Updated S2 K guidelines for the management of bullous pemphigoid initiated by the European Academy of Dermatology and Venereology (EADV)

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GUIDELINE

Updated S2 K guidelines for the management of bullous pemphigoid initiated by the European Academy of Dermatology and Venereology (EADV)

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Abstract

Background Bullous pemphigoid (BP) 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, most frequently, generalized bullous lesions. A subset of patients only develops excoriations, prurigo-like lesions, and eczematous and/or urticarial erythematous lesions. The disease, which is significantly associated with neurological disorders, has high morbidity and severely impacts the quality of life.

Objectives and methodology The Autoimmune blistering diseases Task Force of the European Academy of Dermatology and Venereology sought to update the guidelines for the management of BP based on new clinical information, and new evidence on diagnostic tools and interventions. The recommendations are either evidence-based or rely on expert opinion. The degree of consent among all task force members was included.

Results Treatment depends on the severity of BP and patients' comorbidities. High-potency topical corticosteroids are recommended as the mainstay of treatment whenever possible. Oral prednisone at a dose of 0.5 mg/kg/day is a recommended alternative. In case of contraindications or resistance to corticosteroids, immunosuppressive therapies, such as methotrexate, azathioprine, mycophenolate mofetil or mycophenolate acid, may be recommended. The use of doxycycline and dapsone is controversial. They may be recommended, in particular, in patients with contraindications to oral corticosteroids. B-cell-depleting therapy and intravenous immunoglobulins may be considered in treatment-resistant cases. Omalizumab and dupilumab have recently shown promising results. The final version of the guideline was consented to by several patient organizations.

Conclusions The guidelines for the management of BP were updated. They summarize evidence- and expert-based recommendations useful in clinical practice.

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Conflict of interest

See attachment.

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Introduction

Bullous pemphigoid (BP) constitutes the most common autoimmune subepidermal blistering dermatosis. It is associated with tissue-bound and circulating autoantibodies directed against BP antigen 180 (BP180, BPAG2 or type XVII collagen) and BP antigen 230 (BP230 or BPAG1e – epithelial isoform). The latter are components of junctional adhesion complexes called hemidesmosomes that promote dermal–epidermal cohesion. BP typically develops in patients older than 70 years.[1,2] The mean age of patients at diagnosis in Europe is around 80 years. The severity of itch and cutaneous lesions significantly disturbs the quality of life in affected patients. The disease carries considerable morbidity and a two- to threefold higher mortality compared with the age- and sex-adjusted general population.[3–5]

Its annual incidence has been estimated to range from 6 to 43 new cases per million population per year. Advanced age, concomitant neurologic diseases, poor general condition, and long-term use of high-dose corticosteroids (CS), among others, portend a poor prognosis.[6,7]

The consensus for the management of BP has been updated because of new clinical information, and changes in evidence on existing therapeutic interventions and in outcomes. Specifically, in the past two decades, the incidence of BP seems to have significantly grown, which might be related to raised awareness of atypical non-bullous forms, an increased frequency of dementia and debilitating neurological disorders, which are significantly associated with BP, and finally to an increasing use of drugs potentially triggering BP. In particular, gliptins and immune checkpoint inhibitors have been recognized to increase the risk of and cause BP, respectively, highlighting the importance of a systematic evaluation of drug triggers in the development of BP, and needing to address the question of the usefulness of stopping these drugs. Furthermore, results obtained from either new open or randomized controlled trials (RCTs), assessing immunomodulatory drugs and biologics, as well as novel diagnostic tools, are available. Finally, quality of life as patient-reported outcome and importance of shared-decision making for treatment planning constitute important elements to systematically consider whenever possible.

This consensus further takes into consideration that healthcare settings and modalities are different among European countries, in particular, hospitalization rules, home care availability and the possibility of financial reimbursement for different treatments. The aim of this revised consensus is to make recommendations for the most common situations and is not intended to exhaustively cover specific disease variants of BP, including childhood pemphigoid.[1,2,8] The consensus is also not intended to specifically address and review the predictable and potential side-effects of the proposed drugs. Differences between the recommendations in the present consensus statement of European experts and other national guidelines reflect incomplete knowledge on the matter of optimal treatment modalities in BP due to the paucity of RCTs in this area. The latter may lead to divergent expert opinion on a number of open questions, which ongoing and future studies need to clarify.

Methodology for updating the guidelines

To facilitate this process, a writing group, i.e. LB, NVB, CF and PJ appointed by the EADV Task force *Autoimmune blistering diseases*, revised the first version of the guidelines published in 2015 by reviewing all new relevant knowledge on clinical practice, and evidence about benefits of novel diagnostic and therapeutic interventions and outcomes.

The following syntax was used for specific recommendations based on the following levels of evidence:

- Strong recommendations from large randomized prospective multicentre studies (level of evidence 1): '***is recommended***';
- Recommendations from small randomized or non-randomized prospective multicentre or large retrospective multicentre studies: '***may be recommended***';
- Recommendation pending from case series, or small retrospective single-centre studies: '***may be considered***';
- We have also used: '***may be considered***' when a consensus could not be reached among experts; and
- Negative recommendation: '***is not recommended***'

Thereafter, members of the EADV Task force *Autoimmune blistering diseases* (notation group) were invited to assign scores (ranging from 0 to 5 according to the increasing degree of consensus) to each of the recommendation's statements using the syntax shown above. This process identified the statements of major agreement or disagreement.

Indicated major statements were then voted upon, and the degree of consensus was indicated for all statements. Based on the marks of the notation group, the writing group then prepared a second, third and a fourth version of the guidelines, until each of the statements was given a mark >4 by the voting group. The manuscript was then reviewed by different European patient organizations.

