Table 23.4.1 Immunopathological characteristics of

Table 23.4.1 Immunopathological characteristics of main autoimmune bullous diseases

23.4 Autoimmune bullous diseases 5613 and, in cases of extensive involvement, other differentials such as mucous membrane pemphigoid should be considered. Pemphigoid blisters often burst leaving eroded and weeping areas that are prone to infection. Patients are in significant discomfort with itch and sore- ness during the active stage of the disease. Diagnosis Clinical diagnosis should be followed with histological and im- munofluorescence studies. A skin biopsy from a fresh, intact blister is analysed with light microscopy and a perilesional biopsy is taken from the skin adjacent to a blister with intact epidermis for direct immunofluorescense. Histology with haematoxylin and eosin staining shows a subepidermal cleft with dermal inflammatory cells consisting of eosinophils and neurtorphils. Direct and indirect im- munofluorescence (using serum or blister fluid if no venous access) show linear deposition of IgG and C3 localized along the basement membrane zone (Fig. 23.4.3). Indirect immunofluorescence can be performed on skin that has been artificially split with normal saline, and bullous pemphigoid serum stains the roof of the split. Serum antibodies to BP180 and BP230 can be measured with enzyme linked immunosorbent assay (ELISA) and antibody titre to BP180 might be related to disease activity. Table 23.4.1 Immunopathological characteristics

of main autoimmune bullous diseases Autoimmune bullous dermatosis Target structure Target antigen Immunofluorescence picture Subepidermal diseases Bullous pemphigoid Hemidesmosome BP180, BP230, rarely P200 Linear IgG along the basement membrane zone Mucous membrane pemphigoid Hemidesmosome, anchoring fillament BP180, BP230, laminin 332, α6β4 integrin, collagen VII Linear IgG/IgA along the basement membrane zone Linear IgA disease Hemidesmosome BP180 and its shed ectodomain Linear IgA along the basement membrane zone Epidermolysis bullosa acquisita Anchoring fibrils Collagen VII Linear IgG along the basement membrane zone Dermatitis herpetiformis Microfibrils Likely epidermal tissue transglutaminase Granular deposition in dermal papillae Intraepidermal diseases Pemphigus vulgaris Desmosome Desmoglein1 and 3 Intercellular IgG deposition on epitherlium and mucosa Pemphigus foliaceus Desmosome Desmoglein 1 Intercellular IgG deposition on epithelium Paraneoplastic pemphigus Desmosome Plakins Intercellular and basement membrane zone IgG on epithelium and rat bladder Table 23.4.2 Clinical characteristics and treatment of main autoimmune bullous diseases Autoimmune bullous dermatosis Age group Frequency Clinical features First-line treatment Subepidermal diseases Bullous pemphigoid Elderly with average age of 80 years 7–40 per million population per year Itch, urticated plaques and tense blisters on limbs, trunk, and flexures Topical or systemic steroids, Mucous membrane pemphigoid Middle age and elderly Rare, 1–2 per million population per year Blisters and scarring of oropharynx, oesophagus, ocular, genital, and airway mucosae with or without skin involvement Systemic steroids; dapsone, cyclophosphamide Linear IgA disease Children, young adults and >60 years of age Rare, 0.5 per million population per year Blisters, often at the edge of red plaques (string of pearls) on trunk and limbs (face and genitals in children) with frequent mucosal involvement Dapsone, erythromycin in children Epidermolysis bullosa acquisita All ages 0.25 cases per million population per year Tense blisters and erosions on friction (mechanobullous involvement) with scarring Systemic steroids Dermatitis herpetiformis Young adults, mostly males 4–35 per million population per year Itchy vesicles on extensor areas (e.g. elbows, knees, buttocks) Gluten-free diet, dapsone Intraepidermal diseases Pemphigus vulgaris Middle age but with a peak at 70 years 7 per million population per year in the UK Superficial blisters and erosion on skin and mucosa Systemic steroids Pemphigus foliaceus As pemphigus vulgaris As pemphigus vulgaris. There is an endemic form Superficial blisters and erosions on scalp, chest, and upper limbs without mucosal involvement Systemic steroids Paraneoplastic pemphigus All ages Rare Severe mucosal lesions, erosions, and blistering of the skin mainly on upper body and palmoplantar regions. It is often associated with haematological malignancies Unresponsive to treatment but may improve if the underlying malignancy is treated

