


Bullous Pemphigoid: Risk Factors, Clinical Manifestations, Diagnosis, and Management

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ABSTRACT

Bullous pemphigoid is an autoimmune disease characterized by subepidermal bullae, primarily affecting the elderly population. This disease involves autoantibodies targeting hemidesmosomal proteins, particularly BP180 and BP230, which play a crucial role in dermal-epidermal adhesion. Although bullous pemphigoid may resolve spontaneously, some cases exhibit a chronic course with significant complications. Diagnosis is based on history-taking, physical examination, and supportive investigations, including direct immunofluorescence (DIF) and enzyme-linked immunosorbent assay (ELISA) testing. Management involves topical corticosteroids for localized cases and systemic corticosteroids for more extensive involvement. Immunosuppressive agents such as methotrexate or azathioprine are used as adjunctive therapy. Several factors, including advanced age, neurological comorbidities, and exposure to certain medications, may increase the risk of developing bullous pemphigoid and influence its prognosis. Early recognition of characteristic clinical findings, confirmation through immunopathological examination, and selection of treatment according to disease severity and patient comorbidities are essential to improve clinical outcomes. Long-term monitoring is also required to detect relapse, treatment-related adverse effects, and complications associated with this disease. Although the mortality rate remains high, effective management can help alleviate symptoms and minimize long-term complications.

Keywords: Autoimmune, bullous pemphigoid, DIF, ELISA, immunofluorescence.

ABSTRAK

Pemfigoid bulosa merupakan penyakit autoimun yang ditandai dengan terbentuknya bula subepidermal dan terutama menyerang populasi lanjut usia. Penyakit ini melibatkan autoantibodi yang menargetkan protein hemidesmosomal, khususnya BP180 dan BP230, yang berperan penting dalam adhesi dermoepidermal. Meskipun pemfigoid bulosa dapat mengalami resolusi spontan, sebagian kasus menunjukkan perjalanan penyakit yang kronis dengan komplikasi yang bermakna. Diagnosis ditegakkan berdasarkan anamnesis, pemeriksaan fisik, serta pemeriksaan penunjang, termasuk *direct immunofluorescence* (DIF) dan *enzyme-linked immunosorbent assay* (ELISA). Tata laksana meliputi pemberian *corticosteroid* topikal pada kasus terlokalisasi dan *corticosteroid* sistemik pada kasus dengan keterlibatan yang lebih luas. Agen imunosupresif seperti *methotrexate* atau *azathioprine* dapat digunakan sebagai terapi adjuvan. Beberapa faktor, seperti usia lanjut, komorbid neurologis, dan penggunaan obat-obatan tertentu, dapat meningkatkan risiko terjadinya pemfigoid bulosa serta memengaruhi prognosis penyakit. Pengenalan dini terhadap manifestasi klinis yang khas, konfirmasi diagnosis melalui pemeriksaan imunopatologi, serta pemilihan terapi yang sesuai berdasarkan derajat keparahan penyakit dan komorbiditas pasien sangat penting untuk meningkatkan luaran klinis. Pemantauan jangka panjang juga diperlukan untuk mendeteksi kekambuhan, efek samping terapi, serta komplikasi yang berkaitan dengan penyakit ini. Meskipun angka mortalitas masih relatif tinggi, tata laksana yang tepat dapat membantu mengurangi gejala dan meminimalkan komplikasi jangka panjang. **Arohid Allatib, Angki Perdiyana, Marsita Endy Dhamayanti. Pemfigus Bulosa: Faktor Risiko, Manifestasi Klinis, Diagnosis, dan Tata Laksana.**

Kata Kunci: Autoimun, pemfigus bulosa, DIF, ELISA, *immunofluorescense*.

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INTRODUCTION

Bullous pemphigoid is an autoimmune disease characterized by the formation of subepidermal bullae or blistering.[1] This subepidermal autoimmune disorder accounts for 80% of subepidermal immunobullous cases. The disease typically presents as pruritic bullae, frequently arising over urticarial plaques. Their formation is

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triggered by autoantibodies directed against the hemidesmosomal proteins BP180 and BP230, which incite an inflammatory response and ultimately lead to blister formation.[2,3]

Bullous pemphigoid was first described by Walter Lever in 1953 as the formation of bullae beneath the epidermis with distinctive clinical and histological features. Fourteen years later, Jordon and Beutner identified antibodies at the dermal-epidermal junction in the skin surrounding lesions and in patient serum, confirming that bullous pemphigoid is distinct from pemphigus.[4] Over time, the antigenic targets of this disease were successfully identified as the hemidesmosomal proteins BP180 and BP230.[2,3]

Clinical risk factors associated with higher mortality include advanced age and neurological disorders that are more common among elderly patients, such as dementia (including Alzheimer's disease).[2,3]

MAIN REVIEW

Epidemiology

Bullous pemphigoid is typically diagnosed in individuals over 60 years of age, with peak incidence in the seventh decade of life. Nevertheless, classic bullous pemphigoid may also occur in middle-aged adults and, rarely, in infants and children. No ethnic, racial, or sex predilection has been established for bullous pemphigoid.[2]

The incidence of bullous pemphigoid is rising and may reach 22 to 24 cases per million person-years in the United States and France, with the incidence among individuals over 70 years of age reaching 190–312 cases per million per year.[2] The incidence of this disease is equal between men and women and shows no racial predilection. Although rare, the disease can occur during childhood. Certain HLA class II alleles have been identified, including the DQB1*0301 allele in Caucasian patients, as well as the DRB1*04, DRB1*1101, and DQB1*0302 alleles in Japanese patients.[3]

Clinical Manifestations

The clinical manifestations of bullous pemphigoid (BP) are highly variable, particularly during the early stage or in atypical forms that lack characteristic blistering lesions. The non-bullous phase typically begins with nonspecific symptoms, such as pruritus, sometimes accompanied by papular, urticarial, or eczematous lesions. These atypical manifestations frequently complicate diagnosis. This phase may last from several days to several months, and in some cases, pruritus may be the sole diagnostic clue for BP. This non-classic form is known as non-bullous cutaneous pemphigoid; approximately 20% of BP patients present with this atypical variant. Several subtypes have been identified, namely: (i) eczematous, (ii) urticarial, and (iii) nodular pemphigoid.[5]

