Pemphigus

Enno Schmidt, Michael Kasperkiewicz, Pascal Joly

Lancet 2019; 394: 882–94

Department of Dermatology (Prof E Schmidt MD), **Lübeck Institute for Experimental Dermatology** (Prof E Schmidt), **University of Lübeck, Lübeck, Germany; Department of Dermatology, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA** (Prof M Kasperkiewicz MD); **Department of Dermatology, Rouen University Hospital, Rouen, France** (Prof P Joly MD); **and INSERM Unit 2345, French Reference Center for Autoimmune Bullous Diseases, Normandy University, Rouen, France** (Prof P Joly)

Correspondence to: Prof Enno Schmidt, Department of Dermatology, University of Lübeck, 23538 Lübeck, Germany **enno.schmidt@uksh.de**

See Online for appendix

Pemphigus consists of a group of rare and severe autoimmune blistering diseases mediated by pathogenic autoantibodies mainly directed against two desmosomal adhesion proteins, desmoglein (Dsg)1 and Dsg3 (also known as DG1 and DG3), which are present in the skin and surface-close mucosae. The binding of autoantibodies to Dsg proteins induces a separation of neighbouring keratinocytes, in a process known as acantholysis. The two main pemphigus variants are pemphigus vulgaris, which often originates with painful oral erosions, and pemphigus foliaceus, which is characterised by exclusive skin lesions. Pemphigus is diagnosed on the basis of either IgG or complement component 3 deposits (or both) at the keratinocyte cell membrane, detected by direct immunofluorescence microscopy of a perilesional biopsy, with serum anti-Dsg1 or anti-Dsg3 antibodies (or both) detected by ELISA. Corticosteroids are the therapeutic mainstay, which have recently been complemented by the anti-CD20 antibody rituximab in moderate and severe disease. Rituximab induces complete remission off therapy in 90% of patients, despite rapid tapering of corticosteroids, thus allowing for a major corticosteroid-sparing effect and a halved number of adverse events related to corticosteroids.

Introduction

Pemphigus diseases are life-threatening, chronic, autoimmune blistering diseases characterised by the formation of splits within the epidermis and surface-close epithelia, accompanied by acantholysis, a histopathological term that describes the separation of keratinocytes from each other (figure 1A and 1B). Autoantibodies are mainly of the IgG isoform and directed against two structural proteins of epidermal desmosomes, desmoglein (Dsg) 1 and Dsg3 (also known as DG1 and DG3; figure 2). Desmosomes are cell-cell adhesion structures that connect neighbouring keratinocytes and are essential for the integrity of various tissues including the skin. For improved treatment and prognosis, pemphigus diseases need to be differentiated from pemphigoid diseases, as the other main group of autoimmune blistering disorders. Pemphigoid diseases are a heterogeneous group of disorders, characterised by autoantibodies against structural proteins of the dermal–epidermal junction and tissue destruction that is mainly based on skin inflammation mediated by the Fc receptor, resulting in subepidermal blisters (reviewed by Schmidt and Zillikens[1]). Because prognosis and treatment vary considerably between pemphigus and pemphigoid diseases, an exact diagnosis is needed. Diagnosis cannot be made clinically, but warrants distinct assessment of both serum antibodies and antibodies bound to the skin or mucous membranes.

Search strategy and selection criteria

Data for this Seminar were identified by searches of PubMed with the search term "pemphigus" from Jan 1, 2008, to Jan 31, 2019. Older literature was cited as selected milestone articles or indirectly through review articles. We also searched the reference lists of articles identified by our search strategy and selected those we judged relevant. Review articles and book chapters are cited to provide readers with further information and more references than this Seminar can accommodate.

Two major pemphigus variants can be differentiated, pemphigus vulgaris and pemphigus foliaceus. Pemphigus diseases share some clinical characteristics, such as flaccid blisters and erosions, and, in contrast to pemphigoid diseases,[1] a positive Nikolsky's sign (ie, friction of non-lesional skin does induce intraepidermal disruption and visible erosion; appendix p 18).

The term pemphigus derives from pemphix, the Greek word for blister. Some of the historical aspects of pemphigus are provided in the appendix (p 1).

Epidemiology

Pemphigus vulgaris and pemphigus foliaceus account for 90–95% of pemphigus diagnoses. The relative frequencies of pemphigus vulgaris and pemphigus foliaceus within a population vary greatly between countries, with the relative frequency of pemphigus vulgaris ranging between 95% in Saudi Arabia and 13% in Mali. In Europe and North America, pemphigus vulgaris accounts for 65–90% of pemphigus cases (reviewed by Schmidt and colleagues[2]).

Pemphigus usually manifests between the ages of 45 and 65 years in most populations, with an as yet unexplained lower mean age of onset of about 45 years in South Africa and northeast China (appendix pp 3–4). Reports from the UK and France have highlighted that the age-adjusted incidence of pemphigus is increasing with age.[3,4] In childhood and adolescence, pemphigus is exceedingly rare, with 1–4% of patients with pemphigus vulgaris being younger than 18 years (as reviewed previously[5–7]). Pemphigus foliaceus in children has been described only in individual cases[6,7] outside the endemic areas, but in such areas (discussed later) up to 30% of patients have been reported to be younger than 20 years.[8,9] In most epidemiological studies, a female predominance has been reported, with ratios of males to females between 1:1·1 and 1:1·7 in various populations.[3,10,11]

Incidence and prevalence

The incidence of pemphigus differs considerably between populations, ranging from 0·6 per million per year in Switzerland and 0·8 in Finland, to 8·0 in Greece and

10·0 in Iran. The highest incidences, 16·1 in the USA and 32·0 in Israel, have been recorded in the Jewish population (appendix pp 3–4). The variability is most likely to be related to different genetic backgrounds and trigger factors (discussed later). This notion is supported by observations in Israel (2006–15) and Germany (1989–97), with Israel having a 3·6 times higher incidence of pemphigus vulgaris in patients with Jewish heritage than in those with Arabic background, and Germany having an 8·8 times higher incidence of pemphigus vulgaris in central Europeans than in patients originating from Italy and Turkey.[12,13] In 2014, prevalence was estimated at 95 per million inhabitants for pemphigus vulgaris and 10 per million for pemphigus foliaceus.[11]

Notably, in some rural areas in South America (Brazil, northern Colombia, and Peru) and Tunisia,[14] much higher incidences of pemphigus foliaceus have been noted than in other parts of the world. So-called endemic pemphigus foliaceus was originally described in 1903 and in its most extensive form is known in Brazil as fogo selvagem (wild fire).[8,15] The prevalence of endemic pemphigus foliaceus in the past century reached 3–5% of the population in well studied rural areas of southeastern Brazil and northern Colombia, but has considerably decreased since then.[8,15–17]

Associated diseases and genetics and risk factors

Pemphigus vulgaris and pemphigus foliaceus are associated with various diseases including other autoimmune disorders, psoriasis, neurological and psychiatric disorders, and some malignancies (appendix pp 5–6).[10,18,19]

The strongest evidence for pemphigus vulgaris risk alleles among all populations has been provided for the HLA alleles DRB1*04:02 and DQB1*05:03 (reviewed by Vodo and colleagues[20]). In fact, most patients with pemphigus vulgaris express one of these two alleles. In two meta-analyses of 18 studies on the association of pemphigus vulgaris with alleles of the HLA-DRB1 and HLA-DQB1 genes, DRB1*04, DRB1*08, DRB1*14, DQB1*05:03, and DQB1*03:02 were significantly increased and DRB1*03, DRB1*07, DRB1*15, DQB1*05:01, DQB1*02, DQB1*06:01, and DQB1*03:03 significantly decreased in patients compared with individuals without the disease.[21,22] In 2018, two genome-wide association studies in Chinese patients with pemphigus vulgaris identified DRB1*14,[23,24] DQB1*05:03,[24] and DRB1*04[24] as relevant risk alleles. So far, four non-HLA genes have been associated with pemphigus vulgaris in at least two populations: *DSG3*, encoding the pemphigus vulgaris autoantigen Dsg3; *TAP2*, encoding an ATP-binding cassette transporter involved in antigen presentation; *IL6*, encoding the pleiotropic cytokine interleukin-6; and *ST18*, encoding a transcription factor involved in inflammation and apoptosis overexpressed in skin tissue in pemphigus vulgaris.[20,23,25] In both non-endemic and endemic Brazilian pemphigus foliaceus, HLA DRB1*04 was the most frequently reported susceptibilty allele.[8,26]

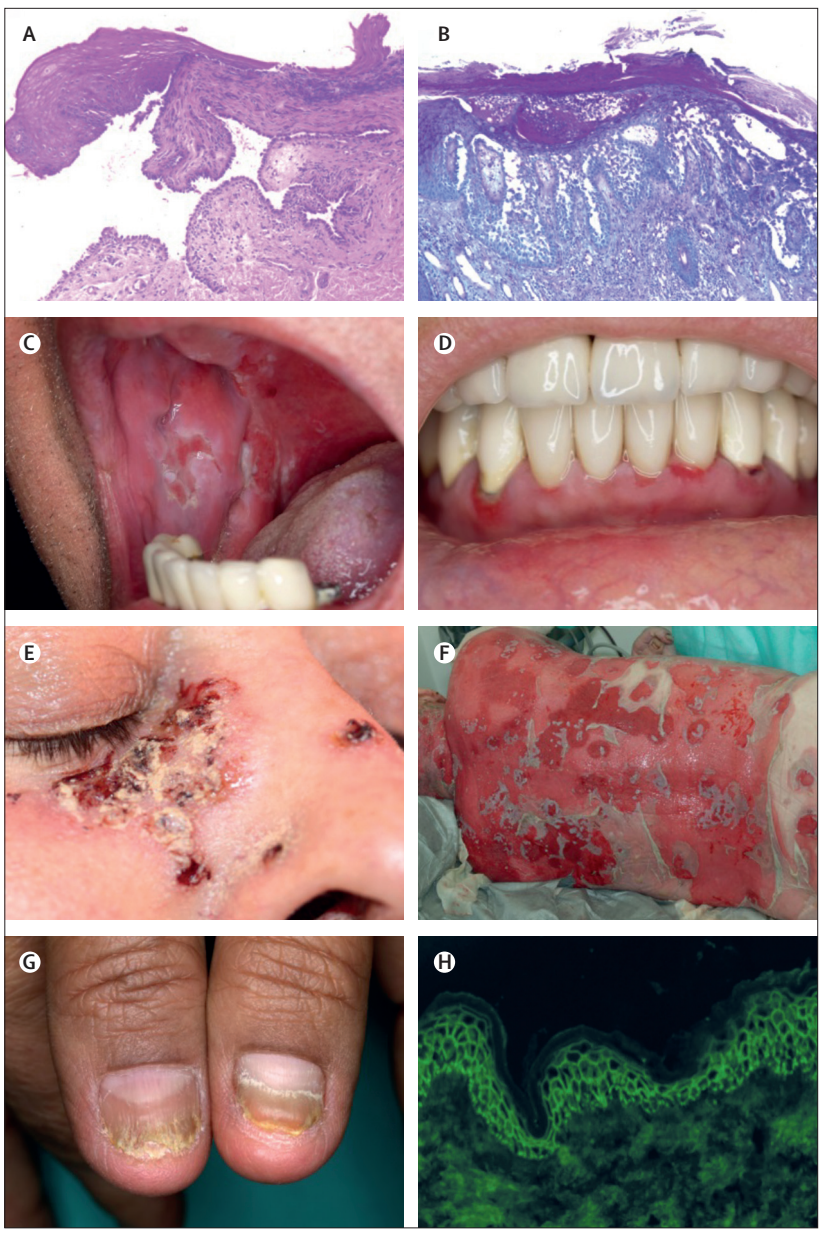

Figure 1: **Pemphigus vulgaris**
Lesional histopathologies of oral (A) and skin (B) biopsies reveal suprabasal splitting and loss of contact between neighbouring keratinocytes (acantholysis). (B) The skin biopsy also shows an inflammatory infiltrate in the serum crust and in the blister directly below the corneal layer. (C) Extensive erosions and enanthema at the right buccal mucosa and palate. (D) Subtle erosions at the lower gingiva close to the teeth. Erosions and crusts on the face (E) and extensive denudation of the entire neck and back (F). (G) Distal onychodystrophy and transverse Beau's line of the thumb nails 8 weeks after massive relapse. (H) Direct immunofluorescence microscopy of a perilesional biopsy specimen shows intercellular deposits of IgG in the epidermis. All images are from the Department of Dermatology of the University of Lübeck (Lübeck, Germany) and the Department of Dermatology of Rouen University Hospital (Rouen, France) and have not been shown previously.

