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Bullous Pemphigoid
From Bench to Bedside

Scott R.A. Walsh,[1] *David Hogg*[2] and *P. Régine Mydlarski*[3]

1 Division of Dermatology, University of Toronto, Toronto, Ontario, Canada
2 Department of Medicine, University of Toronto, Toronto, Ontario, Canada
3 Division of Dermatology, Departments of Medicine and Medical Genetics, University of Calgary, Calgary, Alberta, Canada

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Abstract

Bullous pemphigoid (BP) is a chronic, autoimmune, blistering disease observed primarily in the elderly population. Several clinical variants have been described, including classic (bullous), localised, nodular, vegetating, erythrodermic, erosive, childhood and drug-induced forms. Autoantibodies target the BP230 and BP180 antigens, located in the hemidesmosomal complex of the skin basement membrane zone. Subsequent complement activation recruits chemical and cellular immune mediators to the skin, ultimately resulting in blister formation. Both autoantibodies and complement may be detected by various immunofluorescent, immune electron microscopy and molecular biology techniques. Recent trials suggest that potent topical corticosteroids should be considered as first-line therapy. Tetracycline with or without nicotinamide may benefit a subset of patients with mild BP. Oral corticosteroids should rarely exceed 0.75 mg/kg/day and corticosteroid-sparing agents may be useful for recalcitrant disease.

Bullous pemphigoid (BP) is an autoimmune blistering disorder characterised by the deposition of autoantibodies and complement in the epidermal basement membrane zone (BMZ). Autoantibodies are directed against proteins of the hemidesmosomal complex that anchor basal keratinocytes to the underlying basement membrane. This systematic review of BP is based on data available from literature searches of MEDLINE, EMBASE and the Cochrane Library.

1. Epidemiology

BP is the most common autoimmune blistering disease, with an annual incidence of 6.1–7.0 per million people in European countries.[1-3] The incidence increases with age such that a 90-year-old has a 297-fold higher risk of disease than does a 60-year-old.[3] Earlier studies found no gender bias in disease prevalence;[4] however, when controlling for age-related population gender, BP is almost twice as prevalent in men as it is in women.[3] The disease tends to last anywhere from a few months to up to 10 years,[5-7] and the major mortality comes from age-related causes and treatment complications, rather than the disease process itself.[6] In a multivariate analysis, poor outcome with BP was associated with advanced age, low serum albumin levels reflecting poor physical conditioning, elevated erythrocyte sedimentation rate (ESR) and high dosages of systemic corticosteroids required to control disease.[8-10]

Although BP does not appear to be strongly linked with specific human leukocyte antigen (HLA) class I or II DR antigens,[11,12] some studies have found a weak susceptibility association in specific populations between both BP and cicatricial pemphigoid (CP) and the presence of HLA-DQ7.[13-15] On the basis of a small population series, it has also been suggested that HLA-B7 may be a marker for poor response to immunosuppressive therapy.[16]

2. Association with Systemic Diseases

The coexistence of autoimmune diseases is a well recognised phenomenon of which BP is no exception. Case reports abound of BP in association with rheumatoid arthritis,[17] systemic lupus erythematosus,[18-20] Sjögren's syndrome,[21] multiple sclerosis,[22] myasthenia gravis,[23] primary biliary cirrhosis,[24,25] autoimmune glomerulonephritis,[26,27] factor V inhibitor,[28] ulcerative colitis,[29,30] Crohn's disease,[31] and other autoimmune skin diseases including pemphigus vulgaris[32-37] and pemphigus foliaceus.[38-40] Association with some of these disorders may be coincidental (e.g. single reports of Castleman's disease[41] or myocarditis[42] associated with BP), secondary to medications used to treat comorbid diseases such as ulcerative colitis,[43,44] or due to secondary infection resulting in diseases such as post-infectious glomerulonephritis.[45] Some investigators have questioned whether a true association exists between BP and other autoimmune diseases, or whether the association simply represents reporting bias.[12]

BP may also be associated with amyotrophic lateral sclerosis.[46] In addition to discussing the epidemiological significance of the association, Chosidow et al.[46] suggest a possible interrelation between BP230 (BP antigen 1; BPAG1) and neurofilaments in the pathogenesis of both disorders.

Among the skin disorders, psoriasis may be more prevalent in patients with BP than in the general population.[47] This raises the question as to whether hyperproliferative disorders may help to expose otherwise sequestered autoantigens.

The incidence of malignancy does not appear to be elevated in patients with BP.[48-52] Malignancy and BP are both more common in the elderly population. Hodge et al.[53] examined 124 cases of BP and found a rate of malignancy similar to the population at large. However, with indirect immunofluorescence (IIF), they divided the groups into seronegative and seropositive, and reported a higher likelihood of malignancy (23%) in the seronegative than in the seropositive (4%) group. This probably represents a coincidental finding with small numbers (the seronegative group contained only 35 patients) as IIF, and hence seronegativity, will vary depending on the substrate used. Similarly, isolated case reports of BP resolution after malignancy resection may simply represent the natural history of BP lesions.[54]

3. Pathogenesis

Experiments to elucidate the role of the autoimmune system in BP have incorporated both human *in vivo* and *in vitro* assays with results from murine models. From these data, it is clear that hemidesmosomes are specialised multiprotein junctional complexes located on the ventral surfaces of

basal keratinocytes and attach the epithelial cells to the underlying basement membrane. Autoantibodies against two independent antigens localised to the hemidesmosomes are associated with BP.

The protein BP230 is a member of the plakin gene family and is involved in cytoskeletal architecture in stratified squamous epithelia.[55-58] It is entirely intracellular in location and may provide a way of linking keratin intermediate filaments within the cell to the transmembrane hemidesmosomal proteins β4 integrin and BP180.[59-63] Alternative splicing variants of BP230 capable of binding other cytoskeletal proteins are present in different tissues and even within keratinocytes, suggesting this protein may represent a multifunctional cytoskeletal linking factor.[64] BP230 has long been recognised as the immunodominant antigen in BP.[65]

BP180 (BP antigen 2; BPAG2, collagen XVII) is a trimeric transmembrane protein of identical subunits, each containing an intracellular amino terminus that interacts with BP230 and β4 integrin (among others), a transmembrane domain and an extracellular carboxy-domain.[58,66,67] The extracellular region contains a large non-collagenous (NC16A) domain immediately adjacent to the plasma membrane which interacts with the ectodomain of α6 integrin[68] and a longer collagenous tail structure extending into the lamina densa.[69] This collagenous anchoring domain is interrupted by 15 small non-collagenous segments.[70-72] Tissue distribution of BP180 mirrors that of hemidesmosomes, including expression in buccal, corneal, oesophageal, bladder and skin tissue.[73] Autoantibodies to BP180 are necessary for disease pathogenesis.[74]

