Improving the evidence base in Oral Medicine

A thesis submitted to the University of Manchester for the degree of Doctor of Philosophy in the Faculty of Biology, Medicine and Health

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List of Abbreviations

BISOM/BSOM	British and Irish Society of Oral Medicine
COS	Core outcome set
EAOM	European Association of Oral Medicine
MMP	Mucous Membrane Pemphigoid
PV	Pemphigus Vulgaris
RAS	Recurrent aphthous stomatitis
ROU	Recurrent oral ulcers/ ulceration
WWOM	World Workshop of Oral Medicine
ALU	Aphthous like ulceration

Thesis Abstract

Jennifer Taylor. The University of Manchester

Abstract of Thesis submitted for the degree of Doctor of Philosophy. July 2021

Improving the Evidence Base in Oral Medicine

Background:

Oral medicine is a specialty that cares for patients with conditions of the oral and perioral region. A common group of these conditions are the oro-mucosal diseases which can cause oral ulceration with a wide spectrum of severity for patients leading to potentially significant morbidity and reduction in quality of life. Many of these conditions have no definitive treatment or cure, and as such the aim of management is to improve the patient's condition whilst minimising risk from the treatments given. Evidence based practice is the cornerstone of clinical care. A systematic review of randomised controlled trials with meta-analyses of data, is highest level of evidence available, however, the issue of heterogeneity of outcome measures is often noted and meta-analyses are rarely achieved. To improve this, the development of core outcomes sets has been suggested. Through consensus of relevant stakeholders (including patients, clinicians, and researchers), an agreed set of outcomes is developed. This set of outcomes will then be measured in all future trials for a particular condition – the aim being to reduce heterogeneity and allow for meta- analyses.

Objectives: To evaluate the evidence base of the management of four oral ulcerative conditions (Recurrent Aphthous Stomatitis (RAS), Oral Ulcers in Bechet's Disease, Oral Mucous Membrane Pemphigoid, Oral Pemphigus Vulgaris) and to develop a core outcome set for use in interventional trials for RAS using an interactive consensus process

Settings: Systematic reviews were carried out as part of the Cochrane Collaboration (Recurrent Aphthous Stomatitis (RAS) and Behçet's Disease) and World Workshop of Oral Medicine (WWOM) (Pemphigus Vulgaris (PV), Mucous Membrane Pemphigoid (MMP))

Patient involvement in core outcome set development took place at the University of Manchester, UK in 2014. Consensus process, informed by the patient input and systematic reviews, took place at the British Society of Oral Medicine (BSOM) in Leeds, UK in 2015

Participants: Patients with a diagnosis of RAS who were attending the oral medicine department in Manchester, were involved in the patient information meeting.

Delegates at the BSOM meeting attended the consensus process, including oral medicine specialists, dentists, dental hygienists, dental nurses and research academics.

Design: Mixed methods, including systematic reviews, patient involvement and interactive consensus via clicker technology.

Results:

The four systematic reviews reported heterogeneity of outcomes and no meta-analyses were possible.

The RAS patients identified six important outcomes for inclusion. Systematic review of 73 interventional randomised controlled trials for RAS revealed a total of 313 individual outcomes. This number was reduced to 22 by removing duplication and grouping similar outcomes into domains. Consensus process led to further agreement on the inclusion of 13 outcomes for the COS

Conclusion: Interventional trials for oral conditions should adopt the use of a core outcome set so that future systematic reviews and meta-analyses can be carried out to

provide clinicians with higher quality evidence base than is currently possible due to the heterogeneity of outcome measure used in trials. This project demonstrates a new process for gaining consensus for COS which avoids the need for large scale postal Delphi processes. With ongoing improvements in interactive online programmes, consensus processes will be easier to arrange and will allow for greater and wider participation.

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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Finally, I would like to dedicate this to my Dad who is watching me from the wee clouds above- hopefully you are pleased I finally finished it!

The Author

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She qualified with a Bachelor of Dental Surgery (BDS) in 2000 from the University of Glasgow and completed a two-year longitudinal dental foundation training programme in Southeast Scotland. She successfully passed MFDS in 2002 (Royal College of Surgeons, Edinburgh). This was followed by 2 years working as a senior house officer in maxillofacial surgery in Fife, Scotland.

With a view to furthering a career in maxillofacial surgery – she entered year 3 of MBChB at the University of Manchester – and undertook clinical training in Preston, Lancashire. She qualified as a medical doctor (MBChB) in 2007. In 2011, after medical foundation training in Manchester and two periods of maternity leave, she entered less than full time higher specialty training in oral medicine and completed Intercollegiate Specialty fellowship Examination in 2015.

Following completion of training she worked as a locum consultant in Manchester and made the move back to Scotland in September 2017. Since then, she has been working as a NHS consultant and honorary senior clinical lecturer in Glasgow. In addition to the many roles of her busy clinical job she is involved in teaching and training of undergraduate dental students and dental core trainees. She is the Training Programme Director for Oral Medicine in Scotland.

During the initial stages of the COVID pandemic, she was redeployed back to frontline medicine and worked in the acute COVID receiving unit before contracting the infection and developing COVID pneumonia. Following a substantial recovery period – she resumed her clinical and academic activities in September 2020 and has been working hard to reduce the lengthy clinical backlog caused by the ongoing pandemic.

During her clinical oral medicine training in Manchester, she developed an interest in evidence-based dentistry and recurrent aphthous stomatitis. What started with a clinical question of how best to manage patients with a common, painful, and incurable condition led to the development of this PhD project. Her research aims to improve the quality of evidence through the development of core outcome sets in oral medicine. She disseminated her research widely throughout the prolonged length of her part time

postgraduate degree course, which was carried out alongside her clinical training job. As a result of this, she developed numerous academic relationships on an international scale. To date, as a clinical NHS consultant, she continues her academic interests with her work with Cochrane Oral Health, as a European Association of Oral Medicine RAS position paper lead author, as joint section head of WWOM core outcome set for Oral Lichen Planus and as author of BMJ best practice guidelines on Aphthous stomatitis.

Out-with work, she lives with her husband, two children and the latest addition to the family, a lively spaniel puppy.

Publications from this thesis (listed chronologically):

Brocklehurst P, Tickle M, Glenny AM, Lewis MA, Pemberton MN, Taylor J, Walsh T, Riley P, Yates JM. Systemic interventions for recurrent aphthous stomatitis (mouth ulcers). *Cochrane Database of Systematic Reviews* 2012, Issue 9. Art. No.: CD005411

Taylor J, Brocklehurst P, Walsh T, Riley P, Glenny A-M, Gorodkin R, Pemberton MN. Interventions for the management of oral ulcers in Behçet's disease. *Cochrane Database of Systematic Reviews* 2014, Issue 3. Art. No.: CD011018. DOI: 10.1002/14651858.CD011018

Taylor J, McMillan R, Shephard MK, Setterfield J, Ahmed R, Carrozzo M, Grando S, Mignogna M, Kuten-Shorrer M, Musbah TM, Elia A, McGowan R, Kerr AR, Greenberg M, Hodgson T, Sirois D, World Workshop on Oral Medicine VI: A Systematic Review of the Treatment of Mucous Membrane Pemphigoid, Oral Surgery, *Oral Medicine, Oral Pathology and Oral Radiology* (2015), doi: 10.1016/j.oooo.2015.01.024

McMillan R, Taylor J, Shephard M, Ahmed R, Carrozzo M, Setterfield J, Grando S, Mignogna M, Kuten-Shorrer M, Musbah T, Elia A, McGowan R, Kerr AR, Greenberg MS, Hodgson T, Sirois D
Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology (2015) doi: 10.1016/j.oooo.2015.01.022.

Taylor, J., Walsh, T., Worthington, H., Brocklehurst, P., Pemberton M., Glenny AM. Cochrane and the COMET initiative: developing the evidence base in oral medicine. *British Dental Journal* 223**,** 729–732 (2017).

The inclusion of publication style chapters can lead to duplication with other sections of the thesis; this is acknowledged within the guidelines for this thesis format. The chapters are presented in the most logical order for the thesis but do not necessarily reflect the publication order.

Chapter 1 Introduction

Oral medicine is a dental specialty that aims to give high quality medical care to patients with non-dental, orofacial problems. It acts as a focus for specialist interdisciplinary care of patients with either orofacial manifestations of systemic conditions or localised orofacial problems unrelated to the teeth (Mighell, 2006).

There are a wide range of conditions affecting the maxillofacial region, and management of these conditions within oral medicine practice is primarily medical as opposed to the primarily surgical management of patients under the care of dental, oral, or oral and maxillofacial surgeons.

As well as dental and periodontal conditions; musculoskeletal, salivary gland, neuropathic, potentially malignant/ malignant, and mucosal conditions also come under the remit of oral medicine. Soft tissue disease includes both extra-oral skin conditions and intraoral mucosal disease. The spectrum of severity of conditions affecting these areas is wide and encompasses simple, self-resolving conditions through to progressive diseases that can cause severe morbidity and mortality.

Many diseases and conditions can cause changes to the mucous membranes (mucous lining) of the mouth and in most cases, these represent complex, immune-mediated, auto-inflammatory processes.

Due to the chronic nature of the mucosal diseases, the aim of treatments is primarily to reduce symptoms for patients, in essence most treatments are palliative in nature. The risk-benefit balance for all treatments is considered before commencement, and as always, a high-quality evidence base should support the decisions made by clinicians.

The oral and perioral region has a complex role in the health and wellbeing of patients. Conditions affecting this area can cause significant problems with basic necessary

functions such as breathing, eating, drinking, swallowing, and speaking, through to involvement in the primary senses of smell and taste.

Therefore, the conditions that affect the oral and perioral region can have a significant impact not only on the basic requirements for life (to breathe – to eat – to drink), but in addition they can affect the wellbeing and general health of patients.

Treatment modalities for management of oro-mucosal disease can vary from simple topical treatments through to systemic interventions with potentially serious side effects and often varied efficacy. Severe oro-mucosal disease is thankfully rare; however, this means that access to high quality randomised trials is limited. This thesis includes systematic reviews of treatments for a variety of oro-mucosal and mucocutaneous diseases. These incorporate the most common cause of oral ulceration (Recurrent Aphthous Stomatitis) through to the less common and more severe immunobullous conditions (including Pemphigus Vulgaris and Mucous Membrane Pemphigoid). These conditions, their prevalence, aetiology, and management options are described within each relevant chapter.

The importance of evidence-based practice within the delivery of oral medicine is explored within this introduction, highlighting the role of systematic reviews (such as those produced by Cochrane) and core outcome sets (Taylor et al., 2017).

This following section (a published paper) acts as an introduction to the themes of this thesis and summarises the approaches taken towards improving the evidence by development of a core outcome set.

1.1 Cochrane and the COMET initiative: developing the evidence base in oral medicine

This section has been published in the British Dental Journal (Oral Medicine Special Edition)

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All clinicians in medicine and dentistry aim to deliver evidence-based practice; however, it is widely recognised that the current evidence base for interventions in oral medicine, as with many other specialties, is of a low quality. The highest level of evidence is the systematic review and meta-analysis. The Cochrane Collaboration and the Cochrane Oral Health group produce high quality systematic reviews, however, despite the large number of trials carried out for treatments in oral medicine, the results are often not able to be utilised to guide clinical care due to the various methodological limitations of the trials including the heterogeneity of outcome measures used. To improve the strength of the evidence base this will need to change. The Comet initiative aims to support the development of core outcome sets which are used to allow homogeneity of outcome measures in trials and therefore will allow pooling of data for meta-analysis in future systematic reviews. This paper explores the complexities involved in producing evidence for oral medicine interventions and introduces an approach for developing core outcome sets in oral medicine.

Evidence-based practice

The concept of using research evidence to inform healthcare involving oral medicine, has a long history. One of the earliest accounts of research being undertaken to explore treatment options is the comparative clinical trial reported in James Lind's *Treatise of the scurvy*, published in 1753 (Lind, 2014). Lind was a surgeon on HMS Salisbury. His book details his comparison of interventions for the treatment and prevention of scurvy, along with a critical and chronological account of what had been previously published on scurvy. Scurvy has multisystem manifestations including a number of oral features such as swollen and friable gingivae and spontaneous gingival haemorrhage. At the time it was a common disease among long distance sailors. Lind's work identified the superiority of the citrus fruits over other proposed treatments and, although recognised as important, it took more than 40 years before the results of Lind's experiments were acted upon; this time lag between research findings and changes in practice is still apparent today (Woolf et al., 1999).

This paper will briefly explore how the use of research evidence has developed since then to inform clinical practice focusing on oral medicine. It will also introduce the concept of core outcome sets to help improve future trial data reporting to allow comparison, contrast and combination as appropriate.

Despite the historic use of evidence in informing practice, the term 'evidence-based practice' (EBP) is relatively new, appearing initially as evidence-based medicine in 1992. Over the years EBP has evolved to mean many things to many people. Perhaps the most frequently used and feasible definition of EBP (first applied to evidence-based medicine) is: 'The conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients' (Sackett, 1997).

EBP is not about applying the results of research to all clinical settings and all patients without careful thought and evaluation. Instead, it promotes the integration of best available research evidence with the individual clinician's experience and clinical judgement. In addition to this, the patient's expectations and preferences need to be taken into the decision-making process; a factor often not considered. Only when research evidence, clinical expertise and patient values are considered together can practice be considered evidence-based.

Clearly, in order to practice EBP, there needs to be a strong evidence base. That is, there needs to be relevant, valid research. Despite the promotion of EBP over the last 30 years, it has been estimated that only 15% of all clinical practice is based on sound research evidence (Miller and Kearney, 2004). Variations in practice and the provision of inappropriate care continue. The incorporation of research evidence into the clinical decision-making process may be hampered by several factors (Craig et al., 2001), not least the lack of reliable research addressing a clinical issue.

It has been suggested that the most realistic use of EBP by practitioners at the point of care involves the use of summaries of research evidence (Craig et al., 2001). Sources of secondary research, such as systematic reviews and clinical guidelines, may indeed have an important role to play in helping to close the gap between research evidence and clinical practice (Woolf et al., 1999), providing they themselves are well conducted, address a clinically important question and that there are reliable studies addressing the specified questions.

Cochrane

One organisation aiming to improve the use of research evidence in clinical practice is The Cochrane Collaboration (now known as Cochrane). Cochrane is a global independent network of researchers, professionals, patients, carers, and people interested in health. There are more than 37,000 contributors from over 130 countries. They aim to produce credible, accessible health information that is free from commercial sponsorship and other conflicts of interest. Cochrane believe the need to produce high-quality systematic reviews of research evidence is of increasing importance: 'As access to health evidence increases, so do the risks of misinterpreting complex content; meanwhile the likelihood of any one person getting a complete and balanced picture decreases' (http://www.cochrane.org/about-us). Cochrane is internationally recognised as the benchmark for high-quality information about the effectiveness of healthcare. It focuses predominantly, but not exclusively, on systematic reviews of randomised controlled trials (RCTs). It is acknowledged, however, that RCTs may not be the most appropriate study design to evaluate every clinical research question. Clinicians, policy makers and researchers need to be able to recognise the merits of different study designs in primary research for answering different types of clinical questions (whether they deal with evaluating the effectiveness of preventative or therapeutic interventions, the diagnosis of a particular disease or condition, incidence or prevalence, or perhaps cost-effectiveness of a defined management strategy) .

Cochrane Oral Health (COH)

Cochrane is made up of over 50 Review Groups, of which COH is one. (http://oralhealth.cochrane.org) (Worthington et al., 2010). The scope of COH is to

undertake systematic reviews (predominantly of randomised controlled trials) covering the prevention, treatment and rehabilitation of oral, dental, and craniofacial diseases and disorders. The group has a worldwide network of over 1,650 members from 42 different countries. It maintains a register of references to clinical trials within the scope of the group. This register currently contains around 33,000 references. To date, COH have 154 published systematic reviews and 45 protocols. Their reviews have been used to inform guideline development by organisations such as the National Institute for Health and Care Excellence (NICE), the Scottish Intercollegiate Network (SIGN), the American Dental Association and the Scottish Dental Clinical Effectiveness Programme (SDCEP).

COH are committed to producing high-quality reviews that address priority clinical questions. They are currently working on an international priority setting exercise to ensure they address questions that are most useful for informing clinical decision-making by consumers and clinicians alike. In a previous COH prioritisation exercise carried out in 2014, oral medicine conditions featured in two distinct areas:

- Oral cancer (screening, diagnostic tests, clinical assessment)
- Oral conditions (temporomandibular disorders (TMD), lichen planus, leukoplakia, denture stomatitis).

In undertaking the reviews, COH are keen to ensure they work closely with all relevant stakeholders, in particular guideline developers, to ensure there is minimal duplication of effort and maximum uptake of the findings from their systematic reviews.

Oral medicine and the evidence base

There are several Cochrane reviews in the field of oral medicine, covering a variety of topics (see Table 1). A key criticism of Cochrane reviews, particularly within dentistry, is that there are insufficient trials for the reviews to be useful. However, in the majority of oral medicine reviews, this is not the case with the number of trials included in the latest versions of the reviews ranging from 10–131. Despite the large number of trials in oral medicine, the results produced are often too heterogeneous to be utilised to inform clinical practice.

Review	Review type	Number of RCTs
Interventions for preventing/treating oral mucositis for patients with cancer receiving treatment	Effectiveness	131 trials of prevention; 32 trials of treatment
Interventions for preventing/treating oral candidiasis for patients with cancer receiving treatment	Effectiveness	28 trials of prevention; 10 trials of treatment
Interventions for treating oral lichen planus	Effectiveness	28
Interventions for treating oral leukoplakia	Effectiveness	14
Diagnostic tests for oral cancer and potentially malignant disorders in patients presenting with clinically evident lesions	Diagnostic test accuracy	41
Clinical assessment to screen for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults	Diagnostic test accuracy	13
Systemic interventions for the management of recurrent aphthous stomatitis (mouth ulcers)	Effectiveness	25
Interventions for the management of oral ulcers in Behçet's Disease	Effectiveness	14
Topical interventions for the management of recurrent aphthous stomatitis (mouth ulcers)	Effectiveness	Ongoing review, 77 trials included to date

Table 1. Oral-medicine-related Cochrane reviews

For example, with regard to recurrent aphthous stomatitis (RAS), there are over 25 trials in a review evaluating systemic interventions (see Chapter 2) and 77 trials to date in an ongoing review evaluating topical interventions . The evidence base presented in each review is limited by several factors. Firstly, there is a wide range of interventions being assessed. Twenty-five trials of systemic interventions provide evidence on 21 different interventions; 77 trials of topical interventions provide evidence on over 60 interventions. In most cases, each intervention was assessed in only a single trial; where more than one trial evaluated the same intervention there was variation in dose and duration of the intervention and choice of control group. Such clinical heterogeneity precludes pooling of data. Often, interventions were evaluated with little clinical justification or discussion of biological plausibility and suggested mode of action.

In addition, there was substantial heterogeneity in type and timing of outcome assessment. When evaluating ulcers, this outcome was reported variously as number of ulcers, number of episodes, duration of ulcers/healing time, complete healing, size of ulcers, presence of ulcers, erythema, oedema, exudation, compound/summated RAS index, ulcer severity, site of ulcers, effectiveness index, onset of prodromal phase and recurrence. Other outcomes evaluated include pain (measured in a variety of ways), eating and drinking experience, brushing experience, tolerability/satisfaction with medication, recovery of function, adherence, and daily activity disturbance. The timing of assessments also varied. Some trials reported single episodes of ulceration and others reported multiple episodes (presenting data either cumulatively or per episode). Timeframes were as short as eight hours or as long as six months. In some cases, timing of outcome measurement was unspecified, or based around daily function (for example, before/after meal times). Unless the primary time point of interest is clearly specified *a*

priori, there is potential for the reporting and interpretation of results to be data driven, that is, according to the time point that provides the most favourable result rather than at the time point which is of clinical interest or importance.

To assess the risk of bias in trials the Cochrane Risk of Bias Assessment tool was used (covering selection, performance, detection, attrition and reporting biases) (Higgins et al., 2011b). Out of all 102 trials evaluated to date within the two systematic reviews, only one was considered to be at low risk of bias overall (Lalla et al., 2012). One of the main areas of potential bias was selective reporting. Trials were assessed as being at risk of selective reporting bias due to the lack of reporting of important, expected outcomes (for example, pain), lack of reporting of outcomes listed in the methods section, outcomes reported but not at all listed time points, or summary statistics reported without measures of variability.

Issues regarding lack of accounting for multiplicity following measurement at many time points and reporting at an ulcer level rather than a person level were also apparent, as was analysis within the intervention and comparator groups over time, rather than comparing the groups at a specified time point.

The use of composite scales, providing a summated score based on categorical scores on a range of clinical domains (for example, number of ulcers, size, duration, ulcer-free period, site and pain) were also problematic. Unless scores for individual components are also provided, it is difficult to interpret the findings as improvement could be due to changes in any one of the domains measured or a composite. It is recognised that there is no cure for RAS and therefore all treatments are used to alleviate symptoms. The assessment of their impact therefore is best carried out by the patients themselves. The use of patient reported outcome measures is an important area to consider in RAS and many other oral medicine conditions. The use of a validated quality of life tool to assess

the impact of chronic oral disease would be beneficial as described by Ni Riordain *et al* (Ni Riordain and McCreary, 2012).

Other limitations were apparent in the RAS evidence base, often linked to poor reporting. Although no formal assessment on reporting has been undertaken, there does not appear to be any consistent improvement in the conduct and reporting of RAS trials over time. Recent trials still lack clarity with regard to the inclusion/exclusion of participants within the trials, with the definition of RAS not always being apparent or whether individuals with systemic causes of RAS type lesions had been excluded. Many trials are limited in size, often with insufficient participants to be able to observe a statistically significant effect of treatment in the trial between interventions if one truly existed.

The Cochrane reviews of RAS are not the only reviews to have highlighted limitations of the evidence base in this area. Baccaglini *et al*. undertook a systematic review of RAS interventional trials published from 2005 to 2011 (Baccaglini et al., 2011). They identified considerable methodological flaws in the trial designs. They concluded, 'Improved design, analysis and standardised reporting of clinical trials are needed to maximise study quality, disclose potential sources of bias, and ensure complete assessment of product safety and effectiveness.'

These limitations are not isolated to RAS trials. Clinical trials in other areas of oral medicine have also been compromised due to methodological factors (Baccaglini et al., 2010). Two recent systematic reviews assessing interventions for mucocutaneous pemphigus vulgaris (PV) and mucous membrane pemphigoid (MMP), carried out as part of the Sixth World Workshop of Oral Medicine (WWOM VI) and published in 2014, also concluded that there was inadequate quality of research supporting optimal PV treatment and a lack of high-quality research providing evidence-based MMP

treatments (McMillan et al., 2015, Taylor et al., 2015). Both reviews revealed numerous methodological limitations including heterogeneity of outcome measures used. These reviews are presented in Chapters 4 and 5.

Future trials

Several steps can be undertaken to help overcome the limitations identified. A number of these steps are clearly described in a recent paper by Innes *et al* (Innes et al., 2016). Prospective registration of trial protocols can help overcome issues of reporting biases, specifically outcome reporting bias. Careful attention needs to be given to the choice of intervention being evaluated; interventions should be relevant to current practice and compared with appropriate controls (that is, not sub-clinical doses of alternative treatments). Trials should be methodologically rigorous in their design and fully reported according to the CONSORT statement (www.consort-statement.org).

While single treatment interventions are the most common type of trial design, they do not necessarily reflect how the intervention is used within everyday practice, which often utilises multiple and/or sequential approaches to treatment. This has the potential to reduce the external validity of the study and so other types of trial design should be considered (for example, n-of-1 and stepped interventions) at the design stage.

In addition to examining the effectiveness of interventions, future studies should incorporate an appropriate economic evaluation. As stated in the Cochrane Handbook (Shemilt et al., 2011), the usefulness and applicability of Cochrane reviews can be enhanced by incorporating economics perspectives. Future trials should consider calculating and reporting the costs of interventions evaluated in order to better inform healthcare decision-making.

Outcome sets & the COMET initiative

Importantly, given the huge variation in the choice of outcomes measured, a set of standardised, clinically relevant outcome measures needs to be developed across different topic areas within oral medicine. As described below, this work is currently underway for RAS, registered with COMET (core outcome measures in effectiveness trials; www.comet-initiative.org), and was presented as a poster at the recent European Association of Oral Medicine (EAOM) meeting in Turin (Taylor, 2016). We hope it will be used to inform trials and subsequently reviews in this area.

The COMET initiative is an international collaboration which aims to reduce the heterogeneity of outcome measurements used in trials (www.comet-intiative.org). COMET (core outcome measurements in effectiveness trials) 'brings together researchers interested in the development and application of agreed standardised sets of outcomes, known as a 'core outcome set.' These sets should represent the minimum that should be measured and reported in all clinical trials, audits of practice or other forms of research for a specific condition. They do not imply that outcomes in a particular study should be restricted to those in the core outcome set. Rather, there is an expectation that the core outcomes will be collected and reported to allow the results of trials and other studies to be compared, contrasted and combined as appropriate; and that researchers will continue to collect and explore other outcomes as well' (www.comet-intiative.org). There are a wide variety of core outcome sets that have previously been developed in areas outside of dentistry. These include the CROWN initiative (core outcome sets in women's in newborn health) (http://www.crown-initiative.org/core-outcome-sets/) and OMERACT (outcome measures in rheumatology) (https://www.omeract.org).

Using a suggested framework for the development of a core outcome set, a three stage approach was carried out in the development of a core outcome set for recurrent aphthous stomatitis (COSRAS) (Williamson et al., 2012):

- Identifying existing knowledge: a review of the existing outcome measures in use
- Stakeholder involvement: the opinions of RAS patients with regards to outcome measures
- Consensus methods: Delphi consensus process of clinicians involved in managing RAS patients.

RAS patients were asked about the outcome measures they thought were important and this information was combined with the results of a systematic review of outcome measures in trials of RAS treatments. Removing duplications, over 300 outcomes were condensed into 22 broad outcomes; these included the patient outcomes of choice. These 22 individual outcomes were then presented to oral medicine clinicians at a national speciality meeting (British Society of Oral Medicine) with the aim of gaining consensus on the outcomes to be included in a core outcome set (see Chapter 6).

The difficulty of recruiting adequate numbers of participants to clinical trials is well-known to any triallist and results in the risk of a study being underpowered. The use of a core outcome set in oral medicine trials makes the possibility of allowing combination of the results of different trials in a meta-analysis a realistic possibility, as well as allowing meaningful comparison of different interventions. Ultimately, the strength of the evidence base to guide clinical care will be improved.

1.2 Conclusion

High-quality research informs clinical guidelines and everyday practice. It is important that clinicians maintain up to date knowledge of their subject matter in order to provide the best care for patients. This is especially important in oral medicine as many of the conditions and interventions used to treat have considerable morbidity and in some cases mortality. Cochrane systematic reviews are a useful tool for evaluating and summarising the evidence for clinicians, however, the quality of the evidence produced by the systematic reviews is directly related to the quality of the trials included. Improvements to the methodology of oral medicine intervention trials as described in this paper, the use of patient-related outcomes measures (PROMS) and the future development and use of core outcome sets should improve the quality of the evidence produced to inform clinical care.

1.3 Aims

The aim of this thesis is to improve the oral medicine evidence base. This will be achieved through 2 stages. The first is to evaluate the evidence that is available, and this presented as four published systematic reviews all with commonly found methodological limitations. The second is the development of the first core outcome set of its kind in oral medicine.

i) To determine the clinical effectiveness and safety of systemic interventions in the reduction of pain associated with recurrent aphthous stomatitis, a reduction in episode duration or a reduction in episode frequency

ii) To evaluate the effectiveness of interventions for the management of aphthous like ulcerations in people with Behçet's disease,

iii) To evaluate the efficacy and safety of interventions for oral pemphigus vulgaris

iv) To evaluate the efficacy and safety of interventions for oral mucous membrane pemphigoid

v) To develop a core outcome set for recurrent aphthous stomatitis

Chapter 2 Systemic interventions for recurrent aphthous stomatitis (mouth ulcer)

The first review paper of this thesis is a Cochrane systematic review. This paper sparked my interest in evidence-based dentistry and led to the development of this project and ultimately the registration of my PhD.

I was fully involved in this review from protocol development, screening, data collection through to analysis, discussion and write up. I have presented the findings locally, nationally, and internationally.

This Cochrane Review has been published and is presented here in a format suitable for this thesis.

Systemic interventions for recurrent aphthous stomatitis (mouth ulcer)

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2.1 Abstract

Background

Recurrent aphthous stomatitis (RAS) is the most frequent form of oral ulceration, characterised by recurrent oral mucosal ulceration in an otherwise healthy individual. At its worst RAS can cause significant difficulties in eating and drinking. Treatment is primarily aimed at pain relief and the promotion of healing to reduce the duration of the disease or reduce the rate of recurrence. A variety of topical and systemic therapies have been utilised.

Objectives

To determine the clinical effect of systemic interventions in the reduction of pain associated with RAS, a reduction in episode duration or frequency.

Search methods

We undertook electronic searches of: Cochrane Oral Health Group and PaPaS Trials Registers (to 6 June 2012); CENTRAL via The Cochrane Library (to Issue 4, 2012); MEDLINE via OVID (1950 to 6 June 2012); EMBASE via OVID (1980 to 6 June 2012); CINAHL via EBSCO (1980 to 6 June 2012); and AMED via PubMed (1950 to 6 June 2012). We searched reference lists from relevant articles and contacted the authors of eligible trials to identify further trials and obtain additional information.

Selection criteria

We included randomised controlled trials (RCTs) in which the primary outcome measures assess a reduction of pain associated with RAS, a reduction in episode duration or a reduction in episode frequency. Trials were not restricted by outcome alone. We also included RCTs of a cross-over design.

Data collection and analysis

Two review authors independently extracted data in duplicate. We contacted trial authors for details of randomisation, blindness and withdrawals. We carried out risk of bias assessment on six domains. We followed The Cochrane Collaboration statistical guidelines and risk ratio (RR) values were to be calculated using fixed-effect models (if two or three trials in each meta-analysis) or random-effects models (if four or more trials in each meta-analysis).

Main results

A total of 25 trials were included, 22 of which were placebo controlled and eight made head-to-head comparisons (five trials had more than two treatment arms). Twenty-one different interventions were assessed. The interventions were grouped into two categories: immunomodulatory/anti-inflammatory and uncertain. Only one study was assessed as being at low risk of bias. There was insufficient evidence to support or refute the use of any intervention.

Authors' conclusions

No single treatment was found to be effective and therefore the results remain inconclusive in regard to the best systemic intervention for RAS. This is likely to reflect the poor methodological rigour of trials, and lack of studies for certain drugs, rather than the true effect of the intervention. It is also recognised that in clinical practice, individual drugs appear to work for individual patients and so the interventions are likely to be complex in nature. In addition, it is acknowledged that systemic interventions are often reserved for those patients who have been unresponsive to topical treatments, and therefore may represent a select group of patients.

2.2 Plain language summary

Systemic interventions for recurrent aphthous stomatitis (mouth ulcers)

Mouth ulcers (sores) are one of the most common oral problems and many people suffer with them repeatedly. These can be painful and slow to heal. At its worst, this can cause significant difficulties in eating and drinking. This review found that many different treatments were used to manage this condition, although the evidence of their effectiveness remains inconclusive.

2.3 Background

Recurrent aphthous stomatitis (RAS) is the most frequent form of oral ulceration with a prevalence in the general population ranging between 5% and 60% (Jurge et al., 2006). It is characterised by recurrent oral mucosal ulceration in an otherwise healthy individual (Porter et al., 1998). The peak age of onset is between 10 and 19 years of age, and it can persist into adulthood and throughout the patient's lifespan, with no gender predilection (Ship et al., 2000).

According to Bagan there are three recognised forms (Bagan et al., 1991):

- Minor aphthae are typically round and less that 10 mm in diameter. These are generally pale in colour with an erythematous border and commonly affect non-keratinised mucosa including the labial and buccal mucosa, the borders of the tongue, and the floor of the mouth. Minor aphthae can occur in isolation but characteristically occur in crops of small numbers. Healing is spontaneous and usually takes 7 to 10 days. Episodes of ulceration are usually followed by an ulcer-free period lasting a few days to several weeks before the next episode

occurs (Thornhill et al., 2007). Minor aphthae account for 80% of patients with RAS (Thornhill et al., 2007).

- Major aphthae are similar to minor aphthae but are larger, usually exceeding 10 mm in diameter. Consequently, healing can take longer (20 to 30 days) and may result in scarring (Bagan et al., 1991).
- Herpetiform ulcers are less than 1 mm in diameter and often occur in multiples from 1 to 100. There is a tendency for adjacent ulcers to merge to form a large affected area. Healing takes place within 15 days (Bagan et al., 1991).

The aetiopathogenesis of RAS is multifactoral (Jurge et al., 2006). Some patients have a genetic predisposition, with at least 40% of patients having a positive family history (Sircus et al., 1957). In a review of the literature, Jurge et al suggests that a bacterial or viral aetiology is unlikely and that the immunopathogenesis of the disease is most likely to involve a cell mediated immune response mechanism involving the generation of T-cells (Jurge et al., 2006), interleukins (Sun et al., 2000), and tumour necrosis factor (TNF) (Natah et al., 1998). However, a lymphocyte-mediated mechanism in addition to immune complexes have also been proposed (Jurge et al., 2006), and cross-reactivity between streptococci and the oral mucosa has been demonstrated (Lehner et al., 1991). Local factors can predispose patients to RAS and physical trauma can initiate ulcers in susceptible people (Wray et al., 1981), but RAS is uncommon in patients who smoke tobacco (Salonen et al., 1990). Reduced iron storage has also been reported in 37% of patients (Porter et al., 1993), and psychological illness has also been postulated but this has not been substantiated (Miller and Ship, 1977).

