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Mucous membrane pemphigoid

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Mucous membrane pemphigoid (MMP) is a sub-epithelial vesiculobullous disorder. It is now quite evident that a number of sub-epithelial vesiculobullous disorders may produce similar clinical pictures, and also that a range of variants of MMP exist, with antibodies directed against various hemidesmosomal components or components of the epithelial basement membrane. The term *immune-mediated sub-epithelial blistering diseases* (IMSEBD) has therefore been used. Immunological differences may account for the significant differences in their clinical presentation and responses to therapy, but unfortunately data on this are few. The diagnosis and management of IMSEBD on clinical grounds alone is impossible and a full history, general, and oral examination, and biopsy with immunostaining are now invariably required, sometimes supplemented with other investigations. No single treatment regimen reliably controls all these disorders, and it is not known if the specific subsets of MMP will respond to different drugs. Currently, apart from improving oral hygiene, immunomodulatory—especially immunosuppressive—therapy is typically used to control oral lesions. The present paper reviews pemphigoid, describing the present understanding of this fascinating clinical phenotype, summarising the increasing number of subsets with sometimes-different natural histories and immunological features, and outlining current clinical practice.
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Introduction

Immune-mediated sub-epithelial blistering diseases (IMSEBD), or autoimmune subepidermal blistering disorders are a large family of skin/mucous membrane diseases, which present with fairly common features as a consequence of subepithelial blistering.

It is about 50 years since pemphigoid was recognised as a clinical phenotype distinct from the previously recognised bullous diseases pemphigus and dermatitis herpetiformis (Lever, 1953). A decade later, the *in vivo* linear deposition of immune deposits (immunoglobulins, complement or both) along the epithelial basement membrane zone (BMZ) was recognised to characterise pemphigoid (Beutner *et al*, 1968). The immune deposits at the BMZ were shown to consist predominantly of IgG and C3. Pemphigoid was then recognised actually to be a family of diseases which included conditions such as bullous pemphigoid (BP) and pemphigoid (herpes) gestationis, which generally affect the skin and have only minor oral involvement, and cicatricial pemphigoid (CP) which mainly involves the mucous membranes, most frequently the ocular and oral mucosae (Liu *et al*, 1986).

A number of other sub-epithelial vesiculobullous disorders were subsequently recognised and the term IMSEBD was thus introduced (Chan *et al*, 1993a), recognising that the autoantibodies can be directed against antigens of the BMZ different from the classic 'bullous' pemphigoid antigens. The BP antigen and several newly identified antigens share the feature that IgG is located on the floor of salt-split skin biopsies (Barnadas *et al*, 2001). The antigens include epiligrin (Domloge-Hultsch *et al*, 1994), uncein (Horiguchi *et al*, 1996), 105 kDa protein (Chan and Cooper, 1994), 200 kDa protein (Chen *et al*, 1996; Mascaro *et al*, 2000), type-IV collagen (Ghohestani *et al*, 1997b), and type-VII collagen (associated with epidermolysis bullosa acquisita) (Gammon *et al*, 1984). Thus the clinical entity often previously termed pemphigoid came to be recognised to include CP [now renamed mucous membrane pemphigoid (MMP)], BP, pemphigoid gestationis (PG), anti-p200, anti-p105 and anti-p450 pemphigoid, lichen planus pemphigoides, dermatitis herpetiformis, linear IgA disease, epidermolysis bullosa acquisita (EBA), bullous systemic lupus erythematosus (SLE) and paraneoplastic pemphigus (Verdolini and Cerio, 2003) (Table 1).

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Table 1 Autoimmune bullous skin diseases

Bullae	*Disease*
Intraepithelial	Pemphigus
	Pemphigus vulgaris
	Pemphigus vegetans
	Pemphigus herpetiformis
	Pemphigus foliaceus
	Endemic pemphigus (fogo selvagem)
	Pemphigus erythematous
	Drug-induced pemphigus
	IgA pemphigus
	Paraneoplastic pemphigus
Sub-epithelial	Pemphigoid
	BP
	PG
	Lichen planus pemphigoides
	CP
	MMP
	OCP
	Anti-plectin pemphigoid
	Anti-p105 pemphigoid
	Anti-p200 pemphigoid
	Epidermolysis bullosa acquisita
	Dermatitis herpetiformis Duhring
	Linear IgA disease

Several reviews about this group of lesions had been published in the last years (Scully *et al*, 1999; Zillikens, 1999; Fleming and Korman, 2000; Schmidt and Zillikens, 2000; Casiglia *et al*, 2001; Challacombe *et al*, 2001; Chan, 2001; Chan *et al*, 2002; Stoopler *et al*, 2003a; Verdolini and Cerio, 2003; Yeh *et al*, 2003) and MMP was the subject of a recent international consensus conference (Chan *et al*, 2002).

Mucous membrane pemphigoid

It has long been apparent that MMP itself was neither a single clinical nor immunological entity (Leonard *et al*, 1982, 1984; Manton and Scully, 1988), but a group of chronic blistering diseases that can result in irreversible sequelae (Ahmed *et al*, 1991b; Fleming and Korman, 2000; Chan *et al*, 2002; Yeh *et al*, 2003). Recent molecular biological advances which have helped to unravel this heterogeneity (Chan *et al*, 1993a; Mobini *et al*, 1998) have been noted elsewhere (Sciubba, 1996; Dabelsteen, 1998).

Epithelial biology

Cell-epithelial basement membrane contact is largely via hemidesmosomes, which link the keratinocyte cytoskeletons to the lamina lucida – the superficial part of the epithelial basement membrane (Table 2). The deeper aspect of the epithelial basement membrane is the lamina densa, which is anchored to the underlying papillary dermis by cross-banded anchoring fibrils. The epithelial basement membrane and adjacent area is termed the epithelial BMZ (see Article 1).

The epithelium and BMZ thus have a complex structure and an array of protein molecules is required for normal epithelial integrity. Inevitably, if any one or more of these BMZ proteins is defective or damaged, the result can be loss of cell-basement membrane adhesion, leading to sub-epithelial vesiculation and the clinical phenotype of pemphigoid. The aetiological agents responsible are varied and often unknown but many of the disorders damaging these molecules are of autoimmune aetiology (IMSEBD), can affect several epithelia and may have systemic manifestations (Chan *et al*, 1993a; Eversole, 1994; Weinberg *et al*, 1997) (Table 3). Rare disorders such as epidermolysis bullosa are due to gene mutations affecting these hemidesmosome-associated proteins (Schmidt and Zillikens, 2000).

The clinical phenotype, which is acquired and consists of vesicles, bullae and/or erosions affecting mucosae predominantly, is termed MMP, and it is this condition, which commonly affects the mouth.

Table 2 Main hemidesmosome components

Protein	*Alternate terms*	*Site*	*Disease*
Keratin 5		Basal layer of stratified epithelia	Epidermolysis bullosa simplex
Keratin 14		Basal layer of stratified epithelia	Epidermolysis bullosa simplex
Plectin/HD1		Intracellular	Epidermolysis bullosa simplex with muscular dystrophy
IFAP300		Intracellular	?
P200		Intracellular	?
BPAg1	BP230 or dystonin	Intracellular	Bullous pemphigoid
BPAg2	BP180 or type-XVII collagen	Transmembrane	Cicatricial pemphigoid, bullous pemphigoid
$\alpha 6\beta 4$ integrin		Transmembrane	Cicatricial pemphigoid, junctional epidermolysis bullosa
Laminin 5	Epiligrin or nicein or kalinin	BMZ	Cicatricial pemphigoid, junctional epidermolysis bullosa
Laminin 6		BMZ	?
Ladinin	LAD-1	BMZ	?
Uncein		BMZ	?
Type-VII collagen		BMZ	Epidermolysis bullosa dystrophica, epidermolysis bullosa acquisita
Type-IV collagen		BMZ	?

Table 3 Sub-epithelial vesiculobullous disorders (immune mediated sub-epithelial blistering diseases)

Disease	*Antigen involved*
Pemphigoid	Table 4
Dermatitis herpetiformis	Epidermal transglutaminase (TGase 3)
EBA	Type-VII collagen[a]
Bullous SLE	Type-VII collagen[a]
Toxic epidermal necrolysis	105 kDa
Linear IgA disease	45 kDa
Chronic bullous dermatosis of childhood	97 kDa

Modified from Nousari and Anhalt (1995) and Eversole (1996).
[a]Typically in patients with HLA-DR2.

Epidemiology of MMP

The epidemiology of MMP is unclear. One of every 15 000–40 000 patients treated in an eye clinic may have ocular pemphigoid (OCP) (Mondino and Brown, 1981). Dermatologic data suggest MMP is about seven times less common than BP (Bernard *et al*, 1995). On the other hand, retrospective immunofluorescent studies suggest that MMP is up to three times more frequent than pemphigus, which itself has an annual incidence of 0.5–3.2 per 100 000 population (Daniels and Quadra-White, 1981; Ahmed *et al*, 1991b; Helander and Rogers, 1994; Carrozzo *et al*, 1996; Fleming and Korman, 2000; Chan *et al*, 2002).