Immunoblotting and ELISA studies support the concept that almost all patients with BP have detectable anti-BP180 antibody.[75,76] Furthermore, although BP230 may be the immunodominant antigen in general, [77] some patients have a preponderance of antibodies to BP180 versus BP230, or a combination thereof.[78,79] Male patients may be more likely to have high titres of detectable antibodies only to BP180,[80] which may relate to a poorer prognosis.[81]

Patients with BP have IgG_1-complement-fixing autoantibodies that react with multiple epitopes on both the extracellular and intracellular domain of BP180.[60,82,83] The NC16A domain of BP180, immediately exterior to the plasma membrane, appears to be the most autoantibody-reactive site.[84] This region contains a 14 amino acid major idiotype determinant designated MCW-1.[85,86] The presence of this autoantibody correlates with disease severity[79] and its titre correlates with disease activity.[81,87] The antibody is capable of inducing dermal epidermal junction (DEJ)-separation in cryosections of human skin.[88] This region appears to be important for interaction with α6 integrin and stabilisation of hemidesmosome structure.[68,89] Furthermore, passive transfer of antibody to this region reproduces the disease in a murine model.[74] Subsequent production of non-complement-fixing IgG_4 autoantibody to BP180 appears to occur with chronicity of lesions and can attain high serum levels.[90,91] IgG_4 to either BP180 or BP230 may have a role in mast cell degranulation and subsequent inflammatory cell recruitment (see later in this section).[90,92,93]

Autoantibodies to BP230 are primarily IgG_4 subtype, do not fix complement, do not correlate with disease activity, do not affect prognosis and are felt to be an epi-phenomenon or secondary to epitope spreading.[81,88,91,94,95] However, BP230 is the primary immunodominant antigen in BP and polyclonal antibodies to this sequestered protein are in such high titre that they are detected in the majority of patients.[65,96-99] Furthermore, they are the predominant autoantibody eluted from the BMZ of perilesional skin, which has led some investigators to speculate that they may have a role in the initiation of disease activity.[77] Isotype switching from IgG to IgE may occur with B-cell clones producing autoantibodies to either BP230 or BP180.[100-102] This may account for the hyper-IgE state frequently observed in sera of patients with BP, the presence of occasional IgE deposited at the BMZ, and subsequent serum and tissue eosinophilia secondary to activation of cells expressing the Fcε receptor.[103-105] Titres of IgE directed against the NC16A domain of BP180 parallel both disease activity and severity.[106]

Sera from patients with BP have also been found to inconsistently react with other antigens including 280, 200, 120, 97 and 77 kDa epidermal proteins on immunoblots.[107,108] Many of these proteins may represent differentially processed forms of either BP230 or BP180.[89,109]

Mononuclear cells with a predominantly CD4+ T-lymphocyte profile are the first infiltrating cells to be recognised in BP lesions[93] and activated T cells are found in peripheral blood associated with disease activity.[110] Autoreactive CD4+ cells in BP produce both T helper (T_h)-1 and T_h2 cytokines.[15] The initial production of vesicles appears to favour T_h1 involvement with the production of complement-fixing IgG_1, while chronicity seems to favour T_h2 involvement with the production of IgG_4, IgE and cytokines such as interleukin (IL)-4, IL-5, IL-13 and CD23.[91,100] Thus, the chronic phase of BP may reflect a shift in the T_h1/T_h2 balance.

Production of IgE may activate IgE-bearing cells such as eosinophils and mast cells, resulting in induction of IL-4 and IL-5 expression that may feed back to further stimulate eosinophil chemotaxis and differentiation.[104,111] In fact, blister fluid levels of IL-5 have been found to correlate with severity of disease.[112]

Overall, blister fluid contains many cytokines, including IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, tumour necrosis factor-α and interferon-γ.[112,113] These reflect contributions from both T_h1 and T_h2 lymphocyte subsets. In the murine model, T-cell subset induction was determined primarily by the inciting antigenic stimulation. For example, priming and immunisation with persistent self-antigen favoured development of a T_h1 response, while priming with foreign BP180 favoured a T_h2 response.[114] This suggests that the inciting antigen may alter disease presentation and course.

Autoantibody deposition along the BMZ alone does not induce disease. Subsequent complement deposition and activation through the classical pathway is required for lesion formation.[115,116] Vesiculation does not occur in the absence of either complement-fixing IgG autoantibody or C5,[116] suggesting that this interaction is requisite for induction of disease.

However, antibody and complement are insufficient to induce blistering.[117] Mast cells also appear to play both an early pivotal and a subsequent amplification role in the disease process.[92,93,118] C5a and C3a products released from complement bound to IgG at the BMZ causes degranulation of the local mast cell population. The released mast cell products include both eosinophilic and neutrophilic chemotactic factors. Hence, recruitment of polymorphonuclear cells is much more brisk than that resulting from the innate abilities of C5a/C3a alone. Furthermore, mast cell degranulation appears to be a necessary requirement for blister formation.[118]

Ultimately, blister formation appears to be dependent upon release of elastase and matrix metalloproteinases (MMPs) from recruited eosinophils and neutrophils.[115,119-122] Gelatinase B (MMP9)-deficient mice are resistant to blistering, but this can be overcome by reconstituting the mice with gelatinase B-positive neutrophils.[120] Gelatinase B may require prior activation by a chymase released during mast cell degranulation.[118] It has been proposed that the activated gelatinase B promotes blistering either by cleaving structural proteins at the DEJ or by inactivating protease inhibitors of granulocytes.[120,123] Unlike gelatinase B, neutrophil elastase induces subepidermal blister formation by directly cleaving BP180.[122]

4. Clinical Presentations

The hallmark of BP is widespread tense blisters arising on normal ('non-inflammatory bullae') or erythematous skin ('inflammatory bullae') in an elderly person, often with marked pruritus (figure 1a and b).[5] As the blisters rupture, the eroded bases do not spread further (i.e. Absoe Hansen and Nikolsky negative). Lesions can appear anywhere, but often have a preference for the lower abdomen, groin and flexor surfaces of the extremities,[4,7,124-126] possibly reflecting sites of greatest BP antigen expression.[127] Two-thirds of patients present with pruritic urticarial plaques or localised erythema that progressively become more oedematous prior to bullae