Initial evaluation of bullous pemphigoid

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

Major objectives

- To confirm the diagnosis of BP;
- To assess clinical condition and comorbidities, including cognitive status, search for risk factors, including neurological diseases and potential drug triggers (4.88 ± 0.33);

Table 1 Diagnostic steps in bullous pemphigoid

Clinical examination		
Patient's history	**Physical examination**	**Patient's assessment**
• Date of onset • Evolution of signs and symptoms (including itch) • Recent drug intake	• **Classical bullous form**: symmetric distribution of vesicles and bullae over erythematous and non-erythematous skin (flexural surfaces of the limbs, inner thighs, trunk); rare oral mucosal involvement; no atrophic scarring; no Nikolsky's sign • **Useful diagnostic clinical features**: 1. age older than 70 years; 2. the absence of atrophic scars; 3. the absence of mucosal involvement; and 4. the absence of predominant bullous lesions on the neck and head • **Non-bullous and atypical forms**: excoriations, prurigo, prurigo nodularis-like lesions, localized bullae, erosions, eczematous and urticarial lesions, dyshidrosiform (acral)	• Extension of BP (by BPDAI or daily blister count) • General condition and comorbidities • Laboratory examinations and workup according to patient's condition and therapy choice • Quality of life questionnaire (e.g. Autoimmune Bullous Quality of Life and Itchy Quality Of Life)

Laboratory investigations		
Histopathology (of a recent intact bulla if present)	**Direct immunofluorescence** (using either *perilesional* erythematous skin 1–2 cm away from an active bullae or from *perilesional normal-appearing* skin)	**Immune serological tests**
• Subepidermal bullae containing eosinophils and/or neutrophils • Dermal infiltrate of eosinophils and/or neutrophils • Margination of eosinophils along the dermal–epidermal junction • Non-specific findings in atypical forms	• Linear (with a n-serrated pattern) deposits of IgG and/or C3 along the dermo-epidermal junction • Sometimes IgA and IgE with similar pattern	• **Indirect immunofluorescence microscopy (IIF)** on normal human salt-split-skin (or suction-split): IgG anti-basement membrane antibodies binding to the epidermal side (sometimes epidermal and dermal) of the split • **IIF-based assays using biochips** with multiple antigenic substrates • **ELISA** for antibodies to BP180 and, if negative, for BP230 • **Multivariant ELISAs** using several different autoantigens, including BP180 and BP230

Other immunopathological tests		
Immunoblotting and novel ELISAs	**Fluorescence overlay antigen mapping (foam)**	**Immunohistochemistry**
Search for reactivity with BP180 (BPAG2) and/or BP230 (BPAG1e) Use of different recombinant protein forms of BP180 and/or BP230 produced in various expression systems	Assessment of relative location of detected IgG deposits compared to other proteins within the cutaneous basement membrane zone	In a significant proportion of patients, linear deposits of C3d and C4d along the dermo-epidermal junction can be demonstrated using the same tissue sample obtained for light microscopy studies

For details, see text. The diagnosis of BP is based on a combination of criteria encompassing clinical features and positive direct immunofluorescence microscopy (DIF) findings. The positivity of DIF is essential to reach a correct diagnosis of BP with very few exceptions. Proper classification of BP further requires either clinical criteria or the search and characterization of circulating autoantibodies, most commonly by either indirect IF microscopy or ELISA. The analysis of the n-serration pattern of the linear deposits along the dermo-epidermal junction represents a reliable practical approach to differentiate BP and other pemphigoid forms from epidermolysis bullosa acquisita.

- To specify the type of initial damage and its extent (see definitions and outcome measures for BP)[9];
- To evaluate prognostic factors (age, the Karnofsky Performance Status Scale, neurological diseases, such as dementia, Parkinson's disease and stroke) (4.68 ± 0.14); and
- To consider therapeutic options.

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 should belong to a referral centre or is in contact with a referral centre. Other health professionals who are included in the patient's management according to the clinical presentation, general conditions and comorbidities are as follows:

- The dermatologist in general practice;
- The patient's general practitioner/family physician, alternatively, an internist, a geriatrician;
- Specialized nurses (e.g. elderly care medicine, community health service or home health care);
- Dieticians, psychologists and physiotherapists, often involved in patient care; and
- all other specialists whose expertise might be necessary based on the clinical context (e.g. geriatricians,

endocrinologists, ophthalmologists, oncologists, neurologists, oral medicine specialists or cardiologists) (4.89 ± 0.37).

Clinical examination

Patient's history

- It is recommended to obtain a detailed medical history, including date of onset and evolution of signs and symptoms. Efforts should be made to obtain all relevant information related to comorbidities potentially associated with BP (such as neurological and cardiovascular diseases, cancer, haematological malignancies, thromboembolism, autoimmune diseases, and osteoporosis), as well as to be familiar with the medications for potential use and their side-effects (4.75 ± 0.69)[1,2,10,11];
- BP is strongly associated with neurological disorders, such as multiple sclerosis, Parkinson's disease, dementia and stroke, which raises the question of a causal association or only risk factors. These neurological diseases are usually already present prior to the development of BP[12];
- It is recommended to take an accurate and detailed drug history (drug intake usually within the 6 months prior to the development of symptoms) (4.89 ± 0.31). A recent meta-analysis suggests that the use of diuretics in particular aldosterone antagonists, dipeptidyl peptidase 4 inhibitors, anticholinergics and dopaminergic medications is significantly associated with BP.[11,13] Other drugs whose responsibility remains uncertain have been occasionally reported to be associated with the onset of BP such as NSAIDs, antibiotics, ACE inhibitors, and TNF-alpha inhibitors.

Importantly, it has been increasingly recognized that dipeptidyl peptidase-4 inhibitors (particularly vildagliptin and linagliptin) and immune checkpoint inhibitors are significantly associated with and might cause BP, respectively.[14] With the latter two drug categories, the delay between their starting and BP onset may be long, even more than 1 year.

In general, due to lack of knowledge and contradictory results from studies, no clear recommendations to either stop or to continue the culprit drug can be made. However, if the connection to drug intake is probable or plausible (e.g. timeline from the start of drug intake to development of symptoms), whether or not the culprit drug can be stopped or substituted with no harm, whether or not it is possible to control BP lesions with the usual first-line options in BP treatments, it is recommended to discuss the matter in an interdisciplinary team (4.81 ± 0.64).

With regard to gliptins, there are conflicting results. Some open-label studies suggest the interest of stopping gliptins, but most patients received specific treatment for BP in addition to gliptin discontinuation, confounding thereby the effective beneficial impact of the gliptin withdrawal, while another large study did not show any beneficial effect of stopping the drug.[15,16]Although the effect of cessation of gliptin treatment on the clinical outcome BP remains currently unclear, a switch of the antidiabetic drug class may be considered (4.83 ± 0.47).

Anti-PD-1 and anti-PD-L1 immunotherapies. The number of BP associated with anti-PD-1 (e.g. nivolumab, pembrolizumab) and anti-PD-L1 immunotherapies (e.g. durvalumab, atezolizumab) increases impressively. BP develops as a result of the breakdown of self-tolerance with an activation of the immune response.[17] In clinical practice, it is recommended to carefully evaluate the potential benefits of therapy continuation (in case of response to immunotherapy) particularly when BP lesions can be satisfactorily controlled with therapeutic regimens, which are not expected to significantly reduce the anti-tumour efficacy of immunotherapies. It is recommended to discuss the indication of a transient stop of immunotherapies and/or the use of high doses of systemic CS and/or immunosuppressive drugs with an oncologist (4.20 ± 1.29). Up to now, there is no validated evidence from the literature to indicate the best approach to manage these patients. Continuing the immunotherapy may be considered in patients with a mild/moderate BP, in particular in those who are adequately controlled with a standard topical or oral CS therapy, whereas stopping the immunotherapy may be considered in patients with extensive and recalcitrant BP (4.70 ± 0.94).

