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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

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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.
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Conflict of interest

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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] pemphigus[5] 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 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.

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).

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 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 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

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.[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

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.[27-29] 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-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.[32-35] 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]

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.[14,17,18,22,36-41] 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.[14,17,18,22,36-41,43-51] 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]

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

Laryngeal involvement in MMP 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 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]

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.[79]

Genital and urological involvement in MMP Involvement of the anogenital region can occur, either isolated or with other mucosal sites.[80-82] 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.[80,82,85-90] Distinguishing it from localized vulvar pemphigoid may also pose a challenge. Genital involvement in MMP can be drug-induced or paraneoplastic.[91-95] 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]

Skin involvement in MMP 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]

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.[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.[84,98,106-109]

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 pharyngo-laryngeal, oro-pharyngo-laryngeal and tracheal involvement.[73,79,110,111]

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.[98]

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 BP230.[105,112] Ahmed *et al.* reported that antibodies against the integrin α6 subunit are detected in 80-100% of oral MMP cases.[113-115] These antibodies appear to specifically bind to the extracellular domain of the integrin α6 subunit.[113] In contrast to oral MMP, almost all patients with ocular MMP showed autoantibodies directed against the integrin β4 subunit.[114,116,117] Autoantibodies against the integrin β4 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 β4 subunit, BP180, laminin 332 α3 subunit, γ2 subunit, β3 subunit and LAD-1 in 62.8%, 58%, 28%, 21%, 21% and 19% of cases, respectively. Furthermore, reactivity to the α6 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-α6β4 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.[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.[123-126] 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.[127-129] 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]

Associated factors and comorbidities

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.[63,84,134-140] 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]

Conclusions

Level of evidence 4	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,[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).[144-146] 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.[144,151-153] 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]

Conclusions

Level of evidence 4	MMPDAI is a disease-specific severity scoring tool. It has not been validated. (Murrell 2015)
Level of evidence 4	ABSIS has been proposed for use in MMP, but it is not disease-specific and has not been validated for use in MMP. (Pfütze 2007).
Level of evidence 4	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 4	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,[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.

Conclusions

Level of evidence 4	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)
Level of evidence 1	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.[157-163] 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]

Conclusions

Level of evidence 2	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.
Level of evidence 2	The Cicatrising 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 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 4	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 4	Nash 2017 described a symptomatology scale for laryngeal involvement. This method has not been validated.
Level of evidence 2	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, 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, Zigmond 1983, Layegh 2013, Kouris 2016, Beck 1961, Reilly 1993, Heelan 2015)
Level of evidence 4	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)
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	COMDQ is a validated oral patient-reported outcome measure for use in oral mucosal diseases. It has been validated for use in MMP. (Ní Ríordáin 2011, Ní Ríordáin 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)

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

Acknowledgements

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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.

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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 II

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Abstract

This guideline has been initiated by the task force *Autoimmune Blistering Diseases* of the European Academy of Dermatology and Venereology, including physicians from all relevant disciplines and patient organizations. It is a S3 consensus-based guideline that systematically reviewed the literature on mucous membrane pemphigoid (MMP) in the MEDLINE and EMBASE databases until June 2019, with no limitations on language. While the first part of this guideline addressed methodology, as well as epidemiology, terminology, aetiology, clinical presentation and outcome measures in MMP, the second part presents the diagnostics and management of MMP. MMP should be suspected in cases with predominant mucosal lesions. Direct immunofluorescence microscopy to detect tissue-bound IgG, IgA and/or complement C3, combined with serological testing for circulating autoantibodies are recommended. In most patients, serum

autoantibodies are present only in low levels and in variable proportions, depending on the clinical sites involved. Circulating autoantibodies are determined by indirect IF assays using tissue substrates, or ELISA using different recombinant forms of the target antigens or immunoblotting using different substrates. The major target antigen in MMP is type XVII collagen (BP180), although in 10–25% of patients laminin 332 is recognized. In 25–30% of MMP patients with anti-laminin 332 reactivity, malignancies have been associated. As first-line treatment of mild/moderate MMP, dapsone, methotrexate or tetracyclines and/or topical corticosteroids are recommended. For severe MMP, dapsone and oral or intravenous cyclophosphamide and/or oral corticosteroids are recommended as first-line regimens. Additional recommendations are given, tailored to treatment of single-site MMP such as oral, ocular, laryngeal, oesophageal and genital MMP, as well as the diagnosis of ocular MMP. Treatment recommendations are limited by the complete lack of high-quality randomized controlled trials.
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Conflict of interest

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Diagnostics

Diagnosis of mucous membrane pemphigoid (MMP) is based on clinical findings (see part I) together with detection of antibasement membrane zone (BMZ) autoantibodies. These autoantibodies are tissue-bound, detected by direct immunofluorescence (DIF) microscopy and/or direct immunoelectron microscopy, or circulating when detected either by indirect IF (IIF), ELISA or immunoblotting. Histopathology may be helpful in some cases when MMP, or another autoimmune blistering disease (AIBD), cannot be detected using these methods. About 50% of cases of ocular MMP cannot be confirmed by BMZ autoantibody detection tests. To exclude other cicatrizing conjunctival disorders with a similar disease course, this subset of ocular MMP cases requires an additional panel of investigations before a diagnosis of ocular MMP can be confirmed (see section on Diagnosis of ocular MMP).

Direct immunofluorescence microscopy

Direct immunofluorescence visualizes *in vivo* bound immunoreactants in skin or mucosa and shows linear deposition of IgG and/or IgA and complement C3 along the BMZ in MMP. DIF of a perilesional biopsy is considered the reference standard for diagnosis of MMP.[1] Sensitivities have been reported in a wide range, between 41 and 100%, depending on biopsy site. Mainly retrospective studies have been performed to assess the diagnostic accuracy of DIF, reporting high sensitivities when DIF is used as the reference standard for diagnosis, and lower sensitivities when clinical criteria have been used. Highest sensitivity has been found in MMP whereby both mucosa and skin were affected.[2] DIF biopsies of mucosa have been reported to have sensitivities between 41 and 100%,[2–7] and of skin between 44 and 100%.[2,3,6–11]

Conclusions

Level of evidence 2	DIF is the major diagnostic test, yielding the highest sensitivity for the diagnosis of MMP.

Recommendations

It is recommended that DIF be performed in all patients suspected of having MMP.

Grade of recommendation B

Immunoreactants can also be detected by DIF in non-affected asymptomatic sites.[9,10,12] A recent retrospective study in 251 oral MMP patients compared DIF performed on normal buccal

mucosa with a perilesional punch mucosal biopsy, and detected no significant difference between the two approaches in sensitivity for oral MMP (93.7% vs. 89.6%).[7] Immunoreactants can be detected in a skin biopsy by DIF of affected or non-affected skin (in 44–48%), and may confirm diagnosis of MMP.[2,9,11] A minimum biopsy size of 3–4 mm of skin, and for mucosa, is recommended.[9,13–15] Saline transportation can be used for skin or mucosal biopsies (within 24 h), but is not suitable for conjunctival biopsies.[16,17] Routine testing should be performed for IgG, IgA and complement C3.[2,4,11] IgM and fibrin depositions can also be found in conjunction with other immunoreactants, and as solitary findings in oral lichen planus.[2]

Recommendations

It is recommended that a 3-4 mm punch biopsy be taken for DIF. The biopsy should preferably be taken from perilesional mucosa or skin. If a biopsy of a perilesional location is too painful for the patient, or impractical for the clinician, it can also be obtained from normal mucosa or skin.

Grade of recommendation B

It is recommended to snap-freeze the biopsy, or to use isotonic saline solution (up to 24 hours) or Michel's medium (up to 72 hours) for transportation until processing.

Grade of recommendation C

Negativity of DIF may possibly depend on biopsy site or technical difficulties in cases of conjunctival biopsies, and multiple simultaneous and sequential biopsies may increase the diagnostic yield.[6] Similarly, IgG4 staining may increase the yield of DIF.[18] Positive DIF findings in MMP do not distinguish predominant cutaneous variants of pemphigoid, which should be determined on clinical grounds.[1,12]

Conclusions

Level of evidence 4	Initial negative DIF findings may be due to biopsy site, and/or to a lower amount of tissue-bound autoantibodies in MMP compared to other AIBD, or to technical difficulties in processing mucosal biopsies.

Recommendations

In case of initially negative DIF findings, it is recommended that a sequential biopsy from a different site be performed if clinical suspicion of MMP persists.

Grade of recommendation C

Serration pattern analysis allows for identification of tissue-bound antibodies against type VII collagen.[17,19,20] Serration pattern analysis is often not determinable in mucosal biopsies, but can be performed in biopsies taken from the skin.[17,19,20]

Conclusions

Level of evidence 3	Serration pattern analysis is helpful to identify tissue-bound antibodies against type VII collagen in skin, but often not in mucosal biopsies.

Recommendations

It is recommended that the serration pattern be determined in any skin biopsy for DIF.

Grade of recommendation C

Direct immunoelectron microscopy

Electron microscopy studies allow the analysis of BMZ, including hemidesmosomes, anchoring filaments and anchoring fibrils; these structures cannot be seen by light microscopy. Two techniques of electron microscopy are available: standard transmission electron microscopy and immunoelectron microscopy. Transmission electron microscopy enables precise identification of the level of blister formation, and of structural abnormalities of junction systems which lead to this cleavage. Direct immunoelectron microscopy, like DIF, allows detection of *in vivo* bound IgA, IgG, IgM and/or C3. While DIF gives only linear staining of the BMZ at the dermo-epidermal or chorio-epithelial junction, direct immunoelectron microscopy demonstrates more precise ultrastructural *in vivo* location of antibodies within the dermo-epidermal or chorio-epithelial junctions.