MMP is predominantly a disease of women, with a mean age at onset of 51–62 years (Shklar and McCarthy, 1959; Hardy *et al*, 1971; Ahmed and Hombal, 1986; Silverman *et al*, 1986). Children are rarely affected, to date only 10 cases in the have been reported in the English literature presenting primarily as oral mucosal lesions (Moy *et al*, 1986; Wojnarowska *et al*, 1988; Sklavounou and Laskaris, 1990; Cheng *et al*, 2001; Musa *et al*, 2002; Kuenzli *et al*, 2004).

Aetiopathogenesis

There is no known racial or geographic predilection to MMP but there may be an immunogenetic background and an association with HLA DQB1*0301 (Yunis *et al*, 1994; Delgado *et al*, 1996; Carrozzo *et al*, 2001), especially in OCP (Chan *et al*, 1997a). The HLA-DQB1*0301 allele however, confers a predisposition to all subgroups of MMP and may have a role in T-cell recognition of basement membrane antigens (Setterfield *et al*, 2001). The positive trend between increased allelic expression of HLA-DQB1*0301 in patients with ocular disease and in those with a higher clinical score, further suggests a role for this allele in disease severity (Setterfield *et al*, 2001). Other studies have reported HLA-DQ7(3) positivity in CP and ocular CP (Kirtschig *et al*, 1999). MMP is usually of unknown aetiology but it is occasionally triggered by drugs (Laskaris and Satriano, 1993; Van Joost and Van't Veen, 1993) such as furosemide.

The pathogenesis of MMP probably includes an autoantibody-induced complement mediated sequestration of leukocytes (neutrophils, mainly) with resultant cytokine and leukocyte enzyme release and detachment of the basal cells from the BMZ, and possibly some complement-mediated cell lysis (Eversole, 1994; Kuffer, 1996). However, the mechanism is more complex, and includes molecules such as RANTES, interleukins, tumour necrosis factor alpha (TNF-α), TNF-β, interferon gamma (IFNγ) and more recently identified molecules such as eotaxin (Verdolini and Cerio, 2003).

For example, recently it has been showed that autoantibodies to the human BP180 ectodomain trigger a signal-transducing event that leads to expression and secretion of interleukin-6 and interleukin-8 from human keratinocytes (Schmidt *et al*, 2000, 2001a). This is important because it has recently been shown that dapsone, but not nicotinamide inhibits IL-8, but not IL-6 release from keratinocytes, induced by anti-BP180 IgG, in a dose-dependent fashion as detected by ELISA (Schmidt *et al*, 2001a). This observation suggests that dapsone inhibits the BP IgG-induced IL-8 release from cultured cells by mechanisms at the post-transcriptional level leading to a reduced influx of neutrophils into pemphigoid lesions and the cessation of blister formation (Schmidt *et al*, 2001a).

Involvement of these molecules better explains the typical recruitment of inflammatory cells characteristic of autoimmune bullous disease (Engineer *et al*, 2001). Excellent reviews about the actions and mechanisms of every single cytokine have recently been published (D'Auria *et al*, 1999). In BP, the binding of BP180-specific antibodies to their hemidesmosomal target antigen is not sufficient for blister formation, but must be accompanied by the release of proteases. A recent study showed elevated expression and release of tissue Plasminogen Activator (tPA) from normal human keratinocytes upon stimulation with antibodies to human BP180 (Schmidt *et al*, 2004). Keratinocytes, by secreting tPA, may thus play an active role in the blister formation of BP (Schmidt *et al*, 2004).

However, the recruitment of granulocytes following the local release of cyto-chemokines also contributes to an understanding of the final process which causes dermoepidermal splitting. Recent findings show that the final pathway, which leads to the formation of blisters, includes the release of granular protein with proteolytic activity by eosinophils (Czech *et al*, 1993; Borrego *et al*, 1996), collagenases (Stahle-Backdahl *et al*, 1994; Liu *et al*, 2000b) – both by neutrophils and eosinophils – and neutrophilic elastase (Liu *et al*, 2000a) by neutrophils. All have the capacity to destroy protein binding (Verdolini and Cerio, 2003). In the first phase, there are neutrophilic microabscesses similar to dermatitis herpetiformis, then there are more eosinophils and the tendency to produce scar; examination using polarised light shows bundle of collagen parallel to the surface (Verdolini and Cerio, 2003). In mucosal lesions there is a predominance of plasma cells.

The production of autoantibodies should, in theory, be preceded by presentation of self antigens leading to T helper (Th) cell activation followed by B-cell activation and the subsequent secretion of antibodies

directed against the presented antigen by plasma cells. There are indications that Langerhans cells are the group of antigen presenting dendritic cells (DC) involved in bullous skin diseases. Increased numbers of DCs are detected in the epidermis of patients with pemphigus and pemphigoid (Venning *et al*, 1992). In several different forms of pemphigus and pemphigoid, a strong correlation has been found between the MHC class-II antigen specificities and development of the disease. Possibly, Dsg 1 and Dsg 3 (pemphigus) as well as BP180 and BP230 proteins (BP) are internalised by DCs of individuals that do not develop the disease, but the low affinity of the HLA class-II binding groove with the peptide will circumvent the expression of these immunogenic peptides, avoiding activation of Th cells (Oostingh *et al*, 2002). Pemphigus vulgaris autoantigens and BP180 have been detected in the thymus of healthy individuals, suggesting that the production of autoantibodies in pemphigus and pemphigoid may also be due to clonal escape of autoreactive Th cells (Aho and Uitto, 1999; Oostingh *et al*, 2002). BP180-specific T-lymphocyte clones were detected in patients with BP (Budinger *et al*, 1998; Lin *et al*, 2000) and in patients with linear IgA bullous dermatosis (LABD) (Lin *et al*, 1999). Based on these observations, one may speculate that T cells, autoreactive to specific epitopes, provide direct help to B cells to differentiate into autoantibody-producing plasma cells (Oostingh *et al*, 2002). In conclusion, T cells are involved in the early stages of pemphigoid; Th2 cells, autoreactive to structural components of the skin, can be detected in most patients with these diseases; development of pemphigoid is strongly MHC class-II linked (Oostingh *et al*, 2002). Improved understanding of T-cell involvement in pemphigoid might eventually lead to the development of disease-specific immunomodulatory therapies (Oostingh *et al*, 2002).

In MMP, deposits of immunoglobulins are detectable by immunostaining at the epithelial BMZ and are classically of IgG class (97%) with C3 (78%); however, IgA (27%) or IgM (12%) may be seen (Laskaris and Nicolis, 1980; Daniels and Quadra-White, 1981; Laskaris and Angelopoulos, 1981; Meyer *et al*, 1985; Manton and Scully, 1988; Porter *et al*, 1990; Egan *et al*, 1999b) and this was the first laboratory evidence suggesting that MMP was a heterogenous group of disorders. A recent study of MMP showed that IgG was bound *in vivo* to the dermal-epidermal junction (DEJ) between the location of laminin 5 and type-IV collagen (McGowan and Marinkovich, 2000; Wozniak *et al*, 2003).

Although autoantibodies to BMZ components are involved, patients with MMP rarely have circulating autoantibodies detectable by testing immune reactivity with conventional skin substrates. Mucosal substrates should be used. However, CP can be characterised by detection of circulating autoantibodies to BP180. Autoantibodies in CP target epitopes on both extra and intracellular domains of BP180 and highlight the importance of testing sera for both IgG and IgA reactivity (Nie and Hashimoto, 1999; Schmidt *et al*, 2001b).

Different clinical features between CP and BP appear to correlate with distinct target epitopes on BP180. Previous studies demonstrated that the majority of BP sera react with immunodominant membrane-proximal non-collagenous domain (NC16a) on the extracellular portion of BP180, whereas the C-terminal domains of BP180 were thought to contain the major epitopes in cicatricial phemphigoid (Balding *et al*, 1996; Nie and Hashimoto, 1999; Schumann *et al*, 1999). Probably, CP sera mainly react with the most C-terminal portion, whereas BP sera react with more N-terminal domains (Lee *et al*, 2003). However, recently the Col15 domain has been identified as a hitherto unrecognised epitope region (Schumann *et al*, 2000), positive in 50% of CP sera (Schumann *et al*, 2000) and in 32% of BP sera (Schumann *et al*, 2000). This report is very interesting, because it was recently observed that the Col15 domain of collagen XVII has potential for cell adhesion properties *in vitro* (Schumann *et al*, 2000).

Evidence is now growing that pemphigoid variants may have different autoantibodies, pathogenetic mechanisms and clinical presentations. For example, ocular CP scars more frequently than other variants and is characterised by a more marked infiltration of T cells, Langerhans cells, and macrophages and fibrin deposition (Bhan *et al*, 1982; Sacks *et al*, 1989; Rice and Foster, 1990). Probably the macrophage infiltration is due to increased expression of macrophage colony stimulating factor (m-CSF), mainly by conjunctival fibroblasts and infiltrating inflammatory cells (Razzaque *et al*, 2002). This increase expression of m-CSF may play an important role in the regulation of local proliferation of macrophages in ocular CP and augment or enhance the local inflammatory response and tissue injury consequent to it (Razzaque *et al*, 2002).

