European Dermatology Forum

Guideline on the Diagnosis and Treatment of Autoimmune Bullous Diseases - Pemphigus

Developed by the Guideline Subcommittee “Autoimmune Bullous Diseases” of the **European Dermatology Forum**

Subcommittee Members:
Prof. Dr. Michael Hertl, Marburg (Germany)
Prof. Dr. Hana Jedlickova, Brno (Czech Republic)
Prof. Dr. Sarolta Karpati, Budapest (Hungary)
Prof. Dr. Branka Marinovic, Zagreb (Croatia)
Prof. Dr. Soner Uzun, Antalya (Turkey)
Prof. Dr. Savas Yayli, Trabzon (Turkey)
Dr. Daniel Mimouni, Tel Aviv (Israel)
Prof. Dr. Luca Borradori, Bern (Switzerland)
Prof. Dr. Claudio Feliciani, Rome (Italy)
Prof. Dr. Dimitrios Ioannides, Thessaloniki (Greece)
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Dr. Giovanna Zambruno, Rome (Italy)
Prof. Dr. Detlef Zillikens, Lübeck (Germany)
Dr. Marcel F. Jonkman, Groningen (Netherlands)

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Prof. Dr. Torsten Zuberbier, Berlin (Germany)

Chairman of EDF Guideline Committee:
PD Dr. Alexander Nast, Berlin (Germany)

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EDF Guidelines Secretariat to PD Dr. Nast:
Bettina Schulze, Klinik für Dermatologie, Venerologie und Allergologie, Campus Charité Mitte,
Charité – Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany
phone: ++49 30 450 518 062, fax: ++49 30 450 518 911, e-mail: bettina.schulze@charité.de

Conflicts of interests

Pemphigus. S2 Guideline for diagnosis and treatment

The Work Under Consideration for Publication					
		Claudio Feliciani	**Dimitrios Ioannides**	**Pascal Joly**	**Cezary Kowalewski**
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		Soner Uzun	**Savas Yayli**	**Daniel Mimouni**	**Luca Borradori**
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The Work Under Consideration for Publication					
		Michael Hertl	**Hana Jedlickova**	**Sarolta Karpati**	**Branka Marinovic**
1	Grant	No	No	No	No
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		Giovanna Zambruno	**Detlef Zillikens**	**Marcel F. Jonkman**	
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DEVELOPMENT OF EUROPEAN GUIDELINES AUTOIMMUNE BULLOUS DISEASES

GUIDED BY THE EUROPEAN DERMATOLOGY FORUM (EDF) IN COOPERATION WITH EUROPEAN ACADEMY OF DERMATOLOGY AND VENEROLOGY (EADV)

Pemphigus. S2 Guideline for diagnosis and treatment

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Michael Hertl[1], Hana Jedlickova[2], Sarolta Karpati[3], Branka Marinovic[4], Soner Uzun[5], Savas Yayli[6], Daniel Mimouni[7], Luca Borradori[8], Claudio Feliciani[9], Dimitrios Ioannides[10], Pascal Joly[11], Cezary Kowalewski[12], Giovanna Zambruno[13], Detlef Zillikens[14], Marcel F. Jonkman[15]

Departments of Dermatology, [1]Philipps-University Marburg, Germany; [2]Masaryk University, Brno, Czech Republic; [3]Semmelweis University Budapest, Hungary; [4]School of Medicine University of Zagreb, Croatia; [5]Akdeniz University, Antalya, Turkey; [6]Karadeniz Technical University, Trabzon, Turkey; [7]Tel-Aviv University, Israel; [8]University of Bern, Inselspital, Switzerland; [9]Università Cattolica del Sacro Cuore, Rome, Italy; [10]Aristotle University of Thessaloniki, Greece; [11]Rouen University Hospital, France; [12]Medical University of Warsaw, Poland; [13]L'Istituto Dermopatico dell'Immacolata, Rome, Italy; [14]University of Lübeck, Germany; [15]University of Groningen, The Netherlands