section 23 Disorders of the skin 5614 Treatment and prognosis Patients with bullous pemphigoid are often frail with multiple co- morbidities. The aim of treatment is to control the disease with the least toxic agents. Potent topical steroids applied generously on af- fected areas are effective as sole agents (in mild to moderate dis- ease) or in combination with systemic agents. Oral corticosteroids provide rapid improvement at doses of 0.3–1 mg/kg/day depending on the severity of disease, but high doses are poorly tolerated in older people. The patient should be weaned off corticosteroids slowly to avoid relapse. Anti-inflammatory antibiotics such as tetracyclines and erythromycin are effective in moderate disease and are a good treatment option with low toxicity. In persistent disease other im- munosuppressants may be needed, most commonly azathioprine and mycophenolate mofetil, and rarely immune therapy such as intravenous immunoglobulins, plasmapheresis, and rituximab. Bullous pemphigoid is self-limiting but can last from months to years. Mortality is highest in the first year and is often related to adverse effects of systemic

steroids and immunosuppressants. The early use of anti-inflammatory antibiotics might increase in future and trials are underway to compare the efficacy of these agents with systemic steroids. Mucous membrane pemphigoid Aetiology and epidemiology Mucous membrane pemphigoid is a rare blistering disease with an incidence of 1–2 per million population per year in Western Europe. It affects middle-aged and older individuals with a female preponder- ance. Multiple systems can be involved and patients might present to several specialists including dermatology, ophthalmology, oral medi- cine, respiratory, and gastroenterology. The cause is unknown. Pathogenesis IgG and/or IgA antibodies target components of the basement mem- brane zone. In addition to bullous pemphigoid antigens (mainly BP180 and less commonly BP230), several other antigens have been identified which include laminin 332, collagen VII, and α6β4 in- tegrin. Animal models have shown pathogenicity of the antibodies. Clinical features The predominant feature is mucosal involvement with subse- quent scarring, and skin lesions might also be present. The oral mucosa is the most commonly affected site with blisters, erosions, and desquamative gingivitis (Fig. 23.4.4). There is significant pain Table 23.4.3 Differential diagnoses of autoimmune bullous disease Differential diagnosis Diagnostic clues Inflammatory diseases Eczema Lichen planus Vasculitis Lupus Erythema multiforme Histology confirms the diagnosis. Immunofluorescence tests are negative Infectious diseases Herpes simplex Herpes zoster Impetigo Staphylococcus scalded skin syndrome Skin swabs for virus and bacteria Physical causes of blistering Trauma Burn Ultraviolet light Insect bite History of exposure and spontaneous resolution Genetic diseases Epidermolysis bullosa group Hailey-Hailey disease Family history Drug-induced blistering Fixed drug eruption Pseudoporphyria cutanea tarda Bullous drug reactions Toxic epidermal necrolysis Drug history (e.g. paracetamol, frusemide, antiepileptic drugs) Metabolic causes of blistering Porphyria cutanea tarda Relevant metabolic tests, negative immunofluorescence, and possible history of exacerbation on exposure to sunlight Oedema-induced blisters Oedema is apparent (e.g. in cellulitis) Fig 23.4.1 The basement membrane zone of the skin and mucosa.

 which might lead to reduced oral intake and malnutrition. Ocular involvement is a significant feature and can be subtle initially, but can progress rapidly. Subsequent scarring and symblepharon can lead to blindness (Fig. 23.4.5). Hoarseness, coughing, and stridor are signs of respiratory tract involvement and tracheos- tomy might be required to keep the airways patent. Oesophageal stenosis causes dysphagia and genital tract scarring can lead to structural abnormalities, sexual dysfunction, and micturition problems. Involvement of the skin is often localized and associated with scarring. Diagnosis Clinical signs of mucosal erosions and scarring should prompt the diagnosis. Biopsies should be taken for haematoxylin and eosin staining (from a fresh blister) as well as direct immunofluores- cence (perilesional with intact epidermis). Histology shows a pic- ture similar to that of bullous pemphigoid with a subepidermal cleft, and direct immunofluorescence shows deposition of IgG and or IgA along the basement membrane zone. Indirect immunofluorescence might show low titres of antibodies or be negative. When salt-split skin is used in indirect immunofluorescence, the staining with IgG, and/or IgA can be on the roof or the floor of the split, depending on the targeted antigen. Antibodies to BP180 and BP230 deposit on the roof and those to laminin 332, collagen VII and α6β4 integrin stain the floor. ELISA can further characterize the antibody types. Commercial ELISA is currently available for BP180, BP230, and collagen VII. Treatment and prognosis Treatment of mucous membrane pemphigoid is challenging. The aim is to control the disease to prevent scarring, although this might be inevitable despite treatment. The evidence for various treatments is poor due to lack of large trials and the rarity of the disease. Topical steroids are useful for both skin and oral surfaces. In mild disease,