- It is recommended to evaluate the impact of BP on patients' quality of life related to the BP lesions, in particular painful erosive areas and pruritus (4.84 ± 0.37). For this purpose, whenever possible and feasible, it is recommended to use specific, validated interviews and questionnaires as tools to assess physical, mental and social effects. Various patient-reported outcome measurement information systems are available, including the Dermatology Quality of Life Index (DLQI), the Autoimmune Bullous Quality of Life questionnaire (ABQOL) and Itchy Quality of Life questionnaire (ItchyQoL) (4.62 ± 0.49). The gained information should be considered by caregivers for the choice of the most suitable therapeutic intervention to improve outcome.

Physical examination It is recommended that the physician searches for objective evidence consistent with the diagnosis and assess the general condition of the patient:

- Classical form: severely pruritic bullous dermatosis, with bullae usually arising on erythematous inflamed skin, symmetric distribution (flexural surfaces of the limbs, inner thighs, abdomen), rarely with mucosal involvement and atrophic scarring[1,2,18,19];
- Non-classical/non-bullous forms: pauci-bullous or localized eczema, urticarial lesions, dyshidrosiform (acral) lesions,

erosions, usually without mucosal involvement (oral in particular), excoriations, prurigo, prurigo nodularis-like lesions[18,19];
- Use of validated clinical criteria for BP.[20] When three of the 4 clinical characteristics are present (1. age older than 70 years; 2. the absence of atrophic scars; 3. the absence of mucosal involvement; and 4. the 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 dermo-epidermal junction[20];
- A complete physical examination is necessary, including a check for associated comorbidities (e.g. neurological, cardiovascular diseases, osteoporosis and diabetes) relevant for further management and subsequent therapy[1,2];
- Finally, the extent of BP should be assessed, using, for example, the BP disease activity index (BPDAI) or daily blister count.[9]

Laboratory investigations for the diagnosis of BP

Confirm 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).[1,2,8,20,21] The following steps are recommended for the diagnosis and classification of BP:

- Detection of circulating IgG anti-basement membrane zone (BMZ) autoantibodies by indirect immunofluorescence (IIF) microscopy studies using NaCl-separated normal human skin[1,2,8,21,22];
- Detection of anti-BP180 NC16A IgG autoantibodies and/or anti-BP230 IgG autoantibodies by ELISA[1,2,8,23–25];
- For detection of circulating IgG anti-BMZ autoantibodies, the novel 'multivariant' assays using multiple antigenic substrates, which are IIF-based, are also recommended (4.80 ± 0.40). In these BIOCHIP mosaic assays, various antigenic substrates are combined.[26]

In the rare cases of BP, in which circulating anti-BMZ antibodies are not detectable by either IIF microscopy studies or commercially available ELISA, it is recommended to use additional tests (see Table 1) to increase the diagnostic sensitivity and to exclude another autoimmune disease of the dermo-epidermal junction, in particular anti-p200 pemphigoid or epidermolysis bullosa acquisita (EBA) (4.76 ± 0.52).

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 margination of eosinophils along the dermal–epidermal junction. Nevertheless, in the absence of blistering and in non-bullous forms, histopathological findings may be non-specific, such as the presence of eosinophilic spongiosis.[27]

Direct immunofluorescence microscopy Direct immunofluorescence (DIF) studies represent the most critical test: their positivity is essential for the diagnosis of BP.[1,2,8,20,21] It is recommended to obtain the biopsy specimen for DIF studies from perilesional skin, defined as either erythematous non-bullous skin or normal skin within 1–2 cm from a lesion (4.75 ± 0.53).[21]

For transportation, skin biopsy specimens should be put either in a 0.9% NaCl solution, into a cryotube in liquid nitrogen or in Michel's fixative. Alternatively, for storage and transport of the skin specimen, it is recommended to use either 0.9% NaCl (processing required within 24 and 72 h), liquid nitrogen in a cryotube or Michel's medium (5.0 ± 0).

- DIF studies typically demonstrate linear deposits of IgG and/or C3 along the dermo-epidermal junction; occasionally IgA and IgE are also found with a similar pattern[17,18,25];
- The analysis of the n-serration pattern of DIF may be helpful and specific in combination with IIF studies to differentiate BP from EBA; an n-serrated pattern is suggestive of BP, whereas a u-serrated pattern is typically found in EBA.[28]
- DIF studies using autologous patient's skin biopsy specimen cleaved by 1 M NaCl for IgG (location of IgG deposits after splitting allows differentiation of BP from EBA, anti-laminin-332 and anti-p200 pemphigoid; note: the location of C3 is not reliable).[1,2,21,29]

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 availability, cost and local expertise.

- Search for circulating IgG anti-BMZ antibodies by IIF studies. The latter is recommended to be carried out using 1 M NaCl-separated normal human skin (SSS) as substrate (4.81 ± 0.80). Anti-BMZ IgG autoantibodies characteristically bind to the epidermal side (sometimes epidermal and dermal) of SSS. By this means, IgG autoantibodies are found in up to 80% of cases. The use of non-separated normal human skin or monkey oesophagus as substrate for IIF studies is associated with lower sensitivity[1,2,21,22,30];
- Search for anti-BP180 IgG autoantibodies and anti-BP230 IgG autoantibodies by ELISA. It is recommended to perform first an ELISA for anti-BP180 IgG, and, if negative, for anti-BP230 IgG (4.27 ± 1.00)[1,2,23–25,31];

- Novel ELISA- or IIF-based multivariant assays for the search of autoantibodies against several target antigens in parallel are now commercially available and are also recommended as diagnostic tools (4.68 ± 0.85).[26,32,33]

Diagnostic criteria for BP

It is recommended to make the diagnosis of BP based on the following criteria:

1 *In most cases*, the diagnostic of BP relies on: (i) suggestive clinical features when 3 of the 4 clinical characteristics are present: 1. age older than 70 years; 2. the absence of atrophic scars; 3. the absence of mucosal involvement; and 4. the absence of predominant bullous lesions on the neck and head,[17] (ii) positive DIF and (iii) the presence of serum IgG antibodies labelling the epidermal side of SSS by indirect IF microscopy and/ or reacting with BP180 and/or BP230 by ELISA or IIF (4.57 ± 1.01);
2 *In patients with non-bullous lesions*, the diagnosis of BP can be accepted in patients with: (i) positive DIF studies and (ii) the presence of circulating IgG autoantibodies labelling the epidermal side of SSS by IIF microscopy and/or (iii) reacting with BP180 and/or BP230 by ELISA or IIF (4.94 ± 0.24);
3 *When DIF studies are negative*, it is recommended to perform a new biopsy and to check for any technical problem. In the few patients with persistent negative DIF studies, the diagnosis of BP can be accepted in patients with: (i) suggestive clinical picture (i.e. tense blisters); (ii) consistent histopathological findings (subepidermal cleavage); (iii) presence of circulating IgG autoantibodies binding to the epidermal side of SSS by IIF microscopy studies; and/or (iv) serum reactivity with BP180 and/or BP230 by ELISA or IIF (4.66 ± 0.73).

Other tests Additional tests can also be performed according to clinical context and availability and are listed in Table 1.[25,34–38]

Therapeutic management (see Tables 2 and 3)

Workup and pretherapy screening

The proposed workup and pretherapy screening are depicted in Table 2. The recommendations are largely based on expert opinion.

Objectives

BP is a chronic disease, which usually lasts for several months or even for several years. The latter course is observed particularly in patients who have multiple relapses.[1,2,4,5]

Primary objectives are therefore to control both the skin eruption and itch and to minimize the serious side-effects of the treatment. Specifically, the goals of the management are to:

- Treat the skin eruption, reduce itch and prevent /reduce the risk of recurrence;
- Improve the quality of life of patients; and
- Limit the side-effects related to the newly introduced drugs, particularly in the elderly.

Advanced age in BP patients and the potential presence of comorbidities (neurological, cardiovascular, metabolic, thromboembolic, neoplastic, respiratory, ocular and osteoporosis) make their cases more difficult to manage.[1,2,19,39,40]

Table 2 Suggested workup and pretherapy screening in a patient with newly diagnosed bullous pemphigoid. The recommendations are largely based on expert opinion. It is also advised to regularly verify the updated corresponding recommendations and compare them with the local health practice and system or follow national guidelines if available

• Chest X-ray
• CBC – complete blood count, ESR and C-reactive protein
• Creatinine, blood electrolytes and fasting glucose
• Transaminases, gamma-GT, alkaline phosphatase and bilirubin• Albumin
• Serology for hepatitis B, 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 (TPMT) is optional, when azathioprine is considered as therapeutic
• Glucose 6-phosphate dehydrogenase (G6PDH), if dapsone treatment is considered
• Serum IgA deficiency should be excluded if intravenous immunoglobulins are considered
• Consider detailed clinical neurological examination and brief cognitive assessment of mental status (e.g. perform the Mini-Mental State Examination)
• Check for an underlying neoplasm in line with the patient's age, clinical history and examination and for an infection (in particular, *Mycobacterium tuberculosis*) 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 skin infection
• Consider echocardiography before initiation of therapy with either systemic corticosteroids, dapsone or intravenous immunoglobulins
• SARS-CoV2 infection and vaccination in BP patients: follow carefully the updated governmental recommendations and the guidelines of national and international medical associations, including the International League of Dermatological Societies (ILDS, see https://ilds.org/covid-19/ilds-statement/).

Table 3 Bullous pemphigoid (BP): therapeutic ladder, capsule summary[†]

Mild and moderate BP (BPDAI score <20 and BPDAI score ≥ 20 < 57, respectively)[‡]
• **First choice**
○ **In localized BP**, apply potent or super potent topical corticosteroids on lesions only (*may be considered*[§])
○ **In non-localized mild and moderate BP**
○ Superpotent topical corticosteroids applied twice or once a day, on whole body except the face (*is recommended*)
○ Oral corticosteroids, at an initial dose of 0.5 mg/kg/day prednisone or prednisolone (*is recommended*);
• **Second choice (may be recommended)**
○ Doxycycline
○ Dapsone
Severe BP (BPDAI score ≥ 57)
• **First choice, two treatments *are recommended***
○ Superpotent topical corticosteroids, twice or once a day, on whole body (except the face), or
○ Oral corticosteroids at an initial dose of oral prednisone 0.5 mg/kg/day
– Note: in patients who do not achieve disease control within 1-3 weeks with 0.5 mg/kg prednisone, two options *may be considered*
• to increase the dose of prednisone up to 0.75 mg /kg
• to add superpotent topical corticosteroids
Corticosteroid-dependent or relapsing BP
• **Several alternative choices as adjunctive therapy *may be considered***
○ Combination with or introduction of a conventional immunosuppressive drug
– Methotrexate
– Azathioprine
– Mycophenolate
• **In patients in poor general condition and/or in those with contraindications to immunosuppressive drugs, the following options *may also be considered***
○ Doxycycline
○ Dapsone
○ Omalizumab
Treatment-recalcitrant BP (resistant to 0.75 mg/kg/day of prednisone)
• **Combination with and/or introduction of conventional immunosuppressants *may be considered***
○ Methotrexate
○ Azathioprine
○ Mycophenolate mofetil
• **Other therapeutic options, which have not been validated in this setting, *may be considered* (without any prioritization)**
○ B-cell depletion therapy with anti-CD20 mAb (rituximab)
○ Omalizumab
○ Dupilumab
○ Intravenous immunoglobulins
○ Immunoadsorption

[†]For details, see specific sections in the text; [‡]BPDAI, Bullous Pemphigoid Disease Activity Index; [§]Syntax for specific recommendations: recommendations from large randomized prospective multicentre studies: 'is recommended'; recommendations from small randomized or non-randomized prospective multicentre or large retrospective multi-centre studies: 'may be recommended'; recommendation pending from case series, or small retrospective single-centre studies: 'may be considered'; We have also used: 'may be considered' when a consensus could not be reached among experts.

Whenever possible, it is recommended that caregivers actively include patient participation in decision-making by providing all necessary information about the disease and potential interventions, their benefits and side-effects (4.82 ± 0.49).

Professionals involved and nursing

The initial management, i.e. diagnosis and treatment start, of extended forms of the disease in a polymorbid and elderly patient usually requires hospitalization in a dermatology department. Hospitalization is not a requisite in certain countries due to their specific health system. In pauci-lesional or localized forms, examinations for diagnostic and clinical monitoring can be performed on either an inpatient or an 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 reference centre. Close collaboration between the dermatologist, the treating physician and, if necessary, the nursing staff is therefore fundamental.

