Autoimmune Blistering Disease
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Diagnostic Methodology for Pemphigus and Pemphigoid-
The epidermis generally consists of four layers: basal layer (stratum basale), spinous layer (stratum spinosum), granular layer (stratum granulosum), and cornified layer (stratum corneum). Keratinocytes are the major component of the epidermis. These cells progressively differentiate from basal cells to the finally differentiated, cornified layer, the outermost layer of the epidermis. Several types of intercellular junctions in the epidermis, such as desmosomes and tight junctions, are involved in protection against mechanical stress, physical stimulation or infectious agents. Desmosomes are composed of transmembrane proteins [e.g., desmoglein (Dsg) 1, Dsg3, and desmocollin] and intracellular proteins (e.g., desmoplakin). Desmogleins and desmocollins, which are the cadherin-family proteins, maintain epidermal cohesion in a Ca²⁺-dependent manner. Basal layer, the deepest layer of the epidermis, rests upon the basement membrane zone (BMZ) of dermal-epidermal junction (DEJ). Keratinocytes in basal layers have hemidesmosome, a structure comparable to a half of desmosome, being involved in adhesion in DEJ. Two hemidesmosomal components, BP180 [BPAG2 (bullous pemphigoid antigen 2), or type XVII collagen] and integrin α6β4 are transmembrane proteins which link to BMZ. BP230 (BPAG1) and plectin (HD-1) are cytoplasmic proteins involved in the organization of the cytoskeleton. BMZ is divided into the lamina densa and the lamina lucida. The major component of the lamina densa is type IV collagen. The lamina lucida contains heparan sulfate proteoglycan, fibronectin and Laminin 332 (laminin 5). Laminin 332 serves as a major anchoring protein between the lamina lucida and the lamina densa and connects BP180 and integrin α6β4 in the lamina lucida with type VII collagen. Type VII collagen secures the lamina densa to the dermis through association with desmocollins. Blistering disease is the general term for several diseases with blisters and erosion on the skin and mucous membrane caused by congenital or acquired interruptions of epidermal or epidermal-dermal cohesion. 

This brochure summarizes the clinical manifestations, the mechanism of the blister formation, and the serological diagnosis on various autoimmune blistering diseases.
Pemphigus is a group of autoimmune blistering diseases of the skin and mucous membranes which are characterized histologically by intraepidermal blisters due to acantholysis (i.e., disruption of the intercellular connections between keratinocytes of the epidermis) and immunopathologically by in vivo bound and circulating immunoglobulin G (IgG) antibodies directed against the cell surface of keratinocytes. Most common ages of disease onset is about 40 to 60 years. Nikolsky’s sign (i.e., blistering induced by lateral pressure to the normal-appearing skin) is also a characteristic feature of pemphigus. The target antigens in pemphigus are Dsg1 and 3. 5, 6 members of the cadherin super family. Pemphigus can be classified into pemphigus vulgaris (PV), pemphigus foliaceus (PF), paraneoplastic pemphigus (PNP), and others. The blisters in PV and PF occur in the deeper region of the epidermis (just above the basal layer) and the upper layer, respectively.

**Clinical characterization**

**Pemphigus vulgaris (PV)**

PV is the most common of pemphigus diseases. The majority of patients have painful mucous membrane erosions, especially in the oral cavity (Figure 1). While mucous membranes are mainly affected in mucosal dominant PV (MDPV), in mucocutaneous PV (MCPV), blisters and erosions are not only present on the mucosal area but also on the skin, predominantly the regions prone to pressure and friction, such as scalp, axilla, groin, upper part of back, and buttock. Pemphigus vegetans, a rare form of PV, is characterized by vegetating granulomatous lesions.

**Pemphigus foliaceus (PF)**

PF is characterized by scaly crusted erosions. These lesions are scattered in seborrheic regions such as the scalp, face, and upper trunk, while the mucous membranes are never affected (Figure 2). Symptoms of patients with PF are generally not as serious compared to those of PV. Pemphigus erythematous (Sinead-Usher syndrome), the localized form of PF, is associated with butterfly rash on the face. Fogo selvagem (Brazilian pemphigus foliacous) is the endemic type of PF in the area of South America, especially Brazil.

**Paraneoplastic pemphigus (PNP)**

PNP is an autoimmune mucocutaneous disease associated with underlying malignancy, particularly lymphoproliferative neoplasms. Painful erosions and ulcerations occur in the oral mucous membrane. In addition, many patients with PNP have ocular mucosal lesions and pseudomembranous conjunctivitis, resulting in ankylyloblepharon in severe cases. 7

**Other types of pemphigus**

Herpetiform pemphigus is characterized clinically by erythematous urticarial plaques and vesicles that present in a herpetiform arrangement, histologically eosinophilic spongiosis with minimal or no acantholysis, and serologically IgA autoantibodies against cell surfaces of keratinocytes. Drug-induced pemphigus is induced by drugs such as D-penicillamine or captopril. Neonatal pemphigus is a disease that rarely occurs in infants born to mothers with PV. IgA pemphigus is characterized by tissue-bound and circulating IgA autoantibodies that target the desmocytic proteins or unidentified cell surface antigens in the epidermis.