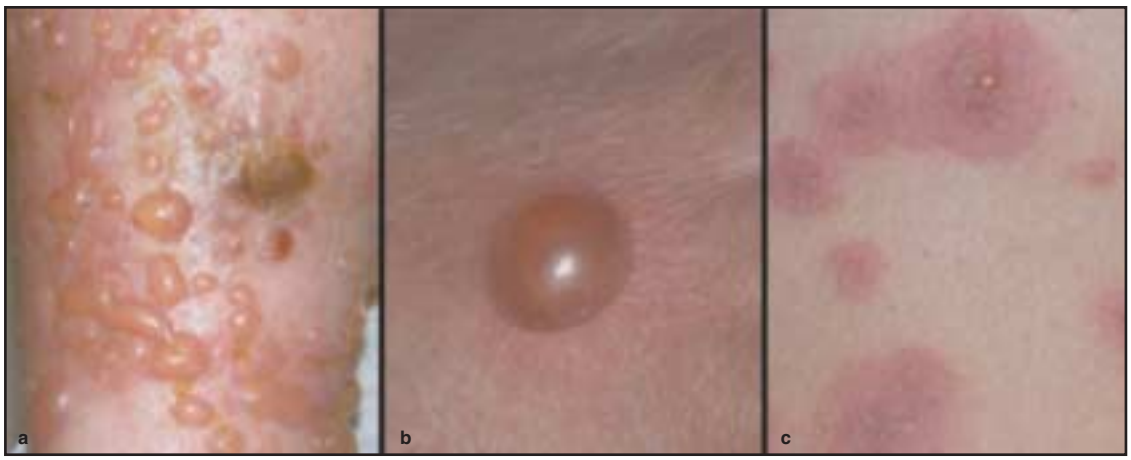

Fig. 1. Clinical variants of bullous pemphigoid: (**a**) classic bullous pemphigoid (tense bullae on an erythematous base); (**b**) localised bullous pemphigoid; and (**c**) urticarial bullous pemphigoid with few vesicles.

formation (figure 1c).[128] This may last from months (urticarial type) to 6 years (eczematous type).[129] If this phase occurs over extended periods of time, the lesions have been referred to as the variants 'non-bullous pemphigoid', 'urticarial pemphigoid' or 'eczematous pemphigoid'.[130-132] Mucous membrane involvement can be seen in up to one-third of BP patients, is usually mild, often not noticed by the patient, non-scarring, limited to the oral mucosa and often spares the lips.[53] Approximately 22–30% of BP cases actually begin in a localised area and subsequently become generalised.[4,52]

Many clinical variants of BP have been described based on positive immunofluorescence (table I).[4,133,134] Localised pemphigoid is characterised by recurrent localised lesions that never go on to a generalised stage (figure 1b).[135-137] It can also occur in sites of trauma or following radiation treatment.[138-142] The most common locations for idiopathic localised BP are the pretibial region (i.e. pretibial pemphigoid) and the hands/feet (i.e. dyshidrosiform pemphigoid).[143] Other similar clinical entities including contact dermatitis, other eczematous processes, bullosis diabeticorum, hydrostatic bullae, bullous tinea pedis and bullous drug eruption must be excluded.[137,143]

Nodular pemphigoid presents as a pruritic, hyperkeratotic papular/nodular eruption with preference for the trunk and extremities in elderly women, resembling prurigo nodularis both clinically and histopathologically. The presence of bullae within hyperkeratotic lesions may precede,[137,144-149] coincide with[150] or follow the nodular eruption,[151,152] or not occur at all.[134,146,153,154] As a result of mechanical trauma, this form of pemphigoid may scar and, hence, has also been termed 'hyperkeratotic scarring pemphigoid'.[136] Whether this variant represents a coincidental expression of both BP and prurigo nodularis or, conversely, results from

Table I. Clinical variants of bullous pemphigoid

Classical pemphigoid (generalised)
non-bullous pemphigoid
urticarial pemphigoid
eczematous pemphigoid
Localised pemphigoid
pretibial pemphigoid
dyshidrosiform pemphigoid
Nodular pemphigoid
hyperkeratotic scarring pemphigoid
Pemphigoid vegetans
Erythrodermic bullous pemphigoid
Vesicular pemphigoid
polymorphic pemphigoid
Erosive bullous pemphigoid
Lichen planus pemphigoides
Childhood bullous pemphigoid
Drug-induced bullous pemphigoid

scratching, thereby exposing sequestered BMZ antigens, has yet to be determined.

Pemphigoid vegetans is an extremely rare variant characterised by well circumscribed, erythematous, erosive, purulent vegetating plaques with peripheral vesicles and pustules, typically located primarily in intertriginous regions.[155-157] These lesions are reminiscent of pemphigus vegetans; however, both histopathology and immunofluorescence are consistent with BP.

Erythrodermic BP may present as generalised exfoliative dermatitis with subsequent onset of tense blisters,[158,159] concomitant presentation of both types of lesions[160] or blisters followed by subsequent erythroderma.[159,161] HLA typing performed on two patients confirmed the presence of HLA-A3 and HLA-DRw53 in both patients.[159]

Vesicular pemphigoid presents with small tense pruritic vesicles, often grouped on the trunk and extremities. The clinical presentation is reminiscent of dermatitis herpetiformis (DH), but both histopathology and immunofluorescence confirm BP.[136,162] Subsequent cases reported in the literature document occasional evolution histopathologically to more typical DH.[163] It is unclear at this time if some of these cases may represent the coincidental coexistence of BP and DH.[164] Polymorphic pemphigoid is a term that has been coined to describe those variants that have both small and large, grouped and scattered vesicles and bullae, which clinically resemble a combination of both DH and BP, but have immunofluorescence findings suggestive of only BP.[165]

An extremely rare variant, erosive BP, has been described recently in two patients.[166] Both patients presented with large eroded areas of skin on the trunk, buttocks and flexor surfaces of the extremities. There was no identified history of pruritus, blisters or urticarial lesions. Their lesions were quite resistant to therapy and both the patients subsequently died from septicaemia. Immunohistochemistry of biopsies taken from peri-lesional skin and immunofluorescence studies were compatible with a diagnosis of BP.