For immunoelectron microscopy, a biopsy must be obtained from clinically normal-appearing skin or mucous membrane adjacent to a lesion within 1–2 cm of the lesions. The minimal diameter size of the biopsy is 6 mm. The sample must be immersed immediately in the appropriate medium[21] and transported within one hour to the laboratory under proper conditions, as any delay will cause it to dry out and result in irreversible damage, making it unsuitable for analysis. Avoid anaesthesia with adrenalin, and taking biopsies of blistered skin, because this often results in artefacts or false-negative results. Details on the detection of binding sites of immune deposits are provided in the Appendix S1.

Conclusions

Level of evidence 4	Direct immunoelectron microscopy is a sensitive and specific assay for detection of tissue-bound IgG and IgA deposits at the dermal-epidermal and/or chorio-epithelial junction.
Level of evidence 4	Direct immunoelectron microscopy enables localization of autoantibodies within the different layers of the basement membrane zone, indirectly reflecting the target antigens, i.e., BP180, laminin 332, and type VII collagen.
Level of evidence 4	The use of direct immunoelectron microscopy is restricted to specialized centers, as the biopsy must be freshly processed and cannot be delivered by mail.

Recommendations

If available, direct immunoelectron microscopy may be recommended for detection of tissue-bound IgG and IgA, in addition to DIF for diagnosis of MMP.
Grade of recommendation C
In particular, direct immunoelectron microscopy may be recommended for precise localization of tissue-bound IgG and IgA in patients with a seronegative MMP.
Grade of recommendation C

Immunoserological tests

Indirect immunofluorescence on tissue substrates IIF detects circulating autoantibodies in the patient's sera through an isotype-specific fluorescent-labelled secondary antibody.[22] In case of MMP, positivity is defined by the detection of linear IgG or IgA along the BMZ of different tissue substrates.[23–30] Compared to bullous pemphigoid, IgG positivity by IIF in MMP occurs less frequently and usually with lower titres.[25,27,31,32] This may be due to the heterogeneity of the target antigens, or the lower amount of autoantibodies in MMP sera. IIF reactivity is largely accounted for by IgG class autoantibodies, but IgA autoantibodies can be detected in about 60% of MMP sera.[27,32,33] Combined IgA and IgG reactivity was associated with more severe disease, compared to the presence IgG autoantibodies alone[32,33] whereas other studies failed to reveal a similar relation.[29,34] One study has reported the presence of circulating anti-BMZ IgE in 24% of 29 MMP patients,[35] but this study awaits confirmation. The sensitivity of IIF depends on the substrate used. Circulating antibodies have been detected in a small percentage of patients on monkey oesophagus substrate, ranging from 2.6% to 8%.[28,29,36] Normal human skin had previously demonstrated higher values (17–35%).[25,31,37] In the salt-split skin technique, normal human or primate skin is incubated in 1 mol/L NaCl until splitting occurs within the lamina lucida of the BMZ.[38] This procedure showed positivity in a significantly greater proportion of MMP patients (36% to 84%).[23,25,27,29,32,39,40] IIF on normal human oral mucosa showed a sensitivity of 85% in a recent study[37], whereas in another study, the same substrate tested negative in all patients.[40] Further investigations are needed to clarify the diagnostic value of oral mucosa as substrate for IIF in MMP. Further details are given in the Appendix S1 and in Table S1.

Conclusions

Level of evidence 3	In MMP, the highest sensitivity of an IIF with a tissue substrate is observed with human/primate salt-split skin.
Level of evidence 3	IgA anti-BMZ reactivity can be found by IIF in about half of serum positive MMP sera on human/primate salt-split skin; IgG anti-BMZ reactivity is detectable in a greater proportion of patients.

Recommendations

It is recommended that IIF on human/primate salt-split skin be used to detect circulating autoantibodies.
Grade of recommendation C
It is recommended that IgG and IgA reactivity be tested by IIF on human/primate salt-split skin.
Grade of recommendation C

Target antigen-specific detection of autoantibodies The target antigens of MMP autoantibodies are components of the epidermal BMZ. Currently, five different target antigens have been identified at the molecular level: BP180 (type XVII collagen), BP230, all three laminin 332 subunits, both subunits of integrin α6β4 and type VII collagen.[1,41] A pathogenic role of MMP IgG autoantibodies against laminin 332 and α6β4 integrin has been described.[42–46] Different methods have been established that enable target antigen-specific detection of serum autoantibodies in MMP sera, including ELISA, immunoblotting, immunoprecipitation and indirect IF microscopy (detailed in the Appendix S1). Five assays (ELISA and IIF) applying four target antigens are highly standardized and widely available; they allow the detection of (i) IgG autoantibodies against the 16th non-collagenous domain of BP180 (NC16A), (ii) C- (and N-terminal) part(s) of BP230 and (iii) the laminin 332 heterotrimer. Other serological test systems are available only in specialized laboratories.

It is noteworthy that the reported sensitivities and specificities of these serological tests, discussed in more detail below, are mainly based on studies of selected and well-characterized patients. In addition, some studies have applied cut-off values for these serological tests in MMP that have been established in bullous pemphigoid, e.g. BP180 NC16A- and BP230-specific ELISA.

Detection of antibodies against BP180. BP180 (also termed type XVII collagen) is the most frequent target antigen in MMP and is recognized by approximately 70% of MMP sera.[14,25,27,29,31,33,34,39,47–58] Immunoblotting has been performed using various substrates, including extracts of human cultured keratinocytes from skin and oral mucosa, epidermis or amniotic membrane; keratinocyte hemidesmosome-rich fraction; enriched preparations of the soluble ectodomain of BP180 in medium of cultured keratinocytes (LAD-1); and various recombinant fragments. With these approaches, IgG autoantibodies to BP180 were found in 30–78% of MMP patients, while IgA were detected in 11–51% of MMP sera.[25,27,31,33,34,39,47–54,56,59] In a

cohort of non-scarring oral MMP cases, 75% showed antibodies against BP180.[54] A different cohort of oral MMP cases showed BP180 reactivity in 46% of the cases and found no significant differences in antibody recognition pattern in patients with restricted oral lesions and patients with also other affected sites.[34]

Several studies described the reactivity of MMP sera with the C-terminal portions of the molecule, whether or not combined with a reactivity to the NC16A portion immunodominant in bullous pemphigoid.[1,25,27,33,48,49,52,54,60,61] A large majority of bullous pemphigoid patients also showed reactivity with the C-terminal portion in addition to reactivity with the NC16A domain of BP180.[62] In addition, direct binding of BP180 to type IV collagen, and the capability of antibodies targeting the C-terminus of BP180 to hinder this binding in oral mucosa keratinocytes, has been recently reported.[59] Importantly, anti-BP180 autoAbs are not limited to the IgG isotype, and testing for IgA reactivity increased the detection rate.[25,27,52,61,63] The soluble ectodomain of BP180, originally described as target antigens of linear IgA disease, LAD-1 or a 97 kDa fragment of LAD-1, is recognized by a portion of MMP sera by immunoblotting.[27,33,51,56,60,64,65] Serum levels of autoantibodies to BP180 did not correlate with disease severity in MMP patients.[29,55,66] In line with this, while the pathogenic relevance of IgG antibodies against the NC16A domain is unclear, its murine homologue has been clearly demonstrated in several mouse models, resulting in predominant skin lesions[67–69]; no mouse model has been reported that mimics human MMP based on antibodies against a C-terminal stretch of BP180. However, the presence of autoantibodies recognizing different target antigens, or multiple BP180 epitopes, or belonging to IgG and IgA isotypes, has been observed in MMP patients with more severe clinical features.[33]

Conclusions

Level of evidence 3	BP180 is the major target antigen in MMP.
Level of evidence 3	Anti-BP180 IgG and/or IgA can be found in the majority of seropositive MMP sera.
Level of evidence 3	C-terminal epitopes on BP180 are frequently recognized

Recommendations

It is recommended that IgG antibodies against BP180 NC16A be looked for every patient with no reactivity, or epidermal IgG reactivity, by IIF on human/primate salt-split skin.

Grade of recommendation C

It is recommended that serum IgG and IgA reactivity be tested against BP180 by immunoblotting and/or ELISA.

Grade of recommendation D

Detection of antibodies against BP230 Autoreactivity against BP230 is detected occasionally in MMP sera, with a frequency ranging from 0% to 40%.[25,29,33,34,47–51,54,55,57,64–66,70–72] Anti-BP230 IgA are absent or less represented than IgG.[34,49] While injection of anti-BP230 antibodies in neonatal mice has resulted in skin lesions, the pathophysiological relevance of antibodies against BP230 in MMP has not yet been demonstrated.[73] In line with this, antibodies against BP230 have not been found to correlate with MMP severity.[29,55,66]

Conclusions

Level of evidence 4	BP230 is targeted by autoantibodies in a minority of MMP patients, usually in conjunction with autoantibodies against BP180 or laminin 332.

Recommendations

It may be considered to search routinely for antibodies against BP230.