**Pemphigus (PV/PF) and anti-desmoglein 1 & 3 IgG autoantibodies**

Dsg1 and Dsg3, the pemphigus target antigens, have different intraepidermal expression patterns in the skin and mucous membranes (Figure 3). In the skin, Dsg1 is distributed throughout the epidermis, but more strongly in the superficial layers, whereas Dsg3 is expressed in the lower part of the epidermis (basal or parabasal layers). In the mucous membranes, on the other hand, Dsg1 and Dsg3 are expressed throughout the mucous membrane, but the expression level of Dsg1 is much lower than that of Dsg3. The clinical features of pemphigus can be explained by “desmoglein compensation theory”, i.e., these antigens can compensate their adhesive functions when they are co-expressed in the same cells. 8, 9 In cases of PV, when only anti-Dsg3 antibodies are present, the blister formations occur only in the deep layers of mucous membranes that lack the compensation by Dsg1 (mucosal-dominant type of PV). Patients who have both anti-Dsg1 and anti-Dsg3 antibodies, the blisters are formed in mucous membranes as well as the skin (mucocutaneous type of PV). On the other hand, in cases where antibodies are present only against Dsg1, the blisters are formed only in the upper epidermis of skin, whereas Dsg1 is present without compensation by Dsg3 (PF). 9
**Overview**

Pemphigoid is a group of diseases characterized histologically by subepidermal blisters and immunopathologically by linear deposition of IgG and complement C3 at basement membrane zone (BMZ) in the skin from patients with circulating IgG against the molecules within the dermal-epidermal junction (DEJ). The target antigens recognized by autoantibodies in patients with bullous pemphigoid (BP) are BP180 (a 180 kDa transmembrane protein), and BP230 (a 230 kDa intracellular protein). The target antigens recognized by autoantibodies in other diseases of this group include type VII collagen in epidermolysis bullosa acquisita (EBA); laminin 332 (laminin 5, epilligrin), one of the target antigens in mucous membrane pemphigoid (MMP); a 97 kDa protein (BP180 degradation product) in linear IgA bullous dermatoses (LAD); and laminin γ1 in anti-p200 pemphigoid. 14–16

**Clinical characterization**

**Bullous pemphigoid (BP)**

The skin lesions of BP are characterized by tense blisters with significant pruritus. Histopathological analysis detects subepidermal blisters and superficial dermal infiltrations of eosinophils, lymphocytes, and macrophages (Figure 4). Mucous membrane erosions are occasionally found in some patients with BP. BP usually occurs in elderly individuals. Herpes gestationis (HG, pemphigoid gestationis), a subtype of BP, occurs during pregnancy and the immediate postpartum period. 17 Histopathology of HG shows subepidermal blisters with eosinophil infiltration.

**Mucous membrane pemphigoid (MMP)**

MMP had been called cicatricial pemphigoid due to scar formation after blisters and erosions. However, not all of the patients have scarring. MMP is a rare autoimmune blistering disease, involving oral and ocular mucous membranes. Linear deposits of IgG and/or complement C3 along BMZ can be detected by direct immunofluorescence assay. A major MMP target autoantigen is BP180. Other target antigens include laminin 332 and BP230. 18

**Epidermolysis bullosa acquisita (EBA)**

EBA is a subepidermal autoimmune skin disease associated with autoimmunity to type VII collagen (Figure 5), which is the major component of anchoring fibrils. The classic presentation of EBA is noninflammatory blistering on the extremities that heal with scar and milia formation. However, the clinical manifestation is varied and inflammatory blisters and erosions can also be observed on any part of the body including the mucous membrane. Histopathology shows subepidermal blisters with different degrees of inflammation and neutrophil infiltration. Direct immunofluorescence assay reveals IgG deposition along BMZ. 19–20

**Dermatitis herpetiformis (Dühring disease)**

Dermatitis herpetiformis (DH) is characterized by chronic eruptions typically on elbows, knees, and back with intense pruritus. The granular deposits of IgA are detected in the papillary dermis by direct immunofluorescence assay. Circulating IgA autoantibodies against transglutaminase have been identified in patients. However, the exact mechanisms on the IgA deposition in the skin remain unclear. In addition, it has been reported that the IgA deposits may be reduced in the patients who go on a long-term gluten-free diet. 21

