Review Article

Bullous Autoimmune Dermatoses

Clinical Features, Diagnostic Evaluation, and Treatment Options

Nina van Beek, Detlef Zillikens, Enno Schmidt

Summary

Background: Bullous autoimmune dermatoses are a clinically and immunopathologically heterogeneous group of diseases, characterized clinically by blisters or erosions of the skin and/or mucous membranes. In Germany, their prevalence is approximately 40 000 cases nationwide, and their incidence approximately 20 new cases per million people per year.

Methods: This review is based on publications that were retrieved by a selective search of the literature focusing on the current German and European guidelines.

Results: Recent years have seen the publication of guidelines, controlled prospective clinical trials, and multicenter diagnostic studies improving both diagnosis and therapy. Specific monovalent and multivariate serological test systems and pattern analysis of tissue-bound autoantibodies allow identification of the target antigens in 80–90% of patients. This enables the precise classification of disease entities, with implications for treatment selection and disease outcome. In 2019, the anti-CD20 antibody rituximab was approved by the European Medicines Agency for the treatment of moderate and severe pemphigus vulgaris, with an ensuing marked improvement in the care of the affected patients. To treat mild and moderate bullous pemphigoid, topical clobetasol proprionate is recommended, in severe disease, combined with systemic treatment, i.e. usually (a) prednisolone p.o. at an initial dose of 0.5mg/kg/d , (b) an immunomodulant, e.g. dapsone or doxycycline, or (c) prednisolone plus an immunomodulant.

Conclusion: The early recognition and precise diagnostic evaluation of bullous autoimmune dermatoses now enables improved, often interdisciplinary treatment, in accordance with the available guidelines. Current research projects are focused on new treatment approaches, an improved understanding of the underlying pathophysiology, and further refinements of diagnostic techniques.

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Autoimmune bullous diseases (AIBD) are prototypical autoantibody-mediated autoimmune diseases in which the effects of the autoantibodies are directly visible on the skin and/or on mucous membranes. If left untreated, these diseases are potentially life-threatening due to superinfection, fluid loss, and severely restricted food intake (1–4, e1, e2).

Clinically, depending on the disease entity, vesicles, blisters, pustules, erosions, excoriations, and erythema on the skin and mucous membranes can be seen. In AIBD, autoantibodies are directed against structural proteins of the skin; in pemphigus diseases, they are directed against desmosomal proteins, which connect neighboring keratinocytes/epithelial cells, and in pemphigoid diseases, against proteins of the basement membrane zone, which connect the epidermis/epithelium and the dermis/lamina propria (*Figure 1*).

Epidemiology

The frequency of AIBD differs significantly depending on the geographic region and population evaluated (2, e3, e4). In Germany and central Europe, bullous pemphigoid is by far the most common AIBD (5, e5–e10) (*Table 1*), with an increasing incidence in recent decades (e8, e11–e13). Possible causes for the increasing incidence of bullous pemphigoid may include an aging population, the association with increasingly frequent neurological diseases and certain medications (see below), and a greater awareness of atypical variants without blistering (overview in [e4]).

The most common AIBDs in children are linear IgA dermatosis and pemphigus vulgaris (6, e14). An association with the human leukocyte antigens HLA-DRB1*04 and HLA-A*10 and a polymorphic variant in the *ST18* gene have been described for pemphigus vulgaris, while an overrepresentation of HLA-DQB1*03:01 and polymorphism in the mitochondrial *ATP8* gene has been described for bullous pemphigoid (1, 2, e3, e15, e16).

Clinical features

Pemphigus diseases

Pemphigus diseases can be classified in 4 main forms based on clincial and immunopathological features: pemphigus vulgaris, in about 70–80% of patients; pemphigus foliaceus, in about 20%; paraneoplastic pemphigus, in about 5%; and IgA pemphigus, in 1–3% (*Table 2*) (2).

FIGURE 1

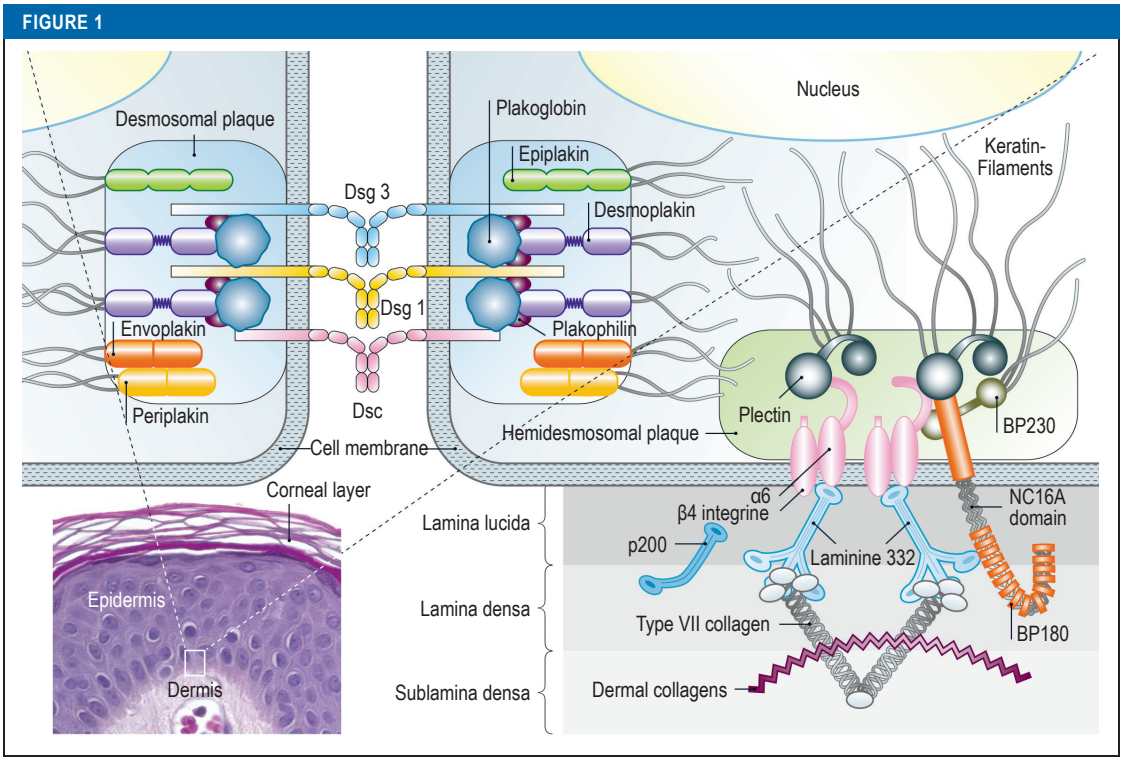

Figure 1: Schematic diagram of the autoantigens in pemphigus and pemphigoid diseases. BP180, type XVII collagen; BP230, dystonin; Dsg, desmoglein; Dsc, desmocollin

