International Journal of Trend in Scientific Research and Development (IJTSRD)
Volume 9 Issue 5, Sep-Oct 2025 Available Online: www.ijtsrd.com e-ISSN: 2456 – 6470

An Overview of Pemphigus Vulgaris: From Clinical Presentation to Therapeutic Advances

Jeevitha M, Ramya G K, Pradesh C, Srinivasan A

Pharm D Student, Department of Pharmacy Practice,
JKKMMRF's Annai JKK Sampoorani Ammal College of Pharmacy, Komarapalayam, Tamil Nadu, India

ABSTRACT

Pemphigus vulgaris (PV) is an uncommon intraepidermal blistering disorder. The mean age of onset is between 40 and 60 years, and the incidence is 2.83 per million population worldwide. The oral mucosa is first affected later developed to skin involvement in the course of illness. It is commonly known that immunological and genetic factors affect the onset of PV. However, the illness may be brought on by or affected by external variables (drugs, food, viruses, etc.). The diagnosis requires a biopsy of the perilesional tissue along with histological and immunostaining analyses. Nikolsky's sign is an important clinical diagnostic criteria. First-line treatment involves systemic corticosteroids, often at 1 mg/kg/day, combined with steroid-sparing agents such as azathioprine or mycophenolate mofetil. In refractory or severe cases, rituximab, IVIG, plasmapheresis, or immunoadsorption are effective adjuncts. With these advances, mortality has dropped from over 60–90% to approximately 5–15%. Continuing research into B cell–targeted biologics and optimized immunomodulatory regimens aims to enhance long term remission and reduce treatment related morbidity.

KEYWORDS: *Pemphigus, Desmoglein, Immunoglobulins, plasmapheresis.*

How to cite this paper: Jeevitha M | Ramya G K | Pradesh C | Srinivasan A "An Overview of Pemphigus Vulgaris: From Clinical Presentation to Therapeutic Advances" Published in International Journal of Trend in Scientific Research and Development (ijtsrd), ISSN: 2456-6470, Volume-9 | Issue-5, October 2025, pp.57-62, URL: www.ijtsrd.com/papers/ijtsrd97416.pdf

IJTSRD97416

INTRODUCTION

Pemphigus vulgaris (PV) is an uncommon intraepidermal blistering disorder. The mean age of onset is between 40 and 60 years, and the incidence is 2.83 per million population worldwide [1]. Pemphigus, a rare, chronic, and noncontagious illness of the skin and mucous membranes, was first mentioned in a 1771 medical literature. It can cause symptoms that range from minor to potentially lethal serum-filled vesicles. Among the first treatments were opium and wine. [4] PV, a severe autoimmune illness with mucocutaneous symptoms, is characterized by blisters on the skin and/or mucosal membranes [2].

The blister production is due to autoantibodies that attack keratinocyte surface molecules, destroying the intercellular material and causing keratinocytes to separate from one another (a process known as acantholysis). PV is a serious autoimmune disorder with mucocutaneous manifestation characterized by the development of blisters on the skin and/or mucosal membranes.[2,3]Six types of pemphigus have been established: vulgaris, vegetans, erythematosus, foliaceus, paraneoplastic pemphigus, and pemphigus IgA [2] PV usually identified between the fourty and fifty years of life, and affects both males and females equally[2]PV patients mostly 90% develop oral lesions over the course of the disease, typically begin with the oral mucosa typically a first area affected. [1] Since PNP is very uncommon and PF rarely affects oral tissues, PV is the most prevalent kind in clinical oral medical practice. The oral mucosal lesions typically presents first in PV patients, later lesions associated with skin in the course of the illness. [5] Particularly on the head, face, axilla, trunk, and groin, cutaneous blisters or erythematous patches are signs of skin involvement in PV. One uncommon cause of persistent oral mucosal ulceration is pemphigus vulgaris. For a year or so, the mouth might be the sole area affected, which could cause a delayed diagnosis and improper management of a potentially lethal illness.[27] PV had an incredibly high death rate until corticosteroid

medication became available in the 1950s.Despite the wide range of currently available treatments, corticosteroids used in combination with other medications continue to be the standard of therapy. Pemphigus mortality has dropped drastically over the past 50 years, and it is now typically caused by side effects from the drugs taken.[26]

