GUIDELINES

European guidelines (S3) on diagnosis and management of mucous membrane pemphigoid, initiated by the European Academy of Dermatology and Venereology – Part I

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Abstract

This guideline on mucous membrane pemphigoid (MMP) has been elaborated by the Task Force for Autoimmune Blistering Diseases of the European Academy of Dermatology and Venereology (EADV) with a contribution of physicians from all relevant disciplines and patient organizations. It is a S3 consensus-based guideline encompassing a systematic review of the literature until June 2019 in the MEDLINE and EMBASE databases. This first part covers methodology, the clinical definition of MMP, epidemiology, MMP subtypes, immunopathological characteristics, disease assessment and outcome scores. MMP describes a group of autoimmune skin and mucous membrane blistering diseases, characterized

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by a chronic course and by predominant involvement of the mucous membranes, such as the oral, ocular, nasal, nasopharyngeal, anogenital, laryngeal and oesophageal mucosa. MMP patients may present with mono- or multisite involvement. Patients’ autoantibodies have been shown to be predominantly directed against BP180 (also called BPAG2, type XVII collagen), BP230, laminin 332 and type VII collagen, components of junctional adhesion complexes promoting epithelial stromal attachment in stratified epithelia. Various disease assessment scores are available, including the Mucous Membrane Pemphigoid Disease Area Index (MMPDAI), the Autoimmune Bullous Skin disorder Intensity Score (ABSIS), the ‘Cicatrising Conjunctivitis Assessment Tool’ and the Oral Disease Severity Score (ODSS). Patient-reported outcome measurements (PROMs), including DLQI, ABQOL and TABQOL, can be used for assessment of quality of life to evaluate the effectiveness of therapeutic interventions and monitor disease course.

Conflict of interest
M. Carrozzo received a grant from AFYX. F. Caux has been advisor, speaker or investigator for Principia Biopharma, Roche Laboratories, Pierre Fabre Dermatologie, LEO, Abbvie and Novartis. G. Geerling has been advisor, speaker or investigator for, and received grants from, Dompé, Chiesi, Novartis, Alcon, Allergan, Santen, Oculus, Tearlab, Tearscience, Theapharma and Visumed. B. Horvath has been advisor, speaker or investigator for, and received grants from, Abbvie, Janssen-Cilag, Solenne B.V, Amgen, Akari Pharmaceuticals, Roche, Novartis, UCB Pharma. P. Joly has been consultant for Roche, Amgen, Principia Biopharma, Argenx, AstraZeneca, Regeneron and Thermofisher. D.F. Murrell has been consultant, investigator, or speaker for Abbvie, Argenx, AstraZeneca, Dermira, Janssen, Lilly, Novartis, Principia Biopharma, Regeneron, Sanofi, UCB. A. Patsatsi has been advisor, speaker, or investigator for Abbvie, Janssen-Cilag, Lilly, Novartis, LEO, UCPEMBiocare, L’Oreal and Genesis Pharma. M. Roth has been speaker for Theapharma and Bayer. E. Schmidt has been consultant for, and received grants and honoraria from, UCB, Biotest, Incyte, Euroimmun, Novartis, ArgenX, AstraZeneca, Fresenius Medical Care, Dompé, Synthonybyondis, Adimirx, Topas, Thermo Fisher and Roche. G. Zambruno has been consultant for Argenx, D. Zillikens has been consultant, speaker, or investigator for Euroimmun, Almirall, UCB, Argenx, Biotest, Fresenius, Miltenyi, Roche, Biogen, Abbvie and Janssen.

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Introduction
Mucous membrane pemphigoid (MMP) comprises a group of autoantibody-mediated subepidermal bullous diseases, characterized by a chronic course with predominant involvement of mucous membranes and a tendency to scarring.1,2 Disease severity varies, ranging from mild/moderate disease with mild gingival inflammation, to severe disease affecting multiple mucosal surfaces. In 2002, a group of experts published a consensus-based guideline for the diagnosis and management of MMP.3 Advances regarding diagnosis and therapeutic options have led to the need for an update of the guideline, an initiative promoted by the European Academy of Dermatology and Venereology (EADV) Task Force for autoimmune bullous diseases (AIBD). The guideline is based on a systematic search and review of the available literature, in combination with a structured consensus process, resulting in a level S3 guideline. The full guideline document with methodology, search strategy, scientific questions and evidence tables is available on the EADV website. It is the fourth guideline initiated by this EADV Task Force, following the guidelines for bullous pemphigoid (BP),4 pemphigus5 and dermatitis herpetiformis.6

Methods
Guideline committee
The guideline committee was established during the EADV Task Force meeting in Geneva, Switzerland, on 16 September 2017. The committee consisted of members of the EADV taskforce for AIBD, as well as selected specialists familiar with MMP, including dermatologists, ophthalmologists, oral medicine specialists, an otorhinolaryngologist and a pathologist. Several national patient organizations, including the German Pemphigus und Pemphigoid Selbsthilfegruppe e.V., the Dutch Netwerk voor Blaarziekten, the British PEM Friends and the Association Pemphigus Pemphigoide France, as well as the International Pemphigus and Pemphigoid Foundation (IPPF), have reviewed the guideline. Finally, the European Dermatology Forum (EDF) has
approved the final version. Conflict of interest forms were collected during the guideline process and approved by the guideline committee.

Aim, scope and targeted audience of the guideline
During the guideline kick-off meeting in Groningen, The Netherlands, on 21 March 2018, the scope and methodology of the guideline and the targeted audience were defined. The aim was to develop a multidisciplinary S3 European guideline, based on both evidence and expert opinion, and useful for all medical specialists who encounter patients with undiagnosed MMP, and treat and/or monitor patients with MMP. In this context, the overall aim is to provide specialists with a diagnostic and therapeutic algorithm. The professionals targeted are healthcare practitioners who may be involved with management of MMP patients in their daily practice. This includes general practitioners, dermatologists, ophthalmologists, otorhinolaryngologists, gynaecologists, urologists, gastroenterologists, dentists, oral medicine specialists and pathologists.

Guideline methodology
This guideline was developed in line with EDF standard operating procedures and in agreement with the quality criteria of the Appraisal of Guidelines Research & Evaluation II (AGREE II) instrument.7

Literature search
During the guideline kick-off meeting, research questions were formulated. Searches were performed per formulated research question. The literature searches were performed in the MEDLINE and EMBASE (OvidSP) databases, published in European languages with no limitations in timeframe. To answer questions regarding management, we used the evidence described in the Cochrane review of Kirtschig et al.8 and in the systematic review by Taylor et al.9 that updated the Cochrane search up to 2013. By using exactly the same keywords, we updated the search from 2013 until June 2019 in the MEDLINE, EMBASE (OvidSP) and Cochrane libraries.

