

## Bullous Pemphigoid (BP) — Causes and Treatment

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**Amongst all autoimmune blistering diseases, bullous pemphigoid is the most common one. Circulating antibodies are produced against the proteins present in the dermo-epidermal junction (DEJ). In this article, we will study epidemiology, pathophysiology, diagnosis, differential diagnosis, therapy and prognosis of bullous pemphigoid.**



### Definition of Bullous Pemphigoid

Bullous pemphigoid (BP) is a **subepidermal immunobullous** disorder affecting elderly people, characterized by pruritus and bullous lesions on the skin. Other diseases that belong to the pemphigoids group include **pemphigoid gestationis, mucous membrane pemphigoid, linear immunoglobulin IgA dermatosis, lichen planus pemphigoid, and anti-p200 pemphigoid.**

### Epidemiology of Bullous Pemphigoid

#### Incidence and prevalence

A variable incidence ranging from 2.5-66 cases/million per year has been seen for BP,

depending on the population being studied. An increased incidence has been noted in the past 10 years, which can be attributed to population aging, increase in the prevalence of debilitating **neurological disorders**, increased use of diuretics and **psycholeptics** and improved diagnostic assays to recognize BP in its very early stages and atypical forms.

## Age

BP is a disease most common in the elderly (pemphigus Vulgaris usually affects middle-aged persons). The mean age of onset is between 69—83 years. The incidence rises with age; it is observed at 190—312 per million/year in those aged 80 years and above.

## Sex

BP is seen more commonly in females, which could be due to the higher life expectancy of women. Few studies report a higher incidence among men after age adjustments were made.

## Ethnicity

The incidence of BP is variable across countries. However, there is a paucity of data to note any differences among various ethnic groups.

## Associated Diseases

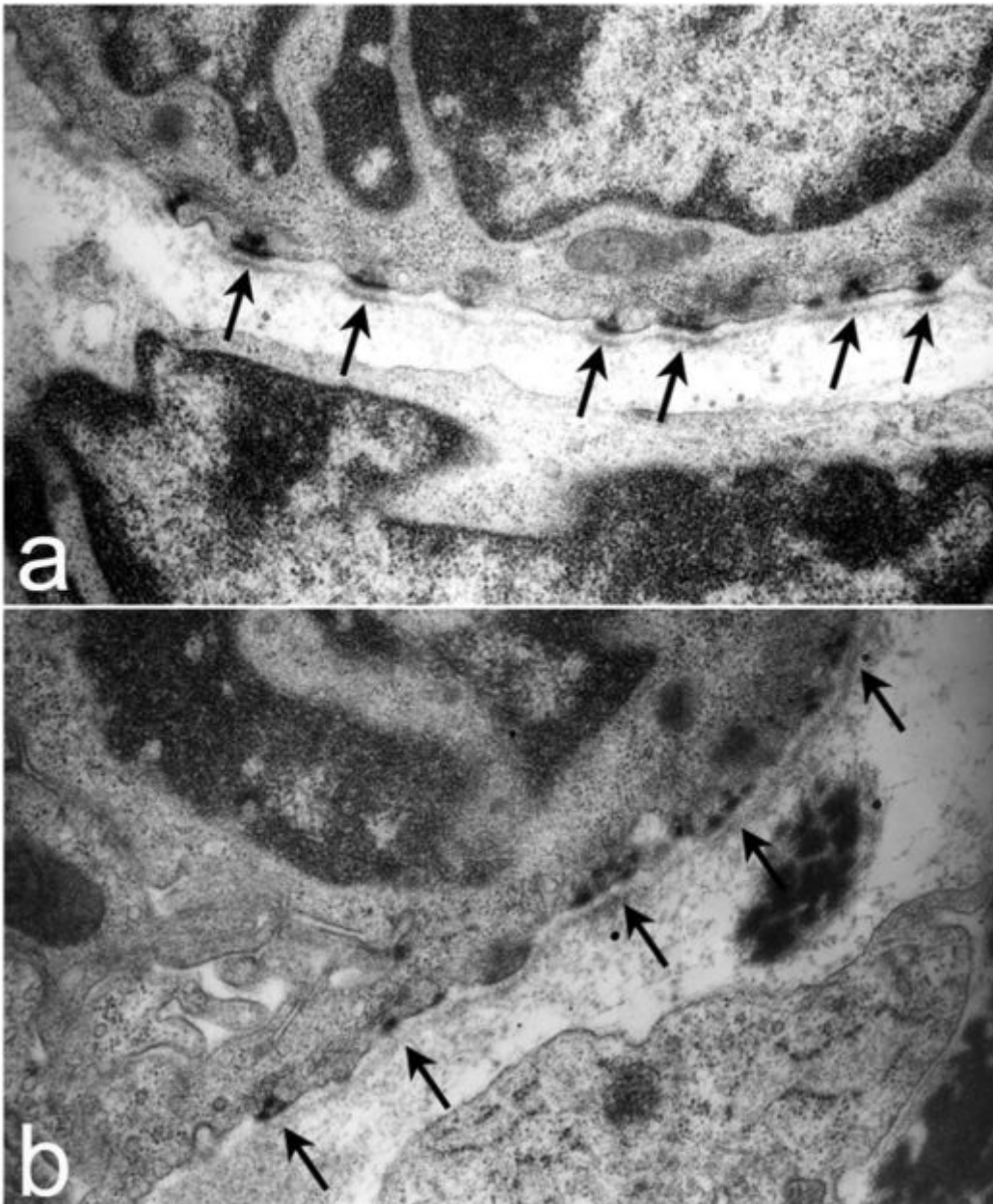
BP has shown association with **neurological** and **psychiatric disorders**. These include cognitive impairment, **Parkinson disease**, **stroke**, **epilepsy**, **multiple sclerosis**, and unipolar and **bipolar disorders**. Studies have shown that 30—50 % of BP patients suffer from **neurological disorders**.