Patients with systemic diseases are also prone to oral ulceration but these manifestations may be secondary to their medical condition and so should be considered separately. These include Behçet's disease, Reiter's syndrome, recurrent erythema multiforme,

coeliac disease, Crohn's disease, ulcerative colitis, anaemia and haematinic deficiency (vitamin B12, folic acid and iron).

For clarity, if there is no associated systemic disease, this will be described as 'RAS'. When the ulceration may be associated with an underlying systemic disease, then this will be described as 'RAS type ulceration'.

Description of the intervention

Treatment is primarily aimed at pain relief and the promotion of healing to reduce the duration of the disease or reduce the rate of recurrence. A variety of topical and systemic therapies have been utilised (Porter et al., 1998), but few studies have demonstrated efficacy. Empirically, effective treatments include the use of corticosteroids, immunosuppressants and topical barriers (Eisen and Lynch, 2001). Mycophenolate mofetil, pentoxifylline, colchicine, dapsone and thalidomide have also been used but with some caution due to the potential for adverse effects. Therapies are principally palliative but none result in permanent remission (Eisen and Lynch, 2001).

Why it is important to do this review

All three clinical types of RAS are associated with varying degrees of morbidity, including pain and difficulties in function. At its worst, RAS can cause significant difficulties in eating and drinking, leading to loss of weight. Given its high prevalence, the prevention of RAS or the reduction of the pain or longevity of the disease are important goals in oral medicine.

This review will focus on the use of systemic interventions in the management of RAS and so will complement the planned Cochrane review examining the use of topical agents.

2.4 Objectives

The objectives of this review are to determine the clinical effectiveness and safety of systemic interventions in the reduction of pain associated with recurrent aphthous stomatitis, a reduction in episode duration or a reduction in episode frequency.

2.5 Methods

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) in which the primary outcome measures assess a reduction of pain associated with recurrent aphthous stomatitis (RAS), a reduction in episode duration or a reduction in episode frequency. However, trials were not restricted by outcome alone and so other measures were considered if relevant to the review e.g. quality of life or a reduction in morbidity e.g. function. We also included RCTs of a cross-over design, provided that the trial included a suitable washout period and no carry-over effects were evident.

Types of participants

Participants with a previous or current history of recurrent aphthous stomatitis, diagnosed on history and clinical examination. We excluded participants with the following conditions: Behçet's disease, Reiter's syndrome, recurrent erythema multiforme or any viral infection. In addition, patients with coeliac disease, Crohn's disease, ulcerative colitis, anaemia and haematinic deficiency (vitamin B12, folic acid and serum ferritin) were also excluded, when sufficient detail is provided in the trial. This was to ensure that patients entering into a trial are for primary lesions, not lesions that are secondary to a medical condition.

Types of interventions

Active treatment included any preventive, palliative or curative interventions administered systemically. Controls were either no active treatment or the administration of a placebo, but head-to-head trials of different interventions were also included, if identified.

Types of outcome measures

Primary outcome measures assessed were:

- pain associated with recurrent aphthous stomatitis;
- episode duration associated with recurrent aphthous stomatitis;
- episode frequency associated with recurrent aphthous stomatitis; and
- safety of the intervention including adverse effects.

Where outcome measurements were taken at multiple time points, the measurements closest to the end of treatment were included in the review. Where cumulative outcome measurements were reported over the total treatment period, these were also included.

Secondary outcome measures assessed included any patient reported outcomes that measure improvements in the patients' quality of life and reduction in morbidity (e.g. function).

Search methods for identification of studies

For the identification of studies included or considered for this review, detailed search strategies were developed for each database searched. These were based on the search strategy developed for MEDLINE (OVID) but revised appropriately for each database (Appendix 1). This search strategy was used in addition to the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomized trials in MEDLINE: sensitivity maximising version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011] (Higgins and Green). The search of EMBASE was linked to the Cochrane Oral Health Group filter for identifying RCTs.

The following electronic databases were searched:

- The Cochrane Oral Health Group's Trials Register (to 6 June 2012)
- CENTRAL (The Cochrane Library, 2012, Issue 4)
- MEDLINE via OVID (1950 to 6 June 2012)
- EMBASE via OVID (1980 to 6 June 2012)
- CINAHL (to 6 June 2012)
- AMED (to 6 June 2012)

Handsearching for this review was done as part of the Cochrane Worldwide Handsearching Programme (see http://us.cochrane.org/master-list).

We checked the bibliographies of included papers and relevant review articles for studies not identified by the search strategies above. We contacted the authors of identified and included studies to identify unpublished or ongoing trials.

Any non-English trials that were identified were translated through The Cochrane Collaboration.

Data collection and analysis

Selection of studies

At least two review authors independently scanned the titles and abstracts obtained from the initial electronic searches in duplicate (Appendix 2). We obtained full text reports for the studies that fulfilled the inclusion criteria. When there was insufficient data in the study title to determine whether a study fulfilled the inclusion criteria, we obtained the full text report and at least two review authors independently assessed them in duplicate. Disagreement was resolved by discussion.

Data extraction and management

All studies meeting the inclusion criteria underwent data extraction and an assessment of risk of bias was made using a data extraction form (Appendix 3). Studies rejected at this and subsequent stages were recorded in the table of excluded studies. At least two review authors independently extracted data from each included study in duplicate using a tool developed for the review. All included trials were discussed in detail by a multidisciplinary team of clinicians, statisticians and methodologists. Differences were resolved by discussion. If a single publication had reported two or more separate studies, then each study would have been data extracted separately. If the findings of a

single study had been spread across two or more publications, then the publications would have been extracted as one. For each study with more than one control or comparison group for the intervention, we extracted the results for each intervention arm. For each trial we recorded the following data:

- Year of publication, country of origin and source of study funding.
- Details of the participants including demographic characteristics and criteria for inclusion.
- Details on the type of intervention and comparisons.
- Details on the study design.
- Details on the outcomes reported, including method of assessment and adverse outcomes.

Assessment of risk of bias in included studies

At least two review authors independently assessed the risk of bias of each included study in duplicate using the Cochrane risk of bias assessment tool. The domains that were assessed for each included study were:

- sequence generation.
- allocation concealment.
- blinding.
- completeness of outcome data.
- risk of selective outcome reporting; and
- risk of other potential sources of bias.

A description of the domains was tabulated for each included trial, along with a judgement on the risk of bias (low, high or unclear), based on the Cochrane Handbook

(Higgins and Green). The following is an example using the domain 'allocation concealment'.

Low risk of bias - adequate concealment of the allocation (e.g. sequentially numbered, sealed, opaque envelopes or centralised or pharmacy-controlled randomisation).

Unclear risk of bias - unclear about whether the allocation was adequately concealed (e.g. where the method of concealment is not described or not described in sufficient detail to allow a definite judgement).

High risk of bias - inadequate allocation concealment (e.g. open random number lists or quasi-randomisation such as alternate days, date of birth, or case record number).

A summary assessment of the risk of bias for the primary outcome across the studies was undertaken (Higgins and Green). For each study, a summary assessment of risk of bias was provided.

Low risk when there is a low risk of bias across all six key domains.

Unclear risk of bias when there is an unclear risk of bias in one or more of the six key domains.

High risk of bias when there is a high risk of bias in one or more of the six key domains.

Measures of treatment effect

For dichotomous outcomes, the estimate of effect of an intervention was expressed as a risk ratio together with 95% confidence interval (CI), where appropriate. For continuous outcomes, mean difference and 95% CI was used to summarise the data for each group.

Unit of analysis issues

If cluster randomised trials had been identified and included, analysis was to be undertaken, whenever feasible, at the same level as the randomisation, or at the individual level accounting for the clustering.

Dealing with missing data

We contacted trial authors for missing data if the report was published from the year 2000 or onwards. We considered it unfeasible to obtain data for trials published prior to this cut-off date.

Assessment of heterogeneity

The significance of any discrepancies in the estimates of the treatment effects from the different trials was to be assessed by means of Cochran's test for heterogeneity, and heterogeneity would be considered significant if $P < 0.1$ (Higgins and Green). The I^2 statistic, which describes the percentage total variation across studies that is due to heterogeneity rather than chance, was to be used to quantify heterogeneity, with I^2 over 50% being considered substantial heterogeneity (Higgins and Green).

Assessment of reporting biases

If there were a sufficient number of trials (more than 10) included in any meta-analysis, publication bias was to be assessed according to the recommendations on testing for funnel plot asymmetry as described in the Cochrane Handbook (Higgins and Green).

Data synthesis

Where appropriate, a random-effects meta-analysis was to be applied to the outcomes should there be four or more RCTs included. If fewer than this, a fixed-effect model would have been used to pool the data. Risk ratios were to be combined for dichotomous data, and mean differences for continuous data, if data had allowed.

Subgroup analysis and investigation of heterogeneity

Had data allowed, sub-group analysis would have been undertaken according to the three classifications of RAS highlighted above: minor, major and herpetiform.

2.6 Results

A total of 1289 studies were identified through the electronic searches (see Figure 1 for flow of studies).

Included studies

A total of 25 trials were included, 22 of which were placebo controlled and eight made head-to-head comparisons (five trials had more than two treatment arms). The interventions used within the trials were diverse, and the mode of action with regard to the management of recurrent aphthous stomatitis (RAS) often unclear. Interventions can be classified by the known primary mode of action of the therapeutic agent (see Table 2). However, for many agents the exact mechanism of action in relation to RAS is unknown. For the purpose of the review, the interventions have been grouped into two categories: immunomodulatory/anti-inflammatory and uncertain (Natural Medicines Comprehensive, 2012).

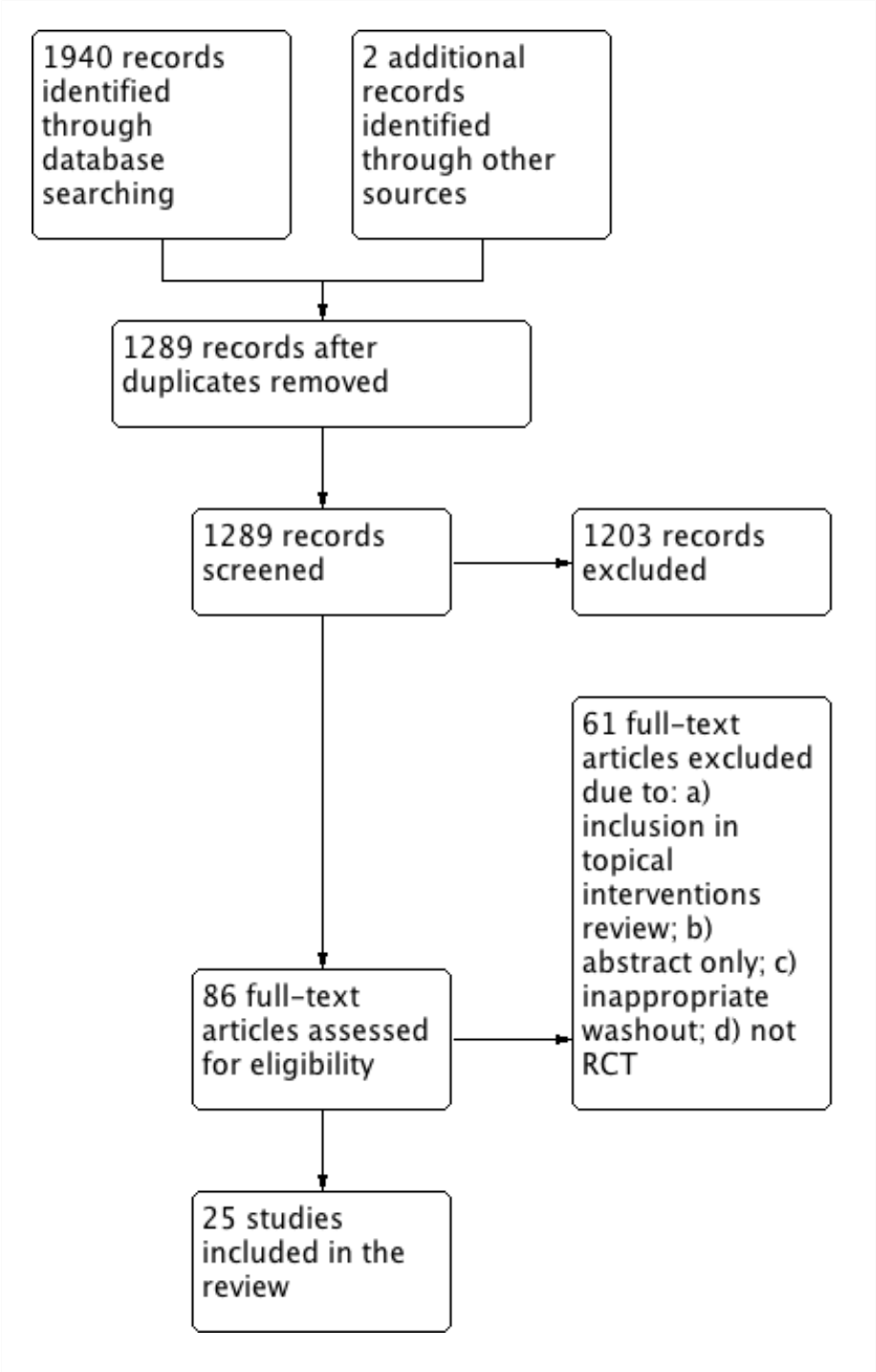

Figure 1. Study flow diagram

Table 2. Systemic agents used in the management of aphthous stomatitis

DRUG CLASS/GROUP	MODE OF ACTION	NOTES
Corticosteroids		
Prednisolone	Anti-inflammatory	
Betamethasone	Anti-inflammatory	Studies of these corticosteroids were not found or included in the review but are included here for completeness. They are not given orally for this indication but some systemic absorption may occur
Beclometasone diproprionate	Anti-inflammatory	
Hydrocortisone	Anti-inflammatory	
NSAID		
Rofecoxib	Cox-2 inhibitor	Withdrawn worldwide after reports of cardiovascular adverse effects
Antimicrobials		
Doxycycline		Downregulate the actions of matrix metalloproteinases, enzymes involved in the breakdown of collagen and which play a key role in the inflammatory and destructive processes of periodontitis (Martindale, 2012)
Tinidazole		
Tetracycline		
Clofazimine	Antimycobacterial	
Dapsone	Antimycobacterial	

Vitamins/Minerals		
Zinc sulphate		
Vitamin B12 ¬		Vitamin B12, a water-soluble vitamin, occurs in the body mainly as methylcobalamin (mecobalamin) and as adenosylcobalamin (cobamamide) and hydroxocobalamin. Mecobalamin and cobamamide act as coenzymes in nucleic acid synthesis (Martindale, 2012)
Herbal/Complementary		
Perilla oil		See Natural Medicines Comprehensive Database monograph (Natural Medicines Comprehensive, 2012)
Soybean oil		
LongoVital		
Camel Thorn		
Beta-glucan		See Natural Medicines Comprehensive Database monograph (Natural Medicines Comprehensive, 2012)
Bee-propolis	Antibacterial	
Miscellaneous		
Colchicine		Colchicine produces a dramatic response in acute gout, probably by reducing the inflammatory reaction to urate crystals; this effect might be due to several actions including decreased lactic acid production by leucocytes. Colchicine also appears to inhibit β-tubulin polymerisation, inhibiting the activation, degranulation and migration of neutrophils, which may mediate some gout symptoms (Martindale, 2012)
Sodium cromoglyctae	Unknown	Stabilisation of mast cell membranes – decreasing release of inflammatory mediators (Martindale, 2012)
Levamisole	Immunostimulant	Modulates cell-mediated immune response (Martindale, 2012)

Montelukast	Leukotriene receptor antagonist	
Pentoxifylline	Vasodilator	Inhibits production of the cytokine TNFα (Martindale, 2012)
Sulodexide	Antithrombotic	
Thalidomide	Immunomodulator	

Footnotes: Table provided by Lindsay Banks, North West Medicines Information Centre, May 2012

In 22 placebo controlled trials, 17 different interventions were assessed (out of a total of 21 interventions included in the review):

Immunomodulatory/anti-inflammatory

Beta-glucan (Koray et al., 2009)

Clofazimine (de Abreu et al., 2009)

Colchicine (de Abreu et al., 2009)

Levamisole (De Cree et al., 1978, DrinnanAj and Fischman, 1978, Meyer et al., 1977, Miller et al., 1978, Olson and Silverman S, 1978, Van de Heyning, 1978, Weckx et al., 2009, Zissis et al., 1983)

Montelukast (leukotriene receptor antagonist) (Femiano et al., 2010)

Pentoxifylline (Thornhill et al., 2007)

Prednisone (Femiano et al., 2010, Femiano et al., 2003)

Sulodexide (Femiano et al., 2003)

Uncertain

Camelthorn (Pourahmad et al., 2010)

Homeopathy (Mousavi et al., 2009)

LongoVital (herbal + vitamin) (Kolseth et al., 2005)

LongoVital (herbal alone) (Bratel et al., 2005, Kolseth et al., 2005)

Propolis (Samet et al., 2007)

Subantimicrobial doxycycline (Preshaw et al., 2007)

Tetracycline (Graykowski and Kingman, 1978)

Vitamin B12 (Volkov et al., 2009)

Multivitamin (Lalla et al., 2012)

Eight trials compared active ingredients:

Colchicine versus clofazimine (de Abreu et al., 2009)

Colchicine versus prednisolone (Pakfetrat et al., 2010)

Prednisone versus montelukast (leukotriene receptor antagonist) (Femiano et al., 2010)

Levamisole versus levamisole (different dose) (Zissis et al., 1983)

Rofexib versus tinidazole (Lu et al., 2004)

Sulodexide versus prednisone (Femiano et al., 2003)

LongoVital (herbal + vitamin) versus LongoVital (herbal alone) (Kolseth et al., 2005)

Perilla cooking oil verus soybean oil (Hamazaki et al., 2006)

Excluded studies

Nine studies were excluded (Dolby and Walker, 1975, Kowolik et al., 1978, Lehner et al., 1976, Nolan et al., 1998, Pedersen et al., 1990a, Pedersen et al., 1990b, Raeste et al., 1981, Sharquie et al., 2008, Yang and Jang, 2009). See Characteristics of excluded studies (Table 3).

Table 3. Characteristics of excluded studies

	Reason for exclusion
Dolby et al, 1975	Following discussion the mode of action was considered to be primarily topical (tablets of cromoglycic acid allowed to dissolve slowly in the mouth)
Kowolik et al, 1978	Cross-over study with no washout period
Lehner et al, 1976	Cross-over study with no washout period
Nolan et al, 1998	Abstract only
Pedersen et al, 1990a	Cross-over study with no washout period and potential for confounding with multivitamins
Pedersen et al, 1990b	Cross-over study with no washout period and potential for confounding with multivitamins
Raeste et al, 1981	Abstract only
Sharquie et al, 2008	No mention of the word 'random'
Yang et al, 2009	Following discussion the mode of action was considered to be primarily topical (local botulinum toxin A injection)

Risk of bias in included studies

A summary of the risk of bias for each study is presented in the Appendix 2 and Figure 2. One of the 25 included trials was assessed as being at overall low risk of bias (Lalla et al., 2012). Eight were assessed as being at unclear risk of bias (Bratel et al., 2005, Femiano et al., 2010, Hamazaki et al., 2006, Koray et al., 2009, Pakfetrat et al., 2010, Pourahmad et al., 2010, Van de Heyning, 1978, Volkov et al., 2009). The remainder were assessed as being at overall high risk of bias.

Allocation (selection bias)

Eleven of the 25 trials were deemed to be at low risk of bias with regard to sequence generation, but only six of these provided information that allowed a judgement of low

risk of bias with regard to allocation concealment (Femiano et al., 2010, Graykowski and Kingman, 1978, Lalla et al., 2012, Miller et al., 1978, Pakfetrat et al., 2010, Thornhill et al., 2007). None of the included trials were judged to be at high risk of selection bias, but typically provided insufficient information to make a clear assessment.

Blinding (performance bias and detection bias)

Fifteen trials were assessed as being at low risk of performance bias, clearly demonstrating blinding of participants/personnel. Only seven were assessed as being at low risk of detection bias (Lalla et al., 2012, Miller et al., 1978, Olson and Silverman S, 1978, Preshaw et al., 2007, Samet et al., 2007, Thornhill et al., 2007, Volkov et al., 2009); one trial was assessed as being at high risk of detection bias as outcome assessment was carried out by investigators unblinded to the treatment groups (Mousavi et al., 2009).

Incomplete outcome data (attrition bias)

Fourteen trials were assessed as being at low risk of attrition bias (Bratel et al., 2005, Femiano et al., 2010, Femiano et al., 2003, Hamazaki et al., 2006, Koray et al., 2009, Lalla et al., 2012, Lu et al., 2004, Mousavi et al., 2009, Pakfetrat et al., 2010, Preshaw et al., 2007, Thornhill et al., 2007, Van de Heyning, 1978, Volkov et al., 2009, Zissis et al., 1983). Five were assessed as being at high risk of attrition bias (de Abreu et al., 2009, DrinnanAj and Fischman, 1978, Graykowski and Kingman, 1978, Meyer et al., 1977, Miller et al., 1978).

Selective reporting (reporting bias)

Only nine of the included trials were judged to be at low risk of reporting bias (Lalla et al., 2012, Meyer et al., 1977, Mousavi et al., 2009, Olson and Silverman S, 1978, Pakfetrat et al., 2010, Pourahmad et al., 2010, Preshaw et al., 2007, Van de Heyning, 1978, Volkov et al., 2009). Eleven were assessed as being at high risk of bias due to a variety of reasons including: no reporting of important outcomes (e.g. pain), lack of reporting of outcomes listed in the methods section, outcomes reported but not at all listed time points, and measures of variance not reported.

Other potential sources of bias

Nine trials were felt to be at low risk of any other potential biases (Hamazaki et al., 2006, Lalla et al., 2012, Mousavi et al., 2009, Pakfetrat et al., 2010, Pourahmad et al., 2010, Samet et al., 2007, Thornhill et al., 2007, Van de Heyning, 1978, Zissis et al., 1983). Six were assessed as being at high risk of bias (DrinnanAj and Fischman, 1978, Kolseth et al., 2005, Meyer et al., 1977, Miller et al., 1978, Olson and Silverman S, 1978, Preshaw et al., 2007) due to reasons including: unclear use of alleviating drugs (e.g. corticosteroids), baseline imbalances in factors such as gender and smoking, and pharmaceutical funding.

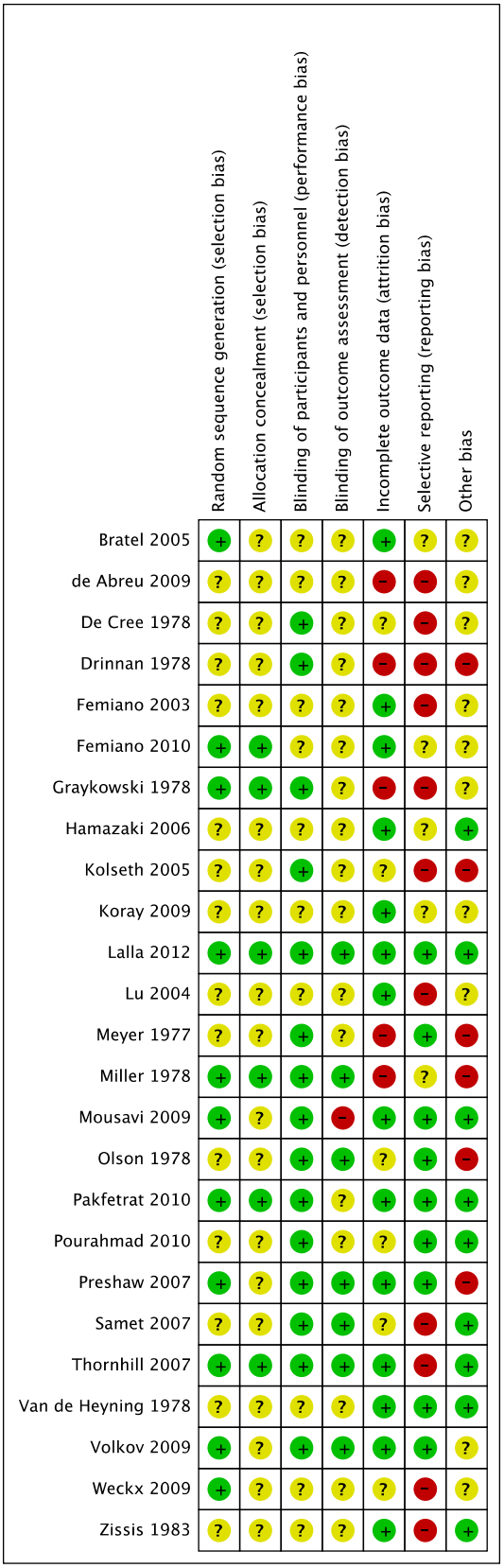

Figure 2. Risk of bias summary

Effects of interventions

Immunomodulatory/anti-inflammatory versus placebo

- Beta-glucan

One trial randomised 31 participants to receive either 10 mg 1.3 to 1.6 beta-glucan twice per day for 20 days or placebo (Koray et al., 2009). The study was at unclear risk of bias. The authors used the ulcer severity score (USS) and report a statistically significant lower mean USS score in the beta-glucan group than in the placebo group (mean difference -4.38; 95% confidence interval (CI) -6.17 to -2.59). No data on the individual scale components (number of ulcers, size, duration, ulcer-free period, site and pain).

There was no reporting of adverse effects.

There is insufficient evidence to support or refute the use of beta-glucan for the treatment of RAS.

- Clofazimine

One trial, assessed as being at high risk of bias, compared clofazimine 100 mg daily for 30 days, then 100 mg every other day (n = 23) with placebo (n = 20) (de Abreu et al., 2009). The authors report that the number of individuals in the clofazimine group who had no further aphthous episodes from beginning treatment until completion of treatment at 6 months was significantly greater than the number in the placebo group (Fisher's exact test P = 0.043) (Table 4). Within group comparisons comparing periodicity, number, duration and size of lesion from initial evaluation on a monthly basis were also made. No statistically significant differences in pain intensity, patient

self-evaluation and physician self-evaluation compared to placebo were observed at 6 months. The number of participants analysed varied across time points and data was not presented in a manner that allowed for further analysis (reported as percentages only).

Clofazimine was associated with an increase in cutaneous adverse effects (Fisher's exact test P = 0.015), but these were reported to be easily controlled.

There is insufficient evidence to support or refute the use of clofazimine for the treatment of RAS.

- Colchicine

The trial by de Abreu et al (2009) also assessed the effect of colchicine (n = 23) compared to placebo (n = 20). The dose of colchicine was 0.5 mg three times per day.The authors report that the number of individuals in the colchicine group who had no further aphthous episodes after beginning treatment until completion of treatment at 6 months was not significantly different from the number in the placebo group (Fisher's exact test P = 1.000) (Table 4). Within group comparisons comparing periodicity, number duration and size of lesion from initial evaluation on a monthly basis were also made. No statistically significant differences in pain intensity, patient self-evaluation and physician self-evaluation compared to placebo were observed at 6 months.

However, the authors report that there was a greater percentage of treatment interruptions in the colchicine group due to gastrointestinal adverse effects (Fisher's exact test P = 0.009).

There is no evidence to support the use of colchicine for the treatment of RAS and potential evidence of harm at a dose of 1.5 mg per day.

- Levamisole

Eight trials (seven assessed as being at high risk of bias and one unclear) compared levamisole with placebo (De Cree et al., 1978, DrinnanAj and Fischman, 1978, Meyer et al., 1977, Miller et al., 1978, Olson and Silverman S, 1978, Van de Heyning, 1978, Weckx et al., 2009, Zissis et al., 1983). Collectively, the trials did not provide data in a way that allowed for meta-analysis (see Table 4). The dose of levamisole was 150 mg per day in all studies, but the duration of treatment varied from 3 consecutive days per episode (with a minimum of 2 weeks between each treatment period) (DrinnanAj and Fischman, 1978), to 11 consecutive days followed by 11 days of no levamisole (for a total of 9 weeks) (Miller et al., 1978).

There is inconsistent evidence regarding the effectiveness of levamisole. Patients receiving levamisole reported more adverse effects than those receiving placebo, however, no adverse effects are reported as requiring withdrawal of the intervention.

- Montelukast (leukotriene receptor antagonist)

One trial assessed as being at unclear risk of bias compared montelukast with placebo (Femiano et al., 2010). The trial randomised 40 participants to receive either 10 mg montelukast orally daily for 1 month followed by alternate days for the second month (n = 20) or to placebo (n = 20). Reported outcomes were days to pain cessation and to ulcer healing for the first month of treatment with respect to first ulcer (single episode), and total number of aphthae for each month of treatment and for the 2 months follow-up. Time in days to resolution of first ulcer was shorter for those receiving montelukast (mean difference -3.95; 95% CI -4.38 to -3.52; $P < 0.00001$) visual analogue scale (VAS) pain mean difference -1.15 (95% CI -1.46 to -0.84; $P < 0.00001$). There was also a significant reduction in the total number of new lesions over the 2-month treatment

period (mean difference -3.90; 95% CI -4.55 to -3.25; P < 0.00001). The study reported equal drug-related adverse effect for those treated with montelukast and placebo.

There is insufficient evidence to support or refute the use of montelukast for the treatment of RAS.

- Pentoxifylline

A single trial assessed as being at high risk of bias compared pentoxifylline 400 mg 3 times daily (n = 14) with placebo (n = 12) for 60 days with a further 60 day follow-up (Thornhill et al., 2007). No statistically significant differences between the groups were reported for pain, number of ulcers and ulcer-free days at the end of treatment. A statistically significant difference in ulcer size was seen, in favour of pentoxifylline. Data for these outcomes are presented as medians only and are therefore not suitable for meta-analysis. There was no statistically significant difference in the proportion of ulcer-free days compared with pre-treatment status (worse, little improvement, substantial improvement) in either group (Table 4).

Patients receiving pentoxifylline reported more adverse events than those in the placebo group but this was not statistically significant (Table 4).

There is insufficient evidence to support or refute the use of pentoxifylline for the treatment of RAS.

- Prednisone

Two trials compared prednisone with placebo in trials that were assessed as being at high (Femiano et al., 2003) and unclear (Femiano et al., 2010) risk of bias. In both trials

the dose of oral prednisone commenced at 25 mg with a phased dose reduction over a 2-month period.

Femiano et al (2003) reports on the number of days to resolution of pain and days to epithelialization of aphthae at 1 month following the start of treatment. Data for these outcomes are presented as ranges only. The trial also reports the number of aphthae per month after the first and second months of therapy; this is reported as the total number of aphthae observed by group, with no estimate of variability. The authors report a statistically significant effect in favour of prednisone.

One significant adverse event (gastritis) was reported for the group receiving prednisone compared to no significant adverse events for the placebo group (Table 4).

The second trial to compare prednisone to placebo, conducted by Femiano et al (2010), evaluated days to pain cessation and to ulcer healing for the first month of treatment with respect to first ulcer (single episode), and total number of aphthae for each month of treatment and for the 2-months follow-up. Time in days to resolution of first ulcer was shorter for those receiving prednisone (mean difference -6.35; 95% CI -6.74 to -5.96; $P < 0.00001$). There was also a significant reduction in the total number of new lesions over the 2-month treatment period (mean difference -4.20; 95% CI -4.84 to -3.56; $P < 0.00001$). The study reported more drug-related adverse effects for those treated with prednisone than placebo.

There is insufficient evidence to support or refute the use of prednisone for the treatment of RAS.

- Sulodexide

The trial by Femiano et al (2003) also compared sulodexide (a low-molecular weight product consisting of heparin and dermatan sulphate chains) with placebo. As discussed previously, the trial was at high risk of bias and data was incompletely presented.

Sulodexide was not associated with significant adverse events.

There is insufficient evidence to support or refute the use of sulodexide for the treatment of RAS.

Other interventions versus placebo

- Camel thorn

A single trial of camel thorn randomised 93 participants to the plant distillate (n = 49) or placebo (n = 44) for the aphthous ulcer episode duration (Pourahmad et al., 2010). The study was assessed as being at unclear risk of bias. The authors report a shorter mean time to complete resolution for camel thorn (mean 4.02 days; range from 3 to 7 days) compared to placebo (mean 8.9 days; range 7 to 14 days), standard deviations not reported. Outcomes of lesion diameter and intensity of pain were analysed at multiple time intervals until 14 days from initial referral. The authors report lower pain and smaller lesions in the camel thorn groups up to 10 days after referral (Table 4).

There were no evidence of adverse effects.

There is insufficient evidence to support or refute the use of camel thorn for the treatment of RAS.

- Homeopathy

Mousavi et al (2009) undertook a placebo-controlled clinical trial of individualised homeopathy. The trial was assessed as being at high risk of bias. One hundred patients

with minor aphthous ulcer were randomised to either a dilution of individualised homeopathic medicines or placebo, in two doses over a 24-hour period and followed up for 6 days. Pain intensity and ulcer size were recorded at baseline, during and at the end of the trial (mornings of days 4 and 6). A statistically significant difference in the number of participants whose ulcers had completely healed by the end of the study was shown, in favour of homeopathy (risk ratio 2.00; 95% CI 1.39 to 2.89; P = 0.0002). The same findings were shown for 'pain free' by the end of the 6-day study (risk ratio 2.00; 95% CI 1.39 to 2.89). A statistically significant difference was reported in mean pain score and mean ulcer size favouring the homeopathic group (Table 4). Summary data are not presented, precluding further analysis.

The authors report that no participant needed to discontinue treatment due to adverse events.