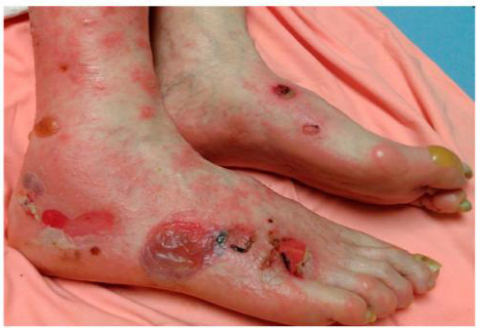
The bullous stage of BP is marked by the appearance of more characteristic vesicles and bullae. In classic BP, tense bullae measuring 1 to 3 cm typically arise on erythematous or normal-appearing skin. When bullae rupture, the affected area forms a crust and typically heals without scarring. However, milia, hyperpigmentation, hypopigmentation, or other post-inflammatory changes may develop at this stage. Lesions are frequently found on the flexor surfaces of the upper and lower limbs, the lower abdomen, and the axillae. Bullae are generally filled with serous fluid, although they may also be hemorrhagic. The Nikolsky and Asboe-Hansen signs are typically negative. Pruritus is generally intense, although it may be minimal in some patients.[2] The clinical appearance of skin lesions in this inflammatory type of BP is shown in **Figure 1**.

In addition to the classic presentation involving tense bullae over an erythematous or urticarial base, a non-inflammatory form of bullous pemphigoid may also present as tense bullae on apparently normal-appearing skin. This non-inflammatory form may be associated with a sparser inflammatory infiltrate on histology (**Figure 2**). Non-bullous lesions frequently represent the initial manifestation of bullous pemphigoid in nearly half of patients (**Figure 3**).[2] Mucosal involvement occurs in approximately 10%–30% of patients, most commonly affecting the oral mucosa. Although cutaneous or mucosal lesions are rarely fatal, mortality among BP patients is six times higher than in a healthy population of the same age.[5]

Etiology

Bullous pemphigoid develops through multiple stages, beginning with autoantibodies targeting hemidesmosomal antigens, which subsequently trigger an inflammatory response and bulla formation.[2,3]

Immunofluorescence (IF) examination reveals autoantibodies targeting the basement membrane zone (BMZ) of the skin, specifically the hemidesmosomes—



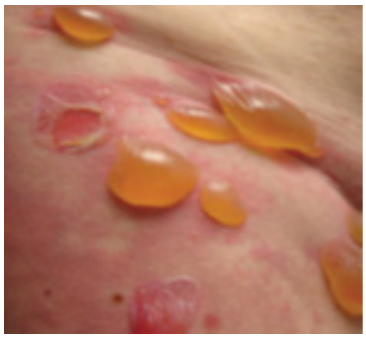


Figure 1. Inflammatory bullous pemphigoid lesions: large, tense bullae, some showing erosion on the dorsum of the foot.[2]

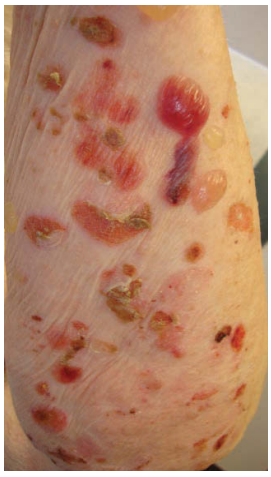


Figure 2. Non-inflammatory bullous pemphigoid lesion.[1,2]

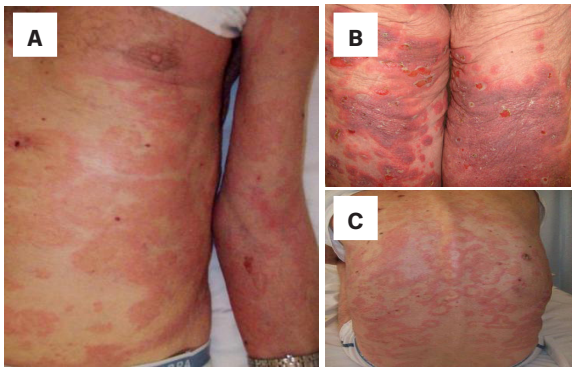


Figure 3. Non-bullous phase cutaneous pemphigoid lesions. (a) Urticarial and polycyclic lesions during the non-bullous phase of bullous pemphigoid; (b) urticarial lesions resembling erythema multiforme in bullous pemphigoid of the thigh; (c) multiple polycyclic and targetoid lesions during the non-bullous phase of bullous pemphigoid.[1,2]

organelles that anchor basal cells to the basement membrane.[2,3] Two major antigens are recognized by these autoantibodies:

1) BP230 (BPAG1): A 230-kDa protein that functions to stabilize keratin filaments in the epidermis.[2,3] In mice lacking BP230, keratin filaments become unstable despite intact dermal-epidermal adhesion.[6] A neuronal isoform of this protein, BPAG1n, is also found in neural tissue and plays a role in stabilizing the sensory neuron cytoskeleton.[7]
2) BP180 (BPAG2, or type XVII collagen): A transmembrane protein with a molecular weight of 180 kDa that plays a role in dermal-epidermal adhesion.[2,3] Its extracellular domain spans the lamina lucida and lamina densa.[8] The NC16A domain of BP180 is the principal region recognized by autoantibodies.[8] The ELISA test measuring antibodies against this domain is highly sensitive and specific for the diagnosis of bullous pemphigoid and can be used to monitor disease activity.[3,5]

Risk Factors and Pathogenesis

Aging is the principal risk factor for bullous pemphigoid (BP), with the majority of cases occurring around 75 years of age and more frequently in women.[4,5] The mechanism by which aging becomes a risk factor for bullous pemphigoid involves several stages. Aging results in an immune system remodeling process known as immunosenescence. In elderly individuals: (a) production of low-affinity immunoglobulins increases, and (b) serum IgG1 and IgG4 levels increase; (c) a chronic, sterile, low-grade inflammatory background is characteristic of aging. This condition (basal cytokine production) may act as a stimulus for the emergence of autoimmunity; (d) infections occur frequently and persistently in the elderly. Within a dysregulated immune system, peptides from infectious agents may cross-react with self-peptides of similar sequence. (e) The $CD4^+CD25^+$ regulatory T-cell compartment tends to decline. These regulatory cells are capable of counteracting autoimmune processes, so a reduction in their numbers may support the development of autoimmunity (**Figure 4**).[4]

More than 50 drugs have been associated with BP, including diuretics (furosemide), antibiotics (ciprofloxacin, amoxicillin), analgesics, and biologic agents, including TNF inhibitors and the anti-diabetic dipeptidyl peptidase-4 (DPP-4) inhibitors. However, the precise mechanism by which these drugs induce BP requires further investigation.[5] A summary of drugs studied in relation to BP is presented in **Table 1.**