EPIDEMIOLOGY

In comparison to Western literature, the epidemiology of pemphigus in India has demonstrated different patterns on a number of counts. From 0.09 to 1.8%, the prevalence of pemphigus among dermatology outpatient attendance has varied greatly. PV has been identified in the majority of pemphigus cases, accounting for 75–92% of all pemphigus patients. Sehgal examined 224 cases that were combined from 5 studies that were published across the nation. In the order of decreasing of frequency, PF, PE, and PVeg are the pemphigus forms following PV in incidence.[25] The crude incidence of pemphigus vulgaris was 0.68 (0.58 to 0.80) per 100 000 person years. This incidence was prevalent in women and in older age groups[24]

ETIOLOGY:

PV is caused by an autoimmune process where normal desmosomal adhesion molecules on keratinocyte cell membranes are targeted by IgG serum antibodies [1]. PV was recognized as an autoimmune illness after circulating antibodies against keratinocyte surfaces were found. [8]. IgG4 ê, ë has been linked to the active phase of the disease, while IgG1 ê, ë has been linked to the remission phase. Serum antibodies of the IgG type are invariably the cause of PV [6]. It is commonly known that immunological and genetic factors affect the onset of PV. However, the illness may be brought on by or affected by external variables (drugs, food, viruses, etc.). Surprisingly, a recent systematic review concluded that smoking is a possible protective factor for PV, although other studies with different methodologies have failed to replicate this result[11]

DIAGNOSIS:

Nonscarring, fragile vesicles and mucosal bullae with variable cutaneous involvement are among the clinical signs and symptoms supporting the diagnosis of PV, a potentially fatal autoimmune vesiculobullous illness. [12] Initially vesiculobullous, oral lesions are prone to rupture, with new bullae forming as the older ones burst and become ulcerated. The diagnosis requires a biopsy of the perilesional tissue along with histological and immunostaining analyses.[9] Antibodies to desmoglein 1 and desmoglein 3 can be measured more sensitively using enzyme-linked immunosorbent tests (ELISA). Since ELISA reactivity and disease activity are correlated, this test can be used to diagnose and track the course of pemphigus in patients [17].On hematoxylin and eosin, histologic findings in PV lesions show suprabasalar acantholysis and infiltration with mostly neutrophils and eosinophils. Suprabasalar acantholysis linked to a modest, superficial mixed inflammatory infiltrate, including some eosinophils, is one of the inconspicuous early signs of pemphigus. More advanced lesions may also exhibit these alterations [12].

IgG and C3 intercellular deposits are visible in the perilesional skin of patients when examined by direct immunofluorescence microscopy [13].Indirect immunofluorescence microscopy can identify circulating autoantibodies in the serum of individuals with pemphigus vulgaris that bind to the keratinocyte intercellular connections in human skin or other substrates, such as the esophagus of monkeys. [13] The typical observation of a whitish superficial layer indicating collapsed bullae, along with quickly rupturing bullae primarily in the buccal mucosa, palate, tongue, and lips, is consistent with PV, according to Davenport et al. [10]An important clinical diagnostic criterion is Nikolsky's sign, which is performed by squeezing the skin lesion with the finger to see if a new blister appears [10]. Shearing caused by rubbing on clinically normal skin is an indirect Nikolsky indication [12]. Another potential symptom is the "indirect Nikolsky" or "Nikolsky II," which is another name for the Asboe-Hansen sign. "Bullaspread" is the term for the phenomena that occurs when a slight pressure on an undamaged bulla causes the fluid to spread beneath the skin away from the pressure site [14]. These symptoms are suggestive of PV, albeit they are not always 100% accurate [12]. It has shown itself to be a very useful clinical diagnostic tool and pathognomic of PV, with a specificity of about 96.3% in oral lesions. Following the clinical diagnosis, histological results usually confirm the lesion. [10] Maternal IgG (autoantibodies against Dsg3) can be transferred across the placenta in pregnant women with active pemphigus, increasing the risk that the unborn child will also have neonatal pemphigus. [14]

CLINICAL MANIFESTATION:

In 90% of patients, oral lesions develop over the course of the disease, and they are the initial symptom in 50% to 70% of cases. Blisters are characterized by painful erosions; they are rarely intact, most likely because to their fragility and susceptibility to breaking. The gingivae, lips, and buccal and palatine mucosa are the most affected. Multiple, irregularly shaped, and varying in size, the erosions extend

peripherally and typically exhibit a delay in re-epithelization. Oral lesions affect the general and nutritional state by making feeding challenging. The conjunctiva, nasal mucosa, pharynx, larynx, esophagus, vagina, penis, and anus are among the other mucous membranes that could be affected.[11] Skin lesions can develop anywhere on the skin, but they are more likely to occur on the scalp, face, chest, axillae, groin, and umbilicus and the palms and soles are typically unaffected. They also arise weeks or months after the commencement of mucosal erosions. Localized or generalized cutaneous involvement is possible. The majority of individuals get clear-content, flaccid blisters on erythematous on normal skin. Painful erosions that bleed readily are caused by the blisters' propensity to burst. Crusts form over these erosions, which have little capacity to heal. Although pigmentary changes may be seen, healing typically leaves no scars behind.[11,14]. Nail dystrophy, paronychia, subungual hematomas, and neonatal pemphigus vulgaris are some furthermore, less common clinical symptoms [11-12]. Nail involvement is typically seen when the disease is severe and, in most cases, responds partially or entirely to systemic therapy[11] Pregnant women with pemphigus can passively transfer pathogenic autoantibodies to their unborn child, causing temporary blisters and skin erosions in the newborns as well as, in approximately 25% of cases, mucous membrane erosions. 34 cases of neonatal pemphigus (31 of pemphigus vulgaris and 3 of pemphigus foliaceus) have been reported[20]

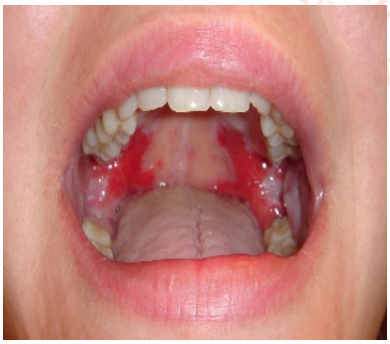

Figure 1: shows oral pemphigus on soft palate of mouth

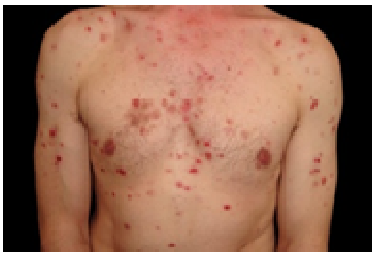

Figure 2: shows cutaneous manifestation of pemphigus vulgaris

Image Source:
https://www.nhs.uk/conditions/pemphigus-vulgaris/

PATHOGENESIS

The inevitably faulty or damage of any one or more of the desmosal proteins which can lead to a lack of cell-cell adhesion and the clinical manifestation of pemphigus-defining vesiculation, erosions, or ulcers. [15] There are four isoforms of desmogleins: Dsg2 is expressed in all desmosome-containing tissues, including the myocardium and simple epithelium; Dsg4 is expressed in hair follicles and may be linked to scalp lesions, which are common in pemphigus; and Dsg1 (160 kDa) and Dsg3 (130 kDa) are only expressed in the squamous stratified epithelium, where pemphigus bullous lesions occur. The desmosome is made up of desmogleins and another class of transmembrane glycoproteins called desmocollins. Whether desmocollins contribute to the etiopathogenesis of pemphigus and the reason they are unable to compensate for the loss of desmoglein function are yet unclear. [16] The difference in Dsg1 and Dsg3 is the basic for this theory with distribution between the skin and mucosa: Dsg1 is expressed throughout the skin, more strongly in the superficial layers, while Dsg3 is concentrated in the lower layers of the epidermis (basal and parabasal), not in the superficial layers; Dsg1 and 3 are expressed in the mucosa, but Dsg3 is abundant than Dsg1. [16] Dsg3 is the primary antigen implicated with mucosal PV. Blisters cannot form in the skin when Dsg3 deficiency is isolated because Dsg1 fully compensated for it. The low Dsg1 concentration in the mucosa, however, is insufficient to make up for the Dsg3 malfunction, resulting in a preponderance of mucosal lesions that do not impact the skin. Dsg1 and Dsg3 are both involved in mucocutaneous PV. As a result, blisters are widely distributed across the skin and mucous membranes. Given that Dsg1 and Dsg3 are expressed throughout the epidermis, it is still unclear why cleavage only takes place in the suprabasal layer and not across the epithelium. Possible explanations include the following: The basal layer is simpler for dermal antibodies to reach, and because there are fewer desmosomes in the basal layer, its intercellular adhesion may be weaker than that of the epidermis' surface.[16] Clinical symptoms similar to PV have been reported to be caused by nondesmoglein autoantibodies against cholinergic receptors (human alpha 9 acetylcholine receptor). When autoantibodies activate these cholinergic receptors, which control keratinocyte adhesion and motility, intracellular signals may be triggered, leading to desmosome disintegration and acantholysis. The successful treatment of PV with the acetyl cholinesterase inhibitors carbachol and pyridostigmine bromide supports the hypothesised role of cholinergic control of keratinocyte adhesion.

