NASZA DERMATOLOGIA Online
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AUTOIMMUNE BASEMENT MEMBRANE AND *SUBEPIDERMAL BLISTERING DISEASES*

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Abstract

Autoimmune mucocutaneous blistering diseases (ABDs) represent a group of conditions that manifest with blisters on the skin and/or mucous membranes. Bullous pemphigoid (BP) is the most common autoimmune mucocutaneous blistering disease. In BP, the location of the blisters is subepidermal and the oral involvement is rare. Variants of BP have been described, including pemphigoid vegetans; however, this disease is not completely characterized. The majority of ABDs have blisters and/or vesicles, that are often pruritic, and manifest autoantibodies to diverse proteins. These proteins include 1) hemidesmosomal plaque proteins(ie, BP230, plectins), 2) transmembrane proteins such as BP180 and α6β4-integrin, which are connected via laminin 332 to type VII collagen and 3) currently uncharacterized 105 kDa and 200 kDa molecules. Other ABDs include drug-induced linear IgA disease, bullous systemic lupus erythematosus (BSLE), dermatitis herpetiformis (DH), cicatricial pemphigoid (CP; also termed mucous membrane pemphigoid), lichen planus pemphigoides (LPP), pemphigoid gestationis (PG), herpes gestationis(HG), chronic bullous dermatosis of childhood (CBDC) and the localized forms of CP, such as Brunsting-Perry pemphigoid. The diagnosis of ABDs requires clinical data; skin biopsies (in 10% buffered formalin) for hematoxylin and eosin (H&E) examination and skin biopsies(in Michel's transport medium) for direct immunofluorescence (DIF). In many ABDs, the histopathologic findings demonstrate a subepidermal vesicle or bulla with a luminal inflammatory infiltrate of neutrophils, eosinophils and/or lymphocytes. In many ABDs, an extensive perivascular and interstitial inflammatory infiltrate is also noted subjacent to the blister in the upper dermis. Normal skin adjacent to an ABD plaque is often excellent for DIF results. Many ABD biopsies reveal autoantibody deposition at the lesional basement membrane zone (BMZ); IgG, IgM, IgA, other immunoglobulins, complement components and fibrinogen may be detected. Indirect immunofluorescence (IIF) yields antibody titer data; the titers usually correlate with disease activity and with ELISA. Linear epitopes are commonly studied by using an immunoblotting (IB) assay. Topical and systemic corticosteroids remain as mainstays of therapy in ABDs; however, multiple other immunosupressors and/or "steroid sparing agents" such as azathioprine have been demonstrated to be of therapeutic value. In the IgA mediated dermatoses, dapsone is often helpful; in addition, liver and blood testing (including G6PD levels) is indicated. The prognosis depends on each case; rapid diagnosis avoids complications and assists in maintaining a good quality of life for each patient.

Key words: bullous pemphigoid; antigens; mucous membrane pemphigoid

Abbreviations and acronyms: Autoimmune mucocutaneous blistering diseases (ABDs), bullous pemphigoid (BP), mucous membrane pemphigoid (MMP), chronic bullous dermatosis of childhood (CBDC), adult linear IgA bullous dermatosis (LAD), lichen planus pemphigoides (LPP), immunohistochemistry (IHC), direct and indirect immunofluorescence (DIF and IIF), hematoxylin and eosin (H&E), antibodies (Abs), basement membrane zone (BMZ), intercellular staining between epidermal keratinocytes (ICS), pemphigus vulgaris (PV), cicatricial pemphigo-id (CP), dermatitis herpetiformis (DH), sodium dodecyl sulfate (SDS), SDS-PAGE (SDS polyacrylamide gel electrophoresis), bullous systemic lupus erythematosus (BSLE); bullous pemphigoid antigens II(180 kDa) and I(230 kDa)(BP180 and BP230), epidermolysis bullosa simplex (EBS), intravenous immunoglobulin (IVIG).

Introduction
Subepidermal autoimmune blisters

Traditionally, the classification of subepidermal blistering diseases has been based on their patterns of inflammation [1-3]. However, some overlap occurs between the traditional categories, especially with subepidermal vesiculobullous diseases in which neutrophils or eosinophils represent the predominant infiltrating cell [1-3].

Special techniques, including electron microscopy, immunoelectron microscopy, immunoblotting, direct immunofluorescence (DIF), indirect immunofluorescence (IIF), IIF/salt split skin, and immunohistochemistry (IHC) has allowed many of the subepidermal blistering diseases to be characterized not only histologically on the basis of the anatomic split level within the BMZ, but also immunologically [4-11]. Further, additional information helps to exclude viral blistering diseases, bullous allergic drug reactions and genodermatoses; this information may be provided via viral serology, viral culture, a history of previous intake of medications (including nonprescription medications) and possible genetic evaluation.

Bullous pemphigoid (BP)

Bullous pemphigoid is the most common autoimmune skin blistering disease (ABD) in the adult population in developed countries, with an estimated incidence that varies from 0.2 to 3 cases per 100,000 inhabitants per year to 1 in 40,000 [12-14]. In undeveloped countries, it seems to be the second more common ABD; however, few pertinent epidemiologic studies have been published, except in Singapore [15-17]. A sex predisposition has not been clearly demonstrated. The course of this disease can be acute, chronic, or relapsing. BP usually manifests in the sixth or seventh decade of life; however, cases have been observed at other ages, including in children [1-3]. The most common clinical presentation includes scattered urticarial papules and plaques on the trunk, arms, and legs early in the disease. The blisters are often large, tense and located on an erythematous base. Sometimes the blisters are not clinically apparent, due to previous rupture. Acral sites may be involved. The most important symptom related by the patients is pruritus, which may be severe; in contradistinction, pemphigus patients often report a burning sensation [1-3,14]. In some patients, the pruritus seems not to be present. Overall, skin lesions are symmetrically distributed, the most common sites are consistently the flexor surfaces of the extremities, the groin, the axillae and the lower abdomen. The lesions generally heal without scarring, but in rare cases milia formation has been described. In some cases, BP is misdiagnosed as urticaria. Specifically, the disease may initially present as tense vesicles and bullae change on an urticarial base. The bullae can reach a size of several centimeters before rupturing [14]. Blisters in the oral cavity are rare, may compromise the oropharynx and are classically non-scarring. Pemphigus vegetans, described as a variant of BP, is discussed below. Occasionally, BP may be induced by medications such as furosemide, captopril, and penicillin; however, BP needs to be immunologically differentiated from blistering allergic drug eruptions [3]. The physiopathologic aspects of BP include cutaneous deposition of autoantibodies, complement, fibrinogen, albumin and other products of proteases; this deposition results in the disruption of adhesive interactions between epidermal basal layer keratinocytes and the cutaneous basement membrane zone (BMZ).

Initial dermatopathology studies in BP were led by Walter F. Lever, M.D. On light microscopy, H&E staining classically reveals a subepidermal blister under an intact epidermis. When clinical blisters arise on erythematous skin, there is often a prominent cellular infiltrate in the papillary dermis consisting of numerous eosinophils, lymphocytes and neutrophils. Papillary dermal microabscesses of neutrophils and eosinophils are present in about 20% of BP cases [3]. The dermal infiltrate in clinically non-inflamed skin lesions is sparse, perivascular, and primarily composed of lymphocytes and histiocytes. Multiple