Teledermatology is starting to be used in some countries. It may be recommended in the follow-up of patients living in nursing home, in particular to communicate with nurses and HCP in charge of the patients (4.79 ± 0.50).

Therapeutic management

Topical treatment Clobetasol propionate 0.05% cream. It is recommended to use 20 to 30 g per day in mild-to-moderate disease and 30 to 40 g/day in extensive disease, initially administered once or twice a day, over the entire body including both normal skin and skin with blisters and erosions, but sparing the face until control of disease activity (CDA) has been achieved (4.40 ± 0.91).[41,42] According to the consensus statement, CDA is defined as the point at which new lesions or pruritic symptoms cease to form and established lesions begin to heal.

Once CDA is achieved, it is recommended to continue high-potency topical CS at the same dosage for 15 days, and then progressively tapered it over a period between 4 months at the earliest, and 12 months (4.36 ± 0.75).

Tapering schedule and dose adaptation

- Daily treatment in the 1st month;
- Treatment for every 2 days in the 2nd month;
- Treatment for 2 times per week in the 3rd month;
- Treatment for once a week starting in the 4th month.

An increasing dose of topical CS (up to 40 g/day) is recommended in patients receiving less than 40g/day of clobetasol propionate 0.05% who do not achieve disease control within 1–3 weeks.[41,42]

Maintenance treatment. Two options may be considered after 4 months of treatment:

- Continue a maintenance treatment for 8 months (hence, the total treatment duration including consolidation and maintenance phases is 12 months), and then stop.[41,42] The dose of whole-body high-potency topical CS 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 high-potency CS should be preferentially applied on previously affected areas and their surrounding areas;
  - Disadvantage: practical and economic difficulties related to continued nursing for a long period and/or cost of topical high-potency CS;
- Stop treatment within 4 months, in particular if BP activity has been rapidly controlled by topical CS and BP is in remission. This approach carries a slightly higher risk of relapse but shows improved safety[41];
- Before discontinuing treatment in patients in remission, it may be considered to perform when available and feasible, an ELISA-BP180 (4.55 ± 0.72), since if the ELISA-BP180 values are lower than 23 IU/mL (as assessed using the test system of MBL international), there is a 90% probability of non-relapse.[43]

Relapse and dose adaptation. In case of a *relapse* (also termed *flare*), defined as appearance of ≥3 new lesions/month, that is 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 patients who have achieved disease control (for definitions, see Ref.[9]) during the dose reduction period, it is recommended to increase the dose to the previous level.[41,42] In patients who experience a relapse after treatment withdrawal, it is recommended to treat using the following doses of clobetasol propionate 0.05% cream or ointment (level of evidence 1)[41]:

- 10 g daily for patients with a localized relapse (to be preferentially applied on previously affected areas and their surrounding areas);
- 20 g daily for patients with mild disease (see below for definition);
- 30–40 g daily for patients with moderate to extensive relapse.

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

Systemic corticosteroid therapy There is evidence that high-dose CS therapy, such as prednisone 1 mg/kg/day, is effective in patients with extensive disease.[42,44–46] However, this therapy has shown to be associated with higher mortality and increased side-effects compared to the whole-body topical use with clobetasol propionate 0.05%.[41,42,44] Therefore, this high dosage of oral CS is not recommended in the initial treatment of BP (4.46 ± 1.10).

A recent prospective observational multicentre study has indicated that a 0.5 mg/kg/day starting dose of prednisone allows disease control to be achieved at day 21 in 75% and 69% of patients with mild and moderate BP, respectively, but in only 46% of patients with severe BP. Disease control at any time during the one-year follow-up was achieved in a high proportion of patients with mild and moderate BP, but in only 62% of patients with severe BP. This 0.5 mg/kg/day starting dose of prednisone was rather well tolerated in particular in patients with a Karnofsky score of ≥70.[47]

- A starting dose of 0.5 mg prednisone /kg daily is therefore recommended in patients with mild/moderate and severe BP (4.79 ± 0.65).

Prednisone doses lower than 0.5 mg/kg have not been validated and seem to be most often ineffective.[48] Systemic

treatment may be accompanied by topical therapy with CS and/or other measures (see below).

Tapering schedule and dose adaptation.

- This initial treatment should be first reduced 15 days after disease control. Earlier reduction in CS doses may be possible.
- In patients who do not achieve disease control within 1–3 weeks with 0.5 mg/kg prednisone, it may be recommended to either increase the dose of prednisone up to 0.75 mg /k day (4.62 ± 0.87) or to add topical CS in addition to the 0.5 mg/kg/day dose of prednisone (4.75 ± 0.60) based on recent evidence.[47]

Maintenance treatment. It is recommended to taper systemic CS doses gradually with the aim of achieving minimal therapy (prednisone 0.1 mg/kg/day, see definitions in Ref.[9]) within 4 to 6 months after initiation of treatment.[42] If the patient is in complete remission (CR) under minimal therapy for 3 to 6 months, it may be recommended to stop the treatment, in particular, in patients with negative or low levels of anti-BP180 Abs (4.72 ± 0.54). Hence, the total treatment duration including consolidation phase and maintenance treatment is usually between 9 and 12 months.

Tapering of CS before discontinuation must be done carefully to avoid possible cortisol deficiency resulting from hypothalamic–pituitary–adrenal axis suppression during the period of CS therapy.

Relapse and dose adaptation. In the case of a relapse during the dose reduction period, it is recommended to increase the dose to the previous level (4.92 ± 0.27).[42]

Adjuvant conventional immunosuppressive / immunomodulant therapy The choice of an adjuvant therapy is dependent upon availability, cost issues, disease severity, practical experience and the presence of specific contraindications. The following options may be considered:

- *Tetracyclines* (doxycycline 200 mg/day orally) alone or in combination with nicotinamide (up to 2 g/day orally).[49,50] A multicentric 'pragmatic' trial, provided evidence that an initial treatment regimen starting with the combination of doxycycline 200 mg/day and topical CS followed by a period in which investigators could switch to oral prednisolone if blister control was not adequate, leads to 74% of blister control in patients with doxycycline-initiated treatment, as well as a better safety profile, when compared to oral prednisolone. The proportion of patients who achieved treatment success with no treatment modification before 6 weeks (patients who only received tetracyclines and topical CS) was 54%.[50] The peculiar design of the RCT, which consisted of an evaluation of a treatment strategy starting with doxycycline and topical CS, then allowing to switch to oral prednisolone, rather than a direct evaluation of the efficacy of doxycycline makes any conclusion difficult.

