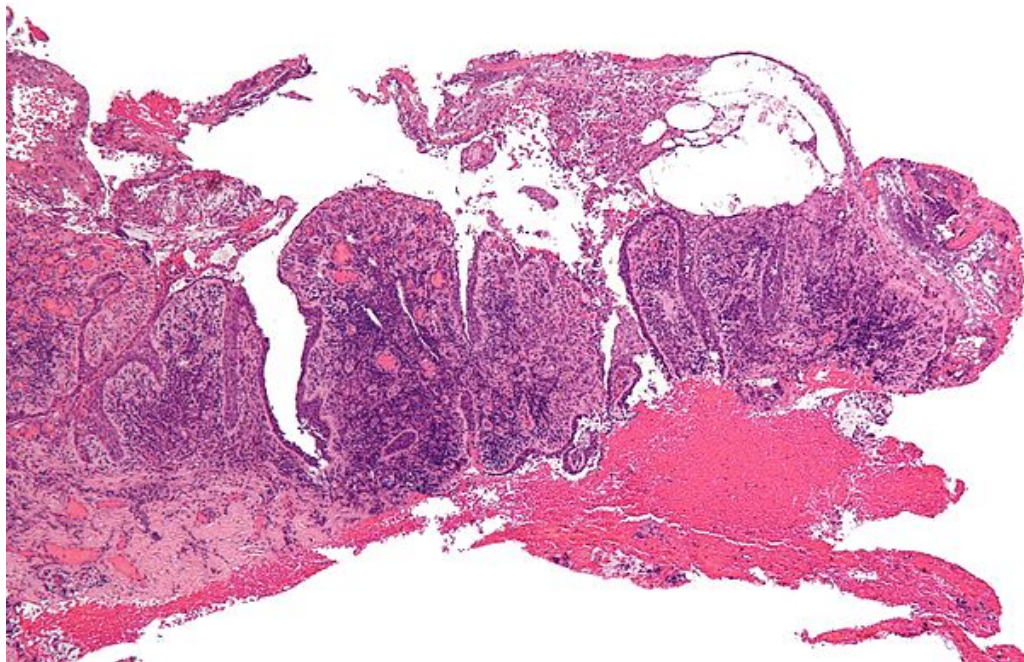


# Pemphigus Vulgaris (PV) — Pathology Outlines and Treatment

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**Pemphigus vulgaris (PV) is a rare, chronic, autoimmune, intraepithelial disease characterized by blister formation involving the skin and mucous membrane. PV is caused by autoantibodies, which are directed against target antigens present on the cell surface of keratinocytes. In this article, epidemiology, pathophysiology, sign and symptoms, differential diagnosis, diagnosis, prognosis and treatment of PV will be discussed.**



## Definition of Pemphigus Vulgaris

The word pemphigus comes from the Greek word “pemphix” which means blister or bubble. Pemphigus Vulgaris (PV) is an immunobullous intraepithelial disease characterized by vesicle formation on the skin and mucous membrane. Target antigens are the cell-cell adhesion molecules referred to as **desmogleins**.

## Epidemiology of Pemphigus Vulgaris

**Incidence and Prevalence:** The frequency of occurrence of the pemphigus group of diseases is known to range from 0.05-2.7/100000/year. Among the different pemphigus diseases, PV is one of the most commonly seen form and its occurrence has some geographical variation. It is common in **the US, Europe, and India**.

**Age:** PV commonly occurs between the fourth and sixth decades of life. However, patients from **Iran, North India, and Pakistan** have shown a younger age of onset with a mean age of 40 years.

**Sex:** PV is known to affect men and women equally with a few studies showing a slightly higher predilection for females.

**Ethnicity:** PV is a disease which affects all ethnic groups, however, it is commonly seen in **Ashkenazi Jews**, Mediterranean, Iranian and Indian populations.

## Etiology of Pemphigus Vulgaris

The cause of PV remains unknown. Certain studies have shown a connection between PV and major histo-compatibility complex (MHC) class II molecules, thus showing possible genetic predisposition.