The mechanism of drug-induced BP involves several stages: (a) A drug may act as an antigen by covalently binding to endogenous proteins. This can alter their antigenic properties by exposing previously hidden antigenic sites or generating new antigens. (b) Low-molecular-weight drugs may become immunogenic through non-covalent binding with molecules such as major histocompatibility complex (MHC) and T-cell receptors (TCR), triggering an immune response. (c) Another proposed mechanism underlying drug-induced BP is molecular mimicry, whereby a drug may be misidentified as a microbial antigen, activating $CD4^+$ T cells and initiating an autoimmune cascade. (d) Inhibition of plasmin by dipeptidyl peptidase-4 inhibitors (DPP-4i) may alter the normal cleavage process of BP180, thereby modifying its antigenicity. (e) Certain drugs may disrupt endogenous regulatory

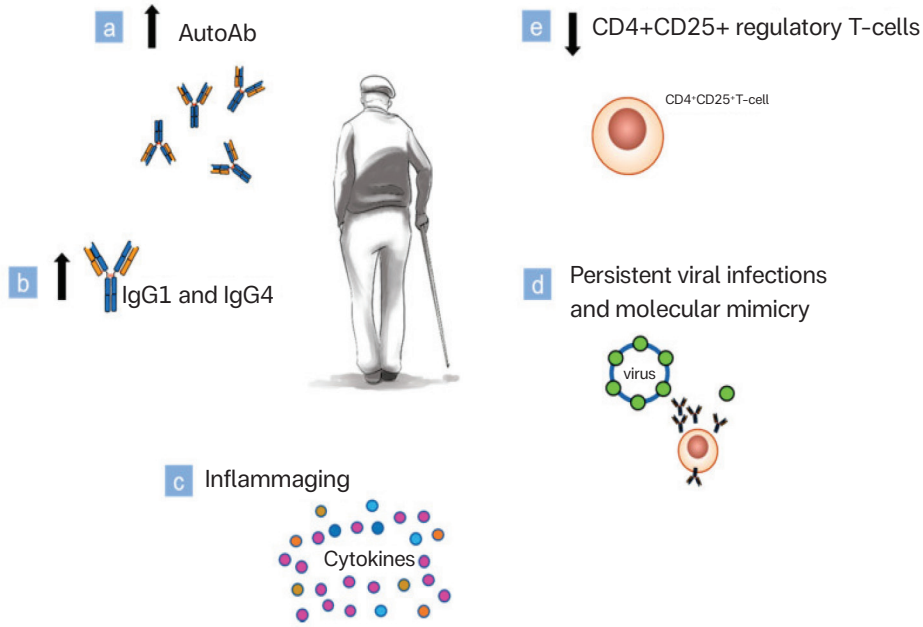


Figure 4. Aging as a risk factor for bullous pemphigoid.[4]

Abbreviations: AutoAb: Autoantibody; CD4: Cluster of differentiation 4; CD25: Cluster of differentiation 25; IgG1: Immunoglobulin G subclass 1; IgG4: Immunoglobulin G4.

Table 1. Drugs associated with bullous pemphigoid.[4]

PD-1/PD-L1 Inhibitors	Antibiotics	ACE Inhibitors	β-Blockers	NSAIDs	DPP-4 Inhibitors	Diuretics	Anti-TNF-α	Others
Pembrolizumab	Actinomycin	Captopril	Atenolol	Azapropazone	Sitagliptin	Furosemide	Adalimumab	Arsenic
Nivolumab	Amoxicillin	Enalapril	Nadolol	Celecoxib	Vildagliptin	Spironolactone	Efalizumab	Doxepin
Durvalumab	Ampicillin	Lisinopril	Practolol	Diclofenac (topical)	Alogliptin	Bumetanide	Etanercept	Clonidine
	Cephalexin		Angiotensin II receptor antagonists	Ibuprofen	Linagliptin		Infliximab	Erlotinib
	Ciprofloxacin		Losartan	Mefenamic acid	Teneligliptin			Escitalopram
	Chloroquine			Phenacetin	Saxagliptin			Everolimus
	Dactinomycin				Anagliptin			Fluoxetine
	Griseofulvin							Flupentixol
	Levofloxacin							Gabapentin
	Metronidazole							Galantamine
	Penicillin							Hydrobromide
	Rifampicin							

Abbreviations: PD-1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; ACE: Angiotensin-converting enzyme; NSAIDs: Nonsteroidal anti-inflammatory drugs; DPP-4: Dipeptidyl peptidase-4; TNF-α: Tumor necrosis factor-alpha.

mechanisms involving T cells. For example, antibodies against immune checkpoints such as PD-1 and PD-L1 may force the immune system into an excessive response, which can also trigger autoimmune reactions (**Figure 5**).[4] Hereditary factors that increase susceptibility to autoimmune disease may also play a role in this relationship.[5]

Although the genetic basis of BP is not yet fully understood, several studies[9–15] have demonstrated a role for the HLA-DQB1*0301 gene in the development of BP. In addition, associations have been found with other genetic abnormalities, such as mitochondrial anomalies (the MT-ATP8 gene), the CYP2D6 isoenzyme, and overexpression of the FcγRIIIa receptor on immune cells.[5]

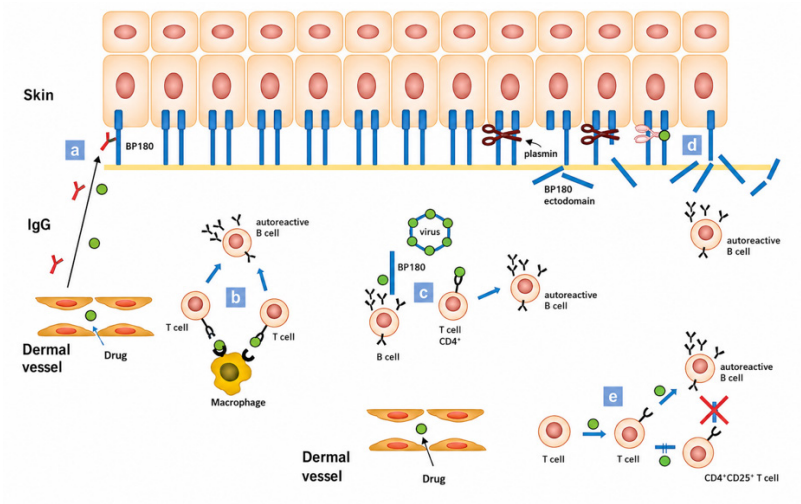


Figure 5. Mechanism of drug-induced bullous pemphigoid.[4]

Abbreviations: BP180: Bullous pemphigoid antigen 180; B-cell: B lymphocytes; T-cell: T lymphocytes; CD4: Cluster of differentiation 4; CD25: Cluster of differentiation 25.