[18] TNF-Alpha and Other Cytokines: There are several lines of evidence indicating that the pemphigus blistering process involves TNF-alpha, interleukin (IL)-6, and IL-1. TNF-alpha and IL-6 levels are elevated both in blisters and serum fluid . Therefore, it appears to suggest that a variety of interrelated signaling cascades are responsible for acantholysis and cell death in Pemphigus. [18]

TREATMENT

The goals of the treatment are listed below:

- To promote the healing of the bullous eruption and eliminate the associated functional impairments from the disease;
- To prevent or significantly reduce the likelihood of recurrences;
- To enhance the quality of life for the patients;
- To minimize the typical side effects that often come with prolonged use of immunosuppressive medications or corticosteroids.[23]

STEROIDS

The mainstay of treatment for pemphigus vulgaris (PV) is still systemic corticosteroids. Achieving quick disease control with corticosteroid monotherapy is one of the main issues with simple people. Within a few weeks, disease activity is usually under control. While it can take months or even years of therapy to achieve total remission without treatment, it only takes a few months to achieve complete remission with little treatment [22]. Systemic glucocorticoids, such prednisolone, are used to treat acute episodes of the disease from the beginning. They are taken orally daily at a dose of 1–1.5 mg/kg. The objective is to use the lowest effective dosage of steroids to induce remission of the patient's disease. The goal of using the lowest dosages is to avoid possible comorbidities such as diabetes, high blood pressure, osteoporosis, and Cushing's syndrome. [19]Second-line treatment in the case of contraindications to glucocorticoids or problems owing to anticipated prolonged usage 4 months) requires the combination or single use of immunosuppressants such as azathioprine, MMF, dapsone, methotrexate, cyclophosphamide, and cyclosporine.[22]

IMMUNOSUPPRESIVE AGENTS

Azathioprine is one of the most often utilized PV adjuvants. The EDF guidelines classify this as a first-line adjuvant immunosuppressant. The dose ranges from 1 to 3 mg/kg/day, depending on the activity of the TPMT enzyme responsible for drug metabolism.[22] Its primary adverse reactions include leukopenia, thrombocytopenia, anemia, pancytopenia, and hepatotoxicity.[21] Adults with PV and high TPMT levels should get standard doses of azathioprine (up to 2.5 mg/kg/d), while those with intermediate or low TPMT levels should receive a maintenance dosage (0.5-1.5 mg/kg/d). [22] Adjuvant azathioprine treatment reduces adverse effects relative to steroid monotherapy, while maintaining clinical remission rates [22]. Mycophenolate mofetil and azathioprine, both steroid-sparing medicines, are regarded first-line adjunctive immunosuppressive treatments in pemphigus and have similar safety and effectiveness profiles.[20] MMF is a steroid-sparing substance that is safe. It is categorized as a first-line adjuvant immunosuppressant according to the EDF guidelines. Weight determines the optimal dosage; for a patient weighing 75 kg on average, a daily dose of 2 g is recommended. With a final dose of 2 g/day, a progressive dose increase of 500 mg/week has been suggested to prevent gastrointestinal side effects. [22] Compared to azathioprine, mycophenolate mofetil is more effective at lowering PV and less hepatotoxic [21]. Cyclophosphamide is categorized as a second-line immunosuppressive adjuvant medication according to the EDF guidelines. It can be administered orally at a dose of 2 mg/kg/day or as an IV infusion of 500 mg. Cyclophosphamide's use is further restricted by its possible long-term side effects, which include lymphopenia, infections, genitourinary issues, infertility, and an increased risk of cancer. [22]

INTRAVENOUS IMMUNOGLOBULINS

Intravenous immunoglobulins (IVIG) neutralize and reduce the development of circulating pemphigus antibodies. For pemphigus intravenous immunoglobulins are classified as an adjuvant therapy for pemphigus. Patients treated with intravenous immunoglobulin have a lower risk of infection or reactivation of chronic infections than those treated with traditional immunosuppressants. [17] The normal dose is 2 g/kg/cycle IV given over 2-5 consecutive days, monthly. [22] IVIG treatment can be utilized to treat refractory disease or when immunosuppressive adjuvants are contraindicated. [22]

