European Dermatology Forum

Guideline on the Diagnosis and Treatment of Autoimmune bullous diseases - Pemphigoid

Developed by the Guideline Subcommittee of the
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Bullous pemphigoid. S2 Guideline for diagnosis and treatment

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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 localised or generalised bullous lesions. In up to 20% of affected patients bullae may be completely absent, and only excoriations, prurigo-like lesions, eczematous lesions, urticated lesions, and/or infiltrated plaques are observed. The disease is significantly associated with neurological disorders. The morbidity of bullous pemphigoid and its impact on 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 under the guidance of the European Dermatology Forum (EDF) in collaboration with the European Academy of Dermatology and Venereology (EADV). It summarises evidence-based and expert-based recommendations (S2 level).

Introduction

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, hospitalisation rules, home-care availability and the possibility of financial reimbursement for different treatments.

The aim of the present guideline is to make recommendations for only the most common situations. They are not intended to cover all specific disease variants of BP exhaustively; [1-3] these are too numerous and too complex to be treated individually. The methodology used to generate this guideline is described in details below (*addendum 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 1**).

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 centre or is in contact with a referral centre. 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 paediatrician;

- 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)..

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 bullae 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 localised 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 1**).[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]
- Immunelectron 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 bullae containing eosinophils and/or neutrophils, associated with a dermal infiltrate of eosinophils and /or neutrophils, or a marginalisation 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 (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: 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 cleaved 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 immunelectron 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 (see Table 2)

2.1 Workup and pre-therapy screening

- CBC – complete blood count, 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 IgA deficiency should be excluded if intravenous immunoglobulins are considered;
- Check for an underlying neoplasm in line with the patient's age, clinical history and examination as well as for an infection (in particular TBC) if appropriate when immunosuppression needs to be initiated;
- Osteodensitometry (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;

- Consider echocardiography before initiation of therapy with either systemic corticosteroids, dapsone, or intravenous immunoglobulins.

2.2 Objectives

Advanced age in affected patients and the potential presence of co-morbidities (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:

- 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 of the disease usually requires hospitalisation in a dermatology department if available. Hospitalisation 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 localised 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 centre 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 paediatrician.

2.4 Therapeutic management

The following recommendations are based on the following level of evidence

(1) Randomised 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) Randomised prospective single centre study (in case of poor methodological quality), retrospective multi-centre study
(3) Case series, retrospective single-centre study
(4) Anecdotal case reports
(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 defined 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 2 times per week in the 3rd month;
- Treatment once a week starting at 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 prednisone /kg/day 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).

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

2.4.2 Localised / 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 localised 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. See above (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 and are listed below.

- 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 co-morbidities (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 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:
    - 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.
- 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 *pneumococcae*. Live attenuated vaccines are contra-indicated.
    - http://www.bccancer.bc.ca/NR/rdonlyres/8B9A8033-61A8-4862-B113-96916C59C04C/12801/ImmunizationGuidelines.pdf
    - http://www.cdc.gov/mmwr/preview/mmwrhtml/00023141.htm)

Other prophylactic measures to consider

- Osteoporosis prophylaxis (if expected duration of systemic corticosteroids >3months);
- 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 § 1.2).

Note: the nursing care required for the application of topical treatments takes usually up to 30 to 45 minutes (encompassing antiseptic baths, bullae 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: at least weekly 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 co-morbidities:
  - 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]

- 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 perfomed:
    - DIF studies and 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 specialised personnel.

4. Information for patients

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

4.1 List of pemphigoid support groups

- Italy: Associazione Nazionale Pemfigo-Pemfigoide Italy (ANPPI): www.pemfigo.it;
- France: Association Pemphigus – Pemphigoïde [53] : www.pemphigus.asso.fr
- Turkey: http://www.turkdermatoloji.org.tr/
- Netherlands: Netwerk Nederland voor Pemphigus en Pemfigoïd: http://www.pemphigus.nl
- USA: International *Pemphigus* Pemphigoid Foundation: http://www.pemphigus.org/
- Germany: Pemphigus und Pemphigoid Selbsthilfegruppe e.V.: http://www.pemphigus-pemphigoid-selbsthilfe.de

References

1 Di Zenzo G, Della Torre R, Zambruno G, Borradori L. Bullous pemphigoid: from the clinic to the bench. *Clin Dermatol* 2012; **30**:3-16.