**Linear IgA dermatosis (LAD)**

LAD is a rare blistering disease with the onset over 40 years or under 10 years of age [chronic bullous diseases of childhood (CBD)]]. The clinical manifestations of LAD are itchy erythematous papules and blisters. Direct immunofluorescence of perilesional skin from the patient with LAD reveals IgA linear deposition along BMZ. A target antigen is the 97 kDa protein, an extracellular domain of BP180. 22

**Anti-p200 pemphigoid (Anti-laminin γ1 pemphigoid)**

Anti-p200 pemphigoid is a blistering skin disease occasionally seen in patients with psoriasis. Recently, laminin γ1 was identified as the target antigen. 23

**Autoimmune Blistering Diseases**

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Staphylococcal scalded skin syndrome (SSSS) and bullous impetigo are blistering diseases caused by exotoxins (exfoliative toxin, ET) produced by *Staphylococcus aureus*. SSSS is common in newborns, infants, and patients with renal failure or immunodeficiency. It is considered that ET disseminated through the bloodstream causes erythema and blisters throughout the body. Nikolsky’s sign is also detected. In bullous impetigo, however, ET produces the blisters locally at the infected area. The mechanisms of blister formation in both diseases had remained unclear until recently, although classic studies showed that ET could induce blisters in neonatal mice in the 1970’s. SSSS and pemphigus foliaceus (PF) share many similar features: (1) only the skin is affected, but not the mucous membrane, (2) the blister formation occurs in the upper epidermis, (3) no necrotic keratinocytes precede the blisters, and (4) injections of ET into neonatal mice induce superficial blisters whose histology is identical to PF. In addition, various experiments indicated that several ET subtypes (exfoliative toxin A, B, and D) induced the blister formation by a cleavage of Dsg1 at G163 through their serine protease activity, while they do not cleave Dsg3. This reflects the histological manifestation in SSSS, of which the lesion is localized in the skin. It is clinically significant that the inactivation of Dsg1 causes superficial skin blisters in two different skin diseases, PF and SSSS. 23, 24)

Epidermolysis bullosa acquisita (EBA) and anti-type VII collagen IgG autoantibodies

Autoantibodies against type VII collagen are associated with dysfunction of anchoring fibrils in dermal-epidermal junctions. Direct immunofluorescence staining shows IgG deposition within the sub-lamina densa of the skin. The localization of autoantibodies is distinct from the deposition in BP. To differentiate EBA from BP, salt-split skin technique (i.e., see page 7) followed by direct immunofluorescence assay is allowed to discriminate EBA from BP. The antibodies from the EBA patients are localized at the dermal side of the separation. Type VII collagen is composed of three identical alpha-chains (290 kDa). Each chain consists of a 145 kDa non-collagen (NC1) domain, a typical collagenous domain, and a 34 kDa non-collagen (NC2) domain. Epitopes recognized by autoantibodies from EBA patients are mainly on NC1. NC2 is also considered to contain minor epitopes. 22)
ELISA kits for the diagnosis of autoimmune blistering diseases

Differential diagnosis of autoimmune blistering diseases with ELISA

MESACUP Anti-Skin Profile ELISA TEST* is an ELISA kit for the qualitative detection of IgG antibodies to Dsg1, Dsg3, BP180, BP230 and type VII collagen in human serum. These anti-skin autoantibodies can be detected simultaneously in a single assay.

For US customers

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For EU customers

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<td>2-8 °C</td>
<td>Recombinant human type VII collagen NC1 and NC2</td>
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<tr>
<td>RG-T7152</td>
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<td>4 wells</td>
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Screening of autoimmune blistering diseases

Interpretation of results with MESACUP Anti-Skin Profile TEST*

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<tr>
<th>MESACUP Anti-Skin Profile TEST*</th>
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Comparison of existing individual ELISA kits for autoimmune blistering diseases and MESACUP Anti-Skin Profile TEST*

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<th>Antigen</th>
<th>MESACUP 2-TEST Desmoglein 1</th>
<th>MESACUP 2-TEST Desmoglein 3</th>
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<td>160</td>
<td>160</td>
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<tr>
<td>Discordance</td>
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<td>Concordance Rate (%)</td>
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Differential diagnosis of pemphigus

Immunofluorescence assay may reveal differences in staining patterns between PV and PF according to the tissue distribution of Dsg1 and 3 (see page 4). However, the immunofluorescence patterns of tissues are difficult to clearly discriminate between the two diseases. MESAUCUP Desmoglein ELISA kits are for measurements of anti-Dsg1 and anti-Dsg3 antibodies in serum, using the recombinant Dsg1 or Dsg3 as the solid-phase antigen. These ELISA kits provide sensitive and specific assays to clearly discriminate between the two diseases.