There is insufficient evidence to support or refute the use of homeopathic medicine for the management of RAS.

- LongoVital (herbal + vitamin)

Forty patients were randomised to receive LongoVital (herbal plus vitamin) or placebo (Kolseth et al., 2005). Outcomes evaluated included the number of ulcer-free days and number of new ulcers over the 4-month treatment period. Data were presented as medians with 95% confidence intervals, so are unsuitable for further analysis. The authors report that there was no statistically significant difference between the groups on these outcomes (Table 4).

Reported adverse events were minor and evenly distributed between the groups.

- LongoVital (herbal alone)

Two trials compared LongoVital (herbal alone) with placebo in trials that were assessed as being at high (Kolseth et al., 2005) and unclear (Bratel et al., 2005) risk of bias. Forty patients were randomised to receive the herbal component of LongoVital alone or placebo (Kolseth et al., 2005). Outcomes evaluated included number of ulcer-free days and number of new ulcers over the 4-month treatment period. Data were presented as medians with 95% confidence intervals, so are unsuitable for further analysis. The authors report that there was no statistically significant difference between the groups on these outcomes (Table 4).

Reported adverse events were minor and evenly distributed between the groups.

In the second trial, 50 participants were randomised to receive either three tablets of LongoVital (n = 25) or a placebo equivalent (n = 25) (Bratel et al., 2005). Outcomes reported included the number of days of ulcers, number of days of pain, mean size of ulcers and general degree of discomfort, as a monthly average for the 6-month duration of treatment. There were no statistically significant differences between the groups for these outcomes: mean difference -0.80 (95% CI -3.30 to 1.70; P = 0.53) (Analysis 1.6); -3.80 (95% CI -9.39 to 1.79; P = 0.18); -0.30 (95% CI -0.56 to 0.04; P = 0.02); -0.30 (95% CI -0.37 to 0.97; P = 0.38).

"Very few and mostly harmless side-effects" were observed in the trial.

There is insufficient evidence to support or refute the use of LongoVital for the treatment of RAS.

- Multivitamin

A single trial at low risk of bias compared a daily multivitamin with placebo in patients who had a validated history of at least three episodes of RAS within the previous 12 months (Lalla et al., 2012). No statistically significant difference was found between groups with regard to mean number of new lesions (mean difference -0.41; 95% CI -1.85 to 1.03; P = 0.58), duration of episodes (mean difference -0.33; 95% CI -2.06 to 1.40; P = 0.71), or average mouth pain during RAS episodes (mean difference -0.05; 95% CI -0.71 to 0.61; P = 0.88). Similarly, the authors report no statistically significant difference between groups with regard to normalcy of diet or compliance with the interventions.

There is insufficient evidence to support or refute the use of multivitamin for the treatment of RAS.

- Propolis

A single trial randomised 19 participants to bee propolis one capsule (500 mg) per day or placebo (Samet et al., 2007). The trial was assessed as being at high risk of bias. Outcomes included patient reported measurements of the number of new ulcers and the duration and severity of outbreaks over a minimum 6-month period. There was no statistically significant difference in the mean number of lesions in the two groups over the treatment period (mean difference -2.6; 95% CI -7.30 to 2.10), although the authors report a statistically significant difference in the reduction of outbreaks based on the difference between expected number of ulcers and observed number of ulcers (Fisher's exact test one sided P = 0.04). They also report an improvement in quality of life favouring the propolis group based on patients volunteering statements of self-reported improvement (Table 4).

Propolis was associated with "low rates of minimal side effects".

There is insufficient evidence to support or refute the use of bee propolis for the treatment of RAS. The components of propolis may vary according to geographical area.

- Subantimicrobial doxycycline

Preshaw et al (2007) compared subantimicrobial dose doxycycline (SDD) 20 mg twice daily for 90 days (n = 25) with placebo (n = 25). The study was judged as being at high risk of bias. Outcomes measured within the study were number of new ulcers, pain (VAS) and additional ulcer treatment. There was no significant difference in the number of ulcers present at the end of the 90-day treatment period (mean difference -0.5; 95% CI -1.10 to 0.10; P = 0.10). Cumulative data was also available for the total number of new ulcers over 90 days (mean difference -16.40; 95 CI% -30.44 to -2.36; P = 0.02). There was a statistically significant difference in the number of new lesions per day, with a mean difference -0.19 (95% CI -0.35 to -0.03; P = 0.02) in favour of SDD, but not in the mean VAS pain per day (mean difference -5.00; 95% CI -11.93 to 1.93; P = 0.16).

No differences in adverse events were reported.

There is insufficient evidence to support or refute the use of SDD for the treatment of RAS.

- Tetracycline

A trial assessed as being at high risk of bias evaluated tetracycline suspension versus placebo. The suspension, containing 250 mg tetracycline, was held in the mouth for 2 minutes and then swallowed, four times per day at new ulcer outbreak, and continued

for 20 doses (5 days) (Graykowski and Kingman, 1978). No statistically significant difference was found with regard to the average number of new lesions/week (mean difference -0.47; 95% CI -1.34 to 0.40; P = 0.29). A statistically significant difference was shown, in favour of tetracycline, for adjusted maximum ulcer size (P = 0.034) and adjusted maximum pain (P = 0.017).

Adverse event rates were comparable between groups.

There is insufficient evidence to support or refute the use of tetracycline for the treatment of RAS.

- Vitamin B12

A single study, assessed as being at unclear risk of bias, randomised participants to sublingual vitamin B12 (1000 mcg daily for 6 months) or placebo (Volkov et al., 2009). A total of 58 participants were included in the trial. The authors provided additional data for analysis. At completion of treatment at 6 months, compared to placebo the treatment group reported lower pain scores (mean difference -1.72; 95% CI -2.70 to -0.74; P = 0.0006), a shorter average duration of RAS episode (number of days) (mean difference -2.86; 95% CI -5.39 to -0.33; P = 0.03) and lower frequency of outbreaks per month (mean difference -8.74; 95% CI -16.62 to -0.86; P = 0.03). During the last 2 months of treatment, statistically significantly more participants receiving vitamin B12 reached a 'no ulcer' status (risk ratio 3.27; 95% CI 1.23 to 8.66; P = 0.02).

No adverse events were associated with receiving vitamin B12 or the placebo in this study.

There is insufficient evidence to support or refute the use of vitamin B12 for the treatment of RAS.

Head-to-head comparisons

Eight trials compared active interventions.

- Colchicine versus clofazimine

One trial, assessed as being at high risk of bias, compared clofazimine 100 mg daily for 30 days, then 100 mg every other day (n = 23) with colchicine 0.5 mg three times per day (n = 23) (de Abreu et al., 2009). The authors report that the number of individuals in the clofazimine group who had no further aphthous episodes after beginning treatment until completion of treatment at 6 months was significantly greater than the number in the colchicine group (Fisher's exact test P = 0.016). Within group comparisons comparing periodicity, number, duration and size of lesion from initial evaluation on a monthly basis were also made. Statistically significant differences in pain intensity, patient self-evaluation and physician self-evaluation at 6 months were observed in the colchicine group compared to the clofazimine group. The authors report higher pain intensity in the colchicine group, greater physician rated improvement and patient rated satisfaction in the clofazimine group (Table 4). The number of participants analysed varied across time points. Data was not presented in a manner that allowed for further analysis.

Clofazimine was associated with an increase in cutaneous adverse effects (Fisher's exact test P = 0.015), but these were reported to be easily controlled. However, the authors report that there was a greater percentage of treatment interruptions in the colchicine group due to gastrointestinal adverse effects (Fisher's exact test P = 0.009)

There is insufficient evidence to support a relative benefit for either colchicine or clofazimine.

- Colchicine versus prednisolone

Pakfetrat et al (2010) randomised participants to 0.5 mg colchicine per day for 3 months (n = 17) or 5 mg prednisolone per day for 3 months (n = 17). The study was judged to be at unclear risk of bias. No statistically significant difference was shown for recurrence during the treatment period (risk ratio 1.30; 95% CI 0.98 to 1.71; P = 0.07) or pain at completion of treatment (mean difference -0.16; 95% CI -1.18 to 0.86; P = 0.76) or number of aphthous ulcers at completion (mean difference -0.13; 95% CI -0.50 to 0.24; P = 0.49).

Colchicine was associated with statistically significantly more adverse effects than prednisolone with nine participants reporting adverse effects on colchicine and two participants reporting adverse effects on prednisolone.

There is insufficient evidence to support a relative benefit for either colchicine or prednisolone.

- Prednisone versus montelukast (leukotriene receptor antagonist)

Femiano et al (2010) assessed as unclear risk of bias compared oral prednisone with montelukast, a leukotriene receptor antagonist. Reported outcomes were number of days to pain cessation and to ulcer healing for the first month of treatment with respect to first ulcer (single episode), and total number of aphthae for each month of treatment and for the 2-months follow-up. Time in days to resolution of first ulcer was shorter in favour of montelukast (mean difference -2.40; 95% CI -2.76 to -2.04; P < 0.00001). There was no significant reduction in the total number of new lesions over the two month treatment period (mean difference -0.30; 95% CI -0.90 to 0.30; P = 0.33).

The study reported more drug-related adverse effects for those treated with prednisone than montelukast.

There is insufficient evidence to support a relative benefit for either prednisone or montelukast.

- Levamisole versus levamisole (different dosage)

Zissis et al (1983) assessed at high risk of bias compared two different doses of levamisole (levamisole 50 mg three times per day for days 1 and 2 compared with levamisole 50 mg three times per day for day 1 and placebo tablet three times per day for day 2). A third group received placebo only. Treatment occurred 2 days per week for 16 weeks. There was some inconsistency in the presentation of the data within the trial. However, the authors report that "All parameters evaluated have been statistically improved in both levamisole groups".

There is insufficient evidence to support a relative benefit for any one particular dose regimen of levamisole.

- Rofexib versus tinidazole

Lu et al (2004) randomised 60 participants to receive either oral rofecoxib for 4 days (50 mg on first day and 25 to 50 mg per day on the following days) or oral tinidazole (1 g per day for 3 days). The trial was assessed as being at high risk of bias. Summary data for mean pain (VAS) and size of ulcer diameter at end of treatment was presented without standard deviations, preventing further analysis (Table 4). The authors report there was no statistically significant difference in total effective rate in the two groups at the end of 4 days (risk ratio 1.17; 95% CI 0.95 to 1.43; P = 0.14).

There is insufficient evidence to support a relative benefit for either rofecoxib or tinidazole.

- Sulodexide versus prednisone

A comparison between sulodexide (n = 10) and prednisone (n = 10) was made in a trial assessed as being at high risk of bias (Femiano et al., 2003). Data for these outcomes are presented as ranges only with no estimates of variability. The trial also reports the total number of aphthae per month with no estimate of variability precluding further analysis. However, the authors report that the effectiveness of systemic sulodexide was similar to that of systemic prednisone, without significant adverse effects (Table 4).

There is insufficient evidence to support a relative benefit for either sulodexide or prednisone.

- LongoVital (herbal + vitamin) versus LongoVital (herbal alone)

A single trial assessed as being at high risk of bias randomised participants to receive the herbal component of LongoVital alone or LongoVital with herbal plus vitamin component (Kolseth et al., 2005). Outcomes evaluated included the number of ulcer-free days and number of new ulcers over the 4-month treatment period. Data were presented as medians with 95% confidence intervals so unsuitable for further analysis. The authors report that there was no statistically significant difference between the groups on these outcomes (Table 4).

Reported adverse events were minor and evenly distributed between the groups (Kolseth et al., 2005).

There is insufficient evidence to support a relative benefit for either LongoVital (herbal alone) or LongoVital (herbal plus vitamins).

- Perilla cooking oil versus soybean oil

Two types of cooking oil were compared in a trial of 33 participants (Hamazaki et al., 2006). The trial was assessed as being at unclear risk of bias. The treatment phase lasted 8 months and assessed the prevalence of minor RAS, time to resolution, fatty acid/dietary analysis and adverse effects. There was no statistically significant difference in the average number of days for resolution of ulcers over the treatment phase (mean difference 0.80; 95% CI -1.83 to 3.43; P = 0.55). No inter-group differences were reported for any other outcome (Table 4). Average and monthly prevalence data were presented as figures only so did not allow for further analysis.

No adverse events were reported.

There is insufficient evidence to support a relative benefit for either perilla or soybean cooking oil.

Table 4. Summary of results not suitable for meta-analysis

Study ID	Comparison	Summary of results	Harms
Drinnan et al (1978)	Levamisole versus placebo	Subjective results: 6/11 improved versus 5/13 improved	"eight subjects reported side effects (generally cacogeusia or nausea)" "no side effects warranted withdrawal"
De Cree et al (1978)	Levamisole versus placebo		"minor side effects included headache, nausea and a metallic taste, never necessitated the discontinuation of therapy"
Olson et al (1978)	Levamisole versus placebo	No statistically significant difference between groups with regard to days between attacks, duration of lesions or patient's evaluation of pain. Investigators clinical evaluation of response to treatment was "significant with $P < 0.005$"	"A total of 15 patients experienced some type of side effect during the double-blind study; 14 of these individuals were taking levamisole. None of the patients had side effects severe enough to warrant discontinuing the medication."
Weckx et al (2009)	Levamisole versus placebo	No statistically significant difference between groups with regard to number of episodes, number of lesions, duration of lesions or pain	"One patient heartburn/weakness, one patient diarrhoea in week 5"
Zissis et al (1983)	Levamisole versus levamisole + placebo versus placebo	Unclear due to inconsistency in the text. However, the authors report that "All parameters evaluated have been statistically improved in both levamisole groups"	"two patients in each group reported unwanted effects"

Meyer et al (1977)	Levamisole versus placebo	Statistically significant differences shown for number of episodes per month (P = 0.029), duration of episodes (P = 0.003), number of lesions/episodes (P < 0.001), size of lesions (P < 0.01) and degree of pain (P = 0.03) (Mann-Whitney U test)	"no one had to discontinue treatment because of side effects"
Miller et al (1978)	Levamisole versus placebo	"The t-tests comparing levamisole and placebo groups revealed no statistically significant difference (P > 0.05) in mean number of ulcers, the mean number of ulcer days, the mean duration of ulcers, or the mean number of ulcers per day"	Adverse effects were experienced by seven of the levamisole subjects while none of the placebo group reported adverse effects. These effects included mild stomach upset or nausea, diarrhoea, sleeplessness and dysgeusia and/or¬dysosmia
Van de Heyning et al (1978)	Levamisole versus placebo	See Analysis 1.7 Decrease in frequency of attacks: RR 4.29 [95% CI 0.72 to 25.39; P = 0.11] Decrease in duration of attacks: RR 4.29 [95% CI 0.67 to 27.24; P = 0.12] Decrease in number of ulcers: RR 7.88 [95% CI 0.51 to 121.96; P = 0.14] Decrease in pain: RR 4.29 [95% CI 0.67 to 27.24; P = 0.12]	"No adverse effects were reported"
Volkov et al (2009)	Vitamin B12 versus placebo	"The duration of outbreaks, the number of ulcers, and the level of pain were reduced significantly (P < 0.05) at 5 and 6 months."	"no known significant toxic effects"
Thornhill (2007)	Pentoxifylline versus placebo	No statistically significant difference between groups for pain, number of ulcers, ulcer-free days and adverse	"69% reported adverse effects…. Dizziness, headaches, stomach upset, increased heart rate

		effects. A statistically significant difference in ulcer size was seen, in favour of pentoxifylline	and nausea. However placebo patients reported similar complaints."
Samet et al (2007)	Bee propolis versus placebo	"a statistically significant reduction of outbreaks in the propolis group (Fisher's exact test , one sided, P = 0.04). Patients in the propolis also self-reported a significant improvement in their quality of life (P = 0.03)"	"low rates of minimal side effects"
Pourahmad et al (2010)	Camel thorn distillate versus placebo	Mean time to complete resolution was 4.02 (range 3 to 7 days) for camel thorn compared to 8.9 (7 to 14 days), P < 0.001 (independent t-test). A statistically significant difference in pain intensity also reported	"No evidence of drug side effects was observed"
Mousavi et al (2009)	Homeopathic medicine versus placebo	Statisitically significant (P < 0.05) reduction in ulcer size and pain was reported for the homeopathic group	"No adverse drug reaction to a treatment solution was reported as a reason for leaving the study"
Graykowski et al (1978)	Tetracycline versus placebo	"Both the placebo and tetracycline groups experienced reductions in ulcer incidence during the treatment period, whereas only the tetracycline group showed significant reductions in ulcer duration, size, and pain"	"side effects recorded in patients taking tetracycline were comparable to those in patients on placebo."
Lu et al (2004)	Rofecoxib versus tinidazole	"The healing rate of the treatment group after 2 days was significantly higher than that of the control group (P < 0.05)....There was no significant differences of total effective rate after 4 days..." Means only presented for pain, size of ulcer at end of treatment but no standard deviations given. Results for these not given in translation	No adverse effects reported in translation

Kolseth et al (2005)	LongoVital (vitamin/herbal supplement) versus LongoVital (herbal component alone) versus placebo	"None of the treatment - response parameters showed any statistically significant differences between any of the groups at any of the test periods"	"Nine of the 52 patients in the study reported mild indigestion problems at the very beginning of the tablet period and they were evenly distributed among the three groups."
Hamazaki et al (2006)	Perilla cooking oil versus soybean cooking oil	No intergroup differences	No adverse events
de Abreu et al (2009)	Clofazimine versus colchicine versus placebo	"A greater percentage of individuals in the clofazimine group had no further aphthous episodes (17% to 44% compared with < = 6% in other groups)	"The clofazimine group showed greater percentage of cutaneous adverse effects (skin pigmentation and drying)…." "skin bronzing did not deter patients…. Dryness was easily controlled" "complaints of dryness" "A significantly greater percentage of treatment interruption occurred in the colchicine group because of gastrointestinal effects."
Femiano et al (2003)	Sulodexide versus prednisone versus placebo	"The effectiveness of systemic sulodexide was almost comparable with that of systemic prednisone in patients with frequent RAS, without significant side effects"	No serious adverse events (one significant adverse event (gastritis) was reported for the group receiving prednisone compared to no significant adverse events for the placebo group)

Footnotes; CI = confidence interval; RAS = recurrent aphthous stomatitis; RR = risk ratio

2.7 Discussion

Summary of main results

Twenty-five randomised controlled trials were included in the review, evaluating the effectiveness of 21 different interventions for the treatment of recurrent aphthous stomatitis (RAS). There was considerable heterogeneity with regard to the comparisons being made within each trial, and the type and timing of outcome assessment. Some trials reported single episodes of ulceration and others multiple episodes (presenting data either cumulatively or per episode). Outcome measures and timing of assessment varied across trials. In most cases, interventions were assessed in single trials. The mode of action by which the intervention was thought to work for the management of RAS not always clear, making grouping of studies difficult. For the purpose of the review, the interventions have been grouped into two broad categories: immunomodulatory/anti-inflammatory and other. Due to heterogeneity and poor reporting in many of the included trials, statistical pooling was not undertaken.

None of the evaluated interventions were shown to be of clear benefit for the treatment of RAS. Statistically significant improvements in outcomes were shown for some interventions, however, given that all trials were judged to be at either high or unclear risk of bias (with the exception of Lalla et al (2012)), it was felt there was insufficient evidence to currently support their use in clinical practice. Further research of these interventions may be warranted: clofazimine, montelukast, prednisone, sulodexide, camel thorn, subantimicrobial doxycycline, vitamin B12.

Overall completeness and applicability of evidence

This review excluded those with ulceration potentially secondary to an underlying medical condition or systemic disease. However, many patients with systemic disease present with RAS type ulceration, for example, Behçet's Disease, Coeliac Disease and vitamin B12 deficiency (Baccaglini et al., 2011). All three forms of RAS type ulceration can occur in patients with simple and complex aphthosis, like Behçet's Disease. However, unlike RAS, patients with Behçet's Disease can present with multisystem disease affecting many mucosal surfaces (Jurge et al., 2006). The prevalence of RAS type ulceration in patients with coeliac disease lies between 3% to 61% (Baccaglini et al., 2011), and this contrasts with a third of the general population (Kleinman et al., 1994). The prevalence of RAS type ulceration in patients with vitamin B12 deficiency ranges from 0 to 42% and studies have found a statistically significant lower daily intake of vitamin B12 in patients that suffer from RAS type ulceration (Kozlak et al., 2010). Given the lack of clarity regarding mode of action of many of the interventions examined in the included trials, the applicability of the review's findings to those with systemic diseases remains unclear.

It is acknowledged that for most people, topical therapies will be the first line of treatment for the management of RAS. A separate review evaluating the effectiveness of topical interventions is being undertaken.

Quality of the evidence

One of the included trials was assessed as being at low risk of bias (Lalla et al., 2012). Eight trials provided insufficient information to make a clear judgement on risk of bias. The remaining 16 trials were assessed being at high risk of bias for at least one of the assessed domains.

The methodological limitations were extensive and this impacted on the quality of the evidence. Specific issues included clarity with regard to the inclusion/exclusion of participants within the trials, with the definition of RAS not always being apparent. In addition, it was not clear in many of the trials whether individuals with systemic causes of RAS had been excluded from the trial (De Cree et al., 1978, Meyer et al., 1977, Weckx et al., 2009), which may lead to a difference in the effect estimates when comparing the results of trials where these individuals have and have not been included.

The risk of selection bias with regard to allocation to intervention groups was judged to be low in only six of the included trials (Femiano et al., 2010, Graykowski and Kingman, 1978, Lalla et al., 2012, Miller et al., 1978, Pakfetrat et al., 2010, Thornhill et al., 2007), and blind outcome assessment evident in only seven trials (Lalla et al., 2012, Miller et al., 1978, Olson and Silverman S, 1978, Preshaw et al., 2007, Samet et al., 2007, Thornhill et al., 2007, Volkov et al., 2009). Given the subjective nature of the outcomes being assessed, this could lead to an important risk of detection bias.

There was an indication of selective outcome reporting in eleven trials. Trials were assessed as being at risk of selective reporting due to the lack of reporting of important outcomes (e.g. pain), lack of reporting of outcomes listed in the methods section, outcomes reported but not at all listed time points, or measures of variance not reported.

Issues regarding lack of accounting for multiplicity following measurement at many time points and reporting at an ulcer level rather than a person level were also apparent, as was analysis within the intervention and comparator groups over time, rather than comparing the groups at a specified time point.

Two trials used the ulcer severity score (USS) (Koray et al., 2009, Thornhill et al., 2007). This provides a summated score based on categorical scores on a range of clinical domains: number of ulcers, size, duration, ulcer-free period, site and pain.

Unless scores for individual components are also provided, it is difficult to interpret the findings as improvement could be due to changes in any one of the domains measured or a composite.

Some trials reported their outcome measure as a cumulative total at the end of treatment, others provided month-by-month data (Meyer et al., 1977). By not deciding a priori the time point of interest then it is easy for the interpretation to be data driven i.e. by reporting the result according to statistical significance at that time point rather than at the time point which is of clinical interest or importance. One trial combined the data from the run-in and treatment phases (Bratel et al., 2005). The use of arbitrary cut-offs was also found to be a problem in one trial as the difference between severe and moderate improvement was determined by the assessors (Mousavi et al., 2009).

Many of the trials were small and may have had insufficient participants to determine a statistically significant difference between interventions, or between intervention and control, if in fact this was present.

Potential biases in the review process

Changes to the original protocol included splitting the review by mode of administration (i.e. topical, systemic and physical) of the intervention. This was to allow more 'user-friendly' reviews. In addition, an exclusion criteria relating to cross-over studies with an inappropriately short washout period was added to the revised protocol. We recognise that post hoc changes to a protocol may potentially bias the results of a review, however, assessment of eligibility, risk of bias and data extraction was undertaken by at least two members of the review team independently. The results were then discussed across the review team and a consensus reached for each trial. Examining each individual study across a multidisciplinary team meant that all the clinical and

methodological issues raised by each trial were discussed thoroughly and openly across the group. Consensus had been reached a priori regarding the types of outcome measures and the timing of the outcome measure (outcome measured nearest to end of treatment), which then determined the selective outcome reporting domain of the risk of bias assessment. This combination of independent and consensual agreement produced a rigorous approach to the assessment process.

Agreements and disagreements with other studies or reviews

Baccaglini et al (2011) undertook a systematic review of RAS trials published since 2005. Again, systemic causes of RAS were excluded. In similarity to this review, there was considerable heterogeneity in the types of ulcers that had been included, how results were reported and the interventions used. This was compounded by a lack of study details and how the outcome data were measured. In similarity with this review, Baccaglini et al (2011) argued that there was substantial evidence of bias, which reduced the quality of the evidence; the randomisation process was poorly described and loss to follow-up was unclear in many of the included studies. Baccaglini 2011 also called for future trials to be carefully planned and reported using universal guidelines, for example Consolidated Standards of Reporting Trials (CONSORT; www.consort-statement.org).

Baccaglini et al (2011) reported both topical and systemic interventions. They found low-dose doxycycline to be effective (Preshaw et al., 2007, Skulason et al., 2009) and minocycline rinses performed better than placebo or tetracycline rinses ((Gorsky et al., 2007); Gorsky 2008); although they also raised the issue of the potential for long-term adverse events when patients are treated for extensive periods of time. In similarity to this review, inconsistent results were found with systemic colchicine, the intervention

being more efficacious with RAS associated with Behçet's Disease (Davatchi et al., 2009, de Abreu et al., 2009). Interventions based on plant extracts with anti-inflammatory, analgesic, or antiseptic properties showed some effectiveness as topical treatments (Amanlou et al., 2007, Babaee et al., 2010, de Armas et al., 2005, Martin et al., 2008, Motallebnejad et al., 2008). Baccaglini et al (2011) also concluded that the use of vitamin B12 for patients with vitamin B12 deficiency or as an intervention in its own right, was found to be efficacious (Biedowa and Knychalska-Karwan, 1983, Volkov et al., 2009). This concurs with Carrozzo 2009 and the US National Health and Nutrition Examination Survey, where patients with RAS had a statistically significantly lower daily intake of vitamin B12 (Kozlak et al., 2010).

2.8 Conclusions

Implications for practice

A wide variety of interventions are currently used for the treatment of recurrent aphthous stomatitis (RAS) in clinical practice, often in a sequential manner, according to the patient's response. In general, systemic interventions are used following ineffective topical therapy.

In this comprehensive systematic review, no single treatment was found to be effective and therefore the results remain inconclusive as regards to the best systemic intervention for RAS. This is likely to reflect the poor methodological rigour of trials, and lack of studies for certain drugs, rather than the true effect of the intervention. It is also recognised that in clinical practice, individual drugs appear to work for individual patients and so the interventions are likely to be complex in nature.

Although comprehensive, this review did not find trials involving several of other systemic interventions used for RAS, for example thalidomide in the absence of any systemic condition, despite its limitations on safety.

Implications for research

Clinical trials in oral medicine have often been compromised due to methodological factors. Careful attention needs to be given to methodological rigour and choice of intervention. Future randomised controlled trials need to ensure they adhere to the CONSORT statement (www.consort-statement.org) and evaluate interventions that are relevant to current practice and compare them with appropriate controls. Cross-over studies should also be carefully planned to incorporate an adequate washout period. In addition, whilst single treatment interventions are the most common type of trial design, they do not necessarily reflect how the intervention is used within every day practice, which often utilises multiple and/or sequential approaches to treatment. This has the potential to reduce the external validity of the study and so other types of trial design should be considered (e.g. n-of-1 and stepped interventions) at the design stage.

A set of standardised, clinically relevant outcomes measures needs to be developed. This work is underway, registered with COMET (Core Outcome Measures in Effectiveness Trials; www.comet-initiative.org), and will be used to inform future reviews and trials in this area.

In addition to examining the effectiveness of interventions, future studies should incorporate an appropriate economic evaluation. This could look at either cost-effectiveness of the intervention or the cost per utility gained.

As it is unclear whether the pathogenesis of RAS is similar or different to that of other RAS type ulceration, this review excluded trials involving patients with relevant

associated systemic disease. However, there may be a wealth of good evidence for successful treatment of RAS type ulceration which may be applicable to treatment of RAS. A Cochrane review of systemic treatments for RAS type ulceration in various systemic diseases would be worthwhile.

2.9 Acknowledgements

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2.10 Contributions of authors

Development of protocol based on the latest Cochrane guidance: Paul Brocklehurst (PRB), Martin Tickle (MT), Mike Lewis (ML), Mike Pemberton (MP), Anne-Marie Glenny (AMG), Jennifer Taylor (JT), Tanya Walsh (TW), Julian Yates (JMY)

Identification of studies: PRB, AMG, JT, Philip Riley (PR), TW

Data extraction: PRB, AMG, JT, PR, TW, JMY

Assessment of risk of bias: PRB, MT, AMG, JT, PR, TW, JMY

Data input/synthesis: PRB, AMG, JT, TW, JMY, PR

Writing of conclusions: PRB, MT, ML, MP, AMG, JT, TW, JMY

2.11 Declarations of interest

There are no financial conflicts of interest and the authors declare that they do not have any associations with any parties who may have vested interests in the results of this review.

2.12 Differences between protocol and review

Splitting the review by mode of administration of the intervention (i.e. topical, systemic and physical) in order to produce more 'user-friendly' reviews; and

an addition of an exclusion criteria relating to cross-over studies with an inappropriately short washout period.

2.13 References for included studies

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UPDATED CLINICAL OPINION

The results of this systemic review were widely regarded as unexpected but unsurprising by clinicians working in oral medicine. Not all clinicians think that Cochrane systematic reviews are a helpful way of summarising our evidence base.

Comments were received with regards to the lack of inclusion of commonly used treatments and I agree that it was surprising not to include randomised controlled trials for systemic steroids, as this is the first line treatment for severe RAS. One reason could be the inclusion of only RCTs or this could be a reflection of the fact that treatment with steroids is widely recognised as standard practice. Perhaps researchers choose not to spend time and money proving what is known (in similarity to the parachute analogy), however this lack of true evidence base is a common scenario in medicine and dentistry.

The papers included in the review do not reflect current practice. Apart from the obvious lack of steroid trials, there were no trials involving azathioprine or mycophenolate (which are medications often the first choice of steroid sparing agents used in practice).

Indeed, the review is now 10 years old and is due an update, which if done, would possibly now include the use of biologic therapies which have increased exponentially in the management of conditions cared for by rheumatology and gastroenterology. The question is – would updating this review give us any further information of benefit to patients? And if not, then can we justify the time spent on such a large piece of work?

In my opinion – updating our evidence base is vital – even if the results are not thought to be helpful in everyday clinical practice. How else will we know what is being researched? How else will we improve the quality of research if we don't systematically critique it?

The pulling together of all research is a useful reference for clinicians, even if the study type of a RCT is a high bar to reach when designing trials, reviewing the highest level of evidence is a reasonable starting point when making clinical decisions as per the hierarchy of evidence.

Chapter 3 Interventions for the management of oral ulcers in Behçet's disease

Behcet's Disease is a multi-system vasculitis and oral ulcers are the most common feature, experienced by 97-99% of patients. The oral ulcers are indistinguishable from RAS in both appearance and behaviour. In this paper, the ulcerations are described as RAS-type ulceration however the term Aphthous like ulceration (ALU) is also widely used to describe aphthous ulcers that present in patients who are not otherwise fit and well.

Bechet's Disease is more common in countries along the old established silk routes in the Middle East and this includes Turkey. This review was instigated in response to a request to speak at the European Association of Oral medicine biannual meeting in Turkey on the topic of evidence base for management of ulcers in Behçet's disease. Rather than present a narrative review, I took the opportunity to carry out a formal systematic review.

I was the lead author of this paper and led the group through the design, search strategies, screening, data extraction, discussion, and conclusions. I have presented the findings internationally.

This Cochrane Review has been published and is presented here in a format suitable for this thesis.

Interventions for the management of oral ulcers in Behçet's disease

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3.1 Abstract

Background

Behçet's disease is a chronic inflammatory vasculitis that can affect multiple systems. Mucocutaneous involvement is common, as is the involvement of many other systems such as the central nervous system and skin. Behçet’s disease can cause significant morbidity, such as loss of sight, and can be life threatening. The frequency of oral ulceration in Behçet's disease is thought to be 97% to 100%. The presence of mouth ulcers can cause difficulties in eating, drinking, and speaking leading to a reduction in quality of life. There is no cure for Behçet's disease and therefore treatment of the oral ulcers that are associated with Behçet's disease is palliative.

Objectives

To determine the clinical effectiveness and safety of interventions on the pain, episode duration, and episode frequency of oral ulcers and on quality of life for patients with recurrent aphthous stomatitis (RAS)-type ulceration associated with Behçet's disease.

Search methods

We undertook electronic searches of the Cochrane Oral Health Group Trials Register (to 4 October 2013); the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2013, Issue 9); MEDLINE via Ovid (1946 to 4 October 2013); EMBASE via Ovid (1980 to 4 October 2013); CINAHL via EBSCO (1980 to 4 October 2013); and AMED via Ovid (1985 to 4 October 2013). We searched the US National Institutes of Health trials register (http://clinicaltrials.gov) and the World Health Organization (WHO) Clinical Trials Registry Platform for ongoing trials. There were no restrictions on language or date of publication in the searches of the electronic databases. We contacted authors when necessary to obtain additional information.

Selection criteria

We included randomised controlled trials (RCTs) that looked at pre-specified oral outcome measures to assess the efficacy of interventions for mouth ulcers in Behçet's disease. The oral outcome measures included pain, episode duration, episode frequency, safety, and quality of life. Trials were not restricted by outcomes alone.

Data collection and analysis

All studies meeting the inclusion criteria underwent data extraction and an assessment of risk of bias, independently by two review authors and using a pre-standardised data extraction form. We used standard methodological procedures expected by Cochrane.