A preliminary report indicates that in real life, only a few BP patients can be managed by doxycycline alone without oral prednisolone. Among the 64 BP patients included in their report, 72% of the patients who were started with tetracyclines alone required additional oral prednisolone, while only 12% of patients were able to continue doxycycline alone throughout the study. In brief, tetracyclines were not able to prevent relapses nor to avoid the need for an increase in prednisolone doses to achieve CDA in many patients.[51]

No consensus could be reached among experts with regard to the use of doxycycline in BP. Therefore, tetracyclines may be considered in combination with topical CS, in particular in patients with contraindications to oral CS or immunosuppressive treatments, with a mild or moderate BP since the benefit of tetracyclines is limited in severe BP (4.62 ± 0.93).

- *Dapsone* (up to 1.5 mg/kg/day orally, up to a maximum of 150 mg/)[52]

The efficacy of dapsone has been tested in a RCT in 54 BP patients who received methylprednisolone at an initial dose of 0.5 mg/kg/day in combination with dapsone 1.5 mg/kg/day or azathioprine 1.5 to 2.5 mg/kg/day. The primary endpoint: time until complete tapering of methylprednisolone could not be compared because the proportion of patients who were able to completely taper methylprednisolone was too low in the dapsone arm (3 of 27 patients; 11%) compared with the azathioprine arm (5 of 27 patients; 18.5%). The median cumulative dose of CS was borderline significantly lower in the dapsone group than in the azathioprine group (1.92 g *versus* 2.65 g; P = 0.06).[53] The results showed that dapsone only allowed a low number of patients to stop CS. They further suggested a potential CS-sparing effect of dapsone, although this CS-sparing effect might have been affected by the non-blind character of the study.

Dapsone is mainly used in Germany, most often in combination with topical CS.[53] A consensus could not be reached among experts on the recommendation of the use of dapsone in BP. Dapsone may be considered, in particular, in patients with contraindications to oral CS or immunosuppressive treatments, with mild and moderate BP (4.56 ± 1.00). However, the prescription of dapsone to older patients with cardiovascular diseases, including coronary artery diseases, requires careful consideration and close monitoring to limit potentially severe complications.

Immunosuppressive drugs

The use of immunosuppressive therapies with a potentially CS-saving effect may be recommended in the presence of

contraindications to oral CS and of comorbidities (such as diabetes, severe osteoporosis and significant cardiovascular problems) or in patients with extensive BP (4.56 ± 0.76). Nevertheless, there is no positive evidence supporting their use as a first-line treatment and they are therefore non-validated.[44–46] The use of immunosuppressive drugs may be recommended either in the large group of patients with relapsing BP or in the few patients having recalcitrant BP who are not adequately controlled by topical or oral CS (4.78 ± 0.77).

In brief, the following molecules may be recommended (see Table 3):

- *Azathioprine*: 1 to 3 mg/kg/day according to TPMT activity[54–56];
- *Mycophenolates* (mycophenolate mofetil 2 g/day, mycophenolic acid 1.44 g/day orally)[55,56];
- *Methotrexate* (5 mg to 12.5 mg, once a week subcutaneously or intramuscularly).[57]

In the case of prescribed low-dose methotrexate to older patients, a careful biologic and clinical monitoring is recommended to avoid toxic complications, in particular, related to renal insufficiency and leucopenia (4.52 ± 0.91).

In an RCT on 300 BP patients, the first-line use of methotrexate (10–12.5 mg weekly) combined with superpotent topical CS for the first month after initiation of therapy allowed a reduction in the 9-month relapse rate from 42% to 25% relative to topical CS alone.[58]

- *Ciclosporin* (3–5 mg/kg/day).[59] 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 (4.90 ± 1.82).

Biologics Biologics may be considered in the few difficult-to-treat cases of BP according to the clinical features and course, response or contraindications to standard therapies as either add-on therapy or monotherapy (4.95 ± 0.46). They target pro-inflammatory key cytokines and cellular functions that contribute to tissue damage in BP. It must be underlined that there is still no strong evidence supporting their use, which is therefore not validated and may not be reimbursed.

- For *B-cell depletion therapy with anti-CD20 monoclonal antibody* (mAb) using rituximab, it is recommended to apply either the rheumatoid arthritis protocol (two 1 g intravenous infusions, 2 weeks apart) or the lymphoma protocol (375 mg/m^2 intravenous infusion, once weekly for 4 weeks) (4.66 ± 0.70). The beneficial effect of rituximab in BP seems lower than in pemphigus in terms of control of disease activity, clinical remission and relapse risk. Potential severe side-effects in the debilitated elderly or as a result of an incidental COVID-19 infection should be kept in mind.[60–62]
- *Intravenous immunoglobulins* (level of evidence 1) (4.48 ± 0.65). In an RCT add-on therapy with intravenous immunoglobulin, 2 g/kg/day in BP cases with no improvement on prednisolone ≥0.4 mg/kg/day showed a trend towards a beneficial effect, which did not, however, reach statistical significance. Potentially severe side-effects in older patients especially the risk of acute renal failure must be underlined.[63]
- *Omalizumab*. Omalizumab is an anti-IgE mAb, which is approved in asthma and spontaneous idiopathic urticaria. Some limited open series have suggested the efficacy of omalizumab in BP patients. Omalizumab may be considered, in particular, in BP patients with urticarial inflammatory lesions and high serum IgE levels (4.52 ± 0.87). Omalizumab may also be considered in patients with neoplasia, which is a contraindication to most immunosuppressive drugs (4.56 ± 0.82).[64]
- *Dupilumab*. Dupilumab is an anti-IL-4 Rα mAb, which is approved in atopic dermatitis. It is off-label in BP (4.36 ± 0.86). An open retrospective series on 13 patients showed that 54% of patients achieved disease clearance, suggesting the potential efficacy of the drug. The drug was well tolerated.[65,66]
- New therapeutic approaches, including blockade of IL-17, IL-12/IL-23, IL-5Rα, eotaxin, neonatal Fc receptor and LTB4/C5aR, are currently being tested in BP (see update in: https://clinicaltrials.gov/ct2/results?cond=bullous+pemphigoid&term=&cntry=&state=&city=&dist=)

Indications of treatment depending on initial BP extent

Localized BP. Localized BP is defined by the presence of lesions involving one body site.

Initial treatment is based on topical clobetasol propionate 10 g per day, which is applied once daily over the involved area. It is recommended to continue treatment until 15 days after CDA followed by a progressive tapering of CS doses over 4 months (4.64 ± 1.11).

