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GUIDELINES

Bullous pemphigoid: Italian guidelines adapted from the EDF/EADV guidelines

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ABSTRACT

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 blister 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 the quality of life are significant. So far, a limited number of national treatment guidelines have been proposed, but no common European consensus has emerged. This guideline for the treatment of bullous pemphigoid has been developed by an Italian group of experts taking in account the Italian legislation and local pharmacological governance. Guidelines are adapted from the original article under the guidance of the European Dermatology Forum (EDF) in collaboration with the European Academy of Dermatology and Venereology (EADV). It summarizes evidence-based and expert-based recommendations (S2 level).

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

The aim of the present guideline is to make recommendations for the Italian dermatological community from the general dermatologist in collaboration with the expert in the field and only the most common situations, but not to cover all specific disease variants of BP exhaustively.[1-3]

Methods

The methodology used to generate this guideline is described in details in the original article published online on the EDF guidelines section (Appendix 1). Adaptation of the Italian guidelines follow the AGREE lines

and rules with an expert in the field group taking in account suggestions from the Cutaneous Immunology group of the Italian Society of Dermatology SIDeMaST.

1. Initial evaluation of bullous pemphigoid

The initial clinical examination should search for features consistent with the diagnosis of BP and evaluate the patient's general condition and potential co-morbidities (Table I).

1.1. Major objectives

— Confirm the diagnosis of BP;
— Search for risk factors and co-morbidities;
— Specify the type of initial damage and its extent (see definitions and outcome measures for BP);[4]
— Evaluate the age-dependent prognosis and general condition (Karnofsky performance status scale);
— 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 center or is in contact with a referral center. Other health professionals who should be included in the patient's management according to the clinical presentation, general conditions and co-morbidities are:
— the consultant dermatologist in general practice;
— the patient's treating physician or, alternatively, a geriatrician, a neurologist, or, very rarely, a pediatrician;
— specialized nurse (*e.g.*, elderly care medicine, community health service, or home healthcare);
— dietician, psychologist, physiotherapist, often involved in patient care;
— all other specialists whose expertise is necessary based on the clinical context (neurologists for example).

TABLE I.—*Diagnostic steps in bullous pemphigoid.*

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

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. The physician should search for recent drug intake (over a 1- to 6-month period) based on their potential triggering role, such as diuretics.[5, 6]

1.3.2. Physical examination

The physician should search for objective evidence required for diagnosis:

— classical form: severely pruritic bullous dermatosis, with blister usually arising from erythematous inflamed skin, symmetric distribution (flexural surfaces of the limbs, medial surface of thighs, abdomen), usually without mucosal involvement and atrophic scarring, and negative Nikolsky's sign;[1, 2, 7, 8]

— 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;[7, 8]

— the extent of BP should be assessed (see for example BP disease activity index BPDAI or daily blister count).[4] Finally, the general condition of the patient and the presence of co- morbidities have to be methodically evaluated.

1.4. Laboratory investigations

— Confirm the diagnosis of BP: the diagnosis is based on a combination of criteria encompassing clinical features, compatible light microscopy findings, and positive specific direct immunofluorescence microscopy (DIF) findings (Table I).[1, 2, 3, 9, 10] A complete blood count frequently shows eosinophilia.

Proper diagnosis and classification of BP may also require:

— use of validated clinical criteria based on patient's characteristics;[10]

— search for circulating IgG anti-basement membrane autoantibodies by indirect immunofluorescence (IIF) microscopy studies;[1, 2, 3, 9, 11]

— search for anti-BP180 (also called BPAG2/type XVII collagen) IgG antibodies and anti- BP230 (also called BPAG1-e, epithelial isoform) IgG antibodies by ELISA.[1, 2, 3, 12-14]

Further technical approaches helpful in confirming the BP diagnosis include (not exhaustive list):

— analysis of n-serrated pattern on DIF;[15]

— biochip technique;[16]

— immunoblotting studies (keratinocyte extracts, recombinant proteins);[1, 2, 13, 14, 17, 18]

— fluorescence overlay antigen mapping (FOAM);[19, 20]

— immunoelectron microscopy studies of a patient's skin biopsy specimen.[21]

1.4.1. Histopathology

A skin biopsy preferably with a recent, intact bulla (placed in formalin solution) for routine histopathological analysis. Typical findings consist of subepidermal blister containing eosinophils and/or neutrophils, associated with a dermal infiltrate of eosinophils and /or neutrophils, or a marginalization of eosinophils along the dermal-epidermal junction. Nevertheless, in the absence of blistering and in non-bullous forms, histopathological findings may be nonspecific, such as the presence of eosinophilic spongiosis.[22]

