

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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Guidelines and Position Statements European guidelines (S3) on diagnosis and management of
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10 7 2021 9 2021 35 9 390472 10.1111/jdv.v35.9 1750 1764 11 2 2021 17 5 2021 22 09 2021 27 09 2021 02 04 2024 © 2021 The Authors. Journal of the European Academy of Dermatology and Venereology published by John Wiley & Sons Ltd on behalf of European Academy of Dermatology and Venereology <https://creativecommons.org/licenses/by-nc-nd/4.0/> This is an open access article under the terms of the <http://creativecommons.org/licenses/by-nc-nd/4.0/> License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made. 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 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.

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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 pemphigus 5 and dermatitis herpetiformis. 6

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 Blaaziekten, the British PEM Friends and the Association Pemphigus Pemphigoïde 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.

During the guideline kickoff 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.

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

During the guideline kickoff 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.

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

John Wiley & Sons, Ltd 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.

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 .

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

Conjunctiva: hyperaemia of bulbar and tarsal conjunctiva, limbitis, loss of plica semilunaris, subepithelial fibrosis, occlusion of lacrimal ductules, fornix shortening, symblepharon, ankyloblepharon, entropion, trichiasis. Redness, tearing, burning, decreased vision, foreign body sensation

Cornea: inflammation, limbitis, corneal vascularization, stem cell failure, erosion, ulceration, perforation, scarring, secondary infection, loss of function, loss of eye

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 meatal stenosis obstructing flow of urine

John Wiley & Sons, Ltd 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.).

List of previous and current terminology for mucous membrane pemphigoid

John Wiley & Sons, Ltd 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.

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 , 12 , 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 , 17 , 18 , 19 , 20 , 21 , 22 , 23 No geographic or racial predilection has been described.

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.

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

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. 27 , 28 , 29 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%). 23 , 30 , 31 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-oral 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. 32 , 33 , 34 , 35 The predominant symptoms upon presentation include discomfort, burning, gingival bleeding, mucosal peeling and difficulty in eating. 25 , 28 Gingival bleeding often results in suboptimal oral hygiene, with subsequent plaque-related marginal gingivitis, leading to chronic periodontitis as a recognized complication. 24

The average age at diagnosis of ocular monosite and multisite MMP ranges from a mean of 60.4–68.2 years. 14 , 17 , 18 , 22 , 36 , 37 , 38 , 39 , 40 , 41 Patients with ocular monosite and multisite involvement seem to be older than those without ocular involvement. 18 , 37 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. 42 An average female proportion of 52% (range 37–81%) has been observed. 14 , 17 , 18 , 22 , 36 , 37 , 38 , 39 , 40 , 41 , 43 , 44 , 45 , 46 , 47 , 48 , 49 , 50 , 51 The mean duration of symptoms prior to diagnosis of ocular MMP ranges from 225 days to 6.4 years. 14 , 36 , 39 , 52 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). 43

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. 49 Limbitis occurs in 12–28% of the eyes. 14 , 15 , 46 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. 53 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. 41 , 54 Furthermore, in late-stage disease, which is often when a definitive diagnosis is made, ocular inflammation may not be the predominant finding. 14

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. 37 , 41 , 49 Although ocular involvement in MMP can occasionally be unilateral, it is usually bilateral. 45 , 55 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. 14 , 45 , 48

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. 56 The most common nasal symptoms and signs consist of epistaxis, rhinorrhea, nasal crusting and nasal obstruction. Examination of the nasal mucosa may reveal atrophic rhinitis, erosive and crusted lesions and synechia. 56 , 57 , 58 , 59 , 60 , 61 , 62 , 63 , 64 Patients with pharyngeal involvement often complain of pharyngalgia, dysphagia or odynophagia, impaired food intake and coughing. 56 , 61 , 63 , 65 , 66 , 67 , 68 , 69 , 70 , 71 , 72 Nasopharyngeal involvement may coexist with involvement of the laryngeal mucosa. 57 , 60 , 65 , 67 , 69 , 70 , 72 , 73 , 74 Clinical signs including erythema, erosions or ulcerations, vesicular lesions and scarring of the pharynx can be seen. 56 , 60 , 61 , 66 , 67 , 69 , 70 , 71

The most common symptoms and signs of laryngeal involvement in MMP are dyspnoea and dysphonia. 72 However, a proportion of MMP patients with laryngeal involvement are asymptomatic. 21 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. 21 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. 21

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. 75 Dysphagia is usually the first and most common symptom to reveal oesophageal MMP, 75 but it may also develop several years after onset of the disease. 76 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. 77 Oesophageal stenosis following oesophageal dilation may occur. The development of blisters, bleeding and oedema may interfere with breathing. 78

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. 79

Involvement of the anogenital region can occur, either isolated or with other mucosal sites. 80 , 81 , 82 In two cohorts of MMP patients, genital lesions were observed in 28–38% of the cases. 83 , 84 Affected patients present with pain and/or pruritus. Examination reveals blisters, vesicles, erosions and ulcers, which may affect the vulvar area and introitus 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 misdiagnosed as lichen sclerosus et atrophicus, lichen planus, pemphigus or even sexual abuse. 80 , 82 , 85 , 86 , 87 , 88 , 89 , 90 Distinguishing it from localized vulvar pemphigoid may also pose a challenge. Genital involvement in MMP can be drug-induced or paraneoplastic. 91 , 92 , 93 , 94 , 95 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. 96 , 97