In pemphigus vulgaris, the mucous membranes close to the surface are always affected, including primarily the oral cavity (*Figure 2a*). Erosions predominate and can also manifest on the mucosa of the pharynx, larynx, esophagus, and genitalia (2, 3). In about half of the cases, flaccid blisters and erosions also appear on the skin, which may involve large areas. This led to a mortality of over 80% before the introduction of the corticosteroids (2, e3, 5). At present, the mortality of patients with pemphigus vulgaris is still two to three times higher than in the general population (e3, 5).

In pemphigus foliaceus, only the skin is affected, with erosions and scaly crusts, predominantly in seborrheic areas on the trunk and head (*Figure 2c*) (2, 3).

Paraneoplastic pemphigus is associated with neoplasia and is clinically similar to pemphigus vulgaris. Characteristic features are pronounced stomatitis, lip involvement, and polymorphic, often lichenoid, skin changes (2, 7, e17). With a mortality of 75–90%, the prognosis is unfavorable, primarily due to neoplasm and bronchiolitis obliterans, which occurs in 5–20% of cases (e3, e18, e19).

In IgA pemphigus, pustules and erosions are the most prominent lesions (e20–e22) (*Table 2*). Furthermore, neonatal pemphigus, pemphigus herpetiformis, and endemic pemphigus foliaceus are described as separate entities; pemphigus vegetans is considered a clinical variant of pemphigus vulgaris with predominant involvement of the axillary and inguinal areas. (2, 3, e23).

The differential diagnoses of pemphigus vulgaris and paraneopalstic pemphigus are severe drug reactions, such as Steven–Johnson syndrome, toxic epidermal necrolysis, stomatitis due to herpes simplex virus, hereditary epidermolysis, mucosal lichen planus, and mucous membrane pemphigoid (MMP). Pemphigus foliaceus must be differentiated from seborrheic dermatitis and impetigo, and IgA pemphigus, from pustular psoriasis as well as from pustular reactions to drugs.

Pemphigoid diseases

Bullous pemphigoid presents with tense blisters (*Figure 2b*), erosions, and urticarial erythema. Non-bullous forms are found in around 20% of cases (e24, e25). Characteristic features are the often severe pruritus and manifestation in old age (mean age of onset, 78 years). Therefore, bullous pemphigoid should be excluded in case of chronic pruritus in old age. Mucosal involvement can be seen in 10–20% of patients (8–10, e26).

Associated diseases that have been described include cardiovascular diseases, psoriasis, diabetes mellitus, hematological malignancies, and degenerative neurological diseases, the latter mostly preceding the skin disease and affecting 30–50% of patients (11, 12, e27–e29). Associations with the use of dipeptidyl peptidase IV inhibitors have also been observed, particularly with vildagliptin, as well as (although to a lesser degree) with spironolactone, loop diuretics, and

drugs for Parkinson's disease (13, e27, e29–e33). Gliptins should be replaced by other antidiabetic drugs in any case, and the other drugs switched to alternatives when possible. The 1-year mortality rates have been reported to range between 8% and 41% (1, e7, e10, e13, e34, e35). Differential diagnoses are bullous erysipelas, impetigo contagiosa, adverse drug reactions, herpes zoster, urticarial eczema, bullous reactions to insect stings, artifactual changes, hereditary epidermolysis, and other pemphigoid diseases.

Predominant involvement of mucous membranes supports the clinical diagnosis of MMP (*Figures 2d, e*). The mucous membranes of the mouth and the conjunctiva are particularly affected, as well as (less frequently) mucous membranes of the nose, pharynx, anogenital region, larynx, esophagus, and trachea. About 25–30% of patients present with additional erosions and blisters on the skin (1, 14).

Lesions of the conjunctiva, nose, larynx, esophagus and trachea in particular heal with scarring, which can lead to blindness, chronic hoarseness, difficulties in breathing and dysphagia, respectively. The main autoantigens are BP180 (in around 75% of patients) and laminin 332 (in up to 25%). Anti-laminin 332 MMP is associated with malignancy in 25–30% of cases, and in these patients, a tumor search is required (14, 15, e36). MMP has a differential diagnosis similar to that of pemphigus vulgaris.

Pemphigoid gestationis usually occurs in the third trimester of pregnancy, with severe pruritus and urticarial erythematous plaques, initially mainly in the periumbilical region. The disease resolves postpartum but usually recurs in subsequent pregnancies (1, e2, e37). As main differential diagnoses, polymorphic eruption of pregnancy and urticaria are to be distinguished. Linear IgA disease is characterized by tense vesicles and blisters, often arranged in an annular pattern, but may also resemble bullous pemphigoid and is a common AIBD in childhood (6, e14). In adults, induction by drugs should be considered; notably, about half of the drug-induced cases are caused by vancomycin (e38). Anti-p200 pemphigoid clinically resembles bullous pemphigoid but shows more palmoplantar involvement (e39). In epidermolysis bullosa acquisita, the inflammatory variant mimics as bullous pemphigoid, MMP, or linear IgA disease. In the mechanobullous variant, which is present in a third of patients, blisters appear on areas most stressed by mechanical forces, such as elbows, knees, and feet. Involvement of the mucous membrane and healing with scarring are common in this variant (16, 17, e40); the most important differential diagnosis is porphyria cutanea tarda.