Lichen planus (LP) pemphigoides (LPP) describes the coexistence of bullous lesions with immunohistochemistry consistent with BP, on both LP lesions and previously unaffected skin.[167-169] Although this entity may represent simultaneous occurrence of two separate diseases, autoantibody profiles reveal that these cases recognise a very specific BP180 epitope not previously identified in cases of BP alone.[170] Similarly, the mean age of these patients (48 years) is significantly younger than that observed with BP alone (75 years).[170] It has been hypothesised that damage caused during basal keratinocytes liquefaction secondary to LP may induce the subsequent production of antibodies to BMZ constituents and the induction of BP.[171] Erythroderma resulting from LPP has also been reported.[172]

Although extremely rare, BP has been reported to occur in childhood.[173] Many earlier cases reported as childhood BP probably represent drug-induced BP (DIBP; see section 5) as there was a history of a medication such as penicillin or sulfasalazine.[174,175] Of those cases with no medication history, childhood BP has occurred as early as 2 months of age, with 81% of patients younger than 8 years of age.[173] Clinically, mucous membrane as well as pronounced involvement on the hands, feet and face, appear to be more common in this younger age group.[173,176] The differential diagnosis requires positive immunofluorescence with C3 and IgG to exclude chronic bullous disease of childhood and other bullous disorders. Other variants including nodular pemphigoid have been reported in the childhood BP grouping.[177]

5. Drug-Induced Bullous Pemphigoid

Several medications have been implicated in precipitating a clinically heterogeneous group of bullous disorders with similarities to BP (table II).[178-202] The majority of the drugs contain free sulfhydryl groups, either within the moiety of the parent compound or within a catabolised metabolite.[179] It has been proposed that the thiol group may allow the molecule to combine with proteins in the lamina lucida, act as a hapten and result in

Table II. Medications and treatments associated with the onset of bullous pemphigoid (BP) and drug-induced BP[178-202]

Likely association[a]	Probable association[b]	Questionable association[c]
Furosemide	Penicillamine	Chloroquine
(frusemide)	Ampicillin	Topical fluorouracil
Phenacetin	Penicillin	UVA with psoralen
Enalapril	Sulfapyridine	UVB
Ibuprofen	Cephalexin	Electron beam
Influenza vaccine	Bone marrow	Captopril
	transplant (with graft	Tetanus toxoid
	vs host disease)	Risperidone
	Fluoxetine	Interleukin-2
	Spironolactone	Omeprazole
	Bumetanide	Sulfonamide
		Amiodarone

a Likely association = rechallenge evidence supports association.

b Probable association = young age group with BP and temporally associated with medication, or spontaneous resolution of BP after drug withdrawal alone (without topical or systemic corticosteroid therapy).

c Questionable association = elderly age group and temporally associated with medication.

autoantibody formation to BMZ proteins. On the other hand, certain sulfur-containing drugs may cause a dermo-epidermal split without immune mediation.[178] Many of the implicated pharmacological agents, vaccines or treatments such as electron beam have only been temporally associated with the onset of BP-like lesions in a middle-aged to elderly age group that is otherwise normally susceptible to developing BP.[181-186] However, temporal occurrence in a younger age group where BP is extremely rare may be more supportive of a causative association.[174,180,187-190] Medications such as penicillamine have repeated citations confirming an overlap reaction mimicking both pemphigus and pemphigoid.[191,192] The best evidence for rash causation is supported by rechallenge with subsequent rash reactivation. Drugs such as furosemide (frusemide),[193,194] phenacetin,[195] enalapril,[196] ibuprofen[197] and influenza vaccinations[198] have been implicated with rechallenge and present a clearer link to rash causation. Spontaneous resolution of BP after drug withdrawal (without topical or systemic corticosteroid therapy) has been described in patients on spironolactone, bumetanide and fluoxetine.[199-201] The rash can appear between 24 hours after consumption of the offending agent to 3 months later.[184,186]

DIBP can mirror the clinical findings of autoimmune BP, but many reports suggest more severe non-scarring mucosal or palm/sole involvement.[174,186,190] Some cases have also been reported that have negative immunofluorescence in the face of a subepidermal blister, which may be more suggestive of a bullous drug reaction than DIBP.[197] Once the offending drug has been withdrawn, the treatment of DIBP is identical to BP (see section 8).

A case-control study of a limited number of patients with BP could not find significant exacerbating or associated medications with expression of BP apart from, possibly, aldosterone antagonists.[202] However, this study was not designed to detect DIBP.

6. Differential Diagnosis

Other autoimmune subepidermal blistering disorders included in the differential diagnoses are: linear IgA bullous dermatosis (LABD); DH; bullous systemic lupus erythematosus (BSLE); CP; epidermolysis bullosa acquisita (EBA); and pemphigoid gestationis (PG). Clinical, histological and immunopathological techniques readily separate LABD, DH and BSLE from BP.

While CP predominantly affects the mucous membranes, BP more commonly affects the skin. Both disorders recognise the same target antigen (NC16A site of BP180),[85,203] but have subtle differences in antibody restriction, prevalent immunoglobulin class and the concentration of complement versus IgG deposited in the BMZ.[204] CP sera typically exhibit a lower lamina lucida/lamina densa staining pattern, whereas the ultrastructural immunolocalisation pattern of BP sera is largely restricted to the upper lamina lucida region.[205]

EBA is often characterised by skin fragility, trauma-induced lesions, absence of inflammation, healing with milia and scarring, and lesions localised to extensor surfaces.[206] However, a subset of patients exists that present with a generalised inflammatory

skin blister phenotype. As such, clinical overlap between EBA and BP occurs. It has been suggested that up to 10% of patients initially diagnosed as BP on clinical grounds, were actually cases of EBA.[207,208] With this in mind, further studies including special immunohistochemical techniques may be necessary for correct diagnosis in specific cases (see section 7).

PG is associated with pregnancy, hydatiform moles, choriocarcinoma and trophoblastic tumours, while BP does not have these associations.[209-211] The trigger in PG is thought to be exposure to paternal tissue via expression of fetal major histocompatibility complex class II antigens in the placenta.[204] Despite these findings, some cases that presented initially as PG, subsequently transformed into classic BP, questioning the distinction between these two entities.[212]

Other blistering disorders including bullous erythema multiforme, generalised fixed drug eruption, impetigo, porphyria cutanea tarda, bullous LP, pemphigus vulgaris and paraneoplastic pemphigus may also be considered in the differential diagnosis of BP. However, each of these entities and the aforementioned autoimmune disorders commonly have unique clinical and histological presentations in a context distinct from BP, making differentiation simple.

Among rare cases in the childhood group, the differential diagnosis of BP includes congenital causes of tense blisters such as variants of epidermolysis bullosa and other genodermatoses such as incontinentia pigmenti.

7. Diagnosis: Clinical, Histological and Immunopathological Techniques

Although the clinical presentation of BP can vary widely with the variants discussed in section 4, the majority of patients present with large tense blisters on either erythematous or clinically normal skin. In an attempt to develop reliable clinical criteria for identification of BP, Vaillant et al.[213] used the gold standard of immune electron microscopy to differentiate among various autoimmune subepidermal bullous disorders and to correlate these with the clinical findings. They found a sensitivity of 90%, with a specificity of 83% when three of four criteria are met clinically: (i) absence of atrophic scars; (ii) absence of head and neck involvement; (iii) absence of mucosal involvement; and/or (iv) age >70 years. However, applicability of these criteria can be severely limited because of the common finding of mucosal lesions in BP patients and earlier age of presentation.