Main results

A total of 15 trials (n = 888 randomised participants) were included, 13 were placebo controlled and three were head to head (two trials had more than two treatment arms). Eleven of the trials were conducted in Turkey, two in Japan, one in Iran and one in the UK. Most trials used the International Study Group criteria for Behçet's disease. Eleven different interventions were assessed. The interventions were grouped into two categories, topical and systemic. Only one study was assessed as being at low risk of bias. It was not possible to carry out a meta-analysis. The quality of the evidence ranged from moderate to very low and there was insufficient evidence to support or refute the use of any included intervention with regard to pain, episode duration, or episode frequency associated with oral ulcers, or safety of the interventions.

Authors' conclusions

Due to the heterogeneity of trials including trial design, choice of intervention, choice and timing of outcome measures, it was not possible to carry out a meta-analysis. Several interventions show promise and future trials should be planned and reported according to the CONSORT guidelines. Whilst the primary aim of many trials for

Behçet's disease is not necessarily reduction of oral ulceration, reporting of oral ulcers in these studies should be standardised and pre-specified in the methodology. The use of a core outcome set for oral ulcer trials would be beneficial.

3.2 Plain language summary

Interventions for managing oral ulcers in Behçet's disease

Review question

This review has been conducted to assess the effects of different interventions, administered systemically or topically, for the prevention or treatment of oral ulcers in people with Behçet's disease. The interventions could be compared with an alternative intervention, no intervention or the administration of a placebo.

Background

Behçet's disease is a chronic disease characterised by a multitude of signs and symptoms including oral and genital ulcerations, skin lesions and inflammatory vascular involvement of the central nervous system and gastrointestinal tract. Although the underlying cause of Behçet’s disease is unknown it is thought to involve a genetic predisposition combined with environmental factors.

Behçet's disease most commonly presents in the third decade. The disease is rare in individuals older than age 50 years and during childhood. Although both sexes are equally affected, it is thought that the disease has a more severe course amongst men.

The oral ulceration that occurs in Behçet's disease can be painful and slow to heal. At its worst, this can cause significant difficulties in eating and drinking.

Study characteristics

Authors from Cochrane Oral Health carried out this review of existing studies and the evidence is current up to 4 October 2013. The review includes 15 studies published from 1980 to 2012 in which 888 participants were randomised. Eleven of the trials were

conducted in Turkey, two in Japan, one in Iran, and one in the UK. Thirteen different interventions were assessed, administered either topically or systemically.

Topical interventions: sucralfate, interferon–alpha (different doses), cyclosporin A, triamcinolone acetonide ointment, phenytoin syrup mouthwash.

Systemic interventions: aciclovir, thalidomide (different doses), corticosteroids, rebamipide, etanercept, colchicine, interferon–alpha, cyclosporin.

Key results

There was insufficient evidence to support or refute the use of any included intervention with regard to pain, episode duration or episode frequency associated with oral ulcers, or the safety of the interventions.

Quality of the evidence

The quality of the evidence ranged from moderate to very low.

3.3 Background

Description of the condition

Behçet's disease is a chronic, relapsing, multisystem inflammatory vasculitis (Chams-Davatchi et al., 2010). It affects both the large and small blood vessels (including veins and arteries) (Mat et al., 2013). It is characterised by a multitude of systemic signs and symptoms. Oral and genital ulcerations, skin lesions, uveitis, and inflammatory vascular involvement of the central nervous system and gastrointestinal tract are common (Dalvi et al., 2012). Although the aetiology of Behçet's disease is unknown it is thought to involve a genetic predisposition combined with environmental factors (Yazici et al., 2012).

The genetic risk factor most strongly associated with Behçet's disease is the human leukocyte antigen (HLA)-B51 allele. HLA-B51 occurs in around 60% of Behçet's disease patients (Gul, 2007, Kose, 2012, Yazici et al., 1980).

Behçet's disease is more frequent in the countries along the 'Silk Road', an ancient trading route, where the prevalence of HLA-B51 is relatively high compared with the other parts of the globe (Yurdakul and Yazici, 2010).

Behçet's disease most commonly presents in the third decade. The disease is rare in individuals older than age 50 years and during childhood. Although both sexes are equally affected, it is thought that the disease has a more severe course amongst men (Yazici et al., 1984).

Diagnosis

Previously, the International Study Group (ISG) Guidelines for the Classification of Behçet's disease were generally accepted as a diagnostic tool (International Study Group for Behçet's, 1990).

The criteria included recurrent oral 'aphthae' (at least three episodes within 12 consecutive months) plus two of the following: recurrent genital ulcers; uveitis or retinal vasculitis; skin lesions that are classified as erythema nodosum (EN)-like lesions, acneiform lesions, pustulosis, or pseudofolliculitis; and a positive pathergy test.

More recently a large group involving people from 32 countries attempted to establish new international guidelines (Davatchi, 2012). Following a prospective, international, multicentre, diagnostic accuracy study, data from over 2556 Behçet's patients from 27 different countries were reviewed. A new diagnostic scoring system was developed. As with the previous diagnostic criteria, oral lesions scored highly along with ocular and genital lesions. In fact 98% of Behçet's patients had oral aphthous ulceration as a feature (Davatchi, 2004).

Oral ulceration in Behçet's disease

The oral ulceration that occurs in Behçet's disease resembles recurrent aphthous stomatitis (RAS). In the oral medicine and dental literature RAS is now commonly used as a term to indicate a primary condition where ulceration is not in association with a systemic disease such as Behçet's. Where a relevant systemic disease is present, various terms including RAS-type ulceration would be used instead. In the general medical literature however, this division of nomenclature is not widely used and the oral ulceration in Behçet's is indistinguishable in appearance and natural history from RAS. It remains unclear whether the ulceration in RAS and RAS-type ulceration shares a common pathogenesis. The term for oral ulceration in association with Behçet’s disease in the international guidelines criteria includes oral aphthosis (ISG 1990) and oral aphthous lesions (Davatchi, 2012). For the purposes of this review we have reviewed

studies where aphthous ulceration is clearly the type of mouth ulceration being investigated, regardless of which precise terminology is used.

RAS is the most common form of oral ulceration with prevalence in the different populations ranging between 5% and 60% (Jurge et al., 2006).

RAS-type ulceration in association with a systemic disease is common. Systemic diseases featuring RAS-type ulceration can include, but are not limited to, coeliac disease, Crohn's disease, vitamin B12 deficiency, iron deficiency anaemia, human immunodeficiency virus infection/acquired immunodeficiency syndrome (HIV/AIDS), cyclic neutropenia, systemic lupus erythematosus (SLE), and Behçet's disease (Baccaglini et al., 2011)..

The frequency of RAS-type ulceration in Behçet's disease is 97% to 100% (Yurdakul and Yazici, 2008). There are a variety of Beḥcet's diagnostic criteria used over many years. Since 1990, the ISG have been most commonly but not exclusively used. Whichever criteria are used, RAS-type ulceration is a major feature with high prevalence.

According to Bagan 1991, there are three recognised forms of RAS (and hence also RAS-type ulceration).

Minor aphthae, typically round and less than 10 mm in diameter. These are generally pale in colour with an erythematous border and commonly affect non-keratinised mucosa including the labial and buccal mucosa, the borders of the tongue, and the floor of the mouth. Minor aphthae can occur in isolation but multiple presentations are also common. Healing is spontaneous and usually takes 7 to 10 days. Episodes of ulceration are usually followed by an ulcer-free period lasting a few days to several weeks before the next episode occurs (Thornhill et al., 2007). Major aphthae are similar to minor aphthae but are larger, usually exceeding 10 mm in diameter, and deeper. Consequently

healing can take longer (20 to 30 days) and may result in scarring (Bagan et al., 1991). Herpetiform ulcers are less than 1 mm in diameter and often occur in multiples, from 1 to 100. There is a tendency for adjacent ulcers to merge.

In Behçet's disease, minor aphthae-type lesions are the most commonly seen type, whereas major and herpetiform types are rare (Hamuryudan et al., 1998, Melikoglu et al., 2005, Yurdakul et al., 2001). This mirrors the frequency of the different forms of aphthae in RAS patients.

Description of the intervention

The cause of RAS is not known; therefore the aims of treatment are primarily pain relief and the reduction of inflammation (Scully, 2006). The cause of RAS-type oral ulceration in Behçet's disease is also poorly understood and, therefore, treatment aimed primarily at the oral ulceration in Behçet's disease is also targeted at pain relief and the promotion of healing to reduce the duration of the disease or reduce the rate of recurrence. A variety of topical and systemic therapies have been utilised (Porter et al., 1998) but few studies have demonstrated efficacy. Empirically, effective treatments include the use of corticosteroids, immunosuppressants, and topical barriers (Eisen and Lynch, 2001). Topical interventions can include mouthrinses, pastes, gels, sprays, injections, laser, and locally dissolving tablets. Many of the topical treatments are available without prescription. Systemic immunomodulators such as mycophenolate mofetil, pentoxyphylline, colchicine, dapsone, and thalidomide have also been used but with some caution due to their potential for adverse effects.

How the intervention might work

As the aetiopathogenesis of RAS-type ulceration in Behçet's disease is not fully understood, the precise mechanisms of how the various topical and systemic interventions influence the disease process are unclear.

Topical interventions for oral ulceration range from inert barriers to active treatments. Providing a barrier for the ulcer (for example with a mucoadhesive paste) should allow the breach in the mucosa to temporarily be protected and therefore noxious stimulants are less likely to sensitise nerve endings. This in theory should provide pain relief. The addition of active compounds to the barrier can potentially give an immunomodulatory effect. Due to the nature of the mucosal layer, there is great variability in the penetration of active compounds through the mucosal barrier, and as such there is great variability in the efficacy of the topical treatments.

Systemic interventions include immunomodulators (colchicine, azathioprine, cyclosporin, thalidomide), corticosteroids, biological agents (interferon; anti-TNF agents such as infliximab, etanercept, adalimumab), and other drugs such as dapsone and daclizumab. As previously stated, the precise mode of action of these interventions is often unclear.

Many of the systemic treatments used in Behçet's disease are given to control the underlying disease process and not primarily for the oral ulceration. Nevertheless, these systemic treatments may also improve the severity and frequency of episodes of RAS-type ulceration in these patients. Where systemic treatments are being used primarily for control of RAS-type ulceration, the risk-benefit ratios are important and may be different to those when trying to control widespread or critical disease. In practice, a combination of systemic therapy for the underlying disease and topical therapy for symptomatic treatment of acute attacks of oral ulceration are frequently used.

Why it is important to do this review

All three clinical types of RAS and RAS-type ulceration are associated with varying degrees of morbidity, including pain and difficulties in function. RAS (and RAS-type) ulceration is a chronic episodic oral mucosal condition which can impact upon the experiences of daily life, such as physical health and functioning (Riordain et al., 2011).

A recent Cochrane review (Brocklehurst et al., 2012) evaluated the evidence for systemic interventions for RAS and an ongoing review by the same author group is evaluating topical interventions for RAS (Taylor 2013). Both of these reviews have specifically excluded trials of interventions for oral ulcers in patients with systemic disease. This therefore excludes trials involving Behçet's patients.

There is, therefore, a population of patients in whom oral ulcers are the most common presenting feature and for whom we have no formal evaluation of the evidence base on which to guide our clinical treatments for them. An evaluation of the evidence for interventions for oral ulcers in this group of patients is therefore essential.

3.4 Objectives

The objectives of this review are to determine the clinical effectiveness and safety of interventions on the pain, episode duration, and episode frequency of oral ulcers and on quality of life for patients with recurrent aphthous stomatitis (RAS)-type ulceration associated with Behçet's disease.

3.5 Methods

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) investigating the effects of interventions for the management of recurrent aphthous stomatitis (RAS)-type ulceration in Behçet's disease were included. We also included RCTs of a cross-over design provided that the trial included a suitable washout period and no carry-over effects were evident. Split-mouth studies were also to be included if it was apparent that there was no risk of contamination of the intervention from one part of the mouth to another (this would be more likely for any topical interventions that was physically applied and retained in one part of the mouth rather than a mouthwash for example).

Studies looking at interventions for the management of any systemic manifestations of Behçet's disease and which also reported on oral ulcers as an outcome measure were included. The oral outcome measures should have been pre-specified in the methodology.

Types of participants

Participants with Behçet's disease with a history of recurrent oral aphthous-type ulcers that were diagnosed clinically were included. Where additional systemic diseases were reported in studies, these were noted.

Types of interventions

Active treatment included any preventive, palliative, or curative interventions administered systemically or topically. Comparators were either standard care, no active treatment, or the administration of a placebo; head to head trials of different interventions were also included.

Types of outcome measures

Primary outcome measures assessed were:

- Pain associated with oral ulcers
- Episode duration associated with oral ulcers.
- Episode frequency associated with oral ulcers.
- Safety of the intervention including adverse effects.

Secondary outcome measures assessed included any patient-reported outcomes that measured a change in the patients' quality of life or in morbidity (e.g. function), or both.

Search methods for identification of studies

For the identification of studies included or considered for this review, we developed detailed search strategies for each database searched. These were based on the search strategy developed for MEDLINE (Ovid) but revised appropriately for each database (Appendix 4). We combined this search strategy with the Cochrane highly sensitive search strategy (CHSSS) for identifying RCTs in MEDLINE: sensitivity maximising version, as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We linked the searches of EMBASE and CINAHL to the Cochrane Oral Health Group filters for identifying RCTs.

Electronic searches

The following electronic databases were searched (Appendix 4):

- Cochrane Oral Health Group Trials Register (to 4 October 2013)

- Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2013, Issue 9)
- MEDLINE via Ovid (1946 to 4 October 2013)
- EMBASE via Ovid (1980 to 4 October 2013)
- CINAHL via EBSCO (1980 to 4 October 2013)
- AMED via Ovid (1985 to 4 October 2013)

There were no restrictions on language or date of publication in the searches of the electronic databases.

We screened the bibliographies of included papers and relevant review articles were checked for studies not identified by the search strategies above.

We searched the following databases for ongoing trials (Appendix 4):

- US National Institutes of Health trials register (clinicaltrials.gov)
- World Health Organization (WHO) International Clinical Trials Registry Platform (apps.who.int/trialsearch/).

Data collection and analysis

Selection of studies

Two review authors (Jennifer Taylor (JT) and Anne-Marie Glenny (AMG)) independently screened the titles and abstracts obtained from the initial electronic searches. Reports from the studies that fulfilled the inclusion criteria were obtained. When there were insufficient data in the study title to determine whether a study fulfilled the inclusion criteria, the full report was obtained and assessed independently by the same review authors. Disagreements were resolved by discussion.

Data extraction and management

At least two review authors (JT, AMG, Tanya Walsh (TW), Paul Brocklehurst (PB), and Philip Riley (PR)) independently extracted data from each included study using a tool developed for the review. All studies meeting the inclusion criteria underwent data extraction and an assessment of risk of bias using a pre-standardised data extraction form. Studies rejected at this and subsequent stages were recorded in the table 'Characteristics of excluded studies'. Differences were resolved by discussion. If a single publication reported two or more separate studies, then the data from each study were extracted separately. If the findings of a single study were spread across two or more publications, then the publications were extracted as one. For each study with more than one control or comparison group for the intervention, the results were extracted for each intervention arm.

For each trial the following data were recorded:

For each trial we recorded the following data:

- Year of publication, country of origin and source of study funding.
- Details of the participants including demographic characteristics and criteria for inclusion.
- Details on the type of intervention and comparisons.
- Details on the study design.
- Details on the outcomes reported, including method of assessment and adverse outcomes.

Assessment of risk of bias in included studies

All review authors assessed the risk of bias in the included studies using the Cochrane's tool for assessing risk of bias. The domains that were assessed for each included study were:

- sequence generation (selection bias)
- allocation concealment (selection bias)
- blinding of participants and personnel (performance bias)
- blinding of outcome assessment (detection bias)
- completeness of outcome data (attrition bias)
- selective outcome reporting (reporting bias)
- risk of other potential sources of bias (other bias).

We tabulated a description of the above domains for each included trial, along with a judgement of the risk of bias (low, high, or unclear), based on the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green).

An example of a risk of bias judgement, based on allocation concealment only, is shown below:

Low risk of bias - adequate concealment of the allocation (e.g. sequentially numbered, sealed, opaque envelopes or centralised or pharmacy-controlled randomisation).

Unclear risk of bias - unclear about whether the allocation was adequately concealed (e.g. where the method of concealment is not described or not described in sufficient detail to allow a definite judgement).

High risk of bias - inadequate allocation concealment (e.g. open random number lists or quasi-randomisation such as alternate days, date of birth, or case record number).

We provided a summary assessment of the risk of bias for the primary outcomes across the studies (Higgins and Green). For each study, we assessed the overall risk of bias according to the following rationales:

Low risk, when there is a low risk of bias across all seven key domains.

Unclear risk of bias, when there is an unclear risk of bias in one or more of the seven key domains.

High risk of bias, when there is a high risk of bias in one or more of the seven key domains.

If high risk of bias is present in one of the seven domains then it took precedence.

Measures of treatment effect

For dichotomous outcomes (for example presence or absence of pain), we expressed the estimate of effect of an intervention as risk ratio (RR) together with 95% confidence interval (CI). For continuous outcomes (for example pain on a visual analogue scale), we used mean differences (MDs) and 95% CIs to summarise the data; in the event that different studies measured outcomes using different scales, we would have expressed the estimate of effect of an intervention as standardised mean difference (SMD) and 95% CI.

Unit of analysis issues

If cluster randomised trials had been included, we would have undertaken data analysis, whenever feasible, at the same level as the randomisation, or at the individual level accounting for the clustering.

Analysis of cross-over studies should take into account the two-period nature of the data using, for example, a paired t-test (Elbourne et al., 2002). We would have entered log RRs or MDs (or SMDs) and standard errors into Review Manager (RevMan) software (Review Manager 2012) using the generic inverse variance method (Higgins and Green).

Dealing with missing data

We contacted trial authors for missing data if the report was published from the year 2000 or onwards. We considered it unfeasible to obtain data for trials published prior to this cut-off date. We used methods as outlined in the Cochrane Handbook for Systematic Reviews of Interventions to estimate missing standard deviations (Higgins and Green).

Assessment of heterogeneity

We assessed clinical and methodological heterogeneity. We further assessed the significance of any discrepancies in the estimates of the treatment effects from the different trials by means of Cochran's Chi2 test for heterogeneity; heterogeneity would have been considered significant if $P < 0.1$ (Higgins and Green). We also used the I2 statistic, which describes the percentage total variation across studies that is due to heterogeneity rather than chance, to quantify heterogeneity; with I2 over 50% being considered substantial heterogeneity (Higgins and Green). .

Assessment of reporting biases

If there had been a sufficient number of trials (more than 10) included in any meta-analysis, we would have assessed publication bias according to the recommendations on testing for funnel plot asymmetry as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green). .

Data synthesis

If data had allowed, we would have performed meta-analysis of studies assessing the same comparisons and outcomes. We would combine RRs for dichotomous outcomes, and MDs (or SMDs if different scales were used) for continuous outcomes, using a random-effects model where there were four or more studies, or a fixed-effect model if there were less than four studies. We would have included data from split-mouth or cross-over studies in any meta-analysis using the generic inverse variance method described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green), combining them with parallel studies using the methods described in Elbourne et al (2002). As meta-analysis was not possible, we presented data in a table format.

Sensitivity analysis

If the number of studies had allowed, we would have undertaken a sensitivity analysis for each intervention and outcome by limiting the analysis to studies at overall low risk of bias.

Presentation of main results

We developed a 'Summary of findings' table for the main outcomes. We assessed the quality of the body of evidence with reference to the overall risk of bias of the included studies, the directness of the evidence, the inconsistency of the results, the precision of the estimates, the risk of publication bias, and the magnitude of the effect. We categorised the quality of the body of evidence of each of the main outcomes as high, moderate, low, or very low.

3.6 Results

A total of 486 articles were identified through our search strategy. Of these, 38 articles appeared to be potentially relevant and full copies were obtained. Following screening of full papers, 15 studies were identified for inclusion (Figure 3). One trial had been completed but had not been fully published as yet (Nct), one trial is ongoing (Nct), and one trial was duplicated and linked to a subsequent included study (Masuda et al., 1989). Twenty studies were excluded.

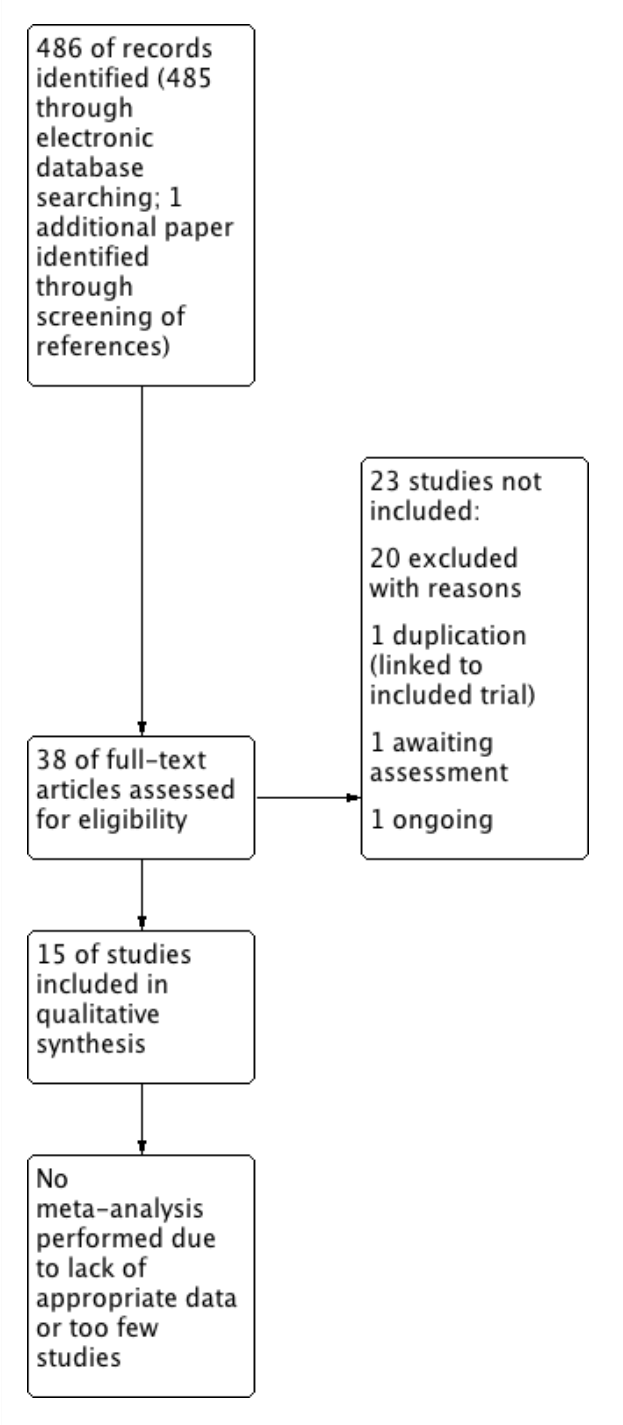


Figure 3. Study flow diagram

Included studies

A total of 15 trials were included in the review (n = 888 randomised participants; 780 evaluated) (see Appendix 5. Characteristics of included studies).

The studies varied in sample size, ranging from 24 to 116. Eleven of the trials were conducted in Turkey, two in Japan, one in Iran, and one in the UK.

One trial was a cross-over design with a washout period (Davies et al., 1988) and the remaining 14 were designed as parallel studies.

The funding source was not stated in six of the trials. Six trials received pharmaceutical company funding and three further trials received funding from research facilities.

The diagnosis of Behçet's disease was not described clearly in all of the studies. Most trials used the International Study Group criteria for Behçet's disease (ISG 1990). The two studies from Japan used the Japanese diagnostic criteria, which were only described in detail in one of the trials, and one trial used the O'Duffy criteria (Aktulga et al., 1980).

Six of the trials evaluated topical interventions applied directly to the ulcers and nine evaluated systemic interventions. The interventions used within the trials were diverse, and the mode of action with regard to the management of oral ulcers was often unclear.

Topical interventions

The six trials evaluating topical interventions assessed five main comparisons (five placebo controlled; two head to head).

Sucralfate versus placebo (Alpsoy et al., 1999, Koc et al., 1992). Interferon–alpha (different doses) versus placebo (Hamuryudan et al., 1991, Kilic et al., 2009). Cyclosporin A versus placebo (Ergun et al., 1997). Triamcinolone acetonide ointment

versus phenytoin syrup mouthwash (Fani et al., 2012). Interferon–alpha 1000 IU versus interferon–alpha 2000 IU (Kilic et al., 2009).

Systemic interventions

The nine trials evaluating systemic interventions assessed nine main comparisons (eight placebo controlled; one head to head).

Aciclovir versus placebo (Davies et al., 1988). Thalidomide (different doses) versus placebo (Hamuryudan et al., 1998). Corticosteroids versus placebo (Mat et al., 2006). Rebamipide versus placebo (Matsuda 2003).Etanercept versus placebo (Melikoglu et al., 2005). Colchicine versus placebo (Aktulga et al., 1980, Yurdakul et al., 2001). Interferon–alpha versus placebo (Alpsoy et al., 2002). Thalidomide 300 mg versus 100 mg versus placebo (Hamuryudan et al., 1998). Cyclosporin versus colchicine (Masuda et al., 1989).

Six of the 15 studies were primarily looking at interventions for oral ulceration (Ergun et al., 1997, Fani et al., 2012, Hamuryudan et al., 1991, Kilic et al., 2009, Koc et al., 1992, Matsuda et al., 2003). Five studies had the management of Behçet's disease as the main aim (Aktulga et al., 1980, Alpsoy et al., 2002, Masuda et al., 1989, Melikoglu et al., 2005, Yurdakul et al., 2001). The remaining studies looked at orogenital ulceration or genital ulceration (Alpsoy et al., 1999, Davies et al., 1988, Hamuryudan et al., 1998, Mat et al., 2006).

A wide range of outcomes were assessed, making comparison across trials difficult. For example, oral ulcers were measured using the following:

number of oral ulcers; mean frequency of ulcers or number of episodes; mean duration of ulcers; ulcer healing time; severity of ulcers; size of ulcers; time to initial response; recurrence of ulcers; time to recurrence of ulcers; complete response, defined as absence

of any oral ulcer of any size during treatment period; percentage change in a patient's total ulcer burden; monthly aphthae count.

Pain measurements included:

pain (e.g. scale of 0 to 3 (0: absent; 1: mild; 2: moderate; and 3: severe)); number of painful days; ratio of painful days to days with ulcers; total monthly pain scores.

Nine of the 15 studies did not report on pain as an outcome measure (Aktulga et al., 1980, Ergun et al., 1997, Fani et al., 2012, Hamuryudan et al., 1998, Hamuryudan et al., 1991, Masuda et al., 1989, Mat et al., 2006, Melikoglu et al., 2005, Yurdakul et al., 2001)

The study by Kilic et al (2009) stated that pain was an outcome but did not describe how it would be measured and did not report any pain data in the results.

Other reported outcomes included measures of 'overall response' or 'positive response' (not specified), 'other disease features', laboratory abnormalities, number and severity of genital ulcers, response of eye disease to treatment, ocular complications, patient-reported general well-being, global disease severity, amount of suppression of pathergy and midstream specimen of urine (MSU) tests, and attacks of arthritis.

Three out of 15 trials failed to report adverse events (Fani et al., 2012, Hamuryudan et al., 1991, Koc et al., 1992). None of the studies reported on issues of cost or reduction of morbidity. One trial described the use of a quality of life assessment tool but did not report any data on quality of life (Kilic et al., 2009).

Excluded studies

Twenty trials were excluded (Table 5. Characteristics of excluded studies). The main reason for exclusion was that following access to the full paper the study did not

actually fulfil the criteria for being a RCT (eight studies) (lack of randomisation, no control group). Three cross-over studies were excluded because of: lack of a washout period, one presented on topical only treatments for genital ulcers, and one reported oral ulcer outcomes but this was ad hoc reporting and not pre-specified. Two papers was rejected as they were letters with insufficient information reported. Both letters were published longer than 10 years ago and we therefore did not obtain any further information from the authors (Convit et al., 1984, Scheinberg, 2002).

Table 5. Characteristics of excluded studies

	Reason for exclusion
Anonymous 1998	Not an RCT
(Azizlerli et al., 1995)	Although mentions placebo 'chosen at random' it is unclear how active intervention arms were allocated
(Bacanli et al., 2006)	Not an RCT
(Ben Slama and Djemil, 2002)	Not an RCT
(Calguneri et al., 1996)	Results presented for whole study not clear at which point the final outcomes were measured i.e. not at point that randomisation stopped (this paper does not present an RCT, it presents RCT+ follow on open study combined)
(Chams-Davatchi et al., 2010)	Topical application – genital ulcers only
(Convit et al., 1984)	Letter (possibly linked to Convit 1972)
(Davatchi et al., 2009)	Cross-over design (4 months each phase, active colchine) but no washout period stated
(Lee et al., 2008)	Open label descriptive study comparing BDRAS versus RAS - no control
(Nanke et al., 2008)	Not an RCT
(Nct)	Not an RCT
(Nct)	No oral outcomes
(Nct)	Trial terminated
(O'Duffy et al., 1998)	Not an RCT
(Pizarro et al.)	Not an RCT

(Scheinberg, 2002)	Letter
(Sharquie et al., 2002)	No washout period
(Sharquie et al., 2013)	Insufficient washout demonstrated; no oral ulcer outcome measures
(Sun et al., 2009)	Not an RCT
(Yazici et al., 1990)	Primary aim ocular manifestations not oral; reject no prespecified oral outcome measures (oral outcomes not described in methods). No trial register registered to check

Risk of bias in included studies

A summary of the risk of bias for each study is presented in Figure 4 and the 'Characteristics of included studies' table (Appendix 5).

Only one trial was assessed as being at low risk of bias (Yurdakul et al., 2001). One of the trials was assessed as having overall unclear risk of bias (Alpsoy et al., 1999). The remaining 13 trials were assessed as at overall high risk of bias.

Allocation (selection bias)

Three of the 15 trials were given an overall low risk of bias for selection bias (both for sequence generation and allocation concealment) (Hamuryudan et al., 1998, Kilic et al., 2009, Yurdakul et al., 2001). Twelve of the 15 were assessed as at overall unclear risk of bias for allocation. Of these 12, the random sequence generation was at low risk of bias for two trials (Davies et al., 1988, Melikoglu et al., 2005) and allocation concealment was at low risk of bias for two (Aktulga et al., 1980, Mat et al., 2006).

Blinding (performance bias and detection bias)

Six trials were shown to be at low risk of bias for blinding (Alpsoy et al., 1999, Davies et al., 1988, Hamuryudan et al., 1998, Kilic et al., 2009, Mat et al., 2006, Yurdakul et al., 2001). Seven trials had an overall unclear risk of bias, of which one had a low risk for detection bias (Hamuryudan et al., 1991) and one had a low risk for performance bias (Koc et al., 1992). Two trials had a high risk of bias for blinding as the interventions used were different in appearance and delivery method (Aktulga et al., 1980, Fani et al., 2012).

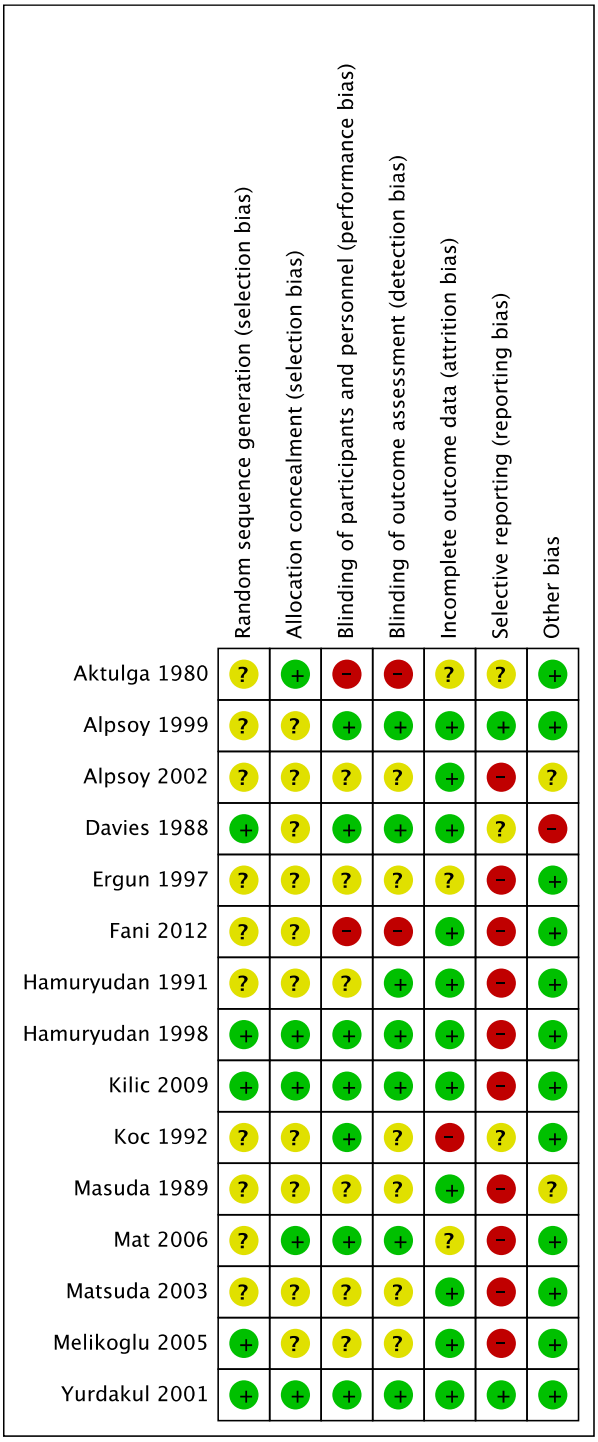


Figure 4. Risk of bias summary

Incomplete outcome data (attrition bias)

One trial was assessed as at high risk of bias due to incomplete data (Koc et al., 1992) as all six dropouts were from the intervention arm and insufficient reasons were presented. Three trials were assessed as at unclear risk of bias (Aktulga et al., 1980, Ergun et al., 1997, Mat et al., 2006). The remaining 11 trials were deemed low risk of bias.

