

# Management of bullous pemphigoid: the European Dermatology Forum consensus in collaboration with the European Academy of Dermatology and Venereology

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## Summary

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Bullous pemphigoid is the most common autoimmune subepidermal blistering disease of the skin and mucous membranes. This disease typically affects the elderly and presents with itch and localized or generalized bullous lesions. In up to 20% of affected patients, bullae may be completely absent, and only excoriations, prurigo-like lesions, eczematous lesions, urticated lesions and/or infiltrated plaques are observed. The disease is significantly associated with neurological disorders. The morbidity of bullous pemphigoid and its impact on quality of life are significant. So far, a limited number of national treatment guidelines have been proposed, but no common European consensus has emerged. Our consensus for the treatment of bullous pemphigoid has been developed under the guidance of the European Dermatology Forum in collaboration with the European Academy of Dermatology and Venereology. It summarizes evidence-based and expert-based recommendations.

The present consensus for the management of bullous pemphigoid (BP) has been prepared bearing in mind that health-care settings and modalities are different among European countries. In particular, hospitalization rules, home care availability and the possibility of financial reimbursement for treatments differ.

The aim of this consensus is to make recommendations for the most common situations. It is not intended to cover exhaustively all specific disease variants of BP, including childhood pemphigoid.<sup>1–3</sup> The various atypical forms of BP are too numerous and their occurrence too rare to be discussed here individu-

ally. The consensus is also not intended specifically to address and review the predictable and potential side-effects of the proposed drugs. The methodology used to generate this consensus, and its limitations, are described in detail in Appendices 1 and 2. Differences between the recommendations in the present consensus statement of European experts and other published national guidelines reflect incomplete knowledge on the matter of optimal treatment modalities in BP due to the paucity of randomized controlled trials in this area. The latter may lead to divergent expert opinion on a number of open questions, which ongoing and future studies will clarify.

## 1 Initial evaluation of bullous pemphigoid

The initial clinical examination should search out features consistent with a diagnosis of BP and evaluate the patient's general condition and potential comorbidities (Table 1).

### 1.1 Major objectives

The major objectives of the management are: (i) to confirm the diagnosis of BP; (ii) to search for risk factors and comorbidities; (iii) to specify the type of initial damage and its extent (see definitions and outcome measures for BP);<sup>4</sup> (iv) to evaluate the age-dependent prognosis and general condition (Karnofsky performance status scale); and (v) to consider therapeutic options.

### 1.2 Professionals involved

The treatment plan for patients with BP should be supervised by a dermatologist familiar with this condition; in most cases, the dermatologist either belongs to a referral centre or is in contact with a referral centre. Other health professionals who might be considered for inclusion in the patient's management according to the clinical presentation, general conditions and comorbidities are: (i) the dermatologist in general practice; (ii) the patient's general practitioner or family physician, or alternatively a geriatrician or neurologist; (iii) a specialized nurse (e.g. elderly care medicine, community health service or home health care); (iv) a dietician, psychologist or physiotherapist, often involved in patient care; and (v) all other specialists whose expertise is necessary based on the clinical context.

### 1.3 Clinical examination

#### 1.3.1 Patient's history

The physician should obtain a detailed medical history specifying the date of onset and evolution of signs and symptoms. Special consideration should further be given to obtaining a relevant history related to either comorbidities potentially associated with BP (such as neurological and cardiovascular diseases) or the potential therapy to be used.<sup>1,2</sup>

The physician should research recent drug intake (over a 1–6-month period) based on potential triggering roles, such as diuretics and psycholeptic drugs (phenothiazine with aliphatic side chains).<sup>5,6</sup>

#### 1.3.2 Physical examination

The physician should search for objective evidence consistent with the diagnosis, and assess the general condition of the patient, as follows.

In the classical form of BP: Severely pruritic bullous dermatosis, with bullae usually arising from erythematous inflamed skin; symmetric distribution (flexural surfaces of the limbs, inner

thighs, abdomen), rarely with mucosal involvement and atrophic scarring.<sup>1,2,7,8</sup>

In the nonclassical and nonbullous forms of BP: Localized eczema, urticarial lesions, dyshidrosiform (acral) lesions, erosions (usually without mucosal involvement; oral in particular), excoriations, prurigo, prurigo nodularis-like lesions.<sup>7,8</sup>

A complete physical exam is necessary, with emphasis on looking for findings from associated comorbidities (e.g. neurological and cardiovascular diseases) relevant for further management and subsequent therapy.<sup>1,2</sup>

Finally, the extent of BP should be assessed (for example BP Disease Activity Index or daily blister count).<sup>4</sup>

### 1.4 Laboratory investigations for the diagnosis of bullous pemphigoid

In confirming the diagnosis of BP, the diagnosis is based on a combination of criteria encompassing clinical features, compatible light microscopy findings and positive direct immunofluorescence microscopy (DIF) findings (Table 1).<sup>1–3,9,10</sup> Proper diagnosis and classification of BP further require one of the following steps.