Data screening and extraction, and methodological evaluation
All identified articles were screened for relevance, based on the title and abstract. If the publication appeared relevant, the full text was reviewed. Relevant findings were extracted and summarized in evidence tables. The level of evidence of the selected studies was graded according to the Oxford Centre for Evidence-Based Medicine (OCEBM) 2011. Recommendations were formulated by the guideline working group and were based on evidence and/or expert opinion. The level of the recommendations was determined by examining the individual levels of the evidence (Table 1).

| Level of recommendation based on level of evidence | Description |
|-----------------------------------------------------|-------------|
| A                                                   | Consistent level 1 studies |
| B                                                   | Consistent level 2 or 3 studies, or extrapolations from level 1 studies |
| C                                                   | Level 4 studies, or extrapolations from level 2 or 3 studies |
| D                                                   | Level 5 evidence, or troublingly inconsistent or inconclusive studies of any level |

Consensus process
All sections with recommendations and tables were discussed within the whole group. Consensus was defined as agreement by at least 80% of the guideline committee. A further meeting took place during the World Dermatology Congress in Milan, in July 2019. During this meeting, several points of consensus were reached regarding the chapters on clinical features and outcome measurements. In a second meeting, during the EADV annual congress in Madrid in October 2019, consensus was reached concerning diagnostics and management.

Clinical presentation
Clinical definition of mucous membrane pemphigoid
MMP is a group of chronic, autoimmune subepithelial blistering diseases predominantly affecting the mucous membranes. MMP should be regarded as a ‘disease phenotype’ shared by a heterogeneous group of blistering diseases, with antibodies targeting different autoantigens. Involved mucosal areas are generally in close contact with the skin, such as mouth, eyes, nose and anogenital region. Other affected mucosal sites include oesophagus, larynx and pharynx. The skin is almost invariably only mildly affected. Mucosal lesions tend to heal with scarring, with the exception of the oral mucosa, which is relatively spared unless severely affected. In serious cases, according to the involved sites, MMP may result in severe comorbidities, life-threatening complications and a significant negative impact on quality of life. An overview of possible clinical manifestations according to the affected mucosal site is depicted in Table 2.

Over the years, different terminology has been used to describe various forms of MMP, based on antigen or affected mucosal site (Table 3). MMP is the most appropriate nomenclature for disease in all patients with more than one affected mucous membrane. The following consensus was reached by the guideline group: single-site terms such as ocular MMP and oral MMP, or ocular monosite MMP and oral monosite MMP, should be applied to patients with involvement of only one specific mucosal site, as the disease in such cases may have different characteristics from those with multisite involvement. In MMP patients with several affected mucosal sites, involvement of one site can be highlighted, as follows: MMP with ocular or oral involvement, or MMP with multisite involvement (oral, ocular, anogenital, etc.).
The autoantibody reactivity and immunoglobulin class profile should not be considered or specified in the terminology and classification of MMP. Therefore, terms such as IgA-MMP, mucosal-dominant EBA or LAD, or alternatively, MMP-like EBA or MMP-like LAD, should be avoided.

Patients with mild and moderate MMP usually present with lesions limited to the oral mucosa, whereas patients with severe MMP often have additional affected sites: ocular, nasopharyngeal, laryngeal, oesophageal, genital mucosae or skin.3 Differentiating between MMP and BP in patients with both oral and skin lesions may sometimes pose a diagnostic challenge. The definitive classification should take into account the area which is predominantly affected, and is more refractory to treatment, as well as the clinical evolution.

**Recommendations**

It is recommended that the term MMP be used for disease in patients with involvement of multiple mucosal sites, whereas terms as ‘ocular (monosite) MMP’ or ‘oral (monosite) MMP’ are recommended for use with MMP patients with single site involvement.

**Grade of recommendation D – expert opinion**

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**Table 2** Overview of possible clinical signs of mucous membrane pemphigoid per affected mucosal site

| Mucosal site               | Clinical signs of mucous membrane pemphigoid                                                                                                                                                                                                 |
|---------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Oral mucosa               | Erythema, blisters, erosions, ulcerations, (rarely) lichenoid changes. Progression to fibrosis and scarring. Discomfort, burning, gingival bleeding, mucosal peeling, difficulty eating                                                                 |
| Ocular mucosa             | Conjunctiva: hyperaemia of bulbar and tarsal conjunctiva, limbitis, loss of plica semilunaris, subepithelial fibrosis, occlusion of lacrimal ductules, fornix shortening, symblepharon, anklyloblepharon, entropion, trichiasis. Redness, tearing, burning, decreased vision, foreign body sensation. Comea: inflammation, limbitis, corneal vascularization, stem cell failure, erosion, ulceration, perforation, scarring, secondary infection, loss of function, loss of eye |
| Laryngeal mucosa          | Erosions, blisters, ulceration, erythema, dyspnoea, dysphonia, fibrosis and scarring (e.g. supraglottic stenosis)                                                                                                                                          |
| Oesophageal mucosa        | Erythema, blisters, erosions, ulcerations. Fibrosis and scarring with web formation, stenosis, or dilatation                                                                                                                                             |
| Tracheal mucosa           | Dyspnoea, cough, dysphonia and wheezing                                                                                                                                                                                                            |
| Genital and urological mucosa | Blisters, vesicles, erosions, and ulcers affecting the vulvar area and introitus vaginae; sometimes mucosal adhesions and scarring. Less specific signs: erythema, oedema, milia, atrophy, or purulent vaginal discharge. Pain and/or pruritus. Recurrent dysuria with negative urine cultures, or mental stenosis obstructing flow of urine |

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**Table 3** List of previous and current terminology for mucous membrane pemphigoid

| Terminology                                      | Reference |
|--------------------------------------------------|-----------|
| Benign Mucous Membrane Pemphigoid, BMMP (Lever 1953) |           |
| Cicatricial Pemphigoid, CP (1980’s)               |           |
| Ocular Cicatricial Pemphigoid, OCP               |           |
| Ocular MMP, OcmMMP                               |           |
| Mucous Membrane pemphigoid, MMP (Chan 2002)      |           |
| Ocular MMP (instead of OCP) and oral MMP         |           |

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**Epidemiology**

**Incidence and prevalence** MMP typically occurs in the elderly, with a mean age between 60 and 80 years at the time of diagnosis. Only case reports or small case series of MMP have been reported in childhood.10 The incidence of MMP is estimated at approximately 1–2 new cases per million people annually in Germany and France.11-13 The incidence of ocular MMP is estimated at 0.7–0.8 million in New Zealand and the United Kingdom.14,15 In 2014, the calculated prevalence of MMP in Germany was 25 cases/million inhabitants, with a female predominance of 30.52/million, versus 18.37/million.13,16-23 No geographic or racial predilection has been described.

**Delay in diagnosis**

The diagnosis of MMP is often significantly delayed, ranging from weeks to several years. In a retrospective cohort study of 105 cases, diagnosis was not made until after more than one year.23 In a prospective national incidence survey, diagnostic delay lasted approximately 21 months.14 Stratification per involved site was not possible, due to frequent involvement of multiple sites and lack of solid data.

**MMP subtypes based on clinical affected site**

Multiple mucosal sites can be affected in patients with MMP (Table 2).

**Oral involvement in MMP** MMP with oral involvement generally affects the middle-aged and elderly, with a mean age between 54–76 years, and a predilection for Caucasian patients.24,25 Diagnostic delays have been reported, ranging from 2 to 60 months from development of the first symptoms to diagnosis.26 In 85% of MMP patients, the oral mucosa is the site of onset, and most
frequently involved. Other mucosal sites may be concomitantly involved. Oral involvement in MMP usually has a gradual progressive onset, characterized by episodes of spontaneous relapses and remissions, with variable mucosal inflammation and ulcerations. Intraoral sites include the gingiva (80%), buccal mucosa (58%), palate (26%), alveolar ridge (16%), tongue (15%) and lower lip (7%). Broadly, three oral phenotypes are recognized: pure gingival lesions, extra-gingival lesions or both. Desquamative gingivitis ranges from localized gingival erythema to generalized inflammation with blistering or ulceration. However, desquamative gingivitis may also be observed in pemphigus vulgaris and in oral lichen planus, which need to be excluded. The labial gingiva is always affected, with lingual and palatal gingiva less frequently involved. Extra-gingival lesions appear as erythematous patches, blisters or erosions. During the healing phase, fibrosis may be observable, with development of reticulated, white striations, mimicking lichen planus. The predominant symptoms upon presentation include discomfort, burning, gingival bleeding, mucosal peeling and difficulty in eating. Gingival bleeding often results in suboptimal oral hygiene, with subsequent plaque-related marginal gingivitis, leading to chronic periodontitis as a recognized complication.