Dermatitis herpetiformis, which is the cutaneous manifestation of celiac disease, is characterized by severe pruritus, excoriated papules, and vesicles with predilection for knees, elbows, and buttocks (4, 18).

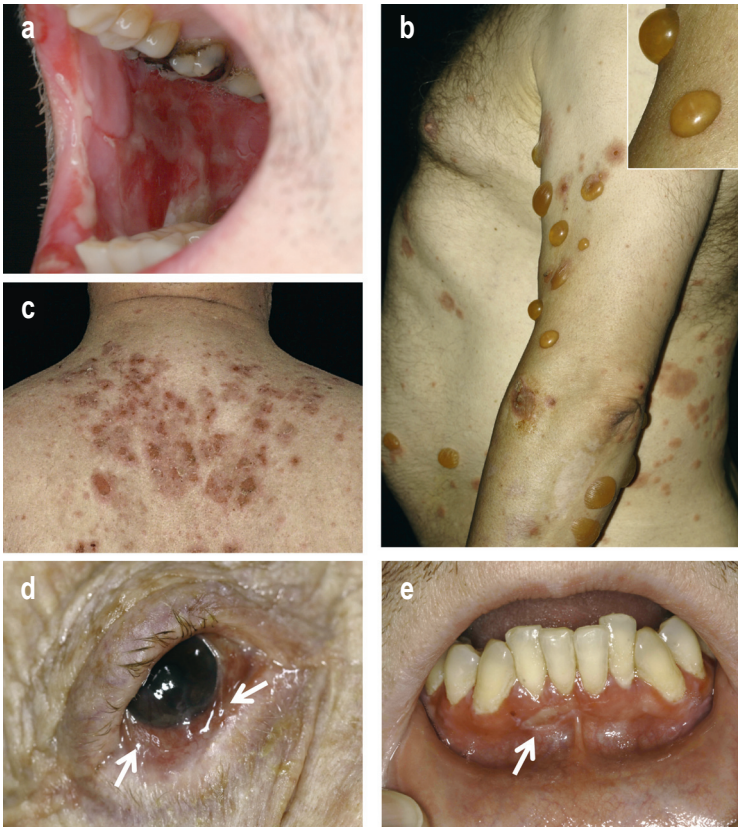

Figure 2: Clinical presentation of selected cases of autoimmune bullous dermatoses
a) Pronounced erosions of the buccal oral mucosa in pemphigus vulgaris.
b) Tense blisters, erythema, and erosions in bullous pemphigoid.
c) Erosions and crusts on the upper back in pemphigus foliaceus .
d) Conjunctival injection and synechiae (indicated by arrows).
e) Gingivitis with erosions (indicated by arrow) in MMP.

Diagnosis

AIBD cannot be diagnosed on the basis of the clinical picture alone. Rather, detection oftissue-bound and/or circulating autoantibodies is required (10).

Direct immunofluorescence

Tissue-bound autoantibodies (primarily IgG and IgA) and complement deposits are detected using direct immunofluorescence (IF) in a perilesional skin/mucosal biopsy and continue to represent the gold standard in AIBD diagnostics (9, 10, 17, 18–21). Direct IF allows a differentiation between pemphigoid diseases with linear deposits on the basement membrane (*Figure 3a, b*), pemphigus diseases with intercellular fluorescence in the epithelium (*Figure 3c*), and dermatitis herpetiformis with granular deposits of IgA along the basement membrane and/or in the tips of the dermal papillae. Linear and intercellular fluorescence together indicate paraneoplastic pemphigus (7, e17).

Of the pemphigoid diseases, linear IgA disease can be differentiated based on predominant IgA deposits along the basement membrane, and epidermolysis bullosa acquisita, based on serration pattern analysis (1). Almost all pemphigoid diseases show an n-serrated pattern (*Figure 3a*); except for epidermolysis bullosa acquisita and bullous lupus erythematosus

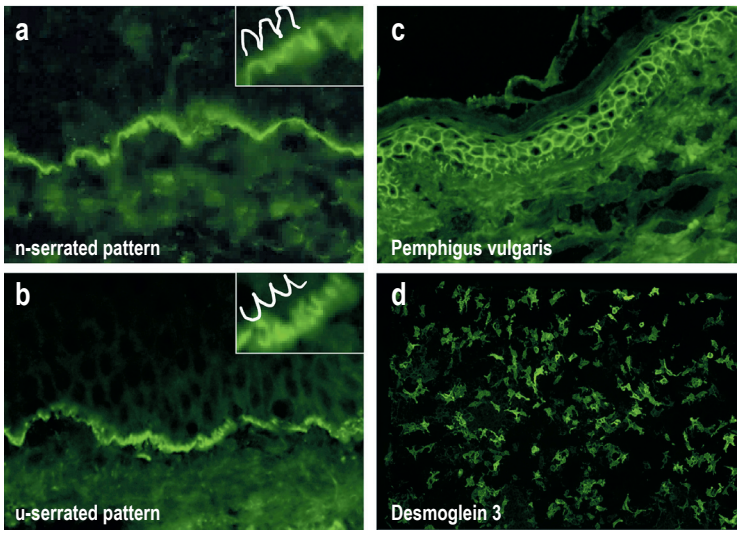

Figure 3: Direct immunofluorescence of perilesional biopsies for the detection of tissue-bound autoantibodies (a–c) and indirect immunofluorescence of the desmoglein 3–specific biochip (d).
a) Linear deposits of IgG on the dermal–epidermal junction in bullous pemphigoid. At 400 x magnification, an n-serrated pattern can be seen (inset), which is found in all pemphigoid diseases with the exception of epidermolysis bullosa acquisita.
b) Linear deposits of IgG on the dermal–epidermal junction zone, with a u-serrated pattern, in epidermolysis bullosa acquisita.
c) Epidermal intercellular deposits of C3 with a reticular pattern, consistent with pemphigus vulgaris
d) IgG reactivity to Dsg3-expressing HEK293 cells of a biochip, typical for pemphigus vulgaris

which reveal a u-serrated pattern (*Figure 3b*) (22, e41, e42).