## Pathophysiology of Bullous Pemphigoid

BP is a subepidermal blistering disorder caused by autoantibodies produced against target antigens present in the **dermal-epidermal junction (DEJ)**.

**Important:** The pathophysiology of **bullous pemphigoid** revolves around **hemidesmosomes**, while **desmosomes** are associated with the pathophysiology of **pemphigus Vulgaris**.

**Hemidesmosomes** connect the basal keratinocytes to the basal lamina in the skin.



**Image:** "Ultrastructure of tracheal hemidesmosomes. Tracheas from P1-2 *Lamc2*<sup>-/-</sup> and littermate control mice were processed for transmission electron microscopy. Littermate control tracheas (a) had well-defined, organized hemidesmosomes with darkened areas in the lamina densa abutting the hemidesmosome (arrows). In contrast, hemidesmosomes in *Lamc2*<sup>-/-</sup> tracheas (b) were less organized, the intracellular component was more diffuse, and the lamina densa directly below the hemidesmosomal areas lacked the electron density seen in the littermate control (arrows)," by Nguyen NM, Pulkkinen L, Schlueter JA, Meneguzzi G, Uitto J, Senior RM. License: [CC BY-SA 2.0](https://creativecommons.org/licenses/by-sa/2.0/)

**Target antigens:** hemidesmosome proteins **BP180 NC16A** (in all patients) and **BP 230** (in some patients). **BP180** is also termed as **BPAG2** and **collagen type XVII**. **BPAG2**

The interaction between the **antigen** and **autoantibodies** causes a cascade of events leading to blister formation. The autoantibodies bind to BP180, which initiates secretion of **IL-6** and **IL-8** from **basal keratinocytes** and also a decrease in expression of BP180. In the next step, complement activation takes place at **DEJ** and **degranulation of mast cells** is also seen. Infiltration of inflammatory cells in the **upper dermis** occurs due to the complement activation and **chemokines**. This leads to a further increase in the secretion of **inflammatory mediators**. In the last step, the **granulocytes** release reactive oxygen species and **proteases** at the level of DEJ leading to the split at DEJ and hence the **blister** formation.