autoantibodies are directed to components of the BMZ.
Initial studies demonstrating the autoimmune nature of BP were led by Ernst Beutner, Ph.D. and Robert Jordon, M.D. [3,5]. These investigators demonstrated the increased diagnostic value of DIF biopsies taken from perilesional blister areas. Serologic studies including indirect immunofluorescence (IIF) can help to confirm the diagnosis, utilizing antigen sources such as normal human skin or monkey esophagus (Fig. 1). The DIF biopsies should be performed at the same time as the cutaneous H&E biopsies. In H&E biopsies, histopathologic findings may vary depending if the biopsy was taken from lesional, lesional border or nonlesional skin [1-4]. In BP, classic DIF of perilesional skin shows deposits of IgG and complement component C3 at the BMZ (Fig. 1). The IgG and C3 deposits are present in a continuous, fine linear pattern along the BMZ. In BP, linear deposits of IgG and C3 are observed in nearly 100% and approximately 90% of the cases, respectively. IgG deposits belong mainly to the IgG4 subclass, and, to a lesser degree, to IgG1 [5]. Other immunoreactant classes are less frequently observed with a similar linear pattern of deposition and usually in association with IgG; these classes include IgM, IgA, IgD, IgE fibrinogen, Complement/C1q and Complement/C3 [19-21]. Using IIF-NaCl split skin, autoantibodies are present predominantly on the blister roof in 90% of BP cases (Fig. 1). IIF is usually performed on normal human or monkey esophagus substrate skin; the skin substrate separates through the lamina lucida on incubation in 1.0 M NaCl. Via non-salt split IIF, the majority of pertinent ABD sera produce an indistinguishable pattern of linear immunofluorescence at dilutions of 1:10 or higher. On salt split skin IIF, these same antibodies bind to either the blister roof (epidermal pattern), blister floor (dermal pattern), or both the roof and floor (combined pattern). The binding patterns have been described in comparison with normal controls. Sera from patients with clinical and histologic features of epidermolysis bullosa acquisita (EBA) show a predominant dermal pattern. However, some sera from patients with BP and EBA show a combined pattern. Indirect immunoelectron microscopy of selected sera show antibodies producing the epidermal and combined patterns are anti-lamina lucida antibodies, and those producing the dermal pattern were anti-sublamina densa antibodies [22-24]. These results show that indirect immunofluorescence on salt split skin is a dependable method for differentiating bullous diseases with anti-lamina lucida versus anti-sublamina densa antibodies, and that differentiating between these antibodies is essential for accurate diagnosis in some patients. The results also suggest that BP anti-lamina lucida antibodies may have more than one antigenic specificity. The autoantibodies detected in sera from patients with BP have been reported to primarily bind to two hemidesmosomal proteins initially detected by immunoblotting (IB) and cDNA cloning as a 180-kD antigen (BPAG II; BP180; Collagen Type XVII), and a 230-kD antigen (BPAGI; BP230. BP230 is a plakin protein family member that promotes the association of hemidesmosomes with keratin intermediate filaments. BP180 is a type II transmembrane collagen that is associated with hemidesmosome anchoring filament complexes, and is believed to harbor all or a portion of the primary pathogenic epitope responsible for the initiation of BP. The extracellular domain of BP180 contains 15 interrupted collagenous domains. Rotary shadowing studies of purified BP180 reveal its intracytoplasmic region to be a globular head, and its ectodomain as a central rod joined to a flexible tail.
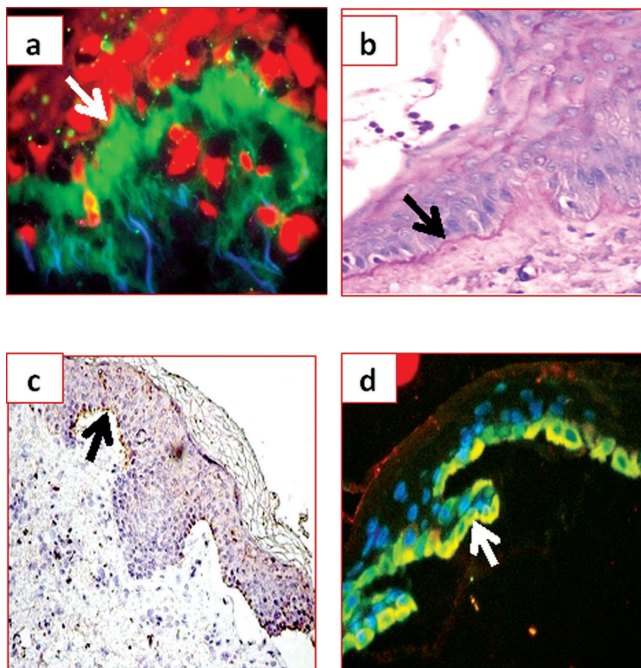
Figure 1 a. DIF of a case of EBA, demonstrating positive antibodies to human FITC conjugated Complement/C3 along the BMZ (green staining; white arrow) (400X). The nuclei epidermal keratinocytes were counterstained with Topro 3 (red staining). **b**. Same case as in a, with PAS positive staining along the BMZ (pink staining; black arrow) (200X). **c**. A case of BP, with positive IHC staining for IgE at the BMZ (brown staining; black arrow). **d**. A BP case, with NaCl salt split skin/IIF and positive staining on the blister roof for FITC conjugated anti-human IgG (yellow staining; white arrow). The nuclei of epidermal keratinocytes were counterstained with Dapi (blue staining).

Immunoelectron microscopy studies indicate that BP180 spans the lamina lucida, and inserts into the lamina densa. BP180 is targeted by autoantibodies from patients with BP, pemphigoid gestationis, cicatricial pemphigoid (CP) and linear IgA dermatosis (LAD) [7-10,25] (Tabl. I).

Enzyme-linked immunosorbent assays (ELISA) for BP180 and BP230 (MCW2 and MCW1, respectively) were developed by a BP research group at the Medical College of Wisconsin. Following further modifications using a fragment named NC16A, these assays are now commercially available. A recent study has shown that the BP180 ELISA is specific for the immunodominant NC16A domain of the BPAGII protein; however, the ELISA is also exclusive of other parts of the NC16A domain [29]. The NC16A finding is consistent with the immunology concept that all conformational epitopes at least carry at least one or more linear epitopes.

Electron microscopy studies on non-inflamed skin lesions from BP patients reveal that dermal-epidermal cleavage occurs within the dermal-epidermal junction, i.e., through the lamina lucida [30-33].

In regard to BP antigen(s), epitope mapping studies of recombinant proteins have formerly shown that autoantibodies from most patients with BP bind a determinant within the sixteenth non-collagenous domain of BP180 (i.e., the portion of its ectodomain that is positioned adjacent to plasma membranes of basal keratinocytes). It also have been shown in some experiments using passive transfer of experimental IgG (developed against the murine homolog of this determinant to neonatal BALB/c mice) produces clinical, histologic, and immunopathologic alterations with similarities to those seen in patients with BP patients. However, no animal or cell culture study has been able shown to reproduce the chronicity of BP [34]. Authors have reported multiple animal models with genetic manipulations; however, many of these studies lack proper controls. Thus, it is difficult to correlate these models to BP in vivo because most animal models lesions only persist for few days, and not reflective the chronic nature of this disease.

In contrast to pemphigus, BP is often a self-limited disease; thus, it may be sufficient to treat the patient symptomatically for a limited period. In general, relapse episodes are not common; systemic corticosteroids represent the most common therapy for generalized BP [33]. Specifically, BP therapy primarily consists of administration of topical and systemic corticosteroids. Topical corticosteroids present less adverse effects compared to systemic steroids [35]. The systemic dosage classically ranges between 0.5 and 1 mg Prednisone/kg/d [36]. The dose of prednisone can be tapered slowly over a period of several months to a maintenance dose of a total of 5 to 10 mg/day. Corticosteroids are often combined with other immunosuppressants in recalcitrant cases; hidroelectrolytic disorders often result from these treatments, especially in the elderly [37]. Because BP affects many senior patients suffering from other medical problems, systemic corticosteriod complications may be severe in these cases. Localized BP can be treated with topical corticosteroids [35-37]. However, the personnel treating these patients need to be aware of secondary cutaneous complicatons (e.g, erysipelas, lymphangitis, sepsis, phlegmons, cutaneous fistulas, atrophy and purpura) in patients treated with topical corticosteroids [38]. Dapsone and sulfonamides, either alone in combination with topical or systemic corticosteroids may also be effective [39]. Specifically, dapsone at a dose of approximately 100 mg/day is initiated at the same time as prednisone. The addition of dapsone often accelerates disease control, and thus allows a faster prednisone taper. Other researchers have describe the use of oral tetracycline, or a combination of tetracycline and niacinamide as successful treatments for BP. Cyclosporine, intravenous immunoglobulin (IVIG), azathioprine, rituximab, and plasmapheresis have all been proposed as additional treatments [40-44] (Tabl. I).

Frequent bacterial, fungal and viral cultures of cutaneous erosions, catheters, and serum cultures will allow detection of secondary infections arising as a result of immunosuppressive therapy. If positive results are found, appropriate therapy should be quickly initiated.