Selective reporting (reporting bias)

Only two of the 15 trials were given low risk of bias for selective reporting (Alpsoy et al., 1999, Yurdakul et al., 2001). Three trials (Aktulga et al., 1980, Davies et al., 1988, Koc et al., 1992) were judged to be at unclear risk of bias and the remaining 10 trials were at high risk of bias. The most frequent reason for allocation of a high risk of bias was failure to report outcome data fully (Alpsoy et al., 2002, Ergun et al., 1997, Hamuryudan et al., 1998, Masuda et al., 1989, Matsuda et al., 2003). Some trials presented only a selection of the pre-specified outcome measures (Kilic et al., 2009) or presented outcomes that were not pre-specified (Mat et al., 2006). One trial did not present the results for the outcomes pre-specified in the trial protocol (Fani et al., 2012). Some trials presented means with no standard deviations (Davies et al., 1988, Kilic et al., 2009) or only a P value (Davies et al., 1988, Kilic et al., 2009). Some trials carried out further analyses to support the findings, however the analyses were not presented (Hamuryudan et al., 1991, Melikoglu et al., 2005).

Other potential sources of bias

Twelve out of 15 trials were thought to have low risk for other potential sources of bias. Two trials were at unclear risk of bias (Alpsoy et al., 2002, Masuda et al., 1989). In one

of these trials (Alpsoy et al., 2002) it was unclear if both the intervention group and the control group received additional analgesia, which in turn could potentially affect the pain outcomes. In the other (Masuda et al., 1989) it was unclear if additional topical therapies had been used. One trial was judged to be at high risk of bias due to concomitant systemic interventions being used (Davies et al., 1988).

Effects of interventions

Topical interventions

Six of the 15 included trials involved topical interventions. Five were placebo controlled (Summary of findings table 1) and one made a head-to-head comparison.

Placebo-controlled trials:

- Sucralfate

Two trials looked at sucralfate suspension versus placebo (Alpsoy et al., 2002, Koc et al., 1992). We were unable to pool the results as the mode of delivery of sucralfate differed between the studies (in one it was used as a mouthwash and in the other it was applied topically to ulcers). The trial by Alpsoy et al (1999) compared sucralfate suspension versus placebo suspension to be used as a mouthwash for two to four minutes after routine oral care and before bed. It included 40 participants and analysed results for 30. It had an unclear risk of selection bias (both for random sequence generation and allocation concealment). The results showed that sucralfate significantly decreased the mean frequency, healing time, and pain in comparison to baseline. However, no statistically significant differences were observed between the intervention

and placebo for any of the oral ulcer outcomes at either end of treatment (three months) or end of follow-up (six months) (Table 6). The trial by Koc et al (1992) included 41 participants (data evaluated for 35) and was at high risk of bias due to incomplete outcome data. It compared the sucralfate suspension and placebo suspension applied to oral ulcers four times a day. No statistically significant differences in number of painful days, number of episodes, or mean duration of episodes were seen at either the end of treatment or end of follow-up (Table 6).

There was insufficient evidence to support or refute the use of sucralfate suspension for oral ulcers in Behcet's disease.

Table 6. Sucralfate versus placebo (topical application)

			Sucralfate			Placebo				
Study	**Outcome**	**Time point**	**Mean**	**Standard deviation**	**N**	**Mean**	**Standard deviation**	**N**	**Mean difference [95% CI]**	**P value**
Alpsoy et al (1999)	Frequency of oral ulcer	End of treatment	3.56	1.3	16	4.36	2.2	14	-0.80 [-2.12, 0.52]	0.23
		End of follow up	3.81	2.1	16	3.57	1.9	14	0.24 [-1.19, 1.67]	0.74
Alpsoy et al (1999)	Healing time	End of treatment	7.19	1.9	16	8.28	2.3	14	-1.09 [-2.61, 0.43]	0.16
		End of follow up	8.31	2.5	16	9.28	2.9	14	-0.97 [-2.92, 0.98]	0.33
Alpsoy et al (1999)	Pain	End of treatment	0.69	0.5	16	1.07	0.8	14	-0.38 [-0.87, 0.11]	0.12
		End of follow up	1.47	0.5	16	1.28	0.6	14	0.19 [-0.21, 0.59]	0.35
Koc et al (1992)	Number of painful days	End of treatment	37.5	17.6	24	28.5	19.0	11	9.00 [-4.25, 22.25]	0.18
		End of follow up	38.5	19.5	24	34.9	23.2	11	3.60 [-12.17, 19.37]	0.65
Koc et al (1992)	Number of episodes	End of treatment	6.4	2.5	24	5.0	2.0	11	1.40 [-0.15, 2.95]	0.08
		End of follow up	6.5	2.0	24	5.5	1.3	11	1.00 [-0.11, 2.11]	0.08
Koc et al (1992)	Mean duration of episodes	End of treatment	10.3	8.3	24	11.3	5.6	11	-1.00 [-5.69, 3.69]	0.68
		End of follow up	8.9	6.9	24	8.2	2.99	11	0.70 [-2.56, 3.96]	0.68

- Interferon-alpha

Two placebo-controlled trials studied the effect of topical interferon-alpha (Hamuryudan et al., 1991, Kilic et al., 2009). Both had a high risk of bias for selective reporting. The trial of 63 patients (61 evaluated) by Hamuryudan et al (1991) compared interferon–alpha 2c as a hydrogel versus placebo hydrogel. Patients applied a thin layer on any ulcer three times a day for 24 weeks. A similar application was made to the upper and lower lip mucosa irrespective of the presence of ulcers. No statistically significant difference was shown for the total number of ulcers throughout the treatment period (**Table 7**).

The Kilic et al (2009) trial compared two different dosages of interferon-alpha lozenges (1000 IU versus 2000 IU) versus placebo in 84 patients. The data presented did not allow for analysis, however the authors reported no statistically significant difference between the total ulcer burden of the intervention (at either evaluated dosage) and placebo groups.

There was insufficient evidence to support the use of interferon-alpha as a topical treatment for oral ulcers in Behçet's disease.

Table 7. Interferon-alpha versus placebo (topical)

			Interferon-alpha			Placebo				
Study	**Outcome**	**Time point**	**Mean**	**Standard deviation**	**n**	**Mean**	**Standard deviation**	**n**	**Mean difference [95% CI]**	**P value**
Hamuryudan et al (1991)	Total ulcers	Duration of treatment (24 weeks)	41.8	24.5	30	40.3	23.0	31	1.50 [-10.43, 13.43]	0.81

Table 8. Triamicinolone acetonide versus phenytoin

			Triamicinolone acetonide		Phenytoin			
Study	**Outcome**	**Time point**	**Number with event**	**N**	**Number with event**	**N**	**RR (95% CI)**	**P value**
Fani et al (2012)	Positive response	7 days	26	30	16	30	1.63 [1.13, 2.34]	0.009

- Cyclosporin A

The trial by Ergun et al (1997) compared cyclosporin A in orabase (70 mg/g of orabase) versus placebo (orabase) in 24 patients. It had a high risk of reporting bias. No data were presented; however the authors reported no clinical improvement in the number, size, and healing time for either group. No adverse effects were seen (Ergun et al., 1997).

There was insufficient evidence to support or refute the use of cyclosporin A in orabase as a treatment for oral ulcers in Behçet's disease at the dose evaluated.

Head-to-head trials:

The trial by Fani et al (2012) included 60 participants and it compared triamcinolone acetonide 0.1% ointment versus phenytoin syrup mouthwash (30 mg in 5 ml). The triamcinolone group applied the ointment to the lesions three times a day. The phenytoin group used two teaspoons of syrup in half a glass of warm water as a mouthwash for four to five minutes, three times a day. The trial had a high risk of reporting bias (Fani et al., 2012). The outcome measure of 'positive response' was not described, however a statistically significant difference was shown in favour of triamcinolone acetonide over phenytoin syrup (risk ratio (RR) 1.63, 95% confidence interval (CI) 1.13 to 2.34; P = 0.009) (**Table 8**).

There was insufficient evidence from this single study to support or refute the use of either phenytoin syrup mouthwash or triamcinolone acetonide as a treatment for oral ulcers in Behçet's disease.

Systemic interventions

Nine of the 15 trials evaluated systemic interventions. Eight out of the nine were placebo controlled (Summary of findings table 2) and one trial was head-to-head.

Placebo-controlled trials:

- Aciclovir

One trial of 36 patients compared acyclovir versus placebo (Davies et al., 1988). The patients were given 800 mg of acyclovir five times a day for one week, followed by 400 mg twice a day for 11 weeks. Patients also received various concomitant treatments. The trial had a high risk of reporting bias. Data weren't presented in a usable format, however the authors reported no statistically significant difference in frequency of oral ulcers between groups.

There was insufficient evidence to support or refute the use of acyclovir as a treatment for oral ulcers in Behcet’s disease at the dose evaluated.

- Thalidomide

One trial recruiting 101 patients compared thalidomide 300 mg daily versus 100 mg daily versus daily placebo (Hamuryudan et al., 1998). It had a high risk of reporting bias. It included only male patients. The authors reported a significant effect on mean numbers of minor oral ulcers from week four of treatment in both thalidomide groups, however oral ulcer data were not presented separate from genital ulcer data. The treatment effect diminished on stopping treatment. There was no reported difference between the 100 mg and 300 mg dosages on oral ulcers. There were significant adverse effects including severe sedation, polyneuropathy, loss of libido, and weight gain. A

greater number of adverse events was seen for the higher dose of thalidomide. Four patients withdrew from the study due to side effects (all from the intervention arm).

There was insufficient evidence to support or refute the use of thalidomide (at either 300 mg or 100 mg daily) as a treatment for oral ulcers in Behçet's disease.

- Corticosteroids

One trial compared intramuscular depot injections of corticosteroids versus saline placebo injections in 86 patients (Mat et al., 2006). The primary aim of the study was to manage genital ulceration in Behçet's disease however they did report on oral ulcers. Patients received 40 mg methylprednisolone by intramuscular injection versus a placebo intramuscular injection every 3 weeks for 27 weeks. The trial had a high risk of reporting bias. Various concomitant treatments were used including colchicine, amitriptyline, non-steroidal anti-inflammatory drugs, and thalidomide. No statistically significant difference between groups was shown with regard to oral ulceration (**Table 9**).

There was insufficient evidence to support or refute the use of intramuscular depot injections of corticosteroids, at the dose evaluated, as a treatment for oral ulcers in Behçet's disease.

Table 9. Depot corticosteroids versus placebo (systemic)

			Depot corticosteroids			Placebo				
Study	**Outcome**	**Time point**	**Mean**	**Standard deviation**	**N**	**Mean**	**Standard deviation**	**N**	**Mean difference [95% CI]**	**P value**
Mat et al (2006)	Mean number of oral ulcers	End of treatment (week 27)	1.8	1.0	41	1.8	1.2	44	0.00 [-0.47, 0.47]	1.00
		End of follow-up (week 35)	1.9	1.6	34	2.0	2.3	40	-0.10 [-0.99, 0.79]	0.83

Table 10. Colchicine versus placebo (systemic)

			Colchicine			Placebo				
Study	**Outcome**	**Time point**	**Mean**	**Standard deviation**	**N**	**Mean**	**Standard deviation**	**N**	**Mean difference [95% CI]**	**P value**
Yurdakul et al (2001)*	Total number of ulcers	24 months	23.2	17.1	57	20.9	14.0	58	2.30 [-3.42, 8.02]	0.43
Study	**Outcome**	**Time point**	**Number with event**		**N**	**Number with event**		**N**	**RR (95% CI)**	**P value**
Aktulga et al (1980)	Improvement in oral ulcer score	6 months	9		14	12		14	0.75 [0.48, 1.17]	0.21

- Rebamipide

One trial of 35 patients compared 300 mg daily rebamipide versus placebo (Matsuda et al., 2003). It had a high risk of reporting bias. Concomitant treatments were allowed but insufficient details were presented to allow full interpretation of the results. The authors stated that rebamipide improved the global evaluation aphthae count and global evaluation pain score in Behçet's disease; data were not presented in a form to confirm or refute this statement.

There was insufficient evidence to support or refute the use of rebamipide, at the dose evaluated, as a treatment for oral ulcers in Behçet's disease.

- Etanercept

The trial by Melikoglu et al (2005) included 40 participants who received either etanercept 25 mg subcutaneously or placebo subcutaneously twice a week for four weeks. It included only males. There was a high risk of reporting bias. The authors reported a statistically significant difference in mean number of oral ulcers with etanercept (weeks one, two, three, and four). The data presented did not allow this statistically significant result to be confirmed at week four. The statistically significant effects disappeared in the follow-up period (Melikoglu et al., 2005).

There was insufficient evidence to support or refute the use of etanercept as a treatment for oral ulcers in Behçet's disease at the dose evaluated.

- Colchicine

Two trials compared colchicine with placebo. One trial of 116 patients compared colchicine (0.5 mg, dose adjusted per weight in kg) versus placebo (Yurdakul et al., 2001). The trial was at overall low risk of bias. The trial authors provided additional data; and no significant difference was noted on the outcome of oral ulcers (**Table 10**). An earlier trial, of 35 patients compared 0.5 mg colchicine, three times a day for six months, with placebo. The colchicine capsule also contained 60 mg of amidone and 40 mg lactose. The placebo contained a diarrhoea producing agent, phenolphtalein. No difference was shown with regard to improvement in RAS (**Table 10**).

There was insufficient evidence to support or refute the use of colchicine as a treatment for oral ulcers in Behçet's disease.

- Interferon-alpha

The trial by Alpsoy et al (2002) compared subcutaneous injections of interferon–alpha (6 x 106 IU) versus placebo subcutaneous injections in 50 patients. The treatment was given three times a week for three months and the patients were followed up for a further three months. The trial had a high risk of reporting bias. Data were not presented in a useable format, however the authors reported a statistically significant decrease in the duration and pain of oral ulceration. There was a high rate of adverse events including alopecia, leukopenia, and diarrhoea and 18 out of 23 patients experienced mild flu like symptoms in the treatment arm (Alpsoy et al., 2002).

There was insufficient evidence to support or refute the use subcutaneous Interferon–alpha as a treatment for oral ulcers in Behçet's disease at the dose evaluated.

- Head-to-head trials

One trial compared cyclosporin (10 mg/kg per day) to colchicine (1 mg daily) for 16 weeks for the management of ocular manifestations of Behçet's disease (Masuda et al., 1989). It included 96 patients (92 evaluated) and also reported on oral ulcers. It had a high risk of reporting bias. The results showed that cyclosporin alleviated oral aphthous ulceration in 70% compared to 20% in the colchicine group (RR 3.3, 95% CI 1.85 to 5.88; $P < 0.0001$). There were multiple adverse events in the cyclosporin arm and three patients withdrew and nine had a dose reduction as a result (**Table 11**).

There was insufficient evidence to support or refute the use of cyclosporin (10 mg/kg per day) or colchicine (1 mg daily) as a treatment for oral ulcers in Behçet's disease at the doses evaluated.

Table 11. Cyclosporin versus colchicine (systemic)

			Ciclosporin		Colchicine			
Study	**Outcome**	**Time point**	**Number with event**	**N**	**Number with event**	**N**	**RR (95% CI)**	**P value**
Masuda et al (1989)	Alleviation of oral aphthous ulcers	Unclear	33	46	10	46	3.3 [1.85, 5.88]	<0.0001

Summary of findings table 1. Topical interventions compared to placebo for managing oral ulcers in Behçet's disease

Patient or population: people with Behçet's disease **Settings:** primary care **Intervention:** topical interventions **Comparison:** placebo	
Outcomes	**Comments**
Pain associated with oral ulcers	5 placebo-controlled trials evaluated topical interventions (sucralfate suspension (2 trials), interferon–alpha (2 trials), cyclosporin A (1 trial). The quality of the evidence ranged from low to very low[1] and there is insufficient evidence to support or refute the use of any evaluated intervention for oral ulcers in Behçet's disease
Episode duration associated with oral ulcers	
Episode frequency associated with oral ulcers	
Safety of the intervention including adverse effects	

Footnotes: [1]Studies downgraded for risk of bias and imprecision. Applicability, indirectness and publication bias were not considered to be of concern.

Summary of findings table 2. Systemic interventions compared to placebo for managing oral ulcers in Behçet's disease

Patient or population: people with Behçet's disease **Settings:** primary care **Intervention:** systemic interventions **Comparison:** placebo	
Outcomes	**Comments**
Pain associated with oral ulcers	8 placebo-controlled trials evaluated topical interventions (aciclovir (1 trial), thalidomide (1 trial), corticosteroids (1 trial), rebamipide (1 trial), etanercept (1 trial), colchicine (2 trials), interferon–alpha (1 trial)). The quality of the evidence ranged from moderate[1] to very low[2] and there is insufficient evidence to support or refute the use of any evaluated intervention for oral ulcers in Behçet's disease
Episode duration associated with oral ulcers	
Episode frequency associated with oral ulcers.	
Safety of the intervention including adverse effects	

Footnotes
[1]Yurdakul et al (2001) downgraded for imprecision alone.
[2]Studies downgraded for risk of bias and imprecision. Applicability, indirectness and publication bias were not considered to be of concern.

3.7 Discussion

Summary of main results

Fifteen randomised controlled trials (RCTs) were included in this review, evaluating the effectiveness of 13 different interventions for the management of oral ulcers in Behçet's disease. There was considerable heterogeneity in the types of interventions evaluated and the way in which the interventions were used. Many of the trials specifically looked at oral ulcers as the primary outcome (six out of 15 trials), however for some of the studies the primary outcomes were related to other manifestations of Behçet's disease or the holistic management of Behçet's disease and the oral aspects were only reported as a secondary outcome.

The outcome measures evaluated and the timing of outcome measures varied widely. Some studies reported on individual ulcer data (size and number of ulcers), some on episodes (number of episodes, number of days with ulcers, number of days with no ulcers), and not all trials reported on pain as an outcome. Three of the 15 trials did not report adverse events or side effects and therefore the safety of the intervention used could not be assessed. Some studies reported data at the end of treatment and some at the end of follow-up. This is of particular clinical relevance as many of the interventions were shown to be beneficial whilst actively on treatment, but on stopping treatment the positive results were not sustained. This would mean that patients would potentially require long-term active treatment.

Twelve of the 15 trials were placebo controlled. There were three head-to-head trials. In the head-to-head trial by Fani et al (2012) no placebo was used. It is possible that the triamcinolone acetonide ointment was being used as an 'active placebo' or as a 'standard treatment' or 'usual treatment' arm, however there is no clear evidence from this review

that triamcinolone is any better than placebo or no treatment for recurrent aphthous stomatitis (RAS)-type ulceration in Behçet's disease. Without a placebo arm to the trial, it is theoretically possible that the benefit shown by the triamcinolone acetonide ointment was because the phenytoin syrup made the symptoms of the RAS-type ulcers worse. Further evidence for the use of topical steroids including triamcinolone acetonide for the management of RAS will be available in the ongoing Cochrane review 'Topical interventions for the management of recurrent aphthous stomatitis' (Taylor et al., 2013).

There was insufficient evidence to support or refute the use of any evaluated interventions for the management of oral ulcers in Behçet's disease.

Overall completeness and applicability of evidence

The diagnosis of Beḥcet's disease was not described clearly in all of the studies. Most trials used the International Study Group criteria for Behçet's disease (International Study Group for Behçet’s, 1990). The two studies from Japan used the Japanese diagnostic criteria, which were only described in detail in one of the trials. One trial used the O'Duffy criteria (Aktulga et al., 1980).

Eleven of the trials were from Turkey and seven of these were from Istanbul, Turkey. Although this may represent the high prevalence of Behçet's disease in that area it also gives a heavy weighting to the evidence from one particular group.

As stated previously, many RCTs are carried out for the treatment of Behçet's disease and not all of them report on the oral outcomes. Where a study reported an oral outcome but this was not pre-specified in the methodology, the study was excluded. This was to avoid ad hoc reporting of results after the trial was finished. It is important that as much information as possible is available for clinicians so they can plan their treatments appropriately. The heterogeneity of outcome measures used in trials for Behçet's disease

was recently systematically reviewed (Hatemi et al., 2014). In the 18 included RCTs that were reviewed, there were nine different oral outcome measurements used. This level of heterogeneity of outcome measures was also a feature in our review and meant that meta-analysis was impossible.

There may be many treatments currently used for Behçet's disease which have a beneficial effect on oral ulcers, however until we have further evidence we can't recommend them for treating the oral ulcers of Behçet's disease.

There was a paucity of RCTs looking at anti-TNF (tumour necrosis factor) treatments. Many of the anti-TNF treatments have been evaluated in open studies. Anti-TNF treatments have the potential to be used to manage the more serious and life threatening or organ threatening aspects of Behçet's disease. As a result of this, the oral aspects of Behçet's disease may not be reported as readily.

Oral ulceration is the most common sign and symptom of Behçet's disease and often pre-dates other systemic involvement. As a result of this, many of the trials were primarily aimed at the management of oral ulceration (six out of the 15 trials). Of these six trials, five were for topical treatments. Whilst the oral aspects of Beḫcet's disease are not considered to be life threatening, they can cause significant morbidity and reduction of quality of life. None of the trials reported on these aspects.

Four of the studies looking at systemic interventions were aimed at orogenital disease and the remaining five studies were for the management of Behçet's disease. There are multiple trials of systemic treatments for Behçet's disease which did not fulfil our criteria for inclusion in this review as they did not report the oral aspects with pre-specified oral outcome measures.

One trial has recently been completed and shows promising results for apremilast compared with placebo for oral ulcers (Nct). Once fully available, the results of this trial will be incorporated in future updates of this review.

Quality of the evidence

One of the 15 trials was assessed as being at low risk of bias (Yurdakul et al., 2001). One was at unclear risk of bias (Alpsoy et al., 1999). The remainder were deemed as at high risk of bias. Of the 13 high risk of bias studies, 10 had a high risk of bias for reporting bias. The main issues with reporting bias were related to inadequate or incomplete reporting. Some studies did not report the pre-specified outcomes, others reported a global evaluation of the outcomes but with no detailed data provided. Inappropriate use of graphs and tables which did not contain useable data was common. Some studies reported that separate analyses were carried out which confirmed their findings, but the separate analyses were never presented.

In previous times the space restrictions from some journals meant authors were required to condense their findings to conform to the limits stipulated. Fortunately, in recent times there is the availability of an online supplement which means that all authors can make all the results available to the reader. In many of the studies a high risk of bias label for reporting bias could have been avoided if additional raw data had been available to this review group.

For topical interventions the quality of the evidence ranged from low to very low; for systemic interventions the quality of the evidence ranged from moderate to very low. The quality of the body of evidence was downgraded due to risk of bias and imprecision.

Potential biases in the review process

The review authors followed the guidelines for conducting this systematic review under the strictest of conditions (Higgins and Green). All abstracts were independently dual screened, and all papers were assessed and had the risk of bias assessment carried out by at least two independent authors. All papers were subsequently reviewed by five of the review authors. The findings were then discussed at a meeting with five of the authors including the three clinical authors.

Agreements and disagreements with other studies or reviews

A previous Cochrane review has looked at pharmacotherapy for Beḫcet's syndrome (Saenz et al., 1998). They included five trials for oral ulceration, four of which are included in this review. The fifth trial (Benamour et al., 1991) was considered to be a controlled clinical trial and therefore not eligible for inclusion in this review. The review by Saenz et al also concluded that there was "insufficient evidence either to support or to refute some of the classic treatments for Behçet's syndrome". The current recommendations for the management of Behçet's disease were written by the EULAR (European League Against Rheumatism) group and published in 2008 (Hatemi and Silman, 2008). This multidisciplinary expert committee carried out a systematic review and presented their findings and recommendations according to the system involved in the disease. The management of oral ulcers is contained in the mucocutaneous section and states that "oral ulcers may be managed with topical preparations". The RCTs included in this review are all noted by the group, and additionally they make recommendations based on various open studies. Colchicine is a readily used systemic treatment in Beḫcet's disease and the authors state "Colchicine is widely used without

any solid proof of its efficacy", which confirms the findings of the colchicine study included in this review (Yurdakul et al., 2001)

Another recent review, 'Behçet's syndrome: Facts and Controversies' (Mat et al., 2013), summarises the RCTS available and comments on the EULAR recommendations. Many of the RCTs described were carried out in the same department that the authors are from (Cerrahpsa medical facility, Istanbul). They also report that data from the open studies on the use of biologic agents is promising (interferon-alpha, anti-TNF). They conclude that "Local treatment for oral and genital ulcers is sufficient".

The findings of our systematic review indicate uncertainty on the effectiveness and safety of local and systemic treatment for oral ulcers.

3.8 Conclusions

Implications for practice

Whilst there is no 'gold standard treatment' for the management of oral ulcers in Behçet's disease, there are a number of treatments which are currently used in practice.

In practice, topical treatments are generally used as first line therapy, however it is often necessary to consider systemic treatments for many patients. When patients have manifestations of Behçet's disease that may cause severe morbidity (for example blindness) or they have multiple morbidities, or they are life threatening, the clinical reasoning for stepping up the treatment to include potentially harmful systemic interventions may be justified. It may be a secondary beneficial outcome that the patient's oral symptoms also improve in these cases. However, there are some patients

who do not have this level of severity of Behçet's disease but they do have severe oral ulceration which can cause significant morbidity and reduction of quality of life (eating, drinking, and speaking). For these patients, it is important that we have the best evidence to guide our clinical decision making.

This review found insufficient evidence to support or refute the use of any of the included topical or systemic interventions for the management of oral ulcers in Behçet's disease.

Implications for research

This review was limited by the poor methodology of many of the trials, which in turn led to huge heterogeneity of outcome measures and timing of outcome measures, and inadequate reporting of results.Future trials for Beḥcet's disease should be appropriately planned, executed, and reported according to the CONSORT guidelines (www.consort-statement.org). The interventions evaluated should be clinically relevant and the controls used should be appropriate. Cross-over trials should have a washout period.

As oral ulcers are the most common feature of Behçet's disease, appropriate pre-specified oral outcome measures should be used for all trials of interventions for Beḥcet's disease. The development of a set of standardised outcome measures for oral ulcer trials is registered with COMET (www.comet-initiative.org). The use of an oral ulcer core outcome set when planning trials will allow homogeneity of outcomes for future systematic reviews. Hatemi et al are leading a group who are currently developing a core set of outcome measures for Behçet's disease (Hatemi et al., 2014), however there is no planned involvement of an oral ulcer related specialty in that group (that is oral medicine, oral surgery, or dentistry).

The inclusion of a quality of life assessment tool such as the Chronic Oral Mucosal Diseases Questionnaire (Riordain et al., 2011) would be advantageous.

As many of the patients will require long term active treatment, the inclusion of an appropriate economic evaluation of the interventions would be appropriate. This could assess the cost effectiveness of treatments.

Further research into the following interventions is warranted:

thalidomide;rebapamide;etanercept;and interferon-alpha.

Further research would most likely change current clinical practice.

3.9 Acknowledgements

The review team would like to acknowledge Anne Littlewood, Jo Weldon, and Janet Lear for their help with the management of this review. We would also like to thank authors of trials for additional data provided.

3.10 Contributions of authors

Development of protocol based on the latest Cochrane guidance: Jennifer Taylor (JT), Philip Riley (PR), Paul Brocklehurst (PB), Mike Pemberton (MP), Anne-Marie Glenny (AMG), Tanya Walsh (TW), and Rachel Gorodkin (RG).

Identification of studies: JT, AMG.

Data extraction: JT, PB, AMG, TW, PR.

Assessment of risk of bias: JT, PB, AMG, TW, PR.

Data input and synthesis: JT, AMG, TW, PB, PR.

Writing of initial report: JT, AMG, PB, TW, MP, AMG, PR, RG.

Addressing feedback following peer review: JT, AMG.

3.11 Declarations of interest

There are no financial conflicts of interest and the review authors declare that they do not have any associations with any parties who may have vested interests in the results of this review.

3.12 Differences between protocol and review

The order of authors has been altered to reflect degree of contribution, however, all authors listed on the protocol remain authors on the full review and all have provided input into its production.

Following peer review the wording around the definition of recurrent aphthous stomatitis (RAS) and RAS-type ulceration has been clarified. This is an amendment to the protocol.

3.13 Published notes

This Cochrane Review is currently not a priority for updating. However, following the results of Cochrane Oral Health's latest priority setting exercise and if a substantial body of evidence on the topic becomes available, the review would be updated in the future.

UPDATED CLINICAL OPINION

The reason for including Behcet's related oral ulcers as a separate review was to ensure we hadn't missed a large section of evidence (as this cohort of patients was excluded in both the systemic and topical RAS reviews)

This review was also not particularly well received by the oral medicine world. The frustration of clinicians was made clear during the question-and-answer session at the European Association of Oral Medicine in Turkey where this paper was presented.

The main complaint was that the findings of the review would not change clinical practice. The most prescribed systemic treatment for oral ulcers in Behcet's Disease is colchicine, and clinically, from experience we know this works, however our clinical experience was not supported by the evidence from this review.

As described in the paper, Behcet's encompasses a spectrum of clinical disease, and whilst oral ulcers are the most reported presentation, they are often the least concerning from a mortality and morbidity perspective. Patients with severe disease are treated with major immunosuppression and often the outcomes on oral symptoms are never measured.

The timing of the searches meant the first publication of a trial on Apremilast was not included. Apremilast has now convincingly shown to be useful for oral ulcers in Behcet's.

In addition, as this review was published 8 years ago– none of the biologic treatments widely used in practice now (infliximab, adalimumab and tocilizumamb), were included.

There is ongoing work within the Behcet's research community around the use of outcome measures. Many of the tools currently in use do not have specific oral outcomes. Often oral ulcers are grouped with genital ulcers as part of the mucocutaneous outcomes. There is ongoing work on the development of core outcome sets in Behcet's Disease.

Chapter 4 World Workshop on Oral Medicine VI: a systematic review of the treatment of mucous membrane pemphigoid

Thus far I have reviewed the evidence for management of RAS and ALU in Behçet's – both conditions which present with oral ulceration that is episodic and non- progressive. The next two chapters will assess the evidence for the management of two persistent, oral ulcerative disorders: Pemphigus Vulgaris (PV) and Mucous Membrane Pemphigoid (MMP). These are the two most common immunobullous diseases seen in oral medicine practice.

The immunobullous diseases are mucocutaneous autoimmune conditions that can be organ damaging and potentially life threatening to patients. They represent the more serious end of the spectrum of disease managed by oral medicine clinicians, often in conjunction with colleagues in Dermatology. They are rare conditions and high quality randomised controlled trials are scarce, therefore, to assess the full body of evidence these systematic reviews were not limited to the evidence from RCTs and, instead, included observational studies as well as interventional designs.

The World Workshop of Oral Medicine was developed in the 1980s to gather international experts in the development of largescale literature reviews on conditions and topics under the care of Oral medicine. Over the years, the scale and remit of the projects has developed and now include consensus and working group developments as well as work under the original theme of systematic reviews (Lockhart et al., 2015).

The group meets on a four-yearly basis with establishment of new research aims and group compositions each time. WWOM V1 was conducted in April 2014 in Orlando, Florida, USA and it involved 89 faculties from 25 countries (Peterson et al.).

By competitive process I was given the role of reviewer alongside my colleague and co-author Dr Roddy McMillan. In a usual WWOM project, the role of reviewer would be directed and supported by a section head of the group. However, due to a variety of factors it was necessary for Dr McMillan and I to lead our group from within. Between us we developed the protocol, search strategy, screening, data extraction and undertook the analysis. In addition, we were fully involved in the discussion and write up.

Permission has been granted from Dr Tim Hodgson on behalf of the WWOM Steering Committee and Dr Roddy McMillan as my co-author, for these published papers to be included in this thesis.

Both papers follow the themes from chapters 3 and 4. The heterogeneity of outcome measures means that meta-analyses cannot be performed. The concept of core outcome sets is raised as an area for potential future research

The following two reviews have been published and are presented here in a format suitable for this thesis.

World Workshop on Oral Medicine VI: A Systematic Review of the Treatment of Mucous Membrane Pemphigoid

Citation: Taylor J, McMillan R, Shephard MK, Setterfield J, Ahmed R, Carrozzo M, Grando S, Mignogna M, Kuten-Shorrer M, Musbah TM, Elia A, McGowan R, Kerr AR, Greenberg M, Hodgson T, Sirois D, World Workshop on Oral Medicine VI: A Systematic Review of the Treatment of Mucous Membrane Pemphigoid, Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology (2015), doi: 10.1016/j.oooo.2015.01.024

4.1 Abstract:

Objective: Determine the efficacy and safety of interventions for mucous membrane pemphigoid (MMP).

Study design: We conducted a systematic review from 2003-2013 according to the Cochrane Collaboration methodology. Randomised (RCTs) or controlled (CCTs) clinical trials and observational studies were included with diagnosis confirmed by clinical, histopathological and immunofluorescence criteria. The primary outcome was lesion remission/healing; several relevant secondary outcomes were also included.