anti-inflammatory antibiotics (tetracyclines, erythromycin) and dapsone are effective. In moderate to severe disease, systemic steroids, and other immunuosuppressants such as azathioprine are often used, but for oesophageal and ocular Fig 23.4.2 Tense and haemorrhagic blisters on background of erythematous skin in bullous pemphigoid. Courtesy of Whittington Health. Fig 23.4.3 IgG autoantibodies binding to the basement membrane zone in bullous and mucous membrane pemphigoid. Fig 23.4.4 Desquamative gingivitis of the gums. Fig 23.4.5 End-stage ocular disease, showing scarring and symblepharon.

section 23 Disorders of the skin 5616 disease the best evidence is for cyclophosphamide. For more re- fractory disease, intravenous immunoglobulins and rituximab may be needed. The disease runs a chronic course and can last for years. The prog- nosis is best for patients with only skin and oral mucosal disease and less favourable for those with ocular, nasopharyngeal, and genital involvement. The presence of antibodies to laminin 332 is thought to be associated with more severe disease. Linear IgA disease Aetiology and epidemiology Linear IgA disease is a rare subepidermal bullous disease that affects both adults and children. There are two peaks of onset; one in child- hood and young adults, and the other after the age of 60 years. The incidence in Western Europe is reported to be 0.5 per million popu- lation per year. Drug-induced linear IgA disease is well-recognized with the most commonly reported drugs being vancomycin and nonsteroidal anti-inflammatory drugs. An association with ulcera- tive colitis has been described and, in some cases, skin symptoms resolve after colectomy. The incidence of lymphoproliferative dis- orders in these patients is also higher. There is a strong association with HLA-B8, HLA-CW7, and HLA-DR3. Pathogenesis Autoantibodies of IgA type react to various antigens of the hemi desmosomes mainly BP180 and its physiologically shed ectodomains but also BP230 and LAD285, and cause a subepidermal split. Clinical features The disease presents with sudden onset of pruritic, urticated plaques, with blisters located around the edge of the plaques in an annular fashion known as ‘string of pearls’ (Fig. 23.4.6). Blisters are often located on trunk, limbs, and oral mucosa; face and genital areas are commonly affected in children along with the nasopharyngeal mucosa. A new consensus suggests that severe mucosal involvement should be classed as mucous membrane pemphigoid instead. Diagnosis Histology is not diagnostic and shows a subepidermal blister with variable infiltration by inflammatory cells. Immunofluorescence studies are essential for diagnosis and are performed on a perilesional skin biopsy and serum, showing deposition of IgA antibodies along the basement membrane zone. In salt-split skin, the antibodies usu- ally stain the roof and rarely the floor or both. Treatment and prognosis Most patients respond well to dapsone and sulphonamide drugs (sulphapyridine, sulphamethoxypyridazine) and some respond to anti-inflammatory antibiotics (tetracyclines, erythromycin). Other immunosuppressants are rarely required. The disease usually re- mits within 3–6 years but can take a chronic course. The prognosis is often good in children and symptoms tend to resolve by puberty. Epidermolysis bullosa acquisita Aetiology, epidemiology, and pathogenesis This is a very rare disease affecting less than 0.25 cases per mil- lion population per year in Western Europe affecting all ages and ethnic groups. It is characterized by IgG autoantibodies against collagen VII, which is a component of the anchoring fibrils in the dermoepidermal junction. An association with Crohn’s disease has been reported. Clinical features Similar to its genetic counterpart, dystrophic epidermolysis bullosa, epidermolysis bullosa acquisita causes mechanobullous fragility in patients. This means that blisters and erosions develop at the site of minor trauma and are often seen on knees, elbows, hands, and feet. There is also an inflammatory subtype that resembles bullous pemphigoid. Mucosal involvement and nail dystrophy are common. Milia (small keratin cysts) and atrophic