In Table I, we present a summary of the more common immunosuppressive agents, their metabolites, their serum half lives and common complications. Previous reports have addressed morbidity and mortality in BP. In a private hospital in Wisconsin, thirty-eight new patients were identified and complete follow-up data were obtained on 37 of the patients. Patients were followed for a minimum of 1 year, or until the time of death. The mean duration of follow-up was 20 months. A Kaplan-Meier analysis of the population indicated a 1 year survival rate of 88.96%, with a 95% confidence interval of 75.6% to 94.2%. The survival rate was considerably higher than that recently reported in several studies from Europe (29%-41% one year mortality). The authors reported that although the age at onset and co-morbidities of our patients were similar to those in the European studies, the rate of hospitalization of our patients was much lower than that of patients from Europe (1.5 days per patient, vs. 11-25 days per patient). The study suggests that differences in practice patterns may be an important factor in the reduced mortality rate in US BP patients compared to those in Europe [45].

Previously, BP has been associated with significant morbidity and mortality rates. In one study, the authors retrospectively studied 94 patients with BP in a Chinese tertiary medical center between 2005 and 2010, to evaluate treatment and prognostic factors for mortality. Cerebrovascular diseases (42.55%) and hypertension (39.36%) represented the most common pre-existing conditions. Cardiopathy, diabetes and psoriasis pre-existed in 24.47%, 22.34% and 5.32% of patients, respectively [46]. Eighty of 94 patients were treated by systemic corticosteroid, specifically prednisone 0.3 mg/kg to 1.5 mg/kg daily. Patients were followed up for a minimum of 1 year or until the time of death. The mean duration of follow-up was 32 months. Kaplan-Meier analysis demonstrated a 1 year survival probability of 76.6% (standard error 4.4%), with a 95% confidence interval (68.04% to 85.16%). Multivariate analysis revealed that increased age, bedridden condition, presence of cerebrovascular diseases at diagnosis, pre-existing cardiopathy and low serum albumin level were associated with an elevated 1 year mortality rate [47]. In a second study, authors in Latin America obtained similar results as those previously described for developing countries [48]. An association has been suggested between neurologic disorders and BP, since Type XVII collagen (BPAGII; BP180) is a component of hemidesmosomes, which connect epidermal basal layer keratinocytes to the underlying basement membrane. In addition, Type collagen XVII has been recently demonstrated in human brain neurons by in situ hybridization.

Skin biopsies for hematoxylin and eosin (H&E) staining and direct immunofluorescence (DIF) are needed to confirm a BP diagnosis. Histopathologic findings of early lesions show subepidermal vesicles, with luminal infiltrates of eosinophils and subjacent, upper dermal, perivascular infiltrates of eosinophils and neutrophils with dilation of infiltrate associated blood vessels [1-3]. The cutaneous H&E biopsy should be placed in 10% buffered formalin, and will produce excellent archival material; however, formalin can form precipitates at high temperatures, and freezing temperatures may produce tissue artifacts. Normal skin adjacent to a BP urticarial plaque is ideal for a DIF biopsy. Almost all biopsies reveal linear Complement/C3 deposition at the basement membrane zone (BMZ), and 80% of biopsies will also show linear immunoglobulin (IgG) deposition at the BMZ [4-6] (Fig. 1). Biopsies for DIF should be placed in Michel's transport media for processing to avoid false negative results; however, when Michel's medium is not available the biopsy may be sent in saline solution.

Several independent research studies have reported mixed results in regards to increased sensitivity and specificity of ELISA testing, in comparison to other diagnostic techniques for BP [49]. Occasionally, BP has been described to be induced by medications such as furosemide, captopril, and penicillin.

Author's note: We recommend carefully differentiating BP from with medication-induced blistering diseases; the medication-induced bullous dermatoses represent a more common presentation of bullae in elderly patients, especially in the USA. In our own immunodermatology practice, blisters caused by medications are much more common than BP

Mucous membrane pemphigoid (MMP), or cicatrical pemphigoid (CP)

CP represents a subepidermal blistering disease, that characteristically presents in the sixth or seventh decade of life. The female-to-male ratio is about 2: 1 [50]. The term cicatricial pemphigoid (CP) has been used for more than 70 years, and originated with pioneers in the study of cutaneous autoimmune bullous diseases [50-60]. However, at the First International Consensus on Mucous Membrane Pemphigoid in 2002 [57], the name for the disease was recommended to be changed to MMP. CP mainly involves oral mucosa, other mucous membranes, and rarely the skin. Gingival involvement is frequent. In a case of desquamative gingivitis, the clip sign suggests the diagnosis of CP. CP is an autoimmune vesiculobullous disease, distinguished clinically by its predilection for oral and ocular mucous membranes and a tendency for the lesions to scar. Considerable heterogeneity exists in terms of age at presentation and the clinical pattern of disease. In rare cases, CP may present in children and adolescents. The mouth is the most frequent site of presentation, and is eventually involved in 85% of cases. There are erosions, irregular ulcers, and vesiculobullous lesions. Ocular involvement is also common, and corneal and conjunctival scarring may lead to blindness. A CP diagnosis is established by clinical, histological and DIF examination. On DIF, linear deposition of IgG and/or IgA are present along the BMZ of biopsies [50-60]. In some reports, autoantibodies to plectin have also been identified. CP differs from BP in that individual lesions heal with scarring that can be deforming, altering vision and/or genitourinary functionality. As in pemphigus vulgaris, any mucosal site can be affected. Involvement of the nasal mucosa can subsequently lead to strictures in the oral and esophageal areas. If the patient is coughing or has a rough voice on initial presentation, possible blistering in the pharynx and larynx should be suspected. An extensive workup should be performed, including consultation with an ENT specialist and a voice therapist. Involvement of the conjunctivae (which manifests clinically as conjunctivitis and xerosis) may result in scarring causing symblepharon, entropion, and later trichiasis [58-60]. Progressive scarring may then lead to blindness. H&E studies show similar results to BP, with subepidermal blisters containing edema fluid, fibrin and inflammatory cells. A dermal perivascular lymphohistiocytic infiltrate with occasional plasma cells and neutrophils can be seen. In general, fewer eosinophils are appreciated than in BP. Conjunctival squamous metaplasia with foci of hyperkeratosis and parakeratosis, accompanied by goblet cell depletion and conjunctival vesicles or bulla is rare. By IIF, the patients usually have low titers of circulating antibodies; IIF on NaCl split skin shows antibodies on the blister floor. By electron microscopy, CP antibodies are located in the lamina lucida.

An interesting recent study investigated the levels of matrix metalloproteinases (MMPs), myeloperoxidase (MPO) and tissue inhibitor of metalloproteinase-1 (TIMP-1) in ocular tears of patients with Stevens Johnson syndrome (SJS) and ocular cicatricial pemphigoid (OCP). The authors performed a prospective, non-interventional cohort study with four SJS patients (7 eyes), 19 OCP patients (37 eyes) and 20 healthy controls who underwent phacoemulsification (40 eyes). The authors evaluated tear washes collected from all patients; these washes were analyzed for levels of MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-12, MPO, and TIMP-1 using a multianalyte bead-based ELISA test. Total MMP activity was also determined, using a fluorometric assay. Correlation studies were performed comparing specific analytes within study groups. The authors reported that MMP-8, MMP-9, and MPO levels were significantly elevated in SJS and OCP tears (SJS>OCP) in comparison to controls. MMP activity was highest in SJS patients, whereas OCP patients and controls displayed lower activities(which were similar to each other). The TIMP-1 levels were decreased in SJS and OCP patients when compared to controls, with levels in OCP patients attaining significance. The MMP-8 to TIMP-1 and MMP-9 to TIMP-1 ratios were markedly elevated in SJS and OCP tears (SJS>OCP) when compared to controls. Across all study groups, MMP-9 levels correlated strongly with MMP-8 and MPO levels, and MMP-8 correlated with MPO, but did not reach significance in SJS patients. The authors also reported that there was no significant relationship between MMP-7 and MPO [61] (Tabl. I). In CP, involvement of the genital and anal mucosa is common. Persistent blistering and scarring of the vaginal mucosa can result in stenosis, which may be discovered and also interfere with screening pelvic examinations [50]. Anal involvement manifests as localized pain and bleeding, which can lead to stenosis if left untreated.