- 1 Use of validated clinical criteria for BP.<sup>10</sup> When three of the four clinical characteristics are present (age > 70 years, absence of atrophic scars, absence of mucosal involvement, absence of predominant bullous lesions on the neck and head), the diagnosis of BP can be made with high specificity and sensitivity in patients with linear IgG and/or C3 deposits along the dermoepidermal junction.<sup>10</sup>
- 2 Detection of circulating IgG antibasement membrane autoantibodies by indirect immunofluorescence (IIF) microscopy studies using NaCl-separated normal human skin.<sup>1–3,9,11</sup>
- 3 Detection of anti-BP180 [also called BP antigen (BPAG)2/type XVII collagen] IgG autoantibodies and/or anti-BP230 (also called BPAG1-e, epithelial isoform) IgG autoantibodies by enzyme-linked immunosorbent assay (ELISA).<sup>1–3,12–14</sup>

#### 1.4.1 Histopathology

Specimens for light microscopy studies should be taken from early bullae arising on erythematous skin and placed in formalin solution. Typical findings consist of subepidermal bullae containing eosinophils and/or neutrophils, associated with a dermal infiltrate of eosinophils and/or neutrophils or a marginalization of eosinophils along the dermoepidermal junction. Nevertheless, in the absence of blistering and in nonbullous forms, histopathological findings may be nonspecific, such as the presence of eosinophilic spongiosis.<sup>15</sup>

#### 1.4.2 Direct immunofluorescence microscopy

DIF studies represent the most critical test: their positivity is essential for the diagnosis of BP.<sup>1–3,9,10</sup> The biopsy specimen for DIF should be obtained from perilesional skin (blistered

Table 1 Diagnostic steps in the evaluation of patients with bullous pemphigoid (BP)

Clinical examination			
Patient's history	Physical examination <sup>a</sup>		Patient's assessment
Date of onset	Classical bullous form: symmetrical		Extension of BP (by BPDAI or daily blister count)
Evolution of signs and symptoms	distribution of vesicles and bullae		General condition and comorbidities
Recent drug intake (over 1–6 months)	over erythematous and nonerythematous skin (flexural surfaces of the limbs, inner thighs, trunk); rare oral mucosal involvement; no atrophic scarring; no Nikolsky sign		Laboratory examinations and work-up according to the patient's condition and therapy choice
Refractory itch of unknown cause in elderly patients	Nonbullous and atypical forms: excoriations, prurigo, prurigo nodularis-like lesions, localized bullae, erosions, eczematous and urticarial lesions, dyshidrosiform (acral)		
Laboratory investigations			
Histopathology (of a recent intact bulla if present)	DIF (perilesional skin)		Immune serological tests
Subepidermal bullae containing eosinophils and/or neutrophils	Linear (n-serrated) deposits of IgG and/or C3 along the dermoepidermal junction		IIF microscopy on normal human salt-split skin (or suction-split): IgG antibasement membrane antibodies binding to the epidermal side (sometimes epidermal and dermal) of the split
Dermal infiltrate of eosinophils and/or neutrophils	Sometimes IgA and IgE with similar pattern		ELISA for antibodies to BP180/BPAG2 and, if negative, for BP230/BPAG1
Marginalization of eosinophils along the dermoepidermal junction			
Nonspecific findings in atypical forms			
Other immunopathological tests			
Immunoblotting	Biochip	Fluorescence overlay antigen mapping	Immunohistochemistry
Search for reactivity with BP180 (BPAG2) and/or BP230 (BPAG1). Rarely, additional targeted autoantigens	IIF with purified BP180 recombinant protein spotted on a slide and transfected cells expressing BP230	Assessment of relative location of detected IgG deposits compared with other proteins within the cutaneous basement membrane zone	In a proportion of patients linear deposits of C3d and C4d along the basement membrane zone can be demonstrated using the same tissue sample obtained for light microscopy studies

BPDAI, Bullous Pemphigoid Disease Activity Index; BPAG, BP antigen. The diagnosis of BP is based on a combination of criteria encompassing clinical features, compatible light microscopy findings and positive direct immunofluorescence microscopy (DIF) findings. The positivity of DIF is essential for the diagnosis of BP. Proper classification of BP further requires searching for and characterizing circulating autoantibodies, most commonly by either indirect immunofluorescence (IIF) microscopy or enzyme-linked immunosorbent assay (ELISA).<sup>9</sup> The following clinical features are diagnostically useful: (i) age > 70 years; (ii) absence of atrophic scars; (iii) absence of mucosal involvement; and (iv) absence of predominant bullous lesions on the neck and head.

skin is to be avoided), and for transportation, skin biopsy specimens should be put into either a cryotube in liquid nitrogen, Michel's fixative or simply 0.9% NaCl solution.