CONTENTS

1 INTRODUCTION

Pemphigus encompasses a group of life-threatening autoimmune bullous diseases characterized by flaccid blisters and erosions of the mucous membranes and skin [1-3]. The severity of the disease is based on its progressive course which is accompanied by an increased body catabolism with loss of body fluids and proteins and secondary bacterial and viral infections which may lead to sepsis and cardiac failure. Before the advent of systemic corticosteroids, the prognosis of pemphigus was almost fatal within two years after making the diagnosis. Pathophysiologically, the underlying intraepithelial blister formation is caused by IgG autoantibodies against the desmosomal adhesion proteins, desmoglein 3 and/or desmoglein 1, on epidermal keratinocytes [4]. Pemphigus is rare and its incidence has been estimated to about 2 new patients per 1 million inhabitants per year in Central Europe. Two main clinical variants are known, pemphigus vulgaris (PV) and pemphigus foliaceus (PF). The pathogenic role of anti-desmoglein 1/3 IgG has been clearly established since the injection of patients' sera or affinity-purified IgG from pemphigus sera into neonatal mice reproduces immune pathologically and clinically the cardinal symptoms of pemphigus within 24 hours [5]. In most patients, disease activity is closely correlated with serum levels of desmoglein-reactive autoantibodies. Due to its rarity, only few prospective controlled clinical trials are available in pemphigus which are limited by the low numbers of patients studied and the lack of statistically significant differences in many studies. A few studies compared different doses of prednisolone, i.v. corticosteroid pulses versus placebo, azathioprine versus mycophenolate mofetil, and the use of adjuvant treatment with methotrexate, cyclosporine, cyclosphosphamide, and high-dose intravenous immunoglobulins [6,7]. The combination of systemic corticosteroids (prednisolone, 1.0-1.5 mg/kg/d) and corticosteroid-sparing immunosuppressive drugs, mostly azathioprine and mycophenolate mofetil, is regarded as standard first-line therapy by most dermatologists.

However, no internationally accepted treatment guidelines exist [8] despite efforts to provide national guidelines in several European countries such as in France [9] and United Kingdom [10]. For this reason, a group of European dermatologists with a longstanding interest and expertise in basic and clinical pemphigus research has sought to define diagnostic and therapeutic guidelines for the management of patients with pemphigus.

1.1 METHODOLOGY OF GUIDELINE PREPARATION

To facilitate this process in the present pemphigus guideline, a working group of European dermatologists followed a strategy which had been previously used by a group of French dermatologists (French guidelines). In a first step, a group of experts (**working group**) wrote the first version of the guidelines which was based on a recently established French guideline for the management of pemphigus [9]. Thereafter, a second group of experts (**notation group**) gave marks (ranging from 0 to 9 according to the increasing degree of consensus) to each of the statements of the first version of the guidelines. This process identified the statements of major agreement or disagreement. Based on the marks of the **notation group**, the **working group** then prepared a second version of the guideline which led to a consensus in all the remaining critical statements. The revised version of the pemphigus guideline was finally passed to the European Dermatology Forum (EDF) for a final consensus of the EDF members.

2 INITIAL EVALUATION OF PEMPHIGUS

The initial clinical examination should seek basic evidence for the diagnosis of pemphigus, as well as screening for co-morbidities.

2.1 MAJOR OBJECTIVES

- To confirm the clinical diagnosis of pemphigus
- To search for risk factors, severity factors and potential co-morbidities based on history and initial clinical evaluation
- To specify the type of initial involvement (skin, mucosa) and its extent
- To evaluate the prognosis depending on the age of the patient, and general condition (Karnofsky score)
- To measure extent and distribution of the lesions by autoimmune Bullous Skin Intensity and Severity Score (ABSIS) or Pemphigus Disease and Area Index (PDAI) (both optional)
- To start treatment

2.2 PROFESSIONS INVOLVED

The treatment plan for patients with pemphigus is the responsibility of an experienced dermatologist, usually a hospital-based dermatologist in a tertiary referral centre, a specialized centre or a member of a network.

