

## 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

# 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

<sup>†</sup>Both authors contributed equally.

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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## 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.<sup>1,2</sup> 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.<sup>3</sup> 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),<sup>4</sup> pemphigus<sup>5</sup> and dermatitis herpetiformis.<sup>6</sup>

## 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 Blaaziekten, 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.<sup>7</sup>

### 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.*<sup>8</sup> and in the systematic review by Taylor *et al.*<sup>9</sup> 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).

**Table 1** Level of recommendation based on level of evidence

|   |  |
|---|--|
| 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.).

**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, ankyloblepharon, entropion, trichiasis. Redness, tearing, burning, decreased vision, foreign body sensation<br>Cornea: 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<br>Less specific signs: erythema, oedema, milia, atrophy, or purulent vaginal discharge. Pain and/or pruritus<br>Recurrent dysuria with negative urine cultures, or meatal stenosis obstructing flow of urine  |

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

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

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.<sup>3</sup> 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**

## 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.<sup>10</sup> The incidence of MMP is estimated at approximately 1–2 new cases per million people annually in Germany and France.<sup>11–13</sup> The incidence of ocular MMP is estimated at 0.7–0.8 million in New Zealand and the United Kingdom.<sup>14,15</sup> 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.<sup>13,16–23</sup> 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.<sup>23</sup> In a prospective national incidence survey, diagnostic delay lasted approximately 21 months.<sup>14</sup> 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.<sup>24,25</sup> Diagnostic delays have been reported, ranging from 2 to 60 months from development of the first symptoms to diagnosis.<sup>26</sup> In 85% of MMP patients, the oral mucosa is the site of onset, and most

frequently involved. Other mucosal sites may be concomitantly involved.<sup>27–29</sup> 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%).<sup>23,30,31</sup> 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.<sup>32–35</sup> The predominant symptoms upon presentation include discomfort, burning, gingival bleeding, mucosal peeling and difficulty in eating.<sup>25,28</sup> Gingival bleeding often results in suboptimal oral hygiene, with subsequent plaque-related marginal gingivitis, leading to chronic periodontitis as a recognized complication.<sup>24</sup>

**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.<sup>14,17,18,22,36–41</sup> Patients with ocular monosite and multisite involvement seem to be older than those without ocular involvement.<sup>18,37</sup> 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.<sup>42</sup> An average female proportion of 52% (range 37–81%) has been observed.<sup>14,17,18,22,36–41,43–51</sup> The mean duration of symptoms prior to diagnosis of ocular MMP ranges from 225 days to 6.4 years.<sup>14,36,39,52</sup> 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).<sup>43</sup>

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.<sup>49</sup> Limbitis occurs in 12–28% of the eyes.<sup>14,15,46</sup> 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.<sup>53</sup> 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.<sup>41,54</sup> Furthermore, in late-stage disease, which is often when a

definitive diagnosis is made, ocular inflammation may not be the predominant finding.<sup>14</sup>

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

**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.<sup>56</sup> 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.<sup>56–64</sup> Patients with pharyngeal involvement often complain of pharyngalgia, dysphagia or odynophagia, impaired food intake and coughing.<sup>56,61,63,65–72</sup> Nasopharyngeal involvement may coexist with involvement of the laryngeal mucosa.<sup>57,60,65,67,69,70,72–74</sup> Clinical signs including erythema, erosions or ulcerations, vesicular lesions and scarring of the pharynx can be seen.<sup>56,60,61,66,67,69–71</sup>

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

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

**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.<sup>79</sup>

**Genital and urological involvement in MMP** Involvement of the anogenital region can occur, either isolated or with other mucosal sites.<sup>80–82</sup> In two cohorts of MMP patients, genital lesions were observed in 28–38% of the cases.<sup>83,84</sup> 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.<sup>80,82,85–90</sup> Distinguishing it from localized vulvar pemphigoid may also pose a challenge. Genital involvement in MMP can be drug-induced or paraneoplastic.<sup>91–95</sup> 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.<sup>96,97</sup>