**Ocular involvement in MMP** The average age at diagnosis of ocular monosite and multisite MMP ranges from a mean of 60.4–68.2 years. Patients with ocular monosite and multisite involvement seem to be older than those without ocular involvement. Younger patients with MMP with ocular involvement appear to present with more severe ocular and systemic disease and, despite immunosuppression, their disease progresses more rapidly. An average female proportion of 52% (range 37–81%) has been observed. The mean duration of symptoms prior to diagnosis of ocular MMP ranges from 225 days to 6.4 years. Mehra et al. reported that the median duration of symptoms until biopsy was longer in cases with ocular involvement than in cases without ocular involvement (2.3 years vs. 1.8 years).

Ocular involvement in MMP commonly presents with symptoms of any non-specific chronic conjunctival inflammation. Many patients initially complain of redness, tearing, burning, decreased vision and foreign body sensation. Limbitis occurs in 12–28% of the eyes. Except for MMP, conjunctivitis with limbitis, without significant corneal involvement, is usually seen only in vernal keratoconjunctivitis. Thus, chronic conjunctivitis with limbitis may be regarded as a distinctive sign of ocular MMP and is associated with more severe disease progression. Infrequently, patients may also present with conjunctival ulceration, swelling and severe hyperaemia. However, these inflammatory signs may be intermittent, relapsing and sometimes minimal, with early clinical signs limited to those of conjunctival cicatrization, often first involving the canthal structures. Furthermore, in late-stage disease, which is often when a definitive diagnosis is made, ocular inflammation may not be the predominant finding.

Untreated, ocular involvement in MMP eventually destroys the lacrimal gland ductules and meibomian gland orifices, impairing both the aqueous and the oily constituents of the tear film, resulting in secondary dry eye. Eyelid malposition, symblepharon and trichiasis eventually develop and, together with secondary dry eye, chronic limbitis and subsequent limbal stem cell failure, contribute to keratopathy. The latter ultimately results in reduced vision due to corneal epithelial defects, neovascularization or even corneal perforation. Although ocular involvement in MMP can occasionally be unilateral, it is usually bilateral. By the time of diagnosis or referral to a tertiary centre, most patients have moderate to severe conjunctival inflammation, with advanced cicatrizing disease and symblepharon formation; this probably reflects the difficulties in diagnosing early ocular MMP.

**Nasopharyngeal involvement in MMP** The frequency of nasal and pharyngeal involvement was at least 35% with a mean age of 60 years as demonstrated in a prospective study of 110 MMP patients. The most common nasal symptoms and signs consist of epistaxis, rhinorhea, nasal crusting and nasal obstruction. Examination of the nasal mucosa may reveal atrophic rhinitis, erosive and crusted lesions and synchie. Patients with pharyngeal involvement often complain of pharyngalgia, dysphagia or odynophagia, impaired food intake and coughing. Nasopharyngeal involvement may coexist with involvement of the larynx mucosa. Clinical signs including erythema, erosions or ulcerations, vesicular lesions and scarring of the pharynx can be seen.

**Laryngeal involvement in MMP** The most common symptoms and signs of laryngeal involvement in MMP are dyspnoea and dysphonia. However, a proportion of MMP patients with laryngeal involvement are asymptomatic. The supraglottis is the most commonly affected site. Swallowing problems are uncommon. MMP with oesophageal involvement may coexist with laryngeal disease and may require independent investigation and management. In one study, the estimated frequency of MMP with laryngeal involvement was 12.2% of MMP cases, with a prevalence in the general population of one case in 10 million persons. The mean age of patients with laryngeal involvement in MMP is approximately 60 years, with equal gender distribution. Laryngeal involvement can result in severe laryngeal obstruction and become life-threatening, in severe cases sometimes requiring surgical interventions. In one report, tracheostomy was required in 10.5% of the cases.

**Oesophageal involvement in MMP** Oesophageal involvement in MMP has a severe scarring potential and is one of the most life-threatening complications. Symptomatic oesophageal disease was
found in approximately 5% of a cohort of 477 MMP patients and often occurs in combination with involvement of additional mucosal sites. Dysphagia is usually the first and most common symptom to reveal oesophageal MMP, but it may also develop several years after onset of the disease. Oesophageal webs are thought to represent an early stage of the disease, whereas oesophageal strictures are more likely to represent a more advanced stage, secondary to scarring with fibrosis. Oesophageal stenosis following oesophageal dilation may occur. The development of blisters, bleeding and oedema may interfere with breathing.

**Tracheal involvement in MMP** Although no data exist about the exact frequency of tracheal involvement in MMP, the latter may manifest with dyspnoea, cough, dysphonia and wheezing. There are anecdotal cases of MMP in which tracheal involvement represents the leading clinical feature of the disease. Severe laryngeal involvement may require tracheostomy.

**Genital and urological involvement in MMP** Involvement of the anogenital region can occur, either isolated or with other mucosal sites. In two cohorts of MMP patients, genital lesions were observed in 28–38% of the cases. Affected patients present with pain and/or pruritus. Examination reveals blisters, vesicles, erosions and ulcers, which may affect the vulvar area and intuitus vaginae, glans penis or foreskin. Mucosal adhesions and scarring may occur. Moreover, less specific signs such as erythema, oedema, milia, atrophy and purulent vaginal discharge can be present. Genital involvement in MMP can be drug-induced or paraneoplastic. Only limited data are available on urological involvement in MMP. Reported signs are recurrent dysuria with negative urine cultures, or meatal stenosis obstructing the flow of urine.

**Skin involvement in MMP** The skin can be mildly affected in MMP and is encountered in 20–35% of MMP patients. In Brunsting-Perry pemphigoid, a variant of MMP, skin lesions present mainly on the head and the neck region consisting of crusts, erosions, blisters and atrophic scars. Mucosal involvement is not always present in this variant. Generalized skin lesions in MMP have also been reported.

**Antigen recognition in MMP**

**BP180 and BP230** BP180 (also termed BP antigen 2 or type XVII collagen) and BP230 (also called BP antigen 1, epithelial isomorph) are haemidesmosomal proteins with a molecular weight of 180 and 230 kD. BP180 is a transmembrane collagenous protein, and BP230 is an intracellular protein of the plakin family of cytolinkers. BP180 is the main target antigen in MMP. In addition to the NC16A domain, C-terminal epitopes are also frequently targeted. In a considerable number of MMP patients, IgA reactivity against BP180 is detected, in addition to IgG autoantibodies. So far, although no specific clinical phenotype has been associated with anti-BP180 reactivity, while one report suggested that a combined IgG and IgA-anti-BMZ reactivity is found in patients with a more severe clinical phenotype. BP230 reactivity is less common and is reported in 9% up to 28% of MMP cases.