Other health professionals who may have supportive functions are:

- The consultant dermatologist in general practice
- The patient's general practitioner
- All other specialists whose expertise is necessary, based on general clinical condition, co-morbidities, such as internists, cardiologists, stomatologists, ophthalmologists, otorhinolaryngologists, gastroenterologists, gynaecologists, urologists, proctologists, rheumatologists, oncologists, and psychologists
- Health nurses in selected cases in which home care is required and applicable, e.g. elderly or disabled patients with residual mucosal or skin lesions following hospitalization
- Dietician, physiotherapist
- Nurse specialist/practitioner

2.3 CLINICAL EXAMINATION

2.3.1 Medical History

- It should specify the time of first onset of symptoms.
- It should specify functional symptoms, i.e. pain, pruritus, intensity of dysphagia, ocular and ENT symptoms, dysuria, anogenital problems and weight loss.
- It should include a haematological, oncologic, endocrine, cardiovascular and infectious medical history to search for risk factors of oral corticosteroid treatment and evolving complications of immunosuppressive therapy.
- It should evaluate anticipated pregnancy, actively practiced contraception (especially if immunosuppressive treatment is being considered).
- It should search for recent drug intake which may potentially induce pemphigus, such as D-penicillamine, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, cephalosporins, phenylbutazone, pyritinol, thiopronine.
- It should assess the psychological tolerance of potential side effects due to treatment, especially corticosteroids.
- It should seek to evaluate the disease impact on quality of life.

2.3.2 Physical Examination

2.3.2.1 General

It should assess the extent of skin lesions and all mucous membranes, the degree of mucosal damage, and functional impairment (dysphagia, dysphonia, weight loss, impairment of vision, dyspareunia).

It should also assess the patient's general condition and co-morbidities:

- Body weight,
- Arterial blood pressure,
- General condition (Karnofsky index), co-morbidities (neoplastic, cardiovascular, musculoskeletal, diabetes etc.),
- Direct Nikolsky’s sign (type I) in normal appearing skin for monitoring of disease activity: ability to split the epidermis on skin areas distant from the lesions by a lateral pressure with a finger,
- Marginal Nikolsky's sign (type II) in perilesional skin for diagnosis: ability to split the epidermis of the skin far beyond the preexisting erosion, extending to a great distance on

the normal-appearing skin, by pulling the remnant of a ruptured blister or rubbing at the periphery of existing lesions.

2.3.2.2 Pemphigus vulgaris (PV)

- Usually begins by with oral mucosal lesions: buccal and/or gingival painful, persisting erosions which interfere with eating. Less common are non-cicatricial ocular lesions, nasal, laryngeal, oesophageal and rectal erosions are also possible.
- Cutaneous involvement (which may appear several weeks or months after the first appearance of mucosal lesions) presents flaccid bullae with clear content, present on non-erythematous skin quickly transforming into post-bullous erosions.
- The lesions may be localized or generalized and predominate at seborrheic areas (chest, face, scalp, interscapular region) and mechanically stressed regions as well as on the extremities.
- The disease is usually not associated with major pruritus.
- Fingernail involvement is possible.

2.3.2.2.1 Pemphigus vegetans

Pemphigus vegetans is a rare but distinct clinical form of PV characterized by verruciform and papillomatous vegetating and/or pustular lesions of the periorificial regions or, more commonly, involving the large folds.

It may present in two forms:

- Neumann type pemphigus vegetans is characterized by periorificial papillomas and
- Hallopeau type pemphigus vegetans by pustular lesions, predominantly involving the large folds.

2.3.2.3 Pemphigus foliaceus (PF)

Including rare pemphigus erythematosus.

- Cutaneous involvement: transient, flaccid bullae or puff pastry-like exfoliation transforming into crusty erosions in seborrheic skin areas (chest, scalp, face, interscapular region).
- More extensive cutaneous involvement in sporadic and endemic pemphigus foliaceus ("Fogo Selvagem", Brazilian pemphigus, Tunisian pemphigus).
- Generally, no mucosal involvement.

2.3.2.4 Paraneoplastic pemphigus (PNP)/paraneoplastic autoimmune syndrome (PAMS)

To be suspected in the context of concomitant malignancy, particularly non-Hodgkin's lymphoma, chronic lymphocytic leukemia, thymoma or Castleman's disease. In up to one third of cases, the underlying malignancy has not been diagnosed at the time of diagnosis. Moreover, the symptoms of PNP/PAMS can preceed the malignancy.

