Bullous Pemphigoid

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Key Points

- Bullous pemphigoid is considered the most common autoimmune blistering disease.
- The target antigens are the BP antigens with molecular weights of 230 and 180 kDa, BPAG1 and BPAG2, respectively.
- Treatment can be divided into three phases: initial control, consolidation, and withdrawal.
- Severity, age of patient, and presence of underlying disease must be considered in determining therapeutic agents and doses.

Definition and Epidemiology

Bullous pemphigoid (BP) is an acquired, non-scarring, subepidermal blistering disease, usually occurring in the elderly, but may rarely affect children and younger adults. BP is considered the most common autoimmune blistering disease. Women and men are equally affected and no racial or geographical predilection is recognized. There is no known specific HLA correlation. BP has been reported in association with a variety of autoimmune diseases, including systemic lupus erythematosus, diabetes mellitus, lichen planus, rheumatoid arthritis, Hashimoto thyroiditis, pemphigus vulgaris, psoriasis, and neurological disorders, particularly dementia and Parkinson's disease. There have been many reports of BP associated with malignancy, although there is much controversy over this association.

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Basic Concepts of Pathogenesis

BP is an autoimmune skin disease and the cause of the autoantibody production remains obscure. The target antigens are the BP antigens with molecular weights of 230 and 180 kDa, BPAG1 and BPAG2, respectively. BP180 is a type II transmembrane protein that spans the lamina lucida and projects into the lamina densa of the epidermal basement membrane. Furthermore the 230-kDa protein called BP230, which was originally identified as the major antigen of BP, is a cytoplasmic component of hemidesmosomes that belongs to the plakin family; it promotes the linkage of keratin intermediate filaments to hemidesmosomes. Antibody binding to BP antigen is postulated to be the initial step in blister formation. Fixation of immunoglobulin G to the basement membrane zone activates the complement cascade (mainly C3, C5a), which causes

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chemotaxis of leucocytes and degranulation of mast cells. Eosinophils and neutrophils are recruited by mast cell-produced factors to the basement membrane zone, where they release tissue-destructive enzymes (proteases) resulting in dermal-epidermal separation. Several drugs have been associated with the onset of BP including furosemide, spironolactone, neuroleptics, sulfasalazine, penicillamine, and captopril. Local irritation and damage to the skin have been all implicated in the induction of disease. Ultraviolet (UV) light or psoralen and UVA (photochemotherapy) and other physical agents including thermal burns, wounds skin grafts, and radiotherapy have been reported to induce BP in normal skin.

Clinical Presentation

Urticarial and figured erythemas are common prodromal eruptions in BP, by weeks or months. In some cases, bullae may not become clinically apparent. Subsequently, large tense blisters arise with a base of normal or erythematous skin (Fig. 11.1). Grouping may be present and lower abdomen, inner thighs, groin, axillae, and flexural aspects of the forearms and the legs are sites of predilection for the lesions. However, localized forms of BP are not uncommon. Pemphigoid nodularis, vegetans, and dyshidrosiform represent some clinical variants of "classical" BP. Nikolsky's sign is negative and mucosal lesions are usually clinically insignificant, consisting of small tense bullae in the oropharynx. The natural history of BP is that of persistent disease with eventual remission occurring within 5 years in the majority of patients. Prognosis is considered fair, but BP is a potentially fatal disease particularly in the elderly, where health may already be fragile.

Diagnosis and Differential Diagnosis

A subepidermal split and a mixed dermal infiltrate of numerous eosinophils, some neutrophils, and lymphocytes are found in biopsy specimens. IgG and/or C3 is deposited along the basement membrane zone in virtually all active cases of BP (direct immunofluorescence), and about 70–80 % of patients are found to have circulation IgG to the