2 Schmidt E, Zillikens D. Pemphigoid diseases. *Lancet* 2013; **26:**381:320-32.

3 Venning VA, Taghipour K, Mohd Mustapa MF *et al*. British Association of Dermatologists' guidelines for the management of bullous pemphigoid 2012. *Br J Dermatol* 2012; **167**:1200-14.

4 Murrell DF, Facid BSD, Joly P *et al*. Definitions and outcome measures for bullous pemphigoid: recommendations by an international panel of experts. *J Am Acad Dermatol* 2012; **66**:479-85.

5 Bastuji-Garin S, Joly P, Picard-Dahan C *et al*. Drugs associated with bullous pemphigoid. A case-control study. *Arch Dermatol* 1996; **132**:272-6.

6 Lloyd-Lavery A, Chi CC, Wojnarowska F *et al*. The associations between bullous pemphigoid and drug use: a UK case-control study. *JAMA Dermatol* 2013; **149**:58-62.

7 Della Torre R, Combescure C, Cortés B *et al*. Clinical presentation and diagnostic delay in bullous pemphigoid: a prospective nationwide cohort. *Br J Dermatol* 2012; **167**:1111-7.

8 Joly P, Baricault S, Sparsa A *et al*. Incidence and mortality of bullous pemphigoid in France. *J Invest Dermatol* 2012; **132**:1998-2004.

9 Pohla-Gubo G, Hintner H. Direct and indirect immunofluorescence for the diagnosis of bullous autoimmune diseases. *Dermatol Clin* 2011; **29**:365-72.

10 Joly P, Courville P, Lok C *et al.* Clinical criteria for the diagnosis of bullous pemphigoid: a reevaluation according to immunoblot analysis of patient sera. *Dermatology*. 2004; **208**:16-20.

11 Kelly SE, Wojnarowska F. The use of chemically split tissue in the detection of circulating anti-basement membrane zone antibodies in bullous pemphigoid and cicatricial pemphigoid. *Br J Dermatol* 1988; **118**:31-40.

12 Zillikens D, Mascaro JM, Rose PA *et al.* A highly sensitive enzyme-linked immunosorbent assay for the detection of circulating anti-BP180 autoantibodies in patients with bullous pemphigoid. *J Invest Dermatol* 1997; **109**:679-83.

13 Di Zenzo G, Thoma-Uszynski S, Fontao L, et al. Multicenter prospective study of the humoral autoimmune response in bullous pemphigoid. *Clin Immunol* 2008; **128**:415-26.

14 Fairley JA, Bream M, Fullenkamp C *et al.* Missing the target: characterization of bullous pemphigoid patients who are negative using the BP180 enzyme-linked immunosorbant assay. *J Am Acad Dermatol* 2013; **68**:395-403.

15. Terra JB, Meijer JM, Jonkman MF, Diercks GFH. The n- vs. u-serration is a learnable criterion to differentiate pemphigoid from epidermolysis bullosa acquisita in direct immunofluorescence serration pattern analysis. *Br J Dermatol* 2013; **169**:100–5.

16 van Beek N, Rentzsch K, Probst *C et al*. Serological diagnosis of autoimmune bullous skin diseases: prospective comparison of the BIOCHIP mosaic-based indirect immunofluorescence technique with the conventional multi-step single test strategy. *Orphanet J Rare Dis* 2012; **7**:49.

17 Labib RSG, Anhalt J, Patel HP *et al*. Molecular heterogeneity of the bullous pemphigoid antigens as detected by immunoblotting. *J Immunol* 1986; **136**:1231–5.

18 Chan YC, Sun YJ, Ng PP, Tan SH. Comparison of immunofluorescence microscopy, immunoblotting and enzyme-linked immunosorbent assay methods in the laboratory diagnosis of bullous pemphigoid. *Clin Exp Dermatol* 2003; **28**:651-6.

19 De Jong MC, Bruins S, Heeres K *et al*. Bullous pemphigoid and epidermolysis bullosa acquisita. Differentiation by fluorescence overlay antigen mapping. *Arch Dermatol* 1996; **132**:151-7.