The tendency to heal with scar formation observed in CP could be due to the specific localisation of the antigen in the BMZ or could depend on the frequent recurrence of the disease in a localised area. However the progressive scarring observed in CP is still partially unexplained but recently the release of soluble fibrogenic factors by inflammatory infiltrating cells has been considered as pathogenically relevant. Recent studies showed the presence of a mixed cytokine pattern in the cellular infiltrate with a corresponding increase of Th2-like activity in fully developed lesions, irrespective of the different sites involved (Caproni *et al*, 2002, 2003;). The pathogenesis of this disease is still incompletely understood, but there is compelling evidence that in CP Th2 cells contribute to the perpetuation of the disease by secreting the inflammatory cytokines IL-5 and IL-13 (Rico *et al*, 1999). These help recruit granulocytes that produce tissue-destroying enzymes. In addition, the constant presence of TGF-β1 mRNA in the different lesional phases of CP, and its overlapping expression in BP suggest that the involvement of additional factors is responsible for the scarring course typical of CP (Caproni *et al*, 2002, 2003).

Other studies showed that the expression of TGF-β1, HSP47, type-I collagen and type-III collagen was

up-regulated in the fibrotic skin of CP patient, and a complex interaction of these molecules may initiate and propagate the fibrotic cascade in the skin of CP patients (Razzaque and Ahmed, 2002).

Antigenic heterogeneity of MMP

The immunological heterogeneity of the clinical phenotype described as MMP has now been confirmed (Leonard *et al*, 1982, 1984; Manton and Scully, 1988; Domloge-Hultsch *et al*, 1992, 1994; Leverkus *et al*, 2001) and it is quite evident that a range of variants exist, resulting from BMZ autoantibodies directed largely against various hemidesmosomal components or components of the lamina lucida (Table 4).

Ten different and distinct basement membrane components have been identified as autoantigens in various subepithelial blistering disorders (Stoopler *et al*, 2003a). Thus far MMP is a heterogeneous group of autoimmune subepidermal blistering diseases associated most commonly with autoantibodies to BP 180 (Bernard *et al*, 1992; Balding *et al*, 1996; Bedane *et al*, 1997) and less frequently with those to laminin 5 or type-VII collagen or to the β4 subunit of $\alpha6\beta4$ integrin (Chan *et al*, 1999; Bhol *et al*, 2000; Roh *et al*, 2000; Schumann *et al*, 2000; Bhol *et al*, 2001; Challacombe *et al*, 2001; Kumari *et al*, 2001b; Leverkus *et al*, 2001), BPAg1 (Balding *et al*, 1996) and rarely against uncein (Horiguchi *et al*, 1996). A recent investigation suggests that a structural variant of the $\alpha6$ integrin is probably involved in the pathogenesis of oral pemphigoid (Bhol *et al*, 2001). Oral pemphigoid sera and anti-$\alpha6$ antibody produced separation of epithelium from basement membrane (blister formation) of normal human buccal mucosa, after 48 h, in organ culture (Bhol *et al*, 2001).

Ultrastructural studies however, have revealed that MMP autoantibodies react with epitopes on the BPAg2 ectodomain that are distinct from those that react with BP autoantibodies (Bedane *et al*, 1997; Kromminga *et al*, 2002). The specific reactivity of MMP autoantibodies is with the lamina lucida/lamina densa interface, particularly with the carboxy-terminal region of BPAg2, a site positioned 'deeper' within epidermal BMZ, while the BP autoantibodies label the upper lamina lucida to the BPAg2 NC16A domain (Prost *et al*, 1987; Bedane *et al*, 1991; Shimizu *et al*, 1995; Balding *et al*, 1996; Bedane *et al*, 1997). Like most patients with BP, a significant subgroup of patients with CP has circulating IgG specific for BP180. Moreover, sera of patients with linear IgA bullous dermatosis (LABD) contain IgA autoantibodies reactive with a 97/120 kDa protein, LABD antigen 1, which is highly homologous to the extracellular portion of BP180. So the presence of IgG and IgA autoantibody responses to BP180 in patients with these three clinically distinct autoimmune bullous diseases and the different clinical manifestations suggest that variable epitopes of BP180 are targeted by the different autoantibody isotypes, resulting in the distinct clinical pictures (Christophoridis *et al*, 2000). This suggests that the autoantibody response may be more epitope-specific than antigen-specific (Parisi *et al*, 2003).

Ocular CP is associated mainly with IgA anti-45 kDa and IgG anti-205 kDa (Smith *et al*, 1993; Tyagi *et al*, 1996; Challacombe *et al*, 2001), the latter recognising a protein in human epithelium that has a complete homology with the cytoplasmatic domain of the β4 integrin (Jones *et al*, 1995; Tyagi *et al*, 1996).

Recently a new variant has been described: binding autoantibodies to laminin 5 causes anti-epiligrin CP (Seo *et al*, 2001; Egan *et al*, 2003; Hisamatsu *et al*, 2003; Vodegel *et al*, 2003). Laminin 5 is an epidermis-specific extracellular matrix consisting of $\alpha3$, $\beta3$ and $\gamma2$ subunits ($\alpha3\beta3\gamma2$) (Hisamatsu *et al*, 2003), utrastructurally overlapping the location of BPAG2 (Domloge-Hultsch *et al*, 1992, 1994). Passive transfer of experimental anti-laminin 5 IgG to neonatal BALB/c mice induced non-inflammatory subepidermal blisters of skin and mucous membranes independent of complement activation or mast cell degranulation (Lazarova *et al*, 1996). Anti-laminin 5 CP is a mucosal-dominant subepithelial blistering disease characterised by IgG anti-BMZ autoantibodies, that bind to dermal side of 1 M NaCl split skin and immunoprecipitate laminin 5 (Hisamatsu *et al*, 2003). The reactivity of anti-laminin 5 CP sera is heterogeneous (Hisamatsu *et al*, 2003), although the previous studies suggested that most sera reacted with the G domains of $\alpha3$ subunit, the subunit probably involved in promoting adhesion of basal keratinocytes to BMZ (Lazarova *et al*, 2001; Egan *et al*, 2003). Some studies demonstrated that human anti-laminin 5 autoantibodies are pathogenic *in vivo* and are able to induce subepidermal blisters in an experimental human skin graft model (Lazarova *et al*, 2000b) or in neonatal mice (Lazarova *et al*, 2000a).

Diseases such as BP and CP, or anti-laminin CP and EBA share the same molecular target but have very different clinical manifestations. Explaining this phenomenon, probably linked to different expressions of MHC, is one of the challenges for the future (Verdolini and Cerio, 2003).

Table 4 Antigens implicated singly or in combination in pemphigoid variants

Disease	*Antigen*
BP	BP230 kDa mainly
	BP180 kDa
	105 kDa antigen
MMP	BP180 kDa mainly
	BP230 kDa
	Laminin 5
	Laminin 6
	Uncein
	β4 Integrin sub-unit
	$\alpha6$ Integrin sub-unit
	200 kDa
	168 kDa
	45 kDa
PG	180 kDa
	230 kDa

MMP with oral lesions

Several MMP variants can present with oral involvement, including patients with antibodies to:

- anti-laminin 5 (epiligrin) and antibody deposition at the lamina lucida/lamina densa interface (Domloge-Hultsch *et al*, 1992, 1994; Kirtschig *et al*, 1995; Shimizu *et al*, 1995; Hashimoto *et al*, 1996; Allbritton *et al*, 1997), most of the anti-laminin-5 autoantibodies being non-complement fixing IgG_4 (Hsu *et al*, 1997);
- laminin 5 and 6 (Chan *et al*, 1997b);
- 168 kDa antigen (Ghohestani *et al*, 1996);
- both 168 kDa and BPAg 2 (Ghohestani *et al*, 1996) or
- both laminin 5 and BPAg 2 (Kawahara *et al*, 1998).

The picture is made even more complex when it is appreciated that new IMSEBD with oral lesions simulating MMP are also being described, such as one associated with antibodies to a 200 kDa antigen, and closely resembling dermatitis herpetiformis (Zillikens *et al*, 1996; Kawahara *et al*, 2000; Zillikens *et al*, 2000).

Recognised subtypes of MMP

MMP has recently been classified into subgroups defined on the basis of the autoantibodies present, which are detected by immunoblot assay. These assays have demonstrated autoantibodies to human β4 integrin (205 kDa), laminin 5, and BP antigen 2 (180 kDa) (Ahmed *et al*, 1991b; Fleming and Korman, 2000; Chan *et al*, 2002; Yeh *et al*, 2003).

It is now clear that at least six subsets of MMP exist, with distinct clinical features in terms of tissues affected, and different patterns of immunopathology and antigenic specificity of autoantibodies (Domloge-Hultsch *et al*, 1992; Chan *et al*, 1993a; Mobini *et al*, 1998) (Table 5).