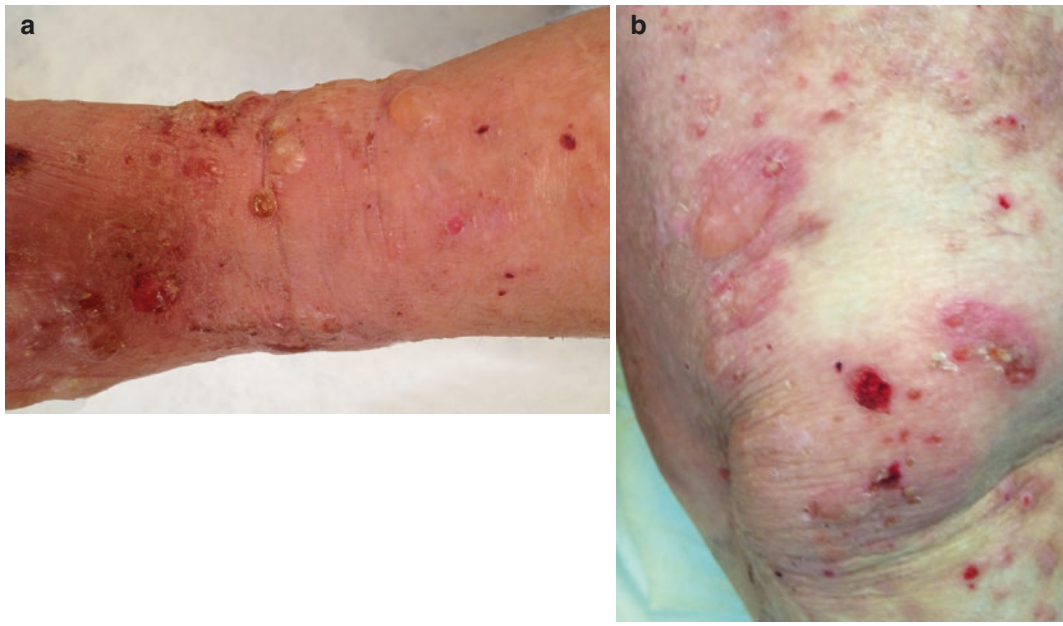


Fig. 11.1 Typical clinical pictures of BP, with tense blisters, erosions, and crusts

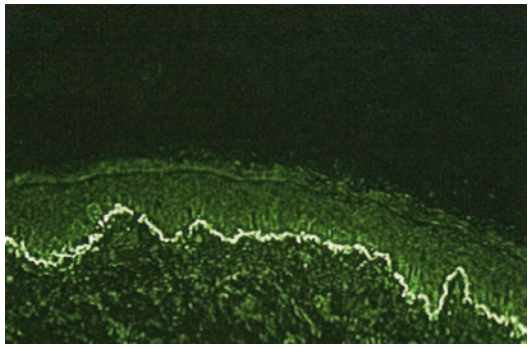


Fig. 11.2 Direct immunofluorescence findings in bullous pemphigoid. Linear deposition of mainly IgG and C3 along the epidermal junction

basement membrane zone of normal stratified squamous epithelia (indirect immunofluorescence) (Fig. 11.2). When 1 mol/L sodium chloride split skin is used as the substrate, circulating autoantibodies from the patient's serum deposit on the roof side of the artificial blister at the dermoepidermal junction (DEJ). In occasional cases, these diagnostic techniques will require supplementation with immunoelectron microscopy, immunoblotting, and immunoprecipitation (Table 11.1).

Table 11.1 Differential diagnosis of bullous pemphigoid

Pemphigoid gestationis	Rare disease of pregnancy and postpartum period
Cicatricial pemphigoid	Scarring autoimmune bullous disease primarily affecting mucosal surfaces
Epidermolysis bullosa acquisita	Trauma-induced blisters healing with scars, different target antigen
Dermatitis herpetiformis	Young adults, pruritic papules and vesicles symmetrically distributed over extensor surfaces. Enteropathy (80 % of cases). HLA-B8-DR3
Linear IgA dermatosis	Younger age group, linear IgA deposition at basement membrane zone (direct immunofluorescence)
Erythema multiforme (bullous)	Typical distribution of lesions, different immunofluorescence findings
Bullous systemic lupus erythematosus	Lesions distributed on sun-exposed areas, subepidermal blisters with neutrophils, different immunofluorescence findings
Other disorders	Porphyria cutanea tarda, drug reactions, insect bite reaction, bullous lichen planus, etc.