Serological diagnostics

Circulating autoantibodies can be detected in the serum of about 90% of AIBD patients. In contrast, this is only possible for about half of the patients with epidermolysis bullosa acquisita or MMP (16, 17, e43). A serological diagnosis in combination with the clinical picture allows an exact assignment to the individual entities and thus a tailored therapy and a more precise prognosis. Anti-laminin 332 MMP and paraneoplastic pemphigus are both facultative and obligatory paraneoplasia, respectively, and a search for an underlying malignancy is indicated (7, 15, e36, e44).

To screen for suspected AIBD, an indirect IF on monkey esophagus and 1 M NaCl–split skin is carried out, which enables a differentiation into pemphigus and pemphigoid diseases (*Figure 4a–c*). The salt-split skin allows a subdivision of binding to the epidermal roof (in the case of autoantibodies against BP180 and BP230) or to the floor (autoantibodies against p200 antigen, laminin 332, and type VII collagen) of the artificial split (*Figures 1 and 4a–c*, *Table 2*) (1, 2, 10, 18, 19, e45).

For the detection of autoantibodies against the most important target antigens of AIBD, sensitive and specific enzyme-linked immunosorbent assays (ELISA) using the recombinant immunodominant regions of the target antigens are available (Euroimmun, Lübeck; MBL, Nagoya, Japan; *Table 2*) (10, e46–e52). For instance, ELISA can detect circulating antibodies against desmoglein 3 in the sera of patients with pemphigus vulgaris, and circulating antibodies against desmoglein 1 in patients with pemphigus foliaceus, in >95% of the cases (3, 23, e47, e52). Serum IgG antibodies against BP180 NC16A can be detected in 80–90% of the sera from patients with bullous pemphigoid.

The diagnostic sensitivity of bullous pemphigoid can be increased by 5–8% by the additional use of the BP230 ELISA, with which 50–60% of patients react (e46, e53). Serum autoantibodies against BP180 NC16A are also found in patients with pemphigoid gestationis as well as in 30–50% of these patients with MMP who have serum antibodies against the epidermal side of human split skin (e54–e57).

For circulating autoantibodies against desmoglein 1, desmoglein 3, BP180 NC16A, and type VII collagen, a correlation with the course of the disease has been shown (3, e47, e48, e58, e59); their determination via ELISA during the course of the disease is recommended to be indcluded in therapy decisions (17, 21, 24). Instead of a step-by-step diagnostic approach, multivariate ELISA systems can be used in which autoantibodies against several target antigens are analyzed in parallel (e51, e60). The indirect IF-based BIOCHIP technology offers a comparable option. It assembles several substrates in so-called BIOCHIP mosaics in a single incubation field of a standard laboratory slide (15, 23, e61–e63) (*Figures 3d and 4d–f*).

The detection of specific autoantibodies that are not (yet) included in commercial assays is carried out in some specialized laboratories (*Table 2 and Box*).

Pathophysiology

The pathophysiology of pemphigus and pemphigoid diseases has been presented in detail in recent reviews (1–3, 25, e1, e64–e67). A common feature of all AIBDs is the presence of T cells and pathogenetically relevant autoantibodies against the respective autoantigens in genetically susceptible individuals (e68–e75). The trigger factors that lead to a breach of tolerance are still largely unknown.

In pemphigus, autoantibody binding is followed by the desmogleins being depleted from the cell surface and further signal transducing events, among others via the p38MAP kinase. Both lead to a weakening of the cell–cell interactions and to the separation of the keratinocytes/epithelial cells called acantholysis (3, 25, e1, e64).

In pemphigoid diseases, the binding of the autoantibodies leads to the local activation of complement and subsequently to the infiltration of inflammatory cells, such as eosinophils, neutrophils, macrophages, and T cells, into the upper dermis. The release of specific proteases from granulocytes, macrophages, and activated mast cells ultimately results in degradation of the proteins of the dermal–epidermal junction,

which appears histologically as subepidermal clefts and clinically as tense blisters and erosions (1, e76). C5aR1, leukotriene B4, the neonatal Fc receptor, eotaxin, the IL-5 receptor, and IL-17A have been identified as key mediators of pemphigoid diseases; clinical studies are currently underway in which some of these are investigated (26–29, e67, e77–e83).

Therapy

German and/or European guidelines have been formulated for bullous pemphigoid, pemphigus vulgaris/foliaceus, MMP, and dermatitis herpetiformis (9, 18, 21, 24, 30, 31, e84) (*eTables 1 and 2*). In addition to an interdisciplinary approach with ENTs, ophthalmologists, gynecologists, general practitioners, infectiologists, paediatricians, and, if necessary, other specialist disciplines, cooperation with patient support groups is recommended, for example with the German pemphigus and pemphigoid self-help group association (*Pemphigus und Pemphigoid Selbsthilfegruppe*, www.pemphigus-pemphigoid-self-help.de) or the International Pemphigus and Pemphigoid Foundation (www.pemphigus.org).

Pemphigus diseases

First-line therapy for pemphigus vulgaris/foliaceus has changed significantly following the approval of the anti-CD20 antibody rituximab for the treatment of moderate and severe pemphigus vulgaris by the European Medicines Agency (EMA) and the US American Food and Drug Administration (FDA). Joly et al. demonstrated that treatment of patients with newly diagnosed pemphigus vulgaris/foliaceus with rituximab (2 × 1 g plus 0.5 g each, in months 12 and 18) plus prednisolone (0.5–1.0 mg/kg/day p.o. for three to six months) was significantly more effective and safer than therapy with oral prednisolone 1.0–1.5 mg/kg/day for 12–18 months (55% difference, 95% confidence interval: [38.4; 71, 7]; $p < 0.0001$) (32). For moderate and severe pemphigus vulgaris/foliaceus, administration of rituximab (2 × 1 g at an interval of 2–3 weeks) is recommended in combination with systemic corticosteroids (tapering over 3–6 months). Alternatively, conventional therapy with prednisolone p.o. 1.0 mg/kg/day plus azathioprine or mycophenols can be applied (*eTable 2*) (24). As an alternative to oral corticosteroids, intravenous corticosteroid pulses can be used (24, 31). The guideline recommends another infusion of rituximab (1 g) after six months in the event of relapse or incomplete remission; in refractory patients, the guideline also recommends high-dose intravenous immunoglobulins (IVIg) or immune apheresis (*eTable 2*) (24). Currrent clinical trials for treatment of pemphigus are evaluating efficacy and safety of inhibition of the Bruton tyrosine kinase or the neonatal Fc receptor, depletion of desmoglein 3–specific B cells using chimeric autoantibody receptor T cells (CAART), and tolerance induction by nanoparticles (27, 33, e1, e85, e86).