1.4.2. Direct immunofluorescence microscopy

DIF studies represent the most critical test: their positivity is essential for the diagnosis of BP.[1, 2, 3, 9, 10]

A biopsy from perilesional skin from a very recent blister (either put into a cryotube for transportation in liquid nitrogen, in Michel's fixative or simply in 0.9% NaCl solution) to demonstrate linear deposits of IgG and/or C3 along the epidermal/dermal-epidermal junction; occasionally IgA and IgE are also found with a similar pattern.[9, 10, 23]

The analysis of the n-serration pattern of DIF may be helpful and specific in combination with indirect IF studies to differentiate BP from epidermolysis bullosa acquisita.[15]

DIF studies on an autologous patient's skin biopsy specimen cleaved by 1 M NaCl for IgG (IgG deposits after splitting allows differentiation of BP from epidermolysis bullosa acquisita, anti-laminin-332 mucous membrane pemphigoid, and anti-p200 pemphigoid (note that the location of C3 is not reliable).[1, 2, 9, 24]

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. [25]

1.4.3. Immune serological tests

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

1.4.3.1.—IIF on normal human skin followed by the 1 M NaCl technique (or suction-split technique): search for anti-basement membrane IgG auto-antibodies binding to the epidermal side (sometimes epidermal and dermal) of the split skin. By this means, IgG antibodies are found in up to 80% of cases. Use of non-separated normal human skin or monkey oesophagus is also possible, however associated with lower sensitivity.[1, 2, 9, 11, 18]

1.4.3.2.—Search first for anti-BP180 IgG antibodies by ELISA, and, if negative, for anti-BP230 IgG antibodies.[1, 2, 12-14, 26]

1.4.4. Other tests

Additional tests may be considered according to clinical context and availability):

— biochip technique. A novel IIF microscopy approach using purified BP180 recombinant proteins and transfected cells expressing BP230 is also available;[16]

— immunoblotting studies using different substrates to assess patient's serum reactivity with BP180 and/or with BP230 or other less frequently targeted antigens;[1, 2, 14, 17, 18]

— FOAM by using either a standard immunofluorescence microscopy or, preferably, laser scanning confocal microscopy.[19, 20] This approach verifies the presence of immune deposits (IgG, C3) in the upper part of the lamina lucida (as compared to structural basement membrane antigens used as topographic reference markers);[19, 20]

— direct immunoelectron microscopy (skin biopsy of peribullous skin) for evidence of immune deposits (IgG, C3) on hemidesmosomes and the adjacent part of the lamina lucida.[21]

2. Therapeutic management

2.1. Workup and pre-therapy screening

— Complete blood count (CBC), ESR and C-reactive protein;
— creatinine, blood electrolytes;
— fasting glucose;
— transaminases, gamma-GT, alkaline phosphatase, 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;
— if available, testing of thiopurine methyltransferase (TPMT) is optional, when azathioprine is considered as therapeutic option;
— glucose 6-phosphate dehydrogenase (G6PDH), if dapsone treatment is considered;
— serum immunoglobulin (IgE for a better characterization of the patients and IgA deficiency 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 TBC) if appropriate when immunosuppression needs to be initiated;
— bone densitometry (optional, if systemic corticosteroid therapy is planned);
— ocular examination (optional, ocular tension and cataract, if corticosteroid therapy is planned);
— local bacteriological sampling if there is any clinical evidence for lesion infection;
— in selected patients consider echocardiography before initiation of therapy with either systemic corticosteroids, dapsone, or intravenous immunoglobulins (Table II).