## Autoantibodies

**IgG antibodies** against **BP180 NC16A** are present in 75—90 % of BP patients, and the level of this antibody correlates with the disease activity. **IgG antibodies** are produced against **C-terminal epitopes** outside the NC16A domain.

IgA and IgE antibodies are also produced against BP180.

## Cellular immune response

**T-** and **B-cells** recognize the NH<sub>2</sub> terminal portion of **BP180 ectodomain** as an antigen, which is associated with a severe BP.

## Cytokines and Chemokines

Increased levels of the following have been found in the sera and blister fluids of BP patients: IL-1, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-15, eotaxin, **monocyte chemotactic protein 4 (MCP-4)**, TNF-α and CCL-18.

## Predisposing factors

Certain factors have been identified to trigger BP such as trauma, burns, skin grafting, **radiotherapy**, **UV radiation** (includes sunlight), **psoralen** and **UVA (PUVA)** and photodynamic therapy. Few case reports have associated BP with **vaccination** against influenza. Drugs are also known to trigger BP. Most common amongst these are furosemide, spironolactone, phenothiazines with aliphatic side chains and **loop diuretics**.

## Summary of the pathogenesis of bullous pemphigoid

A patient with a genetic predisposition to bullous pemphigoid gets exposed to one of the previously mentioned predisposing factors. This is associated with three main abnormal immune responses:

1. An imbalance between **auto-reactive T helper** and **T regulatory cells**.
2. The activation of **Toll-like receptors**.
3. The activation of **Th17 cells**.

Number 1 and 2 abnormal immune responses lead to **B cell** activation and the production of autoantibodies. **IgG4** autoantibodies are responsible for antibody-mediated direct mechanisms of bullous formation in the disease. **IgG1** production results in the activation of the **complement system**. The activation of the complement system along with the production of **IgE** antibodies result in mast cell degranulation, the recruitment of eosinophils and neutrophils, and the release of proteolytic enzymes. The release of proteolytic enzymes is the cause of subepidermal blistering.

The activation of Th17 cells results in the production of **interleukin-17**. The production of this pro-inflammatory mediator is responsible for the recruitment of eosinophils and neutrophils which then follow a similar pathway until subepidermal blistering eventually develops.

# Symptoms of Bullous Pemphigoid

## History

A **prodromal phase** (absent in the pemphigus vulgaris) of several weeks to months may precede the development of blisters. There is **pruritus** in this phase, which may vary in intensity from mild to intractable. Excoriated papules, eczematous or urticarial lesions, **hemorrhagic crusts, and excoriations** may be seen on the skin in this phase.

**Note:** Pruritus is not present in pemphigus vulgaris.

## Presentation

Vesicles and bullae on apparently normal or erythematous skin associated with intense pruritus are characteristic of BP.



**Image:** "Localized flexural bullous pemphigoid: Tense vesicles and bullae in the groins," by Mehta V, Balachandran C - Indian J Dermatol (2008). License: [CC BY 2.0](https://creativecommons.org/licenses/by/2.0/)

Blisters are **dome-shaped** or **tense** (bullae are **flaccid** in pemphigus vulgaris and rupture easily) and may have a diameter of many centimeters containing clear and sometimes hemorrhagic exudates.

Blisters are symmetrically distributed and mostly involve the flexural aspects of the limbs and abdomen; they remain intact for several days. Erosion and yellowish or **hemorrhagic crusts** may develop following mechanical irritation. **Oral mucosae** are involved in 10-20% of the cases. Other mucosae are rarely involved. Lesions heal without scarring; however, erythema in the affected skin may persist for a long time. **Nikolsky's sign** (refer to the article on **Pemphigus Vulgaris** for more details) is **negative** in BP. However, a false Nikolsky's sign may be elicitable.