Pathophysiology

Bullous pemphigoid (BP) is characterized by autoantibodies against BP180 and BP230, with anti-BP180-NC16A IgG titers correlating with disease activity. Inflammatory cells such as eosinophils, neutrophils, and lymphocytes are found in the upper dermis and within the bullous cavity. Proteases such as plasmin and MMP-9 play a role in subepidermal blister formation by degrading the extracellular matrix.[2] A concise overview of the clinical findings and pathogenesis of bullous pemphigoid is presented in **Figure 6**.[16]

In murine model studies, subepidermal blister formation is thought to result from an inflammatory process involving several steps:

(1) Anti-BP180 IgG binds to a pathogenic epitope of the BP180 antigen on the surface of basal keratinocytes (BK).
(2) The interaction between the BP180 antigen and anti-BP180 IgG activates the classical complement (C') pathway.
(3) Complement activation products, namely C3a and C5a, promote mast cell (MC) degranulation.
(4) Proinflammatory mediators such as tumor necrosis factor-α, released by mast cells, recruit neutrophils (PMNs) to the site.

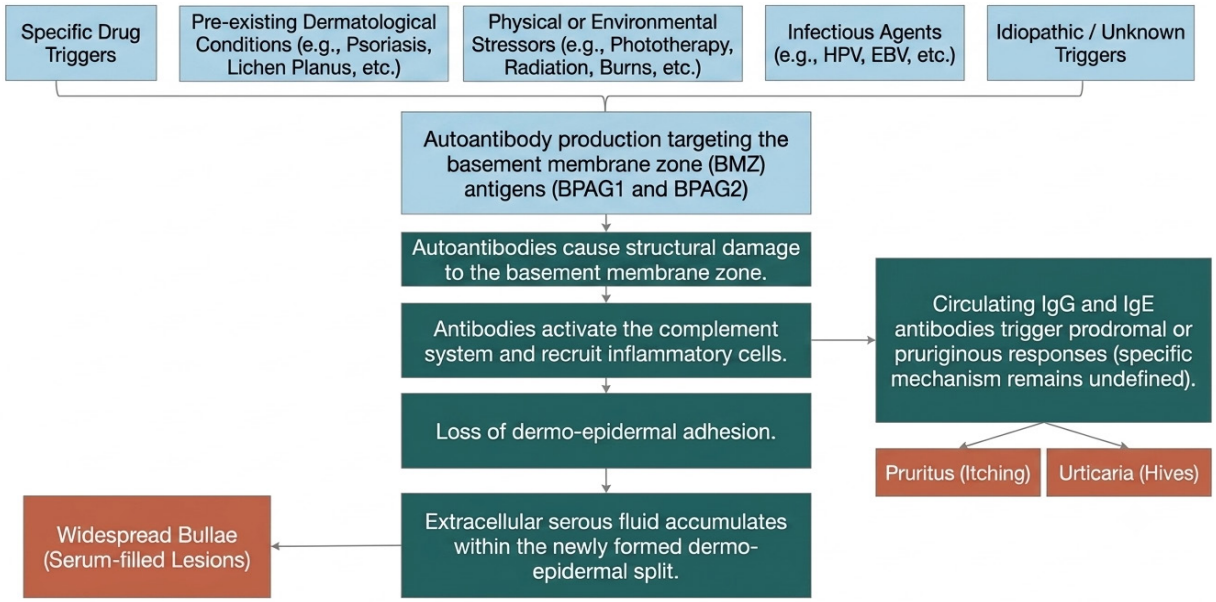


Figure 6. Pathogenesis and clinical manifestations of bullous pemphigoid.[16]

Abbreviations: HPV: Human papillomavirus; EBV: Epstein-Barr virus; BPAG1: Bullous pemphigoid antigen 1; BPAG2: Bullous pemphigoid antigen 2; IgG: Immunoglobulin G; IgE: Immunoglobulin E.

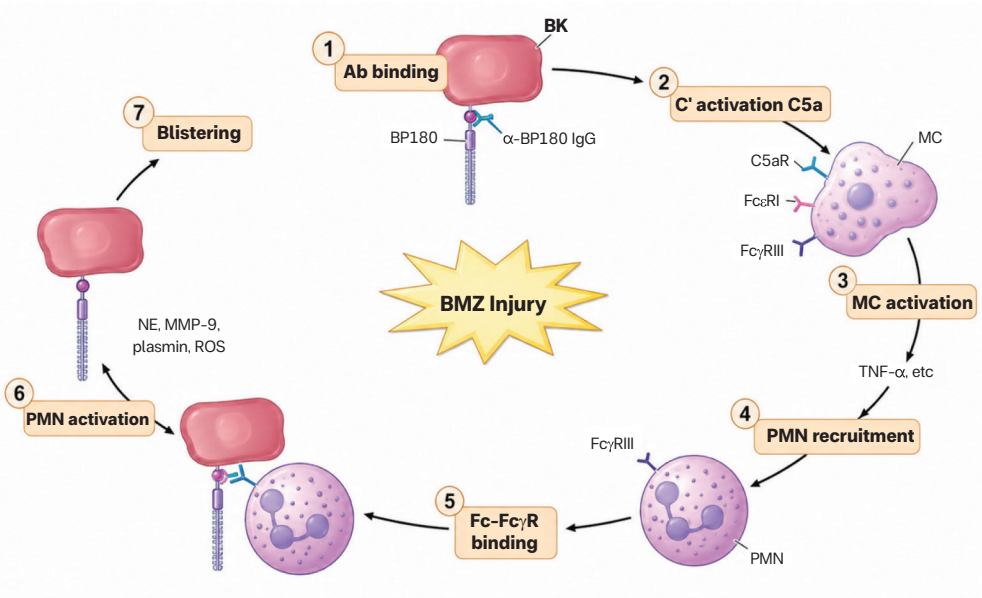


Figure 7. Pathophysiology of blister formation in bullous pemphigoid.[2]

Abbreviations: Ab: Antibody; BK: Basal keratinocyte; NE: Neutrophil elastase, MMP-9: Matrix metalloproteinase-9; ROS: Reactive oxygen species; PMN: Polymorphonuclear neutrophil; BMZ: Basement membrane zone; MC: Mast cell; TNF-a: Tumor necrosis factor-alpha; C5a: Complement component 5a; C5aR: Complement component 5a receptor; FcεRI: High-affinity Fc epsilon receptor I; FcγRIII: Fc gamma receptor III; FcR: Fc receptor.