2.2. Objectives

Advanced age in affected patients and the potential presence of comorbidities (neurological, cardiovascular, neoplastic, metabolic and respiratory) make their cases more difficult to manage.[1, 2, 8, 27, 28]

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

TABLE II.—*Bullous pemphigoid: the therapeutic ladder.*

Localized/limited disease with mild activity	
1st choice	2nd choice
Superpotent topical corticosteroids – in localized disease: on lesions only (3, non-validated) – in mild disease: on whole body except the face (1, validated)	– Tetracycline + nicotinamide (2, non-validated) – Dapsone, sulfonamides (3, non-validated) – Topical immunomodulators (e.g. tacrolimus) (4, non-validated) – Oral corticosteroids (1, validated for prednisone)
Generalized disease	
1st choice	2nd choice
– Superpotent topical corticosteroids on whole body sparing the face (1, validated) – Oral corticosteroids (1, validated for prednisone)	Combination with or introduction of: – tetracycline + nicotinamide (2, non-validated) – azathioprine (1, non-validated) – mycophenolate (1, non-validated) – methotrexate (3, non-validated) – chlorambucil (3, non-validated)
3rd choice	
Combination with and/or introduction of: – anti-CD20 mAb, anti-IgE mAb (4, non-validated) – intravenous immunoglobulins (3, non-validated) – immunoadsorption (4, non-validated)	– plasma exchange (1, non-validated) – cyclophosphamide (3, non-validated)

1: randomized prospective single-center or multicenter study; in case that in the latter the intervention is shown effective and not contradicted by other studies, its use is considered validated; 2: randomized prospective single-center study (in case of poor methodological quality), retrospective multicenter study; 3: case series, retrospective single-center study; 4: anecdotal case reports; 5: expert opinion.

— treat the skin eruption, reduce itch, and prevent/reduce the risk of recurrence;

— improve the quality of life of patients;

— limit the side effects related to the newly introduced drugs, particularly in the elderly.

2.3. Professionals involved

The initial management, *i.e*. diagnosis and treatment start, of extended forms/complicated patients usually requires hospitalization in a dermatology department if available. Hospitalization should be continued until clinical control of the bullous eruption is achieved and most of the post-bullous erosions have regressed. In pauci-lesional or localized forms, 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 center of reference. Close collaboration between the dermatologist, the treating physician and, if necessary, the nursing staff is therefore fundamental. Exceptionally, the disease can occur in childhood. Affected children should be managed jointly by the specialists, including a pediatrician.

2.4. Therapeutic management

The following recommendations are based on the following level of evidence:

— Level 1: randomized prospective single center or multicenter study. In case that in the latter the intervention is shown effective and not contradicted by other studies, its use is considered validated;

— Level 2: randomized prospective single-center study (in case of poor methodological quality), retrospective multicenter study;

— Level 3: case series, retrospective single-center study;

— Level 4: anecdotal case reports;

— Level 5: expert opinion.

2.4.1. EXTENSIVE BP

At present there is no general consensus on the definition of extensive BP.[4] While some experts have de-

fined extensive disease as the occurrence of more than 10 new blisters per day,[29, 30] 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 30 to 40 g/day, initially in two applications, over the entire body including blisters and erosions, but sparing the face (20 g/day if weight <45 kg; level of evidence 1, validated);[29, 30]

Current evidence indicates that 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).[4] Earlier reduction of corticosteroid doses is possible but has not been validated in controlled studies.[29, 30]

Definition of disease control: the time point at which new lesions or pruritic symptoms cease to form and established lesions begin to heal.[4]

Tapering schedule and dose adaptation

— daily treatment in the 1st month;
— treatment every 2 days in the 2nd month;
— treatment twice a week in the 3rd month;
— treatment once a week starting in the 4th month.

In patients who do not achieve disease control within 1-3 weeks, increasing dose of topical steroids (up to 40 g/day) is recommended.[30]

Maintenance treatment

Two options are available after 4 months of treatment:

— continue a maintenance treatment once a week for 9 months (and then stop; level of evidence 1, validated);[29, 30]

— disadvantage: practical and economic difficulties related to continued nursing for a long period and/or cost of topical high potency steroids;

— stop treatment (slightly higher risk of relapse but with improved safety when treatment is stopped within 4 months; level of evidence 1, validated).[30]

Relapse and dose adaptation

In case of a relapse (see definitions and outcome measures for BP) [4] during the dose reduction period, the dose is increased to the previous level (level of evidence 1, validated).[29, 30]

Patients who experience a relapse after treatment withdrawal are treated using the following doses of clobetasol propionate cream (level of evidence 1, validated):[30]

— 10 g daily for patients with a localized relapse;
— 20 g daily for patients with mild disease (see below for definition);
— 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/day, is effective in patients with extensive disease (level of evidence 1, validated).[29, 31-33] However, this therapy has been shown to be associated with higher mortality and increased side effects.[29, 31, 32]

Therefore, the group of experts does not recommend using this dosage in the initial treatment. Doses between 0.5 and 0.75 mg/kg/day of prednisone are suggested, despite lack of evidence in extensive disease.[29, 31-33] Prednisone doses lower than 0.5 mg/kg have not been validated and seem to be ineffective.[34] Systemic treatment may be accompanied by topical therapy with steroids and/or other measures (see below and consider corticosteroid sparing treatments).