In addition to genetic susceptibility traits, environmental factors that trigger the disease have been postulated. Low concentrations of anti-Dsg autoantibodies are present in the sera of about half of clinically unaffected first-degree relatives of patients with pemphigus,[27,28] and in the sera of

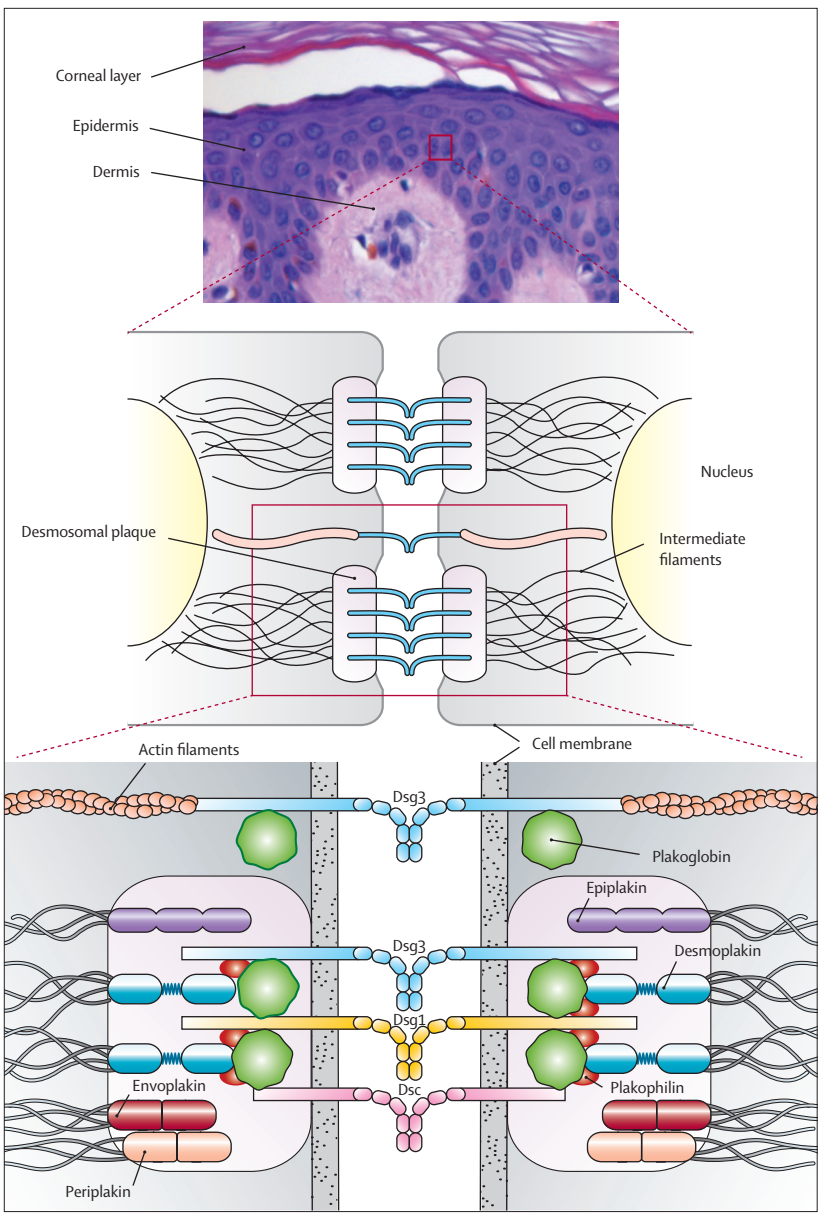

Figure 2: **Schematic diagram of the epidermal desmosome**
Non-desmosomal Dsg is also shown. Although only homophilic transinteractions between Dsg and Dsc molecules are depicted, heterophilic interactions have also been described. Dsg=desmoglein. Dsc=desmocollin. Histopathological image reproduced from Schmidt and Zillikens.[1]

inhabitants of high prevalence areas of endemic pemphigus foliaceus,[15] which suggests more than one triggering factor. In endemic pemphigus foliaceus, the 43·2 kDa salivary protein LJM11 of the sand fly *Lutzomyia longipalpis* was cross-reactive with Dsg1.[29] In non-endemic pemphigus, reported risk factors include the use of particular drugs such as penicillamine and captopril, exposure to pesticides, metal vapour, ultraviolet light, and ionising radiation, sustaining burns, undergoing surgery, and stressful life events.[30–32] Conversely, nicotine (a cholinergic agonist) has a protective effect in pemphigus, which might be explained by the observation that cholinergic agonists are able to reduce acantholysis induced by IgG autoantibodies in pemphigus vulgaris in vitro.[33,34]

Target antigens

Dsg1 and Dsg3 are the major target antigens in pemphigus.[35–40] They belong to the cadherin gene family of Ca^{2+}-dependent transmembrane adhesion molecules found both within and outside of desmosomes (reviewed by Waschke and Spindler[41]). Desmosomes are adherence structures that connect neighbouring cells, including keratinocytes, and enable the cells to withstand mechanical forces (reviewed by Dubash and Green[42]). Several of the structural proteins of desmosomes (figure 2) are recognised by pemphigus autoantibodies. Dsg proteins contain five extracellular domains (EC1–5), a single transmembrane domain, and a cytoplasmic domain containing plakoglobin and plakophilin binding sites. The Dsg molecules interact with each other via their N-terminal EC1 and EC2 domains that are also preferentially targeted by pemphigus autoantibodies.[43,44] In most patients, clinical phenotype is determined by the targeted Dsg molecule. In those with pemphigus foliaceus, lesions are restricted to the skin and autoantibodies solely recognise Dsg1, whereas those with the mucosal-dominant type of pemphigus vulgaris preferentially generate anti-Dsg3 autoantibodies. In patients with the mucocutaneous type of pemphigus vulgaris, which presents with both mucosal and skin lesions, autoantibodies against both Dsg1 and Dsg3 are detected.[45] This remarkable relation of autoantibody specificity to clinical phenotype is reflected in the different expressions of Dsg1 and Dsg3 in the epidermis and surface-close mucosal epithelia. This relation has also guided the assumption that both Dsg molecules can compensate for each other when expressed together in the same cell layer if the adhesive property is compromised in one of the two, as explained by the Dsg compensation theory (appendix p 19).[46] In some patients with the mucocutaneous type of pemphigus vulgaris, autoantibodies are restricted to Dsg3, with skin lesions mainly affecting the face and scalp.[47]

IgG and IgA antibodies against desmocollin (Dsc)1, Dsc2, or Dsc3 have been detected in the sera of less than 5% of patients with pemphigus vulgaris and pemphigus foliaceus in different populations.[48] Increased frequencies of anti-Dsc reactivity have been recorded in the rare variants of pemphigus (ie, IgA pemphigus, pemphigus herpetiformis [appendix pp 1–2], and paraneoplastic pemphigus) and the clinical subtypes of pemphigus vulgaris, pemphigus vegetans, and atypical pemphigus.[48–50] Like the Dsg family of proteins, Dsc molecules are Ca^{2+}-dependent cadherins that form part of the desmosome (figure 2).[41] In addition to antibodies against Dsg1, Dsg3, and Dsc proteins, reactivity against various other molecules such as muscarinic and nicotinic acetylcholine receptors, pemphaxin, mitochondrial proteins, and thyroid peroxidase have been detected in pemphigus by various approaches[51,52] (as reviewed previously[53,54]).

Pathophysiology

The pathophysiology of pemphigus has been the subject of recent comprehensive reviews.[41,52–57] In brief, in genetically susceptible individuals, the autoimmune reaction is driven by autoreactive T lymphocytes and B lymphocytes. Autoreactive T cells are educated (matured) by antigen presenting cells that present specific Dsg peptides via their HLA class II molecules (encoded by the HLA class II risk haplotypes described previously). These CD4 autoreactive T lymphocytes are specific for Dsg molecules and produce IL-10, and drive the generation of Dsg-specific antibodies by B cells (as reviewed previously[55,56,58]). The pathophysiological importance of T lymphocytes in pemphigus vulgaris has also been shown in vitro in transgenic mice expressing HLA-DRB1*04:02 and human CD4 receptor, which on immunisation with human Dsg3, were induced to express human anti-Dsg3 IgG with acantholytic activity.[59]

Ample evidence exists from clinical and experimental observations for the pathogenic relevance of autoantibodies against Dsg1 and Dsg3 in pemphigus, as presented in figure 3. Nevertheless, not all anti-Dsg antibodies are pathogenic, which might explain the finding that in some patients with pemphigus vulgaris, serum concentrations of anti-Dsg3 do not correlate with disease activity (ie, the extent of lesions) and might persist into remission.[54] Pathogenic epitopes on Dsg1 and Dsg3 are Ca^{2+}-dependent and conformational dependent, and typically clustered in the EC1 and EC2 domains, but can be found on all the Dsg extracellular domains (EC1–5).[43,44,68–70]

By contrast with pemphigoid diseases in which a cascade of events including complement activation and effects mediated by antibody Fc receptors are pivotal to autoantibodies inducing subepidermal blister formation,[1] monovalent fragments of anti-Dsg antibodies that lack the Fc portion can also cause acantholysis in vitro and in vivo.[71,72] The exact sequence of events in acantholysis mediated by anti-Dsg antibodies is yet to be fully elucidated; however, three major mechanisms for anti-Dsg IgG binding have been identified: (i) direct interference with Dsg transinteraction (ie, homophilic and heterophilic binding of Dsg molecules to Dsg and Dsc molecules on neighboring cells), an event termed steric hindrance; (ii) remodelling of Dsg expression on the cell surface leading to internalisation and depletion of Dsg from the cell membrane; and (iii) signalling events including p38 mitogen-activated protein kinase, epidermal growth factor receptor, Rho GTPase, MYC proto-oncogene, and caspase pathways that interfere with cytoskeletal architecture[73–75] (as reviewed previously[41,55–57]). Although these three mechanisms are sufficient for acantholysis mediated by anti-Dsg IgG, additional factors, such as non-desmosomal antibodies and soluble Fas ligand (also known as tumor necrosis factor ligand superfamily member 6), might contribute to the pemphigus phenotype.[76]

The pathogenic role of anti-Dsc antibodies in pemphigus is indicated by the clinical phenotype of severe erosions, the microscopic feature of suprabasal splitting in mice deficient in epidermal Dsc1, and the pathogenic effects of anti-Dsc3 IgG in vitro.[77–79] The contribution of antibodies against non-desmosomal antigens to the pathophysiology of pemphigus is suggested by the correlation of serum concentrations of anti-muscarinic acetylcholine receptor IgG with disease severity, and the copathogenic effect of anti-mitochondrial antibodies in addition to anti-Dsg IgG in vitro[80,81] (reviewed by Amber and colleagues[53]).

