A Systematic Review of Management of Ocular Mucous Membrane Pemphigoid: Informing European Guidelines

UNIVERSITY OF BIRMINGHAM | COLLEGE OF MEDICAL AND DENTAL SCIENCES | INSTITUTE OF CLINICAL SCIENCES | INSTITUTE OF INFLAMMATION AND AGEING

Syed Husain[1], Robert J Barry[1,2,3], Saaeha Rauz[1,2]

[1]Academic Unit of Ophthalmology, Institute of Inflammation and Ageing, University of Birmingham
[2]Inflammatory Eye Disease Service, Birmingham & Midland Eye Centre, Sandwell & West Birmingham Hospitals NHS Trust
[3]School of Medicine, Institute of Clinical Sciences, University of Birmingham

BMEC Birmingham & Midland Eye Centre Est 1823 | NHS Sandwell and West Birmingham NHS Trust

Introduction

- Mucous Membrane Pemphigoid (MMP) is a rare, autoimmune disorder primarily affecting the mucous membranes. It is characterised by **autoantibodies directed against basement membrane proteins** in mucosal tissues leading **to blistering, ulceration and scarring**[1].
- Ocular involvement **(ocular MMP) occurs in approximately 70% of cases**, in which progressive inflammation and scarring causes **blindness in up to 20%** of affected individuals[2].
- Ocular MMP is largely managed with **topical and systemic immunosuppression, however surgery may be required** to treat disease complications[3].
- Current management guidelines are based **on outdated consensus recommendations**, and thus an update is required in light of latest evidence[4].

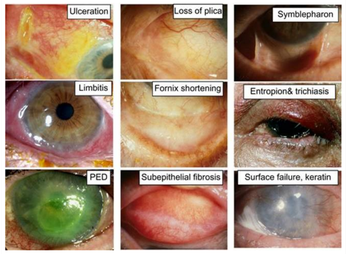


Figure 1: The variety of clinical signs present in ocular MMP[1].

Aims

1. To perform a **systematic review** of existing literature reporting **management of ocular MMP** (OcMMP).
2. Inform **development** of multidisciplinary **European S3 guidelines.**

Methods

Search strategy:

- Electronic searches of MEDLINE, EMBASE and Cochrane databases conducted in 2018. No restrictions on language/date/study design.
- Inclusion criteria: Topical, systemic or surgical treatment for patients with Ocular MMP (OcMMP).
- *Figure 2* details search strategy and study selection process.
- Two reviewers independently screened all studies, with a third reviewer to resolve disagreements on included studies.

Quality of evidence:

- Study quality was graded using Oxford Centre of Evidence Based Medicine (OCEBM) criteria (levels 1-5) where 1 signifies highest quality of evidence.

Outcome measures:

- Primary- Efficacy of topical, systemic or surgical treatment
- Secondary- Adverse events/mortality

Data extraction and synthesis:

- Study data extracted into pre-designed proforma, under relevant PICO headings.
- Data grouped into local, systemic and surgical management.
- Meta-analysis was not conducted due to significant heterogeneity in the methodology of included studies, their interventions and outcomes.