## Pathophysiology of Pemphigus Vulgaris

PV belongs to the immunobullous group of diseases where antibodies are produced against specific **antigens** present in the skin and mucosa. In PV, **antibodies** are produced and targeted against antigens present in the **epidermis** only. Hence it is classified under **intraepidermal immunobullous disorders**.

**Always remember:** Desmosomes act as the junction between two epidermal cells and **hemidesmosomes** connect basal keratinocytes to the basal lamina in the skin.

**Target antigens against which the autoimmune antibodies are produced are:**

- Dsg 1 (Desmoglein 1)
- Dsg 3 (Desmoglein 3)

**Desmogleins** belong to the **cadherin** family of **cell-cell adhesion molecules** and are part of the **desmosome**. Antigen proteins Dsg 1 and Dsg 3 are expressed differently on the skin and mucous membranes. In the skin, Dsg 1 is found throughout the **epidermis** while Dsg 3 is found in the basal and suprabasal layers. In the oral mucosa, Dsg 3 is mainly expressed with a low expression of Dsg 1. Dsg 1 and Dsg3 have to act synergistically in the skin and mucosa to maintain their stability.

In PV, there is a predominance of antibodies against **Dsg 3** and therefore marked blistering of mucosal epithelium.

## Pemphigus Antibodies

The main class of antibodies found in tissue biopsies of PV patients is IgG. **IgM, IgA** and **IgE antibodies** have also been found but are less common in these patients.

## Acantholysis

Acantholysis is the process of separating **keratinocytes** from one another as observed in PV.

Mechanisms which have been described for acantholysis are a steric hindrance by desmoglein **antibodies**, **protease activation** and disruption of intracellular signaling pathways and **apoptolysis** (apoptosis and acantholysis).

## Genetics

Anti Dsg antibodies have been demonstrated in healthy relatives of PV patients suggesting genetic control over the immune mechanism. PV has strong associations with **HLA DRB1\*04, \*14 alleles, DQB1\*0503 and \*0302.**

## Drug Induced

Drug-induced cases of PV are rare and mainly occur with the use of drugs containing thiol compounds such as penicillamine. Non-thiol drugs linked to the disease include ACE inhibitors, glibenclamide, and drugs with phenol groups such as cephalosporins, rifampicin, pyritinol, phenobarbital and aspirin.

## Symptoms of Pemphigus Vulgaris

**Mucosal lesions:** Mucosal lesions are present in almost all patients of PV. The initial clinical presentation is the presence of **oral mucosal lesions**, in 50-70% of PV patients. These lesions may be the only manifestation or may precede the cutaneous lesions. The most commonly observed lesions are irregularly shaped buccal or palatal erosions that heal slowly. Mucosal membranes involved are oral mucosa, conjunctiva, nasopharynx, larynx, esophagus, vulva, and cervix.

**Cutaneous lesions: Flaccid blisters** filled with clear fluid are the most common cutaneous lesions in PV. The skin covering the face, scalp, neck, upper chest and back is the most commonly affected. The skin around the blister may be normal or **erythematous**. The blisters may rupture leaving behind painful erosions which extend at the edges. Erosions usually heal leaving behind post-inflammatory pigmentation (**hypopigmentation or hyperpigmentation**) without scarring.

## Nikolsky's sign

Nikolsky's sign was first described by a Russian dermatologist Pyotr Vasilievich Nikolskiy. Nikolsky's sign can be demonstrated by the application of a firm sliding pressure on the affected skin (i.e. where the blister is present), perilesional skin (skin near the lesion) or the normal skin (skin away from the blister). A positive response is seen when the blister gets extended and/or removal of epidermis adjacent to blister or removal of epidermis on normal skin.

### Different types of Nikolsky's sign:

**Marginal Nikolsky's sign:** Erosion of perilesional skin on the application of pressure is called marginal Nikolsky's sign. This sign is 69 % sensitive in detecting PV.

**Direct Nikolsky's sign:** Erosion of normal-appearing skin on the application of pressure. This sign is 100% specific in detecting PV.