Clinical presentation and differential diagnoses

Pemphigus vulgaris

In most patients with pemphigus vulgaris, the disease originates in the oral cavity, presenting as enanthema and erosions. Nearly all patients with pemphigus vulgaris will develop oral lesions at some stage of the disease. Erosions are mainly found at the buccal mucosa, palate, tongue, and inner side of the lips, whereas on the gingiva, both enanthema and erosions predominate (figure 1C and 1D). Pain is highly variable and ranges from minor discomfort when chewing hard food to the prevention of food intake leading to rapid weight loss. Involvement of the nasal mucosa gives rise to haemorrhagic crusts. Less frequently involved mucosal surfaces than the nasal mucosa are the pharynx, larynx (in up to 40% of patients, often presenting as hoarseness[82]), oesophagus, urethra, glans penis, vulva, and the perianal area. In the mucocutaneous variant of pemphigus vulgaris, skin lesions arise in parallel with mucosal lesions or develop during the course of the disease. Predilection sites of these skin lesions are the scalp, neck, axillae, and upper trunk, but any site of the body can be affected. The skin lesions typically present as flaccid blisters, erosions and crusts, and large areas can become denuded (figure 1E and 1F). Nail involvement is also seen in patients with extended disease (figure 1G).[83] When mechanical friction is applied in perilesional skin, an erosion can be induced, which is a characteristic but not pathognomonic effect in pemphigus termed Nikolsky's sign (appendix p 18). Both mucosal and skin lesions heal without scarring, but in patients with darker skin, hyperpigmentation at affected skin areas might be visible for many months.

Pemphigus vegetans, a clinical subtype of pemphigus vulgaris, presents with papillomatous vegetations mainly located in the intertriginous spaces (eg, the groin, axillae, and intergluteal folds), and with pustules in a grouped or annular distribution.[84]

Differential diagnoses of the mucosal variant of pemphigus vulgaris include mucous membrane pemphigoid, herpes simplex virus infection, oral lichen planus, apthous ulcers, Behçet's disease, erythema multiforme, and Stevens-Johnson syndrome. In the mucocutaneous variant, skin lesions might resemble those seen in pemphigoid diseases, impetigo, varicella zoster virus infection, Grover's disease, bullous drug eruptions

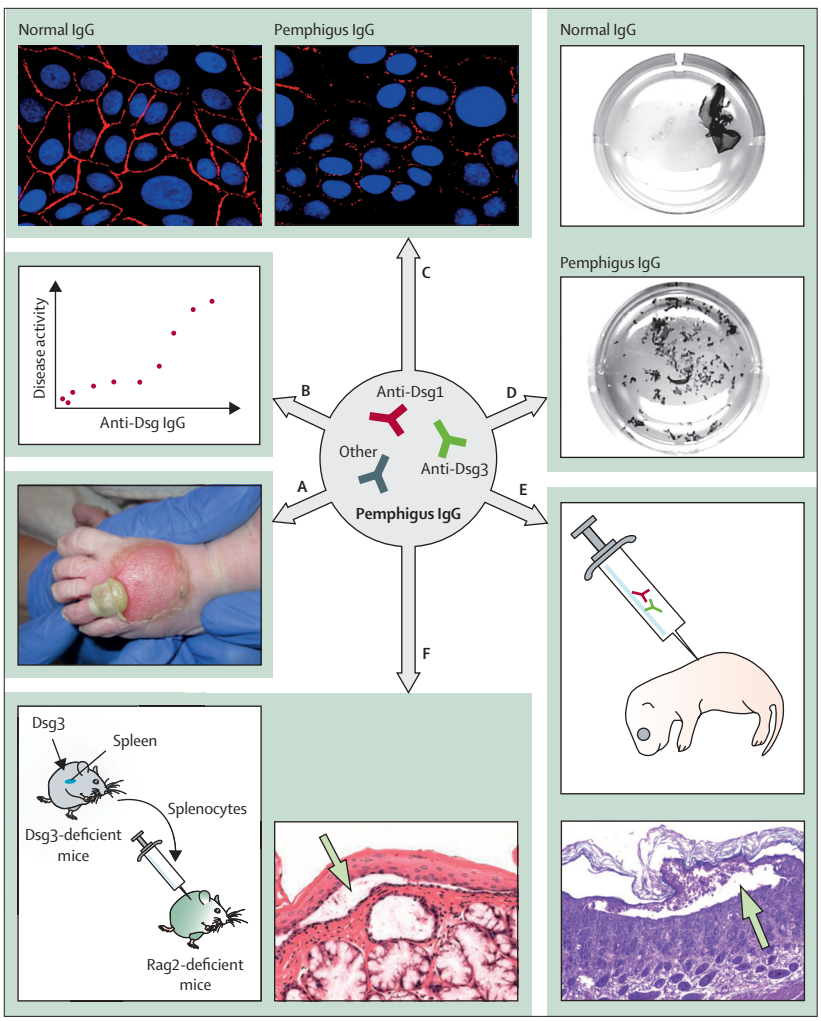

Figure 3: **Pathogenic effects of pemphigus autoantibodies from clinical and experimental findings**
(A) The transplacental transfer of maternal autoantibodies from mothers with pemphigus can cause transient blistering in newborn babies.[60] (B) ELISA values of serum anti-Dsg antibodies parallel disease activity in nearly all patients with pemphigus foliaceus and most with pemphigus vulgaris.[61,62] (C) Degradation of desmosomes (red stain) occurs in cultured keratinocytes after incubation with IgG from patients.[63] (D) Acantholysis of cultured keratinocyte sheets occurs on treatment with IgG from patients.[64] (E) Intraepidermal splitting (arrow) and macroscopic blistering (not shown) occurs in mice injected with sera from patients or monoclonal murine anti-Dsg IgG.[65,66] (F) Anti-Dsg3 antibody production and microscopic (arrow) and macroscopic (not shown) blistering are induced in immunodeficient mice with Rag2 knockout after adoptive transfer of lymphocytes from Dsg3-deficient mice after immunisation with recombinant Dsg3.[67] The actions of other IgGs are debated. The clinical picture in (A) was provided courtesy of Susann Ott (Department of Paediatrics, Klinikum Bayreuth, Bayreuth, Germany) and the histology image in (F) was provided courtesy of Hayato Takahashi and Masayuki Amagai (Department of Dermatology, Keio University School of Medicine, Tokyo, Japan). All other images are from the Department of Dermatology at the University of Lübeck (Lübeck, Germany) and have not been published previously. Dsg=desmoglein. Rag2=recombination activating 2.

including toxic epidermal necrolysis, and dermatitis artefacta. When flexures are predominantly affected, Hailey-Hailey disease (benign chronic familial pemphigus) should be ruled out.

Pemphigus foliaceus

In contrast to pemphigus vulgaris, in pemphigus foliaceus mucosal surfaces are spared and lesions exclusively develop on the skin, predominantly presenting as erythema, so-called puff pastry-like scaling, and crusting (figure 4). Intact blisters are rarely seen because of subcorneal splitting, which allows mechanical destruction of the blister roof (figure 4E). The face, scalp, and seborrhoeic areas of the upper trunk are predilection sites of the lesions (figure 4A–C). The Nikolsky's sign is positive (appendix p 18) and, similar to in pemphigus vulgaris, lesions heal without scarring, but typically result in postinflammatory hyperpigmentations. In mild cases, the clinical presentation mimics severe seborrhoeic dermatitis and Darier's disease. In contrast to pemphigus vulgaris, even in severe forms of pemphigus foliaceus, large eroded areas are not seen and exfoliation might resemble erythroderma also found in severe atopic dermatitis, psoriasis, mycosis fungoides, and drug eruptions. Erosions are also prone to bacterial and herpes virus superinfection.

In pemphigus erythematosus, a clinical subtype of pemphigus foliaceus, lesions mainly involve photodistributed areas such as the face, back, and trunk, and resemble those in cutaneous lupus erythematosus. In sun damaged skin, the clinical features and so-called lupus band-like deposition of immune complexes at the dermal–epidermal junction might be due to tissue destruction induced by UV irradiation in this zone.[85] The clinical presentation of endemic pemphigus foliaceus is described in the appendix (p 1–2).

Rare pemphigus variants

Paraneoplastic pemphigus

Paraneoplastic pemphigus accounts for about 5% of pemphigus cases. Clinical presentation is polymorphous, with flaccid blisters similar to pemphigus vulgaris, pustules, tense blisters similar to bullous pemphigoid, erythema-multiforme-like targetoid erythema and lichenoid lesions.[86,87] The most striking clinical feature is the severe stomatitis with, unlike in pemphigus vulgaris, frequent painful ulcers on the tongue and erosions on the lips that extend to the vermillion border of the lips and resemble those in Stephens-Johnson syndrome (appendix p 20). Other mucosal tissues such as genital, nasal, and ocular can also be affected.[86,88] In almost all patients, a neoplasm is associated with the pemphigus,[86–89] which warrants an extensive tumour search. In 70–80% of patients with paraneoplastic pemphigus, a lymphoproliferative disorder (mostly non-Hodgkin lymphoma and chronic lymphocytic leukaemia) is present, and in the remaining patients, thymoma, malignant solid tumours, and Castleman tumour are typically diagnosed.[86–89] In Asia, the most frequent associated neoplasm is Castleman's disease[90,91] and in some patients, the neoplasm is only detected during the course of pemphigus.[86] In Chinese patients with paraneoplastic pemphigus, myasthenia gravis has been reported in a third of patients.[92] Pulmonary destruction leading to bronchiolitis has been found in 6% of European patients with paraneoplastic pemphigus, but in 20% of Japanese patients, and 70% of the few cases reported in children,

and appeared to be more frequent with underlying Castleman's disease.[86,88,93,94] In Japanese patients, the occurrence of bronchiolitis obliterans was associated with anti-epiplakin antibodies, and explained experimentally by the ectopic expression of Dsg3 in the lung.[95,96] The potential lung involvement led some clinicians to use the term paraneoplastic autoimmune multiorgan syndrome rather than paraneoplastic pemphigus.[97]

Autoantibodies in paraneoplastic pemphigus mainly target Dsg3 and the plakin proteins envoplakin and periplakin (figure 2).[86,87,98–102] In addition, autoantibodies against Dsg1, desmocollins, the plakin proteins, desmoplakin, plectin, epiplakin, bullous pemphigoid antigen (BP)230 (also known as dystonin-e), BP180 (also known as collagen α-1[XVII] chain) and the proteinase inhibitor α2-macroglobulin-like protein 1 have been described (appendix pp 7–8 and figure 2). In contrast to pemphigus vulgaris and pemphigus foliaceus, cytotoxic CD4 and CD8 lymphocytes seem important for tissue destruction in paraneoplastic pemphigus.[103,104] This assumption is in line with the characteristic histopathological findings of lymphocytes in the epidermis, dyskeratotic keratinocytes, and lichenoid and interface dermatitis in patients with paraneoplastic pemphigus.[86,89] Additionally, the transfer of Dsg3-specific CD4 cells and B cells from Dsg3-deficient mice into immunodeficient mice is able to induce skin lesions with similar histopathological findings to those in patients with paraneoplastic pemphigus.[103]

Neonatal pemphigus

Neonatal pemphigus is a transient disease in newborn babies caused by the transplacental passage of autoantibodies from a mother with pemphigus, giving the earliest evidence for the direct pathogenic effect of pemphigus autoantibodies (figure 3; reviewed in Zhao et al[105]). Skin lesions are present in about half of neonates from mothers with pemphigus vulgaris and resolve either spontaneously or with mild topical corticosteroids within 1 to 4 weeks.[106] However, pemphigus vulgaris in pregnancy seems associated with prematurity and fetal death, particularly in mothers with severe clinical disease.