**Laminin 332** Laminin 332, previously known as epiligrin and laminin 5, is a heterotrimer composed of α3, β3 and γ2 subunits, targeted by a subset of MMP patients who usually present with multisite mucosal lesions, with significant association with parhyngo-laryngeal, oro-pharyngo-laryngeal and tracheal involvement.

**Type VII Collagen** Limited data exist on MMP with reactivity against type VII collagen. A number of case reports describe MMP as associated with circulating anti-type VII collagen. In one series encompassing 78 MMP patients, reactivity with type VII collagen was found in 4% of the cases. The latter appeared to have a higher disease severity score.

**The α6 and β4 integrin subunits** The α6 and β4 integrin subunits are components of hemidesmosomes, and belong to the integrin family of heterodimeric cell surface adhesion receptors, which is linked to the cytokeratin network via plectin and BP200. Ahmed et al. reported that antibodies against the integrin α6 subunit are detected in 80-100% of oral MMP cases. These antibodies appear to specifically bind to the extracellular domain of the integrin α6 subunit. In contrast to oral MMP, almost all patients with ocular MMP showed autoantibodies directed against the integrin β4 subunit. Autoantibodies against the integrin β4 subunit bind to the C-terminal end of its intracellular domain.

**Aetiology** The exact pathogenesis and factors responsible for the development of MMP are unknown. Pathogenicity of autoantibodies directed to BP180, laminin 332 and type VII collagen have been demonstrated in vitro, and in animal models for BP. However, no animal model reproduces the clinical features of MMP. In

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dogs, spontaneous onset of MMP has been described. In MMP, genetic susceptibility has also been demonstrated. Several studies have confirmed a link between MMP and HLA class II allele variants, such as HLA-DQB1*0301 or HLA-DRB1*11 in Caucasian MMP patients. A genome-wide association study found 38 single-nucleotide polymorphisms associated with MMP; these polymorphisms need functional validation. In a few cases, drug-induction of MMP has been described. 

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Dipeptidyl peptidase-4 inhibitors may be associated with the induction of MMP. In a cohort of 313 MMP patients, a total of 24 were treated by one dipeptidyl peptidase-4 inhibitor, and 17 had an accountability score, suggesting induction of MMP by the drug. Finally, an increasing number of immune check point inhibitor-triggered cases of MMP has recently been reported. 

Associated factors and comorbidities

One retrospective study reported increased incidence of pernicious anaemia in MMP. Other retrospective cohort studies found no increased risk for autoimmune disease compared with healthy controls. In contrast to BP, so far no report indicates an increased association with diseases of the central nervous system. The potential occurrence of malignancies in MMP is also a matter of controversy. A multicentre retrospective cohort study, which found a malignancy in 11.7% of MMP patients, did not find evidence for an increased rate of malignancy in MMP. Furthermore, MMP patients with anti-laminin-332 reactivity also did not show an increased incidence of malignancy. In contrast, in a small retrospective cohort study with anti-laminin 332 MMP, 20% had a malignancy, while in an another retrospective study with 246 MMP patients, 25% of the anti-laminin 332 MMP patients had a malignancy. 

Conclusions

| Level of evidence | No evidence supports a phenotype association with the target autoantigens. Contradictory evidence exists regarding the association between laminin 332 and an underlying malignancy. |

Recommendations

In case of anti-laminin 332 reactivity, a tumor search, in particular for solid tumors, may be recommended.

Grade of recommendation C

Outcome measurements

Disease assessment scores for multisite involvement

Currently, no published validated scoring methodologies are available for multisite MMP, although methodology for oral MMP has recently been validated. The lack of an agreed unified disease severity score, or a means of combining site-specific severity scores, has hindered interpretation of the few interventional studies in the literature. However, in 2012, an international panel of experts in autoimmune bullous disease proposed a new scoring system: the Mucous Membrane Pemphigoid Disease Area Index (MMPDAI). This was adapted from the validated Pemphigus Disease Area Index (PDAI) and the Bullous Pemphigoid Disease Area Index (BPDAI). MMPDAI is proposed for use in ‘milder’ forms of MMP and is primarily designed to be used by dermatologists.

A further tool advocated for potential use in MMP is the Autoimmune Bullous Skin Disorder Intensity Score (ABSIS). It is based on the amount of body surface area (BSA) involved, and the degree of activity/healing observed in that site. ABSIS scores only skin, oral mucosal sites and genitalia. It has been validated for pemphigus vulgaris but not for MMP.

In addition, Setterfield et al. published an original multisite methodology, which scored each potential site for the severity of involvement and was applicable to all MMP types, including severe cases. Two studies using this methodology showed an association between disease severity and serum autoantibody isotype upon presentation, followed by a longitudinal study relating sequential titres with disease severity. The methodology was subsequently used in two cohort studies, although expanded to include a damage score describing the scarring. Further interventional studies have based response to treatment on previously reported observation endpoint definitions. These include the early observation end point of control of disease activity, late observation end points of partial remission on minimal therapy, complete remission on minimal therapy or off therapy, and relapse/flare, or the extension of established lesions in a patient who has achieved disease control.

Patient-reported pain in the form of a VAS score has also been reported.

Conclusions

| Level of evidence | MMPDAI is a disease-specific severity scoring tool. It has not been validated. (Murrell 2015) |
| Level of evidence | ABSIS has been proposed for use in MMP, but it is not disease-specific and has not been validated for use in MMP. (Plütze 2007). |
| Level of evidence | Multisite oral mucosal disease scoring tool proposed for MMP (Setterfield 1998, 1999), utilized in further treatment studies (Munyangango 2013, Cozzani 2016), has not been validated. |
| Level of evidence | No validated comprehensive disease severity scoring tools are available for use in MMP. Interventional study assessing area of involvement, including mouth, eye, nose, genitals and skin (Thornhill 2000), has not been validated. |
Recommendations

For clinical studies, MMPDAI or ABSIS scoring tools are recommended for use.

Grade of recommendation D

Oral disease assessment

The Oral Disease Severity Score (ODSS) has been proposed as a comprehensive scoring system for the oral lesions of lichen planus, pemphigus vulgaris and mucous membrane pemphigoid. It was developed from the Setterfield et al. multi-site MMP score. The oral aspect of this score was subsequently expanded to become the ODSS, providing a more detailed and sensitive method for detecting subtle changes in disease activity. The ODSS has been independently shown to be a reliable and sensitive tool for oral MMP, and has been validated in a parallel study comparing it with the oral components of MMPDAI, ABSIS and the physician’s global assessment score. ODSS was shown to have greater inter- and intra-observer reliability than the other methods.

Conclusions

Recommendations

In monosite and predominantly oral MMP, application of the ODSS may also be considered for clinical studies and daily practice.

Grade of recommendation B

Ocular disease assessment

None of the scoring systems described above address ocular MMP in enough depth to assess ocular disease activity and progression. These systems have also not been evaluated for the inter- and intra-observer reproducibility of inflammation, scarring and morbidity. Over the last 4 decades, eleven methodologies have been developed specifically to evaluate ocular MMP. However, most of these have focused on evaluation only of conjunctival scarring. One scoring system has also added a simple qualitative grading of conjunctival inflammation, using a 4-point scale, while another system has included this grading for a disease activity index, but excluded scarring and morbidity. Only one system incorporates indices of inflammation (present or absent), as well as another 15 graded indices of scarring and morbidity. Nevertheless, the latter is time-consuming to use, has very limited evaluation of inflammation and has subsequently been used for evaluation of MMP cases in only one case series.