(5) Infiltrating PMNs bind the BP180–anti-BP180 IgG immune complex through interaction between the FcγRIII receptor on neutrophils and the Fc domain of anti-BP180 IgG.

(6) This interaction activates PMNs to release neutrophil elastase (NE), gelatinase B (MMP-9), plasminogen activator (PA), and reactive oxygen species (ROS).

(7) These proteolytic enzymes and ROS act together to degrade BP180 and other extracellular matrix proteins, ultimately resulting in subepidermal blister formation (**Figure 7**).[2]

Diagnosis and Supportive Investigations

The diagnosis of bullous pemphigoid (BP) is based on characteristic clinical findings, the presence of specific autoantibodies (detected via indirect immunofluorescence or ELISA testing), and skin biopsy with direct immunofluorescence (DIF). Specific clinical features together with a positive direct IF result constitute the most important diagnostic criteria. In approximately 10% of patients with negative indirect IF and ELISA results, additional immunopathological testing is required to detect BP-specific autoantibodies, such as anti-BP180 and anti-BP230. In addition, most patients exhibit hypereosinophilia and/or elevated total IgE levels.[5]

Clinical Criteria

Bullous pemphigoid should be suspected in elderly individuals presenting with generalized pruritus, with or without prominent bullae. Initial patient evaluation should include a detailed history to identify comorbidities and

risk factors, along with physical examination. In the typical form, there is no involvement of the head, neck, or mucous membranes.[5]

A complete medical history is essential, including assessment of the severity and duration of pruritus, onset and progression of symptoms, comorbidities, history of malignancy, and medication use within the preceding 1–6 months. Treatment selection is also influenced by the presence of concomitant cardiovascular disease or immunodeficiency.[5]

BP is typically characterized by tense, transparent bullae surrounded by erythematous or urticarial plaques, along with moderate-to-severe pruritus. A previous study demonstrated a sensitivity of 90% and specificity of 83% for the diagnosis of BP when patients met three of the following four criteria:[17]

1) Absence of head and neck involvement
2) Absence of mucous membrane involvement
3) Age over 70 years
4) Absence of atrophic scarring.

However, these clinical criteria require a history of blister formation, which is absent in approximately 20% of patients at the time of diagnosis. Therefore, in patients without bullous manifestations (such as urticarial, erosive, or eczematous lesions) direct IF microscopy and detection of BP-specific antibodies (anti-BP180 and anti-BP230) are essential for the diagnosis of BP.[5]

Immunofluorescence (IF) Microscopy

Direct immunofluorescence (IF) microscopy of perilesional (non-bullous) skin is the gold standard for the diagnosis of autoimmune bullous disorders, including bullous pemphigoid. Although not entirely specific, this technique is highly sensitive for BP.[18] Examination reveals linear and continuous deposition of IgG (predominantly IgG4 and IgG1) and/or C3 along the epidermal basement membrane (BM) (**Figure 8**). IgA and IgE may also be found in a similar pattern, although rarely. Biopsy of an early bulla reveals a subepidermal blister with inflammatory cell infiltration, predominantly eosinophils, neutrophils, and mononuclear cells in the upper dermis, while the blister cavity contains a fibrin network and various infiltrating cells.[5]

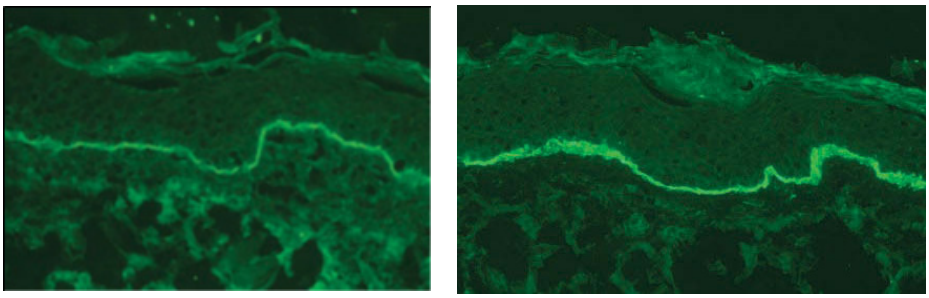


Figure 8. Direct immunofluorescence microscopy of perilesional bullous pemphigoid tissue showing a linear deposition pattern of immunoglobulin G (a) and C3 (b) along the dermo-epidermal junction.[2]

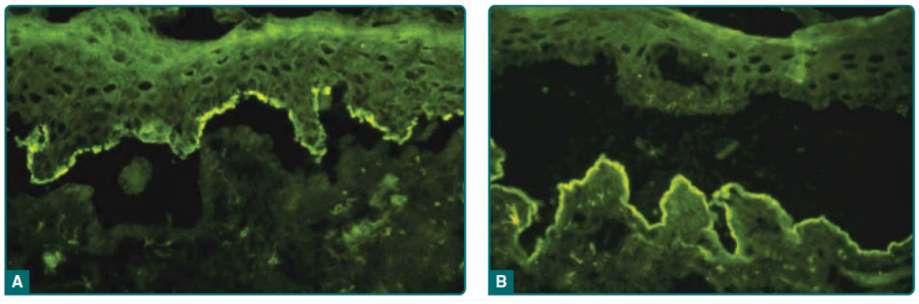


Figure 9. Indirect immunofluorescence. (A) IgG antibodies from bullous pemphigoid serum bind to the epidermal side of an artificially induced split (BP180 and BP230 at the hemidesmosome). (B) IgG antibodies from epidermolysis bullosa acquisita (EBA) serum bind to the dermal side of the split (type VII collagen of the anchoring fibrils).[2]

IgG autoantibodies bound to the BM can also be identified by indirect immunofluorescence (IIF) microscopy, which demonstrates immune deposits on the epidermal side of the blister. Salt-split healthy human skin (skin with separated layers incubated in saline solution) is the most specific substrate for IIF in BP, with a specificity of 100%. Therefore, every patient with a clinical suspicion of BP is recommended to undergo IIF testing using salt-split skin substrate.[5] Findings on IIF examination are shown in **Figure 9**.[2]

Enzyme-Linked Immunosorbent Assay (ELISA)

ELISA is used to detect serum antibodies targeting NC16A, BP180, and BP230. Serum autoantibody titers correlate with disease activity, and high anti-BP180-NC16A titers are associated with an increased risk of relapse, allowing ELISA to be used for therapy adjustment. Low titers of anti-BP180 or anti-BP230 are also found in approximately 4% of patients without BP, particularly those with pruritic dermatoses. In such cases, direct immunofluorescence microscopy (DIF) is required to confirm the diagnosis of BP.[5]