Other rare variants, IgA pemphigus and pemphigus herpetiformis that together account for <5% of pemphigus cases[3] are presented in the appendix (pp 2, 20).

Outcome measures and quality of life

An international panel of experts has defined disease endpoints and therapeutic responses.[107] The best validated and most frequently used scores in clinical studies are the Autoimmune Bullous Skin Disorder Intensity Score (ABSIS; between 0 and 206 according to the extent of skin lesions, number of involved anatomical sites in the oral cavity, and discomfort during food intake) and the Pemphigus Disease Area Index (PDAI; between 0 and 263 based on the number of lesions on the skin, scalp, and mucosa, and region of skin damage).[108,109] In a large prospective multicentre study, on the basis of the quartiles of the disease scores disease activity was defined as mild (<15 for PDAI, <17 for ABSIS), moderate (15–45 for PDAI, 17–53 for ABSIS), and severe (>45 for PDAI, >53 for ABSIS).[108]

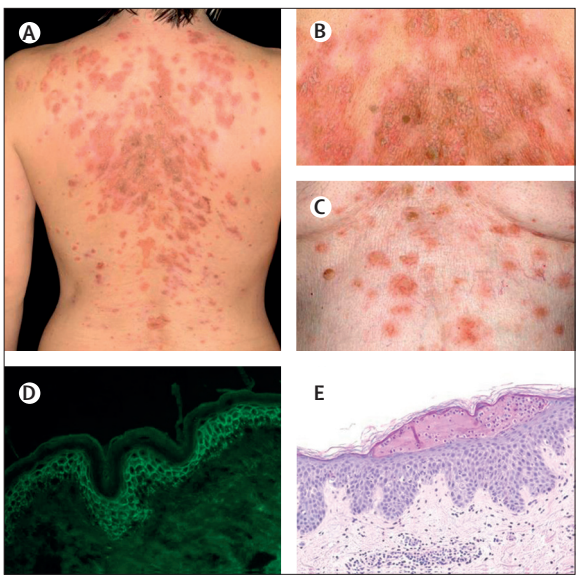

Figure 4: **Pemphigus foliaceus**
Erythema, erosions, and so-called puff pastry-like scaling on the back (A and B) and upper abdomen (C). (D) Direct immunofluorescence microscopy of a lesional skin biopsy showing intercellular deposits of IgG in the epidermis. (E) Histology of a lesional skin biopsy showing a subcorneal split directly below the corneal layer with some inflammatory cells in the blister cavity. All images are from the Department of Dermatology of the University of Lübeck (Lübeck, Germany) and have not been shown previously.

Health-related quality of life in pemphigus has been established via various generic measures in different patient populations and led to heterogeneous, in part contradictory, findings (reviewed by Rencz and colleagues[110]). Although no instrument to specifically assess quality of life in pemphigus is available, a questionnaire for autoimmune bullous diseases has been developed and validated in different languages and populations.[111]

Diagnostic investigations

Diagnosis of pemphigus vulgaris, pemphigus foliaceus, and IgA pemphigus is based on a combination of the clinical presentation, direct immunofluorescence microscopy of a perilesional biopsy, serology, and histopathology of a lesional biopsy (table).[112–114] In these two types, direct immunofluorescence microscopy reveals intercellular deposits of IgG (figure 1H and figure 4D), complement component 3, or both, and in IgA pemphigus, of IgA in the epidermis and mucosal epithelium. The most sensitive substrate for indirect immunofluorescence microscopy for screening of serum autoantibodies is monkey oesophagus,[114] in which immunoreactants stain the epithelium in an intercellular pattern (appendix p 20). Highly sensitive and specific ELISA systems for the

	General frequency (% of cases)	Target antigens*	Clinical hallmarks	Diagnostic clues
Pemphigus vulgaris	60–90%	Dsg3†‡ and Dsg1‡	Nearly always mucosal involvement: mostly oropharyngeal, nasal, and genital	Mucosal lesions, positive Nikolsky's sign, positive direct immunofluorescence microscopy result§, and serum antibodies against Dsg3
Pemphigus foliaceus	10–30%	Dsg1†‡	Crusted erosions, erythema, scales mainly in the seborrhoeic areas; no mucosal lesions	Crusted erosions, no mucosal lesions, positive Nikolsky's sign, positive direct immunofluorescence microscopy result§, and serum antibodies against Dsg1
Paraneoplastic pemphigus¶	5%	Envoplakin†‡, periplakin†, Dsg3†‡, desmoplakin, plectin, epiplakin, BP230‡, BP180‡, Dsc1, Dsc2, Dsc3, Dsg1‡, and α2-macroglobulin-like protein 1†	Severe stomatitis involving the tongue and vermilion; erythema multiforme-like and lichenoid skin lesions; neoplasia, generally leukaemia or lymphoma	Severe stomatitis, neoplasm, dyskeratosis and interface dermatitis, and serum antibodies against Dsg3 and plakins
IgA pemphigus	<3%	Dsc1†, Dsc2, Dsc3, Dsg3, and Dsg1	Flaccid pustules, annular erosions, crusts, and erythematous plaques	Pustules, staining of intercellular IgA in the epithelium by direct immunofluorescence microscopy

Dsg=desmoglein. BP=bullous pemphigoid antigen. Dsc=desmocollin. *Further target antigens of uncertain pathogenic relevance have been described. †Main target antigens. ‡Commercial detection systems are available. §Intercellular deposits of IgG, complement component 3, or both. ¶No official consensus for diagnosis has been reached (appendix pp 9–10).

Table: **Autoantibody specificities and clinical characteristics of pemphigus diseases**

detection of serum IgG against Dsg1 and Dsg3 are commercially available.[112–114] Alternatively, an indirect immunofluorescence microscopy system based on a human cell line that expresses either recombinant Dsg1 or recombinant Dsg3 can be applied (appendix p 20).[114,115] In a recent international prospective multicentre study, anti-Dsg1, anti-Dsg3, or both types of IgG autoantibodies could be detected in 98·5% of more than 300 consecutive pemphigus serum samples.[48] Histopathology of a lesional biopsy might help to reveal subcorneal splitting in pemphigus foliaceus (figure 4E) and suprabasal split formation and acantholysis in pemphigus vulgaris (figure 1A and figure 1B).

For the diagnosis of paraneoplastic pemphigus no official consensus has been reached (suggested diagnostic criteria[87,89,98,99] are shown in the appendix pp 9–10). The presence of anti-plakin antibodies is essential for the diagnosis of paraneoplastic pemphigus, in addition to the clinical presentation of severe stomatitis or lichenoid skin lesions (or both), the presence of a neoplasia, and direct immunofluorescence microscopy of a perilesional biopsy showing intercellular IgG deposits in the epithelium that might or might not be accompanied by linear staining of the basement membrane zone (table).[87,89,98,99] The serum of most patients with paraneoplastic pemphigus will also contain antibodies against Dsg3 (appendix pp 9–10).[100] A sensitive screening substrate by indirect immunofluorescence microscopy is rat bladder, in which serum autoantibodies bind to the plakin-rich urothelium (appendix p 20).[87,98,101] For the detection of anti-plakin antibodies, only BP230 and envoplakin ELISA systems are standardised and widely available.[101] Autoantibody reactivities in paraneoplastic pemphigus are detailed in the appendix (pp 7–8).

Treatment

The availability of evidence-based treatment in pemphigus is hampered by the rarity of the disease and the paucity of randomised controlled trials (RCTs; appendix pp 11–16). Systemic corticosteroids remain the mainstay treatment, and the initial objective of treatment is to control disease activity (figure 5).[112,113,116,117] Most clinicians will use oral prednisone or oral prednisolone as the mainstay corticosteroid treatment, frequently combined with oral azathioprine or a mycophenolate compound (mycophenolate mofetil or mycophenolate sodium). They will also begin to taper the corticosteroid at the end of the consolidation phase, when patients have no new blisters for 2 weeks and healing of about 80% of established lesions has occurred.[107] The objectives during the following maintenance phase are to achieve complete remission, prevent relapses during prednisolone tapering, and avoid as many potential adverse effects as possible.[107] However, relapses occur in up to 50% of patients, and severe adverse events related to immunosuppressants in up to 65% of patients, and only about half of patients are able to stop taking corticosteroid after 3 years.[118–120] Treatment principles in pemphigus have recently been challenged by the first-line use of rituximab, which allowed 70% of patients to achieve remission off-corticosteroids after 6 months and 90% of patients to achieve remission after 2 years.[120]

Recommendations for treatment of pemphigus vulgaris and pemphigus foliaceus are outlined in figure 5.