PLASMAPHERESIS

Plasmapheresis is the process of removing serum IgG antibodies by exchanging plasma with albumin or freshly frozen plasma. This method has been utilized to treat a wide range of antibody-mediated autoimmune diseases. This therapeutic approach is often employed in patients who encounter side effects in corticosteroid therapy, pregnant women, or those who do not react to traditional medicines. [17]

IMMUNOADSORPTION

Immunoadsorption is most effective and safer than plasmapheresis and can be used to treat severe, recalcitrant PV. This method works by rapidly

removing circulating autoantibodies against desmoglein 1 and 3, only IgGs and immune complexes drawn to the absorber and removed from circulation. Some studies have shown that immunoadsorption is more successful when used in combination with immunosuppressive drugs, such as corticosteroids, azathioprine, and rituximab[17].

REFERENCE:

[1] Geng RSQ, Wilken B, Sood S, Sibbald RG, Sibbald C. Biomarkers in Pemphigus Vulgaris: A Systematic Review. Journal of Cutaneous Medicine and Surgery. 2024;28(5):458-462. doi:10.1177/12034754241266136

[2] Ata-Ali F, Ata-Ali J. Pemphigus vulgaris and mucous membrane pemphigoid: Update on etiopathogenesis, oral manifestations and management. J Clin Exp Dent. 2011; 3(3):e246-50. http://www.medicinaoral.com/odo/volumenes/v3i3/jcedv3i3p246.pdf

[3] Buonavoglia, A., Leone, P., Dammacco, R., Di Lernia, G., Petruzzi, M., Bonamonte, D., ... & Dammacco, F. (2019). Pemphigus and mucous membrane pemphigoid: An update from diagnosis to therapy. *Autoimmunity reviews*, *18*(4), 349-358. https://doi.org/10.1016/j.autrev.2019.02.005

[4] Anne-Lise Strandmoe, Jeroen Bremer, Gilles F H Diercks, Antoni Gostyński, Emanuele Ammatuna, Hendri H Pas, Marjan Wouthuyzen-Bakker, Gerwin A Huls, Peter Heeringa, Jon D Laman, Barbara Horváth, Beyond the skin: B cells in pemphigus vulgaris, tolerance and treatment, *British Journal of Dermatology*, Volume 191, Issue 2, August 2024, Pages 164–176, https://doi.org/10.1093/bjd/ljae107

[5] Davis, G., Hathway, R., Shipley, D. *et al.* The management of pemphigus vulgaris and mucous membrane pemphigoid in a joint oral medicine and dermatology clinic: a five-year narrative review. *Br Dent J* **236**, 311–316 (2024). https://doi.org/10.1038/s41415-024-7074-8

[6] Bascones-Martinez A, Munoz-Corcuera M, Bascones-Ilundain C, Esparza-Gómez G (2010) Oral Manifestations of Pemphigus Vulgaris: Clinical Presentation, Differential Diagnosis and Management. J Clin Exp Dermatol Res 1:112. doi:10.4172/2155-9554.1000112

[7] Kumar, Sangeetha Jeevan; Nehru Anand, SP1; Gunasekaran, Nandhini; Krishnan, Rajkumar. Oral pemphigus vulgaris: A case report with direct immunofluorescence study. Journal of Oral and Maxillofacial Pathology 20(3):p 549, Sep–Dec 2016. | DOI: 10.4103/0973-029X.190979

[8] Pettini F, Ballini A, Capodiferro S, et al. Management of oral pemphigus vulgaris: A case report and a clinical update. European Journal of Inflammation. 2015;13(1):53-57. doi:10.1177/1721727X15576854

[9] Sharma, M. (2017). Oral pemphigus vulgaris. *Journal of Kathmandu Medical College*, *4*(3), 100–103. Retrieved from https://jkmc.com.np/ojs3/index.php/journal/article/view/607

[10] Subadra K, S S, Warrier S A (September 15, 2021) Oral Pemphigus Vulgaris. Cureus 13(9): e18005. DOI 10.7759/cureus.18005

[11] Adriana Maria Porro, Camila Arai Seque, Maria Carolina Corsi Ferreira, Milvia Maria Simões, Silva Enokihara, Pemphigus vulgaris*, Anais Brasileiros de Dermatologia, Volume 94, Issue 3,2019,Pages 264-278,ISSN 0365-0596, https://doi.org/10.1590/abd1806-4841.20199011.