General Principles of Treatment

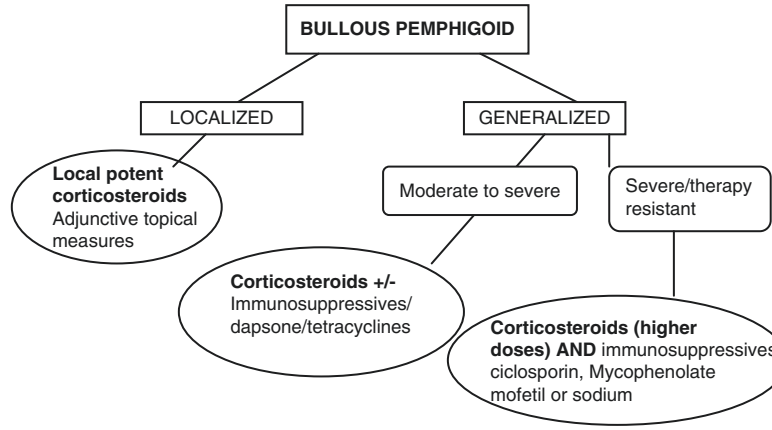
- Treatment can be divided into three phases: initial control, consolidation, and withdrawal. The first objective is stopping or significantly reducing new blister formation. Therapy is introduced and adjusted upward as required and slowly reduced to the lowest possible level while maintaining a low level of disease activity. Complete withdrawal of therapy is carried out if possible.
- The severity of disease, age of patient, and presence of underlying disease (diabetes mellitus, hypertension, peptic ulceration, osteoporosis, malignancy) must be considered in determining therapeutic agents and doses.
- Localized disease may initially be managed with local very potent steroids and adjunctive measures.
- Moderate (20–60 lesions) to severe (more than 60 lesions) disease will usually require systemic steroids in moderate doses alone or in combination with immunosuppressives, dapsone, or tetracyclines.
- Severe therapy-resistant disease requires systemic steroids in higher doses and immunosuppressives, cyclosporin, plasmapheresis, or γ-globulin therapy as adjunctive agents.
- Immunosuppressive agents, due to their delayed onset of action (4–8 weeks), can be started at the same time as systemic steroids. Thus, steroids are used to achieve initial control then tapered at the time when the immunosuppressives are taking effect.

Recommended Therapies (Table 11.2)

Supportive care and adjuvant therapy

Supportive care is essential in cases in which widespread skin denudation and immobility render the patient susceptible to fluid loss, electrolyte imbalance, infection, and thromboembolic events. A bed that spreads pressure is useful in severe disease. The blisters caused by widespread cutaneous and mucosal erosive disease may

Table 11.2 Algorithm of recommended therapies



require frequent oral analgesics, and sedating antihistamines are frequently given in the initial stages of BP to reduce pruritus. Diluted saline or potassium permanganate compresses and baths assist in keeping the lesions clean. Gastric protection, usually with a proton pump inhibitor, should be considered in patients receiving systemic steroids. Calcium supplementations, vitamin D, and bisphosphonate are recommended and have been shown to be effective in preserving bone density in patients receiving systemic corticosteroids, especially in postmenopausal women and men over 50 years.

Topical Therapy

Topical steroids should be considered first-line treatment in localized or moderate BP, and they are also extremely useful adjuvants to systemic therapy when disease is more severe. Very potent topical steroids (clobetasol propionate 0.05 % twice daily) are usually required initially, with tapering to lower potency agents. However, their use in extensive disease may be associated with systemic absorption and adverse events. Triamcinolone acetonide 3.10 mg/mL may be injected weekly to resistant lesions. In the event of secondary infection, topical antibacterial agents may be safely applied. Oral hygiene should be maintained with antiseptic mouthwashes between meals. A soft diet including pureed food and liquid protein supplements is best during active disease. Severe pain may be treated with topical anesthesia (lidocaine (lignocaine) 2 % viscous solution) particularly before meals. Tetracycline mouthwashes (250 mg dissolved in 50 mL of water) may be used to treat oral mucosa infections.

Systemic Corticosteroids

These are most useful drugs in the treatment of BP, rapidly inducing remission in the majority of patients. Our experience and most large series show that the majority of patients respond to 40-80 mg daily of prednisone or prednisolone and it is only rarely necessary to exceed 100 mg daily. In general, doses of prednisolone 0.75–1.0 mg/kg daily in widespread BP are effective within 1–4 weeks in about 60–90 % of the patients. However, depending on the severity of the disease, the doses can be adjusted. For patients with severe involvement, doses of 0.75–1 mg/kg are recommended and lower doses of 0.5 mg/kg for moderate disease and 0.3 mg/kg for mild or localized disease, respectively. Healing of existing lesions and cessation of new blister formation reflect a positive response to therapy. Once the disease is under control, the steroid dose should be tapered slowly and eventually changed to an alternate-day regimen to minimize the steroid side effects. The duration of systemic steroid treatment is likely to be many months and sometimes indefinite. Corticosteroid pulse therapy, in which patients are given 1 g of methylprednisolone intravenously for three consecutive days, may be given for resistant disease. Oral steroids must then be given as maintenance therapy.