Oral corticosteroids are indicated in patients with pemphigus vulgaris and in those with pemphigus foliaceus. The initial dosage is usually 0·5–1·0 mg/kg daily of oral prednisone or prednisolone in patients with moderate pemphigus, and 1·0–1·5 mg/kg daily in those with severe pemphigus.[112,113,116] If lesions do not improve within 10–15 days, the dose is increased. Alternatively, intravenous corticosteroid pulses, such as prednisolone 500–1000 mg daily for 5 consecutive days, or dexamethasone 100 mg daily for 3 consecutive days, can be given. Once disease control is achieved, a decrease of the prednisone or prednisolone dose is

usually proposed, by 25% every 2 weeks until 20 mg daily is reached, then by 2·5 mg weekly until 10 mg daily is reached, with tapering by 1 mg decrements thereafter.[112,113,116] A more rapid tapering of corticosteroids over 3–6 months is proposed in patients treated first-line with a combination of rituximab and prednisone or prednisolone.[120]

Many drugs have been applied to reduce the required dose of corticosteroids and their detrimental adverse effects. Azathioprine and mycophenolate compounds are frequently recommended.[112,113] To our understanding, cyclophosphamide is less frequently used because of its toxicity, with large regional variations apparent. High-dose intravenous immunoglobulins (IVIGs) are mainly applied in severe and recalcitrant pemphigus.[112,113,116] The importance of these conventional corticosteroid-sparing drugs in the treatment of pemphigus is likely to change in the coming years because of the high effectiveness of rituximab.[116,120]

Rituximab, a monoclonal antibody directed against the CD20 antigen on B-lymphocytes, depletes CD20 B cells from the circulation for 6–12 months, and was first introduced in the treatment of paraneoplastic pemphigus in 2001 and of pemphigus vulgaris in 2002.[121] The clinical effectiveness of rituximab was subsequently highlighted in several case series applying different protocols and adjuvants.[122–124] On the basis of these case series and two meta-analyses of collectively more than 500 patients with pemphigus vulgaris or pemphigus foliaceus, researchers found that (1) remission was achieved in 75% of patients after one cycle of rituximab with a mean delay of 3–6 months;[56,120,121,124–126] (2) 80–90% of patients reached complete remission on or off therapy, and on and off therapy with repeated rituximab infusions;[120,121,125,126] (3) relapses were frequent, occurring in 40–60% of patients, particularly in those without maintenance infusions and with increased follow-up time;[123] (4) application of rituximab early in the disease course was associated with a higher proportion of patients in complete remission than in late application as second or third line treatment;[120] and (5) severe adverse events were recorded in 4–10% of patients, including fatal outcomes (in 1–2%).[120,126]

In an RCT[120] of 90 patients with newly-diagnosed pemphigus vulgaris or pemphigus foliaceus showed a large superiority of rituximab over a standard corticosteroid regimen. 89% of patients treated with rituximab (2 × 1 g at baseline and 0·5 g at 12 months and 18 months) combined with short-term prednisolone (0·5–1·0 mg/kg daily for 3–6 months) were in complete remission off therapy at 2 years, compared with 34% of those given prednisone alone (1·0–1·5 mg/kg daily for 12–18 months; p<0·0001). Additionally, in the rituximab group, the cumulative prednisone dose was three times lower (p<0·0001) and the number of severe adverse events two times lower (p=0·0084) than in the prednisone group.[120] On the basis of these data, rituximab has recently been approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of moderate-to-severe pemphigus.

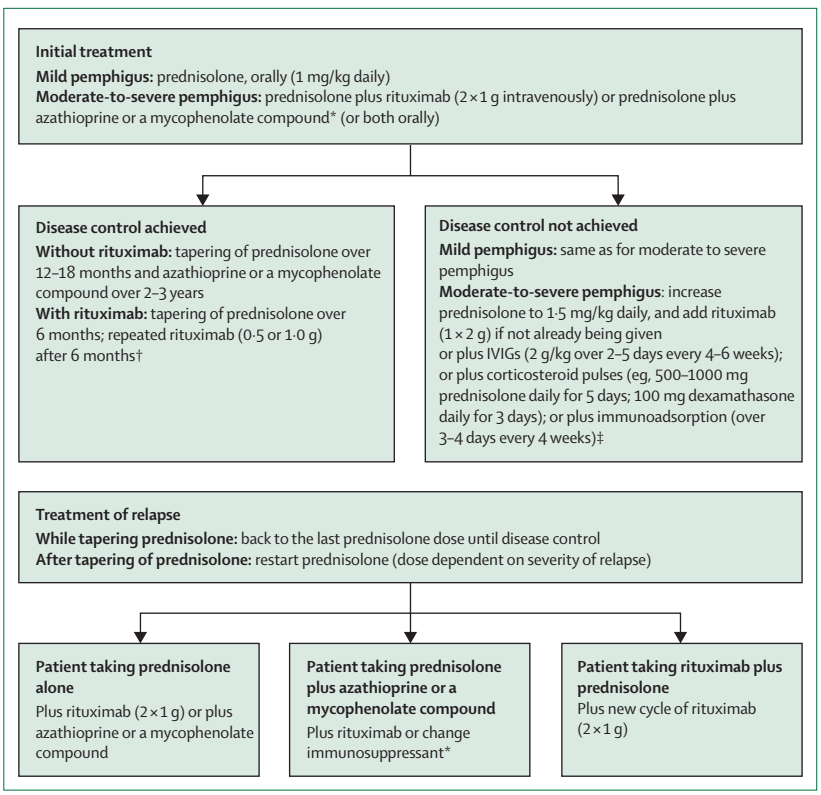

Figure 5: **Treatment algorithm for pemphigus vulgaris and pemphigus foliaceus**
Based on recommendations of an international panel of experts[116] and revised guidelines of the European Academy of Dermatology and Venereology. IVIGs=intravenous immunoglobulins. *If rituximab is not available or contraindicated. †In particular in patients with initially severe pemphigus and high serum concentrations of anti-desmoglein antibodies at month 3; additional rituximab infusions (0·5 g) after 12 months and 18 months might be considered. ‡Might also be used as initial adjuvant therapy in patients with severe pemphigus.

Several arguments favour maintenance infusions of rituximab to reduce the risk of relapses (eg, 6, 12, and 18 months after the initial dose),[120] despite their optimum time and dose being as yet unknown. Patients with high serum concentrations of anti-Dsg1 and anti-Dsg3 at month 3 seem to have an increased risk of relapse (Joly P, unpublished), and might especially benefit from maintenance infusions of rituximab.

In line with the RCTs listed in the appendix (pp 11–16), a Cochrane review and a meta-analysis of RCTs assessing adjuvant therapies, which included ten trials and 559 participants, concluded that azathioprine, mycophenolate compounds, and cyclophosphamide in addition to a corticosteroid were not better at achieving disease control, clinical remission, or avoiding severe adverse events including death than corticosteroid alone.[127,128] Although the adjuvant therapies collectively decreased the risk of relapse by about 30%, analysis of each adjuvant separately showed no single one that was significantly associated with fewer relapses than corticosteroid alone.[127] However, azathioprine and

cyclophosphamide did show a corticosteroid-sparing effect.[127]

Azathioprine at a dose of 2–3 mg/kg daily (with normal thiopurine methyltransferase activity) and mycophenolate compounds (mycophenolate mofetil at a dose of 2–3 g daily and mycophenolate sodium at a dose of 1·44 mg daily) might be considered as first-line corticosteroid-sparing drugs when rituximab is not available or contraindicated (figure 5).[116] Cyclophosphamide at doses of 75–150 mg daily orally or 500–1000 mg monthly intravenously is rarely used in the USA and Europe. Because of its high number of adverse effects and long-term risk of infertility and malignancies, cyclophosphamide might be reserved for patients with refractory disease when rituximab is not available.[109] Methotrexate, cyclosporine, and dapsone have very restricted indications in pemphigus and are reserved for individual treatment situations.

The efficacy of IVIGs in pemphigus has been suggested by several case series[129] and one RCT.[130] This RCT included Japanese patients with pemphigus vulgaris or pemphigus foliaceus who were unresponsive to prednisolone (≥20 mg daily). The endpoint time to escape from the treatment protocol (ie, the length of time a patient adhered to the protocol without any additional treatment) was significantly extended in patients given a single cycle of IVIG at 2 g/kg.[130] In this meta-analysis, IVIG was the only adjuvant that increased the number of patients in whom disease was controlled.[127] IVIGs have a complex mode of action, including saturation of the neonatal Fc receptor, inhibition of antigen presentation, and anti-inflammatory effects of Fc-sialylated IgG (reviewed by Amber and colleagues[131]). The main advantages of IVIGs are that they act rapidly and do not increase the risk of infection. IVIGs are generally infused at a dose of 2 g/kg over 2–5 days with monthly repetitions. In a case series,[132] combining IVIGs with rituximab resulted in long-lasting remission without severe adverse effects.

Plasmapheresis has shown an unfavourable risk-benefit ratio in pemphigus (appendix pp 11–16). By contrast, immunoadsorption does not require plasma substitution, specifically binds Ig molecules, allows the processing of 2–3 plasma volumes, and rapidly removes anti-Dsg IgG from the circulation.[133,134] Immunoadsorption is applied on 3–4 consecutive days at intervals of 3–4 weeks. In an RCT of 72 patients with pemphigus vulgaris or pemphigus foliaceus, immunoadsorption combined with standard therapy (ie, prednisolone at an initial dose of 1 mg/kg daily combined with azathioprine or a mycophenolate compound) led to faster remission and required significantly fewer corticosteroids than standard therapy alone in patients with high disease activity (DRKS00000566). Although the total number of adverse events was lowest in the immunoadsorption plus standard therapy group, the number of severe adverse events was higher in the standard therapy alone group (unpublished). A meta-analysis[126] of patients with pemphigus given various rituximab protocols showed that immunoadsorption-combined regimens resulted in the fastest control of disease activity before completion of rituximab therapy; thus, immunoadsorption might be especially helpful in patients with severe disease during the 2–4 months until rituximab becomes fully effective. Although immunoadsorption is widely available in Europe, it is used mainly in Germany and Austria.

Since paraneoplastic pemphigus is most likely to be triggered by the underlying neoplasm, oncological therapy is paramount. For the autoimmune bullous disease, systemic corticosteroids, rituximab, immunoadsorption, and IVIG have successfully been applied.[89,100]

Before the initiation of corticosteroid or immunosuppressive therapy, complete blood count; blood tests for creatinine, electrolytes, liver enzymes, albumin, fasting serum glucose, and hepatitis B and C and HIV serology; an ocular examination (for glaucoma and cataracts); and the exclusion of tuberculosis are recommended.[116] Additionally, the vaccination status of the patient needs to be updated, and osteoporosis prophylaxis is indicated. Treatments such as nursing care and the treatment of children and pregnant woman are detailed elsewhere.[7,112,135] The involvement of patient support groups is highly recommended (appendix p 17).

Outcomes

The mortality associated with pemphigus vulgaris and pemphigus foliaceus dramatically decreased with the use of corticosteroids in the early 1950s, from approximately 75% to 30% in most regions.[136] Over the past decade, studies from the UK, France, Israel, and Taiwan showed the risk of death to be 1·7 to 3 times higher in pemphigus than in controls.[3,4,12,137,138] Infections, in particular pneumonia and septicaemia, were the most frequent causes of death in different study populations, followed by cardiovascular diseases and peptic ulcer disease.[137,139] Herpes simplex virus DNA was found in the oral mucosa of 30% of treatment-refractory patients with pemphigus vulgaris, and might mimic an exacerbation of the disease.[140] Various comorbidities related to corticosteroid use have been reported in pemphigus vulgaris and pemphigus foliaceus, including Cushing syndrome, infections (particularly opportunistic herpes virus, and fungal infections), osteoporosis, venous thromboembolism, and type 2 diabetes.[138,141,142]

In paraneoplastic pemphigus, mortality is notably higher than for pemphigus vulgaris and pemphigus foliaceus, reaching up to 60% in patients with paraneoplastic pemphigus within 5 years of diagnosis, compared with 20–25% in pemphigus vulgaris and pemphigus foliaceus.[3,88] The main causes of death in paraneoplastic pemphigus are infections, the underlying neoplasm, and bronchiolitis obliterans.[88,93,94]

Increased serum concentrations of anti-Dsg3, mucosal involvement, and younger age at disease onset have been described as risk factors for increased disease duration in

pemphigus vulgaris and pemphigus foliaceus.[143] For patients with pemphigus vulgaris in remission, positive ELISA values for anti-Dsg3 seem to be predictors of relapse.[144] In paraneoplastic pemphigus, erythema multiforme-like skin lesions have been described as predictive of fatal outcome.[88]

Outlook

Although the advent of rituximab has revolutionised the treatment of pemphigus, the possibility of severe adverse events, the 10% of patients who do not adequately respond to rituximab, and those who require a high number of repeated rituximab infusions[120,125,126] indicate the capacity for new treatment modalities. Phase 2 trials are underway of ofatumumab (NCT02613910), an alternative anti-CD20 antibody with increased binding affinity for CD20, and of inhibitors for the neonatal Fc receptor (EudraCT number 2017-002333-40), tyrosine-protein kinase BTK (EudraCT number 2018-002261-19), and B-cell activating factor (NCT01930175). Furthermore, clinical trials are awaited that are based on Dsg-specific immunoadsorption[70,145] and on chimeric autoantibody receptor technology that engineers human T cells to express a chimeric autoantibody receptor consisting of Dsg3 fused to a CD137-CD3-ζ signalling domain, allowing selective depletion of autoreactive B cells.[146]

Contributors

All authors reviewed the literature, collected and interpreted data, and wrote the manuscript. ES prepared the figures.