scarring are often seen at the site of healed blisters. Diagnosis Mechanobullous fragility in adults is an important clinical sign for diagnosis which should be followed by immunopathology studies. A linear deposition of IgG antibodies on the basement membrane zone is seen with immunofluorescence studies. Antibodies are lo- cated to the dermal side of salt-split skin in indirect immunofluores- cence. Antibodies to collagen VII can be confirmed by ELISA. Treatment and prognosis The disease is often refractory. Wound management and avoidance of trauma are important aspects of the treatment; however, systemic agents such as systemic steroids, dapsone, sulphonamide drugs (sulphapyridine and sulphamethoxypyridazine), and immunosup- pressive treatments are often necessary. Refractory disease might respond to intravenous immunoglobulins, immunoadsorption, or rituximab. Although the course of the disease is often chronic, long- term prognosis for patients who respond to immunosuppressants is excellent. Dermatitis herpetiformis Aetiology and epidemiology This is a subepidermal blistering disease that is the cutaneous mani- festation of gluten sensitive enteropathy, or coeliac disease. It affects young adults with a predilection for white males. There is a strong association with HLA DQ-2 and HLA DQ-8 and the incidence is Fig 23.4.6 Annular blistering lesions in linear IgA disease.

 higher among first-degree relatives, with 18% having a family his- tory. The incidence in northern Europe and the United States ranges from 4 to 35 per million population per year with the disease being more common in Scandinavia, western Ireland, and Hungary, and rare in Asia and Africa. Pathogenesis Tissue transglutaminase is the antigen target for coeliac disease and has a homologous structure to epidermal transglutaminase, which is thought to be the antigen for dermatitis herpetiformis. IgA antibodies are deposited in the dermal papillae in dermatitis herpetiformis, which triggers an inflammatory response, neutrophilic infiltrate, and blistering. It is not yet clear whether IgA epidermal transglutaminase antibodies are directly pathogenic. An animal model using genetic- ally primed DQ8 mice has shown that in a minority gluten can induce blisters with the characteristic histology and granular IgA deposition. However this was not associated with circulating antibodies to skin, endomysium, gluten, gliadin, or tissue transglutaminases, nor with enteropathy (see Chapter 15.10.3 Coeliac disease). Clinical features An intensely itchy eruption typically presents on extensor surfaces such as knees, elbows, buttocks, and can also involve the scalp and neck. The rash consists of small vesicles and papules which might not be detected clinically due to intense itch and excoriation. Mucosae are not usually affected. Diagnosis Histology from an intact lesion shows a subepidermal cleft with neutrophils and possibly eosinophils at the dermal papillae. Direct immunofluorescence of uninvolved skin is required to confirm the diagnosis and shows a granular deposition of IgA in the dermal pa- pillae along the basement membrane zone (Fig. 23.4.7). These de- posits might resolve with a gluten-free diet. The presence of antitissue transglataminase and antiendomysial antibodies should be checked to investigate for underlying coeliac disease. Screening for autoimmune thyroid disease and diabetes is also recommended, as are serology tests for other autoimmune dis- eases, if relevant. A commercial ELISA is available in some centres for epidermal transglutaminase antibodies. Treatment and prognosis The main element of the treatment is a gluten-free diet; how- ever, it could take over a year for the skin symptoms to improve with diet alone. Dapsone and sulphonamides (sulphapyridne and sulphamethoxypyridazine) provide fast relief of symptoms while a gluten-free diet, which should be lifelong, takes effect. Symptoms noticeably recur on ingestion of gluten and dietician reviews may be needed to motivate the patient. Titres of epidermal and tissue transglutaminase antibodies can be used to monitor adherence to gluten-free diet and might reduce the need for duodenal biopsies. The prognosis is good in patients who adhere to a gluten-

free diet and the majority will be able to reduce or discontinue dapsone. Intraepidermal diseases Intraepidermal diseases encompass the pemphigus group (pem- phigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus), characterized by flaccid and superficial blisters and erosions on the skin and/or mucosae. Autoantibodies target the intercellular adhe- sion complex (desmosomes, Fig. 23.4.8) between the keratinocytes, which leads to separation of the cells and blister formation within the epidermis. Pemphigus vulgaris Epidemiology and genetics This is the commonest type of pemphigus which affects the mucosal membranes, with or without skin involvement. It is rare in Western Europe (7 per million population per year in the United Kingdom) but is more common in the Middle East, India, North Africa, and among the Jewish population. Middle-aged and young individuals of both sexes can be affected, with a further peak of incidence in the seventh decade. There is a strong association with certain HLA types in different populations and a gene polymorphism in the target antigen (desmoglein 3). Pemphigus can be induced by drugs such as angiotensin-converting enzyme inhibitors and penicillamine. Pathogenesis Autoantibodies target desmogleins which are components of desmo- somes. The main target antigen in pemphigus vulgaris is desmoglein 3 which is found in the lower parts of the epidermis and in mucosal surfaces. Desmoglein 1, which is present in the upper layer of the epidermis, but not in mucosae, might also be targeted. As a result of this antigen-antibody interaction the keratinocyts separate from each other and float within the blister that is formed (acantholysis). Antibodies to desmoglein 3 and desmoglein 1 are usually of the IgG type and are directly pathogenic as proven by several animal studies. The titres of antibodies correlate with disease activity. Clinical features Pemphigus vulgaris often presents with oral blisters and erosions involving the palate, gum, tongue, and buccal mucosa (Fig. 23.4.9). This can lead to dysphagia, dehydration, and malnutrition. Involvement of the skin might be simultaneous or follow the oral manifestations after months. Fragile and superficial blisters on the skin burst easily and are rarely seen intact (Fig. 23.4.10). Scalp, face, and trunk are commonly affected and other mucosal surfaces such as the pharynx and genitalia Fig 23.4.7 IgG antibodies binding to the dermal side of the basement membrane zone of split skin.