ELISA using recombinant proteins derived from BP antigen fragments (such as the BP230 C-terminus, BP180, and the NC16A domain) allows rapid identification of autoantibodies. Anti-BP180 antibodies are detected in 72%–93% of BP patients by ELISA, while anti-BP230 autoantibodies are found in 57%–63% of patients. In clinical practice, the sensitivity of ELISA for BP230 is low (5%–10%) and is used only when the BP180 ELISA result is negative. ELISA is now more commonly used because it is more practical than immunoblotting and immunoprecipitation, which are reserved for specific cases, such as when both BP230 and BP180 ELISA results are negative.[5] The diagnostic algorithm for bullous pemphigoid is shown in **Figure 10**.[19]

Differential Diagnosis

The differential diagnosis of bullous pemphigoid includes subepidermal bullous diseases with autoantibodies,[20–25] subepidermal bullous diseases without autoantibodies,[26–29] intraepidermal bullous diseases with autoantibodies,[30] and intraepidermal bullous diseases without

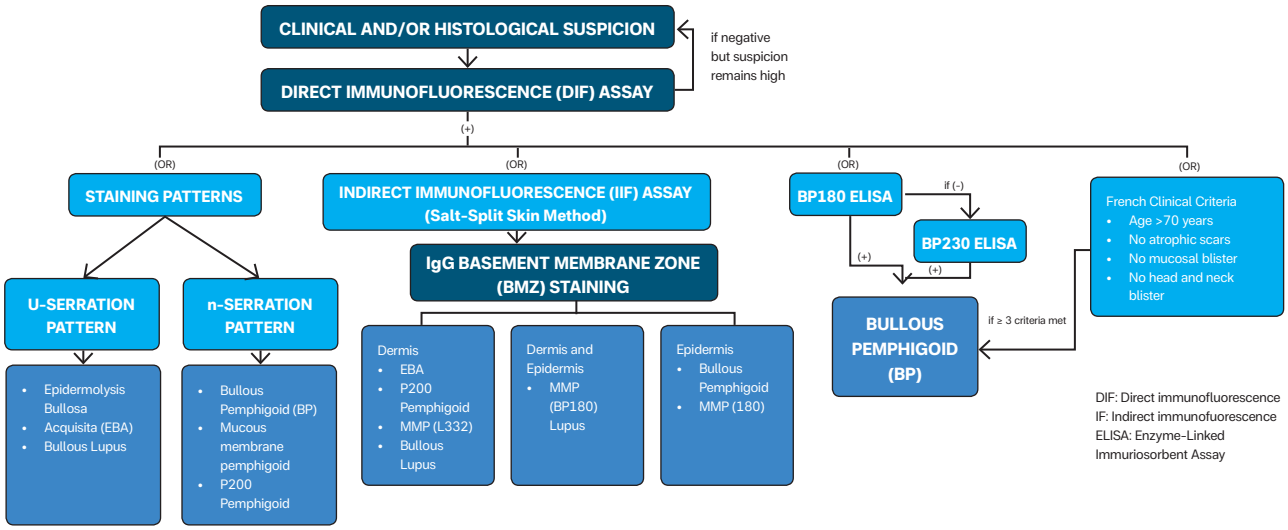


Figure 10. Diagnostic algorithm for bullous pemphigoid.[19]

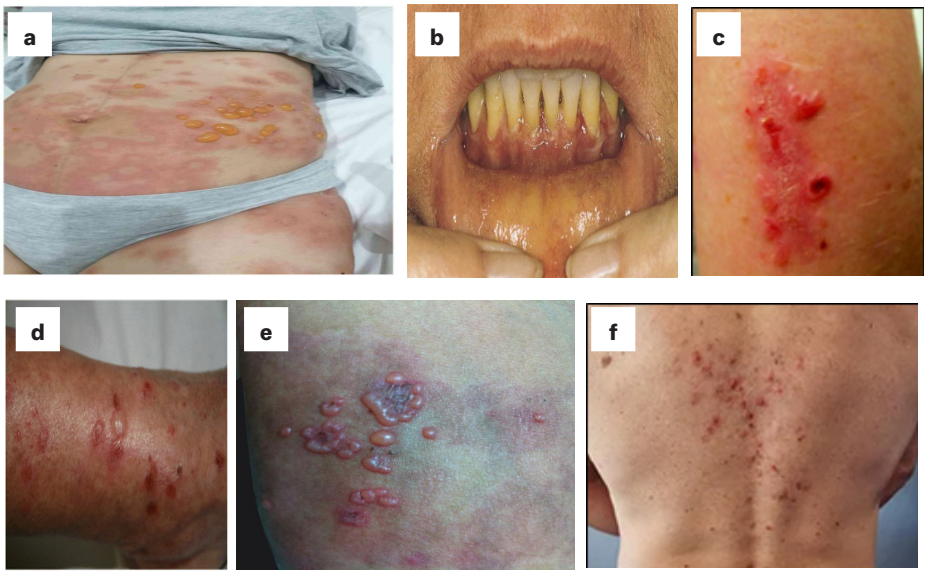


Figure 11. Cutaneous lesions of subepidermal bullous diseases with autoantibodies that form the differential diagnosis of bullous pemphigoid: (a) pemphigoid gestationis, (b) cicatricial pemphigoid, (c) epidermolysis bullosa acquisita, (d) bullous lupus, (e) linear IgA disease, (f) dermatitis herpetiformis.[20–25]

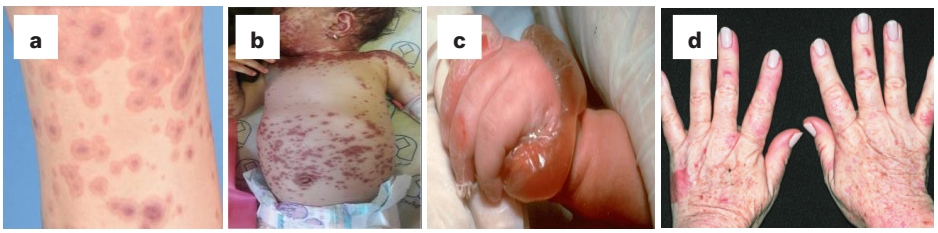


Figure 12. Cutaneous lesions of subepidermal bullous diseases without autoantibodies that form the differential diagnosis of bullous pemphigoid: (a) erythema multiforme, (b) toxic epidermal necrolysis, (c) epidermolysis bullosa, (d) porphyria.[26–29]

autoantibodies.[30–35] Histological examination, direct immunofluorescence (IF), and indirect immunofluorescence can readily distinguish bullous pemphigoid from these conditions.[2]