Grade of recommendation C

Detection of antibodies against laminin 332 Laminin 332 is the second most frequent target antigen of autoantibodies in MMP.[74] Although IIF on salt-split human/primate skin is a sensitive serological test for detection of circulating autoantibodies in MMP, a portion of MMP sera reactive to laminin 332 are negative when tested by IIF; this emphasizes the relevance of using additional techniques for serological diagnosis.[25,39,55] Until very recently, detection of anti-laminin 332 antibodies was limited to specialized laboratories and performed using different inhouse assays, including immunoblotting, immunoprecipitation and ELISA. After comparison of different methods for the detection of anti-laminin 332 antibodies, immunoprecipitation with radiolabelled keratinocyte extracts was found to be the most sensitive technique, followed by immunoblotting with extracellular matrix of cultured human keratinocytes.[50,75,76] In unselected MMP patients, detection in tested sera of antibodies to laminin 332 by immunoblotting or immunoprecipitation ranged from 4% to 31%.[25,27,29,39,49,50] The α3 subunit of laminin 332 was the most frequently targeted chain, followed by the γ2 subunit,[29,56,71,75–80] and IgG4 was the most strongly represented subclass.[76,80,81] Also serum IgE and IgA were reactive with laminin 332 in small subsets of patients.[56,82]

Several ELISAs for detection of anti-laminin 332 IgG have been established.[55,70,76,81,83] When tested on laminin 332 positive sera from MMP patients, this approach showed high sensitivity but limited specificity, ranging from 75% to 94% and from 60% to 98%, respectively.[70,76,83] In a large group of unselected MMP patients, Bernard and coworkers detected laminin 332 antibodies in 20% of sera, with a specificity of 91% (3/32 of healthy controls).[55] Further, a sensitive (100%, $n = 16$) and specific assay (96.9%, $n = 127$), based on detection by IIF of IgG binding to laminin 332 secreted by human keratinocytes, named the keratinocyte footprint assay, has been reported.[84] Moreover, a sensitive and specific assay based on IIF on HEK293 cells expressing

the laminin 332 heterotrimer on the cell surface (biochip mosaic), has recently been developed. When a large cohort of 93 laminin 332 positive MMP patients was assayed, a sensitivity of 84% and specificity of 99.6% were obtained.[80] This assay is highly standardized and widely available.

Another elegant but non-routine method for the detection of anti-laminin 332 serum antibodies is indirect IF microscopy on the skin of patients with inherited junctional epidermolysis bullosa deficient of laminin 332.[85] However, this method requires reactivity on human/primate skin, and the absence of reactivity with any other BMZ antigen. Furthermore, the availability of laminin 332-deficient skin is limited.

Conclusions

Level of evidence 3	Laminin 332 is the second most frequent target antigen in MMP.
Level of evidence 3	Different assays for the detection of serum antibodies against laminin 332 have been established in specialized laboratories. At present, the indirect IF-based biochip mosaic, with recombinant laminin 332 expressed on the cell surface, is the only assay that is highly standardized and available.
Level of evidence 3	Serum levels of anti-laminin 332 IgG were shown to correlate with disease activity.

Recommendations

It is recommended that patients with MMP be tested for anti-laminin 332 reactivity when indirect IF on salt-split human/primate skin reveals dermal binding, or is negative.

Grade of recommendation B

Detection of antibodies against α6β4 integrin Reactivity of MMP sera with α6β4 integrin was originally described by Ahmed's group.[86] By employing immunoblotting and immunoprecipitation with α6β4 integrin-rich tumour cell lysates (e.g. DU145 prostate cancer cells) and different tissue lysates (bovine and human epidermis, gingiva, conjunctiva), they showed that sera of patients with different clinical phenotypes react specifically with one of the two subunits of the integrin.[87–89] They reported that ocular MMP sera, and MMP sera from patients with at least two involved mucosal sites, recognized the β4 integrin subunit, while oral MMP sera reacted with the α6 integrin subunit.[87,88,90] In addition, anti-β4 and anti-α6 IgG serum levels correlated with disease activity and response to therapy.[66,91,92] A limited number of studies from different laboratories have confirmed the results obtained by Ahmed's group, while other authors failed to detect any α6β4 integrin reactivity in MMP patient sera.[14,54,57] Oyama and coworkers reported that 26 of 124 (21%) of MMP patient sera recognized the β4 integrin subunit; they used immunoblotting on placental amnion proteins, of which 23/26 (88%) had ocular involvement, suggesting that the β4 integrin might be a site-specific antigenic determinant in MMP with ocular involvement.[33] More recently, analysis of 43 ocular MMP sera by immunoblotting on hemidesmosome-rich fraction showed IgG reactivity to the cytoplasmic domain of β4 integrin in 42% of sera and to the α6 ectodomain in 19%.[56]

Conclusions

Level of evidence 4	Serum antibodies against α6β4 integrin have been detected in a variable proportion of MMP patients in specialized laboratories using in-house assays, and may be site-specific antigenic determinants in MMP with oral (α6 subunit) or ocular (β4 subunit) involvement. Data on their frequency and site-specific associations remain uncertain. Additional confirmative studies by independent laboratories are needed.

Recommendations

No recommendation on the detection of antibodies against α6β4 integrin can be made based on the current data.

Grade of recommendation D

Detection of antibodies against type VII collagen Type VII collagen (Col7) is the major component of anchoring fibrils and the autoantigen of epidermolysis bullosa acquisita (EBA). The serological diagnosis of EBA has previously been discussed in detail in a consensus paper by a group of international experts.[93] Reactivity with Col7 in MMP is rare and may account for fewer than 5% of cases.[29,94] Several assays for the serological detection of anti-Col7 antibodies have been described, including (i) several ELISA systems that apply recombinant forms of Col7; (ii) immunoblotting of recombinant or forms of Col7; (iii) immunoblotting of cell-derived forms of Col7, e.g. in human dermis or an amnion epithelial cell line; (iv) an IIF-based test which uses a human cell line that expresses the recombinant NC1 domain on the cell surface; and (v) indirect IF on Col7-deficient skin.[93] Two of these assays are highly standardized and widely available: an ELISA that employs the recombinant NC1 domain (sensitivity and specificity for EBA, 92.9% and 100%), and an indirect IF-based biochip mosaic, where recombinant NC1 domain is present on the cell surface (sensitivity and specificity for EBA, 87.5% and 100%).[95–99]

Conclusions

Level of evidence 3	Type VII collagen is a rare target antigen in MMP, comprising <5% of cases.
Level of evidence 3	Two test systems for the detection of serum IgG against type VII collagen, an ELISA and an indirect IF-based assay, are highly standardized and widely available.

Recommendations

It is recommended that patients with MMP be tested for anti-type VII collagen reactivity when indirect IF on salt-split human/primate skin reveals dermal binding, or is negative.

Grade of recommendation B

Further details about the detection of autoantibodies against the individual target antigens are provided in the Appendix S1.

Histopathology

Histopathology is less sensitive and specific in diagnosing MMP compared to DIF, and in a recent study reached a sensitivity of 69.4% in 134 patients.[7] Its main role in MMP is to rule out other diseases, e.g. lichen planus, infectious diseases, pemphigus vulgaris and erythema multiforme. The characteristic histopathological picture shows subepithelial splitting, with a non-specific mixed infiltrate consisting of lymphocytes, histiocytes, plasma cells, neutrophils and eosinophils.[7,100–111] However, less eosinophilic granulocytes than in bullous pemphigoid have been observed.[108] Epithelial changes reminiscent of lichen planus with acanthosis, hypergranulosis, as well as vacuolar degeneration with fibrosis and a band-like infiltrate have also been described.[112] However, in many cases, only a non-specific ulcerative inflammation can be seen, with granulation tissue and scarring. In these cases, one cannot differentiate between MMP and aforementioned differential diagnoses. Scarring is commonly seen in late or recurrent lesions. Conjunctival biopsies often lack a subepithelial split, and instead show epithelial metaplasia, a reduced number of goblet cells, fibrosis and a non-specific chronic infiltrate.[15,100,113,114]

Conclusions

Level of evidence 5	A lesional biopsy for histopathology can be useful to differentiate MMP from pemphigus
Level of evidence 5	Histopathology does not differentiate MMP from other pemphigoid disorders, or MMP subgroups from each other.
Level of evidence 5	When MMP is excluded, a lesional biopsy for histopathology can be useful to consider differential diagnoses.

Recommendations

It is recommended to completely include a small intact blister in the biopsy specimen.
If this is not possible, it is recommended to take the biopsy in such a way that it also contains a small amount of perilesional skin (approximately ¼ of the biopsy) to prevent the blister roof from floating off during processing.

Grade of recommendation B

For an oral, pharyngeal, laryngeal, esophageal or genital biopsy, it is recommended to biopsy mucosa directly adjacent to an erosion.

Grade of recommendation B

It is not recommended to biopsy an erosion.

Grade of recommendation B

A standardized 4% formaldehyde (10% formalin) solution is recommended for storage and transport.

Grade of recommendation B

Diagnosis of ocular MMP

Up to 50% of ocular MMP cases do not meet the immunopathological criteria recommended in the 2002 Consensus for a diagnosis of MMP.[1] Because the current standard of care for the causes of cicatrizing conjunctivitis other than MMP is topical therapy, and not the systemic immunomodulatory therapy required for ocular MMP,[36,115,116] implementation of the Consensus guideline has resulted either in delayed diagnosis in individual patients with ocular MMP, or a diagnosis of a non-MMP severe chronic cicatrizing conjunctivitis.[10,117,118] In both situations, inappropriate treatment with topical therapy has resulted in poor outcomes for individual patients. The background to the opposing recommendations regarding the definition and diagnosis of ocular MMP is described in two recent case series, in which 26/55 (47.3%)[117] and 20/73 (27.4%) patients[10] with ocular MMP did not meet current immunopathological criteria for diagnosis, but in whom the clinical phenotype, disease severity and disease course were identical to that in immunopathology positive ocular MMP cases.