DIF studies typically demonstrate linear deposits of IgG and/or C3 along the dermoepidermal junction; occasionally IgA and IgE are also found with a similar pattern.<sup>9,10,16</sup>

**1.4.2.1 Other tests** The analysis of the n-serration pattern of DIF may be helpful and specific in combination with IIF studies to differentiate BP from epidermolysis bullosa acquisita.<sup>17</sup>

DIF studies are recommended on an autologous patient's skin biopsy specimen cleaved by 1 mol L<sup>-1</sup> NaCl for IgG. The location of IgG deposits after splitting allows differentiation of BP from epidermolysis bullosa acquisita, antilami-

nin-332 mucous membrane pemphigoid and anti-p200 pemphigoid; note that the location of C3 is not reliable.<sup>1,2,9,18</sup>

Immunohistochemistry may be useful for the diagnosis of BP by detecting linear deposits of C3d and C4d along the epidermal basement membrane. Although this approach needs to be validated, it may be helpful in cases in which a second biopsy specimen for DIF studies is not available.<sup>19</sup>

#### 1.4.3 Immune serological tests

Serum samples (tubes sent to the immunology laboratory or to a reference laboratory) are obtained in order to perform either IIF studies or ELISAs. The choice of the approach depends on the availability, cost and local expertise.

Search for circulating IgG antibasement membrane antibodies by IIF microscopy studies. These studies are best carried out using 1 mol L<sup>-1</sup> NaCl-separated normal human skin as substrate. Antibasement membrane IgG autoantibodies characteristically bind to the epidermal side (sometimes epidermal and dermal) of the split skin. By this means, IgG autoantibodies are found in up to 80% of cases. Use of non-separated normal human skin or monkey oesophagus is associated with lower sensitivity.<sup>1,2,9,11,20</sup>

Search for anti-BP180 (also called BPAG2/type XVII collagen) IgG autoantibodies and anti-BP230 (also called BPAG1-e, epithelial isoform) IgG autoantibodies by ELISA. First perform an ELISA for anti-BP180 IgG then, if negative, for anti-BP230 IgG.<sup>1,2,12–14,21</sup>

Note that the above-mentioned IIF studies and ELISA may be positive in pruritic skin diseases other than BP, as well as in healthy subjects. They are confirmatory for BP only together with DIF microscopy studies.

#### 1.4.4 Other tests

Additional tests may be considered according to clinical context and availability, and are listed in Table 1.<sup>14,22–26</sup>

## 2 Therapeutic management

### 2.1 Work-up and pretherapy screening

The proposed work-up and pretherapy screening is depicted in Table 2. The recommendations are based largely on expert opinion.

### 2.2 Objectives

BP is a chronic disease that may last for several years in the absence of treatment and has a tendency to relapse.<sup>1,2</sup> The primary objectives are therefore to control both the skin eruption and itch, as well as to minimize serious side-effects of the treatment. Specifically, the goals of the management are: (i) to treat the skin eruption, reduce itch and prevent/reduce the risk of recurrence; (ii) to improve the quality of life of patients; and (iii) to limit the side-effects related to the newly introduced drugs, particularly in the elderly.

Advanced age in patients with BP and the potential presence of comorbidities (neurological, cardiovascular, neoplastic, metabolic and respiratory) make their cases more difficult to manage.<sup>1,2,8,27,28</sup>

### 2.3 Professionals involved and nursing

The initial management (i.e. diagnosis and treatment start) of extended forms of the disease in a polymorbid elderly patient usually requires hospitalization in a dermatology department. Hospitalization is not a requisite in certain countries due to their specific health systems. In paucile-sional or localized forms of BP, examinations for diagnostic

and clinical monitoring can be performed on an inpatient or outpatient basis depending on the degree of autonomy of the patient.

The management should be coordinated by a dermatologist in contact with treating physicians, specialists and hospital doctors from the centre of reference. Close collaboration between the dermatologist, the treating physician and, if necessary, the nursing staff is therefore fundamental.

### 2.4 Therapeutic management

The following recommendations (summarized in Table 3) are based on the following levels of evidence.

Level 1: randomized prospective single-centre or multicentre studies. In the case of the latter, the intervention is shown to be effective and not contradicted by other studies – its use is considered *validated*. Level 2: randomized prospective single-centre studies (in case of poor methodological quality), retrospective multicentre studies. Level 3: case series, retrospective single-centre studies. Level 4: anecdotal case reports. Level 5: expert opinion.

#### 2.4.1 Extensive bullous pemphigoid

At present there is no general consensus on the definition of extensive BP.<sup>4</sup> While some experts have defined extensive disease as the occurrence of more than 10 new blisters per day,<sup>29,30</sup> there are patients with a lower new blister count whose inflammatory lesions cover a large body surface area or areas.

**2.4.1.1 Topical treatment** Clobetasol propionate 0.05% cream (or ointment), 30–40 g per day, is initially administered in two applications, over the entire body including both normal skin and blisters and erosions, but sparing the face (20 g per day if weight < 45 kg; level of evidence 1, validated).<sup>29,30</sup> Current evidence indicates that the initial treatment should be first reduced 15 days after disease control (for definitions and outcome measures for BP, see recommendations by an international panel of experts).<sup>4</sup> Earlier reduction of corticosteroid doses has not been validated in controlled studies.<sup>29,30</sup>

The definition of disease control is the time point at which new lesions or pruritic symptoms cease to form and established lesions begin to heal.<sup>4</sup>

A tapering schedule with dose adaptation is as follows: (i) daily treatment in the first month; (ii) treatment every 2 days in the second month; (iii) treatment twice per week in the third month; and (iv) treatment once per week starting in the fourth month.