Cutaneous tense blisters (similar to those seen in BP) occur in only 20% of CP patients. Healing occurs with pink, atrophic scarring. In CP, multiple manifestations of the disease exist depending on which protein in the BMZ is the primary antigen involved. Around 90% of patients with CP have been described to have oral erosions. If the oral mucosa is the single mucosal site involved in CP, the condition may be called oral pemphigoid. If the conjuctival mucosa is the only site of CP clinical presentation, the disorder is termed ocular pemphigoid [50-60].

Anti-epiligrin subtype: Another type of CP, termed antiepiligrin cicatricial pemphigoid, occurs when antibodies are formed against laminins 5, 332 and 6 in the basement membrane. This disease is uncommon, and primarily affects mucous membranes but also the skin. The disease is associated with mortality from treatment with systemic immunosuppressive drugs. In this subset, there is an association with solid organ malignancies. Biopsies for H&E staining and DIF should be performed to confirm the diagnosis. Antiendomysial antibodies can be documented, using monkey esophagus as the antigen source for the IIF. Histologically, the findings are almost identical to BP [54,55]. A subepidermal vesicle is seen, with an inflammatory infiltrate of neutrophils and eosinophils in the upper dermis [50-53]. Scarring may be seen in the upper dermis. DIF of perilesional mucosa reveals linear IgG and Complement/C3 deposition at the BMZ in 90 to 95% of patients. Because there are low amounts of circulating antibodies, IIF testing is not generally helpful. The diagnostic findings of CP are summarized in Table I.

Patients with localized oral involvement often respond to topical clobetasol gel, or intralesional triamcinolone (5 to 10 mg/mL, injected sublesionally every 3 weeks as needed). Patients with multiple mucosal sites should be treated with systemic therapy such as dapsone or prednisone. If the lesions are unresponsive, an additional immunosupressor should be utilized in combination with prednisone. In some patients, mycophenolate mofetil is less myelosuppressive and hepatotoxic than corticosteroids. Due to a superior safety profile, mycophenolate mofetil or enteric-coated mycophenolate sodium may gradually replace azathioprine as the first-line adjuvant of choice in the treatment of moderate to severe autoimmune CP. Cyclophosphamide still has a place in the treatment of severe relapsing CP; continuous oral cyclophosphamide provides optimal immunosuppression, but it also produces the highest cumulative dose. Therefore, pulsed cyclophosphamide regimens have been developed and are useful in severe forms of CP. Because of the low incidence and prevalence of these diseases, few randomized controlled studies have compared the efficacy and safety of immunosuppressants such cyclophosphamide with newer treatment options such as rituximab and immunoapheresis. In addition, few studies have been conducted to define optimal dose ranges and optimal durations of immunosuppressive treatments at different stages of CP. We encourage the multidisciplinary collaboration necessary for the diagnosis and proper treatment of difficult cases of CP. Systemic adjuvant immunosuppressive therapy is necessary for patients with progressive disease. In spite of the advances in available immunosuppressive medications and biologics, scarring is a significant complication in many cases [59,62] (Tabl. I). Surgical intervention in general does not cure the disease, though in some occasions with severe sequels, it may be necessary for restoring function and humanizing quality of life. BP alone and bullous lupus rarely involve the oral mucosa. Author's note: Early, strong immunosupressive treatment is advised in CP patients, due to potential scarring damage to the eyes, nasal mucosa and genito-urinary tract. Systemic steroids in combination with immunosuppressive agents such as methotrexate, mycophenalate mofetil, azathioprine or cyclophosphamide are recommended in severe cases.

Localized cicatricial pemphigoid
Localized CP, also known as Brunsting–Perry pemphigoid, is characterized by the occurrence of one or more scarring, plaque-like lesions, usually on the head and neck; the disease is characterized by a lack of involvement of mucous membranes, including on prolonged follow-up. The temple is the most frequent site of presentation, lesions have occurred in tissue transplanted to the site of a pre-existing lesion. The exact relationship of this condition to CP is speculative, although they are thought to be closely related diseases [63,64]. Rare cases may progress to a generalized disease that heals with scarring; however, although the second disorder that could be CP, there is no mucous membrane involvement. In DIF and IIF studies, the most commonly described findings are linear deposits of IgG(but not IgM or IgA) at the epidermal-dermal junction. In few patients, linear Complement/C3 deposition at the BMZ is noted; a few patients also exhibit circulating anti-BMZ antibodies [65,66]. In some cases, DIF has been reported as negative. In other cases the putative antigen(s) have been described to be IgG autoantibodies to laminin-332, BP230 and desmoplakins I and II; and in further cases to a 290 kDa molecule [67,68].

Electron microscopy studies have been shown a subepidermal separation below the basal lamina, and the basal lamina and anchoring fibrils preserved and attached to the intact epidermis along the blister roof [69]. Many authors in the 1980s and 90s considered Brunsting-Perry disease to be a variant of CP. These findings support the concept that localized CP, CP, and disseminated CP are in fact closely related diseases, and may explain the occurrence of scar formation in localized CP [70]. Due to the low incidence of Brunsting-Perry disease, has been difficult to definitively categorize the disorder; in addition, early BP may present with an individual blister, and may be thus improperly categorized as Brunsting-Perry disease.

Pemphigoid vegetans

Pemphigoid vegetans is a rare disease exhibiting clinical similarity to pemphigus vegetans, but with histological and immunopathological features of BP. Only few cases have been reported; the relationship of pemphigoid vegetans to BP thus is not clear. Clinically, pemphigoid vegetans classically presents with multiple, well-circumscribed, erythematous, erosive and vegetating plaques in the axillae, inframammary areas and neck [71-73]. Microscopic examination reveals epidermal hyperplasia, dermal/epidermal junctional separation, and prominent dermal eosinophilia [74]. By DIF, perilesional skin demonstrates linear deposits of IgG at the BMZ, primarily of the IgG4 subclass. On salt split skin IIF, these antibodies are present on the blister roof of normal human skin [75,76]. By immunoblotting (IB) studies, the 230 kD BPAGI antigen is one of the disease antigens in pemphigoid vegetans [76]. Some authors have suggested that pemphigoid vegetans is best classified as a BP variant, after describing a 57 year old man with intertriginous vegetating plaques. The histologic examination and DIF of a biopsy specimen were identical to those of BP. IB studies and IIF of salt-split skin were negative [75,76]. Direct immunoelectron microscopy was consistent with BP [77]. Based on a limited experience, previous authors have reported that pemphigoid vegetans patients seem to improve with tetracycline and/or corticosteroids [78] (Tabl. I).

Pemphigoid gestationis (PG)

Pemphigoid gestationis (also known as herpes gestationis (HG)) is a rare, pruritic, vesiculobullous dermatosis of the late pregnancy and puerperium (post-delivery) periods [79-82]. The most common age of presentation is between 20 and 40 years. It accounts for less than 5% of the dermatoses of pregnancy. The onset of the disease is usually in the second or third trimester of pregnancy with the development of papules and urticarial plaques, initially localized periumbilically and extending towards the thighs and/or extremities. The presence of circinate plaques is not unusual [79]. PG needs to be suspected in presentations of vesicles on extensor surfaces of the elbows, knees or buttocks. Clinically, PG is characterized by severe pruritus. Mucosal lesions are uncommon; untreated lesions may persist through the pregnancy, but classically break down following delivery over several days or weeks [80]. DIF of perilesional skin is helpful in the diagnosis, and the results are similar to those described for BP. The electron microscopy findings seem to be present throughout the entire lamina lucida and the basal cell plasma membrane appeared to be accentuated. The most remarkable ultrastructural changes in normal-appearing skin were the destruction of the basal cell membranes on the dermal side, localized cytoplasmic dissolution, and intracellular edema unaccompanied by inflammatory cells (Tabl. I). Early, nonvesicular lesions showed basal cell degeneration and dermal inflammatory cells. Necrosis and loss of basal cells occurred in the next stage which resulted in microvesicles in which collagen or a well-preserved basal lamina formed the vesicle base. In the later blister stage, the basal lamina was usually lost. It is suggested that damage of basal cell membranes on their dermal side leads to the destruction of basal cells with the subsequent protrusion of epidermal and junctional substances into the dermis. This may result in inflammatory cell infiltration and blister formation. A study in Finland during 2002 to 2011 tested a group of 12 PG pregnancies, evaluating clinical outcome and morphologic and functional placental data [82]. The authors showed that the placental to birth weight ratio was abnormal in half of the pregnancies. In the same study, the authors showed that the PG placentas displayed detachment of basement membranes and undeveloped hemidesmosomes [83]. The authors also reported that ultrasound evaluations of placental function prior to delivery were normal in all but one pregnancy. The authors reported that three (25%) neonates were delivered preterm after 35 gestational weeks, and one pregnancy was complicated by pre-eclampsia and severe fetal growth restriction. The authors reported that the neonatal outcome was uneventful in every PG case [82]. Overall, in pregnancies complicated by PG, slight alterations in ultrastructural morphology of the placental basement membrane have been detected, but umbilical artery Doppler evaluation has indicated no functional placental changes [83]. Thus, placental studies should be further pursued in patients affected by PG. In regard to the autoantigens, it has been shown that PG and BP autoantibodies react with common epitope sites on the extracellular domain of the BP180/BPAGII antigen [83,84]. In some cases, autoantibodies against placental and dermal collagen Type XVII have been also reported (Tabl. I).