Pemphigoid diseases

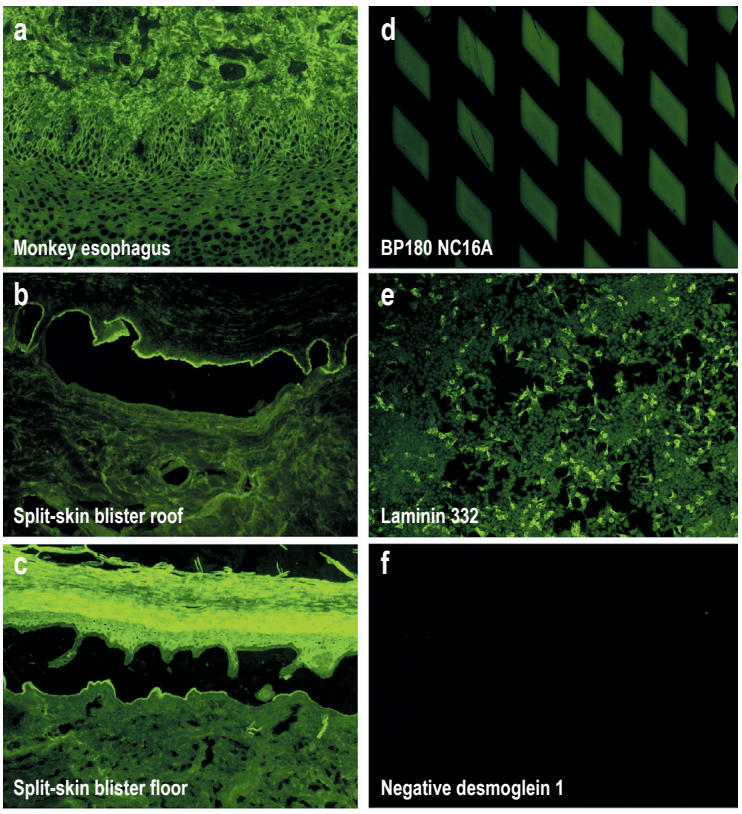

Figure 4: Indirect immunofluorescence on monkey esophagus, salt-split skin, and selected biochips

a) IgG reactivity on monkey esophagus epithelium, with an intercellular pattern typical of pemphigus vulgaris/foliaceus

b) IgG reactivity along the epidermal side of human salt-split skin (using 1M NaCl), fitting to binding of autoantibodies to BP180 and BP230

c) IgG reactivity along the dermal side of human salt-split skin (using 1M NaCl), fitting to binding of autoantibodies to p200, laminin 332, and type VII collagen

d) IgG reactivity to recombinant BP180 NC16A on a biochip, indicative of bullous pemphigoid, pemphigoid gestationis, or mucous membrane pemphigoid

e) IgG reactivity to laminin 332-expressing HEK293 cells of a biochip, indicative of anti-laminin 332 mucous membrane pemphigoid

f) Lack of fluorescence with Dsg1-expressing HEK293 cells of a biochip after incubation with a negative serum

TABLE 1

Incidence and Prevalence

Disease	Incidence/ million inhabitants/year	Prevalence in Germany 2014/million (e9)
Pemphigus vulgaris	0.5–6.8 (e5, 5, e88) Germany: 1.0 (e100)	94.8
Pemphigus foliaceus	< 1 (e89)	10.0
Bullous pemphigoid	6.1–42.9 (5, e5–e8, e10) Germany: 19.6 (40)	259.3
Mucous membrane pemphigoid	0.8–2 (e5, e90, e91)	24.6
Linear IgA disease	0.25–1 (e5, e92)	24.3 for children
Pemphigoid gestationis	0.08–2 (e5, e92) Germany: 2.0 (e5)	13.6 for women
Anti-p200 pemphigoid	Germany: 0.7 (40)	unknown
Epidermolysis bullosa acquisita	0.2–0.5 (5, e5–e8, e10)	2.8

TABLE 2

Target antigens of autoimmune bullous dermatoses and serological diagnostics

Disease	Target antigen	Serological diagnostics*1
Pemphigus diseases		
Pemphigus vulgaris	Dsg 3 Dsg 1	**IIF monkey esophagus:** ICF IgG+ **ELISA, IIF: Dsg3+ Dsg1±**
Pemphigus foliaceus	Dsg 1	**IIF monkey esophagus:** ICF IgG+ **ELISA, IIF: Dsg1+**
Paraneoplastic pemphigus	Envoplakin, periplakin, Dsg 3, desmoplakin I/II, plectin, epiplakin, BP230, BP180, Dsc 1, 2, 3, Dsg1, α2 macroglobulin-like 1	**IIF monkey esophagus:** ICF+, BMF± Monkey-/**rat bladder:** urothelium + **ELISA, IIF: Dsg3±,** Dsg 1±, BP180±, BP230±; **ELISA: envoplakin ±** IB, IP, ELISA: all other target antigens ±
IgA pemphigus	Dsc 1, 2, 3	**IIF monkey esophagus:** ICF IgA ELISA, IIF: Dsc1, 2, 3 IgA±; Dsg3 IgA±
Pemphigoid diseases		
Bullous pemphigoid	BP180, BP230	**IIF monkey esophagus:** BMF+ **IIF salt-split skin:** blister roof+ **ELISA, IIF: BP180 (+ in 80–90%), BP230 (+ in 50–60%)**
Mucous membrane pemphigoid	BP180, LAD-1, laminine332, BP230, (α4β6 integrine)*2	**IIF monkey esophagus:** BMF± **IIF salt-split skin:** blister roof± or blister floor± **ELISA: BP180±, BP230±** IB: LAD-1±; BP180±; **IIF: laminine332±**
Linear IgA disease	LAD-1, type VII collagen	**IIF monkey esophagus:** BMF (IgA)+ **IIF salt-split skin:** blister roof (IgA) + IB, ELISA: BP180 (IgA) ±, LAD-1(IgA)+
Pemphigoid gestationis	BP180 NC16A, BP230	**IIF salt-split skin:** blister roof± IIF complement binding test salt-split skin: blister roof + **ELISA, IIF BP180+, BP230±**
Anti-p200 pemphigoid	p200 protein, laminine γ1	**IIF monkey esophagus:** BMF+ **IIF salt-split skin:** blister roof+ IB: p200+, laminine γ1±
Epidermolysis bullosa acquisita	Type VII collagen	**IIF monkey esophagus:** BMF± **IIF salt-split skin:** blister floor± **ELISA, IIF: type VII collagen+**
Dermatitis herpetiformis	TG2, TG3	**IIF monkey esophagus (IgA):** endomysium + **ELISA (IgA): TG2, TG3, deamidated gliadin +**