An increasing dose of topical steroids (up to 40 g per day) is recommended<sup>30</sup> in patients receiving < 40 g per day of clobetasol propionate 0.05% who do not achieve disease control within 1–3 weeks (level of evidence 1, validated).<sup>29,30</sup>

For maintenance, two options are available after 4 months of treatment.

**Table 2** Suggested work-up and pretherapy screening in a patient with newly diagnosed bullous pemphigoid. It is recommended to verify these recommendations, comparing them with the local health practice and system, and to follow national guidelines if available

Complete blood count, erythrocyte sedimentation rate and C-reactive protein
Creatinine, blood electrolytes, fasting glucose
Transaminases, $\gamma$ -glutamyltransferase, alkaline phosphatase, bilirubin
Albumin
Serology for hepatitis B, hepatitis C and HIV, if immunosuppressive therapy is planned
If patient is of childbearing age (very rare), perform pregnancy test prior to treatment
Testing of thiopurine methyltransferase is optional, when azathioprine treatment is considered
Glucose 6-phosphate dehydrogenase, if dapsone treatment is considered
Serum IgA deficiency should be excluded if intravenous immunoglobulins are considered
Check for an underlying neoplasm in line with the patient's age, clinical history and examination, as well as for an infection (in particular <i>Mycobacterium tuberculosis</i> ) if appropriate when immunosuppression needs to be initiated
Consider performing osteodensitometry if long-term systemic corticosteroid therapy is planned
Consider performing ocular examination (check for ocular tension and cataract) if long-term systemic corticosteroid therapy is planned
Local bacteriological sampling if there is any clinical evidence for lesion infection
Consider echocardiography before initiation of therapy with either systemic corticosteroids, dapsone or intravenous immunoglobulins

**Table 3** Bullous pemphigoid: therapeutic ladder

Localized/limited disease with mild activity
First choice
Superpotent topical corticosteroids; in mild disease, on whole body except the face (1, validated)
In localized disease, on lesions only (3, nonvalidated)
Second choice
Oral corticosteroids (1, validated for prednisone)
Tetracycline + nicotinamide (2, nonvalidated)
Dapsone, sulfonamides (3, nonvalidated)
Topical immunomodulators (e.g. tacrolimus) (4, nonvalidated)
Generalized disease
First choice, primary treatment
Superpotent topical corticosteroids on whole body sparing the face (1, validated)
Oral corticosteroids (1, validated for prednisone)
Second choice, as adjunctive therapy
Combination with or introduction of:
Azathioprine (1, nonvalidated)
Mycophenolate (1, nonvalidated)
Tetracycline + nicotinamide (2, nonvalidated)
Methotrexate (3, nonvalidated)
Chlorambucil (3, nonvalidated)
Third choice
Combination with and/or introduction of:
Anti-CD20 or anti-IgE monoclonal antibody (4, nonvalidated)
Intravenous immunoglobulins (3, nonvalidated)
Immunoadsorption (4, nonvalidated)
Plasma exchange (1, nonvalidated)
Cyclophosphamide (3, nonvalidated)

Key to evidence-based support: (1) Randomized prospective single-centre or multicentre study. If in the case of the latter the intervention is shown to be effective and not contradicted by other studies, its use is considered validated. (2) Randomized prospective single-centre study (in case of poor methodological quality), retrospective multicentre study. (3) Case series, retrospective single-centre study. (4) Anecdotal case reports. (5) Expert opinion.

1 Continue a maintenance treatment for 8 months (total treatment duration including consolidation phase and maintenance treatment is 12 months), and then stop; level of evidence 1, validated.<sup>29,30</sup> The dose of whole-body topical corticosteroids that we propose for this

maintenance therapy (10 g once a week) is lower than that used in the two randomized controlled trials (10 g twice a week) and thus is not validated. The 10-g topical corticosteroids should be applied preferentially on previously affected areas and their surrounding areas. Disad-

vantages are the practical and economic difficulties related to continued nursing for a long period and/or the cost of topical high-potency steroids.

- 2 Stop treatment (slightly higher risk of relapse but with improved safety when treatment is stopped within 4 months; level of evidence 1, validated).<sup>30</sup>

In case of a relapse (also termed a 'flare'), the dose is increased to the previous level (level of evidence 1, validated).<sup>29,30</sup> Relapse is defined as blisters, eczematous lesions or urticarial plaques, or at least one large (10-cm diameter) eczematous lesion or urticarial plaque that does not heal within 1 week, or extension of established lesions or daily pruritus in a patient who has achieved disease control (for definitions, see Murrell *et al.*)<sup>4</sup> during the dose-reduction period.