Mild and moderate BP (BPDAI score < 20 and BPDAI score ≥ 20 < 57, respectively).

It is recommended to define mild/moderate BP as the occurrence of 10 or less new blisters per day or by the presence of few non-bullous inflammatory lesions in different localizations. It is recommended to use the BPDAI scoring system; mild BP corresponds to a severity score lower than 20 points, and moderate BP corresponds to a BPDAI score < 57 points (4.76 ± 0.59).[69]

For the initial treatment of mild to moderate BP, different options are available. The final choice will depend on their availability, practical feasibility and presence of contraindications.

However, only two regimens have shown a significant benefit and are therefore recommended.

- High-potency topical CS with an initial dose of clobetasol propionate of 20 to 30 g per day, applied twice or once a day (4.68 ± 0.62):
- Medium doses of oral CS, that is, oral prednisone 0.5 mg/kg/day (4.90 ± 0.36).

Three other therapeutic options may be considered either alone or in combination with topical or oral CS:

- Doxycycline 200 mg daily (3.83 ± 1.37);
- Methotrexate, 10–12.5 mg/week initially (3.54 ± 1.55) (if no contraindication including renal insufficiency, otherwise reduce doses or avoid)[57,67];
- Dapsone (1 mg to 1.5 mg/kg daily) (3.83 ± 1.30).[52,53,68]

Severe BP (BPDAI score ≥ 57; > 10 new blisters:day. It is recommended to define severe BP by the occurrence of equal or more than 10 new blisters daily on multiple anatomical sites and/or a BPDAI score ≥ 57 (4.80 ± 0.50). This threshold that differentiates BP with limited extent from the extensive type has been calculated in a large series of newly diagnosed patients with BP.[69]

For the initial treatment of severe BP, two first-line options are recommended (4.56 ± 1.12) (level of evidence 1):

- High-potency topical CS: initial dose of clobetasol propionate is 30 to 40 g per day, divided into two daily applications on the entire body (except face and anogenital areas) (4.04 ± 1.55);
- Medium to high dose of oral CS: initial dose of oral prednisone 0.5 mg/kg/day (4.86 ± 0.53). Since only half the patients with severe BP will achieve a CDA with this initial dose of oral prednisone, two options may be considered (4.95 ± 020)[47] in patients not responding to this regimen;
  - ○ secondarily increase in oral prednisone to 0.75 mg/kg/day, or
  - ○ add topical CS in addition to the 0.5 mg/kg/day dose of prednisone.

Although the final choice will depend on their availability, practical feasibility and presence of contraindications for oral CS, high-potency topical CS has been shown to achieve CDA more rapidly compared to oral prednisolone 1 mg/kg daily and results in less severe side-effects and lower mortality (level of evidence 1).

Treatment of corticosteroid-dependent (relapsing) BP

Several therapeutic options can be discussed in patients who have multiple relapses during tapering of topical or systemic CS doses. Data from the literature do not preferentially allow the proposal of a particular option over another.

The addition of a conventional immunosuppressive drug may be recommended in the absence of contraindications, in particular methotrexate (5 to 12.5 mg weekly), mycophenolate mofetil (1 to 3 g daily) or azathioprine (1 to 3 mg/kg daily according to TPMT activity) (4.73 ± 0.83), although the level of evidence is lower for the latter drug.

In patients with poor general condition and/or in those with contraindications to immunosuppressive drugs, doxycycline (200 mg daily), dapsone (1 mg to 1.5 mg/kg daily) or omalizumab may also be considered (4.53 ± 0.90). The prescription of dapsone requires careful consideration and close monitoring (see above).

Treatment of resistant BP

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 CS, there are the following therapeutic options:

- *Conventional immunosuppressants* (see above) such as methotrexate, azathioprine mycophenolate mofetil may be considered (4.75 ± 0.81).[54–57]
- *Other potential therapies* may be considered.It must be underlined that none of the following options is validated in this particular situation of patients with CS-resistant BP. Consequently, these options are mentioned without any prioritization
  - B-cell depletion therapy with anti-CD20 mAb (rituximab) (4.04 ± 1.74)[60,61];
  - Omalizumab (4.31 ± 0.89)[64];
  - Dupilumab (4.30 ± 0.86)[65,66];
  - Intravenous immunoglobulins (4.57 ± 0.59)[70];
  - Immunoadsorption (4.23 ± 1.13).[71,72] The latter may be considered in patients with high levels of circulating anti-BP180 antibodies, and only when the necessary technical expertise is available, because of the risk of severe side-effects, in particular septicaemia.

Other skin care 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 non-adherent, to reduce bacterial super-infection 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.[8,73]

Other general measures, when required or indicated

- Dietary supplements in malnourished patients;
- Vaccinations. Patients receiving oral CS (prednisone at doses of >20 mg per day for >2 weeks) or immunosuppressive therapy should be vaccinated against seasonal

influenza, H1N1 and pneumococcal disease. Live attenuated vaccines are contraindicated;
  - http://www.bccancer.bc.ca/NR/rdonlyres/8B9A8033-61A8-4862-B113-96916C59C04C/12801/ImmunizationGuidelines.pdf
  - http://www.cdc.gov/mmwr/preview/mmwrhtml/00023141.htm)
- SARS-CoV2. Follow carefully the general recommendations regularly updated by the governments of your country, the EADV and the International League of Dermatological Societies (ILDS; see https://ilds.org/covid-19/ilds-statement/). The following common practical advice has been modified by the European League Against Rheumatism (EULAR). Regular updates can be found on: https://www.eulnar.org/eular_guidance_for_patients_covid19_outbreak.cfm
- Patients with an autoimmune blistering disease seem to have a higher risk of suffering from severe forms of SARS-CoV-2 infection when compared to healthy individuals, in particular patients treated with immunosuppressive drugs (rituximab seems to have a particularly high risk). Additionally, patients with autoimmune blistering disease infected with SARS-CoV-2 have a much higher mortality than AIBD patients, who have not been infected with the COVID-19.[62]

It is recommended to use vaccines approved by European Medicines Agency (EMA) in patients with autoimmune bullous diseases such as BP, also when under treatment with immunomodulating or immunosuppressive drugs (4.32 ± 1.40). The mRNA-based vaccines of Pfizer-BioNTech and from Moderna have shown remarkable protection rates. It is also recommended to perform vaccinations preferably when the disease is in a quiet phase and before planned immunosuppression if feasible (4.66 ± 1.04). A vaccination is most effective when the amount of, or level of immunosuppression is low (for oral prednisolone, doses less than 20 mg/daily are considered as low-grade immunosuppression).[73] However, if the risk of a flare of the disease is real, it is not recommended to decrease the immunomodulating or immunosuppressive drugs before vaccination (4.64 ± 1.03).