*1 commercially available tests are indicated in bold
*2 only described for individual patients
BMF, basement membrane fluorescence; Dsg, desmoglein; Dsc, desmocollin; ELISA, enzyme-linked immunosorbent assay; IIF, indirect immunofluorescence; ICF, intercellular fluorescence; IB, immunoblot; IP, immunoprecipitation; LAD-1, soluble ectodomain of BP 180; TG, transglutaminase

For bullous pemphigoid, the current German AWMF guideline recommends a whole-body application of topical 0.05% clobetasol propionate (40 g/day), a superpotent glucocorticosteroid of class IV, for mild as well as moderate cases, if necessary; for severe cases, this is usually recommended in combination with systemic treatment (24). In a controlled randomized study, topical 0.05% clobetasol propionate (40 g/day) had a comparable effect in patients with bullous pemphigoid as prednisolone (0.5 mg/kg/day) (disease control in moderate cases, topical 100% [95; 100]) versus oral 95% [87; 99], p = 0.06; in severe cases, topical 99% [94; 100] versus oral 91% [83; 96], p = 0.02) (34). As a systemic treatment, prednisolone is given orally at 0.5 mg/kg/day, possibly in combination with the (potentially steroid-sparing) agents azathioprine, dapsone, doxycycline, methotrexate, mycophenolate mofetil, or mycophenolate sodium. Alternatively, dapsone, doxycycline, or methotrexate can also be used as the only systemic treatment without oral corticosteroid (24) (see further details, *eTable 1*). In randomized controlled trials in patients with bullous pemphigoid, doxycycline was associated with significantly fewer serious adverse events than oral prednisolone (difference 19.0% [7.9; 30.1], p = 0.001), and dapsone was associated with a lower cumulative corticosteroid dose than azathioprine (p = 0.06) (35, 36). IVIg, immunoadsorption, rituximab, cyclophosphamide, or omalizumab can be used in refractory patients (*eTable 1*) (24, 37–39, e87).

The severity of MMP is distinguished on the basis

BOX

Dermatology departments in Germany that carry out more than 500 non-commercial test systems/year*

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- Department of Dermatology and Allergology, University Hospital Gießen and Marburg, Marburg, Germany
- Department of Dermatology, Venereology, and Allergology and Skin Cancer Center, University Hospital Würzburg, Würzburg, Germany.

* in alphabetical order of the location (e93)

of the risk of scarring, as mild/moderate with exclusive involvement of the skin and oral mucosa, or as severe, with involvement of the eyes, nasal mucosa, pharynx, larynx, esophagus, or trachea. In the case of mild/moderate MMP, topical treatment with highly potent topical glucocorticoids, possibly in combination with immunomodulators, is often sufficient. For severe MMP, treatment with dapsone combined with systemic corticosteroid (prednisolone, either orally 0.5–1.5 mg/kg/day or as an intravenous pulse therapy) or cyclophosphamide (orally or intravenously) is recommended (30, e84). In the case of eye involvement, topical treatments that can be used in addition to lubricants include corticosteroids, tetracyclines, and cyclosporine (30, e84). Timely interdisciplinary treatment of inflammation is crucial before irreversible scarring occurs, especially on the eye.

The systemic treatments for refractory MMP and other pemphigoid diseases and dermatitis herpetiformis are summarized in *eTable 1*.

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► **Supplementary material**

eReferences and eTables:
www.aerzteblatt-international.de/m2021.0136

Questions on the article in the issue 24/2021:

Bullous Autoimmune Dermatoses – Clinical Features, Diagnostic Evaluation, and Treatment Options

cme plus

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Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

Which type of autoimmune bullous diseases mainly has antibodies targeted against the desmoglein 3 antigen?

a) IgA pemphigus
b) Bullous pemphigoid
c) Linear IgA dermatosis
d) Pemphigus vulgaris
e) Mucous membrane pemphigoid (MMP)

Question 2

Which autoimmune bullous disease has the highest prevalence in Germany?

a) Pemphigus vulgaris
b) Pemphigoid gestationis
c) Bullous pemphigoid
d) Epidermolysis bullosa acquisita
e) Pemphigus foliaceus

Question 3

Which is characteristic of bullous pemphigoid?

a) Scaly crusts, manifestation in middle age
b) Manifestation mostly in childhood, severe pruritus
c) Erosion strictly limited to the skin, severe pruritus
d) Manifestation at a young age, usually without pruritus
e) Manifestation in old age, severe pruritus

Question 4

Which autoimmune bullous dermatosis almost always occurs in connection with celiac disease?

a) Epidermolysis bullosa acquisita
b) Dermatitis herpetiformis
c) Linear IgA disease
d) Anti-p200 pemphigoid
e) IgA pemphigus

Question 5

Detection of autoantibodies is part of the serological diagnosis of patients with autoimmune bullous diseases. In what percentage of these patients can circulating autoantibodies be detected in the serum?