Laboratory investigations are non-diagnostic for BP, but may reveal the presence of peripheral eosinophilia in approximately 22–50% of patients.[52,214,215] There may also be an associated elevated serum IgE and ESR.[50,216] When present, the level of peripheral eosinophilia may correlate with both disease activity and response to treatment.[214,217]

Routine histology of a blister in BP demonstrates subepidermal bulla formation that is either infiltrate-poor (taken from a bulla on clinically normal skin) or infiltrate-rich (taken from a bulla on clinically erythematous skin).[5] Biopsies of bullae from inflamed skin are preferable as the large numbers of eosinophils in the dermis and bulla cavity, and the possible presence of papillary microabscesses containing eosinophils, are highly suggestive of BP (figure 2a).[5,218] Furthermore, approximately one-quarter of BP biopsies demonstrate eosinophilic spongiosis, a finding that is frequently associated with peripheral blood eosinophilia.[219] Apart from eosinophil predominance, the infiltrate can include lymphocytes and neutrophils, and may even show neutrophil-predominant papillary microabscesses similar to DH.[5]

To confirm that the bullae are due to antibody deposition at the DEJ, direct immunofluorescence (DIF) for IgG, IgM, IgA and C3 is performed. The biopsy site should be either perilesional skin on the upper body within 2cm of a bulla, or clinically uninvolved skin from the flexor aspect of a forearm or anterior thigh.[220] Biopsy specimens from the lower legs should be avoided because of false-negative results in up to one-third of samples from this region.[194,221] All patients with BP have detectable C3 deposited at the BMZ and >90% have IgG pre-

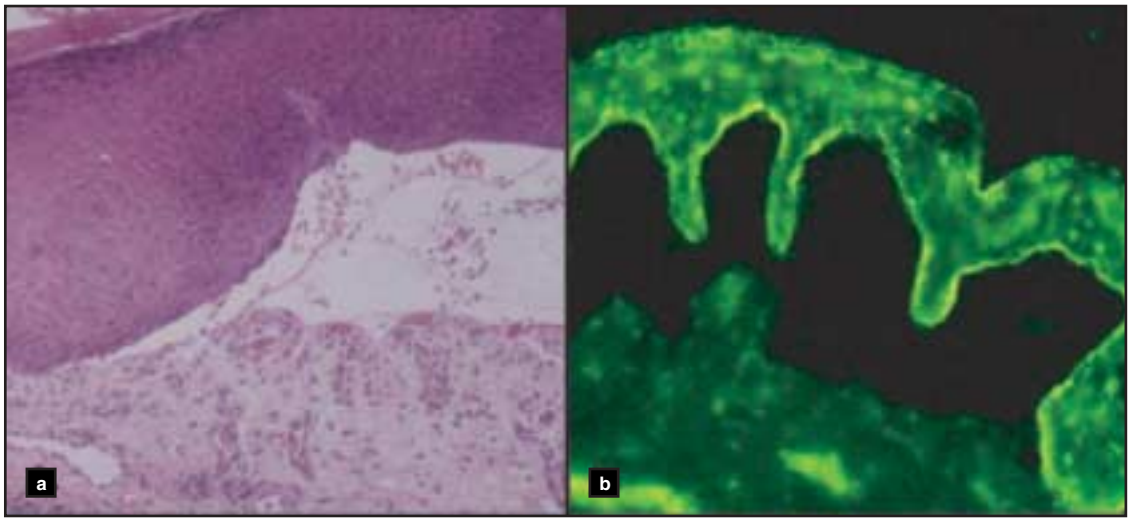

Fig. 2. Pathology of bullous pemphigoid. (**a**) Routine histopathology from the edge of an inflamed blister reveals a subepidermal bulla with an eosinophilic infiltrate in the dermis (haematoxylin-eosin stain; original magnification × 100). (**b**) Indirect immunofluorescence (1 mol/L sodium chloride salt-split skin) demonstrates linear IgG and C3 staining on the roof of the bulla.

sent as detected by DIF.[222] This finding effectively eliminates IgA-predominant diseases such as DH and LABD from the differential diagnosis.

IIF using various substrates can detect circulating IgG to BMZ antigens in 48–88% of cases.[52,53,219] The rate of antibody detection is highly dependent on the substrate used as animal oesophagus (e.g. monkey, guinea pig) may yield misleading results in comparison with human skin substrate.[220] The sensitivity of IIF can be improved dramatically by using split skin with human substrate rather than intact tissue.[108,223] It is thought that this method helps to expose antigens and increase potential antibody binding. However, the specificity of IIF has been questioned with the finding of an increased incidence of circulating anti-BMZ antibodies in healthy, normal, elderly individuals.[224]

The vast majority of patients with BP can be diagnosed on the basis of the clinical scenario, histological pattern and immunological criteria with deposition of C3 and/or IgG along the BMZ on DIF. However, DIF and IIF do not distinguish the precise locations of the antigens that are being recognised by IgG, and thus cannot distinguish between immuno-histologically related disorders such as EBA, BSLE, CP and PG with immunoreactants that bind to the BMZ.

In order to distinguish among these entities, several different techniques can be performed, including: direct or indirect immune electron microscopy; DIF or IIF on salt-split skin (SSS); immunoprecipitation; immunoblotting and Western detection; or immunoperoxidase staining of type IV collagen on a histological sample of a blister. The success of these methods is based upon differential localisation within the BMZ of the different antigens responsible for each disease. The BMZ is composed of four layers: the basal keratinocytes surface containing the hemidesmosomes; the lamina lucida; the lamina densa; and the sub-lamina densa. Antibodies to BP and PG antigens bind primarily to structures located in the hemidesmosome and lamina lucida; antibodies to CP antigens bind to structures located in the hemidesmosome, lamina lucida and lamina densa; and antibodies to EBA and BSLE antigens bind only to the lamina densa and sublamina densa regions.[220]

Direct immune electron microscopy is the gold standard for antibody localisation within the BMZ. However, this method is very time consuming, expensive and not practical in routine clinical settings.

Similarly, indirect immune electron microscopy is affected by the same problems, with the added disadvantage of lower detection rate.