Tapering schedule and dose adaptation

This 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 0.5 mg/kg prednisone, the group of experts proposes to increase the dose of prednisone up to 0.75 mg/kg/day, despite the absence of evidence in the literature.

Maintenance treatment

Systemic steroids doses should be tapered gradually with the aim to stop treatment or to maintain minimal therapy (0.1 mg/kg/day) within 6 months after initiation of treatment.[30]

Relapse and dose adaptation

In case of a relapse during the dose reduction period, the dose is increased to the previous level (level of evidence 1, validated).[29]

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 contra-indications.

The use of an immunosuppressive/immunomodulatory therapy with a potentially corticosteroid saving-effect should be considered in the presence of contra-indications to oral corticosteroids and of co-morbidities (such as diabetes, severe osteoporosis, significant cardiovascular problems). Nevertheless, there is no positive evidence supporting their use as first line treatment and they are therefore non-validated.[31-33]

The following drugs may be considered (level of evidence between 1 and 3):

— tetracyclines (oxytetracycline 2 g/day, doxycycline 200 mg/day orally) alone or in combination with nicotinamide (up to 2 g/day orally);[35]

— azathioprine: 1 to 3 mg/kg/day according to TPMT activity;[36-38]

— mycophenolate (mofetil 2 g/day or sodic 1.44 g/day orally);[37, 38]

— methotrexate (up to 15 mg once a week orally or subcutaneously or IM);[39]

— dapsone (up to 1.5 mg/kg/day orally);[40]

— chlorambucil (2 to 4 mg/day orally);[41]

— cyclosporine (in selected patients 3-5 mg/kg/day).[42]

2.4.2. Localized/limited and mild BP

At present, there is no general consensus about the definition of mild BP. While two studies have defined patients with fewer than 10 new blisters per day as having mild disease,[4, 29, 30] mild disease can be also defined by the presence of few inflammatory non-bullous or localized lesions involving one body site. In the above-mentioned studies around 5 new blisters per day were observed in patients considered as having mild disease.[29, 30]

2.4.2.1. Topical treatment.—Patients with localised/limited BP should be preferentially treated initially with topical steroids applied on lesional skin only (clobetasol propionate 10-20 g/day).[30]

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

Tapering schedule and dose adaptation

Current evidence indicates that initial treatment should be first reduced 15 days after disease control. Earlier reduction of corticosteroid doses may be possible but has not been demonstrated in controlled studies (cf. 2.4.1.1. "Extensive bullous pemphigoid").

In patients who do not achieve disease control within 1-3 weeks with clobetasol propionate 20 g/day, the recommendation is to increase the dose up to 40 g/day.[29, 30]

The use of other lower potency steroids in maintenance therapy has not been validated.

2.4.2.2. Systemic steroid therapy.—There is evidence that 0.5 mg/kg/day prednisone is effective in patients with mild disease (level of evidence 1, validated).[29] Prednisone doses lower than 0.5 mg/kg have not been validated and seem to be ineffective.[31-34] This treatment may be accompanied by topical therapy with steroids and/or other measures (see below).

Maintenance treatment

Systemic steroid doses should be tapered gradually with the aim to stop treatment or to maintain minimal therapy (0.1 mg/kg/day) within 6 months from initiation of treatment. This recommendation of the expert group needs to be validated (level of evidence 5).

Additional measures to obtain or maintain disease control can be considered:

— the choice of an adjuvant or alternative therapy is dependent on its availability, cost aspects, practical experience, and specific contra-indications;

— the use of an immunosuppressive/immunomodulatory therapy with corticosteroid-saving effects should be considered in case of contra-indications 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;[36]

— some evidence supporting the use of tetracyclines and nicotinamide, methotrexate, and dapsone exists, although their use has not been validated in randomized controlled studies of good methodological quality.[31-33] The latter drugs (all off-label) may thus be considered (level of evidence between 1 and 3):

- tetracyclines (oxytetracycline 2 g/day, doxycycline 200 mg/day) plus nicotinamide (up to 2 g/day);[31-33, 35]
- methotrexate (up to 15mg once a week orally or subcutaneously or IM);[39]
- dapsone (up to 1.5 mg/kg/day orally).[40]

2.4.3. Treatment-resistant BP

In the cases of those few patients 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:

— immunosuppressants: see above (such as methotrexate, azathioprine, mycophenolate mofetil);[36-42]

— additional therapies (all off-label):

- intravenous immunoglobulins (level of evidence 3);[43]
- immunoadsorption (level of evidence 4);[44, 45]
- anti-CD20 mAb, anti-IgE mAb (level of evidence 4);[46-48]
- cyclophosphamide (level of evidence 3);[49]
- plasma exchange (level of evidence 1).[34]

2.4.4. 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.