Results: One RCT and 32 observational studies were included in the final analysis. The included RCT with high risk of bias in multiple domains found limited evidence that pentoxiphylline combined with corticosteroid (CS) and cyclophosphamide (CYC) was more effective than standard therapy (CS+CYC alone) for ocular MMP. We summarize the outcomes from 32 observational studies examining 242 patients across 19 unique treatments. Interventions that show promise include rituximab and IVIg.

Conclusions: This systematic review is the most recent since 2003/2009. There is still lack of high- quality research providing evidence-based MMP treatments.

Mucous membrane pemphigoid (MMP) is a heterogeneous group of chronic, autoimmune, subepithelial blistering diseases that predominantly involve the mucous membranes and occasionally the skin. Although the oral and ocular mucosae are the most common sites affected, the nasopharynx, esophagus, larynx, and anogenital region may also be involved (Xu et al., 2013). Affected persons often experience diagnostic delays despite its relatively characteristic and recognizable presentation of MMP. The presentation varies considerably within the spectrum of MMP in terms of sites of involvement and severity of disease. Tailoring treatment to individual patients is considerably limited by a paucity of high-quality clinical trials to demonstrate efficacy of available treatments. Future collaboration between specialized oral medicine clinicians, dermatologists, ophthalmologists, and others working in this field will be essential in developing high-quality clinical trials.

The Sixth World Workshop in Oral Medicine sponsored this systematic review of the efficacy and safety of interventions for MMP.

Epidemiology

MMP is a rare disease, defined as affecting no more than 5 to 7.5 of 10,000 individuals (Dear et al., 2006). The real incidence of MMP is unclear. It was estimated to be 1.3 to 2.0 per million per year in French and German dermatologic studies. However, ophthalmologic and oral cohorts suggest a higher incidence (Scully et al., 1999). Women are more often affected than men, the female-to-male ratio being nearly 2:1. MMP mainly occurs in the older population, commonly observed in those between 50 and 80 years of age. Children are only rarely affected. There is no known racial or geographic predilection (Scully et al., 1999, Xu et al., 2013).

Natural course of disease

MMP typically starts with recurring vesicles or bullae affecting either the mucous membranes or the skin. Extraoral lesions exhibit a pronounced tendency to scarring. Many patients have primary oral involvement of gingivae, buccal mucosa, hard and soft palates, tongue, and uncommonly the lower lip. Oral lesions are usually persistent. Fluid-filled blisters develop and then break, leaving raw, painful ulcers that heal slowly over several days to weeks. The severity of the disease is extremely variable, ranging from occasional blisters to continuous severe blistering and ulceration. The most common oral manifestation of MMP is patchy or generalized gingival sloughing with superficial ulcers and erosions (Bruch-Gerharz et al., 2007), a clinical presentation often referred to as *desquamative gingivitis*, as seen in pemphigus vulgaris and ulcerative lichen planus.

The conjunctiva is the second most common site of involvement, with lesions ranging from conjunctival erosions to scarring and progressive cicatrization that may culminate in blindness. In patients without initial ocular involvement, the annual risk for developing eye lesions is 5% over the first 5 years (Bruch-Gerharz et al., 2007, Di Zenzo et al., 2014). Eye involvement usually begins with erythema and symptoms of burning, irritation, and excessive tearing. Subconjunctival inflammation and scarring may result in the palpebral conjunctiva fusing with the bulbar conjunctiva, resulting in symblepharon or ankyloblepharon. Shrinkage of conjunctivae may lead to entropion, or inward turning of the lid margin onto the corneal surface, with subsequent trauma from the eyelashes (trichiasis). The combination of entropion and trichiasis may result in blindness (Scully et al., 1999).

Scarring lesions can also involve other mucosae: Scarring of the laryngeal mucosa can result in hoarseness and progressive or sudden asphyxiation; scarring of the esophagus can lead to dysphagia; and scarring of the anogenital mucosa can lead to significant morbidity (Xu et al., 2013).

Pathogenesis

MMP is characterized by linear deposition of immunoglobulin G (IgG; 97%), IgA (27%), or C3 (78%) along the epithelial basement membrane zone (BMZ) (Scully et al., 1999, Xu et al., 2013). Autoantibodies are directed against specific adhesion molecules located in the hemi-desmosomes of basal epidermal keratinocytes and the lamina lucida of the BMZ. MMP lesions are widely believed to be the result of a subepithelial loss of adhesion mediated by autoantibodies, although the underlying molecular mechanisms are largely unknown (Bruch-Gerharz et al., 2007). By use of molecular techniques, at least six autoantigens have been identified: bullous pemphigoid antigen of 180 kDa (BP180/collagen type XV11), bullous pemphigoid antigen of 230 kDa (PB230), both subunits of integrin α6β4, laminin 332 (formerly known as laminin 5), and type VII collagen (Schmidt and Zillikens, 2013).

The C-terminal epitopes on BP180 are predominantly recognized (Di Zenzo et al., 2014), although the NC16a domain is also a recognized target. In the majority of patients with anti–laminin 332 reactivity, the α3 chain is targeted (Kirtschig et al., 1995). Autoantibodies to α6 integrin have been described in patients with oral lesions, although not invariably (Di Zenzo et al., 2014), whereas reactivity against β4 integrin has been associated with ocular involvement (Rashid et al., 2006).

Notably, a solid cancer is present in about 30% of patients with anti–laminin 332 MMP.[9] The pathogenic relevance of some of the above-cited autoantibodies in MMP has yet to be demonstrated in vitro and in vivo. Antibodies to both anti−laminin 332 and anti–α6β4 integrin induced noninflammatory subepidermal blisters when injected into mice or human skin grafted onto immunocompromised mice or in organ cultures (Schmidt and Zillikens, 2013).

Ultrastructural analysis has demonstrated that blister formation occurs within the lower lamina lucida and lamina densa (Bruch-Gerharz et al., 2007).

Experimental models of blister formation suggest that the autoantibodies target the adhesion molecules within the basal membrane, interfering with their structural integrity and function. In some lesions, autoantibodies may impair keratinocyte adhesion through steric hindrance or by eliciting a complement-mediated inflammatory reaction at the basement membrane zone. In others, additional amplification factors, including inflammatory cytokines or activated $CD4^+$ T cells, may be necessary to induce the disruption of the basement membrane zone (Bruch-Gerharz et al., 2007).

Etiology

Genetic and environmental factors have a substantial effect on susceptibility to MMP. There are no known racial or geographic predilections, but there may be an immunogenetic background and an association with the common major histocompatibility complex (MHC) molecules. An increased frequency of the HLA-DR4 allele in patients affected by ocular pemphigoid has been reported (Bruch-Gerharz et al., 2007). Furthermore, a prevalence of HLA-DQB1* 03:01 (formerly known as DQB1*0301) was first described in patients with pure ocular MMP and then confirmed in all clinical phenotypes (Ahmed et al., 1991, Delgado et al., 1996, Carrozzo et al., 2001, Setterfield et al., 2001). Very recently, it has been suggested that a genotype of the interleukin 4 receptor A (IL-4RA)-1902 A/A, found in 90% of patients with oral pemphigoid, is associated with a reduced response to IL-4 and it may explain the low likelihood of scarring in this group of patients (Carrozzo et al., 2014). Recent studies have shown that monozygotic twins are discordant for MMP, which argues against genetic susceptibility as the only major risk factor of the disease (Bruch-Gerharz

et al., 2007). A model has been proposed in which relevant portions of the four different peptides derived from BMZ involved in autoimmune response in MMP have potential sites that could be presented by an antigen presenting cell in conjunction with DQB1*03:01 to a T-cell receptor to initiate the process that results in anti-BMZ antibody production (Zakka et al., 2011).

The nature and the role of environmental factors remain unclear in most cases. According to the concept of molecular mimicry antibodies to viruses or drugs with structural similarities to an endogenous antigen within the basal membrane zone may cause an autoimmune process. A few cases of MMP triggered by medications, such as methyldopa, clonidine, and penicillamine have been reported. The availability of epithelial basement membrane zone antigens for immune processing may also be influenced by severe mucosal injury, for example, from burns and severe drugs eruptions, such as Steven-Johnson syndrome (Bruch-Gerharz et al., 2007, Xu et al., 2013).

Diagnosis

Diagnosis of MMP is based on history and on clinical presentation of a predominantly mucosal disease as well as on the presence of certain immunopathologic features.

The most appropriate area to biopsy is the edge of a blister or, in the absence of an intact blister, the area of erythema, erosion, or ulceration and extending also into perilesional tissue (Scully et al., 1999). Classic histopathologic features, including a subepithelial split with a variable inflammatory cells infiltrate, can also be seen in other oral diseases, such as oral lichen planus and erythema multiforme (Scully et al., 1999).

Direct immunofluorescence (DIF) is essential for diagnosis and typically shows a continuous, linear deposition of IgG, C3, less commonly IgA, or a combination of these along the basement membrane zone (Schmidt and Zillikens, 2013, Scully et al., 1999).

Standard indirect immunofluorescence (IIF) is usually negative, as serum samples from MMP patients contain antiepithelial–connective tissue junction autoantibodies at low titers (usually 1:10–1:40) and only in 50% to 80% of cases (Schmidt and Zillikens, 2013). The use of salt split skin (SSS) IIF studies may increase the sensitivity of this technique. SSS-IIF may reveal binding to the roof (epithelial) or floor (connective tissue) depending on the antigen targeted (Schmidt and Zillikens, 2013, Scully et al., 1999). This technique may identify circulating autoantibodies in up to 91% patients for IgG and 64% patients with IgA (Setterfield et al., 1999). Connective tissue binding suggests anti–laminin 332 reactivity (Schmidt and Zillikens, 2013).
Immunoblotting and immunoprecipitation techniques can help in difficult cases, and target antigen can now be achieved with enzyme-linked immunosorbent assay (ELISA) systems, at least for BP180 and laminin 332 (Calabresi et al., 2007, Bernard et al., 2013).

Prognostic indicators

The site of involvement will predict the likelihood of serious sequelae. Pure oral MMP is associated with a relatively low risk of scarring, whereas ocular, nasopharyngeal, esophageal, and laryngeal sites are highly likely to scar with significant associated morbidity. There is evidence suggesting that the presence of both IgG and IgA anti-BMZ antibodies are associated with more severe and persistent disease. Furthermore, the titers of IgG anti-BMZ autoantibodies at the initial presentation correlate with disease activity and predict disease severity (Setterfield et al., 1999).

There is no known correlation between specific BP180 epitopes and disease prognosis. However, there is a well-recognized positive association between antibodies to anti-laminin 332 and an underlying adenocarcinoma in a third of patients (Egan et al., 2001), although the association of anti-laminin 332 with cancers has been questioned in a recent study (Bernard et al., 2013). There is some evidence to suggest a positive correlation between the extent and severity of oral disease and the titer of IgG to α6-integrin (Sami et al., 2002).

Treatment

Treatment of MMP is complex for a number of reasons, including (1) the diversity of pathogenic pathways, (2) rarity of the disease and paucity of randomized controlled trials (RCTs) or controlled clinical trials (CCTs), (3) complex and variable disease activity and severity, and (4) differential effectiveness of treatments on the most common (oral and ocular) manifestations, including an often intransigent course despite extensive therapeutic efforts.

A wide variety of medications have been utilized to treat MMP by disrupting various pathogenic pathways (Di Zenzo et al., 2014). Although systemic corticosteroids (prednisolone 0.5–1.5 mg/kg per day) are effective in achieving rapid control in cases of acute, moderate to severe disease, the adverse effects associated with long-term use limit their value. Immunosuppressant medications, used alone or in combination, include azathioprine, cyclophosphamide, cyclosporine, leflunomide, methotrexate, and mycophenolate mofetil. Biologic agents to reduce autoantibody production include rituximab and intravenous immunoglobulin (IVIg), as well as tumor necrosis factor alpha (TNF-α) inhibitors, such as infliximab, to reduce inflammation. Dapsone and other sulfonamides, as well as cycline antibiotics, have been used extensively in the

treatment of MMP. Other medications used to treat MMP that do not share common mechanisms include colchicine, nicotinamide, and pentoxifylline. Topical corticosteroids and calcineurin inhibitors are used extensively and often as single agents for the treatment of MMP. Finally, MMP has been treated with low-energy laser phototherapy and cryotherapy with mixed results. We discuss these current and emerging therapies in greater detail later, with an emphasis on benefit–risk considerations.

The single, international, comprehensive expert consensus treatment guidelines published in 2002 (Chan et al., 2002) continue to influence clinicians' decision making. Three disease factors influence the choice of medications: site, severity, and rapidity of progression. A summary of the 2002 consensus treatment guidelines is presented in Appendix 7, and full details can be found in the publication (Chan et al., 2002). The guidelines were developed by an international expert panel, but they have not been reviewed and posted at the US Government Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse. Expert opinion and consensus treatment guidelines become important evidence in the absence of directly applicable studies of good quality. We discuss the quality of current evidence in greater detail later.

4.2 Objective

The objective of this systematic review is to determine the clinical effectiveness and safety of topical and systemic interventions for the treatment of MMP.

4.3 Methods

A systematic review was conducted following a detailed protocol consistent with the methodology of the Cochrane Collaboration.

Types of studies

RCTs, CCTs, observational studies (e.g., cohort studies, case series, and case reports) whose primary outcome measures were regression or healing of mucosal lesions were included. However, trials were not restricted by primary outcomes alone, and so other measures were considered when relevant to the review (e.g., time to disease control, time to disease relapse, cumulative glucocorticoid dose, and adverse treatment events, including mortality).

Types of participants

Participants with a diagnosis of MMP confirmed with clinical, histopathologic, and immunofluorescence criteria were included. Patients with a diagnosis of bullous pemphigoid, linear IgA disease, and epidermolysis bullosa aquisita were excluded. Patients with concomitant autoimmune disease or malignancy were also excluded. Participants with drug-induced disease, pediatric cases, and pregnancy cases were included.

Types of interventions

Active treatment included any preventive, palliative, or curative interventions administered topically or systemically with the aim of treating MMP. Treatments administered for the purpose of treating the sequelae of MMP were excluded. Topical interventions for ocular only disease were also excluded.

Types of outcome measures

The primary outcome measure assessed was regression or healing of mucosal lesion(s). Secondary outcome measures assessed were (1) time to disease control; (2) time to disease relapse; (3) cumulative glucocorticoid dose; (4) adverse treatment events, including mortality; (5) quality of life; and (6) any other valid prespecified outcome measure.

Literature search methods

Assisted by a research librarian (RMcG), we searched a number of electronic databases from 2003 to 2013, including (Ovid) Evidence-Based Medicine Reviews (EBMR) – Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects (DARE), MEDLINE via OVID, EMBASE via OVID, and PubMed. The restriction to the last 10 years was to avoid duplication of effort from previous systematic reviews already conducted on the topic. In addition, we searched (1) the bibliographies of included papers and relevant review articles for studies not identified by the search strategies above and (2) for unpublished trials with data (US National Institutes of Health ongoing trials register at www.clinicaltrials.gov and the World Health Organization International Clinical Trials Registry platform at www.who.int/trialssearch).

Language

The electronic search included all non–English language papers, although papers which did not have an English version were not included in the final selection.

Data collection and analysis

Selection of studies

The titles and abstracts obtained from the initial electronic searches were independently reviewed for relevance by two authors (JT, RM). Full manuscripts for those studies satisfying the study criteria were obtained. When the data in an abstract were insufficient to determine their status, the full manuscript was obtained and assessed independently by two of the review authors (DS, JT, MK, MS, RM, TM). Disagreements were resolved by discussion or inclusion of a third author to achieve consensus.

Data extraction

All studies meeting the inclusion criteria had their characteristics independently extracted by three teams of at least two authors (RM, JT; MS, AE; TM, MK, DS) and recorded and using prespecified pro formata. Disagreements among authors were resolved by discussion with a third author and consensus. For RCTs or CCTs, the pro forma was adapted from the Cochrane risk of bias template for RCTs or CCTs (Higgins and Green, 2011), and for observational studies, a separate pro forma was based on the STROBE guidelines (Noah, 2008).

Missing data

We attempted to contact trial authors, where necessary, for missing data if the study was published from 2003 to date.

Methodologic quality assessment (risk of bias) and evidence grading

A two-part risk of bias tool was used to assess the RCTs or CCTs. This assessed eight specific domains (random sequence generation, allocation concealment, blinding of participants, blinding of patient reported outcomes, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and any other risk of bias). Risk of bias for each domain was assessed as "high," "low," or "unclear." A study with one or more "high" risk of bias judgments for any given domains was deemed overall to have a high risk of bias. Individual studies were graded according to the level of evidence (1++ [highest], 1+, 1−, 2++, 2+, 2−, 3, 4 [lowest]) as reported by the Scottish Intercollegiate Guidelines Network.

Data synthesis and measures of treatment effect

For RCTs or CCTs, dichotomous outcomes were to be expressed as an estimated effect of an intervention using a risk ratio with 95% confidence intervals (95%CIs). Continuous outcome data was presented using mean differences and 95%CIs. The outcomes reported by observational studies would be described in narrative form, where appropriate. Where possible, quantitative synthesis (meta-analysis) was to be applied to the outcomes of relevant RCTs.

Presentation of main results

To facilitate critical appraisal of the evidence, the results are separated into three categories: (1) generalized adult MMP, (2) pediatric and pregnancy MMP, and (3) ocular-only MMP. Results for treatment of adult MMP are reported separately from pediatric and pregnancy MMP because of the significant group differences in disease natural history and treatment response. Similarly, we report ocular-only MMP separately from the other studies because of its unique clinical presentation, risk, and

treatment approaches. No studies of generalized adult or pediatric and pregnancy MMP excluded occasional skin lesions; that is, there was no “oral mucosa only” MMP category. RCTs or CCTs and observational studies (case series, case reports) were evaluated separately.

Results of our appraisals are presented below in narrative form for each intervention category, and the detailed characteristics of all included studies, including their evidence grades, were presented online: MMP Interventions. The characteristics of excluded studies were provided online.

4.4 Results

Search process and yield

Figure 5 illustrates the search process. From an initial set of 465 abstracts identified by the electronic searches and dual-reviewed by two of the authors (RM, JT), 314 (67.5%) were excluded, and 151 were selected for full review by three teams of at least two authors (RM, JT; DS, MKS, TM; MS, AE). Of the 151 manuscripts undergoing full review, 1 was an RCT or a CCT and subsequently included in the analyses; 116 were general MMP observational or descriptive studies, of which 21 were subsequently included in the analyses and 95 excluded; 12 were ocular-only studies, of which 8 were subsequently included in the analysis and 4 excluded; 7 were pediatric or pregnancy studies, of which 3 were subsequently included in the analyses and 4 excluded. The remaining 15 papers included a single systematic review and several authoritative reviews and treatment guidelines, of which 2 were excluded and 13 retained as informative and relevant publications but not included in our analyses.

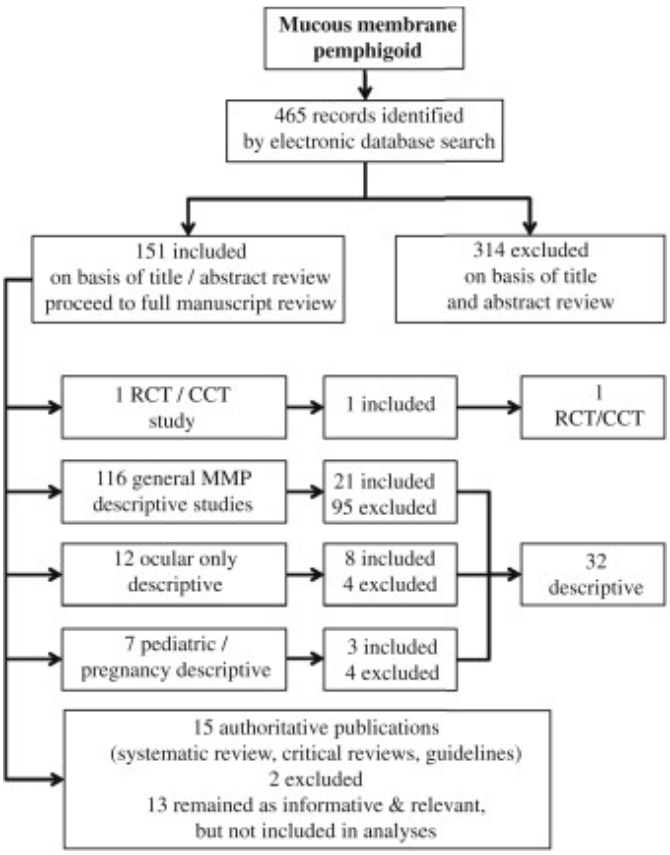


Figure 5. Search process

The reason for excluding each of the 103 manuscripts that underwent full review but were excluded were provided in an online supplement. Only one publication was excluded because it was a non–English language paper: a Portuguese case report of MMP with severe oesophageal stricture (Barbosa Ldo et al., 2011).

Seven authors (RM, JT, MS, RA, DS, JS, MC) met for 2 days (April 7–8, 2014) during the Sixth World Workshop on Oral Medicine (Orlando, FL) for critical discussion and interpretation of the literature.

RCTs or CCTs

A single RCT met the inclusion criteria for our review (El Darouti et al., 2011) (see Figure 6). This study was carried out in Egypt and included 30 patients with ocular cicatricial pemphigoid. Group A (15 patients) were given IV pulsed corticosteroids, cyclophosphamide, and IV pentoxyfylline. Group B (15 patients) were given pulsed IV corticosteroids and cyclophosphamide only. There were 20 "control" healthy patients who had baseline TNF-α blood levels. The control patients did not receive any treatment. The primary outcomes were visual acuity, conjunctival inflammation (0–3), dryness, and cicatrization. There were a number of additional secondary outcomes.

The study had a high risk of performance bias, reporting bias, and other risk of bias. The two arms had differing treatment schedules and therefore were essentially nonblinded. The outcomes listed were not reported clearly, and no raw data were presented. Statistical comparisons did not compare A with B; instead they compared A before and after and B before and after. No baseline characteristics were provided.

El-Darouti 2011

Study type	RCT – randomized controlled parallel trial	
Participants	MMP eye disease patients attending outpatient clinics (1 centre)	
Interventions	• n = 15; **PTX IV** (400mg pentoxyfylline in Ringer solution intravenous (IV) over 3 hours 3 times daily for 3 consecutive days) + standard treatment • n = 15; **"standard treatment"** - pulse steroid therapy (500 mg methylprednisolone in 5% saline administered IV over 3 hours daily for 5 consecutive days) and IV cyclophosphamide (500 mg in 2 L saline given on the first day of the pulse steroid therapy	
Outcomes	• Visual acuity • Conjunctival inflammation (0-3) • Dryness • Cicatrization (Foster staging system) • TNF-α levels Final clinical grading calculated according to some of the outcomes noted above • Excellent – if improved 2 grades • Good if improved 1 grade • Failure if remained on same grade (stationary) • Failure (deteriorated after therapy – poor response) • Conjunctival biopsies before and after	
Risk of bias	**Outcome**	**Comment**
Random sequence generation (selection bias)	low	Quotation: 'computer generated random sequence'
Allocation concealment (selection bias)	low	Quotation: 'sequence was kept in the pharmacy'
Blinding of participants and personnel (performance bias)	high	Comment: regimes differed and no placebo used therefore participants not blinded as to which group they were in
Blinding of outcome assessment (detection bias) (patient-reported outcomes)	high	Comment: as noted above
Blinding of outcome assessment (detection bias) (clinical outcomes)	unclear	Comment: not stated if the clinicians were blinded, but the patients were not and may have told clinicians what they were taking
Incomplete outcome data addressed (attrition bias)	low	Comment: study reports no drop-outs or missing data
Selective reporting (reporting bias)	high	Comment: assessments stated in methods do not appear in the results. All outcome measures are not presented in the results (i.e. bar graphs used, no raw data presented). The *P* values do not represent PTX versus standard therapy groups, they compare PTX before and PTX after.
Other bias	high	Comment: no baseline data given e.g. age of patients in each group and previous treatments
Analysis of results	Clinical response to therapy • **PTX IV** – 12/15; comparing to standard treatment - relative risk 0.5000, 95 % CI 0.1526 to 1.6384, z statistic 1.145, *P* = 0.2523 • **"standard treatment"** – 9/15 Failure to respond • **PTX IV** – 3/15; comparing to standard treatment - relative risk 0.5000, 95 % CI 0.1526 to 1.6384, z statistic 1.145, *P* = 0.2523 • **"standard treatment"** – 6/15 Progression of cicatrisation • **PTX IV** – 0/15 • **"standard treatment"** – 2/15 **Adverse events summary** The side effects in both groups were mainly gastrointestinal in the form of gastric pain and nausea (3 patients in group A and 2 patients in group B). Domperidone was given to control these side effects. Two patients in group B (13.3%) suffered from mild controllable headache. No drug discontinuation was needed. **Summary conclusion of outcomes** The results would suggest no significant clinical benefit of standard therapy and pentoxyfylline over standard therapy alone.	
Grade of evidence		

1++	1+	1-	2++	2+	2-	3	4
		x					

Figure 6. Characteristics of included RCT

Descriptive studies

A total of 32 observational studies (21 adult generalized MMP, 8 ocular-only MMP, and 3 peadiatric- or pregnancy-only MMP) described outcomes for 242 patients across 19 different treatments for MMP (see **Figure 7** and online Supplement Material Table I. The most commonly reported treatments, in decreasing order, were oral corticosteroids, cyclophosphamide, dapsone, and IVIg.

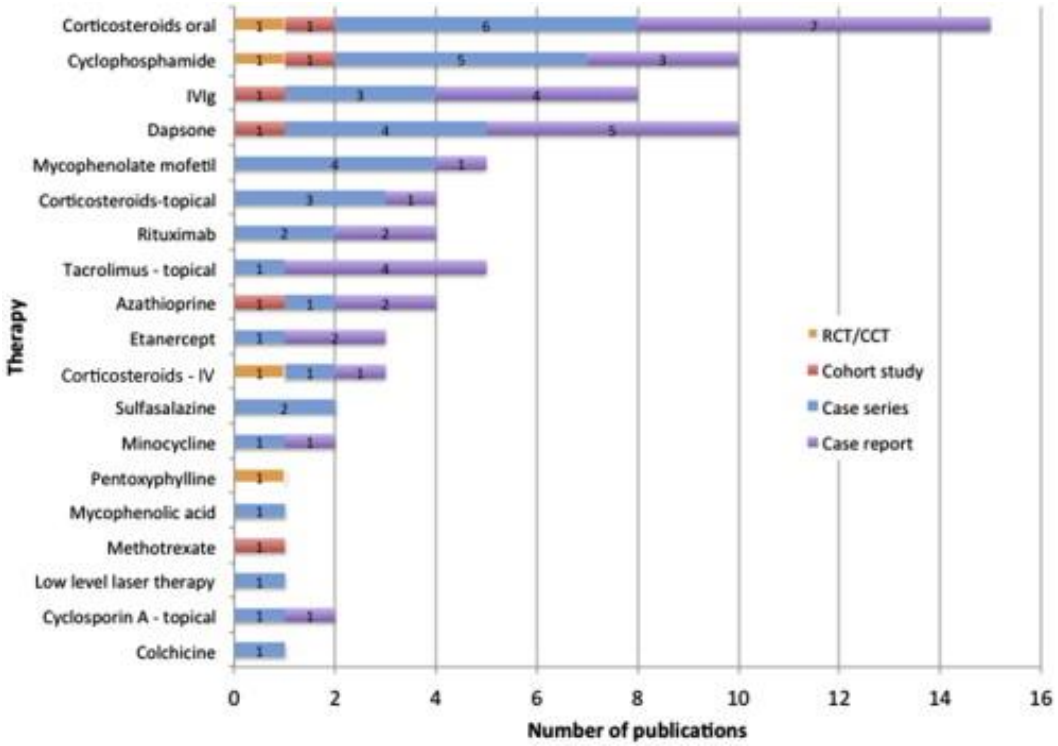


Figure 7. MMP - number of publications by therapy type.

Paediatric and pregnancy studies

No pregnancy cases were included. Three studies involved paediatric patients. These were individual case reports (Kharfi et al., 2010, Lebeau et al., 2004, Schoeffler et al., 2004) of paediatric MMP, ages ranging from 20 months to 9 years. Combinations of

treatments, including corticosteroids, dapsone, topical tacrolimus, and topical cyclosporin, were described. All three cases had a successful outcome.

MMP adult studies

Twenty-one studies, with a combined total of 92 patients, looked at various treatments for adult MMP. Ten case series and 11 case reports were included. Supplementary Material Table II (Appendix 7) describes for each of 19 MMP treatments the characteristics and evidence level of the studies that explored those treatments.

Figure 7 further summarizes for each of the 19 MMP interventions the number and types of study that explored those interventions.

The case series ranged from two participants (Lourari et al., 2011) to 25 participants (Le Roux-Villet et al., 2011). The three largest case series described rituximab (Le Roux-Villet et al., 2011), prednisone/dapsone/colchicine/cyclophosphamide (Chaidemenos et al., 2011), and cyclophosphamide (Munyangango et al., 2013). These three case series are discussed in further detail below.

- Le Roux-Villet et al (2011)

In this study from France, 25 patients were given a combination of rituximab and immunosuppression (dapsone, sulfasalazine, or both). The outcomes were described on the basis of responders (complete response or partial response) and nonresponders. Of the 25 subjects, 2 patients died, 2 patients were nonresponders, 7 patients had complete remission after the second cycle of rituximab, and the remaining 14 patients were partial responders. The authors stated that rituximab appeared to have rapid and dramatic efficacy in patients with severe, refractory MMP. However, the occurrence of severe

infections in patients receiving concomitant conventional immunosuppressants supports the use of rituximab without other immunosuppressants. In the absence of confirmatory studies, rituximab cannot be the first-line drug for MMP. Future prospective studies and registries may be able to accurately evaluate rituximab's safety profile, an optimal regimen, and its risk–benefit ratio in the setting of severe MMP.

- Chaidemenos et al (2011)

This retrospective record review from Greece included 15 patients who received a combination of treatments, including prednisone, dapsone, colchicine, azathioprine, and cyclophosphamide. The outcome measure described was “lesion clearance” or “disease improvement.” The authors concluded that colchicine was effective in 8 of 12 cases, with only 1 withdrawal of treatment because of diarrhea as a side effect. Dapsone caused hemolytic anemia in 2 of 3 patients.

- Mumyangango et al (2013)

This retrospective case series from France included 13 patients. The intervention studied was oral daily cyclophosphamide with adjuvant immunosuppressives, including dapsone with or without sulfasalazine. Primary outcome measure was “active lesion scores.” Four patients remained in complete remission at 6 months after the study; all 4 were also on dapsone. Multiple adverse events were recorded, including lymphopenia in 10 of 15 patients; 6 of these patients had to stop treatment. The authors concluded that cyclophosphamide without corticosteroids had rapid efficacy in patients with severe refractory MMP and that it was safe.

Ocular-only studies

There was 1 cohort study (Letko et al., 2004), 5 case series with 7 (Suelves et al., 2013) to 94 (Thorne et al., 2008) patients, and 2 case reports (Galdos and Etxebarria, 2008, Prey et al., 2007). A full list of interventions attempted was summarized in the online supplement. The cohort study (Letko et al., 2004) from Boston, Massachusetts, included 16 patients with ocular-only MMP. Immunosuppression plus corticosteroids plus IVIg was compared with immunosuppression plus corticosteroids. Group allocation was related to the health insurance provider for each patient (some insurance companies allowed the use of IVIg and others did not). Outcome measures were poorly validated and included a disease activity grade assessed by a nonblinded single assessor. The authors reported positive results for the intervention group (8 of 8 total control) with a low rate of side effects (minimal in 4 of 8), and a failure in the "control" group (2 of 8 total control) and a high rate of side effects (8 of 8).

The largest case series had 94 patients (Thorne et al., 2008), and patients were given a variety of interventions, including cyclophosphamide, oral prednisone, dapsone, mycophenolate mofetil, chlorambucil, and azathioprine. Various ocular outcome measures were reported. The authors reported that treatment with cyclophosphamide and prednisone was strongly associated with the development of ocular remission. Various side effects, including malignancy and infections, were described, and 27 patients stopped treatment because of side effects (Suelves et al., 2013). Eight patients developed malignancy (rate, 0.02/year; 95%CI, 0.01/year–0.05/year), although in 1 patient, 2 malignancies developed. Of the 9 cases of cancer that occurred, 4 were skin cancers (2 basal cell carcinomas and 2 squamous cell carcinomas), 2 were leukemias, 1 was a breast carcinoma, 1 was a laryngeal squamous cell carcinoma, and 1 was a bladder carcinoma (Suelves et al., 2013).

4.5 Discussion

Comparison with previous systematic reviews

There has been little evidence to guide clinicians on the best treatments for MMP. Although there are several authoritative reviews as well as treatment guidelines for single therapies (Durrani et al., 2011, Elad et al., 2011, Eskin-Schwartz et al., 2012, Galdos and Etxebarria, 2008, Gurcan and Ahmed, 2009, Kim and Foster, 2006, Namazi, 2007, Patel et al., 2011) there are only 2 comprehensive, international consensus guidelines (2002, Chan et al., 2002), including the study by Chan et al. (2002) published in English. Finally, a single Cochrane Systematic Review on MMP treatment first published in 2003 (Kirtschig et al., 2003) and last updated in 2009 identified only 2 RCTs with limited evidence for treatment of ocular-only MMP (Foster, 1986). An authoritative review by Di Zenzo et al. (2014)[5] summarized the best therapeutic options for MMP. Although not yet published as a systematic review, the same authors[5] extended the 2009 Cochrane systematic review by using the same methodology and found the same single RCT we identified with limited evidence for treatment of ocular-only MMP with pentoxifylline (El Darouti et al., 2011); they also identified 2 RCTs completed in 1986 (Foster, 1986)(earlier than our 2003 cut-off point) exploring (1) cyclophosphamide plus prednisone to prednisone plus placebo and (2) dapsone versus prednisone. The study concluded that MMP involving the eyes responds best to treatment with cyclophosphamide combined with corticosteroids. However, dapsone is effective in mild to moderate disease and is preferred because of its lower side-effect profile compared with cyclophosphamide. The 2003 systematic review by Kirtschig et al (2003) concluded that there was some evidence to support the author's conclusions but high-quality, reliable evidence was lacking.