Either DIF or IIF on SSS offers a less expensive and technologically simpler method for crudely distinguishing the location of antibody binding.[222] This technique involves separation of the epidermis from the dermis through the lamina lucida via incubation in 1 mol/L sodium chloride. This can be performed on either lesional skin that is then assayed for the site of already-bound antibody (DIF on SSS), or by splitting a substrate skin and adding the patient's sera and subsequently assaying for the site of antibody binding (IIF on SSS) [figure 2b].[206] Hence, SSS separation leaves two surfaces: a roof (the lamina lucida and basal keratinocytes) and a floor (lamina densa and sub-lamina densa). Using this technique, the EBA and SLE (in which the antibodies bind the floor of the blister) can usually be distinguished from BP and PG. In the latter two diseases, antibodies bind the roof (85%), roof and floor (2–10%) or, very rarely, the floor only (3–5%) of the blister.[225,226] Since BP180 extends into the lamina densa, it is possible to have antibodies binding to an epitope in this region. In CP, the antibodies bind to the roof, roof and floor and/or floor only as assessed by either of these methods.[220]

Immunoprecipitation uses radiolabelled extracts from cultured keratinocytes to co-precipitate with antibodies from the serum of a patient with BP. In a similar technique, immunoblotting (i.e. Western blotting) involves assaying an immobilised panel of cultured keratinocyte protein for binding with antibodies from the serum of a patient with BP.[227] Immunoblotting may be more sensitive than immunoprecipitation in detecting BP antibodies.[75] Both of these methods allow detection of small amounts of circulating antibodies and have the advantage that the molecular weight of the specific antigen recognised can be determined (e.g. 180 and 230 kDa proteins in BP vs 290 kDa protein in EBA and SLE). These techniques can be synergistic with IIF on SSS and help to identify cases missed with either technique alone.[78,228,229] However, both techniques using keratinocyte extracts have lower specificity as many unrelated pruritic disorders also have low titres of BMZ antibodies that are detected by these methods.[230] Moreover, false-negative results can be present, depending on polymorphic variation with the source of cultured keratinocyte protein.[99]

The recombinant NC16A region of BP180 has been used to develop an ELISA method for the detection of circulating anti-BP180 antibody in patient sera. The sensitivity and specificity of antibody to this region of BP180 is high for both BP and PG.[231] This technique will also be limited by the potential for false-positive results from low antibody titre in normal human sera.

Antibodies in EBA and SLE specifically recognise collagen VII of the anchoring fibrils in the lamina densa. Collagen IV is situated in the lamina densa above collagen VII. Hence, staining a bulla with anti-type IV collagen antibody may be helpful to distinguish EBA and SLE from BP and PG.[142] As the cleft in BP and PG is at the level of the lamina lucida, anti-type IV collagen will bind to the blister floor. In EBA, the bulla split is below the lamina densa, and staining with anti-type IV collagen will be seen in the blister roof.

In clinical practice, the only reason to progress beyond standard DIF/IIF by using SSS would be in a BP patient whose disease does not follow the expected clinical course or fails to respond to appropriate treatment. Table III reviews an approach to BP with the multitude of immunopathological tests available.

8. Treatment

BP is generally regarded as a benign, self-limited disease of 2- to 5-year duration with rare cases lasting up to 10 years.[4,50,232,233] Exacerbations and remissions are common and tend to be milder than the initial episode.[7,126] Although a benign disease, morbidity can be considerable. The mortality rate averages approximately 27% across different studies of between 3 months and 3 years follow-up, and is often due to factors related to treatment and age.[6,9,234] In fact, present day conventional therapy produces a mortality rate similar to that observed in untreated patients in the past.[234] As the majority of

Table III. An approach to the diagnosis of bullous pemphigoid (BP)

Scenario 1: Classic BP
Clinical context: tense blisters on normal skin or erythematous bases located on the body or extremities of an elderly person in the absence of atrophy or scarring
+
Histopathology (perilesional erythematous skin from upper body preferred): subepidermal bulla with predominant eosinophilic infiltrate ± lymphocytes, neutrophils, fibrin, papillary eosinophilic/ neutrophilic abscesses or eosinophilic spongiosis
+
Direct immunofluorescence or indirect immunofluorescence showing C3 ± IgG in linear deposition along basement membrane zone
Scenario 2: BP variant or unresponsive to standard therapy
Direct immunofluorescence on salt-split skin
or
Indirect immunofluorescence on salt-split skin
guinea pig oesophagus
monkey oesophagus
human tissue
or
Direct or indirect immune electron microscopy (gold standard)
Primarily research tools
Immunoblotting
Immunoprecipitation
Immunoperoxidase staining for type IV collagen
ELISA

patients affected with BP are elderly, have multiple disease comorbidities and are taking multiple medications, they are at high risk for both drug interactions and adverse effects of therapy. Hence, therapy should be directed towards suppressing disease activity with the minimum amount of treatment.[232]

Localised disease is generally self-limited and responds to potent topical corticosteroids such as clobetasol priopionate.[11,137] In earlier open-label studies, several investigators demonstrated that potent topical corticosteroids applied twice daily to hospitalised BP patients could successfully control even moderate and extensive disease in the majority of patients.[235-238] Despite regular use of up to 30 g/day of clobetasol priopionate, there was no pituitary-adrenal axis suppression in patients in these studies. The potent topical corticosteroid could slowly be titrated down to mid- and low-potency strength without significant recrudescence of disease activity.[235] Topical corticosteroids act to inhibit polymorphonuclear leukocyte recruitment, stabilise mast cells and slow lymphocyte production.[235] The beneficial effects may be from the reduction of chemical and cellular immune mediators both locally and through systemic absorption.[238,239]

In a landmark randomised controlled trial comparing the use of potent topical corticosteroids with oral corticosteroids for severe BP in hospitalised patients, Joly et al.[240] suggested that topical corticosteroids twice daily may be more efficacious with lower mortality than high-dose systemic corticosteroids. Using clobetasol priopionate 40 g/day divided twice daily applied to the full body in severe disease, they found better overall survival, control of disease and far fewer life-threatening adverse effects compared with prednisone 1 mg/kg/day. Topical corticosteroid treatment led to a 43% reduction in the 1-year mortality rate compared with systemic treatment. However, topical treatment had equivalent outcomes as systemic treatment with prednisone 0.5 mg/kg/day in moderate disease. Unfortunately, several factors limit the applicability of this study to general practice. Specifically, this study was performed on hospitalised patients in France. In North America patients are not readily hospitalised for the treatment of skin disease and the application of full body topical corticosteroids may pose difficulty for the average elderly person affected with BP.[241,242] Furthermore, the overall 1-year mortality rate in this study was much higher than that reported in most British and American studies.[243,244] Nevertheless, this study highlights the fact that topical treatment should be considered first-line in the treatment of BP.