 might also be involved. The skin is sore and the denuded blisters are prone to infection, which in extensive disease can lead to sepsis. As the erosions heal they can leave small scabbed plaques. Diagnosis Histopathology of an intact blister shows acantholysis and an intraepidermal blister with mixed inflammatory cell infiltrate. The basal cell layer, above which the blister is formed, remains intact and forms a single row of cells in a pattern that is known as ‘tombstoning’. The diagnosis is made with immunofluorescence studies which show labelling of the intercellular space where the IgG antibodies are de- posited (Fig. 23.4.11). Direct immunofluorescence is performed on a biopsy from intact skin or mucosa adjacent to a blister/erosion, and in- direct immunofluorescence utilizes serum added to various substrates rich in desmogleins (e.g. normal human skin and monkey oesophagus). Indirect immunofluorescence and ELISA (for both desmoglein 1 and 3) provide the titre of circulating antibodies and are useful in moni- toring of disease activity and characterizing subtypes of pemphigus. Treatment and prognosis In localized or limited disease, potent topical steroids might be useful; however, systemic steroids at high doses (usually 1 mg/kg) are often needed in the initial stages of the disease to achieve rapid control. The addition of gastric and bone protective measures are essential at this stage. Adjuvant treatment should be introduced to allow reduction of systemic steroids; these include agents such as azathioprine, mycophenolate mofetil, and cyclophosphamide. Rituximab (a monoclonal chimeric anti-CD20 antibody) has shown promising results in the treatment of

pemphigus. It selectively tar- gets the CD20 molecule that is expressed by B cells, which in turn reduces the IgG production by plasma cells. It is thought that early treatment with rituximab is associated with a better outcome as it reshapes the repertoire of B cells, leading to a reduction in the quan- tity of memory B cells after treatment. The downside is the risk of life-threatening infections and thus it should be used for selected pa- tients only. Other treatment options for refractory disease are intra- venous immunoglobulins and immunoadsorption/plasmapheresis. Future treatments might include more targeted therapy such as desmoglein peptides to block the binding sites for autoantibodies. KEY Dsg desmoglein 1 PF + PV DP Desmoplakins PNP PG Plakoglobin PNP intercellular contact layer plasma membrane Dsg desmoglein 3 PV Pemphigus vulgaris PV Pemphigus foliaceus PF Paraneoplastic pemphigus PNP Fig 23.4.8 The desmosome and its target antigens. Fig 23.4.9 Oral erosions on tongue, palate, and labial mucosa in pemphigus vulgaris. Courtesy of Whittington Health.