Differential diagnoses of autoimmune blistering diseases with ELISA

Comparison of existing individual ELISA kits for autoimmune blistering diseases and MESACUP Anti-Skin Profile TEST*

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<tr>
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Disease classification of pemphigus by anti-Dsg antibody profiling

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<tr>
<th>Type of pemphigus</th>
<th>Anti-Dsg1 antibody</th>
<th>Anti-Dsg3 antibody</th>
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<tbody>
<tr>
<td>Mucosal-dominant PV</td>
<td>Positive</td>
<td>Negative</td>
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<tr>
<td>Mucocutaneous PV</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>PF</td>
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Presence of anti-Dsg1 and anti-Dsg3 antibodies in PV, PF, BP, and normal sera

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*U.S. Customers: for research use only (Not for use in diagnostic procedures)

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Differential diagnosis of autoimmune blistering diseases with ELISA

**Differential diagnosis of BP**

MESACUP BP180 TEST is an ELISA kit for the detection of anti-BP180 antibodies in human serum, using the recombinant BP180 NC16a protein as the immobilized antigen. The sensitivity of the kit is 94% (54/64) in patients with BP in the active stage. MESACUP BP230 TEST is an ELISA kit using both the recombinant N-terminal and C-terminal domains of BP230 for detection of anti-BP230 antibodies in human serum. The sensitivity is 58% (37/64) in patients diagnosed with BP in the active stage.

**Clinical sensitivity of anti-BP180 and anti-BP230 ELISA for BP sera**

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<th>Active stage</th>
<th>Remission</th>
<th>Total</th>
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<tbody>
<tr>
<td>MESACUP BP180 TEST</td>
<td>84% (54/64)</td>
<td>60% (153/255)</td>
<td>70% (167/239)</td>
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<tr>
<td>MESACUP BP230 TEST</td>
<td>58% (37/64)</td>
<td>78% (136/175)</td>
<td>75% (175/230)</td>
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**Presence of anti-BP180 and anti-BP230 antibodies in BP, PV/PF, and normal sera**

**Interpretation of results with MESACUP BP180 and MESACUP BP230**

<table>
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<tr>
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<tr>
<td>MESACUP BP230 TEST</td>
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**Clinical manifestation of BP**

The amount of anti-type VII collagen antibodies decreased during the improvement, correlating with the improvement of cutaneous erosions. Amounts of autoantibodies also correspond to the pemphigus disease area index (PDAI). In recent studies, the amount of anti-Dsg1 and anti-Dsg3 antibodies decreased significantly after rituximab and intravenous immunoglobulin (IVIG) therapies.

**Clinical manifestation of PV disease and anti-desmoglein antibody levels**

Clinical data using MESACUP Desmoglein kits suggest that amounts of anti-Dsg1 and anti-Dsg3 antibodies decrease during the improvement, correlating with the improvement of cutaneous erosions. Amounts of autoantibodies also correspond to the pemphigus disease area index (PDAI).

**Clinical manifestation of EBA disease and anti-type VII collagen antibody levels**

These findings strongly suggest the clinical importance of periodic measurements of the autoantibodies in patients with BP.

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**Interpretation of results with MESACUP Anti-Type VII collagen TEST**

<table>
<thead>
<tr>
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<td>MESACUP Anti-Type VII collagen TEST</td>
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**Presence of anti-type VII collagen antibodies in EBA, PV, and normal sera**

**Interpretation of results with MESACUP Anti-Type VII collagen TEST**

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<tbody>
<tr>
<td>MESACUP Anti-Type VII collagen TEST</td>
<td>&lt; 6</td>
<td>≥ 6</td>
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**Clinical manifestation of EBA disease and anti-type VII collagen antibody levels**

The amount of anti-type VII collagen antibodies decreased with the improvement of cutaneous symptoms in a patient with EBA after treatment.

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**Monitoring disease activities by ELISA**

**Clinical manifestation of PV disease and anti-desmoglein antibody levels**

**Monitoring disease activity in muco-cutaneous PV with MESACUP Desmoglein ELISA kits**

**Monitoring disease activity in BP with MESACUP BP180 TEST**

Several clinical studies suggested that the data using MESACAP BP180 TEST demonstrated that the disappearance of blisters correlated with decrease in the amount of anti-BP180 antibody. Additionally, in a previous report on one patient with herpes gestationis (HG), the amount of anti-BP180 antibodies was consistent with the severity of the erythema and blisters of mothers and neonates in the peripartum period. These findings strongly suggest the clinical importance of periodic measurements of the autoantibodies in patients with BP.

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**Clinical manifestation of BP disease and anti-BP180 antibody levels**

**Monitoring disease activity in BP with MESACUP BP180 TEST**

**Monitoring disease activity in EBA with MESACUP Anti-Type VII collagen TEST**

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References