20 Wozniak K, Kazama T, Kowalewski C. A practical technique for differentiation of subepidermal bullous diseases. *Arch Dermatol* 2003; **139**:1007-11.

21 Bédane C, Prost C, Bernard P *et al*. Cicatricial pemphigoid antigen differs from bullous pemphigoid antigen by its exclusive extracellular localization: a study by indirect immunoelectronmicroscopy. *J Invest Dermatol* 1991; **97**:3-9.

22 Machado-Pinto J, McCalmont TH, Golitz LE. Eosinophilic and neutrophilic spongiosis: clues to the diagnosis of immunobullous diseases and other inflammatory disorders. *Semin Cutan Med Surg* 1996; **15**:308-16.

23 Vodegel RM, de Jong MCJM, Meijer HJ *et al*. Enhanced diagnostic immunofluorescence using biopsies transported in saline. *BMC Dermatol* 2004; **4**:10.

24 Gammon WR, Kowalewski C, Chorzelski TP *et al*. Direct immunofluorescence studies of sodium chloride-separated skin in the differential diagnosis of bullous pemphigoid and epidermolysis bullosa acquisita. *J Am Acad Dermatol* 1990; **22**:664-70.

25 Magro CM, Dyrsen ME. The use of C3d and C4d immunohistochemistry on formalin-fixed tissue as a diagnostic adjunct in the assessment of inflammatory skin disease. *J Am Acad Dermatol* 2008; **59**:822.

26 Roussel A, Benichou J, Randriamanantany ZA *et al*. Enzyme-linked immunosorbent assay for the combination of bullous pemphigoid antigens 1 and 2 in the diagnosis of bullous pemphigoid. *Arch Dermatol* 2011; **147**: 293-8.

27 Joly P, Benichou J, Lok C *et al*. Prediction of survival for patients with bullous pemphigoid: a prospective study. *Arch Dermatol* 2005; **141**:691-8.

28. Cortes B, Marazza G, Naldi, L *et al*. Mortality of bullous pemphigoid in Switzerland: a prospective study. *Br J Dermatol* 2011; **165**:368-74.

29 Joly P, Roujeau JC, Benichou J *et al*. Bullous Diseases French Study Group. A comparison of oral and topical corticosteroids in patients with bullous pemphigoid. *N Engl J Med 2002*; **346**:321-7.

30 Joly P, Roujeau JC, Benichou J *et al*. A comparison of two regimens of topical corticosteroids in the treatment of patients with bullous pemphigoid: a multicenter randomized study. *J Invest Dermatol* 2009; **129**:1681-7.

31 Kirtschig G, Middleton P, Bennett C *et al*. Interventions for bullous pemphigoid. *Cochrane Database Syst Rev* 2010; **6**:10.

32 Daniel BS, Borradori L, Hall RP 3rd, Murrell DF. Evidence-based management of bullous pemphigoid. *Dermatol Clin* 2011; **29**:613-20.

33 Singh S. Evidence-based treatments for pemphigus vulgaris, pemphigus foliaceus, and bullous pemphigoid: a systematic review. *Indian J Dermatol Venereol Leprol* 2011; **77**:456-69.

34 Roujeau JC, Guillaume JC, Morel P *et al*. Plasma exchange in bullous pemphigoid. *Lancet* 1984; **2**:486-8.

35 Fivenson DP, Breneman DL, Rosen GB *et al*. Nicotinamide and tetracycline therapy of bullous pemphigoid. *Arch Dermatol* 1994; **130**:753-8.

36 Guillaume JC, Vaillant L, Bernard P *et al*. Controlled trial of azathioprine and plasma exchange in addition to prednisolone in the treatment of bullous pemphigoid. *Arch Dermatol* 1993; **129**:49–53.

37 Beissert S, Werfel T, Frieling U *et al*. A comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil for the treatment of bullous pemphigoid. *Arch Dermatol* 2007; **143**:1536-42.

38 Bystryn JC. Comparative effectiveness of azathioprine or mycophenolate mofetil as an adjuvant for the treatment of bullous pemphigoid. *Arch Dermatol* 2008; **144**: 946.

39 Du-Thanh A, Merlet S, Maillard H *et al*. Combined treatment with low-dose methotrexate and initial short-term superpotent topical steroids in bullous pemphigoid: an open, multicentre, retrospective study. *Br J Dermatol* 2011; **165**:1337-43.