1. *Oral pemphigoid or OMMP* (patients with oral lesions only), has a low frequency of positive indirect immunofluorescence (IIF) findings and no serologic reactivity to BP Ags or to other currently recognised MMP antigens (Chan *et al*, 1993a; Mobini *et al*, 1998). The target antigen is still unclear, though recently antibodies against a 168 kDa oral mucosal protein have been demonstrated in six patients (Ghohestani *et al*, 1996).
2. *Anti-epiligrin pemphigoid* (AECP) (Domloge-Hultsch *et al*, 1992, 1994) (patients with blistering of mucous membranes and skin), which is rare and characterised by serologic reactivity only to the dermal side of salt-split skin, and with a low titre of circulating IgG antibodies to BMZ on IIF which, with immunoprecipitation or immunoblotting have been recognised as anti-laminin 5 (epiligrin) antibodies (Domloge-Hultsch *et al*, 1992, 1994; Allbritton *et al*, 1997; Leverkus *et al*, 1999; Egan and Yancey, 2000; Hsu *et al*, 2000). The target antigen has been identified as the α3 subunit of laminin 5 (epiligrin) (Kirtschig *et al*, 1995) or α3 and γ2 subunits of laminin 5 (Nousari *et al*, 1999) or β3 and γ2-chains of laminin 5 (Fujimoto *et al*, 1999). The disease is underreported (Leverkus *et al*, 1999) probably because of the difficulty of distinguishing it from other forms of CP or EBA (Vodegel *et al*, 2003). It is particularly challenging to distinguish AECP from EBA because anti-BMZ autoantibodies in these patients both bind the dermal side of salt-split skin (Lazarova and Yancey, 1996). This distinction is significant given the recent demonstration that patients with AECP have a higher incidence of a solid cancer compared with the normal population (Egan *et al*, 2001). The diagnosis of AECP is on the basis of the folllowing criteria; (1) chronic subepithelial blistering lesions of mucous membranes and skin, (2) *in situ* and circulating IgG anti-BMZ autoantibodies against the lower lamina lucida at its interface with the lamina

Table 5 Distinctive clinical and immunological features of the main currently recognised MMP subsets

Phenotype	*Clinical profile*	*DIF (fibrin only) positive*	*IIF positive*	*Reactivity to BP Ags*	*Main target antigens*	*New terminology*
Anti-BP Ags mucosal pemphigoid	Oral, mucosal, with or without skin	No	Frequent	Frequent	230 kDa (BP1 Ag), 180 kDa (BP2 Ag), β4 integrin sub-unit, laminin 5	CP
Oral pemphigoid	Oral	No	Rare	No	230 kDa (BP1 Ag), 180 kDa (BP2 Ag), laminin 5, laminin 6, α6 integrin sub-unit, 168 kDa	OMMP
OCP	Ocular, with or without oral	Frequent	Rare	No	Laminin 5, 205 kDa (β4 integrin)	OCP
Anti-laminin 5 or anti-epiligrin pemphigoid	Oral, mucosal and rarely skin	No	Rare	Rare	Laminin 5	Anti-laminin 5 pemphigoid

Modified from Chan *et al* (1993b)) and Dayan *et al* (1999).

densa, and (3) circulating IgG autoantibodies that immunoprecipitate epiligrin/laminin 5 from human keratinocyte extracts, culture media, or both (Yancey *et al*, 1995; Vodegel *et al*, 2003).

3. *Anti-BP Ag mucosal pemphigoid* (Chan *et al*, 1993a) (oral mucosal and skin lesions with or without lesions of other mucosae) with IIF findings similar to BP (high frequency of circulating autoantibodies) and a high frequent reactivity to BP Ags.
4. *Ocular pemphigoid* (patients with ocular lesions, with or without oral lesions) with a low frequency of IgG and C3 and much greater deposits of fibrin in biopsy specimens, negative IIF on salt-split skin and negative serology against BP antigens by immunoblotting and immunoprecipitation (Chan *et al*, 1993a). The sera of these patients recognise a 205 kDa protein showing homology with the β4 integrin, or a 45 kDa protein (Smith *et al*, 1993; Tyagi *et al*, 1996; Hoang-Xuan *et al*, 1999). Some authors showed the presence of immune deposits in the upper lamina lucida of the BMZ in six patients with pure OCP, whereas the immune reactants were located in the lower part of the lamina lucida and in the lamina densa of the BMZ (conjunctiva, buccal mucosa, and skin) in seven patients with OCP and suggested that pure OCP may be a disease entity distinct from mucocutaneous CP (Hoang-Xuan *et al*, 1999).
5. A fifth group consists of patients with antibodies directed against more than one antigen.
6. *Anti-p200 pemphigoid* characterised by autoantibodies to a 200 kDa protein (p200) of the DEJ distinct from all known major DEJ autoantigens and thought to be important for cell-matrix adhesion (Zillikens *et al*, 1996; Kawahara *et al*, 2000; Zillikens *et al*, 2000; Shimanovich *et al*, 2003). The P200 is a non-collagenous protein, which contains N-glycans but lacks O-linked oligosaccharides and chondroitin/heparan sulfate side chains (Shimanovich *et al*, 2003). Anti-p200 pemphigoid is characterised by the binding of circulating IgG autoantibodies to the dermal side of 1 M NaCl split skin and by reactivity of these autoantibodies with a unique 200 kDa antigen on immunoblot of dermal extract (Egan *et al*, 2002). On immunoelectron microscopic examination, these autoantibodies deposit at the lamina lucida-lamina densa interface (Egan *et al*, 2002).

Clinical features

The clinical phenotype known as MMP is therefore not a single entity but includes patients with oral lesions only, and others with involvement of the skin and/or other mucous membranes, or occasionally other systems (Scully and Cawson, 2004). The most common areas of involvement are the oral cavity (85%) and conjunctivae (64%) (Ahmed *et al*, 1991b; Fleming and Korman, 2000; Chan *et al*, 2002; Yeh *et al*, 2003). The oral mucosa is often the initial site of MMP lesions (Alkan *et al*, 2003). When MMP is limited to the oral cavity with no other mucosal involvement, some authors prefer the term *oral mucous membrane pemphigoid (OMMP)* (Anhalt, 1990; Eversole, 1994; Dayan *et al*, 1999) indicating a distinct subset of CP limited to the oral cavity; when MMP is limited to the conjunctivae the term *ocular cicatricial pemphigoid (OCP)* is used (Chan *et al*, 1993b; Shimizu *et al*, 1995; Tyagi *et al*, 1996; Hoang-Xuan *et al*, 1999). Unsurprisingly, although the autoantibody profiles differ between the various subgroups of MMP, the clinical lesions are similar (Ahmed *et al*, 1991b; Fleming and Korman, 2000; Chan *et al*, 2002; Yeh *et al*, 2003).

Oral lesions

Patients often present complaining of soreness, bleeding, pain, dysphagia or peeling of the mucosa (Mobini *et al*, 1998). Vesicles or bullae may occur anywhere on the oral mucosa in MMP, and there can be a positive Nikolsky sign elicited by palpation with a finger, mouth mirror or periodontal probe (Gallagher and Shklar, 1987). The blisters rupture quickly (Figures 1–3), leading to pseudo-membrane covered irregularly shaped erosions with a yellowish slough and surrounded by an inflammatory halo. The gingivae, hard and soft palate, buccal mucosae, and tongue may be involved whereas lips lesions are uncommon. These lesions can sometimes be painful and result in poor nutrition but, despite their painful nature, the oral lesions rarely scar.

Commonly, patients with MMP have oral and especially gingival lesions (Fine and Weathers, 1980; Laskaris *et al*, 1982; Silverman *et al*, 1986; Gallagher and Shklar, 1987). The MMP is one of the main causes of desquamative gingivitis (Laskaris *et al*, 1982; Silverman *et al*, 1986; Scully and Porter, 1997; Stoopler *et al*, 2003b) and, indeed, desquamative gingivitis is the main oral feature of MMP (Gallagher and Shklar, 1987; Venning *et al*, 1988; Stoopler *et al*, 2003b) and may be the presenting feature (Vaillant *et al*, 1990; Stoopler *et al*, 2003b). Chronic soreness is common, especially worse when eating acidic foods. The clinical appearance is of gingival erythema and loss of stippling extending

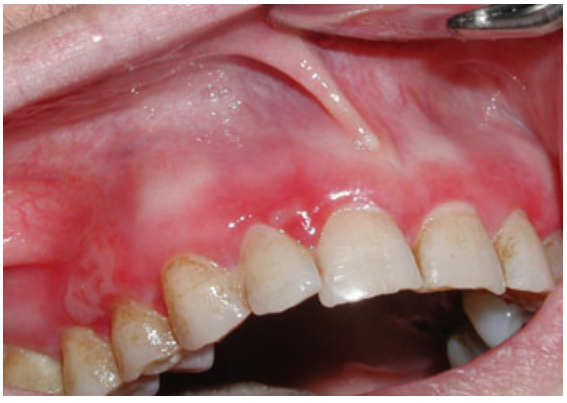

Figure 1 Oral lesion in a patient with OMMP

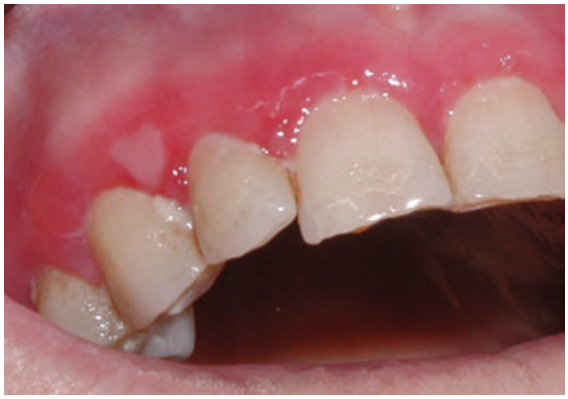

Figure 2 Same case of Figure 2 (blister)

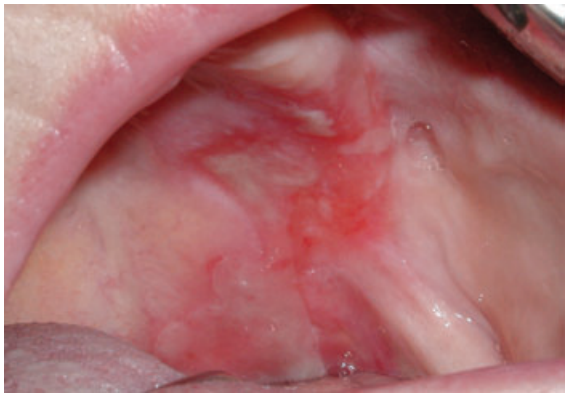

Figure 3 Same case of Figure 2 (rupture of blister)

apically from the gingival margins to the alveolar mucosae. The desquamation may vary from mild almost insignificant small patches to widespread erythema with a glazed appearance.