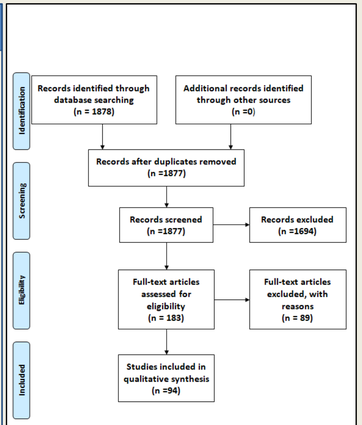


Figure 2: PRISMA flowchart showing screening process for study inclusion

Results

Class of treatment	Sample size range	Study type (no. of included studies)	Summary of evidence (OCEBM level of evidence)
Local measures (Topical and subconjunctival treatments)	1-3497	• Guideline (**1**) • Systematic review (**3**) • RCT (**1**) • Quasi-experimental design (**1**) • Chart review (**1**) • Case series (**9**) • Case report (**2**) • Laboratory studies (**3**)	• Artificial tears and autologous serum (AS) **eye drops may offer short-term (<2 weeks) symptomatic relief,** however they do not influence the immune-mediated disease course. **(Level 1)** • Topical tacrolimus, cyclosporine, tretinoin and ACTH gel improved patient symptoms (mainly dryness and irritation), albeit in limited cases. **(Level 4)** • Despite some reported symptomatic benefit from **punctal plug insertion,** their **efficacy remains inconclusive**, mostly due to heterogeneity in study methodology. **(Level 1)** • For those **intolerant to immunosuppression, subconjunctival mitomycin C** may reduce fibrosis. **(Level 4)** Adverse events: **10/21** included studies reported adverse events; most frequently reported were local allergic reactions to artificial tears.
Systemic (Immunosuppression and/or biological agents)	3-115	• Systematic review (**2**) • Narrative review (**1**) • RCT (**1**) • Cohort (**5**) • Cross-sectional (**1**) • Chart review (**1**) • Case-series (**15**)	• **Oral prednisolone** with or without supplementary loading doses of 1g IV 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 4)** • **Biological therapies** such as anti-CD20 (e.g. rituximab) or anti-TNF-alpha (e.g. infliximab), may be beneficial in patients **resistant to conventional immunosuppression for moderate and severe inflammation** in ocular MMP. **(Level 4)** • **IV Immunoglobulin (IVIG)** can be used, either alone or in combination with anti-CD20 therapy, in **severe sight-threatening disease or resistant cases.** **(Level 4)** Adverse events: **16/26** included studies reported adverse events; 8/9 studies with cyclophosphamide cited nausea, haematuria and malignancy and opportunistic infections. 4/4 studies with rituximab cited leucopenia, anaemia, elevated liver enzymes and infusion reactions.
Surgical (Grafts and prostheses)	5-181	• Systematic review (**2**) • Cohort (**1**) • Chart reviews (**4**) • Case-control (**2**) • Case-series (**38**)	• Potent immunosuppression cover is required for surgical procedures that breach the conjunctiva to provide prophylaxis against severe progression of MMP. **(Level 4)** • In cases of **stem cell failure**, **amniotic membrane grafting, corneal limbal stem cell allograft** and **cultured oral mucosa epithelial cells** may be considered. **(Level 3)** • Keratoprosthesis surgery is high risk. **Good visual outcomes** can be achieved with **osteo-odonto keratoprosthesis** for bilaterally blind patients. **(Level 3)** Adverse events: **35/47** included studies reported adverse events; most related to infection or graft/prosthesis failure.

Recommendations

1. Use of **topical steroids** may only be recommended as an **ancillary short-term treatment** for ocular involvement. **Topical cyclosporine** may be considered as an **adjunct**. Other topical treatment in the form of **lubricants** are recommended to **reduce trauma**.
2. **Systemic therapy** in ocular MMP is recommended according to a **'stepladder approach**' in *Figure 3*.
3. **Rescue surgical procedures** are effective provided inflammation is quiescent for **three months prior to surgery**.

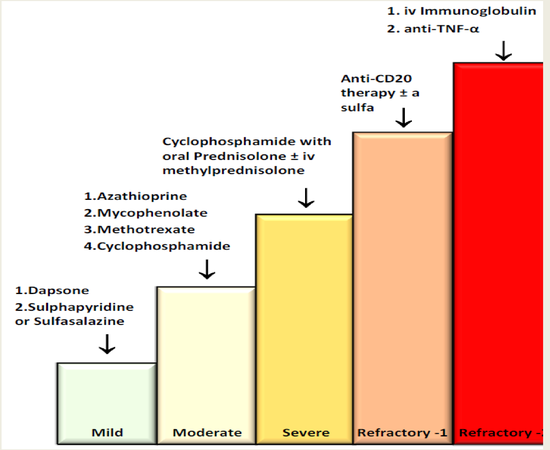


Figure 3: 'Stepladder' approach to systemic immunosuppression

Conclusions

- The **majority of publications** reporting management of ocular MMP are **low quality (level 4).**
- This review will help inform Europoean guidelines for management of MMP, enable development of standardised treatment protocols and spearhead larger scale clinical trials.

References:
1) Dart JK. The 2016 Bowman Lecture Conjunctival curses: scarring conjunctivitis 30 years on. Eye (Lond). 2017 Feb;31(2):301-332. doi: 10.1038/eye.2016.284. Epub 2017 Jan 20. PMID: 28106896; PMCID: PMC5306467.
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