Therapeutically, in mild cases of PG topical corticosteroids and antihistamines (to alleviate pruritus) may be sufficient. However, PG treatment should ideally be coordinated between a nurse, pediatric neonatologist, dermatologist and obstetrician [85-86]. Topical corticosteroids are indicated for pregnant women with skin conditions, but their safety in pregnancy is not fully understood. A recent study reassuringly demonstrated no association of maternal topical corticosteroid exposure with orofacial clefting, preterm delivery, fetal death, low Apgar scores or mode of delivery [86]. Given all available evidence, risk of low birth weight seems to correlate with the total quantity of topical corticosteroid exposure. Due to the possibility that the mother of a baby in gestation may need systemic steroids, risks of prematurity and fetal growth restriction should be monitored. In severe prenatal PG cases and during postpartum exacerbations, prednisone (20-40 mg/d) may be needed in addition to topical steroids [85-86]. The main differential diagnosis is pruritic urticarial papules and plaques of pregnancy (PUPPP), an illness that classically begins in abdominal striae in late first pregnancies, and may present negative findings via DIF and IIF.

Dermatitis herpetiformis (DH)

Dermatitis herpetiformis is an uncommon, chronic, polymorphous pruritic skin disease with subepidermal blistering. DH was first described by Louis A. Duhring, M.D. in 1884 [87]. A male predilection exists; lesions generally present in the fourth decade, although DH has been described in patients from 2 to 90 years of age [88]. DH is most common in Caucasians of northern European descent [89].

Cutaneous manifestations include grouped papulovesicles on an erythematous base, sometimes with excoriations and crusts [89,89]. A symmetric distribution, with lesions on the extensor surfaces of the elbows and knees, back, scalp (often posterior hairline) and buttocks is frequent; however, lesions may sometimes be present on other parts of the body. DH is commonly associated with other autoimmune diseases such as vitiligo, primary biliary cirrhosis, Hashimoto's thyroiditis, Sjögren's syndrome, rheumatoid arthritis, sarcoidosis, lupus erythematosus, type I diabetes and pernicious anemia, among others [90,91]. DH is also commonly associated with celiac disease [92]. Gluten diet allergy typically presents as celiac disease, a common, chronic small intestinal disease. Although DH is highly associated with celiac disease, the gastroenterological symptoms in DH patients are generally mild or not present [92,93].

To confirm the diagnosis of DH, a skin biopsy should be obtained for H&E examination. DIF studies are also indicated, as are serum tests for anti-endomysial and transglutaminase antibodies. Anti-tissue transglutaminase or transglutaminase 2 IgA enzyme-linked immunosorbent assay (ELISA) tests are reported to be of good specificity and sensitivity [94]. The H & E biopsy should be taken from an area near an active DH lesion; the biopsy classically demonstrates a neutrophilic infiltrate within the dermal papillae, and small, punctate subepidermal blisters with luminal neutrophils. Fibrin deposition and leukocytoclasis in the dermal papillary tips are common in DH [95]. DIF classically reveals granular immunoglobulin A (IgA) deposits at the tops of the dermal papillary tips, likened to "snow on the mountain tops". The DH pattern is distinctly different from the DIF pattern seen in linear IgA bullous dermatosis [96]. More complex patterns of immoreactivity have been described via DIF, IIF and immunohistochemistry in DH patients [97] (Tabl. I).

The autoantigen or autoantigens of DH remain obscure, although some authors have suggested that these antigens are transglutaminases [98-100], or part of the BP180/BPAGII antigen. In regards to treatment, a gluten free diet may be helpful; however only less than 30% of the patients with DH present with celiac disease. Dapsone is the gold standard treatment for patients with DH; glucose-6-phosphate dehydrogenase levels should be reviewed before initiating dapsone treatment. Before starting dapsone, it is also recommended to perform a baseline complete blood count (CBC) with differential; renal and liver function tests and urinalysis should be performed. Subsequent monitoring of the CBC should be performed weekly for 1 month, then every other week for 1 month and then every 3 to 4 months. The blood studies are needed to rule out hemolytic anemia and hypersensitivity reactions to dapsone. Other adverse side effects of dapsone include leukopenia, agranulocytosis, cutaneous drug reactions, liver abnormalities, peripheral neuropathy, nephrotic syndrome and pulmonary abnormalities. Documented effective dapsone dosages are from 25 to 400 mg per day, with an average dose of 100 mg per day. Dapsone inhibits neutrophil chemotaxis. Because hemolytic anemia and methemoglobinemia represent well documented side effects, patients need to be educated to recognize these complications. In case of these reactions, it is important to stop the dapsone. The therapy should be stopped if white blood cell count falls below 4000 cells/dl. Signs of peripheral motor neuropathy should be assessed on physical exam. Liver and renal function tests should be evaluated every 3 months, or if symptoms of dysfunction are noted [102-103]. Alternative treatments for DH in patients intolerant to dapsone are sulfasalazine and sulfapyridine, although these agents are not always available. Appropriate doses of 2 to 4 g/day of sulfasalazine, or 1 to 2 g/day of sulfapyridine have been documented [102].

If DH is not controlled sufficiently by these agents, antihistamines and oral steroids may be added (Tabl. I).

Linear IgA bullous dermatosis (LAD)

LAD disease has presented classification challenges. According to some, LAD has two variants. The first variant presents in children as chronic bullous dermatosis of childhood (CBDC); the second variant presents in adults, is either associated with medication allergies or of idiopathic etiology and termed adult linear IgA bullous dermatosis (LAD). Some researchers have postulated these two variants since similar DIF linear deposits of IgA at the BMZ are found in each variant. However, clinically and epidemiologically they seem to be two discrete nosologic entities. The variants demonstrate a bimodal age predilection, with CBDC occurring in children between 6 months and 10 years of age, and rarely persisting after puberty. LAD mainly affects adults over the age of 60 years. Implicated LAD drugs include antibiotics, antihypertensives, and nonsteroidal anti-inflammatory agents (Tabl. I). Vancomycin is the most commonly implicated drug [104-108]. In addition, LAD associations with lymphoproliferative disorders, infections, ulcerative colitis and systemic lupus erythematosus have been described [109-111]. The majority of the reported cases have been induced with medication intake. In addition to the skin, mucosal surfaces with stratified squamous epithelium may also be affected. The incidence of LAD has varied in different studies from 0.22 to 2.3 cases per million per year. Usually LAD patients have bullous and erosive lesions on the trunk and extremities, appearing after taking the medications. The lesions appear as clear or hemorrhagic vesicles or bullae, with an erythematous or urticarial base. The blisters are classically tense, vary in size, and may form annular or circular patterns. In children, CBDC lesions are often localized to the lower abdomen, perineal area, and inner thighs. The face, hands, and feet are not commonly affected. In adults, LAD mainly affects the extensor surfaces, trunk, buttocks, and face. Mucous membranes may be involved; in these cases, the mouth and eyes are most commonly affected. CBDC has been known in the past as juvenile dermatitis herpetiformis, juvenile pemphigoid, and linear IgA disease of childhood. CBDC is characterized by an abrupt onset in the first decade of life and large bullae. CBDC is frequently misdiagnosed as bullous impetigo [104-108]. CBDC lesions may present in characteristic "crown of jewels" or "string of pearls" distributions.