Unlike bullous pemphigoid, cicatricial (mucous membrane) pemphigoid typically presents with predominant—possibly exclusive—mucosal lesions. Cicatricial pemphigoid is characterized by desquamative gingivitis as well as inflammation and scarring of the conjunctiva. When cutaneous blistering does occur, it is usually confined to the head and neck region and may result in scarring. The large, tense bullae characteristic of bullous pemphigoid are typically not found in cicatricial pemphigoid.[2] The differential diagnosis of bullous pemphigoid is grouped into subepidermal bullae with autoantibodies, subepidermal bullae without autoantibodies, intraepidermal bullae with autoantibodies, and intraepidermal bullae without autoantibodies (**Figures 11–14**) (**Table 2**). Bullous pemphigoid must be distinguished from pemphigus vulgaris, particularly because the latter constitutes a medical emergency (**Table 3**).[2]

Management

Therapy is selected based on the extent and rate of bulla formation. If bullae are extensive, with more than 10 new bullae per day, oral prednisone is administered (0.5–0.75 mg/kg body weight/day), with the dose gradually tapered once disease control is achieved. Alternative or adjuvant therapies

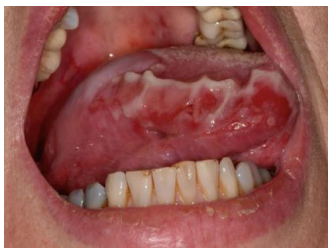


Figure 13. Intraepidermal bullous disease with autoantibodies, showing lesions of pemphigus.[30]

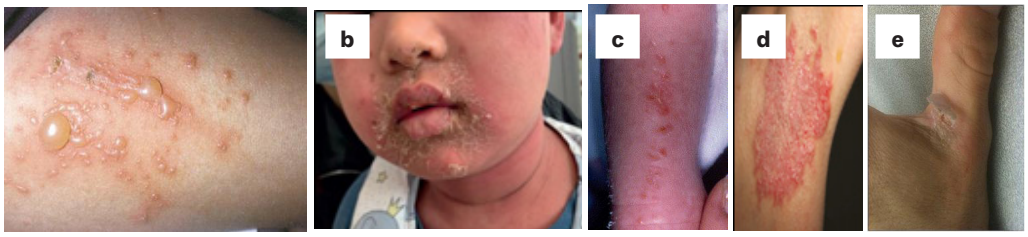
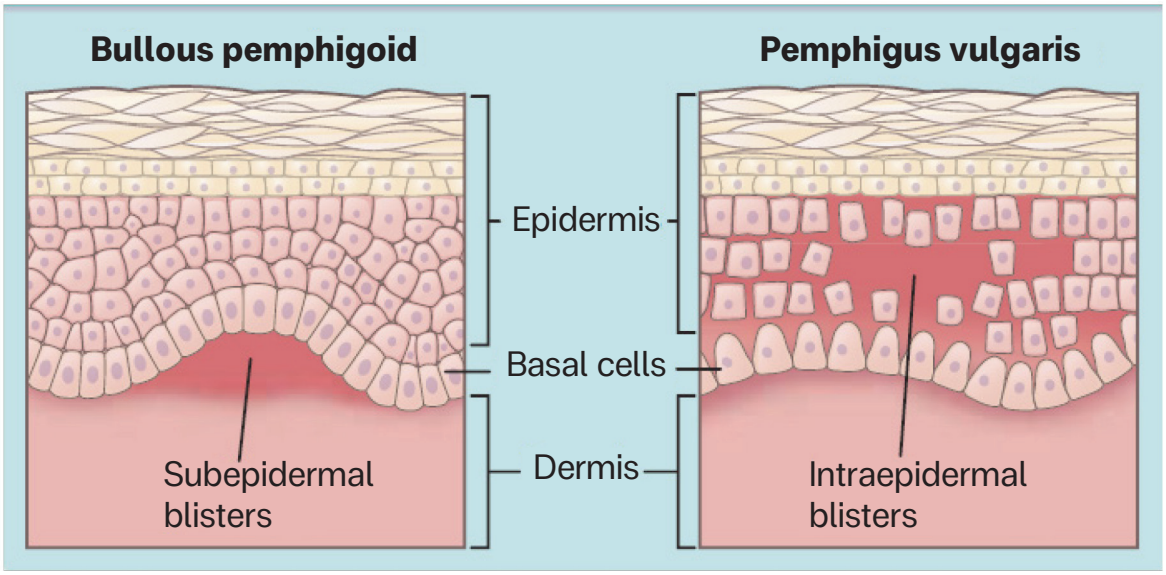


Figure 14. Intraepidermal bullous diseases without autoantibodies that form the differential diagnosis of bullous pemphigoid: (a) allergic contact dermatitis, (b) staphylococcal scalded skin syndrome, (c) incontinentia pigmenti, (d) Hailey-Hailey disease, (e) friction blister.[30–35]

Table 2. Differential diagnosis of bullous pemphigoid.[2]

Subepidermal Bullae with Autoantibodies	Subepidermal Bullae without Autoantibodies	Intraepidermal Bullae with Autoantibodies	Intraepidermal Bullae without Autoantibodies
Pemphigoid Gestationis	Erythema Multiforme and Toxic Epidermal Necrolysis	Pemphigus	Allergic Contact Dermatitis
Cicatricial Pemphigoid	Porphyria		Bullous Impetigo / Staphylococcal Scalded-Skin Syndrome
Epidermolysis Bullosa Acquisita (EBA)	Epidermolysis Bullosa (Genodermatoses)		Friction Blisters
Linear Immunoglobulin A Disease			Hailey-Hailey Disease
Dermatitis Herpetiformis			Incontinentia Pigmenti
Bullous Lupus Erythematosus (described as an EBA phenotype)			

Table 3. Comparison of bullous pemphigoid and pemphigus vulgaris.[2]

Bullous Pemphigoid	Pemphigus Vulgaris
	
Subepidermal bullae, with a predominant eosinophilic infiltrate, followed by neutrophils, lymphocytes, monocytes, and macrophages	Suprabasal bullae with acantholysis; characterized by a "row of tombstones" appearance
Nikolsky sign negative	Nikolsky sign positive