Patients who experience a relapse after treatment withdrawal are treated using the following doses of clobetasol propionate 0.05% cream or ointment (level of evidence 1, validated):<sup>30</sup>

- (i) 10 g daily for patients with a localized relapse (to be applied preferentially on previously affected areas and their surrounding areas);
- (ii) 20 g daily for patients with mild disease (see below for definition) or
- (iii) 30 g daily for patients with extensive relapse.

Additional measures to control disease or for maintenance can be considered and are listed below.

**2.4.1.2 Systemic steroid therapy** There is evidence that high-dose systemic steroid therapy, such as prednisone 1 mg kg<sup>-1</sup> per day, is effective in patients with extensive disease (level of evidence 1, validated).<sup>29,31–33</sup> However, this therapy has been associated with higher mortality and increased side-effects compared with the whole-body topical use of clobetasol propionate 0.05%.<sup>29,31,32</sup> Therefore, the group of experts does not recommend using this dosage in the initial treatment. Doses of prednisone of 0.5–0.75 mg kg<sup>-1</sup> per day are suggested, despite lack of evidence in extensive disease.<sup>29,31–33</sup> Prednisone doses < 0.5 mg kg<sup>-1</sup> have not been validated and seem to be ineffective.<sup>34</sup> Systemic treatment may be accompanied by topical therapy (with steroids and/or other measures; see below).

A tapering schedule and dose adaptation is as follows. The initial treatment should be first reduced 15 days after disease control. Earlier reduction of corticosteroid doses may be possible. In patients who do not achieve disease control within 1–3 weeks with prednisone 0.5 mg kg<sup>-1</sup>, the group of experts proposes to increase the dose of prednisone to 0.75 mg kg<sup>-1</sup> per day, despite the absence of evidence in the literature.

For maintenance treatment, systemic steroid doses should be tapered gradually with the aim of achieving minimal therapy (prednisone 0.1 mg kg<sup>-1</sup> per day, see definitions in Murrell *et al.*)<sup>4</sup> within 4–6 months after initiation of treatment.<sup>30</sup> If the patient is in complete remission under minimal therapy for 3–6 months, the treatment may be stopped (expert opinion). Although this regimen has not been

validated, the recommendation is based on the expected higher relapse rate of BP in patients whose treatment is completely withdrawn after 6 months.<sup>30</sup> Hence, the total treatment duration, including the consolidation phase and maintenance treatment, is usually 9–12 months (expert opinion).

In case of a relapse during the dose-reduction period, the dose is increased to the previous level (level of evidence 1, validated).<sup>29</sup> Additional measures to obtain or maintain disease control can be considered and are listed below.

The choice of an adjuvant or alternative therapy is dependent upon availability, cost issues, practical experience and the presence of specific contraindications. The use of an immunosuppressive/immunomodulatory therapy with a potentially corticosteroid-saving effect should be considered in the presence of contraindications to oral corticosteroids and of comorbidities (such as diabetes, severe osteoporosis, significant cardiovascular problems). Nevertheless, there is no positive evidence supporting their use as a first-line treatment, and they are therefore nonvalidated.<sup>31–33</sup>

The following drugs may be considered (level of evidence 1–3, Table 3). (i) Tetracyclines (oxytetracycline 2 g per day, doxycycline 200 mg per day orally) alone or in combination with nicotinamide (up to 2 g per day orally);<sup>35</sup> (ii) azathioprine 1–3 mg kg<sup>-1</sup> per day according to thiopurine methyltransferase activity;<sup>36–38</sup> (iii) mycophenolates (mycophenolate mofetil 2 g per day, mycophenolic acid 1.44 g per day orally);<sup>37,38</sup> (iv) methotrexate (up to 15 mg once a week orally, subcutaneously or intramuscularly);<sup>39</sup> (v) dapsone (up to 1.5 mg kg<sup>-1</sup> per day orally);<sup>40</sup> (vi) chlorambucil (2–4 mg per day orally);<sup>41</sup> and (vii) ciclosporin (3–5 mg kg<sup>-1</sup> per day).<sup>42</sup> Based on the current lack of evidence for its efficacy and the potential adverse-effect profile, including nephrotoxicity, high blood pressure and neurotoxicity, the use of ciclosporin is not recommended (5, expert opinion).

#### 2.4.2 Localized/limited and mild bullous pemphigoid

While two studies have defined mild BP as the occurrence of fewer than 10 new blisters per day,<sup>4,29,30</sup> it can be also defined by the presence of a few nonbullous inflammatory or localized lesions involving one body site. In the above-mentioned studies around five new blisters per day were observed in patients considered to have mild disease.<sup>29,30</sup>

**2.4.2.1 Topical treatment** Patients with localized/limited BP should be preferentially treated initially with topical steroids applied on lesional skin only (clobetasol propionate 10–20 g per day).<sup>30</sup>

Patients with mild BP with few but disseminated lesions should be treated with clobetasol propionate 20 g per day in one daily application over the entire body (hence on both normal skin and lesions), except for the face (10 g per day if weight < 45 kg; level of evidence 1, validated).<sup>29,30</sup>

A tapering schedule with dose adaptation is as follows. Current evidence indicates that initial treatment should first be

reduced 15 days after disease control. Earlier reduction of corticosteroid doses may be possible but has not been demonstrated in controlled studies. Topical corticosteroids are gradually tapered as mentioned above (section 2.4.1.1), with the aim of stopping treatment 4–12 months after initiation of therapy (level 1).