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

### 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 isoform) are haemidesmosomal proteins with a molecular weight of 180 and 230 kD.<sup>105</sup> BP180 is a transmembrane collagenous protein, and BP230 is an intracellular protein of the plakin

family of cytolinkers.<sup>105</sup> 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.<sup>100</sup> BP230 reactivity is less common and is reported in 9% up to 28% of MMP cases.<sup>84,98,106–109</sup>

**Laminin 332** 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.<sup>73,79,110,111</sup>

**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.<sup>98</sup>

**The  $\alpha 6$  and  $\beta 4$  integrin subunits** 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 cyokeratin network via plectin and BP230.<sup>105,112</sup> Ahmed *et al.* reported that antibodies against the integrin  $\alpha 6$  subunit are detected in 80–100% of oral MMP cases.<sup>113–115</sup> These antibodies appear to specifically bind to the extracellular domain of the integrin  $\alpha 6$  subunit.<sup>113</sup> In contrast to oral MMP, almost all patients with ocular MMP showed autoantibodies directed against the integrin  $\beta 4$  subunit.<sup>114,116,117</sup> Autoantibodies against the integrin  $\beta 4$  subunit bind to the C terminal end of its intracellular domain.<sup>118,119</sup> In a study encompassing 43 ocular MMP sera, Li *et al.*<sup>120</sup> 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.<sup>120</sup> 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.

### 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

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

### Associated factors and comorbidities

One retrospective study reported increased incidence of pernicious anaemia in MMP.<sup>131</sup> Other retrospective cohort studies found no increased risk for autoimmune disease compared with healthy controls.<sup>132,133</sup> 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.<sup>63,84,134-140</sup> 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.<sup>84</sup> 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 another retrospective study with 246 MMP patients, 25% of the anti-laminin 332 MMP patients had a malignancy.<sup>138</sup>

### Conclusions

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| <b>Level of evidence 4</b> | No evidence supports a phenotype association with the target autoantigens. Contradictory evidence exists regarding the association between laminin 332 and an underlying malignancy. |
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### 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,<sup>141</sup> although methodology for oral MMP has recently been validated.<sup>142</sup> 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.<sup>9</sup> 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).<sup>143</sup> This was adapted from the validated Pemphigus Disease Area Index (PDAI) and the Bullous Pemphigoid Disease Area Index (BPDAI).<sup>144-146</sup> 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).<sup>148</sup> 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.<sup>148</sup>

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

Further interventional studies have based response to treatment on previously reported observation endpoint definitions.<sup>144,151-153</sup> 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.<sup>154</sup>

### Conclusions

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| <b>Level of evidence 4</b> | MMPDAI is a disease-specific severity scoring tool. It has not been validated. (Murrell 2015)   |
| <b>Level of evidence 4</b> | ABSIS has been proposed for use in MMP, but it is not disease-specific and has not been validated for use in MMP. (Pfützte 2007).   |
| <b>Level of evidence 4</b> | 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.  |
| <b>Level of evidence 4</b> | 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,<sup>155</sup> pemphigus vulgaris<sup>156</sup> and mucous membrane pemphigoid.<sup>142</sup> It was developed from the Setterfield *et al.*<sup>100</sup> 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,<sup>157</sup> 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

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| <b>Level of evidence 4</b> | ODSS is an oral mucosal disease severity scoring tool, validated for use in lichen planus (Escudier 2007), pemphigus vulgaris (Ormond 2018), and MMP (Ormond, McParland 2020). ODSS was demonstrated to be reliable in MMP. (Reeves 2012) |
| <b>Level of evidence 1</b> | The ODSS and the oral part of both MMPDAI and ABSIS have been validated as disease severity scoring tools for use in oral aspects of MMP.   |

## 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.<sup>157-163</sup> One scoring system has also added a simple qualitative grading of conjunctival inflammation, using a