- Mucosal involvement: initially limited cheilitis and/or ulcerative stomatitis, persisting painful erosions which lead to severe dysphagia. Cicatricial conjunctivitis, keratitis and genital involvement is common. Possible pharyngeal involvement, as well as involvement of the nasal cavity and oesophagus can lead to phagodynia and gastroesophageal reflux.
- Cutaneous polymorphic involvement with symptoms resembling mild lichen planus-like to graft versus host disease-like, erythema multiforme-like, bullous pemphigoid-like, or pemphigus vulgaris-like eruption. Palmar involvement is common.
- Pulmonary involvement (alveolitis, bronchiolitis obliterans, pulmonary fibrosis) is a characteristic and life threatening complication.

2.3.2.5 IgA-pemphigus

- Two clinical variants: subcorneal pustular dermatosis type (SPD) and intra-epidermal neutrophilic type (IEN).
- Cutaneous involvement: pustules on erythematous plaques on extremities (SPD) or pustules in sunflower arrangement on the trunk (IEN).

2.4 LABORATORY INVESTIGATIONS (SUMMARIZED IN TABLE 1)

Confirm the clinical diagnosis of pemphigus.

The diagnosis of pemphigus is based on four criteria:

1) Clinical presentation (see 2.3)
2) Histopathology
3) Direct immunofluorescence microscopy (DIF) of perilesional skin
4) Serological detection of serum autoantibodies against epithelial cell surface by indirect immunofluorescence microscopy (IIF) and/or enzyme-linked immunosorbent assay (ELISA).

2.4.1 Histopathology

Preferentially, a 4 mm- punch excision should be taken of a fresh (<24 h) small vesicle or 1/3 of the peripheral portion of a blister and 2/3 perilesional skin (placed in 4% formalin solution) for routine histopathological analysis: intraepidermal suprabasal acantholysis in PV and PNP, or acantholysis at the granular layer in PF.

2.4.2 Direct immunofluorescence microscopy (DIF)

Skin biopsy of perilesional skin (up to 1 cm from a fresh lesion), put into a cryotube for transportation in a cylinder of liquid nitrogen, or in saline (delivery <36 h) or Michel's fixative for DIF analysis:

- DIF: IgG and/or C3 deposits at the ICS of epidermal keratinocytes.
- The epithelial cell surface staining for in vivo IgG depositions is normally granular in DIF, and not smooth such as in IIF.
- IgA deposits with an epithelial cell surface pattern in addition to IgG may be present in a minority of cases. When only IgA is found, the diagnosis of IgA pemphigus is established.
- Epithelial cell surface deposits can sometimes be associated with linear deposits of IgG or C3 along the dermal-epidermal junction, suggestive of PNP/PAMS or pemphigus erythematosus, or the coexistence of pemphigus and pemphigoid.
- In specialized laboratories, plugged hairs can be utilized for DIF for the diagnosis of pemphigus.

2.4.3 Immune serological tests

In addition to DIF, IIF and additional techniques with defined native or recombinant proteins are commonly used to detect serum autoantibodies in patients with pemphigus.

2.4.3.1 Indirect immunofluorescence microscopy (IIF)

- IIF test on monkey oesophagus or human skin to search for autoantibodies against proteins of epidermal keratinocytes.
- The epithelial cell surface pattern by IIF on substrates is smooth and reticular, which is also referred to as “chicken wire”, “honeycomb”, or "fishnet-like" pattern.

2.4.3.2 ELISA

- Detection of anti-desmoglein 1 (Dsg1) (PF/cutaneous PV) and/or anti-desmoglein 3 (Dsg3) IgG autoantibodies (mucosal PV) by ELISA (commercial kits are available).
- The detection of IgG autoantibodies by ELISA is positive in more than 90% of cases.
- In general, the ELISA index correlates with t
- he extent and/or activity of disease (see remark above and prognostic value for relapse, helping to guide treatment). Large prospective cohort studies are however missing in this context to provide reliable data about predictive value.
- In case of atypical presentation or the suspicion of an unrelated autoimmune bullous

disorder, additional immunopathological tests may be performed, such as IIF on rat bladder and immunoblot/immunoprecipitation.