40 Bouscarat F, Chosidow O, Picard-Dahan C *et al*. Treatment of bullous pemphigoid with dapsone: retrospective study of thirty-six cases. *J Am Acad Dermatol*. 1996; **34**:683-4.

41 Chave TA, Mortimer NJ, Shah DS, Hutchinson PE. Chlorambucil as a steroid-sparing agent in bullous pemphigoid. *Br J Dermatol* 2004; **151**:1107-8.

42 Barthélémy H, Thivolet J, Cambazard F *et al*. Cyclosporin in the treatment of bullous pemphigoid: preliminary study. *Ann Dermatol Venereol* 1986; **113**:309-13.

43 Gaitanis G, Alexis I, Pelidou SH *et al*. High-dose intravenous immunoglobulin in the treatment of adult patients with bullous pemphigoid. *Eur J Dermatol* 2012; **22**:363-9.

44 Müller PA, Bröcker EB, Klinker E *et al*. Adjuvant treatment of recalcitrant bullous pemphigoid with immunoadsorption. *Dermatology* 2012; **224**:224-7.

45 Meyersburg D, Schmidt E, Kasperkiewicz M, Zillikens D. Immunoadsorption in dermatology. *Ther Apher Dial* 2012; **16**:311-20.

46 Schmidt E, Seitz CS, Benoit S *et al*. Rituximab in autoimmune bullous diseases: mixed responses and adverse effects. *Br J Dermatol*. 2007; **156**:352-6.

47 Hall RP 3rd, Streilein RD, Hannah DL *et al*. Association of serum B-cell activating factor level and proportion of memory and transitional B cells with clinical response after rituximab treatment of bullous pemphigoid patients. *J Invest Dermatol* 2013; **133**:2786-8.

48 Fairley JA, Baum CL, Brandt DS *et al*. Pathogenicity of IgE in autoimmunity: successful treatment of bullous pemphigoid with omalizumab. *J Allergy Clin Immunol* 2009; **123**:704-5.

49 Gual A1, Iranzo P, Mascaró Jr JM. Treatment of bullous pemphigoid with low-dose oral cyclophosphamide: a case series of 20 patients. *J Eur Acad Dermatol Venereol*. 2013;Apr 13. doi: 10.1111/jdv.12155. [Epub ahead of print]

50 Fichel F, Barbe C, Joly P *et al*. Clinical and immunologic factors associated with bullous pemphigoid relapse during the first year of treatment: a multicenter, prospective study. *JAMA Dermatol* 2014; **150**:25-33.

51 Bernard P, Reguiai Z, Tancrède-Bohin E *et al*. Risk factors for relapse in patients with bullous pemphigoid in clinical remission: a multicenter, prospective, cohort study. *Arch Dermatol* 2009; **145**: 537-42.

52 Le Roux-Villet C, Prost-Squarcioni C, Oro S *et al*. Role of the nurse in care of bullous pemphigoid. *Rev Infirm* 2010; **160**:38-40.

53 Bernard P, Bedane C, Prost C *et al*. Centres de référence des maladies bulleuses auto-immunes. Société Française de Dermatologie.[Bullous pemphigoid. Guidelines for the diagnosis and treatment. Centres de référence des maladies bulleuses auto-immunes. Société Française de Dermatologie. *Ann Dermatol Venereol* 2011; **138**:247-51.

Table 1. Diagnostic steps in the evaluation of patients with bullous pemphigoid

Table 2. Bullous pemphigoid: therapeutic ladder

Addendum 1.

Methods

The methodology on which the guidelines is based, is derived from recommendations made by the French Health Agency (HAS) (http://www.has-sante.fr/portail/jcms/c_1340879/fr/protocoles-nationaux-de-diagnostic-et-de-soins-pnds). Two committees - a writing committee and a voting committee - were created. Each committee comprised 8 different experts from different European countries and Israel. None of the experts served in both committees.