Histologic H&E sections of LAD classically reveals a subepithelial blister, with a predominance of luminal neutrophils. Neutrophils are also present in the upper dermis; these may form papillary dermal microabscesses and leukocytoclasis. The DIF findings feature linear deposits of IgA at the BMZ, and may also include IgG and Complement/C3 in a linear pattern at the BMZ. Note that the LAD DIF IgA deposition differs from DH, in that the IgA deposits in DH are primarily granular and located at the dermal papillary tips [104-108] (Tabl. I).

Interestingly, some researchers have postulated that LAD and DH represent variable expressions of the same disease; both variants would theoretically share an identical target antigen (a 97 kDa or 285 kDa antigen in the upper lamina lucida) [105]. However, such an antigen association has not been definitively proven.

The LAD antigen was originally identified as a 97 kDa peptide; however, some studies have also shown LAD reactivity to BP180. Anti-laminin 5 mAbs also localize to the blister floor in LAD. Some authors have also tried to describe a nosologic association of LAD and BP. Specifically, the hypothesis cites DIF results in each disease showing deposits of IgG and IgA to multiple similar molecules; in addition, immunoblotting results show IgG and IgA antibodies to subunits of laminin-332, Type VII collagen, laminin-γ1, BP230/BPAGI and BP180/BPAGII recombinant proteins. However, these reports require careful analysis, and further confirmation [112,113]. CBDC is often a self-limited disease; most patients enter remission within 2 years. However, full treatment of CBDC and LAD require identification of any offending drug(s) or agent(s), and immediate withdrawal. Especially in LAD, such actions alone may result in resolution of skin lesions within days to weeks. Finally, both LAD and DH are usually responsive to dapsone; alternatively, sulfapyridine or sulfamethoxypyridazine are also effective (Tabl. I). In LAD, severe cases may also require oral steroids [114-115].

Subepidermal autoimmune bullous diseases with antibodies to 105- or 200-kDa BMZ proteins

In recent years, two new pemphigoid-like diseases have been postulated. Specifically, the first disorder would exhibit autoantibodies to a 105-kDa lamina lucida protein, and be known as deep lamina lucida pemphigoid; the second disorder would exhibit autoantibodies to a BMZ protein of 200 kDa [116-117]. According to the authors, patients with these conditions responded well to systemic corticosteroids. We further describe these entities in the next two paragraphs.

Deep lamina lucida (anti-p105) pemphigoid

Anti-p200 pemphigoid: Anti-p200 pemphigoid represents a unique subepidermal blistering disease. The disease presents with clinical similarity to BP, but without scarring. In DIF, the disease resembles DH or LAD, with additional linear deposits of IgG and complement/C3 along the BMZ [117]. Disseminated small blisters and erosions are often present. Palmoplantar involvement has been also described. Large, tense bullae may also be the dominant lesion [118]. Anti-p200 pemphigoid is associated with psoriasis in some patients. The antibodies are usually of the IgG4 subclass, and directed against a 200 kDa protein in the lower lamina lucida which is distinct from either laminin 5 or Type VII collagen. A recent study found that the autoantigen in this condition is a non-collagenous glycoprotein, and is synthesized by keratinocytes and fibroblasts; the autoantigen is distinct from nidogen-2 (Tabl. I). Another report described a subepidermal bullous disease with clinical features of BP and erythema multiforme, and non-scarring mucous membrane involvement. The immune response was directed against a 200 kDa protein at the BMZ, and the disease was responsive to both tetracycline and niacinamide [117-119]. Because few cases have been described of these anti-p105 and anti-p200 pemphigoid diseases, caution is recommended when interpreting these results (Tabl. I).

Epidermolysis bullosa acquisita (EBA)

EBA is a chronic, autoimmune, subepidermal bullous disease with clinical features similar to the genetic form of dystrophic epidermolysis bullosa [120-123]. EBA has been differentiated from other bullous diseases on the basis of distinctive clinical and histologic and immunodermatologic features, establishing diagnostic criteria for the disease. Specifically, these include 1) clinical lesions resembling dystrophic epidermolysis bullosa, 2) adult onset of the disease, 3) a negative family history of dystrophic epidermolysis bullosa, and 4) exclusion of other bullous diseases [124]. EBA is characterized by subepidermal blisters and autoantibodies to Type VII collagen, the major component of BMZ anchoring fibrils. Indeed, additional evidence from mouse models supports a pathogenic role of autoantibodies against Type VII collagen in EBA. Type VII collagen is unique to stratified squamous epithelium; it consists of 3 identical α chains, each with a molecular weight of 290 kDa. The amino terminus of Type VII collagen contains a large, globular non-collagenous domain termed NC1; a small noncollagenous domain termed NC2 lies at the carboxyl terminus. Anchoring fibrils are formed as a consequence of an antiparallel alignment of individual Type VII collagen molecules, that subsequently unite via disulfide bonds within the NC2 tails. Once a tail-to-tail dimer is formed, the NC2 domain is proteolytically cleaved, leaving a long, thread-like macromolecule characterized by a central rod with large, globular NC1 head domains at each end. Type VII collagen dimers then aggregate laterally to form anchoring fibrils. Once considered a diagnosis of exclusion from a group of heterogeneous blistering disorders, EBA is now recognized as a polymorphic, yet distinct, subepidermal blistering disease [125,126]. Ocular involvement in EBA should not be confused with drug induced pemphigoid (pseudo–ocular cicatricial pemphigoid), which is self-limiting, and usually develops after long term use of glaucoma medication. Of several proposed subclassifications, one includes 3 different skin manifestations of the disease: 1) a non-inflammatory form of EBA, affecting trauma-prone areas of the skin, 2) a generalized inflammatory blistering eruption, and 3) a CP-like disease, mainly affecting mucous membranes. A second subclassification divides EBA into two main clinical types: 1) mechanobullous and 2) inflammatory EBA. Mechanobullous EBA, referred to as classic EBA, presents with skin fragility, blisters and dystrophic changes on trauma-prone areas. Inflammatory EBA resembles other autoimmune subepidermal bullous diseases. Further subclassifications of EBA include patients with the dermolytic, or noninflammatory variant of EBA; these patients have trauma induced blisters and erosions on none inflamed skin, atrophic scars, milia, nail dystrophy, and/or oral erosions. Other inflammatory EBA patients have widespread inflammatory blisters that mimic those seen in patients with BP. Some patients may transition from the inflammatory to the dermolytic form of the disease [127-129]. All forms of EBA are difficult to treat, and treatment is often unsatisfactory. EBA is typically chronic; many patients also have underlying inflammatory bowel disease Systemic corticosteroids alone, or in combination with azathioprine or cyclophosphamide may not be effective in controlling the disease. Some intractable cases of EBA have successfully been treated with intravenous immunoglobulin or rituximab. Some patients may respond to dapsone or cyclosporine; a small number of patients have also been successfully treated with colchicine or extracorporeal photopheresis [124] (Tabl. I).

Direct immunofluorescence of perilesional skin revealed linear BMZ deposition of IgG and Complement/C3. ELISA testing detects anti-COL7 autoantibodies, confirming the diagnosis of EBA [130] (Fig. 1). An ELISA for EBA has correlated disease activity with positivity [131]. Extracutaneous EBA manifestations include ocular, oral mucosal, esophageal, anal, vaginal, tracheal and laryngeal lesions.

Ocular involvement in EBA predominantly presents with scaring, and resembles lesions observed in patients with MMP. Rarely, laryngeal involvement may cause hoarseness, impaired phonation, loss of voice, and may lead to irreversible respiratory distress with esophageal strictures. Patients may not be able to swallow food and thus require endoscopic esophageal dilations, which may have to be repeated if disease activity cannot be controlled [132-134].

In multiple cases, EBA has also been associated other diseases such subacute cutaneous systemic lupus erythematosus, diabetes mellitus, cryoglobulinemia, ulcerative colitis, Crohn's disease and psoriasis. Interestingly, regarding the association of EBA with psoriasis, in the 4 patients described so far, EBA presented subsequent to psoriasis [132-134]. However, most of these findings are anecdotal reports, establishing no definitive pathogenic interaction of psoriasis and EBA.