- IIF on rat bladder (in suspected cases of PNP/PAMS with extracts of epidermal keratinocytes) is highly specific but less sensitive.

2.4.3.3 Immunoblot and immunoprecipitation

Diagnosis of PNP/PAMS: immunoblot and immunoprecipitation with keratinocyte extracts will reveal evidence of serum IgG/IgA autoantibodies against:

- Envoplakin (210 kDa) and periplakin (190 kDa), commercial ELISA now availabe.
- Desmoglein 3 (130 kDa), desmoglein 1 (160 kDa), desmocollins, desmoplakins I and II, BP180/BPAG2, BP230/BPAG1, plectin (500 kDa), and alpha-2-macroglobulin-like-1 (A2ML-1, 170 kDa).

IgG antibodies against envoplakin and periplakin and/or A2ML1 confirm the clinical diagnosis of PNP/PAMS. IgG against desmoplakins I and II, BP230/BPAG1 and plectin may be present in other forms of pemphigus.

Combining two of three serological techniques (IIF on rat bladder, immunoblot and immunoprecipitation) is sufficient for making the diagnosis of PNP/PAMS (sensitivity almost 100%).

2.4.4 Work-up before corticosteroid or immunosuppressive therapy

- Complete blood count;
- Creatinine, blood electrolytes;
- Transaminases, gamma GT, alkaline phosphatase;
- Total serum protein, albumin;
- Fasting serum glucose;
- Hepatitis B, C and HIV;
- Chest X-ray.

Recommended, on indication or optional:

- Serum IgA deficiency should be ruled out prior to IVIG treatment;
- Thiopurine methyltransferase (TPMT) activity, when azathioprine is considered;
- Abdominal sonography is optional;
- Quantiferone or PPD is recommended in case of elevated risk for TB;
- G6PD serum activity, bilirubine, reticulocytes if dapsone is considered;
- ß HCG to exclude pregnancy in females of childbearing age;

- Osteodensitometry is recommended prior to glucocorticoid treatment;
- Ocular examination (glaucoma, cataract) is recommended.

3 THERAPEUTIC MANAGEMENT

3.1 OBJECTIVES

Control and healing of the bullous skin and/or mucous lesions is the primary objective as well as attempting to minimize, as much as possible, serious side effects of treatment.

The treatment aims are:

- Healing of the bullous eruption and disappearance of the functional impairment associated with the disease;
- Prevent/strictly limit the appearance of recurrences;
- Improve the quality of life of the patients;
- Limit common side-effects usually associated with long-term immunosuppressive or corticosteroid treatment.

3.2 PROFESSIONALS INVOLVED

- The initial management, diagnosis and treatment of extensive manifestations of the disease usually requires hospitalization in a dermatology department.
- This is continued until clinical control of the bullous eruption is achieved.
- In limited forms of pemphigus, additional diagnostic examinations and clinical monitoring can be either performed in an inpatient or outpatient setting.
- Overall management is coordinated by the dermatologist in liaison with the referring dermatologist, the general physician and other medical specialists and hospital doctors from the centre of reference and/or geographical area (if a reference centre exists in the particular country).
- Specialists and health professionals involved are identical to those listed in the initial evaluation (see §2.2).
- Exceptionally, the disease can occur during childhood, and children should be supported by a multidisciplinary team, jointly by a reference centre, a paediatric dermatology department or a paediatrician.

3.3 THERAPEUTIC MANAGEMENT (SUMMARIZED IN TABLE 2)

3.3.1 First-line treatment

- Systemic corticosteroid therapy (predniso(lo)ne at 0.5 mg to 1.5 mg/kg/day).
- Control of PF generally requires lower doses than PV.
- If initial control of PV is not reached within 2 weeks, a higher predniso(lo)ne dose (up to 2 mg/kg) is optional.