Standard treatment for BP has classically relied upon systemic corticosteroids. Early studies suggested that prednisone, prednisolone and methylprednisolone were equivalent for disease treatment.[245,246] However, one small study suggested that prednisone may have slightly higher efficacy than prednisolone metasulfobenzoate sodium.[247] It has also been recognised that BP is frequently corticosteroid responsive and patients often improve within 24 hours if given high-dose pulsed intrave-

nous corticosteroids.[248,249] Nevertheless, it became further apparent that lower doses of an oral corticosteroid were as efficacious as higher doses, and had fewer adverse effects and complications.[250,251] In fact, the frequency of adverse events associated with corticosteroids increase with higher dosages.[233,240,246] Adverse effects of systemic corticosteroids are numerous and include diabetes mellitus, hypertension, cataracts, osteoporosis, bone fracture/osteonecrosis, gastrointestinal bleeding, sepsis/severe infections and psychosis.[240] This has led experts to recommend maximum starting doses of ≤0.75 mg/kg/day.[233,246] Although the majority of patients will achieve prolonged clinical remission after an initial course of oral corticosteroids, as many as 12–24% of BP patients are resistant to such treatment.[234] These patients will require either a different approach or a corticosteroid-sparing agent. Furthermore, elderly patients with BP often have comorbid diseases such as diabetes, peptic ulcer disease or hypertension that may become aggravated if disease treatment must rely upon systemic corticosteroids.

Several open-label studies and case series suggested that antibacterials such as tetracycline (1–2g divided four times daily), erythromycin (400mg three times daily) or minocycline (50–100mg once daily) may control disease activity alone,[252] with nicotinamide (2g divided four times daily),[253,254] or as adjuvant therapy with oral[255,256] or topical corticosteroids.[257,258] A small randomised, open-label study comparing combination therapy with tetracycline and nicotinamide with oral prednisone in mild-to-moderate BP found equivalent efficacy between the two treatment arms, but significantly fewer complications in the antibacterial group.[259,260] However, a small sample size and insufficient power limit the interpretations of these study findings.

Improvement with tetracyclines is generally seen within 1–3 weeks of commencing therapy.[249,257,259] Members of the tetracycline family and nicotinamide inhibit granulocyte chemotaxis and secretion.[261-263] Adverse effect profiles are generally favourable: tetracycline is associated with phototoxicity, candidiasis and gastrointestinal upset; minocycline is associated with vertigo, pneumonitis, drug-induced lupus, candidiasis, hyperpigmentation and, rarely, a hypersensitivity reaction; and nicotinamide is associated with flushing, pruritus, nausea, headache and, rarely, hepatotoxicity.[260] Unlike other tetracyclines, doxycycline does not appear to be helpful in the treatment of BP.[264] Recent guidelines recommend a trial of tetracycline and nicotinamide as first-line treatment for mild-to-moderate disease.[233,246] Furthermore, these agents may be helpful as corticosteroid-sparing adjuvants.

Although controversial, the classic corticosteroid-sparing adjuvant has been azathioprine. Early studies suggested that adjuvant usage of low-dose azathioprine (1.5 mg/kg/day) with prednisone could shorten both the length of therapy and the total prednisone dose by 30% in comparison with prednisone alone.[11] A controlled study using azathioprine 2.5 mg/kg/day with prednisone compared with prednisone alone found a reduction of 45% in the amount of corticosteroid required to control disease in the azathioprine group.[265] Additional case series using azathioprine reinforced the potential to significantly decrease or withdraw systemic corticosteroid treatment in many patients.[266] However, in a subsequent larger controlled trial, Guillaume et al.[267] found no advantage to the combination of azathioprine 100–150 mg/kg/day and prednisolone compared with prednisolone alone. In fact, severe complications from treatment were more common in the azathioprine group. Limitations to this study include under-dosage of azathioprine and the strict adherence to specific prednisolone dosages despite continued disease activity.[268] In contrast, in most clinical situations, the corticosteroid-sparing agent is added once control of the disease has been achieved with oral corticosteroids. The corticosteroid dosage is then tapered and stability is maintained with the second-line, less toxic agent. Azathioprine is metabolised in red blood cells by hypoxanthine guanine phosphoribosyl transferase of the salvage pathway to 6-thioguanine, which becomes incorporated into DNA and RNA synthesis and blocks further elongation. As azathioprine affects the salvage pathway, it is not

overly specific for lymphocytes, and has effects upon many rapidly dividing cell types. It has a delayed onset of action and may not reach optimal effect for several weeks. Adverse effects of azathioprine include bone marrow suppression, gastrointestinal distress, hypersensitivity syndromes, hepatotoxicity and an increased risk of malignancy.[243] Risk of bone marrow suppression can now be minimised and the drug administered appropriately by determining thiopurine methyltransferase levels before starting therapy. This enzyme catabolises the drug and its active intermediates into inactive metabolites. A low endogenous level of this enzyme correlates with a high risk of potential adverse effects. Both allopurinol and captopril may increase the concentrations of azathioprine into the toxic range. Current guidelines suggest that the addition of azathioprine should only be considered if the corticosteroid dose cannot be reduced to an acceptable level without recrudescence of disease activity.[233]

Low-dose methotrexate has been used either in conjunction with potent topical corticosteroids,[217] or as an oral corticosteroid-sparing agent to control disease activity.[269] In both of these case series methotrexate was started at 5 mg/week and increased by 2.5 mg/week until control of disease activity was achieved (total 5–12.5 mg/week). Response occurred within days to a maximum of 1 month. Methotrexate inhibits the enzyme dihydrofolate reductase (DHFR) in the reduction of folate to tetrahydrofolate and, thus, inhibits purine synthesis.[270] It is a protein-bound drug and can be displaced by salicylates, NSAIDs, phenytoin or tetracyclines. It should not be used in conjunction with these medications or with other inhibitors of the DHFR pathway including sulfonamides and dapsone. Adverse effects of methotrexate include nausea, stomatitis, alopecia, myelosuppression, pneumonitis/pulmonary fibrosis, hepatotoxicity, immunosuppression-related malignancies and teratogenicity. Myelosuppression and stomatitis can be minimised by the addition of folic acid 1 mg/day without decreasing drug efficacy. Methotrexate may represent a relatively benign alternative that can help to reduce prednisone dosage by up to 30 mg/week[269] or may be successful as systemic monotherapy with adjunctive topical corticosteroids.[217] It should also be considered in patients with concomitant psoriasis and BP.[233]

Mycophenolate mofetil is a promising immunosuppressive candidate for the treatment of BP. Thus far, it has only been used in isolated case reports as either corticosteroid-sparing[271,272] or as a second-line monotherapy agent in corticosteroid-resistant disease.[273] Mycophenolate mofetil is catabolised to mycophenolic acid, which inhibits inosine monophosphate dehydrogenase in the *de novo* purine synthesis pathway of guanine. As lymphocytes are more dependent upon *de novo* synthesis of nucleotides, this drug has a greater effect on these cells than on other actively replicating cell types. The typical dosage range has been between 2 and 3 g/day divided twice daily. The major adverse effects of this drug include gastrointestinal intolerance, leukopenia, increased viral/bacterial infections with immunosuppression and a theoretical risk of immunosuppression-related malignancies. As it does not produce hepatonephrotoxicity, it can be used in patients with kidney or liver problems.[273]