Declaration of interests

ES reports personal fees from Roche, grants from the German Research Foundation and Euroimmun, and grants and personal fees from Fresenius Medical Care, Biotest, Union Chimique Belge, and argenx, during the conduct of the Review. ES also reports grants and personal fees from Novartis, TxCell, True North Therapeutics, Incyte, and Amryt Pharma, and personal fees from Genetech, outside of the submitted work. PJ reports personal fees from Principia Biopharma, argenx, Lilly, Novartis, Abbvie, Amgen, and Uriage, personal fees and non-financial support from Roche, Janssen, Bristol-Myers Squibb, and Pierre Fabre, outside of the submitted work. MK declares no competing interests. No authors within the past 3 years had stocks or shares, equity of a relevant company, a contract of employment or a named position on a company board. No organisation other than *The Lancet* has asked the authors to write, be named on, or submit the paper.

Acknowledgments

This Seminar is dedicated to Marcel F Jonkman, Groningen, Netherlands, who contributed enormously to the field of research on pemphigus and who passed away at the height of his career after a short and severe illness. We miss his vast clinical knowledge, sharp intellect, clear concepts, and strong beliefs in scientific discussions. This work was supported by the German Research Foundation under Germany's Excellence Strategy (grant number EXC 2167).We acknowledge researchers who have contributed to this field whose work was not cited directly but through review articles because of space limitation. We thank Stephanie Goletz, Florian Heck, Sabrina Tofern, and Marina Kongsbak-Reim for their help with the immunofluorescence and histopathological photographs, and Carolin Mahlerwein for the graphical design of figure 2.

References

1 Schmidt E, Zillikens D. Pemphigoid diseases. *Lancet* 2013; **381:** 320–32.
2 Schmidt E, Borradori L, Joly P. Epidemiology of autoimmune bullous diseases. In: Murrell D, ed. Blistering diseases, 1st edn. Heidelberg: Springer, 2015: 251–64.
3 Jelti L, Cordel N, Gillibert A, et al. Incidence and mortality of pemphigus in France. *J Invest Dermatol* 2018; **139:** 469–73.
4 Langan SM, Smeeth L, Hubbard R, Fleming KM, Smith CJ, West J. Bullous pemphigoid and pemphigus vulgaris—incidence and mortality in the UK: population based cohort study. *BMJ* 2008; **337:** a180.
5 Mintz EM, Morel KD. Treatment of chronic bullous disease of childhood. *Dermatol Clin* 2011; **29:** 699–700.
6 Mintz EM, Morel KD. Clinical features, diagnosis, and pathogenesis of chronic bullous disease of childhood. *Dermatol Clin* 2011; **29:** 459–62.
7 van Beek N, Schmidt E. Chapter 74: Autoimmune bullous diseases. In: Höger P, Kinsler V, Yan A, eds. Harper's textbook of pediatric dermatology, 4th edn. Chichester: Wiley-Blackwell, in press: 868–97.
8 Aoki V, Rivitti EA, Diaz LA. Update on fogo selvagem, an endemic form of pemphigus foliaceus. *J Dermatol* 2015; **42:** 18–26.
9 Diaz LA, Sampaio SA, Rivitti EA, et al. Endemic pemphigus foliaceus (fogo selvagem): II. Current and historic epidemiologic studies. *J Invest Dermatol* 1989; **92:** 4–12.
10 Kridin K. Pemphigus group: overview, epidemiology, mortality, and comorbidities. *Immunol Res* 2018; **66:** 255–70.
11 Hubner F, Recke A, Zillikens D, Linder R, Schmidt E. Prevalence and age distribution of pemphigus and pemphigoid diseases in Germany. *J Invest Dermatol* 2016; **136:** 2495–98.
12 Kridin K, Zelber-Sagi S, Bergman R. Pemphigus vulgaris and pemphigus foliaceus: differences in epidemiology and mortality. *Acta Derm Venereol* 2017; **97:** 1095–99.
13 Hahn-Ristic K, Rzany B, Amagai M, Brocker EB, Zillikens D. Increased incidence of pemphigus vulgaris in southern Europeans living in Germany compared with native Germans. *J Eur Acad Dermatol Venereol* 2002; **16:** 68–71.
14 Morini JP, Jomaa B, Gorgi Y, et al. Pemphigus foliaceus in young women. An endemic focus in the Sousse area of Tunisia. *Arch Dermatol* 1993; **129:** 69–73.
15 Warren SJ, Lin MS, Giudice GJ, et al. The prevalence of antibodies against desmoglein 1 in endemic pemphigus foliaceus in Brazil. *N Engl J Med* 2000; **343:** 23–30.
16 Goncalves GA, Brito MM, Salathiel AM, Ferraz TS, Alves D, Roselino AM. Incidence of pemphigus vulgaris exceeds that of pemphigus foliaceus in a region where pemphigus foliaceus is endemic: analysis of a 21-year historical series. *An Bras Dermatol* 2011; **86:** 1109–12.
17 Abreu-Velez AM, Hashimoto T, Bollag WB, et al. A unique form of endemic pemphigus in northern Colombia. *J Am Acad Dermatol* 2003; **49:** 599–608.
18 Kridin K, Zelber-Sagi S, Comaneshter D, Batat E, Cohen AD. Pemphigus and hematologic malignancies: a population-based study of 11 859 patients. *J Am Acad Dermatol* 2018; **78:** 1084–89.e1.
19 Schulze F, Neumann K, Recke A, Zillikens D, Linder R, Schmidt E. Malignancies in pemphigus and pemphigoid diseases. *J Invest Dermatol* 2015; **135:** 1445–47.
20 Vodo D, Sarig O, Sprecher E. The genetics of pemphigus vulgaris. *Front Med* 2018; **5:** 226.
21 Yan L, Wang JM, Zeng K. Association between HLA-DRB1 polymorphisms and pemphigus vulgaris: a meta-analysis. *Br J Dermatol* 2012; **167:** 768–77.
22 Li S, Zhang Q, Wang P, et al. Association between HLA-DQB1 polymorphisms and pemphigus vulgaris: a meta-analysis. *Immunol Invest* 2018; **47:** 101–12.
23 Gao J, Zhu C, Zhang Y, et al. Association study and fine-mapping major histocompatibility complex analysis of pemphigus vulgaris in a Han Chinese population. *J Invest Dermatol* 2018; **138:** 2307–14.
24 Zhang SY, Zhou XY, Zhou XL, et al. Subtype-specific inherited predisposition to pemphigus in the Chinese population. *Br J Dermatol* 2018; **180:** 828–35.
25 Sarig O, Bercovici S, Zoller L, et al. Population-specific association between a polymorphic variant in ST18, encoding a pro-apoptotic molecule, and pemphigus vulgaris. *J Invest Dermatol* 2012; **132:** 1798–805.
26 de Sena Nogueira Maehara L, De-Souza-Santana FC, Porro AM, et al. HLA class II alleles of susceptibility and protection in Brazilian and Dutch pemphigus foliaceus. *Br J Dermatol* 2018; **178:** e212–14.

27 Brandsen R, Frusic-Zlotkin M, Lyubimov H, et al. Circulating pemphigus IgG in families of patients with pemphigus: comparison of indirect immunofluorescence, direct immunofluorescence, and immunoblotting. *J Am Acad Dermatol* 1997; **36:** 44–52.

28 Ahmed AR, Mohimen A, Yunis EJ, et al. Linkage of pemphigus vulgaris antibody to the major histocompatibility complex in healthy relatives of patients. *J Exp Med* 1993; **177:** 419–24.

29 Qian Y, Jeong JS, Maldonado M, et al. Cutting edge: Brazilian pemphigus foliaceus anti-desmoglein 1 autoantibodies cross-react with sand fly salivary LJM11 antigen. *J Immunol* 2012; **189:** 1535–39.

30 Wolf R, Tamir A, Brenner S. Drug-induced versus drug-triggered pemphigus. *Dermatologica* 1991; **182:** 207–10.

31 Daneshpazhooh M, Fatehnejad M, Rahbar Z, et al. Trauma-induced pemphigus: a case series of 36 patients. *J Dtsch Dermatol Ges* 2016; **14:** 166–71.

32 Morell-Dubois S, Carpentier O, Cottencin O, et al. Stressful life events and pemphigus. *Dermatology* 2008; **216:** 104–08.

33 Nguyen VT, Arredondo J, Chernyavsky AI, Pittelkow MR, Kitajima Y, Grando SA. Pemphigus vulgaris acantholysis ameliorated by cholinergic agonists. *Arch Dermatol* 2004; **140:** 327–34.

34 Lai O, Recke A, Zillikens D, Kasperkiewicz M. Influence of cigarette smoking on pemphigus – a systematic review and pooled analysis of the literature. *J Eur Acad Dermatol Venereol* 2018; **32:** 1256–62.

35 Eyre RW, Stanley JR. Identification of pemphigus vulgaris antigen extracted from normal human epidermis and comparison with pemphigus foliaceus antigen. *J Clin Invest* 1988; **81:** 807–12.

36 Eyre RW, Stanley JR. Human autoantibodies against a desmosomal protein complex with a calcium-sensitive epitope are characteristic of pemphigus foliaceus patients. *J Exp Med* 1987; **165:** 1719–24.

37 Amagai M, Klaus-Kovtun V, Stanley JR. Autoantibodies against a novel epithelial cadherin in pemphigus vulgaris, a disease of cell adhesion. *Cell* 1991; **67:** 869–77.

38 Hashimoto T, Ogawa MM, Konohana A, Nishikawa T. Detection of pemphigus vulgaris and pemphigus foliaceus antigens by immunoblot analysis using different antigen sources. *J Invest Dermatol* 1990; **94:** 327–31.

39 Korman NJ, Eyre RW, Klaus-Kovtun V, Stanley JR. Demonstration of an adhering-junction molecule (plakoglobin) in the autoantigens of pemphigus foliaceus and pemphigus vulgaris. *N Engl J Med* 1989; **321:** 631–35.

40 Koch PJ, Walsh MJ, Schmelz M, Goldschmidt MD, Zimbelmann R, Franke WW. Identification of desmoglein, a constitutive desmosomal glycoprotein, as a member of the cadherin family of cell adhesion molecules. *Eur J Cell Biol* 1990; **53:** 1–12.

41 Waschke J, Spindler V. Desmosomes and extradesmosomal adhesive signaling contacts in pemphigus. *Med Res Rev* 2014; **34:** 1127–45.