In patients who do not achieve disease control within 1–3 weeks with clobetasol propionate 20 g per day, it is recommended to increase the dose to 40 g per day (see section 2.4.1.1).<sup>29,30</sup> The use of lower-potency steroids in maintenance therapy has not been validated.

**2.4.2.2 Systemic steroid therapy** There is evidence that prednisone 0.5 mg kg<sup>-1</sup> per day is effective in patients with mild disease (level of evidence 1, validated).<sup>29</sup> Prednisone doses < 0.5 mg kg<sup>-1</sup> have been proposed for mild disease.<sup>3</sup> As these doses have not been validated and seem to be ineffective, they cannot be recommended here.<sup>31–34</sup> The systemic treatment may be accompanied by topical therapy with steroids and/or other measures (see below).

For *maintenance treatment*, systemic steroid doses should be tapered gradually with the aim of attaining minimal therapy (prednisone 0.1 mg kg<sup>-1</sup> per day) within 4–6 months of initiation of treatment. Although the optimal duration remains unclear, the expert group recommends a total treatment duration (consolidation phase and maintenance treatment) of 4–12 months (5, expert opinion).

Additional measures to obtain or maintain disease control can be considered (Table 3). The choice of an adjuvant or alternative therapy is dependent on its availability, cost aspects, practical experience and specific contraindications. The use of an immunosuppressive or immunomodulatory therapy with corticosteroid-saving effects should be considered in case of contraindications to oral corticosteroids and of comorbidities (such as diabetes, severe osteoporosis, significant cardiovascular disorders). Of note, there is evidence for increased side-effects associated with the use of azathioprine.<sup>36</sup>

Some evidence supporting the use of tetracyclines plus nicotinamide, methotrexate, and dapsone exists, although their use has not been validated in randomized controlled studies of good methodological quality.<sup>31–33</sup> The latter drugs may thus be considered (level of evidence 2 and 3). (i) Tetracyclines (oxytetracycline 2 g per day, doxycycline 200 mg per day) plus nicotinamide (up to 2 g per day);<sup>31–33,35</sup> (ii) methotrexate (up to 15 mg once a week orally, subcutaneously or intramuscularly)<sup>39</sup> and (iii) dapsone (up to 1.5 mg kg<sup>-1</sup> per day orally).<sup>40</sup>

Consider the recommendation for extensive BP (section 2.4.2.1).

### 2.4.3 Treatment-resistant bullous pemphigoid

In the cases of those few patients with generalized disease who remain below the controllable level (unresponsive)

despite several weeks of intensive therapy with combined topical and systemic steroids, the following therapeutic options might be considered.

Firstly, immunosuppressants (see above; including methotrexate, azathioprine and mycophenolate mofetil).<sup>36–39,41,42</sup> Secondly, additional therapies: (i) intravenous immunoglobulins (level of evidence 3);<sup>43</sup> (ii) immunoadsorption (level of evidence 4);<sup>44,45</sup> (iii) anti-CD20 monoclonal antibody, anti-IgE monoclonal antibody (level of evidence 4);<sup>46–48</sup> (iv) cyclophosphamide (level of evidence 3);<sup>49</sup> and (v) plasma exchange (level of evidence 1).<sup>34</sup>

### 2.4.4 Other skincare measures

The use of baths containing antiseptics and/or wheat starch is recommended. In cases of extensive erosive lesions, the latter may be covered by bandages using different types of dressings, preferably nonadherent, to reduce bacterial superinfection and pain, as well as to promote healing.

It is better to leave small and medium blisters intact and to puncture and drain larger blisters leaving the blister roof in place, as it forms a natural dressing. If the blister is already broken remove only the fluttering skin.<sup>3,50</sup>

### 2.4.5 Other general measures, when required or indicated

Other measures include the following.

- 1 Dietary supplements in malnourished patients.
- 2 Vaccinations. Patients receiving corticosteroids (prednisone at doses of > 20 mg per day for > 2 weeks) or immunosuppressive therapy should be vaccinated against seasonal influenza, H1N1 and pneumococci. Live attenuated vaccines are contraindicated.<sup>51,52</sup>
- 3 Osteoporosis baseline screening and prophylaxis if the expected duration of systemic corticosteroids is > 3 months. Vitamin D and calcium supplement is recommended at initiation of glucocorticoid treatment.<sup>53</sup> Treatment with bisphosphonates (alendronate, risedronate) is recommended in patients at risk (postmenopausal women, men aged > 50 years on glucocorticoid treatment > 3 months) to prevent osteoporosis.<sup>53</sup>
- 4 *Mycobacterium tuberculosis* prophylaxis/therapy (if necessary).
- 5 *Pneumocystis jirovecii* prophylaxis (optional).