4-point scale,<sup>149</sup> while another system has included this grading for a disease activity index, but excluded scarring and morbidity.<sup>143</sup> Only one system<sup>164</sup> 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.<sup>165</sup>

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

## Conclusions

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| <b>Level of evidence 2</b> | Two grading schemes for conjunctival scarring disease, which include disease activity, scarring, and morbidity/loss of vision parameters, are required to fully phenotype ocular MMP and meet an evidence level of B or C. One of these was designed for Stevens-Johnson syndrome (Sotozono 2007), a disease with a phenotype similar to that of ocular MMP, but the parameters have not been assessed for inter- and intra-observer variability. |
| <b>Level of evidence 2</b> | The Cicatrizing Conjunctivitis Assessment Tool tool (Ong 2020) meets all these requirements. It is semi-quantitative, unlike the other tools, which are all qualitative; it has been shown to be comparable to the most comprehensive (Sotozono 2007) and widely used (Tauber 1992, evaluating scarring only) previous systems. It is ready for use as a phenotyping tool for ocular MMP.   |

## Recommendations

The validated Cicatrizing 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.<sup>21</sup> Although their proposal has not been validated, it has been referred to in other case series.<sup>72,168</sup>

### Conclusions

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| <b>Level of evidence 4</b> | 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. |
| <b>Level of evidence 4</b> | Nash 2017 described a symptomatology scale for laryngeal involvement. This method has not been validated.  |
| <b>Level of evidence 2</b> | 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.<sup>169,170</sup> 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.<sup>171</sup> 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.<sup>172</sup> Often, however, the QOL burden is independent of objective disease burden and clinical severity.<sup>172,173</sup>

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),<sup>174-176</sup> Activities of Daily Living (ADLs),<sup>177</sup> 12-item General Health Questionnaire (GHQ-12),<sup>178-180</sup> Hospital Anxiety and Depression scale (HADS),<sup>181,182</sup> Clinical Depression Questionnaire (CDQ),<sup>176,183</sup> Beck Depression Inventory (BDI),<sup>184,185</sup> and The Work Productivity and Activity Impairment Questionnaire-Specific Health Problem (WPAIQ-SHP).<sup>186,187</sup>

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.<sup>188-195</sup> The DLQI is the first validated dermatology-specific QOL instrument.<sup>188,196</sup> Currently, the SF-36 and the DLQI are the most often reported measures for evaluating QOL in AIBD.

The Oral Health Impact Profile (OHIP)<sup>197</sup> is the most common generic instrument used in the field of oral medicine.<sup>198</sup> 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.<sup>199</sup> 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,<sup>150,200,201</sup> and its validity and reliability have been well established.<sup>202</sup> Further, the Chronic Oral Mucosal Disease Questionnaire (COMDQ)<sup>203</sup> 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.<sup>203-207</sup> 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.<sup>172,208</sup> 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)<sup>173</sup> is the first validated patient-centred tool to allow quantitative measurement of treatment-specific impact on QOL in AIBD.<sup>209</sup>

## Conclusions

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| <b>Level of evidence 4</b> | SF-36, ADLs, GHQ-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 1976, Zigmund 1983, Layegh 2013, Kouris 2016, Beck 1961, Reilly 1993, Heelan 2015) |
| <b>Level of evidence 4</b> | DLQI, DQOLS, DSQL, 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)   |
| <b>Level of evidence 4</b> | OHIP is a validated generic oral patient-reported outcome measure. It has not been validated for use in MMP. (Slade 1994).  |
| <b>Level of evidence 4</b> | COMDQ is a validated oral patient-reported outcome measure for use in oral mucosal diseases. It has been validated for use in MMP. (Ní Riordáin 2011, Ní Riordáin 2016)   |
| <b>Level of evidence 4</b> | 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)   |

## Recommendations

The following patient-reported outcome measures may be considered for patients with MMP:

Generic - SF-36 , DLQI  
Oral - COMDQ , OHIP  
AIBD - ABQOL , TABQOL

**Grade of recommendation D**

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### 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.