42 Dubash AD, Green KJ. Desmosomes. *Curr Biol* 2011; **21:** R529–31.

43 Tsunoda K, Ota T, Aoki M, et al. Induction of pemphigus phenotype by a mouse monoclonal antibody against the amino-terminal adhesive interface of desmoglein 3. *J Immunol* 2003; **170:** 2170–78.

44 Futei Y, Amagai M, Sekiguchi M, Nishifuji K, Fujii Y, Nishikawa T. Use of domain-swapped molecules for conformational epitope mapping of desmoglein 3 in pemphigus vulgaris. *J Invest Dermatol* 2000; **115:** 829–34.

45 Amagai M, Tsunoda K, Zillikens D, Nagai T, Nishikawa T. The clinical phenotype of pemphigus is defined by the anti-desmoglein autoantibody profile. *J Am Acad Dermatol* 1999; **40:** 167–70.

46 Stanley JR, Amagai M. Pemphigus, bullous impetigo, and the staphylococcal scalded-skin syndrome. *N Engl J Med* 2006; **355:** 1800–10.

47 Baykal C, Azizlerli G, Thoma-Uszynski S, Hertl M. Pemphigus vulgaris localized to the nose and cheeks. *J Am Acad Dermatol* 2002; **47:** 875–80.

48 Mindorf S, Dettmann IM, Kruger S, et al. Routine detection of serum antidesmocollin autoantibodies is only useful in patients with atypical pemphigus. *Exp Dermatol* 2017; **26:** 1267–70.

49 Ishii N, Teye K, Fukuda S, et al. Anti-desmocollin autoantibodies in nonclassical pemphigus. *Br J Dermatol* 2015; **173:** 59–68.

50 Muller R, Heber B, Hashimoto T, et al. Autoantibodies against desmocollins in European patients with pemphigus. *Clin Exp Dermatol* 2009; **34:** 898–903.

51 Sajda T, Hazelton J, Patel M, et al. Multiplexed autoantigen microarrays identify HLA as a key driver of anti-desmoglein and -non-desmoglein reactivities in pemphigus. *Proc Natl Acad Sci USA* 2016; **113:** 1859–64.

52 Nguyen VT, Ndoye A, Shultz LD, Pittelkow MR, Grando SA. Antibodies against keratinocyte antigens other than desmogleins 1 and 3 can induce pemphigus vulgaris-like lesions. *J Clin Invest* 2000; **106:** 1467–79.

53 Amber KT, Valdebran M, Grando SA. Non-desmoglein antibodies in patients with pemphigus vulgaris. *Front Immunol* 2018; **9:** 1190.

54 Ahmed AR, Carrozzo M, Caux F, et al. Monopathogenic vs multipathogenic explanations of pemphigus pathophysiology. *Exp Dermatol* 2016; **25:** 839–46.

55 Pollmann R, Schmidt T, Eming R, Hertl M. Pemphigus: a comprehensive review on pathogenesis, clinical presentation and novel therapeutic approaches. *Clin Rev Allergy Immunol* 2018; **54:** 1–25.

56 Kasperkiewicz M, Ellebrecht CT, Takahashi H, et al. Pemphigus. *Nat Rev Dis Primers* 2017; **3:** 17026.

57 Spindler V, Eming R, Schmidt E, et al. Mechanisms causing loss of keratinocyte cohesion in pemphigus. *J Invest Dermatol* 2018; **138:** 32–37.

58 Hertl M, Eming R, Veldman C. T cell control in autoimmune bullous skin disorders. *J Clin Invest* 2006; **116:** 1159–66.

59 Eming R, Hennerici T, Backlund J, et al. Pathogenic IgG antibodies against desmoglein 3 in pemphigus vulgaris are regulated by HLA-DRB1*04:02-restricted T cells. *J Immunol* 2014; **193:** 4391–99.

60 Wu H, Wang ZH, Yan A, et al. Protection against pemphigus foliaceus by desmoglein 3 in neonates. *N Engl J Med* 2000; **343:** 31–35.

61 Schmidt E, Dahnrich C, Rosemann A, et al. Novel ELISA systems for antibodies to desmoglein 1 and 3: correlation of disease activity with serum autoantibody levels in individual pemphigus patients. *Exp Dermatol* 2010; **19:** 458–63.

62 Harman KE, Seed PT, Gratian MJ, Bhogal BS, Challacombe SJ, Black MM. The severity of cutaneous and oral pemphigus is related to desmoglein 1 and 3 antibody levels. *Br J Dermatol* 2001; **144:** 775–80.

63 Farb RM, Dykes R, Lazarus GS. Anti-epidermal-cell-surface pemphigus antibody detaches viable epidermal cells from culture plates by activation of proteinase. *Proc Natl Acad Sci USA* 1978; **75:** 459–63.

64 Ishii K, Harada R, Matsuo I, Shirakata Y, Hashimoto K, Amagai M. In vitro keratinocyte dissociation assay for evaluation of the pathogenicity of anti-desmoglein 3 IgG autoantibodies in pemphigus vulgaris. *J Invest Dermatol* 2005; **124:** 939–46.

65 Anhalt GJ, Labib RS, Voorhees JJ, Beals TF, Diaz LA. Induction of pemphigus in neonatal mice by passive transfer of IgG from patients with the disease. *N Engl J Med* 1982; **306:** 1189–96.

66 Schulze K, Galichet A, Sayar BS, et al. An adult passive transfer mouse model to study desmoglein 3 signaling in pemphigus vulgaris. *J Invest Dermatol* 2012; **132:** 346–55.

67 Amagai M, Tsunoda K, Suzuki H, Nishifuji K, Koyasu S, Nishikawa T. Use of autoantigen-knockout mice in developing an active autoimmune disease model for pemphigus. *J Clin Invest* 2000; **105:** 625–31.

68 Li N, Aoki V, Hans-Filho G, Rivitti EA, Diaz LA. The role of intramolecular epitope spreading in the pathogenesis of endemic pemphigus foliaceus (fogo selvagem). *J Exp Med* 2003; **197:** 1501–10.

69 Di Zenzo G, Di Lullo G, Corti D, et al. Pemphigus autoantibodies generated through somatic mutations target the desmoglein-3 cis-interface. *J Clin Invest* 2012; **122:** 3781–90.

70 Langenhan J, Dworschak J, Saschenbrecker S, et al. Specific immunoadsorption of pathogenic autoantibodies in pemphigus requires the entire ectodomains of desmogleins. *Exp Dermatol* 2014; **23:** 253–59.

71 Payne AS, Ishii K, Kacir S, et al. Genetic and functional characterization of human pemphigus vulgaris monoclonal autoantibodies isolated by phage display. *J Clin Invest* 2005; **115:** 888–99.

72 Rock B, Labib RS, Diaz LA. Monovalent Fab' immunoglobulin fragments from endemic pemphigus foliaceus autoantibodies reproduce the human disease in neonatal Balb/c mice. *J Clin Invest* 1990; **85:** 296–99.

73 Diercks GF, Pas HH, Jonkman MF. The ultrastructure of acantholysis in pemphigus vulgaris. *Br J Dermatol* 2009; **160:** 460–61.

74 Sokol E, Kramer D, Diercks GFH, et al. Large-scale electron microscopy maps of patient skin and mucosa provide insight into pathogenesis of blistering diseases. *J Invest Dermatol* 2015; **135:** 1763–70.

75 Jennings JM, Tucker DK, Kottke MD, et al. Desmosome disassembly in response to pemphigus vulgaris IgG occurs in distinct phases and can be reversed by expression of exogenous Dsg3. *J Invest Dermatol* 2011; **131:** 706–18.

76 Lotti R, Shu E, Petrachi T, et al. Soluble Fas ligand is essential for blister formation in pemphigus. *Front Immunol* 2018; **9:** 370.

77 Chen J, Den Z, Koch PJ. Loss of desmocollin 3 in mice leads to epidermal blistering. *J Cell Sci* 2008; **121:** 2844–49.

78 Rafei D, Muller R, Ishii N, et al. IgG autoantibodies against desmocollin 3 in pemphigus sera induce loss of keratinocyte adhesion. *Am J Pathol* 2011; **178:** 718–23.

79 Spindler V, Heupel WM, Efthymiadis A, et al. Desmocollin 3-mediated binding is crucial for keratinocyte cohesion and is impaired in pemphigus. *J Biol Chem* 2009; **284:** 30556–64.

80 Lakshmi MJD, Jaisankar TJ, Rajappa M, et al. Correlation of antimuscarinic acetylcholine receptor antibody titers and antidesmoglein antibody titers with the severity of disease in patients with pemphigus. *J Am Acad Dermatol* 2017; **76:** 895–902.

81 Chen Y, Chernyavsky A, Webber RJ, Grando SA, Wang PH. Critical role of the neonatal Fc receptor (FcRn) in the pathogenic action of antimitochondrial autoantibodies synergizing with anti-desmoglein autoantibodies in pemphigus vulgaris. *J Biol Chem* 2015; **290:** 23826–37.

82 Mahmoud A, Miziara ID, Costa KC, Santi CG, Maruta CW, Aoki V. Laryngeal involvement in pemphigus vulgaris: a proposed classification. *J Laryngol Otol* 2012; **126:** 1041–44.

83 De D, Kumar S, Handa S, Mahajan R. Fingernail involvement in pemphigus and its correlation with disease severity and other clinicodemographic parameters. *Br J Dermatol* 2018; **180:** 662–63.

84 Zaraa I, Sellami A, Bouguerra C, et al. Pemphigus vegetans: a clinical, histological, immunopathological and prognostic study. *J Eur Acad Dermatol Venereol* **25:** 1160–67.

85 Oktarina DA, Poot AM, Kramer D, Diercks GF, Jonkman MF, Pas HH. The IgG "lupus-band" deposition pattern of pemphigus erythematosus: association with the desmoglein 1 ectodomain as revealed by 3 cases. *Arch Dermatol* 2012; **148:** 1173–78.

86 Ohzono A, Sogame R, Li X, et al. Clinical and immunological findings in 104 cases of paraneoplastic pemphigus. *Br J Dermatol* 2015; **173:** 1447–52.

87 Joly P, Richard C, Gilbert D, et al. Sensitivity and specificity of clinical, histologic, and immunologic features in the diagnosis of paraneoplastic pemphigus. *J Am Acad Dermatol* 2000; **43:** 619–26.

88 Leger S, Picard D, Ingen-Housz-Oro S, et al. Prognostic factors of paraneoplastic pemphigus. *Arch Dermatol* 2012: **148:** 1165–72.

89 Anhalt GJ, Kim SC, Stanley JR, et al. Paraneoplastic pemphigus. An autoimmune mucocutaneous disease associated with neoplasia. *N Engl J Med* 1990; **323:** 1729–35.

90 Wang L, Bu D, Yang Y, Chen X, Zhu X. Castleman's tumours and production of autoantibody in paraneoplastic pemphigus. *Lancet* 2004; **363:** 525–31.

91 Liu Q, Bu DF, Li D, Zhu XJ. Genotyping of HLA-I and HLA-II alleles in Chinese patients with paraneoplastic pemphigus. *Br J Dermatol* 2008; **158:** 587–91.

92 Wang R, Li J, Wang M, et al. Prevalence of myasthenia gravis and associated autoantibodies in paraneoplastic pemphigus and their correlations with symptoms and prognosis. *Br J Dermatol* 2015; **172:** 968–75.

93 Mimouni D, Anhalt GJ, Lazarova Z, et al. Paraneoplastic pemphigus in children and adolescents. *Br J Dermatol* 2002; **147:** 725–32.