In 2012, independent of outside financial support or backing, the voting committee held a 2-day meeting in Frankfurt, the purpose of which was to grade approximately 150 items (from 0 indicating total disagreement to 9 indicating total agreement) relating to key sentences or proposals in the first draft of the guideline compiled by the writing committee. Mean and standard deviation of the 150 items were then calculated. All items graded lower than 7, plus those showing conflicting marks were re-discussed by members of the writing committee and a subsequent second draft was produced. Modified items were then submitted to a second vote by the voting committee to ensure that a mean of higher than 7 had been reached. The draft was emailed to members of the writing committee. Only minor modifications were allowed at this stage. C.F. and L.B. were responsible for collecting and incorporating them into the final text.

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 • Recent drug intake (over 1 to 6 months) • Refractory itch of unknown cause in elderly	• Classical bullous form: symmetric distribution of vesicles and bullae 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, localised bullae, erosions, eczematous and urticarial lesions, dyshidrosiform (acral)	• Extension of BP (by BPDAI or daily blister count) • General condition and co-morbidities • Laboratory examinations and work-up according to patient's condition and therapy choice
LABORATORY INVESTIGATIONS		
HISTOPATHOLOGY (of a recent intact bulla if present)	**DIF** (perilesional skin)	**IMMUNE SEROLOGICAL TESTS**
• Subepidermal bullae containing eosinophils and/or neutrophils • Dermal infiltrate of eosinophils and/or neutrophils • Marginalisation 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)**	**IMMUNOHISTO-CHEMISTRY**
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 patients linear deposits of C3d and C4d along the basement membrane zone can be demonstrated using the same tissue sample obtained for light microscopy studies

Table 2. Bullous pemphigoid - Therapeutic ladder

Localised/limited disease with mild activity	
1st choice	2nd choice
• Superpotent topical corticosteroids: - In localised 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)
Generalised disease	
1st choice	2nd choice
• Superpotent topical corticosteroids on whole body sparing the face (1, validated) • Oral corticosteroids (1, validated for prednisone)	<u>Combination with or introduction of:</u> • Tetracycline + nicotinamide (2, non-validated) • Azathioprine (1, non-validated) • Mycophenolate (1, non-validated) • Methotrexate (3, non-validated) • Chlorambucil (3, non-validated)
3rd choice	
<u>Combination with and/or introduction of:</u> • 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)	

Key to evidence-based support: (1) Randomised 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) Randomised prospective single centre study (in case of poor methodological quality), retrospective multi-centre study; (3) Case series, retrospective single-center study; (4)Anecdotal case reports; (5) Expert opinion.

(

Conflicts of interests

Pemphigoid. S2 Guidelines for diagnosis and treatment

The Work Under Consideration for Publication					
		Claudio Feliciani	**Pascal Joly**	**Marcel F. Jonkman**	**Detlef Zillikens**
1	Grant	No	No		Euroimmun Inc. Miltenyi Inc. Fresenius Inc. Biostest Inc. Dompé Inc.
2	Consulting fee or honorarium	No	No	Roche, Genetech	No
3	Support for travel to meetings for the study or other purposes	No	No	No	No
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	No	No	No	No
5	Payment for writing or reviewing the manuscript	No	No	No	No
6	Provision of writing assistance, medicines, equipment, or administrative support	No	No	No	No
7	Other	No	Roche provides Rituximab for a study which I am conducting	No	No

* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	No	Novartis Abbott Janssen	No	No
2	Consultancy	No	No	Glaxo Smith Kline, Stiefel	No
3	Employment	No	No	No	No
4	Expert testimony	No	No	No	No
5	Grants/grants pending	No	No	No	No
6	Payment for lectures including service on speakers bureaus	No	No	Abbvie	No
7	Payment for manuscript preparation	No	No	No	No
8	Patents (planned,	No	No	No	Euroimmun Inc.

	pending or issued)				
9	Royalties	No	No	No	No
10	Payment for development of educational presentations	No	No	No	No
11	Stock/stock options	No	No	No	No
12	Travel/accommodations/meeting expenses unrelated to activities listed**	No	No	No	Fresenius Inc. Miltenyi Inc. Abbott Inc. Roche Pharma Inc. UCB Inc.
13	Other (err on the side of full disclosure)	No	No	No	No

* This means money that your institution received for your efforts.
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Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	No	No	No	No