23.4 Autoimmune bullous diseases 5619 Pemphigus foliaceus Epidemiology and genetics This is a rare subtype of pemphigus with a sporadic and an endemic form. The endemic form (fogo selvagem) is seen in Brazil, Colombia, and Tunisia, and is thought to be related to insect exposure as it af- fects individuals living in rural areas near rivers, and resolves when they move away. A slight preponderance for young females has been found in North Africa. Both sporadic and endemic forms share similar HLA II alleles. Pathogenesis Autoantibodies to desmoglein 1 target this component of the ad- hesion complex that is located in the upper layer of epidermis, below the stratum corneum (subcorneal). Blisters are more super- ficial than pemphigus vulgaris. Animal studies have confirmed the pathogenicity of the antibodies. A similar clinical picture is seen with staphylococcal scalded skin syndrome where the toxin cleaves desmoglein 1, leading to superficial blisters. Clinical features Erosions and crusting are seen in a seborrhoeic distribution af- fecting scalp, face, torso, and upper limbs. In contrast to pemphigus vulgaris, mucosal surfaces are not involved. Diagnosis Histology shows a subcorneal split and immunofluorescence shows antibody deposition in the intercellular space. Indirect immuno- fluorescence (positive on substrates rich in desmoglein 1 and nega- tive for desmoglein 3) and ELISA (positive for desmoglein 1 and negative for desmoglein 3) can differentiate pemphigus foliaceus from pemphigus vulgaris. Treatment and prognosis The treatment is similar to that of pemphigus vulgaris with topical treatment and systemic steroids to achieve remission. Steroid sparing agents should be used as per treatment of pemphigus vulgaris. The disease can take a chronic course but eventually remits. Elucidating environmental factors that trigger the endemic dis- ease might lead to better understanding of the disease pathogenesis in future. Paraneoplastic pemphigus Epidemiology and genetics This is a rare subtype of pemphigus that was first recognized as an entity in 1990. It is associated with an underlying malignancy, which is often haematological, such as non-Hodgkin’s lymphoma, chronic lymphocytic leukaemia, and Castleman’s disease. Its genetic basis is not well characterized and seems to be different to other subtypes of pemphigus. Fig 23.4.10 Erosions and excoriations in pemphigus. Courtesy of Whittington Health. Fig 23.4.11 Immunofluorescence demonstrating antibody binding in the epidermis in pemphigus.

 Pathogenesis There are antibodies against various antigens of the adhesion complex, mainly plakins, which are also found in transitional and other types of epithelia, but also desmogleins and bullous pemphigoid antigens. Clinical features Patients present with severe mucosal erosion and skin eruption involving a large area of the body. There can be involvement of the palms and soles with blisters mimicking erythema multiforme, as well as nasopharynx, genital, and respiratory mucosal erosions. A lichenoid type of eruption might also be

seen. There is often multiorgan involvement and the patients are unwell with respiratory failure as the usual cause of death. Diagnosis Histology shows intraepidermal cleavage and possibly basal cell ne- crosis and is not diagnostic. Direct immunofluorescence of uninvolved skin shows both intercellular and intraepidermal desposition of antibodies. A sub- strate with transitional epithelia such as rodent bladder (devoid of desmogleins) is used in indirect immunofluorescence to confirm the presence of antibodies to plakins. The patients should be investi- gated for underlying malignancy if not known. Treatment and prognosis The disease is resistant to treatment but might improve if the underlying malignancy is treated. Immunosuppression is needed to improve the skin symptoms. Prognosis is poor and most patients die. FURTHER READING Bolotin D, Petronic-rosic V (2011). Dermatitis herpetiformis. Part I: epidemiology, pathogenesis, and clinical presentation. J Am Acad Dermatol, 64, 1017–24. Bolotin D, Petronic-rosic V (2011). Dermatitis herpetiformis. Part II: diagnosis, management, and prognosis. J Am Acad Dermatol, 64, 1027–33. Chan LS, et al. (2002). The first international consensus on mucous membrane pemphigoid: definition, diagnostic criteria, patho- genic factors, medical treatment, and prognostic indicators. Arch Dermatol, 138, 370–9. Colliou N, et al. (2013). Long-term remissions of severe pemphigus after rituximab therapy are associated with prolonged failure of desmoglein B cell response. Sci Transl Med, 5, 175ra30. Harman KE, Albert S, Black MM (2003). Guidelines for the manage- ment of pemphigus vulgaris. Br J Dermatol, 149, 926–37. Lloyd-lavery A, et al. (2013). The associations between bullous pem- phigoid and drug use: a UK case-control study. JAMA Dermatol, 149, 58–62. Taghipour K, et al. (2010). The association of bullous pemphigoid with cerebrovascular disease and dementia: a case-control study. Arch Dermatol, 146, 1251–4. Venning VA, et al. (2012). British Association of Dermatologists’ guidelines for the management of bullous pemphigoid 2012. Br J Dermatol, 167, 1200–14. Wojnarowska F, et al. (1988). Chronic bullous disease of childhood, childhood cicatricial pemphigoid, and linear IgA disease of adults: a comparative study demonstrating clinical and immunopathologic overlap. J Am Acad Dermatol, 19(5 Pt 1), 792–805.

Revision #1
Created 2026-01-22 16:43:05 UTC by Omar Ayman
Updated 2026-01-22 16:43:05 UTC by Omar Ayman