Systemic corticosteroids can be combined with an immunosuppressive adjuvant at the start of therapy, particularly in cases of increased risk of corticosteroid therapy, complications due to expected prolonged use (> 4 months) or dose dependency above minimal therapy (> 10 mg/day). However, there is only fair evidence that addition of adjuvants is superior to treatment with glucorticoids alone.

Intravenous corticosteroid pulses do not appear to have additional benefit on top of conventional first line treatment with oral predniso(lo)ne and immunosuppressive adjuvants [11].

3.3.2 Immunosuppressive adjuvants

Based on the current evidence, adjuvants have only a steroid-sparing effect, and may lead to steroid-free remission [7,12-16].

3.3.2.1 First line adjuvants

- Azathioprine (1-3 mg/kg/day). Start first week 50 mg /day to detect idiosyncratic reactions (and in case stop immediately), and then raise to desired dose. Check TPMT activity before treatment [17].
- Mycophenolate mofetil (2g/day) or mycophenolic acid (1440 mg/day). Consider to raise daily dose by 1 capsule per week for better gastrointestinal tolerance.

3.3.2.2 Second line adjuvants

- Anti-CD20 monoclonal antibody, such as rituximab 2 x 1g i.v. (2 weeks apart) or 4x375 mg/m^2 (each 1 week apart) [18-21].
- Intravenous immunoglobulins (IVIG, 2g/kg/month) [22].
- Immunoadsorption (2 cycles à 4 days, 4 weeks apart) [18,23,24].

- Cyclophosphamide (500 mg as i.v. bolus or given orally at 2 mg/kg/day) [25,26].
- Methotrexate (10-20 mg/week) [27].
- Dapsone 100 mg/day or up to ≤ 1.5 mg/kg/day [28].

3.3.3 Additional supportive treatment

- Intralesional injections of corticosteroids (triamcinolone acetonide) may be beneficial for isolated lesions of oral mucosa, lips, and skin.
- Topical treatment with potent corticosteroids (clobetasol propionate) or calcineurin inhibitors applied directly to the lesions, and oral typical corticosteriods (such as triamcinolone acetonide gel) directly to oropharyngeal erosions for use in combination with systemic therapy, may be beneficial [29,30].
- The use of baths containing antiseptics such as chlorhexidine is recommended.
- If there are erosive lesions, they may be covered by using different low adhesive wound dressings or local emollients, and compresses.
- Analgesics (paracetamol, metamizol, and opioids) may be necessary.
- Gels containing local anesthetics may be used for application at the mucosal surfaces.
- Proper dental care is required.
- Nutritional management with the help of a dietician or a nutritionist if malnutrition is related to oral involvement or systemic corticosteroid therapy.

3.3.3.1 Measures in prolonged corticosteroid therapy

- Osteoporosis baseline screening and prophylaxis.
- Vitamin D and calcium supplementation is mandatory.
- Ophthalmologic evaluation.
- Oral topical antifungals recommended for prophylaxis of oro-intestinal conditions.
- Systemic antifungals, antiviral, and antibiotic treatment should be used when clinically indicated.
- H2-blockers or proton pump inhibitors are recommended to prevent gastric/duodenal ulcers.
- Anti-thrombotic prophylaxis in case of high risk of thrombosis.
- Psychological support if required.
- Physiotherapy is often necessary if prolonged corticosteroid therapy is required.

3.3.3.2 Vaccinations

Adjuvant immunosuppressants and rituximab contraindicate the use of live vaccines.

It is recommended that patients receiving oral corticosteroids or immunosuppressive therapy may be vaccinated against seasonal influenza, H1N1, tetanus, and pneumococci. The level of protection is questionable during systemic immunosuppression.

4 MONITORING

Pemphigus often shows a chronic (relapsing) course which requires close monitoring of clinical symptoms and of potential side effects inherent to chronic immunosuppressive treatment. Thus, a multidisciplinary approach is commonly required.

4.1 OBJECTIVES

- To evaluate the efficacy and safety of treatment.
- To plan the gradual reduction of immunosuppressive treatment, and the duration of maintenance therapy or its discontinuation.