The main differential diagnosis of EBA is the dystrophic epidermolysis bullosa (DEB) and other genetic forms of DEB. DEB is due to a genetic defect in the gene encoding Type VII collagen; as previously noted, this molecule represents a primary component of anchoring fibrils, structures that attach the epidermis and its underlying BMZ to the papillary dermis. Thus, DEB patients have decreased normal functioning anchoring fibrils, due to structural defects [135-136]. EBA patients have a similar functional problem; however, their decrease in functionality is due to an abnormality in their immune system, in which they produce anti-Type VII collagen antibodies that attack the anchoring fibrils.

Bullous systemic lupus erythematosus (BSLE)

BSLE represents a rare blistering disease, presenting in patients who 1) meet American College of Rheumatology (ACR) criteria for systemic lupus erythematosus (SLE) and 2) displaying clinical lesional blisters. In addition, BSLE may present in patients with a vesiculobullous eruption, who do not fulfill complete ACR SLE clinical diagnostic criteria for SLE [137-138]. BSLE displays a clinical spectrum including herpetiform vesicles, large hemorrhagic bullae, and a disseminated urticarial, erythematous eruption associated with tense blisters, erosions, and crusting. Sometimes the lesions are limited to sun-exposed areas of the body, and can be triggered by sun exposure [139]. BSLE may also present with renal and or other clinical abnormalities [138]. BSLE skin biopsies typically demonstrate subepidermal blistering with a prominent neutrophilic luminal infiltrate. By DIF, BSLE usually presents with linear BMZ deposits of IgG; however, other immunoreactants such as IgA, IgM, and Complement/C3 may be also seen at the BMZ and accentuated on the blister floor [140]. The best antigen most clearly associated with this disease is Type VII Collagen; by electron microscopy, the antibodies are located under the BMZ lamina densa. In the limited cases found in the literature, patients responded better to dapsone than corticosteroids [141]. The differential diagnosis includes lichen planus pemphigoides (LPP), and bullous allergic drug eruptions (Tabl. I).

Lichen planus pemphigoides (LPP)

LPP, a rare skin disorder, has been generally considered to represent a mixture of the clinical, histopathologic and immunologic patterns of lichen planus (LP) and BP [142-144]. LPP is characterized by the development of tense blisters, often located on the extremities, in a patient with lichen planus. LPP is predominantly idiopathic; however, in rare cases it has been associated with drug administration. One pertinent example was development of the disease after the use of captopril [145].

Histologic changes include a mild, perivascular infiltrate of lymphocytes; sometimes, there are a few eosinophils and neutrophils beneath the blister and a lichenoid, lymphohistiocytic infiltrate at the BMZ. Occasionally, Civatte bodies are present in the basalilar epidermis at the margins of the blister. LPP needs to be distinguished from vesiculobullous dermatomyositis, in which a subepidermal blister occurs with a weak infiltrate of lymphocytes in the upper dermis. Interface changes are usually very mild in this condition, in contrast to LPP [142-144]. If the bullae develop in papules of lichen planus in contradistinction to uninvolved skin, there is usually a much heavier dermal and lichenoid infiltrate (Tabl. I).

One study represented a clinicopathological study of nine cases of LPP, including immunofluorescence, ultrastructural and immuno-electronmicroscopic observations. In LPP, DIF classically demonstrates IgG and Complement/C3 along the BMZ and on the Civatte bodies [145]. In this study, DIF did indeed reveal immunologic characteristics of LP in skin and mucosal lesions, with deposits of IgG and Complement/C3, usually on blister roofs; an ELISA to BP180/BPAGII was also positive. The main differential diagnosis of LPP is LP. LPP serum has further been documented to react with a novel epitope within the C-terminal NC16A domain of BP180/BPAGII [146]. In cases of LPP resistant to steroid treatment, other immunosupressors may be added.

Conclusions and personal notes

In ABDs, the blisters are produced via a variety of pathologic mechanisms; the most common mechanism involves the presence of autoantibodies that activate complement, proteases and other secondary cell signaling processes. The clinical presentation of each disease seems to depend on the level within the skin that the blister cleavage occurs. The proper diagnosis of autoimmune blistering diseases requires skin biopsy for H&E review, as well as specialized testing techniques including direct and indirect immunofluorescence, salt split skin, immunoblotting, ELISA, immunoprecipitation and electron microscopy. In patients with significant skin involvement, morbidity and mortality is often associated with inadequate therapy, lack of electrolytic balance control and secondary infections with bacteria, parasites and viruses. Treatment should include family support and education regarding chronic disease care.

In addition, we recommend caution when interpreting pertinent medical literature. Specifically, recently suggested subvariants of an ABD may not be validated over time. Further, only a few laboratories provide full expertise for the workup of ABDs. ABDs should at least be investigated at the clinical, histologic and immunopathologic levels. In addition, advanced studies may be needed in molecular biology and electron microscopy, and should be performed when clinically indicated.

Bullous Pemphigoid

· Usually elderly patients (over 70 years).
· Most commonly affected areas are the trunk and extremities; head and mucous membranes are seldom affected.
· Blisters present on erythematous skin; sometimes chronic urticaria-like lesions are present without blistering.
· Pruritus is common, and lesions heal without scars.

H&E: Subepidermal bullae are present. Vacuolar degeneration of the epidermal basaloid layer may be noted. Eosinophils are present within the blister lumens, and also present within a superficial dermal infiltrate. The base of the blister re-epithelializes quickly and the blister may then appear intraepidermal.

DIF: Normal skin adjacent to a lesion is ideal for DIF. Classic findings include linear IgG and Complement/C3 at the BMZ. However, recent studies have also shown positive staining of dermal blood vessels, neurovascular packages and eccrine sweat glands.

Salt split skin/IIF: Positive staining is usually present along the blister roof; however, in some cases positive staining may be noted on both the blister roof and floor.

Antigens via immunoblotting: BP230/BPAGI, BP180/BPAGII, desmoplakins.

ELISA: Commercially available against BP180 NC16A, and BP230

Electron microscopy: Ultrastructural alterations of superficial epidermal keratinocytes have been described using scanning electron microscopy.

Treatment: In localized lesions such as the Brusting-Perry variant, topical corticosteroids are the treatment of choice, supplemented by antihistamines. If the lesions progress, addition of systemic corticosteroids usually provides fast and effective control. Initial doses of oral prednisone are recommended at 0.5 to 1.0 mg/kg per day. The dose of prednisone can be tapered gradually over a period of months to a maintenance dose between 5 and 10 mg/day. If lesions are intractable to prednisone at 10 mg/day, an immunosuppressive agent such as azathioprine or mycophenolate is warranted. If lesions are refractory to conventional therapy, try intravenous immunoglobulin or rituximab are recommended. For moist cutaneous erosions, topical soaks with aluminum acetate (Domeboro®) for 10 minutes three times a day are often helpful.

Differential diagnosis: Bullous amyloidosis, dermatitis herpetiformis, EBA, disease lineal by IgA, chronic bullous disease of childhood, erythema multiforme and pemphigus, cicatricial pemphigoid, toxic epidermal necrolysis, allergic contact dermatitis.

Mucous Membrane Pemphigoid

· Commonly affects mucous membranes of the mouth, pharynx, larynx, esophagus, conjuctiva, genital areas and anus; skin involvement is less frequent.
· Disease has a tendency to scar and form strictures; conjunctival involvement may lead to blindness.
· Initial lesions may be blisters on the skin, and erosions on the mucous membranes. Erosions are more common than vesicles on mucous membranes.

H&E: Subepidermal bullae and vesicles with a chronic dermal inflammatory infiltrate. Dermal proliferation of capillaries and associated granulation tissue, with subsequent fibrosis and scarring. The dermal infiltrate contains neutrophils; later eosinophils appear. Sometimes vacuolar changes can be seen along the BMZ.

DIF: Linear IgG and Complement/C3 deposition at the BMZ. IIF on NaCl salt split skin shows antibodies on the blister floor.