A review of these ocular MMP scoring systems concluded that none met the need for a validated scoring system of the three parameters of inflammation, scarring and morbidity that cause progression in ocular MMP. Only two out of the 11 systems available, measuring conjunctival scarring using different quantitative methods, have been validated for inter and intra-observer variability, and compared with another methodology. A scoring system called the Cicatrising Conjunctivitis Assessment Tool was developed to meet the requirements identified by Lee et al., and has been validated, by calculation of inter- and intra-observer levels of agreement, for reproducible scoring of the three functional categories of inflammation, scarring and morbidity. Although the validation study was carried out on MMP subjects, it is applicable to all causes of cicatrizing conjunctivitis. It was developed from previously described tools and includes the use of a fornix depth measurer (FDM) for scarring assessment.

Conclusions

Recommendations

The validated Cicatrising Conjunctivitis Assessment Tool is recommended for disease assessment in ocular MMP.

Grade of recommendation B
Otorhinolaryngological disease assessment
None of the scoring systems described above address otorhinolaryngological MMP in enough depth to evaluate and assess either progression of disease in the hypopharynx or larynx, or the effect of interventional studies. These systems have also not been evaluated for the required inter- and intra-observer reproducibility of inflammation, scarring and morbidity. Currently, no validated tool exists for these purposes. However, in a systematic review, Higgins et al. proposed a disease/damage assessment of laryngeal MMP.21 Although their proposal has not been validated, it has been referred to in other case series.72,168

Conclusions

| Level of evidence | Higgins 2010 proposed a staging system for laryngeal mucous membrane pemphigoid. It quantifies disease severity and provides standardized reporting. This method has not been validated. |
|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Level of evidence | Nash 2017 described a symptomatology scale for laryngeal involvement. This method has not been validated.                                                                                      |
| Level of evidence | No validated comprehensive disease severity scoring tools are available for use regarding otorhinolaryngological involvement in MMP.                                                              |

Recommendations

For clinical studies, it is recommended that an otorhinolaryngological version of the MMPDAI scoring tools be validated.

Grade of recommendation D

Patient-reported outcome measurements
PROM use has a positive impact both on diagnosis and treatment, and on the relationship between patients and clinicians.169,170 Quality of life (QOL) is increasingly recognized as an important clinical outcome and basis for understanding patient care within the field of dermatology. QOL assessment can be used to evaluate the effectiveness of therapeutic interventions, monitor disease course, and provide a patient-based end point for clinical trials. PROM is an instrument that enables patients to assess their health, without external interpretation.171

The clinical manifestations and treatment options available for management of MMP can place a significant burden on everyday life, with physical, economic, social and psychological consequences.172 Often, however, the QOL burden is independent of objective disease burden and clinical severity.172,173

A variety of questionnaires and psychometric tools exist to assess QOL in AIBD; these can be categorized as generic, skin-specific or disease-specific. A number of studies have evaluated QOL in AIBD by using generic tools such as the Medical Outcome Study 36-item Short Form (SF-36),174-176 Activities of Daily Living (ADLs),177 12-item General Health Questionnaire (GHQ-12),178-180 Hospital Anxiety and Depression scale (HADS),181,182 Clinical Depression Questionnaire (CDQ),176,183 Beck Depression Inventory (BDI),184,185 and The Work Productivity and Activity Impairment Questionnaire–Specific Health Problem (WPAIQ-SHP).186,187

The literature also mentions several dermatology-specific instruments that evaluate QOL in AIBD, including the Dermatology Life Quality Index (DLQI), Dermatology Quality of Life Scales, Dermatology Specific Quality of Life Instrument, Itchy QOL and Skindex-29.188-195 The DLQI is the first validated dermatology-specific QOL instrument.188,196 Currently, the SF-36 and the DLQI are the most often reported measures for evaluating QOL in AIBD.

The Oral Health Impact Profile (OHIP)197 is the most common generic instrument used in the field of oral medicine.198 The OHIP was originally developed with 49 questions across seven domains; a shortened version was subsequently derived with 14 questions, referred to as OHIP-14.199 This was developed to provide a comprehensive measure of self-reported dysfunction, discomfort and disability resulting from oral conditions. In oral MMP studies, the Visual Analogue Scale (VAS) is the most commonly used PROM,150,200,201 and its validity and reliability have been well established.202 Further, the Chronic Oral Mucosal Disease Questionnaire (COMDQ)203 is the first validated specific QOL measure developed in the field of oral medicine to evaluate chronic conditions of the oral mucosa, and has been translated into other languages. The reliability and validity of this tool have also been confirmed.203-207 Finally, the Autoimmune Bullous Disease Quality of Life (ABQOL), a validated 17-item questionnaire, is the only disease-specific tool used for patients with AIBD.172,208 Its specificity promises to capture the small changes in AIBD which generic tools may miss. The ABQOL can be used to quantify the effect of a patient’s AIBD on their QOL, and capture changes in disease status, which may not be apparent during routine clinical review. Treatment of MMP may be associated with a significant risk of medical complications and a severe impact on QOL, an impact which is difficult to differentiate from the burden of the disease itself. The Treatment of Autoimmune Bullous Disease Quality of Life (TABQOL)173 is the first validated patient-centred tool to allow quantitative measurement of treatment-specific impact on QOL in AIBD.209
Conclusions

Level of evidence 4
SF-36, ADLs, GHO-12, CDQ, HAD, BDI, WPAIQ-SHP are validated generic patient-reported outcome measures. (Ware 1992, Terrab 2005, Tabolli 2008, Masahiro 2000, Goldberg 1988, Paradisi 2009, Ghodsi 2012, Paradisi 2009, Ghodsi 2012, Krug 1978, Zigmund 1983, Layegeh 2013, Kouris 2016, Beck 1981, Reilly 1993, Heelan 2015)

Level of evidence 4
DLQI, DQOLS, DSQI, ItchyQOL, Skindex-29 are validated dermatology-specific patient-reported outcome measures. (Finlay 1994, Basra 2008, Morgan 1997, Anderson 1997, Desai 2008, Alshamekh 2019, Chren 1996)

Level of evidence 4
OHIP is a validated generic oral patient-reported outcome measure. It has not been validated for use in MMP. (Slade 1994).

Level of evidence 4
COMDO is a validated oral patient-reported outcome measure for use in oral mucosal diseases. It has been validated for use in MMP. (Ni Riordáin 2011, Ni Riordáin 2016).

Level of evidence 4
ABQOL and TABQOL are validated AIBD-specific patient-reported outcome measures. ABQOL has been validated for use in MMP. (Sebaratnam 2013, Kalinska-Bienias 2017, Patsatsi 2017, Yang 2017, Sebaratnam 2015, Tjokrowidjaja 2013, Chen G 2018, Alshamekh 2019).