Note that it is recommended to verify these recommendations, comparing them with the local health practice and system, and to follow national guidelines if available.

## 3 Monitoring

### 3.1 Objectives

The aims of monitoring are to evaluate the efficacy, safety and tolerance of the treatment, gradually to reduce and/or adapt treatment, and to decide when to discontinue treatment.

### 3.2 Professionals involved, including nursing

The specialists and health professionals involved are identical to those listed in the initial evaluation (section 1.2).

Note that the nursing care required for the application of topical treatments takes usually up to 30–45 min (encompassing antiseptic baths, bullae count, application of topical steroids, and bandaging).

### 3.3 Frequency of consultations

The frequency of the follow-up visits and of laboratory tests has to be adapted to (i) the patient's clinical condition; (ii) the severity and evolution of the disease; (iii) the treatments used; and (iv) the local health practice and system.

Treatment efficacy is monitored and evaluated essentially by clinical examination. In the scenario of generalized disease, the following visit frequency is suggested. (i) Weekly to biweekly until disease control, then (ii) monthly for the next 3 months, and then (iii) every 2 months to three times a year until treatment is stopped; the monitoring frequency has to be adapted to the disease course.

### 3.4 Clinical examination and laboratory monitoring

The clinical follow-up is identical to that performed during the initial assessment and consists of firstly, examination for skin disease activity (check for blisters, eczematous/urticarial-like lesions, intensity of itch etc.); and secondly, checking for possible treatment-related side-effects and comorbidities. The follow-up should include the following examinations and tests.

- 1 The degree of skin atrophy, purpura and skin infections
- 2 Blood pressure, cardiovascular insufficiency (corticosteroids), respiratory disorders and infections (corticosteroids, immunosuppressants)
- 3 Analysis of white blood cells, liver and kidney tests (immunosuppressants) and glycaemic value (corticosteroids)
- 4 Immune serological analyses. Determination of anti-BP180 IgG by ELISA at days 0, 60 and 150 is useful during treatment because IgG autoantibody fluctuations measured at these specific end points may predict outcome.<sup>13,54,55</sup> A small decrease – no more than approximately 20% – in anti-BP180 IgG serum levels between days 0 and 60 is a factor associated with disease relapse within the first year of therapy.<sup>54</sup> Furthermore, a low or negative anti-BP180 IgG level by ELISA ( $< 23 \text{ U mL}^{-1}$ , i.e.  $< 2$  times the upper limit of one of the commercially available kits) at day 150 has a good negative predictive value, as in this case the probability of durable remission is approximately 90%.<sup>55</sup>
- 5 Depending on the drug used, other specific examination, which may be required and necessary (e.g. for dapsone)
- 6 Osteodensitometry and ocular examination if indicated (according to the treatment regimen, and the patient's age and condition).

### 3.5 Discontinuation of treatment

The optimal duration of treatment has not been defined.<sup>29–33</sup> Based on clinical experience, we recommend an average treatment duration of 4–12 months according to the presence of either mild or generalized disease (see above), except in cases of steroid resistance or steroid dependence.

Discontinuation of treatment is recommended in patients who are free of symptoms for at least 1–6 months under minimal therapy with oral prednisone ( $0.1 \text{ mg kg}^{-1}$  per day), clobetasol propionate (10 g per week) or immunosuppressants. The choice of discontinuation of treatment is further affected by the patient's overall general condition and presence of distinct comorbidities.

Prior to cessation of treatment, DIF studies and/or ELISA for BP180 should be performed. In case of positive DIF or BP180 ELISA (if  $> 27 \text{ U mL}^{-1}$ ), there is an increased risk of relapse.<sup>55</sup> Be aware of and check for potential adrenal insufficiency caused by exogenous steroid use, even after topical application.

#### 3.5.1 Monitoring after treatment discontinuation

A follow-up visit is recommended in the third month after treatment discontinuation, as this period seems sufficient to detect most relapses of BP.<sup>30,54,55</sup> Patients or their caregivers should be informed that reappearance of itch, excoriations and/or inflammatory cutaneous lesions justifies medical assessment to exclude relapse.

### 3.6 Potential complications

BP can cause permanent complications directly related to either the disease itself or the treatments used. Affected patients seem to show a significantly increased mortality rate compared with control populations.<sup>1,2,8,27,28</sup> In this context, proper management of affected patients is necessary and requires specialized personnel.

## 4 Information for patients

Patients or their families must be informed about the disease, its prognosis, available treatments, possible adverse reactions and therapy-related complications. Furthermore, the need for regular clinical follow-ups to monitor disease activity and to carry out tests to gauge and monitor treatment tolerance must be fully explained. Patients should also be informed of the existence of local or national patients' associations. The purpose of these associations is to promote knowledge of the disease; to improve patients' access to information, care and social services and to interlink them. Thus, a better overall management of the disease can be achieved by promoting cooperation between patients, patients' families, patients' associations and healthcare professionals. Patients' associations can also help in referring patients to either referral centres or their network of correspondents.