**Wet Nikolsky's sign:** Application of sliding pressure creates erosion with a moist glistening skin at the base.

**Dry Nikolsky's sign:** Application of sliding pressure creates erosion with a dry base.

**False Nikolsky's sign or Sheklakov's sign:** Application of sliding pressure creates erosion in sub-epidermal blistering disorders such as **bullous pemphigoid**. This sign is elicited in a ruptured blister with some of the skin of the deroofed blister remaining in the

corners of the blister which gets pulled, thus extending the erosion. The erosion gets extended to the surrounding normal skin and heals rapidly.

**Pseudo-Nikolsky's sign:** In this sign, the application of sliding pressure on the affected skin or on erythematous areas leads to erosion. **Pseudo-Nikolsky's sign** is elicited in cases of **toxic epidermal necrolysis (TEN)**, **Stevens-Johnson syndrome**, **bullous ichthyosiform erythroderma** and burns (few cases). In these cases, the epidermal cells undergo necrosis, hence leading to erosion.

## Bulla spread sign (Asboe-Hansen sign)

In this sign, mechanical pressure is applied on the roof of an unruptured blister. A positive sign is elicited when an extension of the blister occurs. In PV, the application of pressure leads to an extension of the blister with a sharp angle. In **bullous pemphigoid**, the application of pressure causes the blister to extend creating a rounded border.

## Other Clinical Findings in Pemphigus Vulgaris

**Nail dystrophies**, **acute paronychia**, and **subungual hematomas** have been seen in PV.

## Clinical Variant of Pemphigus Vulgaris

**Pemphigus vegetans:** It is a rare variant of PV showing vegetating erosions in the flexural areas. This variant has two subtypes: one is the **Neumann type** which is severe and other is the **Hallopeau** type which is milder.

## Diagnosis of Pemphigus Vulgaris

**Tzanck smear:** It is a side lab cytologic smear prepared by gently scraping the base of a deroofed blister. The tissue that is scraped out is smeared on a clean glass slide and kept in open air to dry. This slide is then stained with **Giemsa stain**. Typical changes following acantholysis are seen in this smear. The **tzanck cell** is the name given to the **acantholytic cell** of PV.

The smear, when examined under a light microscope, shows the tzanck cell. The tzanck cell is a rounded epidermal cell with a nucleus which is **dysmorphic** or **hypertrophic** and nucleoli which are hazy or absent. The cytoplasm is abundant and takes up basophilic staining. There is a tendency of the cytoplasm to get condensed at the periphery of the cell membrane leading to deep **basophilic staining** at the edges of the cell membrane (**mourning edge**) and a relatively empty area around the nucleus (**perinuclear halo**). This test is known to be 100 % sensitive and 43.5 % specific for PV.

**Histopathology:** A skin biopsy of the blister shows **intercellular edema** with loss of intercellular attachments as the earliest change. A characteristic **row of tombstones appearance** is seen on the floor of the blister where the basal cells, which remain attached to the basement membrane separate from one another. Blister cavities contain **acantholytic cells**.

**Direct immunofluorescence (IF) test:** In this test, skin or mucosal biopsy is taken from the **perilesional skin** and transported in **Michel's medium**. The basic principle of direct IF test: antibodies are labeled with **immunofluorescent dyes**, which then bind as per their target antigen (tissue antibodies and complement) mainly **IgG** and

**complement protein 3 (C3).** This is the most accurate way to diagnose **mucosal pemphigus**. The characteristic appearance under fluorescence microscope is a 'fishnet' pattern of IgG around the **keratinocytes**.

It has been observed that DIF can be done even on plucked hairs in PV patients. The pilar sheath epithelium of anagen hair shows similar findings under DIF as the skin; hence can be a more acceptable diagnostic test.

**Indirect IF test:** This test is done to detect circulating antibodies mainly IgG and IgA. For this test, a number of epithelial substrates are used such as the esophagus of a monkey, guinea pig, normal human skin and the lip and esophagus of a rabbit. The patient's serum is put on these epithelial substrates in the first step and in the next step the same tissue substrate is covered with fluorescent dye-labeled antihuman IgG. Circulating antibodies are detected in 80 % of patients.