In a minority of patients, dapsone has been successfully used as either sole treatment or as an adjunct to systemic or topical corticosteroids. Success rates range from 14% to 44% in open-label studies and isolated case reports.[274-276] Remission was typically apparent in 2 weeks from start of therapy in responders. Dapsone inhibits neutrophil chemotaxis, suppresses the generation of damaging oxygen intermediates in neutrophils and inhibits the myeloperoxidase-peroxide-halide system.[277] Potential adverse effects include nausea, fatigue, headache, haemolytic anaemia, leukopenia, agranulocytosis, methaemoglobinaemia, hepatitis, psychosis, rashes and peripheral neuropathy. Glucose-6-phosphate dehydrogenase levels must be assessed before commencing of therapy with sulfones. Related sulfonamides such as sulfapyridine may also demonstrate limited success in controlling BP.[274,276] Sulfones may offer greater success at controlling dis-

ease in those patients who have a high neutrophilic infiltrate on biopsy.[274,276]

Several alternative immunosuppressive therapies have been reported in the literature, but with insufficient numbers or trials to currently recommend them as treatment options. In an open-label study of 26 patients, Milligan and Hutchinson[278] used chlorambucil (0.1 mg/kg/day reduced to maintenance dosage of 2 mg/day) as a corticosteroid-sparing agent. Although successful in both controlling disease and limiting prednisone dosage, several patients developed thrombocytopenia and one patient had significant bone marrow suppression. Cyclophosphamide, in both oral and pulsed therapy, has been used successfully in severe, treatment-resistant cases with or without concomitant corticosteroids.[279,280] The potential adverse effects of this treatment, including myelosuppression, haemorrhagic cystitis and neoplasia (5–10%), severely limit this drug as an option in the treatment of BP. Ciclosporin has had mixed results in case reports and, even at high doses, may not control disease activity.[281-283] Leflunomide, a novel immunomodulatory agent inhibiting dihydro-orotate dehydrogenase and, thus, *de novo* synthesis of pyrimidines, has been reported as a successful corticosteroid-sparing agent in a single case.[284]

Several open-label or retrospective studies have reported success with plasmapheresis as monotherapy[285] or as a corticosteroid-sparing agent in BP.[285,286] Similarly, success with photophoresis in treatment-resistant BP has been reported in a few patients.[287] Two early controlled studies suggested that plasmapheresis was beneficial as a corticosteroid-sparing measure, but the expense and lack of reduction of adverse events over prednisone severely limit its efficacy.[288,289] A subsequent controlled study did not find an appreciable difference between oral prednisone alone and oral prednisone plus plasmapheresis.[267] Many of these studies are difficult to evaluate as they have used different protocols for plasmapheresis. However, in light of the extreme cost and low benefit with potential severe adverse outcomes, plasmapheresis cannot be currently recommended as either a corticosteroid-sparing or second-line monotherapy in BP.

A costly treatment option, intravenous immunoglobulin (IVIg) therapy at 2 g/kg/cycle (one cycle = 1 month) for a minimum of four cycles has been advocated as an effective option in both nonresponsive disease as monotherapy and as a corticosteroid-sparing agent when adverse effects have been encountered.[234,290] Earlier studies suggesting limited efficacy of IVIg did not use appropriate doses or

Table IV. Treatment algorithm for bullous pemphigoid (BP)

Mild-to-moderate disease
First-line
topical clobetasol propionate bid
Second-line
tetracycline (1–2g divided bid) or
erythromycin (400mg tid) or
minocycline (50–100 mg/day)
± nicotinamide (2g divided qid)
prednisone (0.5–0.75 mg/kg/day)
Third-line
methotrexate, azathioprine, mycophenolate mofetil, dapsone, IVIg
Moderate-to-severe disease
First-line
prednisone (0.5–0.75 mg/kg/day)
± topical clobetasol propionate bid
± tetracycline/erythromycin/minocycline
± nicotinamide (2g divided qid)
Second-line
methotrexate 5 mg/week increasing by 2.5 mg/week
azathioprine (administered according to TPMT levels)
mycophenolate mofetil (2–3g divided bid)
IVIg (2 g/kg/cycle)
Third-line
dapsone (50–100 mg/day)
chlorambucil (0.1 mg/kg/day)
cyclophosphamide (pulsed or oral)
leflunomide (20 mg/day)
plasmapheresis/photophoresis
Specific indications
Localised pemphigoid: topical clobetasol propionate bid
Neutrophil-heavy infiltrate on biopsy: dapsone 50–100 mg/day
BP with concomitant psoriasis (>15% total body surface area): methotrexate 5–15 mg/week

bid = twice daily; **IVIg** = intravenous immunoglobulin; **qid** = four times daily; **tid** = three times daily; **TPMT** = thiopurine methyl transferase.

length of therapy.[291-293] Duration of therapy was up to 2 years, and relapse was frequent within 10 months if IVIg was abruptly discontinued rather than tapered. By increasing the intervals between infusions from 4 to 6, 8, 10, 12, 14 and finally 16 weeks, the risk of relapse may be minimised.[293] Potential adverse effects of IVIg include headache, nausea, fatigue, flushing, haemolytic anaemia, aseptic meningitis, stroke/thrombosis, renal failure, congestive heart failure, acquired infections, and anaphylactic or hypersensitivity reactions.[293] Several theories exist regarding the mechanisms by which IVIg exerts its action including functional blockade of Fc receptors, increasing catabolism and elimination of immune complexes, inhibiting complement-mediated damage, anti-idiotype suppression of autoantibodies and cytokine modulation.[294] At present, it appears that IVIg may be a reasonable but costly alternative in treatment-resistant, severe cases where the battery of other immunosuppressive agents is contraindicated.

Table IV lists an approach to the treatment of BP based on the data outlined in this section. Guidelines have recently been published for the management of BP.[233]

9. Conclusion

BP is an autoimmune subepidermal bullous disorder more commonly observed in the elderly population. Autoantibody formation against specific antigens of the BMZ leads to complement activation and subsequent amplification/recruitment of chemical and cellular immune mediators, ultimately resulting in blister formation. BP may present as several distinct clinical variants ranging from pruritic nodules to classic blisters or drug-induced disease. Potent topical corticosteroids represent the first line of therapy. If systemic agents are required, treatment must be aimed at balancing efficacy with toxicity.

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Correspondence and offprints: Dr *P. Régine Mydlarski*, Division of Dermatology, University of Calgary, 3330 Hospital Dr NW, Calgary, Alberta, Canada T2N 4N1.
E-mail: regine.mydlarski@ucalgary.ca