[Image:](#) "Bullous pemphigoid in a 72-year-old bedridden female," by Ashashyou. License: [CC BY-SA 4.0](#)

## Clinical Variants of Bullous Pemphigoid

### Localized bullous pemphigoid

In many patients, the disease remains confined to certain body parts, most commonly the **lower extremities** (especially the pretibial area). Other areas where localized BP has been reported are the flexures, palms, soles, genital area, umbilicus, around stomata and **hemodialysis fistula**. This disease may remain localized or progress to classical BP.

### Childhood bullous pemphigoid

Childhood BP has been reported most frequently in the first year of life (**infantile BP**) and at the age of 8 years. Infantile BP was reported following **vaccination**. In infants, blisters form in the **acral areas** (palmar, plantar). In older children, the **genital area** is involved in 50 % of the cases.

Other clinical variants of BP have been described depending on the cutaneous manifestations. These include dyshidrosis form, **prurigo nodularis-like**, prurigo-like, erythrodermic, **ecthyma gangrenosum-like**, **intertrigo-like**, papular, eczematous, **lymphomatoid papulosis-like**, vegetating, vesicular and toxic **epidermolysis-like pemphigoid**. About 20 % of BP patients may present with such atypical presentations at the time of diagnosis.

## Diagnosis of Bullous Pemphigoid

Diagnosis is made based on the clinical picture, **direct IF microscopy** and **serology**.

About 90 % of the patients can be diagnosed by the clinical picture and specific serological tests such as **ELISA** and **indirect IF microscopy**. Direct IF microscopy is the confirmatory test to obtain a definite diagnosis. Biopsy of perilesional skin is taken for DIF and the characteristic **n-serrated pattern** is noted.

Through a light microscope, the histopathology of the lesional skin shows a **subepidermal splitting** with a **dense eosinophil-rich infiltrate** within the papillary dermis and at the **dermo-epidermal junction (DEJ)**. The infiltrate also contains **neutrophils, macrophages, and T-lymphocytes**.

Electron microscopy of the blister shows the split to be at the level of **lamina lucida**.

Direct Immunofluorescent microscopy of perilesional skin **reveals linear deposits of IgG** (mainly IgG1 and IgG4), C3, few IgA and IgE along the DEJ. The pattern that is observed is called **n-serrated pattern**.

## Differential Diagnosis of Bullous Pemphigoid

- Pemphigus group of diseases
- Mucous membrane pemphigoid
- Linear IgA disease, EBA, and anti-p200/laminin  $\gamma$ 1 pemphigoid
- **Dermatitis herpetiformis**
- Differentials for the prodromal phase: localized or generalized drug reactions, **contact, and allergic dermatitis, prurigo, urticaria, urticarial vasculitis**, arthropod reactions, scabies, **ecthyma, pityriasis lichenoides**.

## Therapy of Bullous Pemphigoid

Systemic and topical steroids are the mainstay of treatment for BP. As the disease occurs in the elderly, **systemic steroids** and **steroid-sparing immunosuppressants** are used at a minimum dose as is required. The main aim of therapy is to reduce inflammation and autoimmune activity. Steroids inhibit the various inflammatory pathways and immunosuppressants suppress the overactive immune system through various mechanisms.

The recommendations of the European Dermatology Forum and the European Academy of Dermatology and Venereology, published in 2015, for the treatment of bullous pemphigoid are summarized below:

### Localized or mild disease

The localized or mild disease has been defined as the occurrence of less than 10 new blisters per day or presence of **non-bullous inflammatory** or localized lesions involving a single body site.

**First choice:** lesional application of **very potent topical steroids** (0.05 % clobetasol propionate ointment) applied twice a day in case of mild BP only.

**In patients having mild BP with few disseminated lesions:** whole-body application of very potent topical steroids (0.05 % clobetasol propionate ointment).

**Second choice:** Oral prednisolone in doses of 0.5 mg/kg/day.

## Extensive disease

- > 10 new lesions/day or inflammatory lesions covering a large body surface area.

### First-line therapy:

- Very potent topical corticosteroids on the whole body surface to be applied twice a day.
- Oral steroids (prednisolone).