Antigens via immunoblotting: BP-180 kDa carboxyl domain, laminin-5, laminin 332, α6β4-integrin.

ELISAs: BP180 NC16A, BP230.

Electron microscopy: The antibodies are localized in the lamina lucida.

Treatment: Topical steroids and intralesional steroids injected soon after diagnosis may prevent scarring. Patients with localized oral, ocular or genital involvement often respond to topical Clobetasol® gel or intralesional triamcinolone(at a dose of 5 to 10 mg/ml, injected sublesionally every 3 weeks as required). If these treatments are not successful, systemic steroid therapy may be of value. If then refractory to prednisone at 10 mg/day, an immunosuppressive agent such as azathioprine or mycophenolate is recommended. If lesions are refractory to conventional therapy, IVIg or rituximab may be helpful. To aid in healing moist cutaneous erosions, topical soaks with aluminum acetate (Domeboro®) for 10 minutes three times a day are often helpful.

Differential diagnosis: Candidiasis, lichen planus, Behcet's disease.

Pemphigoid Gestationis

· A rare disease, usually occurring in the third trimester of pregnancy or postpartum period.
· Commonly, lesions are located in the periumbilical region, on extremities and on the trunk.
· The lesions are primarily vesicles, with some elevated erythematous plaques that resemble urticarial lesions.
· Pruritus is common.

H&E: Pemphigoid gestationis resembles BP, with additional necrotic keratinocytes and prominent edema of the dermal papillae.

DIF: Linear BMZ deposition of IgG and Complement/C3 may be found, as well as the HG factor (indirect IIF/Complement).

Antigens via immunoblotting: BP 180 kDa (posible).

ELISAs: BP180 NC16A, BP230.

Table I. Summary of subepidermal autoimmune blistering diseases.

Electron microscopy: Immuno-electron microscopy using a multistep peroxidase antiperoxidase method revealed the in vivo deposition of IgG at the basal plasma cell membrane that extended into the lamina lucida. It also showed the marked degenerative and necrotic changes of the basal cells in the involved areas of skin. It appears that at the histological as well as at the ultrastructural level, the blister of HG results from degenerative changes in the basal cells and is initially located in the epidermis.

Treatment: Topical steroid creams can be used in mild cases if only a limited area of skin is affected. Even if the rash is quite extensive using a strong steroid cream may be worthwhile before steroid tablets are given. Oral antihistamines (only those suitable for use during pregnancy) can be used to relieve itching. Treatment for more severe disease (with blistering) is usually with high doses of steroid tablets to get the disease under control rapidly. This needs careful monitoring and should involve the obstetricians and paediatricians as well as the dermatologists, to look after the health of both mother and baby.

Dermatitis Herpetiformis

· Usually affects extensor surfaces, with predilection for elbows, knees, sacral region, buttocks, chest, scalp and around the hair line. In rare cases, generalized lesions are seen.
· The primary lesions consist of small papules, vesicles and excoriations; the excoriations are often secondary to scratching of lesions.
· Significant lesional pruritus is present.

H&E: Neutrophils below the epidermal basement membrane, and papillary dermal edema; subepidermal small, punctate clefts or vesicles containing primarily neutrophils.

DIF: Usually granular deposits of IgA, present at tips of the dermal papillae along the BMZ. Recently, deposits of other immunoglobulins and complement have been documented in the dermal papillary tips as well as around dermal papillary blood vessels.

Antigens: Possible transglutaminases.

ELISA: BP 180.

Electron microscopy: Abnormal collagen fibers in the dermis; specifically, many misshapen fibrils are noted with frayed ends and associated amorphous material. The BMZ basal lamina shows considerable alterations. In some regions, it may be completely obliterated. When present, it has demonstrated breaks, thickening, and increases in electron density.

Treatment: In patients that have associated celiac disease and/or gluten intolerance, a gluten free diet is suggested. However, due to the difficulty of maintaining the diet, well documented gastrointestinal pathologic alterations are encouraged before prescribing this diet. Dapsone is the treatment of choice; if an alternate therapy is needed, sulfapyridin is recommended.

Differential diagnosis: Eczema, atopic dermatitis, papular urticaria, neurotoxic excoriations, bullous pemphigoid and pemphigoid gestationis.

LAD/CBDC

Lesions appear as clear or hemorrhagic vesicles or bullae, with an erythematous or urticarial base. The blisters are usually tense, vary in size, and may form annular or circular patterns. In children, lesions are often localized to the lower abdomen, perineal area, and inner thighs.

H&E: Classically, a subepidermal bulla with neutrophils. In addition, neutrophils are present in the upper dermis; these neutrophils may form papillary microabscesses, associated with fibrin and leukocytoclasis.

DIF: Mainly linear deposits of IgA at the BMZ.

Antigens via immunoblotting: A possible 97 kDa (BP 180-like) antigen. Also, possible soluble ectodomain of BP180 (LAD-1).

ELISA: Tissue transglutaminase ELISA has been partially successful.

Treatment: Removal of any eliciting medication; additional dapsone of sulfapyridin. Some patients require low-dose prednisolone therapy to suppress blister formation.

Differential diagnosis: Dermatitis herpetirformis, bullous pemphigoid, epidermolysis bullosa acquisita, cicatricial pemphigoid, bullous lupus erythematosus, lichen planus, toxic epidermal necrolysis.

Epidermolysis Bullosa Acquisita

Blisters often form following pressure, rubbing or trauma.

H&E: A subepidermal blister, with a clean separation between the epidermis and dermis.

DIF: Mainly linear deposits of IgG and Complement/C3 at the BMZ. On salt split skin/IIF, immunreactants are located on blister floor.

Antigens via immunoblotting: 290 kDa (Type VII collagen).

Differential diagnosis: Dermatitis herpetirformis, bullous pemphigoid, cicatricial pemphigoid, bullous lupus erythematosus, lichen planus, toxic epidermal necrolysis.

ELISA: Anti-COL7 autoantibodies NC1.

Electron microscopy: Localization of immune deposits by inmunoelectron microscopy is the "gold standard" for diagnosis. Immune deposits are found within the sub-lamina densa zone of the cutaneous BMZ.

Treatment: Proper nutrition, avoiding trauma and Domeboro for macerated lesions. Antibiotic baths, steroids, and other immunosupressors as needed. Good dental hygiene.

Table I. Summary of subepidermal autoimmune blistering diseases (continued).

Bullous Lupus Erythematosus
Lesions vary in appearance from herpetiform vesicles to large hemorrhagic bullae. A spectrum of lesions may be present simultaneously, featuring an urticarial, erythematous eruption associated with tense blisters, erosions and crusting
H&E: Subepidermal blistering with a prominent neutrophilic infiltrate.
DIF: Linear BMZ IgG antibodies are most common, present on the blister floor on salt split skin/IIF. In addition, similar deposits of IgA, IgM and Complement/C3 can be found.
Antigens via immunoblotting: Disease is often associated with Type VII collagen.
ELISA: Positive in some cases to BP180.
Electron microscopy: It has been shown that the basement membrane split is below the BMZ lamina densa.
Treatment: Patients respond better to dapsone than to corticosteroids.
Differential diagnosis: Bullous pemphigoid, cicatricial pemphigoid, LAD/CBDC, lichen planus pemphigoid, epidermolysis bullosa acquisita, bullous drug eruptions.

Lichen Planus Pemphigoid
Characterized by development of tense blisters, often located on the extremities, in a patient with lichen planus.
H&E: Subepidermal blistering. Dermal histologic changes include a mild perivascular infiltrate of lymphocytes and histiocytes; sometimes, there may be a few eosinophils and neutrophils beneath the blister, and a lichenoid infiltrate under the BMZ.
DIF: Immunological characteristics of lichen planus, with deposits of IgG and Complement/C3 along the BMZ and Civatte bodies.
Antigens via immunoblotting: BP180, and additional 200 and 220 kDa antigens.
ELISAs: BP180 NC16A, BP230
Treatment: Corticosteroids; if unsuccessful, other immunosuppressors may be added.
Electron microscopy: The LPP antigen seems to localize similarly to BP antigens, but is different from the EBA antigen.
Differential diagnosis: Lichen planus, bullous lichen planus, bullous lupus erythematosus.

Table I. Summary of subepidermal autoimmune blistering diseases (continued).

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