The subset of ocular MMP cases with undetectable autoantibodies requires an additional panel of investigations before a diagnosis of ocular MMP can be confirmed, to exclude other cicatrizing conjunctival disorders with a similar disease course. These investigations include both conventional histopathology and a careful clinical history, and systemic examination outlined below.[10,117–121]

1 DIF on the conjunctiva and/or tissue from other sites. Patients with DIF showing IgG, IgA, and/or C3, either in the conjunctiva or from another site, meet the currently widely adopted 2002 Consensus criteria. Biopsy of normal skin or oral mucosa may be positive when a conjunctival biopsy is DIF negative in ocular MMP.[117]
   a Where possible, bulbar conjunctival biopsies should be taken from uninflamed conjunctiva because of the reduced sensitivity in inflamed conjunctiva.[9,122] When they are taken from inflamed conjunctiva, this should be recorded.
   b Biopsies should be taken from another non-lesional site if the conjunctiva is inflamed, and because multiple biopsies improve the detection of a positive DIF.[6] Non-lesional skin gives results similar to those of uninflamed

conjunctiva,[9] and buccal mucosal DIF may also be positive when the conjunctival is negative. More data are needed regarding the numbers of biopsies that are optimal to provide good DIF sensitivity.

c Conjunctival DIF should also include staining for fibrinogen to identify lichen planus, which shows shaggy discontinuous fibrinogen deposits at the BMZ.[1]

2 Routine conjunctival histopathology is needed to exclude sarcoid and ocular surface tumours, both of which may present with inflammation and scarring. Ocular surface tumours are usually, but not always, unilateral.

3 Serology tests: Patients with positive IIF, or the presence of antibodies to epithelial BMZ proteins, can be diagnosed as having ocular MMP providing the clinical features are consistent. These tests are generally less often positive than DIF[1], and it is important to be aware that a variable proportion of age- and sex-matched healthy controls have positive serology findings (see Table S1).

4 When both DIF and serology are negative, and the other diseases that may cause cicatricial conjunctivitis have been excluded, this immunopathology negative subset of patients can be diagnosed as having ocular MMP. However, if the disease course or response to therapy is not as expected, all tests should be repeated.

Conclusions

Level of evidence 3	Ideally, bulbar conjunctival biopsies are taken from uninflamed conjunctiva, where possible, because of the reduced sensitivity in inflamed conjunctiva.
Level of evidence 3	Non-lesional skin gives similar results to uninflamed conjunctiva, and buccal mucosal DIF may also be positive when the conjunctival is negative.
Level of evidence 3	Ocular surface tumors are usually, but not always, unilateral.

Recommendations

In ocular MMP, it is recommended that the following investigations be performed:
DIF of non-inflamed conjunctiva and buccal mucosal biopsies; histopathology of a lesional (inflamed and thickened, but not ulcerated) conjunctival biopsy; and serology.
When DIF biopsies are taken from inflamed conjunctiva this should be recorded.

Grade of recommendation D

Conjunctival DIF should also include staining for fibrinogen, as shaggy discontinuous deposits at the BMZ are suggestive of lichen planus.

Grade of recommendation D

If uninflamed conjunctiva is not available for biopsy it is recommended to proceed with a biopsy as outlined in the section on ***DIF***.

Grade of recommendation C

If the initial DIF is negative it is recommended to proceed with a biopsy as outlined in the section on ***DIF***.

Grade of recommendation D

Routine conjunctival histopathology is recommended to exclude sarcoid and ocular surface tumors, both of which may present with inflammation and scarring.

Grade of recommendation D

It is recommended that subjects with circulating antibodies to epithelial BMZ proteins be diagnosed as having ocular MMP, providing the clinical features are consistent. Serological tests are generally less often positive than DIF.

Grade of recommendation D

Algorithm for the diagnosis of MMP

The recommended algorithm for the diagnosis of MMP is shown in Fig. 1.

Differential diagnoses of MMP

When repeated DIF and serology are negative, the diagnosis of MMP cannot be made, with the exception of individual cases of ocular MMP. In these rare cases, differential diagnoses need to be considered by an experienced ophthalmologist.

If multiple sites are involved, in particular the eyes, only few differential diagnoses remain, including pemphigus vulgaris (intraepithelial splitting by histopathology, antibodies against desmoglein 3, intercellular binding of autoantibodies in the epithelium by DIF), erythema multiforme, Steven Johnson syndrome and toxic epidermal necrolysis.

In single-site MMP, the following differential diagnoses may be addressed:

Oral MMP: Herpes simplex virus infection, *Candida* infection, lichen planus, aphthous stomatitis, systemic lupus erythematosus, erythema multiforme, Steven Johnson syndrome, toxic epidermal necrolysis, leukoplakia, Crohn's disease, malnutrition, radiation mucositis and chemotherapy-induced mucositis.

Ocular MMP: Rosacea, viral and bacterial infections, atopic keratoconjunctivitis, trauma, malignant tumours, Sjögren's syndrome, systemic lupus erythematosus, sarcoidosis.

Genital MMP: Lichen sclerosus et atrophicus, erosive lichen planus, pemphigus and sexual abuse.

Laryngeal MMP: Pemphigus, epidermolysis bullosa and malignancy.

Conclusions

Level of evidence 3	In case MMP cannot be diagnosed according to the diagnostic algorithm for MMP, a number of differential diagnoses need to be addressed.

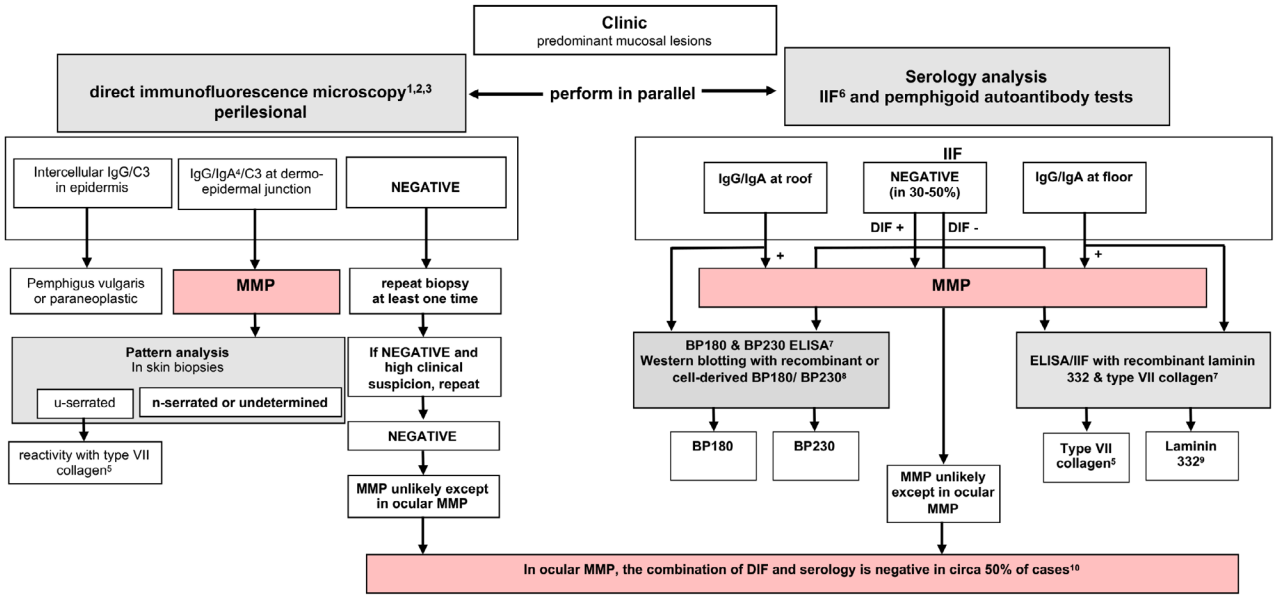

Figure 1 Diagnostic algorithm and work-up, and diagnostic criteria for mucous membrane pemphigoid. [1]Alternatively or in addition, direct immunoelectron microcopy can be performed. [2]A positive DIF from any site is diagnostic for MMP, providing the clinical phenotype at the site that has not been biopsied is consistent with MMP. [3]If ocular MMP is suspected, take biopsies from the least inflamed bulbar conjunctiva of both eyes together with another site (buccal mucosa or skin). Also take an additional lesional biopsy for routine histopathology to exclude both ocular surface neoplasia and sarcoid (which may present in the conjunctiva). [4]Patients with predominant or exclusive IgA deposition could also be classified as having linear IgA disease. [5]Patients with reactivity with type VII collagen could also be classified as having Epidermolysis Bullosa Acquisita. [6]On human/primate salt-split skin. [7]Commercially available (for IgG antibodies). [8]Only available in specialized diagnostic centers. [9]Associated with a malignancy in 25–30% of patients; a tumor search is indicated. [10]A diagnosis of immunopathology unconfirmed ocular monosite MMP can be made by exclusion of the more than 25 other causes of cicatrising conjunctivitis (CC). MMP is the most common cause of CC in most developed countries. Causes of CC, except for sarcoid & surface neoplasia: (i) have a history consistent with another cause of conjunctival disease; (ii) are positive on routine histopathology for neoplasia or sarcoid; or (iii) are DIF+ for another immuno-bullous disease. If, after initiating appropriate therapy for immunopathology negative ocular monosite MMP, the disease course or response to therapy is not as expected, then this algorithm (both for DIF in ocular cases and serology) should be repeated and alternative diagnoses considered (e.g., severe ocular rosacea which can be difficult to differentiate from ocular MMP. DIF, direct immunofluorescence microscopy; ELISA, enzyme-linked immuno sorbent assay; IIF, indirect immunofluorescence microscopy; MMP, mucous membrane pemphigoid.