[12] Venugopal, Supriya S., and Dédée F. Murrell. "Diagnosis and clinical features of pemphigus vulgaris." *Dermatologic clinics* 29.3 (2011): 373-380, doi:10.1016/j.det.2011.03.004

[13] Mihai S, Sitaru C. Immunopathology and molecular diagnosis of autoimmune bullous diseases. J Cell Mol Med. 2007 May-Jun;11(3):462-81. doi: 10.1111/j.1582-4934.2007.00033.x. PMID: 17521373; PMCID: PMC3922353.

[14] Costan, V., Popa, C., Hâncu, M.F., PorumbAndrese, E., & Toader, M.P. (2021). Comprehensive review on the pathophysiology, clinical variants and management of pemphigus (Review). Experimental and Therapeutic Medicine, 22, 1335. https://doi.org/10.3892/etm.2021.10770

[15] Scully C, Challacombe SJ. Pemphigus Vulgaris: Update on Etiopathogenesis, Oral Manifestations, and Management. Critical Reviews in Oral Biology & Medicine. 2002;13(5):397-408. doi:10.1177/154411130201300504

[16] Porro, Adriana Maria, Camila Arai Seque, and Maria Carolina Corsi Ferreira. "Pemphigus vulgaris." *Anais brasileiros de dermatologia* 94

(2019): 264-278. https://doi.org/10.1590/abd1806-4841.20199011

[17] Popescu, I.A., Statescu, L., Vata, D., Porumb-Andrese, E., Patrascu, A.I., Grajdeanu, I., & Solovastru, L.G. (2019). Pemphigus vulgaris - approach and management (Review). Experimental and Therapeutic Medicine, 18, 5056-5060. https://doi.org/10.3892/etm.2019.7964

[18] Raviraj, J.1; Nayak, Ajay G.2. Current Pathophysiological Aspects and Therapeutic Modalities for Pemphigus Vulgaris: A Review. Journal of Indian Academy of Oral Medicine and Radiology 19(4):p 503-511, October–December 2007.

[19] Sanders, W.J. A brief review of pemphigus vulgaris. *biomed dermatol* **1**, 7 (2017). https://doi.org/10.1186/s41702-017-0008-1

[20] Kasperkiewicz M, Ellebrecht CT, Takahashi H, Yamagami J, Zillikens D, Payne AS, Amagai M. Pemphigus. Nat Rev Dis Primers. 2017 May 11;3:17026. doi: 10.1038/nrdp.2017.26. PMID: 28492232; PMCID: PMC5901732.

[21] Gregoriou, S., Efthymiou, O., Stefanaki, C., & Rigopoulos, D. (2015). Management of pemphigus vulgaris: challenges and solutions. Clinical, Cosmetic and Investigational Dermatology, 8, 521–527. https://doi.org/10.2147/CCID.S75908

[22] Joly, Pascal, et al. "Updated S2K guidelines on the management of pemphigus vulgaris and foliaceus initiated by the european academy of dermatology and venereology (EADV)." Journal of the European Academy of Dermatology and Venereology 34.9 (2020): 1900-1913.

[23] Santoro FA, Stoopler ET, Werth VP. Pemphigus. Dent Clin North Am. 2013 Oct; 57(4):597-610. doi: 10.1016/j.cden.2013.06.002. Epub 2013 Aug 12. PMID: 24034068; PMCID: PMC3883438.

[24] Langan SM, Smeeth L, Hubbard R, Fleming KM, Smith CJ, West J. Bullous pemphigoid and pemphigus vulgaris--incidence and mortality in the UK: population based cohort study. BMJ. 2008 Jul 9;337(7662):a180. doi: 10.1136/bmj.a180. PMID: 18614511; PMCID: PMC2483869.

[25] Amrinder J Kanwar, Dipankar De; Pemphigus in India; 2011:77:4;439-449 doi: 10.4103/0378-6323.82396; PMID: 21727691

[26] Cholera, Mimansa, and Nita Chainani-Wu. "Management of pemphigus vulgaris." *Advances in therapy* 33 (2016): 910-958.

[27] Tamgadge, Sandhya, et al. "Pemphigus vulgaris." *Contemporary clinical dentistry* 2.2 (2011): 134-137.