Grade of recommendation D

Recommendations

The following patient-reported outcome measures may be considered for patients with MMP:
Generic - SF-36, DLQI
Oral - COMDO, OHIP
AIBD - ABQOL, TABQOL

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References

1 Schmidt E, Zillikens D. Pemphigoid diseases. Lancet (London, England) 2013; 381: 320–332.
2 Bernard BBL. Pemphigoid group. In Bologna JL, JV Schaffer I Cerroni, eds. Dermatology, Elsevier Limited, 2018: 510–526.
3 Chan LS, Ahmed AR, Anhalt GJ et al. The first international consensus on mucous membrane pemphigoid: definition, diagnostic criteria, pathogenic factors, medical treatment, and prognostic indicators. Arch Dermatol 2002; 138: 370–379.
4 Feliciani C, Joly P, Jonkman MF et al. Management of bullous pemphigoid: the European Dermatology Forum consensus in collaboration with the European Academy of Dermatology and Venereology. Br J Dermatol 2015; 172: 867–877.
5 Hertl M, Jedlickova H, Karpati S et al. S2 Guideline for diagnosis and treatment – Guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV). J Eur Acad Dermatol Venereol 2015; 29: 405–414.
6 Caproni M, Antiga E, Melani L, Fabbi P. Guidelines for the diagnosis and treatment of dermatitis herpetiformis. J Eur Acad Dermatol Venereol 2009; 23: 633–638.
7 Brouwers MC, Kho ME, Browman GP et al. AGREE II: advancing guideline development, reporting and evaluation in health care. CMAJ 2010; 182: E839–E842.
8 Kirtschig G, Murrell D, Wojnarowska F, Khumalo N. Interventions for mucous membrane pemphigoid and epidermolysis bullosa acquisita. Cochrane database Syst Rev 2003: CD004056.
9 Taylor J, McMillan R, Shephard M et al. World Workshop on Oral Medicine VI: a systematic review of the treatment of mucous membrane pemphigoid. Oral Surg Oral Med Oral Pathol Oral Radiol 2015; 120: 161–171e20.
10 Khari M, Khaled A, Anane R et al. Early onset childhood cicatricial pemphigoid: a case report and review of the literature. Pediatr Dermatol 2010; 27: 119–124.
11 Bertram F, Brocker EB, Zillikens D, Schmidt E. Prospective analysis of the incidence of autoimmune bullous disorders in Lower Franconia, Germany. J Dtsch Dermatol Ges 2009; 7: 434–440.
12 Zillikens D, Wever S, Roth A, Weidenthaler-Barth B, Hashimoto T, Brocker EB. Incidence of autoimmune subepidermal blistering dermatoses in a region of Central Germany. Arch Dermatol 1995; 131: 957–958.
13 Bernard P, Vaillant L, Labelle B et al. Incidence and distribution of subepidermal autoimmune bullous skin diseases in three French regions. Bullous Diseases French Study Group. Arch Dermatol 1993; 131: 48–52.
14 Radford CF, Rauz S, Williams GP, Saw VPJ, Dart JKG. Incidence, presenting features, and diagnosis of cicatrising conjunctivitis in the United Kingdom. Eye (Lond) 2012; 26: 1199–1208.
15 Bobba S, Devlin C, Di Girolamo N et al. Incidence, clinical features and diagnosis of cicatrising conjunctivitis in Australia and New Zealand. Eye 2018; 32: 1636–1643.
16 Hubner F, Recke A, Zillikens D, Linder R, Schmidt E. Prevalence and age distribution of pemphigus and pemphigoid diseases in Germany. J Invest Dermatol 2016; 136: 2495–2498.
17 Thorne JE, Anhalt GJ, Jabs DA. Mucous membrane pemphigoid and pseudopemphigoid. Ophthalmonology 2004; 111: 45–52.
18 Hong GH, Khan IR, Shifiers A, Okeacu G, Thorne JE. Incidence and clinical characteristics of ocular involvement in mucous membrane pemphigoid. Ocal Immunal Inflamm 2019; 7: 1–5.
19 Daneshpazhooh M, Chams-Davatchi C, Payandemehr P, Nassiri S, Valikhani M, Safai-Naragh Z. Spectrum of autoimmune bullous diseases in Iran: a 10-year review. Int J Dermatol 2012; 51: 35–41.
20 Loget J, Barbe C, Duvert-Lehembre S et al. The regibul register: a tool for monitoring the distribution and incidence of autoimmune bullous dermatoses in three french regions, 2010 to 2015. Acta Derm Venerol 2018; 98: 380–381.
21 Higgins TS, Cohen JC, Sinacori JT. Laryngeal mucous membrane pemphigoid (MMP): a systematic review and pooled-data analysis. Laryngosope 2009; 119(Suppl 3): S267.
22 Higgins GT, Allan RB, Hall R, Field EA, Kaye SB. Development of ocular disease in patients with mucous membrane pemphigoid involving the oral mucosa. Br J Ophthalmol 2006; 90: 964–967.
23 Laskaris G, Sklavounou A, Stratigos J. Bullous pemphigoid, cicatricial pemphigoid, and pemphigus vulgaris. A comparative clinical survey of 278 cases. Oral Surg Oral Med Oral Pathol 1982; 54: 656–662.
24 Jascholt I, Lai O, Zillikens D, Kasperkiewicz M. Periodontitis in oral pemphigus and pemphigoid: a systematic review of published studies. J Am Acad Dermatol 2017; 76: 975–978.e3.
25 Arduino PG, Broccolotti R, Carbone M et al. Describing the gingival involvement in a sample of 182 Italian predominantly oral mucous
70 Lambsi S, Dulguerov P, Lafitte E, Leuchter I. Paraneoplastic mucous membrane pemphigoid with ocular and laryngeal involvement. BMJ Case Rep 2017; 2017.
71 Murono S, Nakamishi Y, Fujimoto M, Yoshizaki T. Hypopharyngeal presentation of cicatricial pemphigoid: videofluorographic and direct laryngoscopic findings. J Laryngol Otol 2013; 127: 429–431.
72 Nash R, Hughes J, Kuchai R, Sandison A, Sandhu G. Assessment and management of laryngeal mucous membrane pemphigoid: our experience in six patients and a proposed severity scale. Clin Otolaryngol 2017; 42: 752–756.
73 Amber KT, Bloom R, Hertl M. A systematic review with pooled analysis of clinical presentation and immunodiagnostic testing in mucous membrane pemphigoid: association of anti-laminin-332 IgG with oropharyngeal involvement and the usefulness of ELISA. J Eur Acad Dermatol Venereol 2016; 30: 72–77.
74 Murata S, Sumikawa Y, Takahashi H et al. Case of mucous membrane pemphigoid with immunoglobulin G antibodies to the beta 3 subunit of laminin-332 showing clinically Stevens-Johnson syndrome-like general involvement and may be linked to antibasement membrane IgG production. Acta Derm Venereol 2008; 88: 204–206.
75 Zehou O, Raynaud JJ, Le Roux-Villet C et al. Oesophageal involvement in 26 consecutive patients with mucous membrane pemphigoid. Br J Dermatol 2017; 177: 1074–1085.
76 Sárdy M, Borovaya A, Horváth ON et al. Successful rituximab treatment of juvenile bullous pemphigoid with esophageal scarring due to epitope spreading. JDDG J Ger Soc Dermatol 2016; 14: 618–621.