We summarized in an online supplement the recommendations of the single, international, comprehensive expert consensus treatment guidelines published in

2002(Chan et al., 2002). Di Zenzo et al. (2014) emphasizes the importance of careful risk assessment, particularly when making treatment decisions for mild to moderate MMP, which can be effectively treated with a (potent) topical agent plus one systemic medication. The authors point out the high rates of adverse effects (AEs) and discontinuation of therapy reported in previous studies: cyclophosphamide 77% AE, minocycline 67% discontinuation rate, mycophenolate mofetil 41% AE, and dapsone 14% discontinuation rates. Such rates of complications, and even deaths, have resulted from medications commonly used to treat MMP, and this only emphasizes the need for high-quality RCTs that very carefully characterize initial mucocutaneous lesion activity and disease severity.

A significant methodologic limitation adversely affecting the quality of and comparison between clinical trials and observational studies is lack of common, validated methods for assessing disease severity and therapeutic endpoints and outcomes with differentiation between oral mucosal disease and ocular mucosal disease. A significant advance has just been published (international, expert consensus recommendations for assessing disease activity and therapeutic outcome) (Murrell et al., 2015), and, if followed in future studies, it could overcome historical limitations and more accurately allow comparison of treatment efficacy for MMP. In addition to definitions of disease activity, the international expert panel introduces a Pemphigoid Disease Area Index (PDAI) specific to MMP-oral and MMP-ocular. Validation studies of the expert definitions and outcomes measures are already being planned (personal communication). A summary of the consensus recommendations were provided in the online supplement and full details can be found in the publication (Murrell et al., 2015).

A final point worth emphasizing for MMP is that topical treatments can effectively control mild to moderate disease, especially in the oral cavity. Although no study has explored the technique specifically, a common practice among oral medicine clinicians

to enhance the topical treatment of generalized desquamative or erosive gingivitis is the use of a custom-made, soft drug-delivery oral stent covering the gingivae to extend drug contact time and absorption (Lee et al., 1991). Additionally, there has long been interest in the relationship between dental plaque-associated gingivitis and MMP-associated desquamative or erosive gingivitis. Painful erosive gingivitis often compromises a patient's effective control of dental plaque with toothbrushing and dental flossing methods. Although not included in this systematic review because the intervention was not the treatment of MMP, an Italian group has recently described case-control differences in periodontal health status due to differences in oral hygiene in patients with MMP compared with healthy controls(Arduino et al., 2011). The same authors then developed a pilot program of periodontal hygiene instruction combined with periodontal therapy and demonstrated significant improvement in periodontal health status and MMP lesion activity(Arduino et al., 2012). Although these preliminary findings have not been replicated, the results suggest that optimal dental hygiene education and control of dental plaque–associated gingivitis—even when painful gingival lesions are present—will improve periodontal health and gingival inflammation in patients with MMP and erosive gingivitis lesions.

Potential biases in the review process

Several studies had incomplete or missing data that we were unable to obtain from the authors. As our review only assessed the published literature, there is a risk of publication bias, as there may be unpublished studies that may provide further useful data. Indeed, a search (US National Institutes of Health ongoing trials register at www.clinicaltrials.gov and World Health Organization International Clinical Trials Registry platform at www.who.int/trialssearch) for recent and ongoing or recently

completed clinical trials did reveal 4 ongoing and recruiting studies, 2 studies not yet recruiting, and 2 completed trials. Of the 2 completed trials, 1 had data (Clinical Trial Evaluating Rituximab in Ocular MMP; 3 patients entered and completed the trial; only baseline data were available for comparison with treatment; and no serious AEs occurred) and the second trial did not have data (naturalistic observational cohort study: no study intervention).

4.6 Conclusions

There continues to be a paucity of high-quality clinical trials of interventions for MMP. Clinical practice is presently guided by descriptive evidence and expert guidelines published in 2002. Future studies of MMP treatment would be significantly improved by strict adherence to newly published expert recommendations on definitions of disease activity and outcome measures.

Presently, research evidence is of insufficient quality to determine the optimal therapies for the treatment of MMP. Interventions that show promise include rituximab and IVIg. We have summarized in Figure 8 a treatment algorithm, adopted from the 2002 guidelines and modified on the basis of the literature published since that time. We emphasize that this algorithm is our summary of current best practices and has not been validated. Further high-quality research would very likely have an important impact on our clinical decision making. For clinicians, this review is a summary of the most recent available evidence, which can be used to guide clinical decision making.

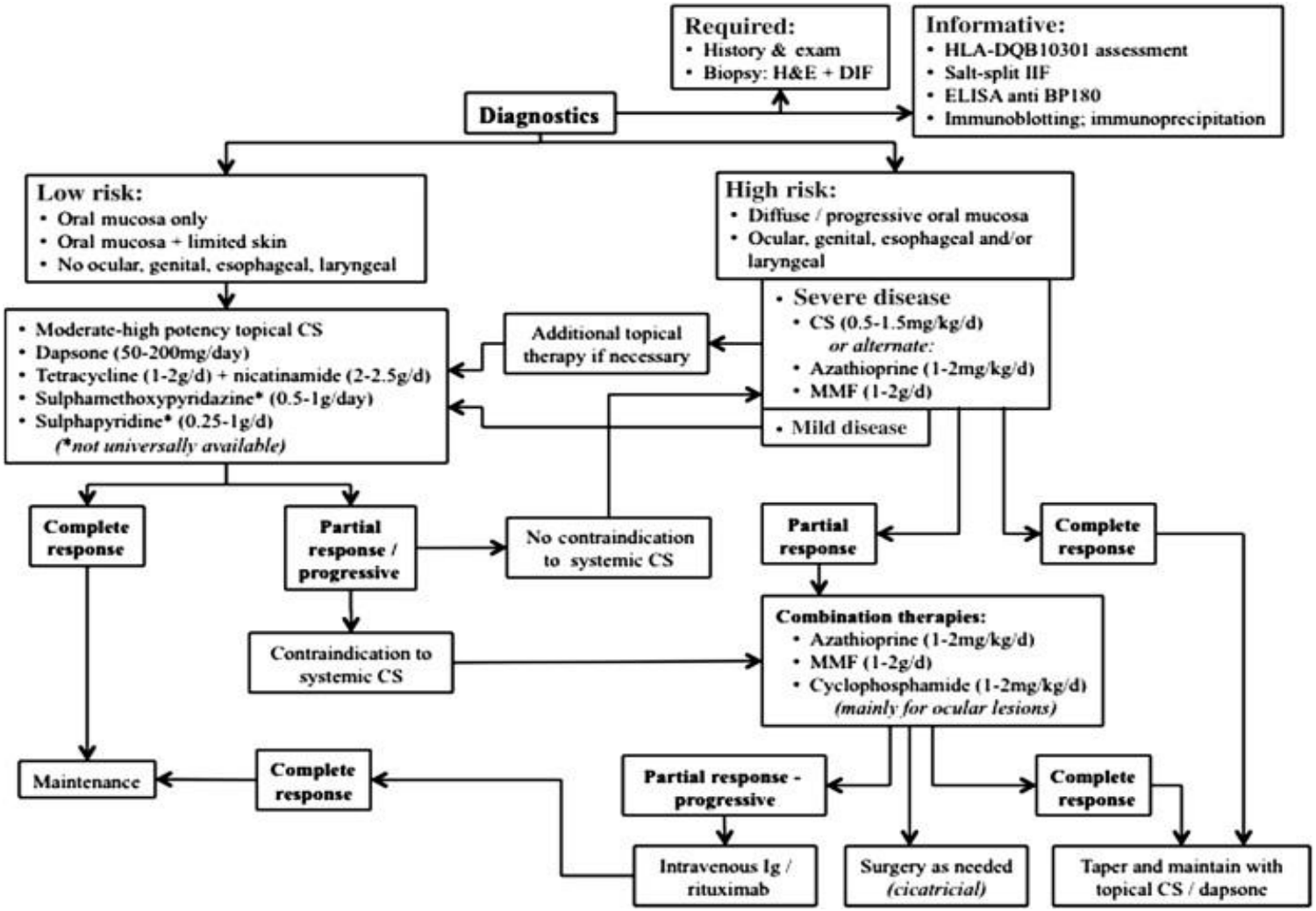


Figure 8. **Summary Treatment Algorithm for MMP**

Chapter 5 World Workshop on Oral Medicine VI: A Systematic Review of the Treatment of Mucocutaneous Pemphigus Vulgaris

This is the second of the two papers I co-authored as part of the WWOM. I was involved from the protocol development throughout the entire process of screening, data extraction and write up.

Cited as: McMillan R, Taylor J, Shephard M, Ahmed R, Carrozzo M, Setterfield J, Grando S, Mignogna M, Kuten-Shorrer M, Musbah T, Elia A, McGowan R, Kerr AR, Greenberg MS, Hodgson T, Sirois D. World Workshop on Oral Medicine VI: a systematic review of the treatment of mucocutaneous pemphigus vulgaris. Oral Surg Oral Med Oral Pathol Oral Radiol. 2015 Aug;120(2):132-42.e61. doi: 10.1016/j.oooo.2015.01.022.

5.1 Abstract

Objective: To determine the efficacy and safety of interventions for pemphigus vulgaris (PV).

Study Design: We conducted a systematic review from 2003 to 2013 according to the Cochrane Collaboration methodology. Randomized controlled trials (RCTs) or controlled clinical trials (CCTs) and observational studies were conducted along with diagnosis confirmed by clinical, histopathologic, and immunofluorescence criteria. Primary outcomes were disease remission and mortality; several relevant secondary outcomes were also included.

Results: Fourteen RCTs or CCTs and 110 observational studies were included in the final analyses. RCTs or CCTs demonstrated considerable heterogeneity in outcome measures, and all had a high risk of bias for at least 1 of 8 domains. Of the studies, 96.8% (120) described the use of oral corticosteroids. Azathioprine and mycophenolate-mofetil were the most commonly cited treatments. An increasing number of studies described biologic therapies (rituximab, intravenous immunoglobulin [IVIg]). Evidence supporting recent comprehensive treatment guidelines was reviewed.

Conclusions: We found persisting wide variations in treatment practice and inadequate quality of research supporting optima

Pemphigus vulgaris (PV) belongs to a group of life-threatening blistering diseases characterized by intra-epithelial blister formation resulting from the loss of adhesion of keratinocytes (acantholysis), with associated autoantibodies directed to the intercellular junctions of keratinocytes(Mihai and Sitaru, 2007). PV typically involves the mucosal surfaces, with or without associated skin involvement, and the oral mucosa is the initial site of lesions in the vast majority of patients (Kneisel and Hertl, 2011, Sirois et al., 2000). The pre-dominant and commonly exclusive involvement of the oral mucosa, the morbidity and mortality of the illness, frequent delay in diagnosis, and lack of treatment consensus all suggest a need for increased awareness of PV among primary dental and medical as well as specialized oral medicine and dermatology clinicians. The Sixth World Workshop in Oral Medicine sponsored this systematic review of treatment efficacy for PV involving the oral mucosa, with or without cutaneous lesions.

Epidemiology

The pemphigus group of diseases comprises four major entities: (1) PV, (2) pemphigus foliaceus, (3) immuno- globulin A (IgA) pemphigus, and (4) paraneoplastic pemphigus or paraneoplastic autoimmune multiorgan syndrome (PAMS). The immunopathologic mechanisms of PAMS differ appreciably from those responsible for the lesions of classic pemphigus (Czernik et al., 2011). As its name suggests, PV is the most common variant, with an incidence of 0.1 to 0.5 per 100,000 people per year and even higher rates in certain populations (Venugopal and Murrell, 2011). Individuals of Mediterranean and Jewish decent (particularly Ashkenazi Jews) have the greatest risk for developing PV; and a genetic predisposition for disease development has been suggested in several candidate gene-driven and genome wide association studies (Todd

et al., 1988, Sarig et al.). PV affects individuals of all ages but usually occurs in adults, with a peak incidence between 40 and 60 years (Kneisel and Hertl, 2011).

Natural course of disease

PV is a lifelong blistering disease that affects the mucosal surfaces lined by stratified epithelium (especially the oral mucosa but also the nasal, laryngoesophageal, genital, anal, and conjunctival mucosa), and/or the skin (Kneisel and Hertl, 2011). The oral cavity is frequently the site of initial presentation (Sirois et al., 2000), and the buccal mucosa, palate, and gingiva are the most commonly affected areas (Scully and Mignogna). Since mucosal blisters erode quickly, erosions are often the only clinical findings. Most patients also develop cutaneous involvement manifesting as flaccid blisters on normal-appearing or erythematous skin. As in the oral mucosa, the blisters rupture rapidly, resulting in painful erosions that bleed easily. A positive Nikolsky sign can be elicited in patients with PV by applying pressure at the edge of a blister ("marginal" Nikolsky sign) or on normal-looking skin ("direct" Nikolsky sign), and this serves as a nonspecific indicator of active acantholysis (Grando et al., 2003).

Before the introduction of therapy with oral cortico- steroids in the 1950s, PV was invariably fatal, with a mortality rate of up to 90% (Herbst and Bystryn, 2000). Although corticosteroid treatment is lifesaving, the high dose and prolonged courses required for disease control are associated with significant adverse events, including death (Rosenberg et al., 1976, Ahmed and Moy, 1982). Mortality remains relatively high level (approximately 5%-10%); however, after therapy, the majority of patients eventually achieve complete and long-lasting remission (Alexandroff and Harman, 2009, Herbst and Bystryn, 2000, Scully and Mignogna).

Pathobiology

Historically, PV is believed to result from the deleterious action of autoantibodies directed against the desmosomal cadherins, desmoglein 1 (Dsg1) and Dsg3, resulting in acantholysis and subsequent blistering (Stanley and Amagai, 2006). Early observations led to the development of the Dsg compensation hypothesis, which proposes that the clinical phenotype of pemphigus is defined by the anti-Dsg autoantibody profile (Amagai et al., 2009). Specifically, anti- Dsg3 antibody alone is associated with the mucosal variant of PV, whereas both anti-Dsg1 and anti-Dsg3 antibodies are associated with the mucocutaneous variant.

In recent years, however, evidence has emerged supporting a more complex pathophysiologic signaling mechanism for PV, and the role of anti-Dsg antibodies as triggers of the disease has been disputed (Grando, 2012). According to the multiple hit hypothesis, proposed by Grando (Grando, 2000), multiple PV autoantibodies act synergistically to target different cell membrane antigens, including not only molecules that mediate cell-to-cell adhesion but also molecules that regulate cell shape. Recent proteomics studies have identified a number of new pathophysiologically relevant self-antigens in PV, including several mitochondrial proteins (Kalantari-Dehaghi et al., 2013a, Kalantari-Dehaghi et al., 2013b). The binding of these pathogenic antibodies to keratinocytes triggers an array of intracellular signaling cascades, culminating in apoptolysis (Grando et al.). The term apoptolysis encompasses the structural damage (acantholysis) and death (apoptosis) of keratinocytes, which occur in a stepwise fashion. During this process, the antibody-mediated interference with kera- tinocyte shape and adhesion leads to weakening of the intracellular junctions and collapse of the cytoskeleton, with consequent shrinkage of the basal keratinocytes. Because basal cells shrink more compared with supra- basal keratinocytes, suprabasal acantholysis occurs.

As acantholysis advances, secondary production of auto- antibodies is stimulated, leading to rounding up (“tombstoning”) and apoptosis of acantholytic cells.

Diagnosis

The diagnosis of PV is made on the basis of clinical signs, histopathology, immunopathology, and serology. The characteristic histopathology of PV reveals a suprabasal cleavage with acantholysis, as well as retention of a single layer of basal keratinocytes along the basement membrane (“tombstoning”). On direct immunofluorescence (DIF), intercellular deposition of IgG and C3 can be demonstrated (Venugopal and Murrell, 2011). As immune deposits precede the appearance of acantholysis in the suprabasal epithelium, DIF is considered more sensitive than conventional histopathology (Scully and Mignogna). Indirect immunofluorescence (IIF) and enzyme-linked immunosorbent assay (ELISA) are serologic studies that can detect circulating autoantibodies against epithelial cell- surface antigens. IIF is usually performed after positive DIF studies are obtained, to help guide prognosis and therapy (Scully and Mignogna, Ettlin). PV sera demonstrate a characteristic netlike intercellular staining of IgG with an epithelial substrate. Similarly, ELISA for IgG antibodies to Dsg1 and Dsg3 provides a simple and highly sensitive approach to confirm the initial diagnosis of PV (Grando, 2012).

Treatment

Treatment of PV is complex, and a wide variety of interventions directed at multiple pathogenic pathways have been reported (Kasperkiewicz and Schmidt, 2009,

Kasperkiewicz et al., 2012). Although systemic corticosteroid therapy (prednisolone 0.5-1.5 mg/kg weight) re- mains the cornerstone of initial treatment to achieve disease control, long-term use is associated with significant adverse effects and is a major source of morbidity and mortality (Ahmed and Moy, 1982, Bystryn and Steinman, 1996, Rosenberg et al., 1976). Successful treatment of PV usually requires strategies that disrupt multiple pathogenic pathways, including production of desmoglein-reactive antibodies, presence of circulating antibodies, and antibody-mediated apoptolysis. A wide variety of immunosuppressive and anti-inflammatory steroid- sparing adjuvant therapies that maintain therapeutic benefit while reducing adverse effects have been re- ported, as well as techniques to reduce antibody load (plasmapheresis, immunoadsorption) and biologic or biopharmaceutical agents to reduce autoantibody pro- duction (intravenous immunoglobulin therapy [IVIg], rituximab) and inflammation (etanercept, infliximab) (Bystryn and Steinman, 1996, Ruocco et al., 2013). Despite a considerable volume of published reports for a rare disease and the "orphan disease" designation easing the pathway to approved indication, the number of interventions available to treat PV remains limited, with no consensus on optimal therapeutic strategies (Meurer, 2012, Ahmed and Dahl, Mimouni et al., Ahmed, 2007)

The treatment of PV has been the subject of several authoritative and systematic reviews (Alexandroff and Harman, 2009, Kasperkiewicz et al., 2012, Bystryn and Steinman, 1996, Martin et al., 2011, Martin et al., 2009, Scully and Mignogna, Mirceva et al.). This study extends that body of work, uniquely investigating the current evidence supporting the efficacy and safety of treatments for PV involving the oral mucosa, with or without cutaneous lesions.

5.2 Objectives

The objectives of this systematic review were to deter- mine the clinical effectiveness and safety of topical and systemic interventions for the treatment of PV involving the oral mucosa, with or without cutaneous lesions.

5.3 Methods

A systematic review was conducted following a detailed protocol consistent with the methodology of the Cochrane Collaboration. Key aspects of the protocol are summarized here, and additional detailed aspects of the protocol were provided as online supplementary material within the published paper.

Inclusion criteria

A systematic literature search was limited to papers published from 2003 to 2013 to avoid duplication of effort from previous published systematic reviews.

Studies or publications

Randomized controlled trials (RCTs), controlled clinical trials (CCTs), observational studies (e.g., cohort studies, case series and case reports) whose primary outcome measures were remission and mortality were included. However, trials were not restricted by primary outcomes alone, and other measures were considered (see "Outcome Measures"). To focus this review on PV involving the oral mucosa, we

included studies (1) investigating topical or systemic treatments for mucosal or mucocutaneous disease and (2) describing the systemic management of disease only affecting the skin (with the assumption these treatments would similarly benefit mucosal lesions). Studies describing only topical treatment for cutaneous lesions were excluded.

Participants

Participants with a diagnosis of PV were included if they adhered to accepted criteria in all three diagnostic domains: clinical presentation, histology, and immunofluorescence. We also included participants with drug-induced disease, as well as paediatric and pregnancy cases of PV, as long as the same three criteria were met.

Participants with the following characteristics were excluded: a diagnosis of paraneoplastic pemphigus or PAMS, pemphigus foliaceus (PF), pemphigus vegetans, diagnosis of other concomitant autoimmune diseases, or a malignant comorbidity.

Interventions

Active treatment included any preventive, palliative, or curative intervention administered topically or systemically aimed at the treatment of PV.

Outcome measures

Primary outcome measures were (1) remission and (2) mortality. Secondary outcome measures included time to disease control, time to disease relapse, pemphigus severity score, cumulative glucocorticoid dose, serum antibody titers, adverse treatment events, quality of life, and any other relevant outcome measure where reported.

Search methodology

Assisted by a research librarian, we searched a number of electronic databases from 2003 to 2013, including Evidence-Based Medicine Reviews (EBMR); Cochrane Central Register of Controlled Trials (CENTRAL) (OVID); Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects (DARE); MEDLINE (OVID); EMBASE (OVID); and PubMed. The detailed search strategy was provided as online supplementary material. In addition, we searched the bibliographies of included papers and relevant review articles for studies not identified by the search strategies above.

The electronic search included all non-English language papers, although papers which did not have an English version were not included in the final selection. Non-English language papers excluded from the study were listed in the online supplementary material.

Data collection and analysis

Selection of studies.

The titles and abstracts obtained from the initial electronic searches were independently reviewed for relevance by two authors (JT, RM). Full manuscripts for those studies satisfying the study criteria were obtained. When the data in an abstract were insufficient to determine their status, the full manuscript was obtained and assessed independently by the review authors (DS, JT, MK, MS, RM, TM). Disagreements were resolved by discussion or inclusion of a third author to achieve consensus.

Data extraction.

Each of the included studies were independently assessed, and data were extracted by at least two authors using prespecified pro formata (see online supplementary material). For RCTs or CCTs, the pro forma was adapted from the Cochrane risk of bias template for RCTs or CCTs (Higgins et al., 2011a), and for observational studies, a separate pro forma was based on the STROBE guidelines (Noah, 2008).

Missing data

We attempted to contact the trial authors, where necessary, for missing data if the study was published from 2003 to the present date.

Methodological quality assessment and evidence grading

The Cochrane risk of bias tool was used to assess quality of the RCTs or CCTs across eight domains: (1) method of randomization, (2) allocation concealment, (3) blinding of participants, (4) blinding of patient re- ported outcomes, (5) blinding of outcome

assessors, (6) incomplete outcome data, (7) selective outcome reporting, and (8) any other risk of bias. Risk of bias for each domain was assessed as "high," "low," or "unclear." A study with one or more "high" risk of bias judgments for any given domain was deemed overall to have a high risk of bias. Individual studies were graded according to the level of evidence (1++ [highest], 1+, 1, 2++, 2+, 2, 3, and 4 [lowest]) as reported by the Scottish Intercollegiate Guidelines Network (SIGN) (http://www.sign.ac.uk/pdf/sign50.pdf).

Data synthesis and measures of treatment effect

For RCTs or CCTs, dichotomous outcomes were expressed as an estimated effect of an intervention using a risk ratio with 95% confidence intervals (CIs). Continuous outcome data were presented using mean differences and 95% CIs. The outcomes reported by observational studies were described in narrative form, where appropriate.

Where possible, quantitative synthesis (meta-analysis) was applied to the outcomes of relevant RCTs.

Presentation of main results

To facilitate critical appraisal of the evidence, the results are separated into three categories: (1) RCTs or CCTs, (2) observational studies (including drug- induced PV), and (3) paediatric and pregnancy PV. Results for treatment of adult PV are reported separately from paediatric and pregnancy PV because of the significant group differences in the disease's natural history and in treatment responses. RCTs or CCTs and paediatric and pregnancy results are described in the Results section which follows

and are summarized in the online Supplementary Material Tables TI and TII, and observational studies are described only in the online Supplementary Material (Tables TI and TII). Outcomes for specific interventions are described independently in the online Supplementary Material (Tables TI, TII) and cross-referenced to a narrative description of the RCTs or CCTs and, if relevant, to the observational studies assessed to be of adequate quality. The characteristics of excluded studies are provided in the online Supplementary Material Appendix A4.

5.4 Results

Figure 9 illustrates the search process. From an initial set of 1051 papers identified by electronic search and an additional 3 by manual search, a grand total of 1054 papers underwent initial title or abstract review by two authors. Of the 1054 papers, 682 (64.7%) were excluded, and 372 were selected for full manuscript review: 231 that clearly met the criteria and 141 that were uncertain after abstract review. Of the 372 manuscripts undergoing full review, 23 were RCTs or CCTs, of which 14 were subsequently included in the analyses and 9 excluded; 302 were observational or descriptive studies, of which 94 were subsequently included in the analyses and 208 excluded; and 49 were paediatric or pregnancy studies, of which 16 were subsequently included in the analyses and 33 excluded. The reason for excluding each of the 250 excluded full-text papers is provided in the online Supplementary Material Appendix A4; additionally Appendix A2 lists the non-English language reports also excluded from the analyses.

Seven authors met for 2 days (April 7-8, 2014) during the Sixth World Workshop on Oral Medicine (Orlando, Florida, USA) for critical discussion and interpretation of the literature.

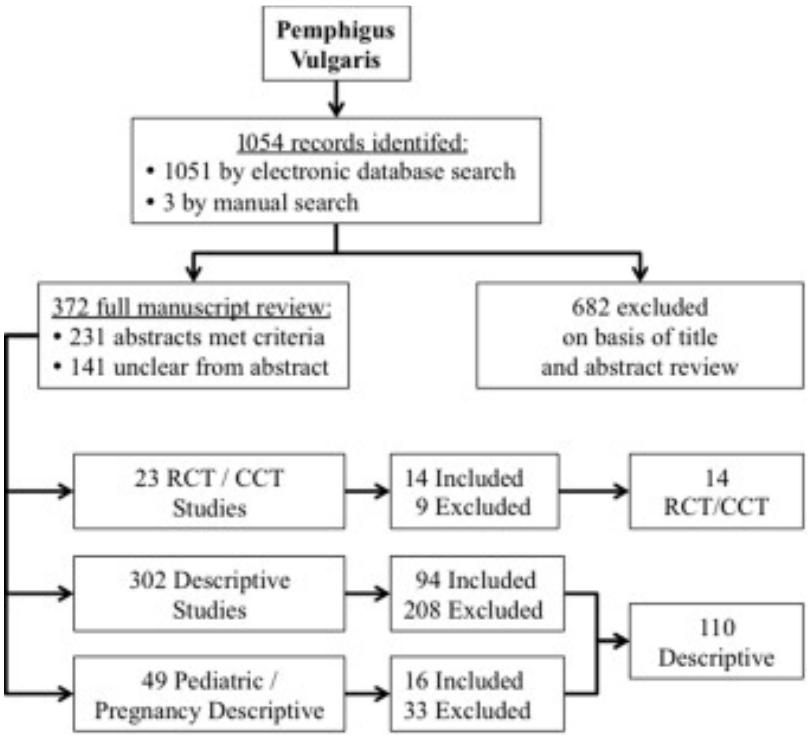


Figure 9. Study flow process

Randomized controlled trials or controlled clinical trials

Detailed characteristics of the 14 RCTs or CCTs meeting criteria and included in the final analyses are summarized in the online Supplementary Material Appendix A5. Two studies were classified as CCTs (el-Darouti et al., 2009, Shahidi-Dadras et al.), 1 was an "n- of-1" trial (Arnold et al., 2009), 1 was a "split-mouth" RCT (Nazemi-Tabrizi et al., 2012), and 1 was a parallel RCT with a crossover arm for treatment failures (Werth et al., 2008). The remaining 9 studies were parallel RCTs (Amagai et al., 2009, Beissert et al., 2010, Beissert et al., 2006, Chams-Davatchi et al., 2007, Fiorentino et al., 2011,

Ioannides et al., 2012, Mentink et al., 2006, Parmar et al., 2013, Rose et al., 2005). Two of the included RCTs were multinational trials (Beissert et al., 2010, Mentink et al., 2006), 1 study was unclear with regard to where it was conducted (Fiorentino et al., 2011), although the authors of the study were based in the United States, and the remainder of the RCTs or CCTs were conducted in single countries. Eight of the RCTs or CCTs used placebo controls, although the placebo arms were combined with some form of active treatment in all cases (Arnold et al., 2009, el-Darouti et al., 2009, Amagai et al., 2009, Beissert et al., 2010, Beissert et al., 2006, Mentink et al., 2006, Werth et al., 2008, Fiorentino et al., 2011, Rose et al., 2005).

Outcomes.

All of the RCTs or CCTs used clinical outcome measures except for 1 study (Parmar et al., 2013), which used IIF and DIF as surrogate outcome markers of disease control. There was considerable heterogeneity in the outcome measures employed by the RCTs or CCTs (see online Supplementary Material Appendix A5), with only "time to remission," "complete healing," and PV antibody titers being used in more than one study. Standardized disease scoring, such as described in the consensus statement on definitions of disease, endpoints, and therapeutic response for pemphigus (Murrell et al.), was used by only 1 study (Ioannides et al., 2012). One study claimed to adhere to the consensus statement but did not report any outcomes that could substantiate the claim (Parmar et al., 2013). Reduced dosage of corticosteroids was used as a surrogate marker for treatment efficacy in several studies; however, there was variation in how the steroid dosages were calculated (e.g., cumulative dose over 1 year, cumulative dose until remission). Because of the heterogeneity of outcomes for each of the studied interventions, quantitative analysis (meta-analysis) could not be conducted. Analyses of

the relevant outcomes (relative risks and 95% CIs) from the RCTs or CCTs are summarized in detail in the online Supplementary Material Appendix A5.

Quality assessment and evidence grade.

Figure 10 illustrates the risk of bias outcome in detail for each RCT or CCT study across all 8 risk domains, and Figure 11 illustrates the risk of bias outcomes as percentages across all 14 studies. Appendix A5 in the online Supplementary Material summarizes in detail the risk of bias outcome across 8 domains for each of CCTs had an outcome of high risk of bias for at least 1 of the eight domains (and one study had 7 or 8 areas assessed as high risk of bias), thus reducing the overall quality of evidence of all selected RCTs or CCTs to 1e ("meta-analyses, systematic reviews, or RCTs with a high risk of bias") (http://www.sign.ac.uk/pdf/sign50.pdf).

Four of the RCTs or CCTs were explicitly nonblinded designs (Ioannides et al., 2012, Shahidi-Dadras et al., 2007, Beissert et al., 2006, Chams-Davatchi et al., 2007), and of the others, 4 were found to have a high risk of bias in at least one of the domains covering blinding (Amagai et al., 2009, Beissert et al., 2010, Chams-Davatchi et al., 2007, Parmar et al., 2013 {Nazemi-Tabrizi, 2012 #315). High risk of bias outcomes featured prominently on the "selective outcome reporting" domain, as many of the studies failed to adequately report prespecified outcomes or the outcomes one should reasonably expect to find in such a study. An example of a high risk outcome in the "other risk of bias" domain was the risk of bias intrinsic to the "N-of-1" study design(Arnold et al., 2009) - a design better suited for stable, chronic diseases rather than for relapsing-remitting diseases, such as PV. Moreover, post hoc analyses(Beissert et al., 2010, Mentink et al., 2006) and baseline inequalities between study arms (el-Darouti et al., 2009) were seen as further examples of "other risk of bias."