Recommendations

In case MMP cannot be diagnosed according to the diagnostic algorithm for MMP, it is recommended that the following interventions be performed to address major differential diagnoses:

- detection of serum autoantibodies against desmoglein (for pemphigus vulgaris)
- review of lesional biopsy (for toxic epidermal necrolysis, lichen planus, etc.)
- swabbing for *Herpes simplex* virus infection
- swabbing for *Candida* infection

Grade of recommendation D

Management

Aim of therapy and multidisciplinary care

The aim of treatment is to stop the inflammation, and hereby the progression of scarring, especially of conjunctivae, larynx, oesophagus and genital mucous membranes. Surgical release of scarring and strictures is indicated only after the inflammatory phase of MMP has been fully controlled for several months.

Management of MMP requires a multidisciplinary team, involving specialists from dermatology, ophthalmology, otorhinolaryngology, gastroenterology and gynaecology/urology. Systemic treatment is ideally co-ordinated by a specialist, collaborating with the clinicians treating the complications of disease at other sites of involvement. In centres focusing on the management of MMP, often an established multidisciplinary team (dermatologist, ophthalmologist, stomatologist, otorhinolaryngology, etc.) is involved in the diagnostics and follow-up of the patients, including management of complications, and depending on the affected sites.

Mild MMP (moderate) and severe MMP are defined according to Chan *et al.*: patients with mild MMP have disease occurring only in oral mucosa, or in oral mucosa and skin. Patients

with severe MMP have disease occurring in any of the following sites: ocular, genital, nasopharyngeal, oesophageal and/or laryngeal mucosae.[1]

Conclusion

Level of evidence 5	The aim of treatment in MMP is to stop inflammation, and hereby stop progression of scarring, especially of eyes, larynx, esophagus, and genital mucous membranes.

Recommendations

It is recommended that newly diagnosed MMP patients be screened by an ophthalmologist, an oral medicine specialist or an experienced dermatologists and an otorhinolaryngologist at baseline, and during follow-up in case of clinical symptoms.

Grade of recommendation D

Topical medications

Oral MMP Topical therapies available for use in oral MMP include a broad range of corticosteroids, or the calcineurin inhibitor tacrolimus. There are no randomized placebo-controlled trials to support efficacy of topical therapies in MMP. Evidence is based largely upon small case series or RCTs conducted to study mixed oral vesiculoerosive disease. Nevertheless, the findings of these studies are frequently used in clinical practice.

Topical corticosteroid therapy was advocated in the First Consensus statement on MMP[1] for mild to moderate MMP as a first-line approach, and more recently, the available evidence was evaluated in a systematic review.[123] This therapy is often used in clinical practice for mild or moderate disease oral MMP as first-line therapy, and in more severe disease, it is used in addition to systemic therapy for patients with multisite or single-site disease. Topical steroids, particularly the superpotent clobetasol propionate, can lead to remission.[124,125] The latter corticosteroid is the most frequently used topical ointment, while betamethasone sodium phosphate tablets 0.5mg may be diluted in water and used for rinsing for 2–3 min before discarding, between one and four times per day. Fluticasone propionate 400 micrograms (1 mg/mL) may also be used twice daily as a mouthwash. Corticosteroid metered-dosed inhalers may be sprayed directly onto active lesions. The frequency of use is tailored to the severity of the disease, with one application ideally before sleep, as saliva flow is reduced overnight and the length of contact is therefore optimized; applications can be tapered as lesions improve.

For gingival lesions, use of a custom-made, soft drug-delivery tray covering the gingivae to extend drug contact time and absorption, has been described.[126] This is a method sometimes used in routine clinical practice, though no study has compared its efficacy with other methods of application. Adjuvant analgesic, anti-inflammatory and anti-infectious therapy can be additionally used, e.g. chlorhexidine 0.12–0.20%.

There are case reports demonstrating efficacy of topical tacrolimus in localized oral MMP, and reporting complete remission within 2–3 months. However, the cost is greater, and tolerance may be lower due to oral burning upon application.[127–129] No good evidence supports the use of topical cyclosporine for oral MMP. Further details on the topical treatment of oral MMP are provided in the Appendix S1.

Conclusions

Level of evidence 4	Evidence for use of topical therapy in MMP is limited to small case series or RCTs conducted in mixed oral vesiculoerosive diseases. Evidence supports the use of topical corticosteroids for MMP.

Recommendations

Topical corticosteroids can be recommended as first-line therapy in mild/moderate MMP, and as adjunctive therapy in moderate to severe oral MMP.

Grade of recommendation D

Ocular MMP Historical evidence suggests that topical therapy does not alter the natural history of the disease, and offers only variable symptomatic relief.[130–133] But in patients intolerant to immunosuppression, or where it is not safe to administer immunosuppression, then topical steroids, combined with systemic matrix-metallo proteinase inhibitors (tetracyclines), are a useful alternative for treating mild disease. Subconjunctival steroids, such as triamcinolone, may provide temporary benefit, but relapses may occur, together with complications such as cataract, glaucoma or localized scleral thinning. Topical tacrolimus and ciclosporin have been used in isolated cases with limited response.[134–137] Topical treatment in the form of lubricant drops, gels and ointments should be used to reduce trauma. These lubricants should preferably be free of preservatives to avoid iatrogenic toxicity. Serum eye drops may be used as alternative, or in addition, to provide nutrients to severely dry ocular surfaces.

Conclusions

Level of evidence 4	Topical therapies may offer symptom relief, but do not influence immune-mediated disease course.
Level of evidence 4	Subconjunctival corticosteroids, such as triamcinolone, may provide temporary benefit, but relapses may occur, together with complications such as cataract, glaucoma, or localized scleral thinning. Topical tacrolimus and ciclosporin have been used in isolated cases with limited response.

Recommendations

Use of topical steroids may be recommended as an ancillary short-term treatment for ocular involvement. Topical cyclosporine may be considered as an adjunct. Other topical treatments in the form of lubricants are recommended to reduce trauma. Serum eye drops can substitute the nutrient effect of tears in severe dry eye.

Grade of recommendation C

In cases of intolerance of immunosuppressive drugs, topical therapies combined with systemic tetracyclines may be recommended as a useful alternative for mildly inflamed ocular disease.

Grade of recommendation D

Genital MMP Only case reports on genital MMP have been presented in the literature. Topical corticosteroids, particularly clobetasol propionate, can lead to remission in juvenile MMP.[138,139] Topical tacrolimus was reported to be effective as monotherapy in one case report of juvenile MMP.[140] In two case reports, topical corticosteroids were ineffective in controlling the progression of juvenile MMP, and dapsone was added.[141,142] Farrell *et al*. reported remission of three patients with juvenile genital MMP treated with topical clobetasol propionate cream and tetracycline combined cream. Two patients required systemic corticosteroids, sulphones, azathioprine and dapsone.[143] Topical therapy in adult MMP is often not sufficient to achieve remission of genital lesions.[144,145]

Recommendations

In mild/moderate genital MMP, high-potency topical corticosteroids alone may be considered as first-line therapy.

Grade of recommendation C

Systemic medications

Disease control has previously been defined as the point at which new inflammatory lesions cease to form and established lesions begin to heal.[146] Immunosuppressive agents need to be chosen with a 'stepladder' approach, beginning with drugs that have the fewest side effects.

Recommendations

It is recommended that patients be defined as refractory when no disease control has been achieved after 12 weeks of adequately administered therapy.

Grade of recommendation D

Tetracyclines Tetracyclines are generally used as antibiotics due to their efficacy in controlling bacterial proliferation and growth. In addition to these effects, tetracyclines have been shown to have also anti-inflammatory and collagenolytic properties. In light of their anti-inflammatory action, tetracycline has been proposed as first-line agent in mild/moderate MMP, also due to its better side-effect profile as compared to corticosteroids and other conventional immunosuppressive agents.[147,148] Most patients included in the studies taken into consideration have been switched to tetracyclines due to adverse effects with previous treatments. On the other hand, minocycline has been stopped in five out of nine patients included in a case series of predominantly oral MMP due to its side effects, mainly vertigo and gastric upset.[149] In this case series with a follow-up of 2 years, only one patient achieved persistent remission with no relapse.

Conclusion(s)

Level of evidence 4	Tetracyclines, in particular tetracycline (possibly associated with oral nicotinamide), may be effective in the treatment of mild/moderate MMP, with less side effects compared with corticosteroids.

Recommendations

Tetracyclines, i.e tetracycline 1,500 mg/day, may be considered as a first-line treatment in mild/moderate MMP. In refractory cases, oral corticosteroids, mycophenolate or azathioprine may be added.