a) ca. 90 %
b) ca. 70 %
c) ca. 50 %
d) ca. 20 %
e) ca. 10 %

Question 6

Which technology is used to detect autoantibodies against the most important target antigens in autoimmune bullous dermatoses?

a) Polymerase chain reaction (PCR)
b) Immunoprecipitation
c) Fluorescence In Situ Hybridization (FISH)
d) Matrix-Assisted Laser-Desorption-Ionization (MALDI)
e) Enzyme-linked immunosorbent assay (ELISA)

Question 7

In addition to conventional therapy, which treatment is recommended for moderate and severe pemphigus vulgaris?

a) Rituximab (1 g/day for 3 months) as a monotherapy
b) Azathioprine as monotherapy
c) Rituximab in combination with systemic corticosteroids
d) Mycophenolate mofetil (500 mg/day) as a monotherapy
e) Azathioprine combined with mycophenolate mofetil

Question 8

Which types of autoimmune bullous diseases are most common in children?

a) Linear IgA dermatosis and pemphigus vulgaris
b) Bullous pemphigoid and mucous membrane pemphigoid (MMP)
c) Epidermolysis bullosa acquisita and pemphigus foliaceus
d) IgA pemphigus and dermatitis herpetiformis Duhring
e) Dermatitis herpetiformis Duhring and bullous pemphigoid

Question 9

Which pattern is typically seen in the direct immunofluorescence of perilesional biopsies in epidermolysis bullosa acquisita?

a) An N-serrated pattern
b) A U-serrated pattern
c) An A-serrated pattern
d) An O-serrated pattern
e) A Y-serrated pattern

Question 10

What is known about the occurrence of pemphigoid gestationis?

a) It is usually most pronounced at the beginning of pregnancy
b) The disease stops immediately postpartum
c) After recovery from the disease, it will not occur in subsequent pregnancies
d) Urticarial erythematous plaques do not appear on the abdomen
e) It usually occurs in the third trimester of pregnancy

Supplementary material:

Bullous Autoimmune Dermatoses

Clinical Features, Diagnostic Evaluation, and Treatment Options

by Nina van Beek, Detlef Zillikens, and Enno Schmidt

Dtsch Arztebl Int 2021; 118: 413–20. DOI: 10.3238/arztebl.m2021.0136

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eTABLE 1

Treatment options for pemphigoid diseases and dermatitis herpetiformis

Disease/ severity	Treatment	
	Medication*2	Adverse drug reactions*11
Bullous pemphigoid*1 (24)		
Mild (< 10% body surface area)	Topical 0.05% clobetasol propionate (level B)	Skin atrophy
Moderate (10–30% body surface area)	Topical 0.05% clobetasol propionate (level B) ± systemic treatment	Skin atrophy
	Systemic treatment Prednisolone*3 p.o. 0.5 mg/kg/day (level B) or	Hypertension, diabetes, osteoporosis, AI, infections
	Dapsone*7 ± prednisolone*3 p.o. 0.5 mg/kg/day (level C) or	Dapsone: hemolytic anemia, GI complaints, methemoglobinemia, agranulocytosis
	Doxycycline (200 mg/day) (level B) ± nicotinamide (level D) ± prednisolone*3 p.o. 0.5 mg/kg/day or	Doxycycline: GI complaints, sensitivity to light
	Azathioprine*5 (level C) + prednisolone*3 p.o. 0.5 mg/kg/day or	Azathioprine: myelo- and hepatotoxicity, arthralgias, infections
	Methotrexate (≤ 20 mg /week) (level D) ± prednisolone*3 p.o. 0.5 mg/kg/day or	Methotrexate: myelo- and hepatotoxicity, infections, kidney dysfunction, possible reactivation
	Mycophenols*6 (level C) + prednisolone*3 p.o. 0.5 mg/kg/day	Mycophenols: GI complaints, infections, (rarely) myelotoxicity
Severe (> 30% body surface area)	Topical 0.05% clobetasol propionate + systemic treatment (see above)	(see above)
Refractory to treatment	IVIg (level D)*9	Headache, chills, flushing, fever, hypertension, nausea
	Immunadsorption (level D)*10	Hypotension, thrombosis, bradycardia, anaphylaxis, herpes zoster infection, sepsis
	Rituximab*8 (level D)	Infusion reaction, infections, reactivation of hepatitis B, PML
	Cyclophosphamide (level E) Omalizumab (level E)	Myelotoxicity, hemorrhagic cystitis, carcinogenicity, infertility, infections

Disease/ severity	Treatment	
	Medication*2	Adverse drug reactions*11
MMP*1 (30, e84)		
Mild/moderate (only oral cavity and skin are affected)	Topical corticosteroids class III/IV and/or dapsone*7 (level D), methotrexate (≤ 20 mg/week) (level E) or tetracycline (level E)	(ADRs of these drugs are described above) GI complaints, dizziness
Mild, refractory to treatment	+ Prednisolone*3 p.o. 0.5–1.5 mg/kg/day (level C) and/or azathioprine*5 or mycophenols*6 (level D)	(ADRs of these drugs are described above)
Severe (involvement of conjunctiva, nasopharynx, larynx, trachea or esopha-	Dapsone*7 (level C) + cyclophosphamide p.o./i.v. and/or prednisolone*3 p.o. 0.5–1.5 mg/kg/day (or i.v. steroid pulse*4) (all: level D)	(ADRs of these drugs are described above)
Severe, refractory to treatment	Dapsone*7 + rituximab 2 × 1 g*8 (level D) If still refractory: + IVIg*9 (level D)	(ADRs of these drugs are described above)
Linear IgA disease (e96, e97)	Topical corticosteroids class III/IV or prednisolone*3 p.o. 0.25–0.5 mg/kg/day ± dapsone*7 (all: level D)	(ADRs of these drugs are described above)
Refractory to treatment	Prednisolone*3 p.o. 0.5 mg/kg/day + Sulfasalazine/-pyridine (level D) Doxycycline (200 mg/day) (level E) Cholchicine (level E) IVIg*9, azathioprine*5, or mycophenols*6 (all, level E)	(see above) GI complaints, hepato- and nephrotoxicity, myelotoxicity (see above) GI complaints, hepato- and nephrotoxicity, myelotoxicity (see above)
Pemphigoid gestationis (e37)	Topical 0.05% clobetasol proprionate or prednisolone*3 p.o. 0.25–0.5 mg/kg/day (level D)	(ADRs of these drugs are described above)
Refractory to treatment	Immunadsorption*10, rituximab*8 (only postpartum) (level E)	(ADRs of these drugs are described above)
Anti-p200 pemphigoid (e39)	Topical 0.05% clobetasol proprionate ± prednisolone*3 p.o. 0.25–0.5 mg/kg/day ± dapsone*7 or doxycycline 200 mg/day (level E)	(ADRs of these drugs are described above)
Epidermolysis bullosa acquisita (39, e98, e99)		
Mild (< 10% body surface area)	Topical 0.05% clobetasol proprionate + dapsone*7 or colchizine (level E)	(ADRs of these drugs are described above)
Moderate/severe	Prednisolone*3 p.o. 1.0–2.0 mg/kg/day or i.v. steroid pulses*4, tapering over course+ azathioprine*5, mycophenols*6 or dapsons*7 (all: level E)	(ADRs of these drugs are described above)
Refractory to treatment	+ Rituximab*8 and/or IVIg*9 (both level E)	(ADRs of these drugs are described above)
Dermatitis herpetiformis*1 (18)	Gluten-free diet (life-long) ± dapsone*7 (until skin lesions have healed) (level D)	(ADRs of these drugs are described above)