Ocular lesions

Ocular manifestations have been quite common in some stomatological series, ranging from 3 to 48% (Silverman *et al*, 1986; Gallagher and Shklar, 1987; Lamey *et al*, 1992; Vincent *et al*, 1993) and are important since they may culminate in blindness (Figure 4). A survey of 401 reported patients (Shklar and McCarthy, 1971; Laskaris *et al*, 1982; Silverman *et al*, 1986; Gallagher and Shklar, 1987; Manton and Scully, 1988) reveals that whereas the oral mucosa was affected in 100%, the ocular mucosa was concomitantly involved in approximately 39.4% of the cases and the skin and other mucosa were affected to a much lesser extent (Dayan *et al*, 1999).

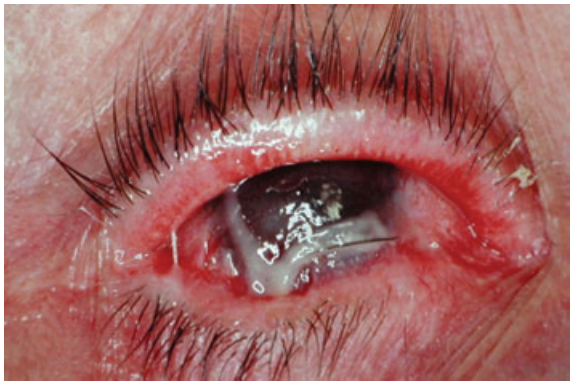

Figure 4 Ocular involvements in MMP

Eye involvement usually begins as chronic conjunctivitis with symptoms of burning, irritation, photophobia and excess tearing (Ahmed *et al*, 1991a, b; Mutasim *et al*, 1993). In most patients, the symptoms affect one eye initially. Then, if left untreated, the disease can involve the other eye within a period of 2 years. Vesicles are rarely seen in the conjunctiva and ulceration is seen only in advanced aggressive disease. Scarring following repeated fibrosis can lead to the fusion of the scleral and palpebral conjunctivae (symblepharon) or the superior and inferior palpebrae (ankyoblepharon). The conjunctiva may contract and invert the eyelid margins (entropion), leading to inversion of eyelashes onto the corneal surface with subsequent irritation (trichiasis). The combination of entropion and trichiasis may lead to blindness (Ahmed *et al*, 1991b; Mutasim *et al*, 1993; Fleming and Korman, 2000; Chan *et al*, 2002).

Less common lesions

Cutaneous involvement is uncommon (up to 25% of patients) and is limited to the face, neck, scalp, axilla, trunk and extremities (Ahmed *et al*, 1991b; Fleming and Korman, 2000; Chan *et al*, 2002; Yeh *et al*, 2003).

Some patients may have lesions of other stratified squamous epithelia such as of the larynx (Miziara *et al*, 2002; Whiteside *et al*, 2003), subglottis (Cole *et al*, 2000), oesophagus (Egan *et al*, 1999a; Sallout *et al*, 2000; Park *et al*, 2002), or nasal (Miziara *et al*, 2002), vulva (Ikegaya *et al*, 1999), penis (Fueston *et al*, 2002) or anus (Mutasim *et al*, 1993; Lilly *et al*, 1995), where scarring may cause serious complications. In rare cases, CP is disseminated (Provost *et al*, 1979; Kurzhals *et al*, 1995; Poon and McGrath, 1999).

There are several reports of the simultaneous presence of clinical and serological features of pemphigus and pemphigoid in the same patient (Sami and Ahmed, 2001; Sami *et al*, 2001), and occasionally reports of other autoimmune diseases (Nayar *et al*, 1991).

Association with malignancy

Patients with AECP present a higher incidence of a solid cancer compared with the normal population (Egan *et al*, 2001). A review of reported cases in Japan disclosed that 5 of 16 cases (31.2%) were complicated by internal malignancies (Matsushima *et al*, 2004). There are also reports of cancers of lung (Gibson *et al*, 1997; Lish *et al*, 1997; Setterfield *et al*, 1999b; Matsushima *et al*, 2004), endometrium (Lenz *et al*, 1998), cervix (Leverkus *et al*, 1999), colon (Leverkus *et al*, 1999) and stomach (Fujimoto *et al*, 1998; Taniuchi *et al*, 1999; Uchiyama *et al*, 2000) and of non-Hodgkin's lymphoma (Shannon *et al*, 2003).

Some cases of CP have been associated with B-cell lymphoproliferative disorders (Aractingi *et al*, 1999).

Diagnosis

The differential diagnoses of MMP may include pemphigus vulgaris, and bullous SLE (Scott and Ahmed, 1998) as well as pemphigoid subtypes and other IMSEBD. The management can only be carried out appropriately if there is an accurate diagnosis, and this is based on the history, examination, and biopsy with histological and direct immunofluorescent (DIF) examination (Ahmed *et al*, 1991b; Helander and Rogers, 1994; Scott and Ahmed, 1998; Nousari and Anhalt, 1999; Fleming and Korman, 2000; Yancey and Egan, 2000; Chan *et al*, 2002; Yeh *et al*, 2003).

Routine histopathology of a properly obtained specimen will demonstrate sub-basilar cleavage. The most appropriate area to biopsy is not an erosion, which will show loss of the epithelium one wishes to study, but a vesicle or perilesional tissue. Some suggest inducing a vesicle by rubbing the mucosa first before taking a biopsy (Siegel and Balciunas, 1994).

It is better to avoid gingival biopsy since the chronic inflammation of gingivitis may confuse the histological picture. Also obtaining a diagnostic gingival biopsy can be technically challenging and result in a periodontal defect (Siegel and Anhalt, 1993).

Histopathology

The MMP is histologically characterised by junctional separation at the level of the basement membrane giving rise to a sub-basilar split as in other forms of pemphigoid. Classical histopathological features include a subepithelial split with a chronic inflammatory infiltrate containing eosinophils, lymphocytes, and neutrophils as well, in the lamina propria (Figure 5). However, routine biopsy of a patient suspected of having MMP is often not enough to fully differentiate the disease from other mucocutaneous disorders.

Direct immunofluorescence (DIF)

The DIF is often helpful in making the broad diagnosis of pemphigoid if immunostaining shows deposits of IgG and C3 in a homogeneous linear manner in the BMZ along the dermoepidermal junction. This procedure involves performing an incisional biopsy from a perilesional site adjacent to a new vesicle or bulla. The specimen should be transferred in a specific transport media (Michel's solution) or snap-frozen on liquid nitrogen, and must be processed in a timely manner. The tissue is then incubated with fluoresceinated antibodies against IgG, complement and fibrinogen, and examined under a fluorescent microscope. In some cases, additional biopsies may be necessary to demonstrate the presence of immune deposits in the BMZ. The following recommendations by the Consensus Statement may enhance positive results (Chan *et al*, 2002):

1. In patients with single-site mucosal involvement, a biopsy specimen should be obtained from tissue next to the areas of inflammation.
2. When patients present with multiple-site involvement, the biopsy should be taken from tissue adjacent to an inflamed non-ocular site.
3. Patients who present with both skin and mucosal involvement should have a skin biopsy taken from an inflamed lesion.
4. For patients with ocular involvement requiring a biopsy, the procedure should be performed cautiously both to minimise injury and additional scarring.

Essentially all patients with MMP and CP have, on DIF, *in vivo* bound IgG, IgA or C3, presenting as a homogeneous line in the BMZ of lesional and perilesional mucosa. Deposition of C3 in the BMZ is detected in almost all patients, sometimes is the sole immunologic reactant, and is considered diagnostically significant. The DIF analysis of biopsy specimens of MMP where the epithelium is separated from the underlying connective tissue may show IgG deposits on the basal pole of the epithelial cells in an interrupted linear pattern (Siegel and Anhalt, 1993).

DIF is thus useful in several ways: first, a positive result confirms the diagnosis of IMSEBD. Second, DIF differentiates IgG-mediated diseases [BP, MMP, HG and acquired epidermolysis bullosa (EBA)] from IgA-mediated diseases (dermatitis herpetiformis and linear IgA disease) (Mutasim, 1997).