Conflicts of interests

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The Work Under Consideration for Publication					
		Giovanna Zambruno	**Dimitrios Ioannides**	**Cezary Kowalewski**	**Hana Jedlickova**
1	Grant	No	No	No	Clinical trial sponsored by Euroimmun
2	Consulting fee or honorarium	No	No	No	No
3	Support for travel to meetings for the study or other purposes	No	No	No	No
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	No	No	No	No
5	Payment for writing or reviewing the manuscript	No	No	No	No
6	Provision of writing assistance, medicines, equipment, or administrative support	No	No	No	No
7	Other	No	No	No	No

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Relevant financial activities outside the submitted work					
1	Board membership	No	No	No	No
2	Consultancy	No	No	No	No
3	Employment	No	No	No	No
4	Expert testimony	No	No	No	No
5	Grants/grants pending	Dompé S.p.A. research grant “Possible role of IL-8 in pemphigus pathogenesis” (2011-2013)	No	No	No
6	Payment for lectures including service on speakers bureaus	No	No	No	No
7	Payment for manuscript preparation	No	No	No	No
8	Patents (planned, pending or issued)	No	No	No	No
9	Royalties	No	No	No	No
10	Payment for development of	No	No	No	No

	educational presentations				
11	Stock/stock options	No	No	No	No
12	Travel/accommodations/meeting expenses unrelated to activities listed**	No	No	No	No
13	Other (err on the side of full disclosure)	No	No	No	No

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Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	No	No	No	No

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The Work Under Consideration for Publication					
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1	Grant	No	No	No	No
2	Consulting fee or honorarium	No	No	No	No
3	Support for travel to meetings for the study or other purposes	No	No	No	No
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	No	No	No	No
5	Payment for writing or reviewing the manuscript	No	No	No	No
6	Provision of writing assistance, medicines, equipment, or administrative support	No	No	No	No
7	Other	No	No	No	No

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Relevant financial activities outside the submitted work					
1	Board membership	No	No	No	No
2	Consultancy	No	No	No	No
3	Employment	Semnmelweis University	No	No	No
4	Expert testimony	No	No	No	No
5	Grants/grants pending	OTKA	No	No	No
6	Payment for lectures including service on speakers bureaus	Peter Pazmany Catholic University	No	No	No
7	Payment for manuscript preparation	No	No	No	No
8	Patents (planned, pending or issued)	No	No	No	No
9	Royalties	No	No	No	No
10	Payment for development of educational presentations	Peter Pazmany Catholic University	No	No	No
11	Stock/stock options	No	No	No	No
12	Travel/accommodations/meeting expenses unrelated	Support for annual EADV meeting travel/	No	No	No

	to activities listed**	accommodation 2013 by EGIS			
13	Other (err on the side of full disclosure)	No	No	No	No

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Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	No	No	No	No

Conflicts of interests

Pemphigoid. S2 Guidelines for diagnosis and treatment

The Work Under Consideration for Publication					
		Savas Yayli	**Michael Hertl**	**Luca Borradori**	
1	Grant	No	No	No	
2	Consulting fee or honorarium	No	No	No	
3	Support for travel to meetings for the study or other purposes	No	No	No	
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	No	No	No	
5	Payment for writing or reviewing the manuscript	No	No	No	
6	Provision of writing assistance, medicines, equipment, or administrative support	No	No	No	
7	Other	No	No	No	

* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	No	Biogen Idec, Roche AG	No	
2	Consultancy	No	UCB Pharma	No	
3	Employment	No	No	Government	
4	Expert testimony	No	No	No	
5	Grants/grants pending	No	Fresenius Comp., Biogen Idec, MBL Corp.	No	
6	Payment for lectures including service on speakers bureaus	No	Biogen Idec, MEDAC Comp., MSD Pharma, Biotest Comp., Dermapharm	No	
7	Payment for manuscript preparation	No	No	No	
8	Patents (planned, pending or issued)	No	No	No	
9	Royalties	No	No	No	
10	Payment for development of educational	No	No	No	

	presentations				
11	Stock/stock options	No	No	No	
12	Travel/accommodations/meeting expenses unrelated to activities listed**	No	Astellas Pharma, Janssen Cilag	No	
13	Other (err on the side of full disclosure)	No	No	No	

* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	No	Co-sponsoring of ongoing clinical trial “Efficacy of immunoadsorption in pemphigus” by German Research Council and Fresenius Company	No	