94 Nikolskaia OV, Nousari CH, Anhalt GJ. Paraneoplastic pemphigus in association with Castleman's disease. *Br J Dermatol* 2003; **149:** 1143–51.

95 Hata T, Nishimoto S, Nagao K, et al. Ectopic expression of epidermal antigens renders the lung a target organ in paraneoplastic pemphigus. *J Immunol* 2013; **191:** 83–90.

96 Tsuchisaka A, Numata S, Teye K, et al. Epiplakin is a paraneoplastic pemphigus autoantigen and related to bronchiolitis obliterans in Japanese patients. *J Invest Dermatol* 2016; **136:** 399–408.

97 Amber KT, Valdebran M, Grando SA. Paraneoplastic autoimmune multiorgan syndrome (PAMS): beyond the single phenotype of paraneoplastic pemphigus. *Autoimmun Rev* 2018; **17:** 1002–10.

98 Poot AM, Diercks GF, Kramer D, et al. Laboratory diagnosis of paraneoplastic pemphigus. *Br J Dermatol* 2013; **169:** 1016–24.

99 Zimmermann J, Bahmer F, Rose C, Zillikens D, Schmidt E. Clinical and immunopathological spectrum of paraneoplastic pemphigus. *J Dtsch Dermatol Ges* 2010; **8:** 598–605.

100 Amagai M, Nishikawa T, Nousari HC, Anhalt GJ, Hashimoto T. Antibodies against desmoglein 3 (pemphigus vulgaris antigen) are present in sera from patients with paraneoplastic pemphigus and cause acantholysis in vivo in neonatal mice. *J Clin Invest* 1998; **102:** 775–82.

101 Probst C, Schlumberger W, Stocker W, et al. Development of ELISA for the specific determination of autoantibodies against envoplakin and periplakin in paraneoplastic pemphigus. *Clin Chim Acta* 2009; **410:** 13–18.

102 Joly P, Thomine E, Gilbert D, et al. Overlapping distribution of autoantibody specificities in paraneoplastic pemphigus and pemphigus vulgaris. *J Invest Dermatol* 1994; **103:** 65–72.

103 Takahashi H, Kouno M, Nagao K, et al. Desmoglein 3-specific CD4+ T cells induce pemphigus vulgaris and interface dermatitis in mice. *J Clin Invest* 2011; **121:** 3677–88.

104 Nousari HC, Deterding R, Wojtczack H, et al. The mechanism of respiratory failure in paraneoplastic pemphigus. *N Engl J Med* 1999; **340:** 1406–10.

105 Zhao CY, Chiang YZ, Murrell DF. Neonatal autoimmune blistering disease: a systematic review. *Pediatr Dermatol* 2016; **33:** 367–74.

106 Kardos M, Levine D, Gurcan HM, Ahmed RA. Pemphigus vulgaris in pregnancy: analysis of current data on the management and outcomes. *Obstet Gynecol Surv* 2009; **64:** 739–49.

107 Murrell DF, Dick S, Ahmed AR, et al. Consensus statement on definitions of disease, end points, and therapeutic response for pemphigus. *J Am Acad Dermatol* 2008; **58:** 1043–46.

108 Boulard C, Duvert Lehembre S, Picard-Dahan C, et al. Calculation of cut-off values based on the Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) and Pemphigus Disease Area Index (PDAI) pemphigus scoring systems for defining moderate, significant and extensive types of pemphigus. *Br J Dermatol* 2016; **175:** 142–49.

109 Hebert V, Boulard C, Houivet E, et al. Large international validation of ABSIS and PDAI pemphigus severity scores. *J Invest Dermatol* 2019; **139:** 31–37.

110 Rencz F, Gulacsi L, Tamasi B, et al. Health-related quality of life and its determinants in pemphigus: a systematic review and meta-analysis. *Br J Dermatol* 2015; **173:** 1076–80.

111 Sebaratnam DF, Hanna AM, Chee SN, et al. Development of a quality-of-life instrument for autoimmune bullous disease: the autoimmune bullous disease quality of life questionnaire. *JAMA Dermatol* 2013; **149:** 1186–91.

112 Harman KE, Brown D, Exton LS, et al. British Association of Dermatologists' guidelines for the management of pemphigus vulgaris 2017. *Br J Dermatol* 2017; **177:** 1170–201.

113 Hertl M, Jedlickova H, Karpati S, et al. Pemphigus. S2 Guideline for diagnosis and treatment – guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV). *J Eur Acad Dermatol Venereol* 2015; **29:** 405–14.

114 Schmidt E, Goebeler M, Hertl M, et al. S2k guideline for the diagnosis of pemphigus vulgaris/foliaceus and bullous pemphigoid. *J Dtsch Dermatol Ges* 2015; **13:** 713–27.

115 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.

116 Murrell DF, Pena S, Joly P, et al. Diagnosis and management of pemphigus: recommendations by an international panel of experts. *J Am Acad Dermatol* 2018; published online Feb 10. DOI:10.1016/j.jaad.2018.02.021.

117 Amagai M, Tanikawa A, Shimizu T, et al. Japanese guidelines for the management of pemphigus. *J Dermatol* 2014; **41:** 471–86.

118 Almugairen N, Hospital V, Bedane C, et al. Assessment of the rate of long-term complete remission off therapy in patients with pemphigus treated with different regimens including medium- and high-dose corticosteroids. *J Am Acad Dermatol* 2013; **69:** 583–88.

119 Herbst A, Bystryn JC. Patterns of remission in pemphigus vulgaris. *J Am Acad Dermatol* 2000; **42:** 422–27.

120 Joly P, Maho-Vaillant M, Prost-Squarcioni C, et al. First-line rituximab combined with short-term prednisone versus prednisone alone for the treatment of pemphigus (Ritux 3): a prospective, multicentre, parallel-group, open-label randomised trial. *Lancet* 2017; **389:** 2031–40.

121 Schmidt E, Goebeler M, Zillikens D. Rituximab in severe pemphigus. *Ann NY Acad Sci* 2009; **1173:** 683–91.

122 Ahmed AR, Spigelman Z, Cavacini LA, Posner MR. Treatment of pemphigus vulgaris with rituximab and intravenous immune globulin. *N Engl J Med* 2006; **355:** 1772–79.

123 Colliou N, Picard D, Caillot F, et al. Long-term remissions of severe pemphigus after rituximab therapy are associated with prolonged failure of desmoglein B cell response. *Sci Transl Med* 2013; **5:** 175ra30.

124 Joly P, Mouquet H, Roujeau JC, et al. A single cycle of rituximab for the treatment of severe pemphigus. *N Engl J Med* 2007; **357:** 545–52.

125 Ahmed AR, Shetty S. A comprehensive analysis of treatment outcomes in patients with pemphigus vulgaris treated with rituximab. *Autoimmun Rev* 2015; **14:** 323–31.

126 Wang HH, Liu CW, Li YC, Huang YC. Efficacy of rituximab for pemphigus: a systematic review and meta-analysis of different regimens. *Acta Derm Venereol* 2015; **95:** 928–32.

127 Atzmony L, Hodak E, Leshem YA, et al. The role of adjuvant therapy in pemphigus: a systematic review and meta-analysis. *J Am Acad Dermatol* 2015; **73:** 264–71.

128 Martin LK, Werth V, Villanueva E, Segall J, Murrell DF. Interventions for pemphigus vulgaris and pemphigus foliaceus. *Cochrane Database Syst Rev* 2009; **1:** CD006263.

129 Czernik A, Toosi S, Bystryn JC, Grando SA. Intravenous immunoglobulin in the treatment of autoimmune bullous dermatoses: an update. *Autoimmunity* 2012; **45:** 111–18.

130 Amagai M, Ikeda S, Shimizu H, et al. A randomized double-blind trial of intravenous immunoglobulin for pemphigus. *J Am Acad Dermatol* 2009; **60:** 595–603.

131 Amber KT, Maglie R, Solimani F, Eming R, Hertl M. Targeted therapies for autoimmune bullous diseases: current status. *Drugs* 2018; **78:** 1527–48.

132 Ahmed AR, Kaveri S, Spigelman Z. Long-term remissions in recalcitrant pemphigus vulgaris. *N Engl J Med* 2015; **373:** 2693–94.

133 Behzad M, Mobs C, Kneisel A, et al. Combined treatment with immunoadsorption and rituximab leads to fast and prolonged clinical remission in difficult-to-treat pemphigus vulgaris. *Br J Dermatol* 2012; **166:** 844–52.

134 Kasperkiewicz M, Shimanovich I, Meier M, et al. Treatment of severe pemphigus with a combination of immunoadsorption, rituximab, pulsed dexamethasone and azathioprine/mycophenolate mofetil: a pilot study of 23 patients. *Br J Dermatol* 2012; **166:** 154–60.

135 Kushner CJ, Concha JSS, Werth VP. Treatment of autoimmune bullous disorders in pregnancy. *Am J Clin Dermatol* 2018; **19:** 391–403.

136 Bystryn JC, Steinman NM. The adjuvant therapy of pemphigus. An update. *Arch Dermatol* 1996; **132:** 203–12.

137 Huang YH, Kuo CF, Chen YH, Yang YW. Incidence, mortality, and causes of death of patients with pemphigus in Taiwan: a nationwide population-based study. *J Invest Dermatol* 2012; **132:** 92–97.

138 Hsu DY, Brieva J, Sinha AA, Langan S, Silverberg JI. Comorbidities and inpatient mortality for pemphigus in the United States. *Br J Dermatol* 2016; **174:** 1290–98.

139 Chams-Davatchi C, Valikhani M, Daneshpazhooh M, et al. Pemphigus: analysis of 1209 cases. *Int J Dermatol* 2005; **44:** 470–76.

140 Kumar S, De D, Handa S, et al. Identification of factors associated with treatment refractoriness of oral lesions in pemphigus vulgaris. *Br J Dermatol* 2017; **177:** 1583–89.

141 Wormser D, Chen DM, Brunetta PG, et al. Cumulative oral corticosteroid use increases risk of glucocorticoid-related adverse events in patients with newly diagnosed pemphigus. *J Am Acad Dermatol* 2017; **77:** 379–81.

142 Leshem YA, Atzmony L, Dudkiewicz I, Hodak E, Mimouni D. Venous thromboembolism in patients with pemphigus: a cohort study. *J Am Acad Dermatol* 2017; **77:** 256–60.

143 Saha M, Bhogal B, Black MM, Cooper D, Vaughan RW, Groves RW. Prognostic factors in pemphigus vulgaris and pemphigus foliaceus. *Br J Dermatol* 2014; **170:** 116–22.

144 Daneshpazhooh M, Zafarmand Sedigh V, Balighi K, et al. Immunologic prediction of relapse in patients with pemphigus vulgaris (PV) in clinical remission. *J Am Acad Dermatol* 2016; **74:** 1160–65.

145 Hofrichter M, Dworschak J, Emtenani S, et al. Immunoadsorption of desmoglein-3-specific IgG abolishes the blister-inducing capacity of pemphigus vulgaris IgG in neonatal mice. *Front Immunol* 2018; **9:** 1935.

146 Ellebrecht CT, Bhoj VG, Nace A, et al. Reengineering chimeric antigen receptor T cells for targeted therapy of autoimmune disease. *Science* 2016; **353:** 179–84.