The skin can be mildly affected in MMP and is encountered in 20–35% of MMP patients. 17 , 25 , 43 , 83 , 98 , 99 , 100 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. 101 , 102 Generalized skin lesions in MMP have also been reported. 103 , 104

BP180 (also termed BP antigen 2 or type XVII collagen) and BP230 (also called BP antigen 1, epithelial isoform) are haemidesmosomal proteins with a molecular weight of 180 and 230 kD. 105 BP180 is a transmembrane collagenous protein, and BP230 is an intracellular protein of the plakin family of cytolinkers. 105 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. 100 BP230 reactivity is less common and is reported in 9% up to 28% of MMP cases. 84 , 98 , 106 , 107 , 108 , 109

Laminin 332, previously known as epiligrin and laminin 5, is a heterotrimer composed of $\alpha 3$, $\beta 3$ and $\gamma 2$ subunits, targeted by a subset of MMP patients who usually present with multisite mucosal lesions, with significant association with pharyngo-laryngeal, oro-pharyngo-laryngeal and tracheal involvement. 73 , 79 , 110 , 111

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. 98

The $\alpha 6$ and $\beta 4$ 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 BP230. 105 , 112 Ahmed et al . reported that antibodies against the integrin $\alpha 6$ subunit are detected in 80-100% of oral MMP cases. 113 , 114 , 115 These antibodies appear to specifically bind to the extracellular domain of the integrin $\alpha 6$ subunit. 113 In contrast to oral MMP, almost all patients with ocular MMP showed autoantibodies directed against the integrin $\beta 4$ subunit. 114 , 116 , 117 Autoantibodies against the integrin $\beta 4$ subunit bind to the C terminal end of its intracellular domain. 118 , 119 In a study encompassing 43 ocular MMP sera, Li et al . 120 reported reactivity with the integrin $\beta 4$ subunit, BP180, laminin 332 $\alpha 3$ subunit, $\gamma 2$ subunit, $\beta 3$ subunit and LAD-1 in 62.8%, 58%, 28%, 21%, 21% and 19% of cases, respectively. Furthermore, reactivity to the $\alpha 6$ subunit in the ocular MMP sera was found in only 23.3% for IgG and 18.6% for IgA. 120 Since the presence of anti- $\alpha 6\beta 4$ integrin antibodies in MMP has not been confirmed in independent laboratories, the findings described remain to be validated.

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 dogs, spontaneous onset of MMP has been described. 121 , 122 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. 123 , 124 , 125 , 126 A genome-wide association study found 38 single-nucleotide polymorphisms associated with MMP; these polymorphisms need functional validation. 126 In a few cases, drug-induction of MMP has been described. 127 , 128 , 129 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. 130 Finally, an increasing number of immune check point inhibitor-triggered cases of MMP has recently been reported. 128

One retrospective study reported increased incidence of pernicious anaemia in MMP. 131 Other retrospective cohort studies found no increased risk for autoimmune disease compared with healthy controls. 132 , 133 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. 63 , 84 , 134 , 135 , 136 , 137 , 138 , 139 , 140 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. 84 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. 138

Currently, no published validated scoring methodologies are available for multisite MMP, 141 although methodology for oral MMP has recently been validated. 142 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. 9 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). 143 This was adapted from the validated

Pemphigus Disease Area Index (PDAI) and the Bullous Pemphigoid Disease Area Index (BPDAI). 144 , 145 , 146 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). 148 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. 148

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. 100 , 147 The methodology was subsequently used in two cohort studies, although expanded to include a damage score describing the scarring. 98 , 149 Thornhill et al. scored sites including the mouth, eye, nose, genitals and skin as areas of involvement, but not the pharynx and larynx. 150

Further interventional studies have based response to treatment on previously reported observation endpoint definitions. 144 , 151 , 152 , 153 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. 154

The Oral Disease Severity Score (ODSS) has been proposed as a comprehensive scoring system for the oral lesions of lichen planus, 155 pemphigus vulgaris 156 and mucous membrane pemphigoid. 142 It was developed from the Setterfield et al . 100 multisite 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, 157 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.

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. 157 , 158 , 159 , 160 , 161 , 162 , 163 One scoring system has also added a simple qualitative grading of conjunctival inflammation, using a 4-point scale, 149 while another system has included this grading for a disease activity index, but excluded scarring and morbidity. 143 Only one system 164 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. 165

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. 141 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. 157 , 163 A scoring system called the Cicatrising Conjunctivitis Assessment Tool 166 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 37 , 164 , 167 and includes the use of a fornix depth measurer (FDM) for scarring assessment. 163

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

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 , 175 , 176 Activities of Daily Living (ADLs), 177 12-item General Health Questionnaire (GHQ-12), 178 , 179 , 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 , 189 , 190 , 191 , 192 , 193 , 194 , 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 , 204 , 205 , 206 , 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

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

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