However, caution must be recommended in utilizing this type of therapy, particularly concerning the effects of prolonged systemic steroid therapy which are numerous: diabetes mellitus, hypertension, gastrointestinal bleeding, osteoporosis, cataracts, and increased susceptibility to bacterial, fungal, and viral infections. Immunosuppressive and metabolic adverse events are considered dose dependent. Appropriate monitoring includes urinalysis for glucose, fluid imbalance, blood pressure, and body weight. Routine biochemistry may be done at weekly or twice weekly intervals in the first instance, dropping to monthly thereafter. Osteoporosis profile tests and ophthalmological examination for cataracts should be performed as a baseline and thereafter every 6 months, particularly in postmenopausal women.

Immunosuppressive Agents

Azathioprine

This drug is most commonly employed in combination with steroids and sometimes for maintenance following steroid withdrawal. The usual dose is 50–100 mg daily. Azathioprine dose can be optimized with regard to myelosuppression risk by prior assay of thiopurine methyltransferase (TPMT). However a normal TMPT lever does not totally preclude myelotoxicity. The usual dose of azathioprine use, the steroid maintenance dose, may be significantly reduced and in some instances discontinued. Side effects of azathioprine include dose-dependent bone marrow depression, idiopathic hepatitis, increased susceptibility to infection, teratogenicity, and increased risk of internal and cutaneous liver function tests and urinalysis. The full blood count and renal and liver function tests are repeated weekly for 8 weeks and then monthly.

Cyclophosphamide

Cyclophosphamide is more toxic than other immunosuppressive drugs used for BP. It may be considered only for exceptionally refractory disease. The drug may be given initially in doses of 100–200 mg daily and 3 weeks later in maintenance doses of 100 mg daily. A pulsed steroid cyclophosphamide regimen is effective in severe cases of BP, permitting low cumulative steroid doses. Dexamethasone 100 mg i.v. given on three consecutive days, with the addition on day 1 of cyclophosphamide 500 mg, is given per day between pulses. The pulses are initially repeated every 2 weeks, reducing to every 10 weeks in combination with ongoing oral cyclophosphamide over a period of 6 months. Side effects include nausea and vomiting, bone marrow depression, hemorrhagic cystitis, and increased risk of malignancy. Monitoring is as for azathioprine, with the addition of urinalysis weekly for the first 8–12 weeks and every 2 weeks thereafter. Cardiac monitoring is required during pulse therapy.

Chlorambucil

Chlorambucil has been used as a steroid-sparing agent in the treatment of BP with excellent results. However, its use is not recommended except in special cases because of concern about the induction of hematological malignancy (acute myeloid leukemia). The drug is initially given at 0.1 mg/kg per day in combination with prednisolone 40–60 mg/day. The chlorambucil dose is reduced over 6 weeks to a maintenance dose of 2 mg daily. Prednisolone is gradually withdrawn over a 4-month period, chlorambucil being discontinued some weeks later. There is a 50 % reduction in the cumulative dose of prednisolone. Side effects include bone marrow suppression, which can be severe, often resulting in transient dose-related thrombocytopenia. Appropriate monitoring is with baseline and weekly blood counts. Hematological malignancies may be related to a cumulative dose of 1 g or more of the drug.

Cyclosporin

Cyclosporin cannot be recommended in the routine treatment of BP. However it has been used in the treatment of BP at doses of 5–8 mg/kg per day as a single agent or of 5 mg/kg per day in combination with steroids. According to our experience, combined therapy has a significant steroid-sparing effect and induces remission of BP in all patients, with monotherapy being less successful. The side effects include hypertension, renal dysfunction, raised lipids, hypertrichosis, gum hyperplasia, susceptibility to infection, and

increased risk of malignancy. Baseline blood pressure should be recorded, and the laboratory investigations required include complete blood picture, urea, serum creatinine, creatinine clearance, liver function tests, fasting lipids, and urinalysis. Serum creatinine should be repeated every 2 weeks for the first month with all the other previously mentioned laboratory parameters.