Serologic assays

There are serologic assays that can be used to detect circulating antibodies to confirm the diagnosis of MMP, including IIF and immunoblot assays.

There are two IIF techniques:

1. IIF is performed by incubating patient serum with an epithelial substrate, such as human buccal mucosa, human skin, monkey oesophagus or guinea pig labial mucosa and marking the specific antigens with fluorescein-labeled, anti-human IgG. Using this method, antibody titers of MMP autoantibodies can be determined.
2. Normal human skin or mucous membrane is incubated with 1 mol sodium chloride solution to

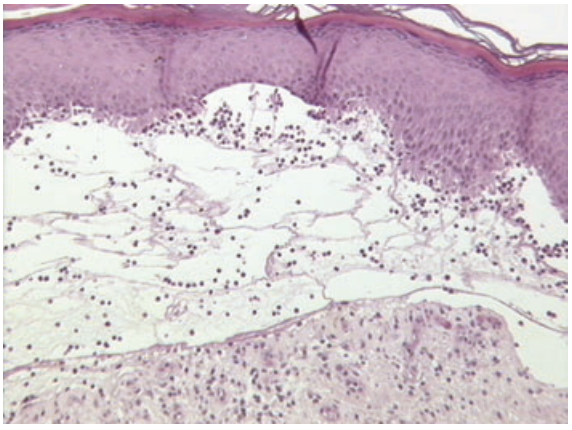

Figure 5 Histological aspects of a bulla in a case of OMMP

separate the epithelium from the connective tissue at the site of the lamina lucida (Gately and Nesbitt, 1994; Kelly and Wojnarowska, 1988); this provides a more sensitive assay (Lazarova and Yancey, 1996), can demonstrate anti-BMZ antibodies (Kelly and Wojnarowska, 1988), and allows the distinction between antigens located on the epidermal side of the split and those located on the dermal side (Kelly and Wojnarowska, 1988; Gately and Nesbitt, 1994; Barnadas *et al*, 1999).

IIF using monkey oesophagus substrate, can detect low titres of anti-BMZ antibodies in CP sera. IIF using salt-split skin substrate elicits autoantibodies to human B4 integrin and BPAg2, which bind to the epidermal side, and autoantibodies to laminin 5, which bind to the dermal side.

Immunoblot assays, which are more specific than IIF, can detect specific autoantibodies in CP sera, as described earlier (Fleming and Korman, 2000; Chan *et al*, 2002).

Some cases of pemphigoid with negative DIF can be positive to IIF (Mutasim and Adams, 2000) but circulating anti-BMZ autoantibodies are found in about half of these patients (Yancey and Egan, 2000) and a clinical study suggested that serial titres of IgG and IgA may therefore be useful in the assessment and management of CP (Setterfield *et al*, 1999a). However, the various subsets of MMP show different expressions of autoantibodies in patients' sera. Patients with MMP who present with only ocular involvement (OCP) rarely exhibit circulating IgG antibodies (Parisi *et al*, 2003). They also have no serologic reactivity to BP antigens or BMZ antigens. Patients with MMP confined to the oral cavity (OMMP) often also do not have circulating IgG antibodies, but linear deposits of complement and immunoglobulin, particularly IgG, along the BMZ are usually detected by using DIF testing. Patients exhibiting both mucosal disease and skin lesions show circulating IgG autoantibodies to BPAG2. Lastly, subgroups of MMP that involves multiple mucosal surfaces without significant skin disease show variable expression of circulating IgG autoantibodies and DIF testing.

Differentiating between MMP, BP and EBA

Even after routine histopathological and immunopathological studies, it can still be difficult to differentiate between MMP, BP and EBA. Oral lesions are more common MMP than in BP but are indistinguishable clinically and by light microscopy and conventional immunostaining though eosinophils are more prominent in BP (Laskaris and Nicolis, 1980; Laskaris *et al*, 1982). The MMP and BP may be differentiated ultrastructurally, but this is not routinely available. Therefore, the distinction remains based on the clinical presentation; if the disease is predominantly cutaneous, a diagnosis of BP is made, whereas if it is predominantly mucosal, especially when associated with scarring, a diagnosis of MMP is more appropriate (Mutasim *et al*, 1993). The EBA may also present clinical, histopathological and immunopathological features indistinguishable from MMP (Ahmed *et al*, 1991b; Mutasim, 1997). In doubtful cases, the very best distinction can be achieved by using human skin split in 1 M sodium chloride through the lamina lucida prior to IIF examination. If immune deposits are limited to the floor (dermal side) of the induced cleavage, the diagnosis is most likely to be EBA, whereas if deposits are also on the roof side, the diagnosis is MMP (Mutasim *et al*, 1993).

If the serum does not contain detectable antibodies, concentrated serum should be used (Korman and Watson, 1996). If these results are negative, two other tests can be performed.

1. A split may be induced chemically in intact perilesional tissue for DIF examination in a way similar to IIF, when epidermal and dermal fluorescence indicates MMP (Gammon *et al*, 1990) or
2. A definitive diagnosis may be obtained determining the antigen-binding specificity of circulating antibodies using immunoblotting or immunoprecipitation (Mutasim, 1997). EBA sera, unlike MMP, label the 290 kDa major component and a minor 145 kDa protein from dermal extracts.

Immunogold electron microscopy

Direct and indirect immunogold electron microscopy can be useful to identifiy autoantibodies, complement, and fibrin deposits contributing to the diagnosis of rare entities (Hoang-Xuan *et al*, 1999; Robin *et al*, 1999; Karpouzis *et al*, 2002), but the technique is difficult and expensive.

Laser scanning confocal immunomicroscopy

Recently a simple and very sensitive immunofluorescence (IF) assay based on confocal laser scanning microscopy has been described (Kazama *et al*, 1998; Schmidt *et al*, 2002). Laser scanning confocal microscopy allows precise localisation of *in vivo*-bound IgG in skin and thus offers a rapid method for the differentiation of MMP from BP and EBA (Wozniak *et al*, 2003). This method is of special value in those patients in whom circulating autoantibodies are not detectable (Wozniak *et al*, 2003).

Management

The MMP is neither a single entity nor has a predictable natural history. In some patients the disease is localised and has a slowly progressive course without complications; in others it is devastating, with severe morbidity. Because of the difficulties in the differential diagnosis and limited available data, it is not clear if the pemphigoid subtypes account for different outcomes. No reliable objective prognostic criteria are available, though it has been suggested that a dual antibody response with IgG and IgA signifies more persistent and severe MMP (Setterfield *et al*, 1998). However, not all patients with MMP have detectable circulating autoantibodies (Chan *et al*, 1993a; Mutasim, 1997).

Clinical trials of treatments for MMP are few, often include only a limited number of patients and most certainly include patients with heterogeneous entities (Mobini *et al*, 1998). Reliable data from randomised controlled trials in MMP are not available, and so most of the therapeutical experience is from studies on BP.

Pemphigoid limited to the oral cavity

The OMMP seems to have a relatively benign course compared with that of other pemphigoid variants involving the oral cavity and other mucosae and the skin (Mobini *et al*, 1998). Thus patients with oral lesions alone are best being treated with topical drugs, and indeed they typically respond adequately.

Patients should also take measures to avoid trauma, including avoiding hard foods (Ahmed *et al*, 1991b; Fleming and Korman, 2000; Chan *et al*, 2002; Yeh *et al*, 2003). It seems prudent to improve oral hygiene since, in similar disorders; this may improve DG (Holmstrup *et al*, 1990).

Topical anti-inflammatory agents

Corticosteroids

Patients with pemphigoid limited to the oral cavity can often be managed with local therapies, including topical corticosteroids and intralesional steroid injections (Ahmed *et al*, 1991b; Fleming and Korman, 2000; Chan *et al*, 2002; Yeh *et al*, 2003). Topical corticosteroids remain the mainstay treatment (Lozada and Silverman, 1980; Silverman *et al*, 1986; Lozada-Nur *et al*, 1991; Lamey *et al*, 1992; Vincent *et al*, 1993; Lozada-Nur *et al*, 1994; Carrozzo *et al*, 1997) though some advocate systemic dapsone (see below). Candidosis may complicate treatment but can be prevented by adding antimycotics (e.g. miconazole gel and/or chlorhexidine mouthwashes) (Carrozzo *et al*, 1997).

Triamcinolone acetonide 0.1–0.5% as an aqueous rinse or ointment is rarely adequate to control MMP (Vincent *et al*, 1993) and so the more potent fluorinated steroids such as fluocinonide 0.05% or clobetasol propionate 0.05% (2–3 applications per day for 9–24 weeks) in an adhesive medium (Lozada and Silverman, 1980; Lamey *et al*, 1992; Lozada-Nur *et al*, 1994; Carrozzo *et al*, 1997) are usually required. Intralesional triamcinolone acetonide (in a dilution of 5.0–10 mg ml^{-1}) (Ahmed *et al*, 1991b) can be useful to treat isolated erosions (Urbanek and Cohen, 1971). For gingival lesions, these corticosteroids are typically more effective if used in a vacuum-formed custom tray or veneer (Aufdemorte *et al*, 1985; Wray and McCord, 1987; Lamey and Jones, 1988; Lilly *et al*, 1995; Carrozzo *et al*, 1997; Gonzalez-Moles *et al*, 2003). Clobetasol 17-propionate 0.05% in Orabase plus 100 000 IU cm^{-3} of nystatin administered in trays is effective for gingival lesions (Gonzalez-Moles *et al*, 2003), and an aerosol of beclomethasone dipropionate or budesonide (50–200 μg) may be valuable for patients with palatal, pharyngeal, nasal and esophageal MMP (Ahmed *et al*, 1991b; Huilgol and Black, 1995).