Grade of recommendation C

Dapsone Dapsone, a well-known anti-leprosy drug, is effective in several dermatologic diseases due to its anti-inflammatory properties. The corticosteroid-sparing effect of dapsone could be explained by several mechanisms, including oxygen-radical scavenging, reduction in tumour necrosis factor (TNF)-α and dysregulation of lymphocyte function. Dapsone is used to treat both mild/moderate and severe cases of different autoimmune bullous diseases, usually in association with corticosteroids. Prior to initiation of therapy, the patient's glucose-6-phosphate dehydrogenase (G6PD) level should be checked to be normal, since low levels are associated with a higher incidence of haemolytic anaemia.

Due to its anti-inflammatory properties, dapsone is regarded as a first-choice treatment for mild/moderate MMP. In a cross-sectional retrospective review, seven out of 20 patients with oral MMP were maintained successfully on dapsone 50–150 mg/day.[150] However, possible side effects caused by dapsone: haemolytic anaemia, skin rash, malaise and gastrointestinal problems, have led to high discontinuation rates in different trials.[151–154]

Conclusions

Level of evidence 4	Dapsone may lead to disease control in mild/moderate MMP. However, adverse effects are quite common. Confirmation of the G6PD status prior to dapsone initiation is necessary.

Recommendations

Dapsone, at a dosage of 1-1.5 mg/kg/day, alone or in combination with topical corticosteroids, may be recommended as first-line treatment for mild/moderate MMP. Careful monitoring of possible onset of side effects is required.

Grade of recommendation C

In refractory cases, oral corticosteroids, mycophenolate mofetil, or azathioprine may be added.

Grade of recommendation C

In severe MMP, dapsone in combination with oral corticosteroids or cyclophosphamide may be considered as a first-line treatment.

Grade of recommendation C

In refractory cases, rituximab (first step), intravenous immunoglobulins (second step), or a TNF-alpha inhibitor (third step) can be added.

Grade of recommendation C

Mycophenolate mofetil Mycophenolate mofetil (MMF) is a prodrug of mycophenolic acid and inhibits the *de novo* pathway of guanosine nucleotide synthesis. T- and B-lymphocytes are critically dependent on this pathway for their proliferation, but the potent cytostatic effects of MMF inhibit proliferative responses of T- and B-lymphocytes to both mitogenic and allospecific stimulation. Mycophenolic acid also suppresses antibody formation by B-lymphocytes. The use of MMF for the treatment of mild/moderate or severe MMP has been investigated in few clinical trials.[153,155–157] Its efficacy in controlling inflammatory lesions and its safety, either in monotherapy or in association with corticosteroids, have been confirmed in all these studies.

Conclusions

Level of evidence 4	MMF is an effective agent for treatment of mild/moderate MMP, with minimal side effects. However, the drug cannot always prevent disease progression in severe refractory cases.

Recommendations

MMF, at a dosage of 2 g/day, alone or in combination with topical/oral corticosteroids, tetracycline or dapsone, may be recommended as second-line therapy in patients with mild/moderate MMP.

Grade of recommendation C

Cyclophosphamide Cyclophosphamide is an oxazaphosphorine-substituted nitrogen mustard alkylating agent, with powerful cytotoxic and immunosuppressive effects. It is used to treat haematological and solid cancers as well as autoimmune diseases, including refractory and/or severe autoimmune bullous diseases. Main side effects of cyclophosphamide are haemorrhagic cystitis, infertility and bladder cancer.

Different clinical studies on cyclophosphamide, administered orally or intravenously, demonstrated its effectiveness in severe MMP,[158–163] and it has been shown to be effective for many years.[164] Both oral and intravenous pulsed cyclophosphamide showed a high rate of efficacy, preventing relapses in ocular MMP and allowing to taper corticosteroids. It induced sustained clinical remission both as monotherapy[160] and in combination with corticosteroids[158,161,163] or pentoxyfilline.[163]

Conclusions

Level of evidence 4	Patients with severe MMP, particularly with ocular presentation, have rapidly benefited from cyclophosphamide, also experiencing prolonged remissions. Early initiation of therapy could decrease the risk of relapses.

Recommendations

Cyclophosphamide, administered either orally at an initial dosage of 2 mg/kg/day or intravenously at a pulsed dosage of 500 mg monthly, may be recommended as first-line treatment in severe MMP, either alone or in combination with oral corticosteroids or dapsone.

Pentoxyfylline may be added to the treatment with cyclophosphamide plus corticosteroids in patients with severe MMP.

Grade of recommendation C

Corticosteroids Systemic corticosteroids are widely used for their excellent anti-inflammatory and immunosuppressive effects. A wide range of dermatoses, including autoimmune bullous diseases, are successfully treated with systemic steroids. However, the chronic courses of treatment required favour the onset of side effects, such as osteoporosis, adrenal suppression, hyperglycaemia, dyslipidaemia, cardiovascular disease, Cushing's syndrome and psychiatric disturbances. Steroids may be administered orally, intravenously or through intramuscular injections.

Although systemic corticosteroids (initial oral prednisone 0.5–1.5 mg/kg/day) are effective in achieving rapid control in cases of acute, severe disease, the adverse effects associated with long-term use limit their value. Systemic corticosteroids are usually associated in combination with MMF as second-line treatment in mild/moderate MMP[153,157] and in combination with cyclophosphamide in severe MMP.[162,163] The use of systemic corticosteroids has also been investigated in combination with rituximab.[165] Studies focusing on systemic corticosteroids in monotherapy have not been found, but in clinical practice, they are widely used, even at high dosages, for controlling flare-ups.

Conclusions

Level of evidence 4	Corticosteroids are useful adjuvant agents in both mild/moderate and severe cases. Their side effects limit a prolonged use.

Recommendations

Oral corticosteroids, i.e., prednisone at an initial dosage of 0.5-1 mg/kg/day tapering over the next 8-12 weeks, may be considered in combination with a corticosteroid-sparing immunosuppressive agent.

Grade of recommendation C

Methotrexate Methotrexate is an antifolic and antimetabolic drug widely used for autoimmune and haematological diseases. It is used in dermatology as a steroid-sparing immunomodulating agent. Its mechanism of action is based on its interference with DNA synthesis and replication, as well as the inhibition of rapidly dividing cells.

McCluskey *et al.* reported that an approximately 15-month course of methotrexate therapy led to complete control and/or suppression of conjunctival inflammation in 10 out of 12 (83%) patients with ocular MMP.[166] Moreover, only 24% of patients developed side effects requiring cessation of methotrexate therapy, and these were reversible. In a retrospective, non-controlled, case series study involving 11 patients with severe ocular MMP, Shi *et al.* demonstrated that low-dose methotrexate improved visual acuity in three patients.[167]

Conclusions

Level of evidence 4	Methotrexate monotherapy may be considered as first-line systemic treatment of ocular MMP.

Recommendations

Methotrexate, at an initial dosage of 7-15 mg/week, alone or in combination with topical corticosteroids, may be considered as first-line treatment in patients with mild/moderate MMP. In refractory cases, oral corticosteroids may be added.

Grade of recommendation C

Azathioprine Azathioprine is a synthetic purine analog derived from 6-mercaptopurine, which is thought to act by disrupting nucleic acid synthesis, and has recently been found to interfere with T-cell activation. Albeit originally developed for its anticancer properties, azathioprine is nowadays more widely used for its immunosuppressant properties. One of the most recognized uses of azathioprine in dermatology is as treatment for autoimmune bullous disorders, including MMP.

Azathioprine showed a low success rate as compared to methotrexate and dapsone, and its discontinuation due to adverse effects (gastrointestinal, headache, malaise, dizziness, elevated liver function tests and myelosuppression) was higher than in patients treated with other immunosuppressants. In fact, successful treatment was achieved in 43% and 47% of MMP patients treated with azathioprine by Pasadhika *et al.* and Saw *et al.*, respectively.[153,168] In MMP with ocular involvement, an evaluation of 115 patients on a variety of therapies found that azathioprine had a success rate (no conjunctival inflammation) of 38/80 (47%) and qualified success (partial inflammation control) in 19/80 (24%), with failure in 23/80 (29%). However, the side-effect profile was poor, resulting in discontinuations in 24/60 (40%). For the latter reason, mycophenolate was recommended for use in this study, instead of azathioprine (except as a second-line agent for patients not tolerating mycophenolate), because of the higher success rate in 27/46 (59%) and improved tolerance, resulting in discontinuations of 15% (5/34).[153]

Conclusions

Level of evidence 4	Successful treatment of MMP was achieved in around 50% of MMP patients treated with azathioprine, but with a poorer side effect profile than the other drugs used in this study (dapsone, sulfapyridine, mycophenolate and cyclophosphamide).

Recommendations

Azathioprine, at an initial dosage of 1.5-2 mg/kg/day, in combination with topical corticosteroids, tetracyclines or dapsone, may be considered as a second-line therapy in mild/moderate MMP.