Bullous Pemphigoid	Pemphigus Vulgaris
Asboe-Hansen sign negative	Asboe-Hansen sign positive
Urticarial lesions precede tense bullae	Flaccid bullae may occur anywhere on the skin surface; erosions are most commonly observed
Mucous membrane lesions in approximately ~10% of cases	Mucous membrane lesions are commonly found
BPAg1 (230 kDa) or BPAg2 (180 kDa) / type XVII collagen	Desmoglein 3 (130 kDa); desmoglein 1 (160 kDa)
DIF reveals IgG deposition along the basement membrane	DIF reveals IgG deposition in an intercellular pattern

include azathioprine, mycophenolate mofetil, tetracycline, or other immunosuppressive agents. For localized cases (fewer than 5–10 new bullae per day), topical therapy such as clobetasol cream is used. Monitoring should include comorbidities such as diabetes, hypertension, infection, and other chronic diseases, with hospitalization considered as clinically indicated.[2]

Although no randomized controlled trials exist, oral prednisone remains the mainstay of therapy. Studies have also shown that potent topical steroids, such as 0.05% clobetasol propionate cream applied twice daily, are effective for moderate-to-severe bullous pemphigoid and may be safer than oral prednisone. However, high-potency topical treatment can result in significant systemic absorption, which may cause both local and systemic effects.[2]

Topical treatment can be costly and difficult to apply, which may pose a barrier for many patients. In elderly patients, complications of systemic glucocorticoid therapy (such as osteoporosis, diabetes, and immunosuppression) can be severe. Therefore, it is important to minimize the total dose and duration of oral glucocorticoid therapy. An initial prednisone dose of 0.75 to 1.0 mg/kg/day, or even lower, may be sufficient to control the disease. In addition, immunosuppressive agents such as methotrexate, azathioprine, and mycophenolate mofetil are frequently used concomitantly with prednisone for a steroid-sparing effect, although very few controlled trials have addressed this approach. Once new blister formation has been successfully halted (the consolidation phase), careful tapering of prednisone is recommended. A weekly reduction of 5 mg until a dose of 30 mg is reached is advised, after which an alternate-day tapering regimen is typically initiated. Prednisone tapering must be adjusted according to clinical response and patient tolerability. Most cases can be controlled with low-dose prednisone combined with an immunosuppressive agent.[2] A summary of the management algorithm for bullous pemphigoid is shown in **Figure 15**.[36]

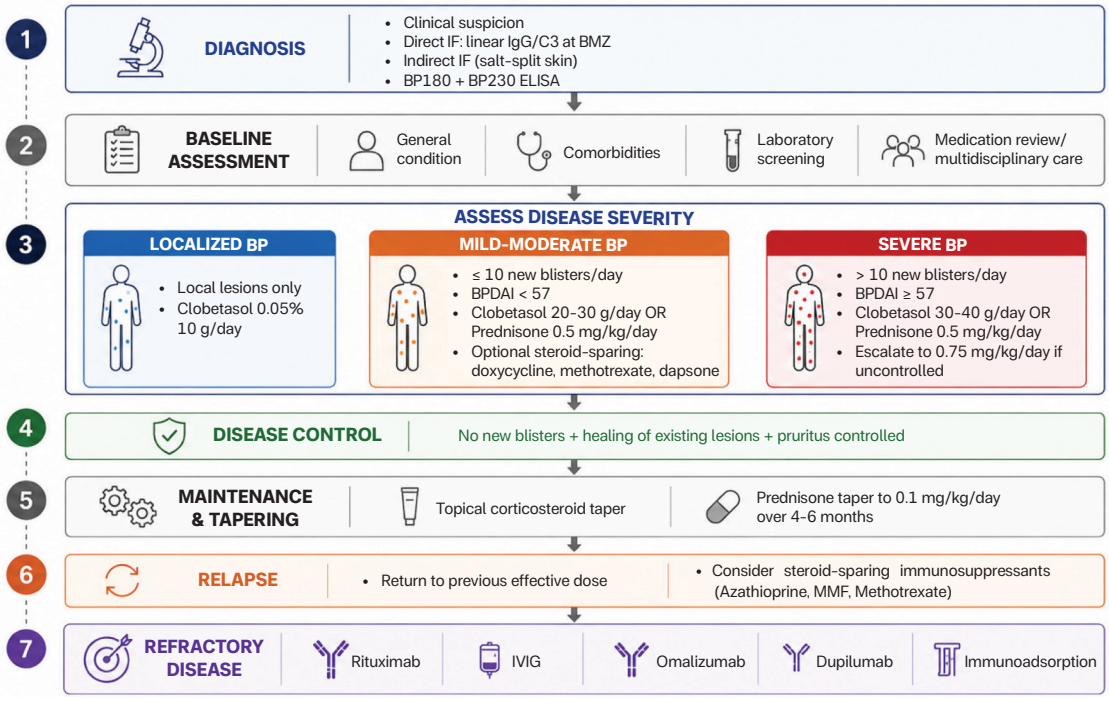


Figure 15. Management algorithm for bullous pemphigoid.[36,38,39]

Abbreviations: IF: Immunofluorescence; IgG: Immunoglobulin G; ELISA: Enzyme-Linked Immunosorbent Assay; BP: Bullous pemphigoid; BPDAI: Bullous pemphigoid disease area index; MMF: Mycophenolate mofetil; IVIG: Intravenous immunoglobulin.

Prognosis

Bullous pemphigoid is characterized by a fluctuating disease course with occasional spontaneous remission, even without treatment. Localized BP tends to resolve spontaneously, and spontaneous remission may also occur in extensive or widespread BP lesions.[37] Remission may occur prior to the use of systemic corticosteroids and may develop after 15 months of active disease. In treated patients, disease duration ranges from 9 weeks to 17 years, with a median treatment period of 2 years and a remission rate of 50% after a minimum of 3 years. Clinical remission can occur even in patients with severe, widespread lesions following treatment with oral corticosteroids or azathioprine. The reported early mortality rate among untreated patients reaches 25%. Recent studies indicate a one-year mortality rate among bullous pemphigoid patients of approximately 19% to 40% in Europe and approximately 6% to 19% in the United States.[2]

CONCLUSION

Bullous pemphigoid is an autoimmune disease characterized by subepidermal blistering, associated with high morbidity and mortality, particularly among the elderly. Even with early treatment, its prognosis is comparable to that of end-stage heart disease, with mortality rates reaching up to 40% within 12 months of diagnosis, partly attributable to comorbidities and the use of immunosuppressive agents. Early diagnosis and identification of triggering factors are essential to improve prognosis. Given that the majority of patients are elderly with multiple comorbidities, treatment selection must account for coexisting conditions and minimize adverse effects. Close monitoring during treatment and follow-up is also required to improve patients' quality of life.

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