Table 1. Pemphigus: diagnostic algorithm

Histopathology	***Additional considerations***
1) Suprabasal loss of epidermal adhesion (PV, PNP, IgA-IEN) **2)** Subcorneal loss of epidermal adhesion adhesion (PF, IGA-SPD)	Ad 1 and 2) The biopsy should include preferentially a fresh entire blister or at least part of a blister with perilesional skin. Characteristic is an eosinophilic epidermal infiltrate (PV), neutrophilic epidermal infiltrate (PF, IgA-SPD, IgA-IEN) or interface dermatitis (PNP).
Direct immunofluorescence microscopy	***Additional considerations***
1) Anti epithelial cell surface IgG deposits in the epidermis (PV, PF) 2) Anti epithelial cell surface IgA deposits in the epidermis (IgA-SPD, IgA-IEN) ***3)*** Anti epithelial cell surface IgG deposits and C3 and/or IgG deposits at the dermal-epidermal junction (PNP)	Ad 1-3) The biopsy should be taken from perilesional skin.
Indirect Immunofluorescence microscopy	***Additional considerations***
1) Anti epithelial cell surface IgG deposits on the epithelium of monkey esophagus (PV, PF, PNP) 2) Anti epithelial cell surface IgA deposits on the epithelium of monkey esophagus (IgA-SPD, IgA-IEN) ***3)*** Anti epithelial cell surface IgG reactivity with the epithelium of rat/monkey bladder (PNP)	Ad 1) Majority of PV, PF and PNP sera are positive on monkey esophagus. Ad 2) Only ca. 50% of the IgA pemphigus sera show reactivity with monkey esophagus Ad 3) Standard substrate to detect IgG reactivity against plakins
Enzyme-linked immunosorbent assay (ELISA)	***Additional considerations***
1) **Desmoglein 3-ELISA** (PV, PNP) 2) **Desmoglein 1-ELISA** (PF, PV, PNP) 3) **Periplakin/Envoplakin-ELISA** (PNP) 4) **Desmocollin 3-ELISA** (PNP, IgA-IEN) ***5)*** **BP230-ELISA** (PNP)	Ad 1) Dsg3-ELISA positive in mucosal PV and PNP. In general, IgG titers relate to disease activity. Ad 2) Dsg1-ELISA positive in cutaneous PV and frequently in PNP. In general, IgG titers relate to disease activity. Ad 3) Additional serological parameter for PNP; sensitivity of the ELISA at 85-90% Ad 4) Dsc3-ELISA frequently positive in atypical pemphigus, i.e. clinical cases reminiscent of PV or PF which lack IgG reactivity against Dsg3 and/or Dsg1. Ad 5) BP230-ELISA frequently positive in PNP but of minor diagnostic importance.

IgA-IEN, intraepidermal neutrophilic type of IgA pemphigus; IgA-SPD, subcorneal pustular dermatosis type of IgA pemphigus; PF, pemphigus foliaceus; PNP, paraneoplastic pemphigus; PV, pemphigus vulgaris.

Table 2. Pemphigus: therapeutic algorithm

1st line treatment	***Comments***
1) **Predniso(lo)ne**	Ad 1) Initially 0.5 mg to 1.5 mg/kg/day. Optimal dose not validated. Taper by 25% reduction in bi-weekly steps, at <20 mg/d more slowly. Add proton pump inhibitors/H2 blockers, vitamin D, and calcium
2nd line treatment *(in refractory disease or in case of contraindications to glucocorticoids)*[1]	***Comments***
1) **Azathioprine** or **2a) Mycophenolate mofetil** or **2b) Mycophenolic acid** or **3) Cyclophosphamide**	Ad 1) 1-3 mg/kg/day. Check TPMT activity prior to treatment. Start with 50 mg/d. Steroid-sparing effect demonstrated. Ad 2a) 2g/day. Steroid-sparing effect demonstrated. Raise daily dose by 1 capsule/ week to increase GI tolerance. Ad 2b) 1440 mg/day. Steroid-sparing effect demonstrated. Raise daily dose by 1 capsule/ week to increase GI tolerance. Ad 3) 500 mg as i.v. bolus or given orally at 2 mg/kg/day. Steroid-sparing effect demonstrated. Consider secondary sterility, hemorragic cystitis and secondary cancer
3rd line treatment *(in refractory disease or in case of contraindications to immunosuppressants)*	***Comments***
1) **Anti-CD20 monoclonal antibody (rituximab)** 2) **Intravenous immunoglobulins** 3) **Immunoadsorption** 4) **Dapsone** 5) **Methotrexate**	Ad 1) 2 x 1g i.v. (2 weeks apart) or 4x375 mg/m2 (each 1 week apart). Exclude hypersensitivity to mouse proteins. PML is a rare but potentially fatal complication. Ad 2) (2g/kg/month). Exclude IgA deficiency before treatment. Has been used in combination with rituximab and cyclophosphamide. Ad 3) 2 cycles à 4 days (2.5-fold total plasma volume/d), 4 weeks apart. Has been used in combination with rituximab and cyclophosphamide. Ad 4) 100 mg/day or up to ≤ 1.5 mg/kg/day. Check serum G6PD activity before treatment. Steroid-sparing effect demonstrated. Ad 5) 10-20 mg/week. Substitute folate 5-15 mg on the following day.

[1]Immunosuppressants are commonly used in combination with glucocorticoids. Based on the current evidence, they have a glucocorticoid-sparing effect and may lead to glucocorticoid-free remission.