Dapsone and Sulfonamides

BP may respond well to dapsone or the sulfonamides (sulfapyridine and sulfamethoxypyridazine) either alone or in combination with other agents. Dapsone is started at 50 mg daily and increased to 100 mg daily after 5–7 days if no response is apparent. Response is rapid, within 2 weeks. Dapsone may be used in combination with topical steroids or may be added (150–300 mg daily) to prednisolone or azathioprine therapy, achieving adequate control of disease activity and permitting a reduction in the steroid dose. Although these are not drugs of first choice for BP, they may be useful in the management of patients in whom corticosteroids are contraindicated or not tolerated. Side effects include dose-related hemolysis and methemoglobinemia, cutaneous hypersensitivity reactions, peripheral neuropathy, hepatic damage, and renal failure. Monitoring should be with baseline tests and electrolytes. Glucose-6-phosphate dehydrogenase deficiency must be excluded prior to commencing therapy. Estimation of methemoglobinemia is obtained as clinically indicated.

Alternative and Treatment Suggestions

Topical Tacrolimus

The use of topical tacrolimus is limited due to local irritation and high price compared to topical steroids. It may be used as an alternative in localized disease as it is not implicated in skin atrophy.

Mycophenolate Mofetil (MMF) or Sodium (MMS)

MMF is an inhibitor of purine synthesis in activated T and B cells and is considered a generally well-tolerated immunosuppressive agent. They are both used for prevention of allograft rejection in transplantation medicine. MMF is a well-tolerated and effective corticosteroid-sparing agent in autoimmune bullous disease, and several suggest that complete remission is achieved more frequently with the use of MMF over azathioprine, with less hepatotoxicity. They have been reported as effective in controlling BP in doses of 0.5–1 gr twice daily, both as adjunct to systemic prednisolone and as monotherapy following disease relapse.

Anti-inflammatory Antibiotics/ Niacinamide

Tetracyclines and niacinamide (nicotinamide) may be considered as treatment in adults, perhaps in combination with topical corticosteroids. Niacinamide is used between 500 and 2,500 mg daily, usually started at 500 mg and then gradually increased. Tetracycline has been used at doses of 500–2000 mg daily, doxycycline at 200–300 mg daily, and minocycline at 100–200 mg daily. Minocycline has a worse side-effect profile and therefore is not the first choice. Erythromycin should be considered for treatment, particularly in children and perhaps in combination with topical corticosteroids. Side effects include gastrointestinal symptoms, photosensitivity, headache, benign intracranial hypertension, hyperpigmentation (minocycline), and candidosis. The combination of tetracycline 500 mg four times daily or minocycline 100 mg twice daily and niacinamide 500 mg twice daily is efficacious in some BP patients.

Plasmapheresis

Plasmapheresis is used as an adjuvant to corticosteroids in the treatment of BP, showing a steroid-sparing effect. Prednisolone is administered in combination with eight large-volume plasma exchanges over 4 weeks. In our experience a higher mean daily steroid dose is required to control disease activity when steroid is given alone (1 mg/kg) than with the dual therapy (0.6 mg/kg). The mild side effects of fever, chills, and hypertension are relatively common. However, the potential difficulties include maintaining venous access, a bleeding tendency, electrolyte imbalances, allergic reactions, pulmonary edema, and septicemia.

Deaths may also occur. Frequent observation of vital signs and cardiac monitoring are required during the procedure. It is suggested that weekly full blood examination, electrolytes, coagulation studies, and liver function tests are carried out.

Gammaglobulins

Gammaglobulins given alone in a dose of 100–400 mg/kg for five consecutive days do not appear to be more than temporarily effective in the treatment of BP. The possible steroid-sparing effect awaits further investigation.

Methotrexate

Methotrexate (5–15 mg weekly) can be effective at controlling BP in elderly patients, either as monotherapy or in combination with topical or systemic steroids**.**

Biologic Agents

Only a few reported cases have been treated with tumor necrosis factor-α (anti-TNF-α) and the anti-CD20 agent, rituximab. Regarding anti-TNF-α agents, there is conflicting evidence as to whether these agents treat or induce BP. Until further supportive evidence is available, their role in BP remains limited.

Childhood Bullous Pemphigoid

Due to its rarity and benign nature, preference should be given to low-toxicity treatments (e.g., erythromycin) and topical steroids.

Further Reading

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