Ciclosporin

Preliminary reports indicated that topical ciclosporin could be effective in the treatment of oral lesions of MMP (Eisen *et al*, 1990; Azana *et al*, 1993) but it is expensive.

Tacrolimus

Topical tacrolimus has been used to treat CP (Letko *et al*, 2001; Hall *et al*, 2003; Assmann *et al*, 2004; Chuh, 2004; Gunther *et al*, 2004). The potency of tacrolimus therapy for CP can probably be explained by its possible down-regulating effect on local T lymphocytes. Daily application of topical tacrolimus 0.1% ointment (Protopic) in addition to oral prednisone (40 mg day^{-1}) succeeded in healing the condition and allowed tapering of the prednisone dose (Gunther *et al*, 2004). Continuation of topical tacrolimus alone resulted in complete resolution of erosions after 3 months and prevented progression (Assmann *et al*, 2004; Gunther *et al*, 2004). There were no side effects to tacrolimus or any systemic uptake of the drug.

Tetracyclines

Topical tetracyclines have reportedly been of benefit in a single report (Bauco van der Wal and Jonkman, 1997).

Recalcitrant pemphigoid or not limited to the oral cavity

Patients with large oral and/or multiple oral lesions, extensive mucous membrane involvement (especially ocular), or recalcitrant disease, may need aggressive systemic therapy (Burton *et al*, 1978; Rogers *et al*, 1982; Rogers and Mehregan, 1988; Ahmed *et al*, 1991b; Bauco van der Wal and Jonkman, 1997; Foster and Ahmed, 1999; Fleming and Korman, 2000; Chan *et al*, 2002; Miserocchi *et al*, 2002; Sami *et al*, 2002b; Yeh *et al*, 2003). The treatment of choice is based on the extent and severity of disease (Ahmed *et al*, 1991b; Fleming and Korman, 2000; Chan *et al*, 2002; Yeh *et al*, 2003).

The main treatments available, shown in Table 6, are anti-inflammatory and/or immunosuppressive. Dapsone has frequently been used in the initial treatment of CP, since morbidity and mortality are most often due to complications of systemic therapy, as the drugs used are potentially toxic and the patients often elderly (Ahmed *et al*, 1991b; Nayar and Wojnarowska, 1993). If patients fail to respond to dapsone, systemic steroids or alternative immunosuppressive agents have been used, or a combination of high-dose intravenous corticosteroids and cyclophosphamide (Yeh *et al*, 2003). Figure 6 summarises a suggested approach to the care of patients with MMP.

Systemic anti-inflammatory agents

Dapsone

Dapsone, a synthetic sulfone with anti-inflammatory properties, appears to suppress neutrophil adherence, inhibits the synthesis of prostaglandins E2 and thereby can modulate several vesiculobullous disorders, including MMP (Booth *et al*, 1992; Ciarrocca and

Table 6 Principal treatment modalities in mucous membrane pemphigoid

Topical corticosteroids	Beclomethasone dipropionate
	Betamethasone valerate
	Budesonide
	Clobetasol propionate
	Fluocinonide
Systemic corticosteroids	Prednisone
Other immunosuppressives	Azathioprine
	Cyclophosphamide
	Cyclosporine
	Methotrexate
	Thalidomide
	Tacrolimus
	Mycophenolate mofetil
	Leflunomide
	Mitomycin C
	Etanercept
Dapsone	
Sulphonamides	Sulfapyridine
	Sulfamethoxypyridazine
	Sulfasalazine
Tetracyclines	Tetracycline
	Doxycycline
	Minocycline
Intravenous immunoglobulin therapy	
Plasmapheresis	

Greenberg, 1999). Several authors consider dapsone the drug of choice for patients with MMP (Rogers *et al*, 1982; Fine, 1995; Huilgol and Black, 1995; Mobini *et al*, 1998), with/without topical corticosteroids (Ciarrocca and Greenberg, 1999), but others have reported disappointing results (Matthews *et al*, 1989; Nayar and Wojnarowska, 1993). Furthermore, dapsone often has to be discontinued because of adverse effects including headaches, haemolytic anemia, methaemoglobinaemia, bone marrow suppression or hepatotoxicity (Matthews *et al*, 1989; Nayar and Wojnarowska, 1993; Huilgol and Black, 1995), especially in patients of Asian, Negro or Mediterranean descent (Nayar and Wojnarowska, 1993), in whom glucose-6-phosphate dehydrogenase deficiency should also first be excluded. To minimise adverse effects the following regimen using dapsone has been recommended: 25 mg/day for 3 days, then 50 mg/day for 3 days, then 75 mg/day for 3 days, then 100 mg/day for 3 days and on the 17th day of therapy 150 mg/day (Rogers *et al*, 1982). However, even with this regimen, intolerance is not uncommon (Nayar and Wojnarowska, 1993).