4.1.1 Definitions for disease outcome parameters [31]

- *Control of disease activity*: The time at which new lesions cease to form and established lesions begin to heal.
- *End of consolidation phase*: The time at which no new lesions have developed for a minimum of 2 weeks, approximately 80% of lesions have healed, and when most clinicians start to taper steroids.
- *Complete remission on therapy*: A *complete remission on therapy* is defined as the absence of new or established lesions while the patient is receiving minimal therapy.
- *Complete remission off therapy*: A *complete remission off therapy* is defined as the absence of new and/or established lesions while the patient is off all systemic therapy for at least two months.
- *Relapse/flare*: Appearance of ≥3/month new lesions/mo that do not heal spontaneously within 1 week, or by the extension of established lesions, in a patient who has achieved disease control.
- *Minimal therapy*: Prednisolone (or the equivalent) at ≤10 mg/day and/or minimal adjuvant therapy for at least 2 months.

4.1.2 Approach to be maintained after consolidation phase

- The evolution is usually slowly favourable, often requiring a period of 1 to 3 months for complete healing of lesions.

- Progressive reduction of oral corticosteroid treatment: start taper steroids as early as disease control is reached, or up to the end of consolidation phase.
- Taper predniso(lo)ne by 25% reduction in bi-weekly steps (at <20mg more slowly!).
- If reappearance of <3 lesions during tapering of oral corticosteroid therapy occurs, go back to last dose.
- At relapse, re-increase oral corticosteroid therapy, and go two steps back in previous dose until control of the lesions is achieved within two weeks, then resume gradual decrease of systemic corticosteroids. If disease control is not reached go back to initial dose.
- If oral corticosteroids are given alone: add an immunosuppressant (especially in case of early stage relapse occurring despite continued high dose corticosteroid treatment).
- If oral corticosteroids are already combined with an immunosuppressant: discuss a change in first line immunosuppressant or the use of a second line immunosuppressant including immunoadsorption, IVIG or rituximab.
- The extent of immunosuppressive therapy increases the risk of side-effects.
- The persistence of high levels of anti-Dsg1 by ELISA has a positive predictive value for skin relapses, while the persistence of anti-Dsg3 IgG does not necessarily indicate a mucosal relapse.

4.1.2.1 Immunoadsorption

Immunoadsorption is an option in patients who have not sufficiently responded to first line treatment, i.e. glucocorticoids in combination with azathioprine or mycophenolate. Immunoadsorption is considered most effective in combination with systemic immunosuppresive drugs [18,23,24].

- Generally, four treatments of immunoadsorption are performed on four consecutive days (2.5-fold plasma volume/day).
- Treatment is repeated in four-week intervals.
- Immunoadsorption reduces serum IgG concentration against Dsg1 and Dsg3 by 80%.
- Contraindications include severe systemic infections, severe cardiovascular diseases, hypersensitivity against components of the immunoadsorption column, treatment with angiotensin converting enzyme inhibitors, and extensive hemorrhagic diathesis.

4.1.2.2 Anti-CD20 monoclonal antibody (Rituximab)

Rituximab is indicated in patients who remain dependent on more than 10 mg predniso(lo)ne combined with an immunosuppressive adjuvant [18-21].

- A course of intravenous rituximab 2 x 1000 mg (2 weeks apart or 4 x 375 m^2/1 week apart.

The need for immunosuppressive adjuvants in rituximab therapy is unclear.

- Treatment can be repeated with single infusion of 500 mg rituximab in case of clinical relapse or as early as 6 months after treatment [32].
- Commonly, clinical relapses occur not before the second year after treatment initiation.
- Rituximab can be combined with short term (< 4 mo) systemic corticosteroids and long term (>12 mo) immunosuppressive treatment.
- The incidence of unforeseen fatal infections such as progressive multifocal leukoencephalopathy (PML) cannot be estimated due to the rarity of pemphigus.

4.1.2.3 Management of IVIG treatment

A course of IVIG treatment (2 g/kg/cycle) is applied i.v. over 2-5 consecutive days (monthly) [22].

- Treatment is generally combined with systemic corticosteroids (initially) and immunosuppressive adjuvants.
- Treatment should be performed over several days to avoid headache and nausea.
- Aseptic meningitis is a rare but meaningful side effect of IVIG treatment which needs to be kept in mind in patients who commonly experience episodes of migraine.
- Even though rare, complete IgA deficiency is a contraindication for IVIG treatment.