#### 4.1 List of pemphigoid support groups (selection)

France:

Association Pemphigus – Pemphigoïde:<sup>56</sup> [www.pemphigus.asso.fr](http://www.pemphigus.asso.fr).

Germany:

Pemphigus und Pemphigoid Selbsthilfegruppe e.V.: <http://www.pemphigus-pemphigoid-selbsthilfe.de>; Pemphigus-Forum: <http://www.pemphigus-forum.de>.

International Pemphigus Pemphigoid Foundation: <http://www.pemphigus.org/>.

Italy:

Associazione Nazionale Pemfigo-Pemfigoide Italy: [www.pemfigo.it](http://www.pemfigo.it).

The Netherlands:

Netwerk Nederland voor Pemphigus en Pemfigoïd: <http://www.pemphigus.nl>.

Turkey:

Turkish Society of Dermatology: <http://www.turkdermatoloji.org.tr/>.

U.K.:

Bullous Pemphigoid Support Group: <http://www.patient.co.uk/support/bullous-pemphigoid-support-group>.

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## Appendix 1

### Methods

The present consensus statement was prepared according to the guidelines of the European Dermatology Forum, which are summarized on their website.<sup>57</sup> The consensus followed the recommendations on guidelines for research and evaluation II provided by the AGREE Research Trust, May 2009,<sup>58</sup> as well as those of the French government.<sup>59</sup>

Specifically, to facilitate further the preparation of the consensus statement, two committees – a writing committee and a voting committee – were created. Each committee comprised eight different experts. None of the experts served in both committees. In 2012, independent of outside financial support or backing, the voting committee held a 2-day meeting in

Frankfurt, the purpose of which was to grade approximately 150 items (from 0 indicating total disagreement to 9 indicating total agreement) relating to key sentences or proposals in the first draft of the consensus compiled by the writing committee. The mean and SD of the 150 items were then calculated. All items graded lower than 7, plus those showing conflicting marks, were discussed further by members of the writing committee and a subsequent second draft was produced. Modified items were then submitted to a second vote by the voting committee to ensure that a mean > 7 had been reached. The draft was e-mailed to members of the writing committee. Only minor modifications were allowed at this stage. Nevertheless, all potential studies relevant for the management of BP, which were published up to 31 December 2013, were considered further and evaluated during the preparation of the final manuscript. C.F. and L.B. were responsible for collecting and incorporating them into the final text. Based on the grading system of the Association of the Scientific Medical Societies of Germany, this consensus is classified as the S2e-guideline.<sup>60</sup>

Finally, the authors have included only a limited number of relevant references. While all available randomized prospective single-centre or multicentre studies have been included and referenced in the present consensus, the authors have voluntarily cited only a selected number of representative retrospective single- or multicentre studies, case series or anecdotal case reports to support their statements, but have specified the level of available evidence.

## Appendix 2

### Disclaimer and limitations

It is recognized that according to the different health systems in various countries and under certain conditions, it might not be feasible to follow this consensus. Based on the results of ongoing and future studies, the recommendations are subject to change. Consequently, the authors can take no responsibility for dosage or treatment decisions taken in this rapidly

changing field. Failure to adhere to the recommendations should not necessarily be considered negligent. Steps that can be considered part of every physician's general obligations when prescribing drugs (inquiring about allergies and intolerance reactions, and identifying potential contraindications) are not reported. It was considered obvious, and not declared, that all patients should be informed about the specific risks associated with any given systemic therapy. Finally, this consensus will not serve as an instrument, in part or in whole, as a defence in a negligence claim.

## Appendix 3

### Conflicts of interest

P.J. is conducting a study for which Roche provides rituximab; and is a board member for Novartis, Abbott and Janssen. M.F.J. receives consultancy fees or honoraria from Roche and Genetech; is a consultant for GlaxoSmithKline and Stiefel and has received payment for lectures from AbbVie. D.Z. has received grants from Euroimmun, Miltenyi, Fresenius, Biotest and Dompé; is involved with patents with Euroimmun; and has received travel or meetings expenses from Fresenius, Miltenyi, Abbott, Roche and UCB Pharma. G.Z. has received a research grant from Dompé. H.J. has received a grant for a clinical trial sponsored by Euroimmun. S.K. is employed by Semmelweis University; has grants from OTKA; has received payment for lectures and educational presentations from Peter Pazmany Catholic University; and has been reimbursed for travel or meetings expenses by EGIS. M.H. is a board member for Biogen Idec and Roche; is a consultant for UCB Pharma; has received grants from Fresenius, Biogen Idec and MBL Corp; has received speakers fees from Biogen Idec, MEDAC Ltd, MSD Pharma, Biotest and Dermapharm; has been reimbursed for travel or meetings expenses by Astellas and Janssen Cilag; and is being sponsored for an ongoing clinical trial by the German Research Council and Fresenius. L.B. is a government employee.