**ELISA (Enzyme Linked Immunosorbent Assay):** Recombinant Dsg 1 and Dsg 3 proteins are being used to detect circulating antibodies in patients' sera.

## Differential Diagnosis of Pemphigus Vulgaris

Differentials for mucosal lesions: Acute herpetic stomatitis, erythema multiforme, **aphthous ulcers**, lichen planus or mucous membrane pemphigoid.

Differentials for cutaneous lesions: Linear Ig A disease, **erythema multiforme**, pemphigoid and its variants.

## Therapy for Pemphigus Vulgaris

### Systemic Therapy

Systemic corticosteroids are the mainstay of therapy in combination with a steroid-sparing immunosuppressant.

**Initial treatment:** Prednisolone is started in doses of 0.5-1 mg/kg/day with steroid-sparing immunosuppressant and appropriate topical therapy. Steroid dose is titrated as per the clinical response.

**For patients with aggressive and generalized disease:** IV pulses of 1 mg methylprednisolone or 100 mg dexamethasone with IVIG, immunoabsorption, and plasmapheresis have been used with variable results.

### Steroid-Sparing Immunosuppressants

**Azathioprine:** used in doses of 2–3 mg/kg/day with prednisolone was found to be effective in many studies.

**Mycophenolate mofetil:** in doses of 1–3 mg/day was found to be as effective as azathioprine with fewer side effects and longer remission.

Cyclophosphamide is an anti-B cell drug that has a number of side effects. Hence it is reserved for PV patients not responding to azathioprine and mycophenolate mofetil.

Intravenous Immunoglobulin is one of the newer treatment options which have also proved to be effective treatment options for PV.

**Rituximab** is a **monoclonal anti-CD 20 antibody** which causes depletion of **B lymphocytes**. It can be combined with conventional steroid therapy with minimal side effects. Reactivation of **viral hepatitis** and increased risk of infections due to excessive immunosuppression needs to be taken care of.

## Other Therapies

**Immunoabsorption and plasmapheresis:** Plasmapheresis is the removal of circulating antibodies from the plasma and has shown limited benefits. Immunoabsorption involves selective removal of IgG and has shown to induce remission. However, simultaneous therapy with steroids and immunosuppressants needs to be administered so as to suppress rebound production of antibodies.

Cyclosporine, methotrexate, infliximab (TNF-alpha inhibitor), acitretin, gold, dapsone, extracorporeal photophoresis, and adalimumab have been used with variable results.

## Topical Therapy

In a case of localized oral disease, potent topical steroids or intralesional steroids may reduce the requirement for systemic steroids.

Good oral hygiene is essential to prevent infections.

**Potassium permanganate** and topical antiseptics to reduce the risk of skin infections.

Emollients on skin to reduce frictional stress on affected skin.

## Progression and Prognosis of Pemphigus Vulgaris

The disease' course in PV is chronic with average disease duration of 10 years. Early oral involvement is known to be an adverse prognostic factor. Patients with an early age of onset and Asian ancestry have shown a prolonged disease activity. The presence of Dsg 1 and Dsg 3 antibodies is associated with more active disease. PV is known to have a mortality rate of 5—15 %.

## References

Griffiths, C., Barker, J., Bleiker, T., Chalmers, R. J., Creamer, D., & Rook, G. A. (2016). Rook's textbook of dermatology. Chichester, West Sussex: John Wiley & Sons Inc. PP 1395-1403.

Urbano F.L. Review of clinical signs. Nikolsky`s sign in Autoimmune Skin Disorders. Hospital Physician. January 2001

Seshadri D, Kumaran MS, Kanwar AJ. Acantholysis Revisited: Back to basics. Indian J Dermatol Venereol Leprol 2013;79:120-6.

Shetty VM, Subramaniam K,Rao R. Utility of Immunofluorescence in dermatology. Indian Dermatol Online J 2017;8:1-8.

Kelly, B., & Shimoni, T. (2009). Reintroducing the Tzanck smear. American journal of clinical dermatology, 10(3), 141-152.

[Pemphigus Vulgaris](https://www.emedicine.com/derm/topic140.htm) via [emedicine.medscape.com](https://www.emedicine.com)

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