4.2 SCHEDULING AND CONTENT OF CONSULTATIONS

Evaluation of the efficacy of treatment is primarily based on clinical symptoms.

The frequency of disease management (physical exam, additional exams) must be adapted:

- to the patient's clinical condition;
- to the severity and disease course during treatment;
- to the therapeutics used (monitoring, tolerance, side effects).
- There are two clinical scores, ABSIS and PDAI, which are currently being tried on research base for their usefulness as clinical outcome parameters for the evaluation of the extent and activity of pemphigus.
- Initially, follow-up visits should be offered on a two-weekly basis until clinical disease control is achieved.
- Then, for the next 3 months, monthly clinical follow-ups are recommended, and in the consolidation phase, patients should be seen on a monthly or bi-monthly basis.

4.2.1 Clinical Examination

The clinical follow-up is identical to that carried out during the initial assessment, it should seek to clarify:

- if the disease is clinically controlled (mucosal, mucocutaneous or cutaneous lesions);
- if adverse effects related to treatment are present or absent;
- diabetes, high blood pressure, cardiac insufficiency (corticosteroids);
- respiratory disorders, anaemia, hepatitis (dapsone, methotrexate);
- infections, notably respiratory, hepatitis (corticosteroids, immunosuppressants);
- mental disorders (corticosteroids);
- myopathy, osteoporosis, avascular bone necrosis, glaucoma, cataract (glucocorticoids);
- haematological abnormalities (leukopenia), (immunosuppressants).

4.2.1.1 Serological monitoring of disease activity

Determination of serum autoantibodies at the initiation of treatment, after 3 months, and every 3 to 6 months based on the evolution, or in case of relapse by:

- ELISA: anti-Dsg1 and/or Dsg3 IgG.
- If ELISA is not available: IIF microscopy utilizing monkey oesophagus.

4.3 DISCONTINUATION OF TREATMENT

- Discontinuation of treatment is primarily based on the clinical symptoms but may be also supported by the findings of Dsg ELISA and/or IIF. In some clinical departments, negative direct IF microscopy of a skin biopsy is a prerequisite of termination of treatment.
- Discontinuation of systemic corticosteroids may be proposed in patients in complete remission on minimal therapy (prednisolone or equivalent at ≤10 mg/day). The adjuvants may be stopped 6-12 months after achieving complete remission on therapy.

4.4 POSSIBLE SEQUELAE

Pemphigus may cause permanent sequelae due to the involvement of skin, conjunctivae, oral, pharyngeal, laryngeal, oesophageal, anogenital, and anal mucosa but also due to side effects of treatment, justifying request for recognition or help from departmental disability centres.

5 INFORMATION FOR PATIENTS

Patients and their families must be informed about the disease, its clinical course and prognosis, treatment, relapse signs, possible adverse events associated with treatment.

- Patients should be informed about the existence of patients' self support groups.
- The purpose of these associations is to promote knowledge about the disease, provide comfort and share the experience of patients regarding daily life, and to provide information dissemination. It may contribute to a better overall management of the disease by promoting cooperation between patients, patient associations and health professionals. Patients are also informed about referral centres.
- Patients should be alerted to potential triggers such as drugs, operations, radiation, and physical trauma.
- There is insufficient evidence to give dietetic restrictions.

5.1 LIST OF PEMPHIGUS SUPPORT GROUPS

- International Pemphigus and Pemphigoid Foundation
  www.pemphigus.org
- Pemphigus-Pemphigoid-France
  www.pemphigus.asso.fr
- Pemphigus Vulgaris Network
  www.pemphigus.org.uk
- Pemphigus und Pemphigoid Selbsthilfe e. V.
  www.pemphigus-pemphigoid-selbsthilfe.de
- Pemphigus-Forum
  www.pemphigus-forum.de
- Associazione Nazionale Pemfigo/Pemfigoide Italy
  www.pemfigo.it
- Netwerk Nederland Pemphigus en Pemfigoïd
  www.pemphigus.nl

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