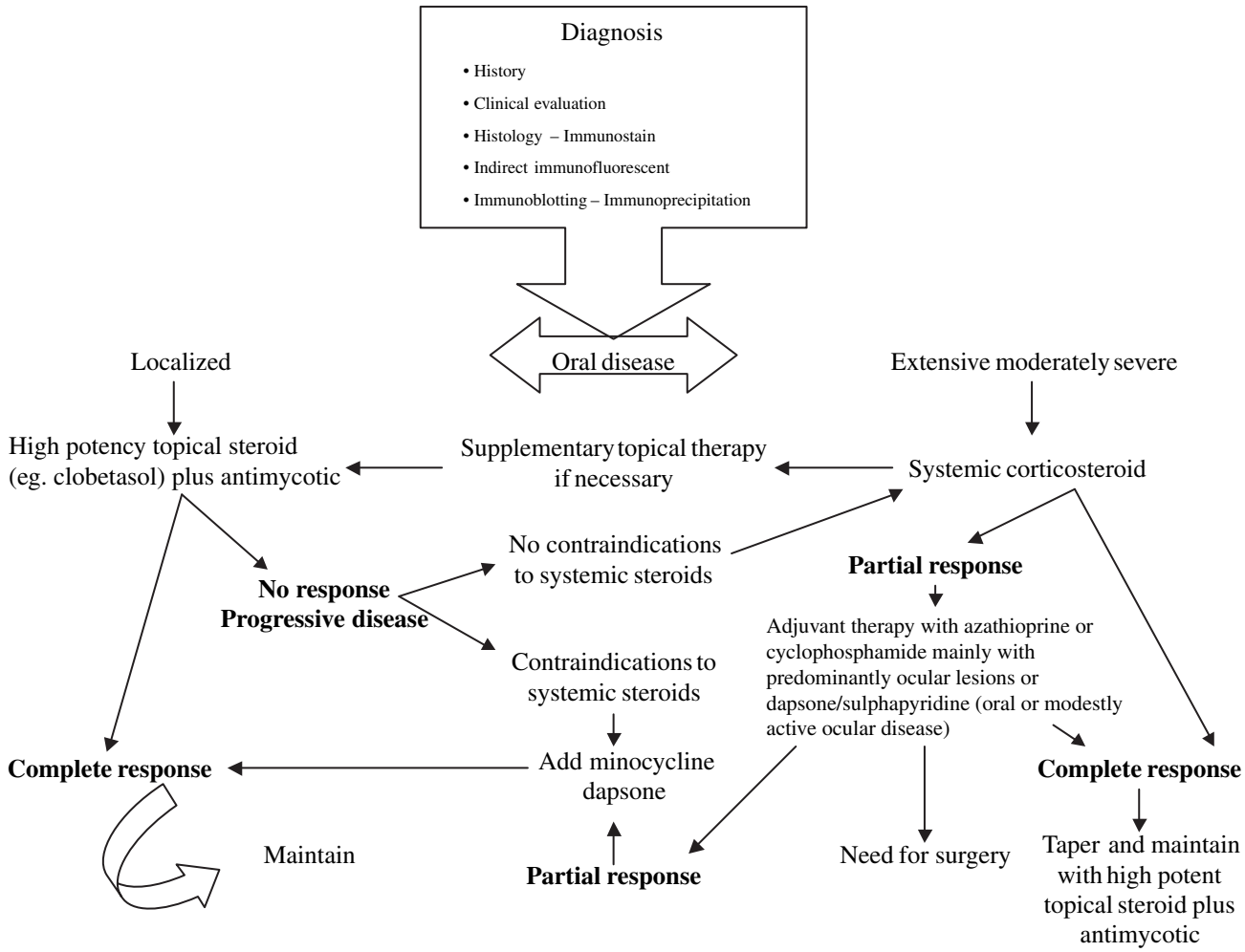

Figure 6 Algorithm for treatment of MMP

Systemic immunosuppressives

Corticosteroids

Treatment with a short plasma half-life systemic corticosteroid (e.g. prednisone) (Truhan and Ahmed, 1989) may be effective (Lozada, 1981; Ahmed *et al*, 1991b; Huilgol and Black, 1995; Carbone *et al*, 1998). Since most adverse effects have been observed when steroids are administered for more than 2 weeks (Lozada-Nur *et al*, 1994), short courses of high dose (1–2 mg/kg/day) prednisone are advocated to permit either early withdrawal from the steroid, or earlier and more effective drug tapering (Silverman *et al*, 1986). The initial dose should be slowly tapered down as soon as the disease is under control, but this can take several months (Nayar and Wojnarowska, 1993). An alternative approach is to use a lower dose of systemic prednisone (40 mg/day for 5 days) followed by 10–20 mg day^{-1} for 2 weeks (Vincent *et al*, 1993). Prednisone therapy may usefully be combined with high potency topical steroids (e.g. clobetasol) to control oral lesions (Vincent *et al*, 1993; Carrozzo *et al*, 1997), or used along with other immunosuppresive agents or with dapsone (Foster, 1986; Mutasim *et al*, 1993). If complete remission is achieved with such a two-drug regimen, the dosage of the second drug is maintained while the prednisone is tapered and eventually discontinued, at which point careful tapering of the other drug is attempted (Fine, 1995). It is worthy of note that the benefit of immunosuppressants may take up to 6 weeks to become apparent (Nayar and Wojnarowska, 1993).

Azathioprine or cyclophosphamide

Azathioprine (1–2 mg/kg/day) or cyclosphosphamide (0.5–2 mg/kg/day) can be used for MMP (Dave and Vickers, 1974; Brody and Pirozzi, 1977; Foster, 1986; Ahmed *et al*, 1991b; Nayar and Wojnarowska, 1993; Epstein *et al*, 2001) but unfortunately neither is usually sufficient alone (Fine, 1995), and both can have several adverse effects that should be carefully monitored (Ahmed and Moy, 1981; Ahmed and Hombal, 1984). Both drugs can induce bone marrow suppression and azathioprine may induce cholestasis, whereas cyclosphamide can induce alopecia, haemorrhagic cystitis and has potential teratogenic and carcinogenic effects (Ahmed and Moy, 1981; Ahmed and Hombal, 1984).

A recent Cochrane review found two small RCTs of MMP with severe ocular involvment (Kirtschig *et al*, 2003). In the first trial cyclophosphamide was superior to prednisone after 6 months of treatment and in the second trial all 20 patients treated with cyclophosphamide responded well after 3 months of treatment, but only 14 patients responded to the treatment with dapsone (Kirtschig *et al*, 2003). One report has recommended pulsed intravenous cyclophosphamide for the treatment of CP (Musette *et al*, 2001).

Methotrexate

Low-dose oral methotrexate has been suggested as first-line systemic therapy in the treatment of OCP: progression of conjunctival cicatrisation was prevented in 72% of eyes with OCP and 90% of eyes with drug-induced OCP, with 92% of patients experiencing no adverse effects (McCluskey *et al*, 2004).

Tumor necrosis factor antagonists

Thalidomide controlled previously resistant disease in one report (Duong *et al*, 2002) and one patient with long-standing recalcitrant CP responded rapidly and lastingly to therapy with the TNF-α antagonist etanercept (Sacher *et al*, 2002).

Mycophenolate mofetil

Mycophenolate mofetil has recently been reported to show promise for several dermatologic conditions, including pemphigoid (Liu and Mackool, 2003).

Leflunomide

One patient with severe CP that led to laryngeal and subglottic stenosis and involvement of both eyes and the oral, nasal, and nasopharyngeal mucosae has been effectively treated with leflunomide over 8 months with no relapses (Boedeker *et al*, 2003). Leflunomide is an isoxazole derivative, chemically unrelated to any hitherto applied immunosuppressants, which exhibits a strong anti-inflammatory action via its abilty to block dihydroorotate dehydrogenase, a key enzyme of *de novo* pyrimidine synthesis (Wozel and Pfeiffer, 2002). Adverse effects are mild, dose-related and reversible, suggesting leflunomide is a safe immunosuppressant (Wozel and Pfeiffer, 2002).

Sulphonamides

Sulfasalazine is considered as an alternative to dapsone, and so may be useful in OCP patients with previous dapsone-related adverse effects (Le Rouic *et al*, 1999; Doan *et al*, 2001).

Sulfapyridine (1.5–3 g/day in divided doses) alone or in combination with dapsone is reportedly successful in controlling MMP (Rogers, 1986).

A recent report on 25 patients indicated that, with appropriate monitoring, sulfamethoxypridazine is an effective and safe treatment for MMP, comparing favourably with other systemic agents (Thornhill *et al*, 2000) but others have found it less beneficial than sulfapyridine (McFadden *et al*, 1989; Nayar and Wojnarowska, 1993).

Tetracyclines

Tetracyclines have a range of anti-inflammatory and immunosuppressive activities in addition to their antibacterial effects, including anti-collagenase activity, suppression of leucocyte chemotaxis, inhibition of lymphocyte blast trasformation, and other actions (Thong and Ferrante, 1979; Humbert *et al*, 1991).

One preliminary report described a beneficial response of desquamative gingivitis to 100 mg/day of doxycycline for 8 weeks (Ronbeck *et al*, 1990).

Minocycline, (50–100 mg/day for 3–39 months) used alone in 10 patients with MMP who had not responded to a wide range of therapies was successful in four patients with gingival lesions (Poskitt and

Wojnarowska, 1995a; Ozog *et al*, 2000). The main side effects were nausea, vomiting, dizziness, photosensitivity, hyperpigmentation and candidiasis (Kim and Greenberg, 2001). Other rare but serious side effects reported include drug-induced lupus, serum sickness-like reaction and hypersensitivity syndrome reaction.

The combined use of tetracycline and nicotinamide (500 mg to 2.5 g/day) seemed to produce a better clinical response in isolated cases (Mallon and Wojnarowska, 1994; Poskitt and Wojnarowska, 1995b; Dragan *et al*, 1999; Kreyden *et al*, 2001; Sakamoto *et al*, 2002) though there is a need for controlled trials. Potential adverse effects reported with nicotinamide therapy may include hepatotoxicity, pruritus and flushing, though these have been reported mainly in patients taking much higher doses than those used in combination therapy (Fivenson *et al*, 1994).

Intravenous immunoglobulin therapy

In patients unresponsive to conventional therapy such as high-dose systemic corticosteroids and/or immunosuppressive agents, an alternative treatment modality can be the use of intravenous immunoglobulin (IVIg) therapy (Foster and Ahmed, 1999; Letko *et al*, 2000; Ahmed and Colon, 2001; Jolles, 2001; Kumari *et al*, 2001a; Leverkus *et al*, 2002; Sami *et al*, 2002b). In a recent study 15 patients received an IVIg dose of 1–2 g/kg per cycle and all 15 patients had an effective clinical response, with a prolonged clinical remission (Sami *et al*, 2002b). The IVIg improved the quality of life in all 15 patients and demonstrated a steroid-sparing effect with no serious adverse effects (Sami *et al*, 2002b). Patients treated with IVIg therapy had a fast rate of decline in the antibody titres (Sami *et al*, 2002a). The regulation of IL-1 could be one of the mechanisms, amongst others, by which IVIg may exert its beneficial effect in the treatment of CP, since the levels of serum IL-1α and IL-1β were statistically significantly lower in CP patients with active disease after IVIg therapy, with statistically significantly higher levels of IL-1Ra (Kumari *et al*, 2001a).

Another patient unresponsive to different immunosuppressive treatment regimens including steroids and mycophenolate mofetil, and with severe conjunctival scarring was treated with addition of IVIg (1 g/kg body weight on two consecutive days) every 4 weeks and obtained a dramatic improvement of conjunctivitis and gingivitis (Leverkus *et al*, 2002). Clinical improvement correlated with the serum's IgA immunoblot reactivity against LAD-1 (the soluble ectodomain of BP180) (Leverkus *et al*, 2002). The IVIG therapy has also reportedly been successful in the treatment of CP in patients who had failed to respond to multiple combinations of immunosuppressive agents (Yeh *et al*, 2003)

Plasmapheresis

One patient with ocular lesions persisting despite corticosteroids and immunosuppressive agents, when treated with a combination including double-filtration plasmapheresis, improved (Hashimoto *et al*, 2000). Two other patients with severe oral CP, both resistant to corticosteroids and other standard immunosuppressive therapies, remitted when treated with the combination of plasma exchange and subsequent cyclophosphamide, and by follow up at 6 and 9 years, had no symptoms of active disease and have not required any further immunosuppressives (Bohn *et al*, 1999).

Surgery

Surgery is not a treatment for MMP but in some patients oral mucosa is used to correct ocular lesions (Shore *et al*, 1992), and surgery may be necessary to deal with scarring to prevent severe complications such as blindness, upper airway stenosis or oesophageal stricture (Foster, 1986; Hanson *et al*, 1988). Surgical procedures may however aggravate the disease and hence it is of utmost importance that there should be good control of the disease before any surgery is undertaken (Ahmed *et al*, 1991b; Nayar and Wojnarowska, 1993).

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