77 Sallout H, Anhalt GJ, Al-Kawash FH. Mucous membrane pemphigoid presenting with isolated esophageal involvement: a case report. Gastrointest Endosc 2000; 52: 429–433.
78 Goedicke H. Cicatricial pemphigoid: Bullae blossoming before one’s eyes. Am J Respir Crit Care Med 2013; 187: 3904.
79 Jalil RA, Abdou YG, Rosen SA, Dammad T. Mucous membrane pemphigoid causing central airway obstruction. J Bronchol Interv Pulmonol 2017; 24: 334–338.
80 Hoque SR, Patel M, Farrell AM. Childhood cicatricial pemphigoid confined to the vulva. Clin Exp Dermatol 2006; 31: 63–64.
81 Saad RW, Domloge-Hultsch N, Yancey KB, Benson PM, James WD. Childhood localized vulvar pemphigoid is a true variant of bullous pemphigoid. Arch Dermatol 1992; 128: 807–810.
82 Lebeau S, Mainetti C, Masouye I, Saurat JH, Borradori L. Localized childhood vulval pemphigoid treated with tacrolimus ointment. Derma tology 2004; 208: 275–283.
83 Setterfield J, Theron J, Vaughan RW et al. Mucous membrane pemphigoid: HLA-DQB1*0301 is associated with all clinical sites of involvement and may be linked to antibasement membrane IgG production. Br J Dermatol 2001; 145: 406–414.
84 Bernard P, Antonicelli F, Bedane C et al. Prevalence and clinical significance of anti-laminin 332 autoantibodies detected by a novel enzyme-linked immunosorbent assay in mucous membrane pemphigoid. JAMA Dermatology 2013; 149: 533–540.
85 Marren P, Valken D, Mallon E, Wojnarowska F. Vulval cicatrical pemphigoid may mimic lichen sclerosus. Br J Dermatol 1996; 134: 522–524.
86 de Waard MM, Jonkman MF. Vulvar geloalkalized pemphigoid. NTvDv 2008; 18: 204–207.
87 Wentworth A, Mangold A, Siegfried E, Camilleri M, Javed ATM. Childhood mucous membrane pemphigoid of the oral and genital mucosa. Pediatr Dermatol 2017; 34: S100–S121.
88 Goldstein AT, Anhalt GJ, Kligman D, Burrows LJ. Mucous membrane pemphigoid of the Vulva. Obstet Gynecol 2005; 105(5 II): 1188–1190.
89 Edwards L. Dermatologic causes of vaginitis: a clinical review. Dermatol Clin 2010; 28: 727–735.
90 Levine V, Sanchez M, Nestor M. Localized vulvar pemphigoid in a child misdiagnosed as sexual abuse. Arch Dermatol 1992; 128: 804–806.
91 Van Joost T, Faber WR, Manuel H. Drug-induced anogenital cicatricial pemphigoid. Br J Dermatol 1980; 102: 715–718.
92 Lenz P, Hsu R, Yee C, Yancey K, Volc-Platzer B, Stingl GKR. Cicatricial pemphigoid with autoantibodies to laminin 5 (epiligrin) in a patient with metastatic endometrial carcinoma. Hautarzt 1998; 49: 31–35. In German.
93 Fukuchi O, Sako A, Matsuoka H et al. Anti-laminin-332 mucous membrane pemphigoid with autoantibodies to $\varepsilon$3, $\beta$3 and $\gamma$2 subunits of laminin-332 as well as to BP230 and perilakin associated with adenocarcinoma from an unknown primary site. J Dermatol 2013; 40: 61–62.
94 Mitsuya H, Ito K, Ishii N, Hashimoto T, Terui T. Metastatic ovarian carcinoma-associated subepidermal blistering disease with autoantibodies to both the p200 dermal antigen and the $\gamma$2 subunit of laminin 5 showing unusual clinical features. Br J Dermatol 2008; 158: 1354–1357.
95 Ormond MHT. Bevacizumab associated mucous membrane pemphigoid. Oral Dis 2010; 16: 516–572.
96 Venning VA, Frith PA, Bro J, Millard PR, Wojnarowska F. Mucosal involvement in bullous and cicatricial pemphigoid. A clinical and immunopathological study. Br J Dermatol 1988; 118: 7–15.
97 Ramlogan D, Couchman BH, McGeorge A. Cicatricial pemphigoid: a diagnostic problem for the urologist. J Urol Surg Edinb 2000; 45: 62–63.
98 Cozzani E, Di Zenzo G, Calabresi V et al. Autoantibody profile of a Cohort of 78 Italian patients with mucous membrane pemphigoid: correlation between reactivity profile and clinical involvement. Acta Derm Venereol 2016; 96: 768–773.
99 Yasukochi A, Tey K, Ishii N, Hashimoto T. Clinical and immunological studies of 332 japanese patients tentatively diagnosed as anti-BP180-type mucous membrane pemphigoid: a novel BP180-C-terminal domain enzyme-linked immunosorbent assay. Acta Derm Venereol 2016; 96: 762–767.
100 Setterfield J, Shirlaw PJ, Kerr-Muir M et al. Mucous membrane pemphigoid: a dual circulating antibody response with IgG and IgA signifies a more severe and persistent disease. Br J Dermatol 1998; 138: 602–610.
101 Jedlickova H, Niedermeier A, Zgárová S, Hertl M. Brunsting-Perry pemphigoid of the scalp with antibodies against laminin 332. Dermatol Pract Concept 2011; 222: 193–195.
102 Chandan N, Juhi ME, Tsoukas MM. Brunsting-Perry pemphigoid: a case with antigen identification. Int J Dermatol 2018; 57: e41–e43.
103 Kurzhals G, Stolz W, Maciejewski W, Karpaci S, Meurer M, Breit R. Localized cicatricial pemphigoid of the Brunsting-Perry type with transition into disseminated cicatricial pemphigoid. Report of a case proved by preembedding immunogold electron microscopy. Arch Dermatol 1995; 131: 580–585.
104 Imstpef V, Cazzaniga S, Beltramelli H, Borradori L, Feldmeyer L. Brunsting-Perry pemphigoid: a retrospective case series of a frequently unrecognized condition. J Am Acad Dermatol 2020.
105 Goletz S, Ziliikens D, Schmidt E. Structural proteins of the dermal-epidermal junction targeted by autoantibodies in pemphigoid diseases. Exp Dermatol 2017; 26: 1154–1162.
106 Horváth B, Niedermeier A, Podstawa E et al. IgA autoantibodies in the pemphigoids and linear IgA bullous dermatosis. Exp Dermatol 2010; 19: 648–653.
107 Ghobestani RF, Nicolas JF, Rousselle P, Claudey AL. Diagnostic value of indirect immunofluorescence on sodium chloride-split skin in differential diagnosis of subepidermal autoimmune bullous dermatoses. Arch Dermatol 1997; 133: 1102–1107.
108 Carrozzo M, Cozzani E, Brocchieri R et al. Analysis of antigens targeted by circulating IgG and IgA antibodies in patients with mucous membrane pemphigoid predominantly affecting the oral cavity. J Periodontol 2004; 75: 1302–1308.
109 Murakami H, Nishioka S, Setterfield J et al. Analysis of antigens targeted by circulating IgG and IgA autoantibodies in 50 patients with cicatricial pemphigoid. J Dermatol Sci 1998; 17: 39–44.
110 Hayakawa T, Furumura M, Fukano H et al. Diagnosis of oral mucous membrane pemphigoid by means of combined serologic testing. Oral Surg Oral Med Oral Pathol Oral Radiol 2014; 117: 483–496.
therapy for metastatic melanoma and review of the lite. Front Med 2018; 5: 268.