2.4.5. Other general measures, when required or indicated

Dietary supplements in malnourished patients (taking in account that many patients are diabetics).

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 pneumococcal. Live attenuated vaccines are contraindicated (www.cdc.gov/mmwr/preview/mmwrhtml/00023141.htm).

Other prophylactic measures to consider:

— osteoporosis prophylaxis (if expected duration of systemic corticosteroids >3 months);

— TBC prophylaxis/therapy (if necessary);

— *Pneumocystis jirovecii* prophylaxis (optional).

3. Monitoring

BP is a chronic disease which can last for several years in the absence of treatment and has a tendency to relapse.[1, 2, 50, 51]

3.1. Objectives

— To evaluate the efficacy, safety and tolerance of the treatment;

— to gradually reduce and/or adapt treatment, and decide its discontinuation.

3.2. Professionals involved

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

Note: the nursing care required for the application of topical treatments takes usually up to 30 to 45 minutes (encompassing antiseptic baths, blister count, application of topical steroids, bandaging). It is better to leave small and medium blisters intact as the roof of the blister forms a natural dressing. If the blister is broken remove the fluttering skin.[52]

3.3. 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 (treatment efficacy is essentially monitored and evaluated by clinical examination);

— follow-up frequency: several times 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 should 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:

— 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 (corticosteroids), respiratory disorders and infections (corticosteroids, immunosuppressants);

analysis of WBC, liver and kidney tests (immunosuppressants) and glycaemic value (corticosteroids);

immunoserological analyses: determination of anti-BP180 IgG antibodies by ELISA at days 0, 60, and 150 is useful during treatment because IgG antibody fluctuations measured at these specific endpoints may predict outcome.[13, 50, 51] 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.[50] Furthermore, a low or negative anti-BP180 IgG level by ELISA — less than 23 U/mL, *i.e*. less than two times the upper limit of one of the commercially available kits — at day 150 has a good negative predictive value, since in this case the probability of durable remission is approximately 90%:[51]

- total serum IgE

— depending on the drug used, other specific examination may be required and necessary (*e.g*. for dapsone);

— osteodensitometry, if indicated (according to patient's age and conditions).

3.5. Discontinuation of treatment

The optimal duration of treatment has not been defined.[27-31] Based on clinical experience, we recommend an average treatment duration of 6 to 12 months, except in cases of steroid- resistance or steroid-dependence.

Discontinuation of treatment is recommended in patients free of symptoms for at least 3 to 6 months under minimal therapy with oral prednisone (0.1 mg/kg/day), or clobetasol propionate (20 g/week), or immunosuppressants.

Prior to cessation of treatment, the following exams should be performed:

— DIF studies or ELISA-BP180. In case of either positive DIF studies, or

— ELISA-BP180 (if value >27 U/mL) there is an increased risk of relapse.[51]

Be aware and check for potential adrenal insufficiency caused by exogenous steroid use, even after topical application.

3.6. 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, 8, 27, 28] In this context, proper management of affected patients is necessary and requires specialized personnel.

4. Information for patients and general practitioners

Pemphigoid is a rare disease, and cost of treatment and follow-up diagnostic laboratory tests are covered by the Italian Health System. Each regional area organizes a register (usually on regional platform) for rare diseases and selected regional hospital centers for legal certification of rare diseases. Bullous pemphigoid's number code is RL0040. Usually, off-label treatments should be approved by a regional committee via the register of rare diseases, then the local pharmacy provides the drug for free to the patient.

Patients or their families must be informed about the disease, its prognosis, available treatments, possible adverse reactions and therapy-related complications. Furthermore, the need of 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 centers or their network of correspondents.[53]

4.1. List of pemphigoid support groups

Italy: Associazione Nazionale Pemfigo-Pemfigoide Italy (ANPPI): www.pemfigo.it

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