*1 German and/or European therapy guidelines are available for these diseases
*2 Level of evidence: level A, meta-analyses of prospective, controlled trials; level B, high-quality prospective, controlled trials; level C, lower-quality prospective controlled trials; level D, larger case studies; level E, small case studies, case reports
*3 or prednisolone equivalent
*4 dexamethasone 100 mg/day for three consecutive days, or prednisolone 500–1000 mg/day, every 3–4 weeks, eventually every 6–8 weeks
*5 2.0–2.5 mg/kg/day with normal thiopurine methyltransferase levels
*6 mycophenolate mofetil (2 g/day), mycophenolate sodium (1440 mg/day)
*7 1.0–1.5 mg/kg/day with normal glucose 6-phosphate levels
*8 or biosimilar
*9 2 g/kg for 2–5 days every four weeks; after six months, interval extension (37)
*10 on 3–4 consecutive days with regenerable adsorbers every 3–4 weeks, for 8–16 weeks
*11 important adverse drug reactions (ADRs) are indicated; note that this list is not comprehensive
ADR, adverse drug reactions; AI, adrenal insufficiency; GI, gastrointestinal; IVIg, intravenous immunoglobulins; MMP, mucous membrane pemphigoid; PDAI, Pemphigus Disease Activity Index; PML, progressive multifocal leukoencephalopathy.

eTABLE 2

Treatment options for pemphigus diseases

Disease/ severity	Treatment	
	Medication*2	Adverse drug reactions*11
Pemphigus vulgaris/ Pemphigus foliaceus*1 (24)		
Mild (PDAI ≤ 15)	Prednisolone*3 p.o. 1.0–1.5 mg/kg/day or i.v. steroid pulses*4 (level C)	Hypertension, diabetes, osteoporosis, AI, infections
	± azathioprine*5 (level C)	Myelo- and hepatotoxicity, arthralgias, infections
	mycophenoles*6 (level C)	GI complaints, infections, (rarely) myelotoxicity
	dapsone*7 (only for pemphigus foliaceus) (level E)	Hemolytic anemia, GI complaints
Moderate, severe (PDAI > 15)	Rituximab 2 × 1 g*8 (level B)+	Infusion reaction, infections, reactivation of hepatitis B, PML
	prednisolone*3 p.o. 1.0 mg/kg/day or i.v. steroid pulses*4 (tapering over 3–6 months; level B) ± azathioprine*5 or mycophenols*6 (level C)	(ADRs of these drugs are described above)
	prednisolone*3 p.o. 1.0–1.5 mg/kg/day or i.v. steroid pulses*4 + azathioprine*5 or mycophenols*6 (level C)	
Refractory to treatment	IVIg*9 (level D)	Headache, chills, flushing, fever, hypertension, nausea
	Immunadsorption*10 (level D)	Hypotension, thrombosis, bradycardia, anaphylaxis, herpes zoster infection
Paraneoplastic pemphigus (2, 3)	Treatment of neoplasm + prednisolone*3 p.o. 0.5–1.0 mg/kg/day or i. v. steroid pulses*4 eventually in combination with rituximab*8, IVIg*9, immunadsorption*10 (all: level E)	(ADRs of these drugs are described above)
IgA pemphigus (2, 3, e94, e95)	Dapsone*7 and/or acitretine +	Hemolytic anemia, GI complaints, teratogenicity
	Prednisolone*3 p.o. 0.5–1.0 mg/kg/day (all: level E)	Hypertension, diabetes, osteoporosis, AI, infections

*1 German and/or European therapy guidelines are available for these diseases
*2 Level of evidence: level A, meta-analyses of prospective, controlled trials; level B, high-quality prospective, controlled trials; level C, lower-quality prospective controlled trials; level D, major case studies; level E, small case studies, case reports
*3 or prednisolone equivalent
*4 dexamethasone 100 mg/day for three consecutive days, or prednisolone 500–1 000 mg/day, every 3–4 weeks, eventually every 6–8 weeks
*5 2.0–2.5 mg/kg/day with normal thiopurine methyltransferase levels
*6 mycophenolate mofetil (2 g/day), mycophenolate sodium (1 440 mg/day)
*7 1.0–1.5 mg/kg/day with normal glucose 6-phosphate
*8 or biosimilar
*9 2 g/kg for 2–5 days every four weeks; after six months, interval extension (37)
*10 on 3–4 consecutive days with regenerable adsorbers every 3–4 weeks, for 8–16 weeks
*11 not a comprehensive list

ADR, adverse drug reactions; AI, adrenal insufficiency; GI, gastrointestinal; IVIg, intravenous immunoglobulins; PDAI, Pemphigus Disease Activity Index; PML, progressive multifocal leukoencephalopathy.