130 Gaudin O, Seta V, Alexandre M et al. Gliptin accountability in mucous membrane pemphigoid induction in 24 out of 313 patients. Front Immunol 2018; 9: 1030.

131 Nayar M, Wojnarowska F, Venning V, Taylor CJ. Association of autoimmune and cicatricial pemphigoid: is there an immunogenetic basis? J Am Acad Dermatol 1991; 25(6 Pt 1): 1011–1015.

132 Malik M, Gurcan HM, Ahmed AR. Coexistence of mucous membrane pemphigoid and connective-tissue disease. Clin Exp Dermatol 2010; 35: 156–159.

133 Siassipour A, Katz I. Oral mucous membrane pemphigoid associated with hypothyroidism: a retrospective study and a case report. Quintessence Int 2017; 48: 569–573.

134 Nayar M, Wojnarowska F. No association between cicatricial pemphigoid and malignant disease. Br J Dermatol 1991; 125: 193–194.

135 Egan CA, Lazarova Z, Darling TN, Yee C, Yancey KB. Anti-epiligrin cicatricial pemphigoid: clinical findings, immunopathogenesis, and significant associations. Medicine (Baltimore) 2003; 82: 177–186.

136 Letko E, Gurcan HM, Papadopoulos GN, Christen W, Foster CS, Ahmed AR. Relative risk for cancer in mucous membrane pemphigoid associated with antibodies to the β4 integrin subunit. Clin Exp Dermatol 2007; 32: 637–641.

137 Malik M, Gurcan HM, Christen W, Ahmed AR. Relationship between cancer and oral pemphigoid patients with antibodies to α6β4 integrin. J Oral Pathol Med 2007; 36: 1–5.

138 Goletz S, Probst C, Komorowski L et al. A sensitive and specific assay for the serological diagnosis of antilaminin 332 mucous membrane pemphigoid. Br J Dermatol 2019; 180: 149–156.

139 La Placa M, Balestri R, Tartari F et al. Mucous membrane pemphigoid-associated malignancies: case series and a brief overview of the literature. Dermatol Pract Concept 2019; 9: 119–125.

140 Schulze F, Neumann K, Recke A, Zillikens D, Linder R, Schmidt E. Malignancies in pemphigus and pemphigoid diseases. J Invest Dermatol 2015; 135: 1445–1447.

141 Lee BWH, Tan JCK, Radjenovic M, Coronoe MT, Murrell DF. A review of scoring systems for ocular involvement in chronic cutaneous bullous diseases. Orphanet J Rare Dis 2018; 13: 83.

142 Ormond M, McParland H, Thakrar P et al. Validation of an Ocular Disease Severity Score (ODSS) tool for use in oral mucous membrane pemphigoid. Br J Dermatol 2020; 183: 78–85.

143 Murrell DF, Marinovic B, Caux F et al. Definitions and outcome measures for mucous membrane pemphigoid: recommendations of an international panel of experts. J Am Acad Dermatol 2015; 72: 168–174.

144 Murrell DF, Dick S, Ahmed AR et al. Consensus statement on definitions of disease, end points, and therapeutic response for pemphigus. J Am Acad Dermatol 2008; 58: 1043–1046.

145 Rosenbach M, Murrell DF, Bystryn J-C et al. Reliability and convergent validity of two outcome instruments for pemphigus. J Invest Dermatol 2009; 129: 2404–2410.

146 Wijayanti A, Zhao CY, Boetiger D et al. The reliability, validity and responsiveness of two disease scores (BPDAL and ABSIS) for bullous pemphigoid: which one to use? Acta Derm Venereol 2017; 97: 24–31.

147 Setterfield J, Shirlaw PJ, Bhogal BS, Tilling K, Challacombe SJ, Black MM. Cicatricial pemphigoid: serial titres of circulating IgG and IgA antibasement membrane antibodies correlate with disease activity. Br J Dermatol. 1999;140: 645–650.

148 Pfütze M, Niedermeier A, Hertl M, Eming R. Introducing a novel histocompatibility complex class II markers in clinical variants of cicatricial pemphigoid. J Invest Dermatol 1999; 112: 241–248.

149 Sherbinin A, Schmitt J, Auer C et al. Establishment of a novel indicator in mucous membrane pemphigoid for outcome prediction. Br J Dermatol 2013; 168: 381–390.
195 Chren M-M, Lasek RJ, Quinn LM, Mostow EN, Zyzanski SJ. Skindex, a quality-of-life measure for patients with skin disease: reliability, validity, and responsiveness. J Invest Dermatol. 1996;107:707–713.

196 Basra MKA, Fenech R, Gatt RM, Salek MS, Finlay AY. The Dermatology Life Quality Index 1994–2007: a comprehensive review of validation data and clinical results. Br J Dermatol. 2008;159:997–1035.

197 Slade GD, Spencer AJ. Development and evaluation of the Oral Health Impact Profile. Community Dent Health 1994;11:3–11.

198 Ni Riordain R, McCreary C. The use of quality of life measures in oral medicine: a review of the literature. Oral Dis 2010;16:419–430.

199 Locker D, Allen PF. Developing short-form measures of oral health-related quality of life. J Public Health Dent 2002;62:13–20.

200 Ni Riordain R, Shirlaw P, Alajbeg I et al. World Workshop on Oral Medicine VI: patient-reported outcome measures and oral mucosal disease: current status and future direction. Oral Surg Oral Med Oral Pathol Oral Radiol 2015;120:152–160.e11.

201 Arduino PG, Lopetuso E, Carcieri P et al. Professional oral hygiene treatment and detailed oral hygiene instructions in patients affected by mucous membrane pemphigoid with specific gingival localization: a pilot study in 12 patients. Int J Dent Hyg 2012;10:138–141.

202 Bijur PE, Silver W, Gallagher EJ. Reliability of the visual analog scale for measurement of acute pain. Acad Emerg Med 2001;8:1153–1157.

203 Ni Riordain R, Meaney S, McCreary C. A patient-centered approach to developing a quality-of-life questionnaire for chronic oral mucosal diseases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;111:578–586, 586.e1–2.

204 Li M, He S-L. Reliability and validity of the Chinese version of the chronic oral mucosal diseases questionnaire. J Oral Pathol Med 2013;42:194–199.

205 Ni Riordain R, Hodgson T, Porter S, Fedele S. Validity and reliability of the Chronic Oral Mucosal Diseases Questionnaire in a UK population. J Oral Pathol Med 2016;45:613–616.

206 Rajan B, Ahmed J, Shenoy N, Denny C, Ongole R, Binnal A. Assessment of quality of life in patients with chronic oral mucosal diseases: a questionnaire-based study. Perm J 2014;18:e123–e127.

207 Shirzad A, Bijani A, Mehrjari M, Motallebnejad M, Mohsenitavakoli S. Validity and reliability of the persian version of the chronic oral mucosal diseases questionnaire. Casp J Intern Med 2018;9:127–133.

208 Sebaratnam DF, Okawa J, Payne A, Murrell DF, Werth VP. Reliability of the autoimmune bullous disease quality of life (Abqol) questionnaire in the USA. Qual Life Res. 2015;24:2257–2260.

209 Chen G, Yang B, Zhang Z. Chinese version of the treatment of autoimmune bullous disease quality of life questionnaire: Reliability and validity. Indian J Dermatol Venereol Leprol. 2018;84:431–436.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Glossary table of terms, previously used to describe variants of mucous membrane pemphigoid, which should be avoided.