**The second choice of drugs**, along with the first line of treatment, can be started as adjunctive therapy or as alternative therapy:

- Azathioprine
- Mycophenolate
- Tetracycline + nicotinamide
- Methotrexate
- Chlorambucil

**The third choice** can be started in combination with the first line or can be introduced as alternative therapy:

- Anti-CD20 or anti-IgE monoclonal antibody
- Intravenous immunoglobulins
- Immunoabsorption
- Plasma exchange
- Cyclophosphamide

**Note:** The recommended duration of treatment is 4–12 months depending upon the nature of the disease (mild or extensive).

## Progression and prognosis of bullous pemphigoid

Few studies have shown that BP patients are three times at a higher risk of developing **pulmonary infection** and **embolism** as compared to controls.

BP is a chronic self-limiting disease and may last for years when untreated. Relapses may occur in 50 % of the patients and observation shows that they are more common in those suffering from extensive disease, dementia and high serum levels of **anti-BP180 NC16A antibodies**. The duration of the disease is usually 3–6 years.

The mortality rates in the first year of the disease were studied to be between 10 to 40 %. Certain risk factors have been found leading to increased mortality (less fatal than **pemphigus vulgaris**) among BP patients such as old age (greater than 80 years), extensive disease, high doses of **prednisolone** (> 35 mg/day), low serum albumin levels (3.6 g/dL), presence of **heart disease, diabetes** or **neurological diseases**.

## Review Questions

The correct answers can be found below the references.

**1. A 75-years-old patient of Parkinson's disease presents with intense itching all over the body that has developed over the past 6 months and with the presence of tense bullae on the limbs. Nikolsky's sign is negative. Which of the following is the most probable diagnosis?**



- A. Pemphigus vulgaris
- B. Bullous pemphigoid
- C. Dermatitis herpetiformis
- D. Mucous membrane pemphigoid

**2. An 80-year-old female patient was diagnosed with bullous pemphigoid. Her DIF test of perilesional skin was positive for BP. Which of the following is the most likely finding in the DIF test?**

- A. Fishnet appearance
- B. Immunofluorescence along the basement membrane
- C. N-serrated appearance
- D. Maze-like appearance

**3. A 70-year-old male was diagnosed with bullous pemphigoid. At present, he has one bulla on the leg and itching on the legs. What is the treatment of choice?**

- A. Oral prednisolone in the dose of 1mg/kg/day.
- B. Mild topical steroids like hydrocortisone.
- C. Very potent topical steroids.
- D. Very potent topical steroids with oral prednisolone in the dose of 1 mg/kg/day.

## 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 1404-1417.

Essentials in Dermatology, Venereology, Leprology Cosmetology. Jaypee Brothers Medical Publishers; First edition (2015). PP 151.

Schmidt, E., & Zillikens, D. (2013). Pemphigoid diseases. The Lancet, 381(9863), 320-332.

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

1. Feliciani, P. Joly, M.F. Jonkman, G. Zambruno, D. Zillikens, D. Ioannides et al. Management of bullous pemphigoid: the European Dermatology Forum consensus in collaboration with the European Academy of Dermatology and Venereology. British Journal of Dermatology (2015) 172, pp867-877

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.

Borradori, L., & Sonnenberg, A. (1999). Structure and function of hemidesmosomes: more than simple adhesion complexes. Journal of Investigative Dermatology, 112(4), 411-418.

D'Auria, L., Cordiali, F. P., & Ameglio, F. (1999). Cytokines and bullous pemphigoid. European cytokine network, 10(2), 123-134.

<http://emedicine.medscape.com/article/1062391-overview#a6>

<http://www.uptodate.com/contents/epidemiology-and-pathogenesis-of-bullous-pemphigoi>

[d-and-mucous-membrane-pemphigoid](#)

Bullous pemphigoid: Etiology, pathogenesis, and inducing factors: Facts and controversies | <https://doi.org/10.1016/j.clindermatol.2013.01.006>

**Correct answers:** 1B; 2C; 3C

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Notes