Grade of recommendation C

Rituximab Rituximab is a chimeric monoclonal antibody directed against CD20, which is a cell surface marker expressed by B cells. Recently licensed for moderate/severe pemphigus,[169] it has a long record in refractory autoimmune blistering diseases, including MMP.[170–172] Le-Roux-Villet *et al.* found that 17 out of the 25 patients with severe refractory MMP included in their study showed a complete response after one cycle, and five additional patients after a second cycle, yielding a 88% response rate. Three patients (all receiving concomitant high-dose immunosuppressants) developed severe infectious complications.[173] In this study, immunosuppressant regimens were discontinued at the initiation of rituximab and 88% of patients were continued on maintenance dapsone or sulfasalazine. You *et al.* found that 46 eyes (77.0%) in 26 MMP patients treated with rituximab alone, or in combination with other immunomodulatory treatments, achieved clinical remission, with an average sustained remission time of 24.5 months.[174]

Maley *et al.* studied 24 patients treated with rituximab added to conventional immunosuppression, and 25 treated only with conventional immunosuppression. They found that 100% of patients in the rituximab group achieved disease control compared with 40% in the conventional group ($P < 0.01$), with a mean time to disease control of 10.17 and 37.7 months ($P = 0.02$).[165] Recently, Lamberts *et al.* observed in a cohort of 14 MMP patients treated with rituximab 1 g at day 1 and at day 14, disease control in 85.7%, partial response in 64.3%, and complete response in 28.6% patients, with a relapse rate of 75%

during follow-up.[175] Since 2018, an open-label, phase 3 clinical trial comparing the safety and effectiveness of RTX vs oral cyclophosphamide is ongoing (NCT: 03295383).

Conclusions

Level of evidence 4	Rituximab, alone or combined with other immunosuppressants or intravenous immunoglobulins, is effective in patients with severe, refractory MMP. The onset of adverse events, particularly severe infections, is a common concern in patients treated with rituximab.

Recommendations

Rituximab, either at an initial dose regimen of 375 mg/m^2 each week for 4 consecutive weeks, or of 1 g given 15 days apart, may be recommended as a second-line treatment in severe MMP, and as third-line treatment in mild/moderate MMP refractory to conventional immunosuppressants.

Grade of recommendation C

Intravenous human immunoglobulins Intravenous immunoglobulins (IVIg) are a purified IgG preparation derived from pooled human plasma, and contain more than 95% of unmodified IgG, which has functionally intact Fc-dependent effector functions. IVIg may be a therapeutic option in several dermatologic diseases, including autoimmune bullous diseases, and is usually applied at a dose of 2 g/kg body weight over 2–4 days at monthly intervals.[176] IVIg are used when conventional therapies are contraindicated, or when the disease is progressive despite conventional systemic therapies. Adverse events are usually mild, self-limiting and apparently predominantly infusion-related. The most frequent are headache, back pain, chills, flushing, fever, hypertension, myalgia, nausea and vomiting. The major limitation of IVIg is their cost.

IVIg have been reported as an effective and safe treatment for progressive MMP unresponsive to conventional therapies. Letko *et al*.[177] compared two groups of ocular MMP – one treated with IVIg and the second with conventional therapies – revealing a faster, more effective, and safer response in the first group. Leuci *et al*.[178] showed that the efficacy of IVIGs is persistent for a long time. Foster *et al*. and Steger *et al*. confirmed the favourable response of severe and progressive ocular MMP to combination therapy with rituximab and IVIg.[179,180] Despite evidence of progressive scarring in some of their patients, blindness was prevented. Adverse events reported were limited (headache and nausea), and the authors did not induce discontinuation of the therapy in almost all but two patients described by Segura *et al*.[181]

Conclusions

Level of evidence 4	IVIGs are effective and safe for severe MMP. Their good safety profile makes them a favorable option for immunocompromised patients who cannot be treated with conventional immunosuppressive regimens.

Recommendations

IVIGs may be recommended as third-line treatment for severe MMP, unresponsive to conventional immunosuppressants and/or rituximab. It is also recommended when a patient is at high risk of developing adverse events to conventional therapies.

Grade of recommendation C

Anti-TNFα drugs Increased levels of TNFα have been observed in the sera of MMP patients, compared with controls. The use of anti-TNFα drugs in MMP is supported only by case reports or case series, such as that by Canizares *et al*. reporting on the effectiveness of etanercept in three patients with ocular MMP.[182] Etanercept is a recombinant human dimeric fusion protein consisting of the extracellular ligand-binding domain of the TNFα receptor fused to the Fc portion of the human IgG1.

Conclusions

Level of evidence 5	Controlled trials are needed to confirm the effectiveness and safety of anti-TNFα drugs for MMP.

Recommendations

TNFα inhibitors may be considered as fourth-line therapy for severe MMP.

Grade of recommendation C

Algorithm for the treatment of MMP

The recommended algorithm for the treatment of MMP is shown in Fig. 2.

Systemic medical management of ocular, oral, genital, laryngeal and oesophageal MMP

Ocular MMP

Conclusions

Level of evidence 4	Systemic oral corticosteroids (prednisolone), with or without supplementary loading doses of 1g intravenous corticosteroids (methylprednisolone) preceding oral therapy, tapering over 3 months until adjunctive immunosuppressive agents take full effect, are useful for moderate and severe inflammation in ocular MMP.
Level of evidence 4	Biological therapies such as anti-CD20 (e.g., rituximab) or anti-TNF-α may be beneficial in patients resistant to conventional immunosuppression for moderate and severe inflammation in ocular MMP.
Level of evidence 4	IVIg can be used, either alone or in combination with anti-CD20 therapy, in severe sight-threatening disease or resistant cases of ocular MMP.
Level of evidence 3	Good control of inflammation with systemic immunosuppression is required to minimize progression of conjunctival scarring. Inflammation progresses without visible inflammation.
Level of evidence 4	Subconjunctival mitomycin has been described to reduce fibrosis with mixed results in fewer than 15 subjects reported before 2004.

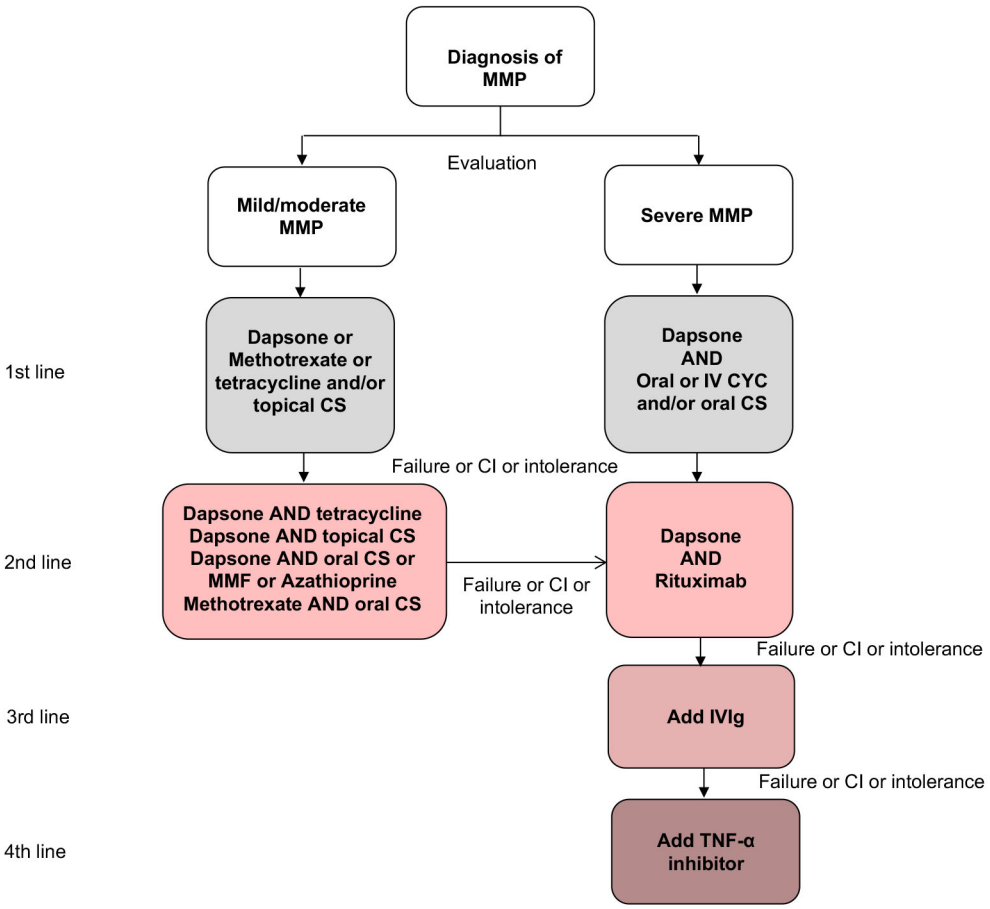

Figure 2 Algorithm for treatment of mucous membrane pemphigoid. CI, contraindication; CS, corticosteroid; CYC, cyclophosphamide; IV, intravenous; IVIg, Intravenous Immunoglobulin; MMF, mycophenolate mofetil; MMP, mucous membrane pemphigoid; TNF, tumour necrosis factor.

Recommendations

Systemic therapy in ocular MMP is recommended according to the stepladder approach detailed in **Fig. 3**.

Grade of recommendation D

Good control of inflammation with immunosuppression is required to limit progression of conjunctival scarring.

Grade of recommendation B

Oral MMP

Conclusions

Level of evidence 4	Topical treatment, in particular clobetasol propionate ointment in adhesive paste, is a first-line option in mild/moderate oral MMP. Dapsone, possibly associated with oral or topical corticosteroids, is a first-line agent in severe oral MMP. Combination of systemic corticosteroids, dapsone and immunosuppressive agents, notably mycophenolate mofetil, should be reserved for severe cases.