- Osteoporosis baseline screening and prophylaxis if expected duration of systemic CS is more than 3 months. Prolonged treatment with superpotent topical CS seems also to be associated with an increased risk of osteoporosis[74];
- Vitamin D and calcium supplement is recommended at the initiation of glucocorticoid treatment[75];
- Treatment with bisphosphonates (i.e. alendronate, risedronate) is recommended in patients at risk (postmenopausal women, men >50 years on glucocorticoid treatment >3 months) to prevent osteoporosis[75]; check for regular updates of corresponding guidelines (see,.e.g., https://link.springer.com/article/10.1007%2Fs00198-018-4704-5);
- *Mycobacterium tuberculosis* prophylaxis/therapy (if necessary);
- *Pneumocystis jirovecii* prophylaxis (optional).

Note: It is recommended to regularly verify the updated recommendations and compare them with the local health practice and system or follow national guidelines if available.

Monitoring

Objectives

- To evaluate the efficacy, safety and tolerance of the treatment;
- To gradually reduce and/or adapt treatment, and to decide when to discontinue treatment.

Professionals involved including nursing

Specialists and health professionals involved are identical to those listed in the initial evaluation (see § 1.2).

Note: The nursing care required for the application of topical treatments takes usually up to 30 to 45 min (encompassing antiseptic baths, bullae count, application of topical CS, bandaging).

Frequency of consultations

Frequency of the follow-up visits and of laboratory tests has to be adapted to:

- The patient's clinical condition;
- The severity and evolution of the disease;
- The treatments used; and
- The local health practice and system.

Treatment efficacy is essentially monitored and evaluated by clinical examination. In the scenario of generalized disease, the following visit frequency is suggested:

- Weekly to biweekly until disease control, then
- Monthly for the next 3 months, and then
- Every two months to three times a year until treatment is stopped;
- Monitoring frequency has to be adapted to the disease course.

Clinical examination and laboratory monitoring

The clinical follow-up is identical to that performed during the initial assessment and consists of:

- Examination for skin disease activity (check for blisters, eczematous/urticarial-like lesions, intensity of itch, *etc.*);
- Check for possible treatment-related side-effects and comorbidities:

○ Degree of skin atrophy, purpura and skin infections;

- ○ Blood pressure, cardiovascular insufficiency (as a result of CS), respiratory disorders and infections (CS, immunosuppressants);
- ○ Analysis of WBC, liver and kidney tests (immunosuppressants) and glycaemia (CS);
  - Immunoserological analyses. Determination of anti-BP180 IgG by ELISA (as detected using the kit of MBL, Nagoya, Japan, at days 0, 60 and 150) is useful during treatment because IgG autoantibody levels at these endpoints may predict outcome.[24,43,76] A decrease of no more than ±20% of ELISA-BP180 values between days 0 and 60 is a predictive factor for disease relapse within the first year of therapy.[76] Furthermore, low and negative values by the ELISA-BP180 (MBL, Nagoya, Japan), that is values lower than 27 U/mL (which are less than two times the upper limit) at day 150, have a good negative predictive value, implying a probability of durable remission of around 90%[43]; The corresponding cut-off values for the ELISA-BP180 of Euroimmun have not been made precise yet.
  - Depending on the drug used, other specific examination may be required and necessary (e.g. for dapsone);
  - Osteodensitometry and ocular examination if indicated (according to the used treatment regimen, patient's age and condition).

Discontinuation of treatment

- The optimal duration of treatment has not been defined.[41,42,44–46] Based on clinical experience, the group of experts recommend a treatment duration between 9 and 12 months according to the presence of either mild or generalized disease (see above), except in cases of CS resistance or CS dependence;
- Discontinuation of treatment is recommended in patients who are free of symptoms for at least one to 6 months under minimal therapy with oral prednisone (0.1 mg/kg/day), clobetasol propionate (10 g/week) or immunosuppressants; treatment discontinuation is further affected by the patient's overall general condition and presence of distinct comorbidities;
- Anti-BP180 ELISA (i.e. > 27 U/mL, as assessed using the MBL assay), and to a lesser degree DIF studies have been reported to have a predictive value for the occurrence of relapse after stopping the treatment.[43] It may be considered to apply these assays before stopping treatment (4.52 ± 1.11);
- Be aware and check for potential adrenal insufficiency caused by exogenous CS use, even after topical application.

Monitoring after treatment discontinuation

- A follow-up visit is recommended in the third month after treatment discontinuation, since this period seems sufficient to detect most relapses of BP[41,43,76];
- Patients or their caregivers should be informed that reappearance of itch, excoriations and/or inflammatory cutaneous lesions justify medical assessment to exclude relapse.

Potential complications

BP can cause permanent complications directly related to either the disease itself or to the treatments used. Affected patients seem to show a significantly increased mortality rate compared to control populations.[1,2,19,39,40] In this context, proper management of affected patients is necessary and requires specialized personnel.

Information for patients

It is recommended to inform patients or their families about the disease, its prognosis, available treatments, possible adverse reactions and therapy-related complications (4.96 ± 0.20). 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 health professionals. Patients' associations can also help in referring patients to either referral centres or their network of correspondents.

List of pemphigoid support groups (selection)

- France: Association Pemphigus – Pemphigoïde: www.pemphigus.asso.fr
- Germany: Pemphigus und Pemphigoid Selbsthilfegruppe e.V.: http://www.pemphigus-pemphigoid-selbsthilfe.de.
- International Pemphigus Pemphigoid Foundation: http://www.pemphigus.org/
- Italy: Associazione Nazionale Pemfigo-Pemfigoide Italy (ANPPI): www.pemfigo.it;
- Netherlands: Netwerk Nederland voor Pemphigus en Pemfigoïd: https://www.netwerkblaarziekten.nl
- Turkey: http://www.turkdermatoloji.org.tr/
- UK: https://www.pemfriendsuk.co.uk

Data availability statement

Data sharing is not applicable to this article as no new data were created or analysed in this study.

Qualifying statement

Decisions to follow these recommendations must be based on professional clinical judgement, consideration of individual patient circumstances and available resources. All possible care has been undertaken to ensure the publication of the correct

dosage of medication and route of administration. However, it remains the responsibility of the prescribing clinician to ensure the accuracy and appropriateness of the medication they prescribe.

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