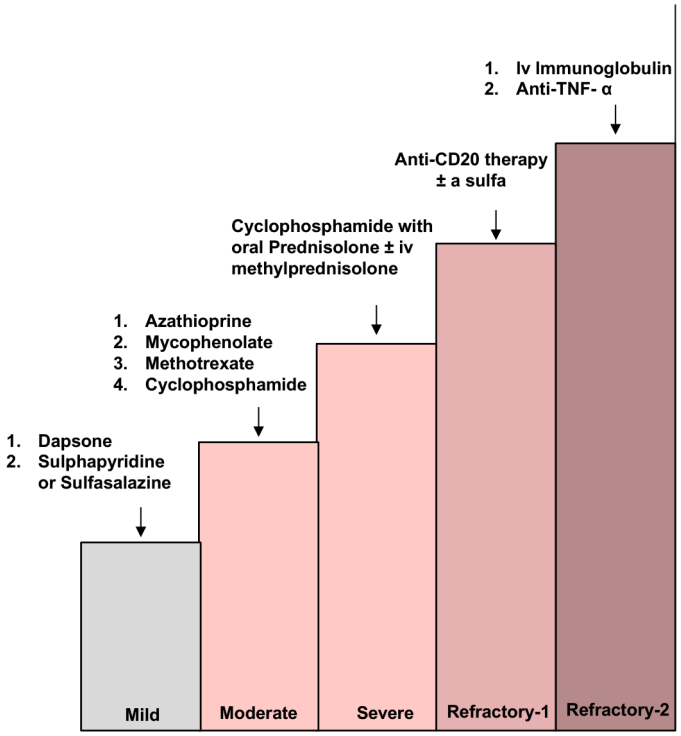

Figure 3 Algorithm for systemic treatment of ocular mucous membrane pemphigoid. The complete legend is shown in the Appendix S1.

Recommendations

In mild/moderate MMP, oral corticosteroids in combination with dapsone may be recommended as first-line regimen.
Grade of recommendation C
High-dose oral tetracyclines may be considered as second-line agents.
Grade of recommendation C
Combination of systemic corticosteroids, dapsone, and immunosuppressive agents, notably mycophenolate mofetil, may be recommended for severe cases.
Grade of recommendation C

See also above recommendations for topical treatment in ocular disease.

Laryngeal MMP

Conclusions

Level of evidence 4	Dapsone should be the first therapeutic option in mild/moderate laryngeal MMP, while prednisone plus cyclophosphamide should be initiated in unresponsive cases. In severe laryngeal MMP, high dose prednisone combined with cyclophosphamide (or azathioprine) should be regarded as first-line treatment. Rituximab may be considered in severe laryngeal MMP refractory to traditional immunosuppressants. Surgical approach by endoscopic CO_2 laser and dilatation is useful to maintain laryngeal airway, but should be avoided during active phase of the disease.

Recommendations

Oesophageal MMP

In severe laryngeal involvement of MMP, high-dose oral corticosteroids in combination with cyclophosphamide or azathioprine may be considered the first-line regimens. In severe cases, rituximab may be recommended as a second-line treatment option.

Grade of recommendation C

In mild/moderate laryngeal involvement of MMP, dapsone may be considered.

Grade of recommendation C

In laryngeal involvement of MMP, surgical treatment by CO_2 laser excision or dilatation is recommended to treat scarring, but is not recommended during the active phase of the disease.

Grade of recommendation C

Conclusions

Level of evidence 4	Dapsone, cyclophosphamide, and azathioprine can be used to treat esophageal mucous membrane pemphigoid.

Recommendations

In mild/moderate esophageal MMP involvement, dapsone may be recommended as first-line treatment; prednisone plus cyclophosphamide may be considered as second-line treatment.

Grade of recommendation C

In severe esophageal MMP involvement, high-dose oral corticosteroids in combination with cyclophosphamide or azathioprine may be considered the first-line regimen.

Grade of recommendation C

Endoscopic dilatation may be recommended, and should be done by expert operators, to treat cicatricial stenosis upon obtaining disease control by using medical treatment.

Grade of recommendation C

Genital MMP

Conclusions

Level of evidence 4	Dapsone, cyclophosphamide, and azathioprine can be used in the treatment of genital mucous membrane pemphigoid..

Recommendations

In mild/moderate genital MMP involvement, dapsone may be recommended, with or without topical corticosteroids (classes III and IV).

Grade of recommendation C

In severe or refractory genital involvement of MMP, high-dose oral corticosteroids in combination with cyclophosphamide, or azathioprine, or mycophenolate mofetil may be considered.
In severe or refractory genital involvement of MMP, high-dose oral corticosteroids in combination with cyclophosphamide, or azathioprine, or mycophenolate mofetil may be considered.

Grade of recommendation C

See also above recommendations for topical treatment in genital disease.

Details on systemic treatment of single-site MMP are shown in the Appendix S1.

Rescue procedures in ocular involvement

Conclusions

Level of evidence 4	Potent immunosuppression cover is required for surgical procedures that breach the conjunctiva, to provide prophylaxis against severe progression of ocular MMP.
Level of evidence 3	In cases of stem cell failure, amniotic membrane grafting, corneal limbal stem cell allograft, and cultured oral mucosal epithelial cells may be considered.
Level of evidence 3	Keratoprosthesis surgery is high risk. Good visual outcomes can be achieved with the osteo-odonto keratoprosthesis for bilaterally blind patients.

Recommendations

For incisional conjunctival surgery, potent immunosuppression is recommended.

Grade of recommendation B

Ocular reconstructive surgery with stem cell replacement surgery may be considered in the bilaterally blind.

Grade of recommendation B

Osteo-odonto keratoprosthesis may be beneficial for patients with bilateral corneal blindness caused by MMP.

Grade of recommendation B

Details on rescue procedures and additional local measures in ocular involvement in MMP are shown in the Appendix S1.

Oral hygiene advice

MMP, among other disorders causing desquamative gingivitis, may potentially intensify the development and progression of plaque-related periodontal disease. A number of studies have described the gingival status in patients with MMP.[183–186] A systematic review showed an increased incidence of periodontitis in patients with desquamative gingivitis (MMP, $n = 65$) compared to healthy individuals.[187] This review showed that patients had worse periodontal parameters, including bleeding upon probing clinical attachment level of the periodontal ligament, probing depth, plaque index and/or gingival index/recession. Patients with a diagnosis of MMP >5 years were also shown to have more recession and furcation involvement.[183] Desquamative gingivitis may indirectly increase the long-term risk for developing periodontal disease via plaque accumulation when pain associated with such lesions impairs capacity to perform efficient oral hygiene practices. In addition, discomfort associated with

gingival lesions could predispose patients to less frequent dental visits. A direct effect of MMP on periodontitis may also be plausible based on the possible shared pathogenic mechanisms between antibody and bacterial-induced inflammatory tissue damage.

Improving oral hygiene is prudent, as this may reduce the chronicity of the disease and the need for complex treatments. In conjunction with medical therapy, the avoidance of trauma and elimination of infection is beneficial. There is evidence for the beneficial effect of conservative treatment in improving the clinical parameters and severity of MMP lesions or symptoms. Non-surgical periodontal therapy, consisting of scaling and root planing, and effective bacterial plaque control can be effective in reducing the gingival manifestations, representing a complementary treatment to the use of corticosteroids.[188–192] A recent systematic review evaluated the efficacy of daily hygiene and professional prophylaxis for treatment of desquamative gingivitis, regardless of its aetiology.[192] This review concluded that the combination of appropriate daily gingival hygiene techniques at home, and the performance of periodontal treatment, including scaling and root planning, decreased pain-perception, disease activity, dental plaque and gingival bleeding. General dentists, hygienists and periodontists therefore play a key role in controlling the oral manifestations of MMP. Patients should be instructed in the maintenance of good oral hygiene, using toothbrushes with soft or extra-soft bristles, applying the modified Bass brushing technique, and using dental floss. In their review, Garcia-Pola *et al*. also recommended rinsing with chlorhexidine twice daily, initially with a concentration of 0.2%, and a maintenance concentration of 0.12% for one to four weeks.

Information for patients

Written information is provided by the EADV webpage and the patient support groups. The purpose of these associations is to promote knowledge about the disease, to furnish comfort and share the experience of patients regarding daily life, and to disseminate information. Such information may contribute to a better overall management of the disease by promoting cooperation between patients, patient associations and health professionals. Patients are also informed about referral centres

Recommendations

It is recommended that patients and their families be informed about the disease, its clinical course and prognosis, treatment, relapse signs, and possible adverse events associated with treatment.
It is recommended that patients be informed about patient support groups for MMP (see list below).

List of support groups for patients with MMP:

International Pemphigus and Pemphigoid foundation: www.pemphigus.org

Pemphigus und Pemphigoid Selbsthilfegruppe e.V.: www.pemphigus-pemphigoid-selbsthilfe.de

Association Pemphigus Pemphigoïde-France: www.pemphigus.asso.fr

Pemfriends: www.pemfriends.co.uk

Associazione Nazionale Pemfigo/Pemfigoide:

Netwerk voor Blaarziekten: www.netwerkblaarziekten.nl

Pemfigus Hastaları Yardımlaşma ve Dayanışma Dernegi: www.pemfigus.org.tr

Future perspective and gaps in knowledge

Several important gaps in knowledge that exist were formulated by the guideline working group:

-Effectiveness and sequence of the different drugs used in MMP

-Ocular MMP: laser therapy and plugging eyelashes

-Validation of outcome measurements

-Scoring system for multisite MMP

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Supporting information

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

Appendix S1. Supplementary material.