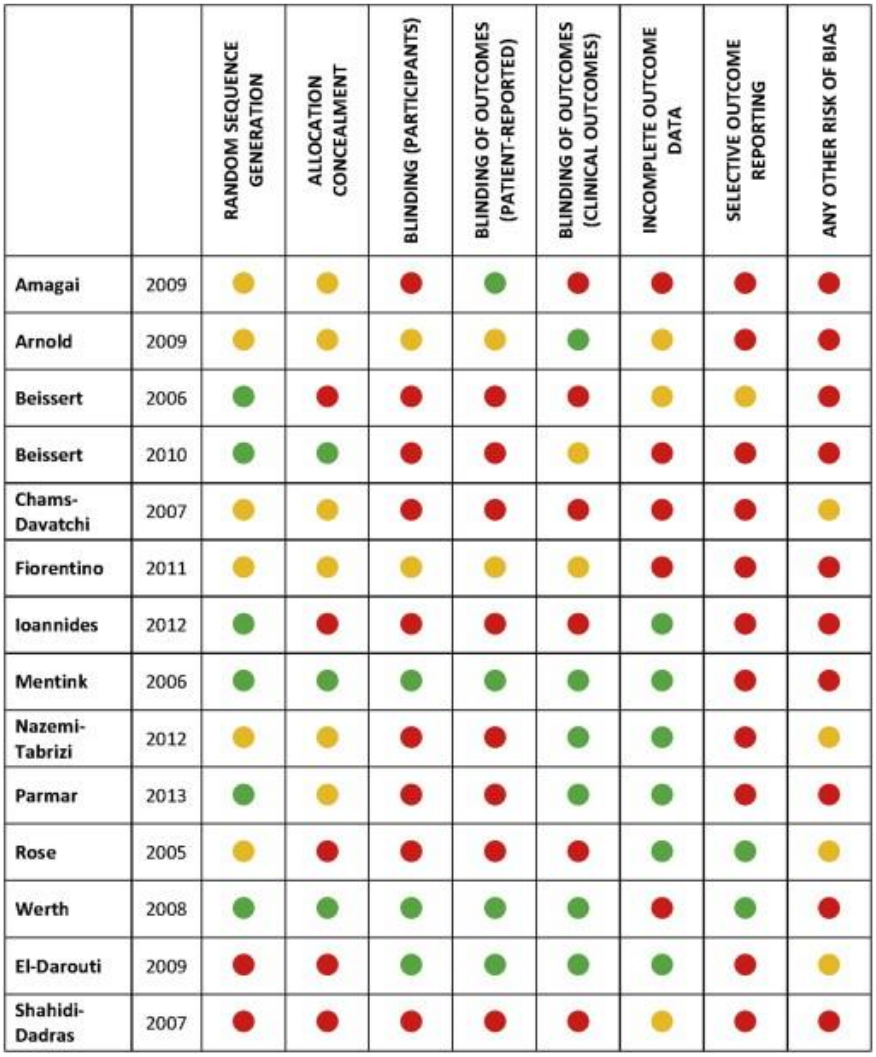


Figure 10. Risk of bias summary

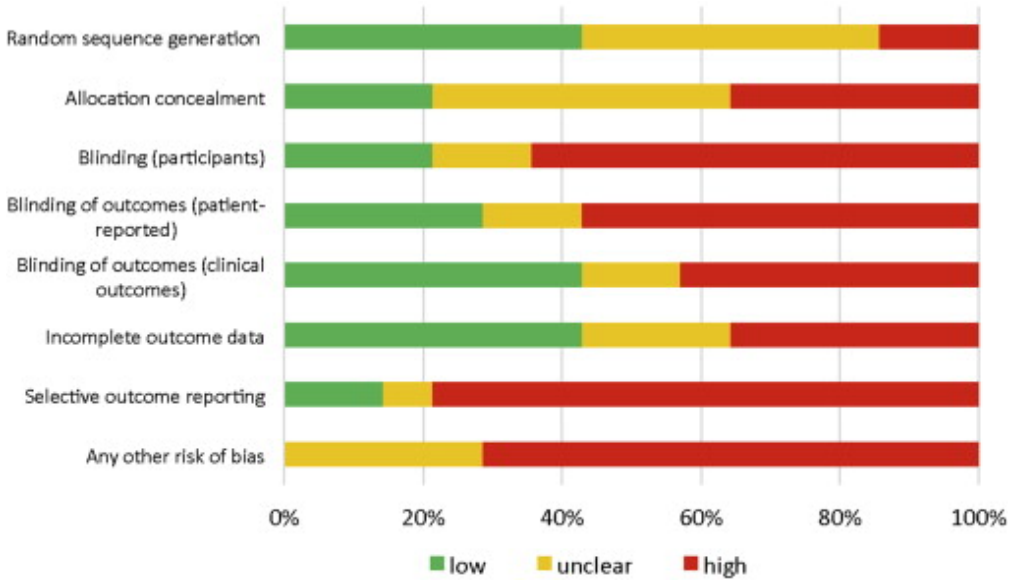


Figure 11. Risk of bias judgements as percentages across all studies

Paediatric and pregnancy studies

A total of 6 case series (5 paediatric, 1 pregnancy) and 10 case reports (6 paediatric, 3 pregnancy, and 1 maternal and neonatal) were included in the paediatric and pregnancy selection. Table TI in the online Supplementary Material summarizes in detail the design, intervention, level of evidence, and summary of outcomes (therapeutic and adverse effects) for each study. Two studies were included in the paediatric and pregnancy section as well as in the case series section, as they had mixed cohorts of adult and paediatric patients (Ahmed et al., 2006, Kanwar et al., 2013).

By definition, all reports were assessed with grade 3 level of evidence (nonanalytic studies, e.g., case reports, case series); thus, there was insufficient quality of evidence to support any single treatment for the management of PV in paediatric, pregnancy, or neonatal cases. Nonetheless, there are valuable qualitative observations or insights. The adverse effects of prolonged systemic corticosteroids (e.g., weight gain, cushingoid features, and acne) were described in several studies of paediatric PV. Pregnancy and

maternal cases of PV tended to be managed with oral and/or topical steroids antenatally, with 1 series suggesting benefit with IVIg monotherapy and 1 case employing immunopheresis combined with adjuvant oral steroids. Only 1 case of neonatal PV was included, as neonatal cases reported in the literature tended not to involve biopsy or blood testing as part of the diagnostic process. The neonatal case included in our review (Fenniche et al., 2006) had cutaneous PV lesions affecting the cheek, neck, and legs and which resolved spontaneously after 3 weeks following use of an unspecified topical treatment. This pattern of cutaneous involvement affecting areas of skin exposed to friction in utero and birth trauma, with spontaneous resolution following minimal if any treatment, was mirrored by other neonatal PV papers excluded from the review.

Interventions in the management of PV in adult patients

Despite the poor quality and evidence across all studies in this systematic review, there are valuable (qualitative) insights and observations that can influence clinical decision making to improve treatment outcome or reduce adverse effects. We identified a total of 32 individual interventions for the management of adult PV among the studies included in this review; among those interventions the RCTs or CCTs described 8 systemic and 2 topical treatments. Drug-induced PV was described in 1 case report(Laguna et al., 2008), which described PV flares associated with cocaine use: Remission was achieved with cessation of cocaine use rather than any active therapy.

Only 2 RCTs (Parmar et al., 2013, Nazemi-Tabrizi et al., 2012), and 2 case series(Ahmed et al., 2006, Kumaran and Kanwar, 2006) did not use oral corticosteroids. This means that of the studies included in our final analysis, 96.8% (120 of 124) described the use of oral corticosteroids. This suggests that the effectiveness of systemic

corticosteroids is well established in the treatment of PV; this study is unlikely to provide any further evidence that will change current practice in that respect.

Figure 12 contains a summary of adult PV treatments in order of frequency of citation. Table II in the online Supplementary Material summarizes adult PV treatments in alphabetical order. In both Figure 12 and in the online Supplementary Material Table II, oral corticosteroids and drug-induced PV are omitted, as they are discussed earlier in the text. All RCTs or CCTs in online Supplementary Material Table II contain a detailed summary of the study intervention and outcome; observational studies are summarized only if each study is the only study that cites that particular intervention or is primarily focused on the intervention in question.

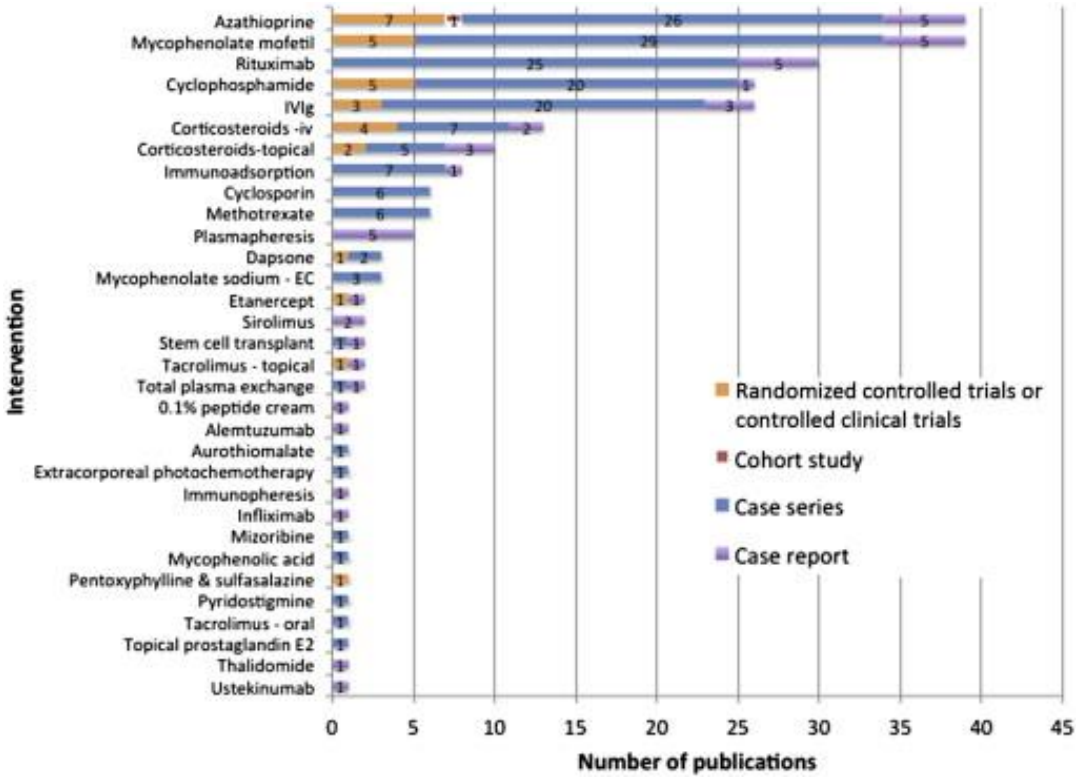


Figure 12. Number of publications per intervention

As pentoxyfylline and sulfasalazine were only re- ported in 1 study (el-Darouti et al., 2009), in which both drugs were both taken together as a combined treatment in the active arm, these drugs were described as one treatment for the purpose of the results.

The authors note that although azathioprine was cited in more papers than any other intervention, very rarely was it the medication of primary focus and more often was used as an adjuvant treatment to the primary medication. This was in contrast to mycophenolate mofetil, which, over the last 10 years, has been the primary study medication in many publications. The authors suggest this may, in part, be related to azathioprine being a well-established steroid-sparing adjuvant in PV compared with mycophenolate mofetil, thus prompting researchers to investigate the role of mycophenolate mofetil as a potential alternative to azathioprine. Furthermore, the authors note that there has been an upsurge in the number of studies looking at novel approaches to the management of PV: largely biologic therapies, in particular rituximab and IVIg. The authors also note that the data from the present study support the suggestion made by Schultz et al (Schultz et al., 2011). that there are wide variations in standard practice among different regions. As an example, such treatments as cyclophosphamide are used rarely, if at all, in some centers, whereas it is standard therapy elsewhere.

5.5 Discussion

Comparison with previous systematic reviews

A Cochrane review on interventions to treat PV and PF was published in 2009 (Chrysomallis et al., 1994) and identified an additional 5 RCTs not included in our

review, as they had been published earlier than our selected review period. The 5 studies described the following interventions:

- Oral prednisone alone versus prednisone and cyclo- phosphamide 100 mg/day versus prednisone and cyclosporine 5 mg/kg/day in 28 participants with PV (Chrysomallis et al., 1994)
- Oral prednisolone alone versus oral prednisolone and 10 large-volume plasma exchanges over 4 weeks in 33 participants with PV and 7 with PF (Guillaume et al., 1988)
- Oral methylprednisolone alone versus oral methyl- prednisolone and cyclosporine 5 mg/kg in 29 participants with PV and 4 with PF (Ioannides et al.)
- Glucocorticoids alone versus glucocorticoids plus traditional Chinese medicine (Tianpaochuang #1) in 40 participants with unspecified pemphigus (Luo et al., 2003)
- Oral prednisolone 45 to 60 mg/day versus oral prednisolone 120 to 150 mg/day in 19 participants with PV and 3 with PF (Ratnam et al., 1990)

The Cochrane review concluded that all five of the aforementioned studies provided inconclusive results relating to the efficacy of the described interventions.

Potential biases in the review process

This review included a broad range of outcome measures, including surrogate outcomes, some of which may have arguable clinical validity. Several studies had incomplete or missing data that we were unable to obtain from the authors. This review

excluded studies that did not have an English language version, thus reducing the number of potentially valid studies for analysis.

As our review only assessed published literature, it runs the risk of publication bias, as there may be unpublished studies containing further useful data. Indeed, a search (US National Institutes of Health ongoing trials register at www.clinicaltrials.gov and World Health Organization International Clinical Trials Registry platform at www.who.int/trialssearch) for recent and ongoing or recently completed clinical trials did reveal completed studies with data or without data: 4 completed, randomized, blinded, controlled trials, of which 2 studies indicated data were available and 2 indicated data were not available. Upon careful review, our systematic review had failed to include outcomes from only 1 of these studies (infliximab vs. placebo), which had been published later than our search timeframe (Hall et al., 2015); the other 3 trials were captured in our review(Beissert et al., 2010, Chams-Davatchi et al., 2007, Fiorentino et al., 2011) (interventions: mycophenolate mofetil plus corticosteroid vs. corticosteroid plus placebo; azathioprine with prednisone vs. placebo with prednisone; and etanercept as a steroid-sparing agent).

Clinical decision making in the absence of high-quality research evidence: Expert consensus opinion and clinical guidelines as evidence

Clinicians face the challenge of making treatment decisions with or without supporting high-quality research evidence. The Oxford Center for Evidence-Based Medicine (OCEBM) developed revised Levels of Evidence in 2011 specifically as a "short-cut for busy clinicians, researchers or patients to find the likely best evidence" (http://www.cebm.net). As elaborated in the 2011 OCEBM revision, the "best" evidence to support clinical decisions, in the context of each patient's individual

symptoms and condition, may be found in "lower" evidence sources such as observational studies, case series and expert opinion. Indeed, the OCEBM emphasizes that "no evidence ranking system or decision tool can be used without a healthy dose of judgment and thought" ((http://www.cebm.net)). The US Government Agency for Healthcare Research and Quality (AHRQ) has championed efforts to get evidence into practice through the Evidence-based Practice Centers program but also recognizes the value of "…evidence from expert committee reports or opinions and/or clinical experience of respected authorities…in the absence of directly applicable studies of good quality" (Guirguis-Blake et al., 2007). The AHRQ also established the National Guideline Clearinghouse to facilitate getting evidence in the form of clinical practice guidelines into practice. Among others, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group (Brozek et al., 2009) and the Appraisal of Guidelines, for Research, and Evaluation (AGREE I, II) (Brouwers et al., 2010) represent robust approaches for separately grading the quality of evidence and strength of recommendations for high-level RCTs or CCTs as well as lower level consensus reports or clinical practice guidelines.

Given the inconclusive evidence supporting PV treatments from this and previous systematic reviews, we summarize in this section the strength of evidence and quality of recommendations from expert consensus reports and clinician guidelines. A search of the National Guideline Clearinghouse (http://www.guideline.gov) for published PV treatment guidelines identified only one guideline directly focusing on pemphigus, originally reviewed in 2004 and revised in 2011 (Meggitt et al., 2011). However, that single guideline limited its scope to the safe and effective use of a single adjuvant medication rather than comprehensive treatment recommendations. A search of the biomedical literature for published PV treatment guidelines identified three authoritative consensus guidelines for the diagnosis and treatment of PV, in each instance developed

by expert membership of national or multinational professional dermatology societies: a European guideline in 2014 (Hertl et al., 2015), a French guideline in 2011 (Joly et al.), and a UK guideline in 2003 (Harman et al., 2017). Although none of the three published guidelines have been reviewed and included in the National Guideline Clearinghouse, each extensively references the available evidence and includes a formal process for developing expert consensus opinion, even where quality research evidence is lacking.

Future evidence-based care for PV

This systematic review reveals persisting wide variations in practice and inadequate high-quality evidence supporting optimal treatments for PV. Nonetheless, the detailed summary of the therapeutic and adverse effects of 32 individual treatments for PV can be an invaluable resource for clinicians to facilitate optimal clinical decision making. Importantly, two recent advances, never before available, provide future opportunities for significant progress in evidence-based treatment of PV: (1) recent publication of the first comprehensive, international consensus guidelines on the diagnosis and treatment of PV (Hertl et al., 2015) (summarized in online Supplementary Material Table III) and (2) consensus on and validation of definitions of disease activity, endpoints, and therapeutic response (McMillan et al., 2015). The findings of this systematic review, coupled with these key recent advances, provide a framework to enable significant progress toward validating current treatment recommendations and exploring novel therapies.

5.6 Conclusions

The consensus statement on pemphigus and pemphigoid (Schultz et al., 2011) suggests the requirement for international, multicenter PV studies coupled with the "generation of consensus terminology and criteria for the description of disease severity and response to treatment." There are several outcome measures specific to PV (Rahbar et al., 2013), and a consensus on disease endpoints has been established (McMillan et al., 2015). Moreover, the consensus statement (Schultz et al., 2011) suggests moving toward "an international algorithm for treatment." This systematic review reveals persisting wide variations in practice and inadequate high-quality, evidence-based research supporting treatment consensus for PV.

In conclusion, there is insufficient quality of research evidence to establish optimal therapies in the treatment of PV. Future high-quality research to validate current guidelines and to explore novel therapies would very likely have an important impact on our confidence in the efficacy and safety of available PV interventions and influence our clinical decision making.

Clinicians may use the results and detailed data from this systematic review, combined with the summary of a recent authoritative treatment guideline, as the most current summary of the available evidence supporting the safety and efficacy of PV treatments. This information will facilitate the discussion of the benefit and risk of specific treatments with individual patients, taking account of their condition, values, and preferences when making clinical decisions.

5.7 Acknowledgements

The authors would like to gratefully acknowledge the following organizations, individuals, and companies, which provided unrestricted financial support of WWOM VI: American Academy of Oral Medicine, European Association of Oral Medicine, Anonymous gifts from patients of Dr. David Sirois, New York University College of Dentistry, Biocosmetics, Elsevier, Johnson and Johnson, The Oral Cancer Foundation, and Unilever.

UPDATED CLNICAL OPINION

The reviews undertaken as part of the WWOM differ to the Cochrane reviews in that all observational studies were included. This allowed us to assess a larger body of evidence which was essential in these rare conditions as there is a paucity of high-quality trials.

The reviews have been cited widely and act as a large body of information for clinicians. However, unless reviews such as these are updated – they quickly become less useful. The introduction of biologics is rapidly changing how we manage our patients, and in MMP and PV we are more likely to move onto these newer treatments than persevere with the older style treatments.

The evidence base is developing and recognised scoring systems for the oral manifestations of these conditions have been validated.

There is no ongoing work that I am aware of, in the area of a core outcome set for these diagnoses as yet.

Chapter 6 COSRAS: Development of a core outcome set for recurrent aphthous stomatitis using an interactive consensus process

Thus far, through the systematic evaluation of treatments for RAS, ALU in Behçet's, oral MMP and oral PV, I have demonstrated that there are methodological issues inherent in multiple trials, most commonly a heterogeneity around the area of outcome measurements. These issues mean that data cannot be pulled together, to allow meta-analyses and give the highest level of evidence to support clinical decision making. This is a particular problem in oral medicine as many of the conditions we manage are uncommon and therefore the likelihood of multiple largescale high quality RCTs is limited. The use of meta-analyses would allow us to pool data from multiple studies, however until all trial design incorporate a standard outcome set, these issues will continue.

This next chapter presents a COS development project, which, at the time it was carried out, was the first in the specialty of oral medicine.

I am the lead author and developed the project with my supervisors from concept to final write up. The project was a long process over 2 years and was the first COS development project in oral medicine. Following dissemination of the project at international conferences, interest from other dental specialties led to development of COS in other areas of dentistry and the use of the methodology as a basis for other projects.

This paper is presented in a format suitable for publication. The abstract for a poster summarising the project was published and presented at EAOM 2016.

6.1 Abstract

Background: RAS is a highly prevalent disease which can cause pain and suffering for patients. Many of the treatments can cause significant side effects. Despite the large numbers of trials for treatments for RAS, there is no universally accepted best treatment. Due to the heterogeneity in trial design and choice of outcome measures used, no meta-analyses of the existing literature has been possible. The development of a core outcome set for trials of interventions for RAS is warranted.

Objective: To develop a core outcome set for use in interventional trials for RAS using an interactive consensus process

Settings: Patient involvement took place at the University of Manchester, UK.

Consensus process took place at the British Society of Oral Medicine (BSOM) in Leeds, UK in May 2015

Participants: Patients with a diagnosis of RAS who were attending the oral medicine department in Manchester, were involved in the patient information meeting.

Delegates at the BSOM meeting attended the consensus process, including oral medicine specialists, dentists, dental hygienists, dental nurses and research academics.

Design: Mixed methods, including systematic reviews, patient involvement and interactive consensus via clicker technology.

Results: Patients agreed on six important outcomes for inclusion.

Systematic review of 73 interventional randomised controlled trials for RAS revealed a total of 313 individual outcomes. This number was reduced to 22 by removing duplication and grouping similar outcomes into domains. Consensus process led to further agreement on the inclusion of 13 outcomes for the COS

Conclusion: Interventional trials for RAS should adopt the use of a core outcome set so that future systematic reviews and meta-analyses can be carried out to provide clinicians with higher quality evidence base than is currently possible due to the heterogeneity of outcome measure used in trials. This project demonstrates a new process for gaining consensus for COS which avoids the need for large scale postal Delphi processes. With ongoing improvements in interactive online programmes, future consensus will be easier to arrange and will allow for greater and wider participation.

6.2 Introduction

Recurrent aphthous stomatitis (RAS)

RAS is the most frequent form of oral ulceration with a prevalence (population dependent), estimated to be between 5-60% (Jurge et al., 2006). It has a multifactorial aetiopathogenesis (Ship et al., 2000). It can cause significant morbidity and reduced quality of life for patients. There is no known cure for RAS and treatment is currently aimed at palliation of symptoms.

The term aphthae (from the Greek word aphtha meaning eruption) has been used to describe mucosal ulceration since the time of Hippocrates (460-370 BC). Aphthae are described as a round or ovoid ulcers with well circumscribed margins. They exhibit an erythematous halo which surrounds the grey or yellow appearance of the floor of the ulcer.

Recurrent aphthous stomatitis usually presents in late childhood, peaks in the early 20s then settles into middle age. Patients will report the presence of one or more ulcers affecting various areas of the intra-oral mucosa. These ulcers appear on a recurrent basis in so called ‘crops’ or ‘episodes’ and the time between episodes of ulcers can vary between patients. There is usually a prodromal period, (a preceding nonspecific period where patients are aware an attack is imminent). The ulcers appear to be most painful in the first few days of an attack, and patients will report finding it difficult to eat and drink. The ulcers appear red initially before the actual ulcer appears (break in the epithelial lining). Once formed, the ulcer has a sloughy grey/yellow base with a surrounding erythematous halo. Healing rates are entirely variable, although it is thought that super-infection of the ulcer with the commensal oral flora can cause more painful and longer lasting ulcers.

Recurrent aphthous ulcers are characterised according to their history and presentation and are often classified into three subgroups (major, minor and herpetiform) according to the size, duration and other clinical features of the ulcers. Patients with RAS are otherwise completely healthy and have no underlying disease, however RAS-type ulceration can be a feature of many other systemic diseases such as Behçet's Disease, Crohn's Disease and HIV infection.

Aetiopathogenesis

The aetiopathogenesis of RAS is multifactorial and not fully understood. There seems to be a genetic basis which together with various factors such as immune mediated response, local and systemic factors and possible microbial aspects, lead to the development of the aphthous ulcers.

There is almost certainly a genetic predisposition present (Albanidou-Farmaki et al.) this is demonstrated by the increased frequency of human leucocyte antigen (HLA) types and previous family history of recurrent mouth ulcers. The following HLA types are examples of the many that have been linked to RAS. HLA 2 (Challacombe et al.), HLA B12 (Lehner et al., Malmström et al., 1983), HLA-B51 (Shohat-Zabarski et al., 1992), HLA-DR4 (Ozbakir et al.), DR5 and A28 (Albanidou-Farmaki et al.) and DRw9 (Sun et al., 1991).

More recently an association with toll-like receptors (TLR) and tumour necrosis factor (TNF) have been proposed and further research in this area is on-going.

Various other implicating factors have been suggested such as food sensitivities, haematinic deficiencies, cessation of smoking, stress, products for intra oral use such as toothpastes (Wardhana and Datau, Atkin et al., Bao et al., Gavic et al.)

The proposed aphthous process begins microscopically as lymphocytic cells invade the epithelial area involved, causing swelling. This pre-ulcerative stage is then accompanied by pain as a localised vasculitic process takes place with an associated dense mononuclear cell infiltrate. Ulceration then follows with a fibrinous overlying layer containing lymphocytes, neutrophils and plasma cells. The final stage of regeneration follows this resulting in healing of the ulcer. The length of this process varies from ulcer to ulcer and patient to patient.

Genetic Factors

There is understood to be a genetic basis or predisposition to recurrent aphthous stomatitis. A strong family history is common. There are various proposed associations between recurrent aphthous stomatitis and the HLA (human leukocyte antigen) gene family. The HLA gene family is responsible for the production of proteins known as the HLA complex which in turn is responsible for allowing the body to recognise 'own' proteins as opposed to those produced by 'foreign invaders' such as viruses or bacteria.

Immunology

Immune mediated factors are also involved in the development of aphthous ulceration. Interleukins are a group of signalling molecules known as cytokines which are involved in the regulation of the immune response. They are expressed by various white blood cells including CD4 t-helper lymphocytes, monocytes and macrophages. The most important interleukins associated with RAS are IL2 (Boers-Doets et al.), IL10 (Buño et al., 1998), IL1b and IL6 (Bazrafshani et al., 2002) and the precursor CD4 and CD 25 (Lewkowicz et al., 2008).

More recently there has been new evidence of the association of tumour necrosis factor (TNF) (Eguia-del Valle et al.), toll like receptors (TLR) (Gallo et al., 2012, Borra et al., 2009, Hietanen et al., 2012) and Cytokine polymorphism (Wu et al., 2018).

Local Factors

There are numerous local factors that are associated with recurrent aphthous stomatitis. Physical trauma or injury has been reported to be a causative factor (Wray et al., 1981). For example, a young patient receiving orthodontic therapy with a background of recurrent aphthous stomatitis will report increased number of episodes during orthodontic treatment due to mechanical rubbing of the mucosal surfaces against the orthodontic brackets and wires.

There has been a longstanding negative association with smoking habits and RAS. Patients often report that after stopping smoking they develop recurrent aphthous stomatitis or their previous recurrent aphthous stomatitis worsens in severity (Shapiro et al., 1970, Chellemi et al., 1970, Axell and Henricsson, 1985, Bookman, 1960, Dorsey, 1964, Salonen et al., 1990, Tuzun et al., 2000, Atkin et al., 2002, Sawair, 2010). This has led to further research into treatments of recurrent aphthous stomatitis with nicotine products.

Sodium lauryl sulphate (SLS) is a detergent agent added to most toothpaste that can be bought freely at chemists and supermarkets. It is this detergent that allows the foaming of toothpaste when brushing and gives a ‘zingy’ fresh feeling after brushing. It has been reported to be associated with RAS (Healy et al., 1999, Shim et al., 2012), although some consider this a causal link.

Systemic factors

There are many systemic factors associated with the appearance of recurrent oral aphthous ulceration. These can vary from nutritional deficiencies to complex systemic diseases such as Behçet's Disease. There is no agreed consensus as to whether the ulcers in patients with a systemic underlying disease are the same as the ulcers in RAS. The appearance and clinical behaviour of the ulcers can be very similar. The aphthous ulcers seen in combination with systemic disease resemble RAS in appearance and behaviour and can be described as RAS-like ulcers or Aphthous like ulcers (ALU)

Diagnosis and management

Diagnosis of RAS is made on the history and clinical findings on examination. There is no specific test and mucosal biopsies are only recommended to exclude a different cause of ulceration e.g. immunoobullous disease.

When considering a diagnosis of RAS, other systemic causes of oral ulceration must be excluded and therefore routine blood tests are carried out as standard. The blood tests usually requested are full blood count, and haematinics (Vitamin B12, folate and ferritin). Many specialists also advocate an autoimmune screen for coeliac disease as the presence of aphthous like ulcers may precede other symptoms.

Treatments for RAS can be broadly divided into topical and systemic (although it is accepted that many treatments will have a combined topical/systemic effect).

Topical interventions

There are a wide variety of topical treatments used for RAS. These vary from treatments widely available for patients to buy, treatments available by prescription from a doctor

or dentist to treatments that are prescribed off-licence for use in RAS. Topical treatments can be broadly divided into the following categories:

Numbing agents

For example, acetyl-salicylic acid based products such as ‘bonjela’ cause local irritation and damage to nerve endings causing numbness. Benzydamine hydrochloride spray or mouthwash causes short term numbness to allow patients to eat and drink and maintain oral hygiene. Topical anaesthetics have also been tried such a lignocaine gel 5%.

Barriers

For example ‘orabase’ is a sticky substance that if applied correctly can adhere to mucous membranes. It is thought that the pain from the ulcer is secondary to it being an ‘open wound’ and by covering it, the pain is decreased. Often steroid pastes or immunosuppressant pastes are mixed with it to improved availability of the active ingredient adjacent to the ulcer.

Antiseptic

Examples include mouthwashes and gels such as chlorhexidine gluconate. This is due to the theory that a ‘super infection’ with commensal oral bacteria causes increased inflammation and therefore increased pain from the ulcers.

Antimicrobial

Topical antimicrobials are used generally as a mouthwash. For example doxycycline 100mg capsules dissolved in water and rinsed in the mouth for 4 minutes then being spat out seems to have an immunomodulatory effect. It is not thought to be the antimicrobial effect that is beneficial in the treatment of recurrent aphthous stomatitis.

Corticosteroids

This forms the biggest subgroup of topical treatments. Various ways of using steroids topically in the mouth have been suggested. These include as a paste or cream such as adcortyl, amelxanox, betamethasone valerate and triamcinolone, as a mouth wash betnesol – soluble betamethasone tablets - (500mcg betamethasone soluble tablets dissolved in 10-20mls of water and rinsed in the mouth for 4 minutes before being spat out), as a slow dissolving tablet 2.5mg hydrocortisone tablets, as a spray (Becotide inhaler (beclomethasone diproprionate 100mcg) as used for asthma but instead directed as a spray to the ulcers, or Flixonase as used for allergic rhinitis).

Immunomodulators

Tacrolimus ointment also known as ‘protopic’ ointment.

Unknown mode of action

Sodium lauryl sulphate-free toothpastes, botulinum toxin injections, herbal remedies.

Systemic interventions

A multitude of systemic treatments are currently used in clinical practice (see Chapter 2). There is no standard way of classifying these treatments as often the precise mode of action is not fully understood. However, treatments include: antimicrobials and antivirals (e.g acyclovir, dapsone, doxycycline, tetracycline and clofazimine); vitamin and food supplements (e.g vitamin B12, multivitamins, and beta-glucan); herbal remedies with an unknown mode of action (e.g camelthorn, homeopathy, longovital, bee propolis); anti-inflammatories (e.g. sulodexide and montelukast); corticosteroids (e.g. prednisolone and prednisone); thalidomide; pentoxifylline; colchicine; immunosuppressant treatments (e.g azathioprine and mycophenolate mofetil).

Other interventions

Treatments advocated for the management of possible causative factors are included here and these include stress management and cognitive behavioural therapy. Treatment of underlying deficiencies or disease is also crucial. In particular there is evidence that managing a patient's underlying systemic disease for example Crohn's disease will have a beneficial effect on the patient's aphthous ulcers (which confirms the theory that the ulcers in this case are part of the systemic disease process).

Despite the high prevalence of RAS and the vast array of treatments currently used, there are no agreed guidelines with regards to management. There is no gold standard treatment. Various topical agents are used in practice and for severe symptoms, systemic interventions are required. Individual clinicians have preferred treatment regimens which can involve the use of sequential interventions. These have variable success rates which are rarely scientifically evaluated. Many of the interventions can cause significant adverse reactions.

The heterogeneity of trial design in interventional oral medicine trials is well recognized (Baccaglini et al., 2011). In the Cochrane Systematic Review 'Systemic Interventions for Recurrent Aphthous Stomatitis' (Chapter 2) it was noted that outcome measures and timing of assessment varied across trials (Brocklehurst et al., 2012). A further review assessing interventions for the management of RAS-type ulceration in Behcet's Disease also found substantial heterogeneity, with the authors concluding 'that the use of a core outcome set for oral ulcers would be beneficial' (Taylor et al., 2013).

Core outcome sets

A core outcome set is an agreed standardised set of outcome measures that should be collected as a minimum for all trials in a particular clinical area. The aim of a core outcome set is to standardise the outcomes so that comparisons can be made across studies and data pooling can be carried out during meta-analysis. At the time of developing this study, no widely accepted standardised format for the development of a core outcome set was available. However the comet initiative (www.cometinitiative.org) aims to provide resources that support and guide the development of such core outcome sets (Williamson et al., 2012).

The key stages for development of a COS include:

- **Patient involvement -** the patients who have personal experience of the condition should be involved in agreeing the outcome measures most important to them, ideally from the concept and early planning stages of a core outcome set project.
- **Identifying existing knowledge -** the outcome measures already in use in trials should be gathered and included.

- **Consensus methods -** the relevant stakeholders should agree by consensus which outcomes are of most importance. Consensus processes for core outcome set development are usually carried out using a Delphi process.

6.3 Methods

Patient Involvement

To ensure the development of a COSRAS was informed by RAS patient opinion, a group of RAS patients was gathered at an early stage in the process. We acquired a small grant from NIHR Research Design Service and held a patient information meeting in July 2014. Long-term RAS patients attending University Dental Hospital of Manchester oral medicine clinic were given the opportunity to take part in a RAS information meeting. These patients had previously been treated with a wide variety of interventions over many years with varying degrees of clinical benefit.

Patients interested in taking part were subsequently invited by letter to attend an informal patient group meeting. The meeting allowed the patients to share their experiences of living with RAS and in addition the topic of outcomes was raised and discussed openly. The patients were able to share their opinions of what they felt was important to measure in a trial of treatments for RAS. The meeting was run by a non-clinical researcher to allow patients freedom to express their thoughts and promote open discussion. The meeting was recorded with consent from the participants.

The following questions were raised for discussion by the non-clinical researcher.

- When thinking about treatments for mouth ulcers, what outcomes do you think should be measured?

- What would make you think a treatment had been successful?

Identifying existing knowledge

Trials were identified from two Cochrane systematic reviews. These two reviews were ranked in the top 10 Cochrane reviews in the specialty of oral medicine in the Cochrane Oral Health Group priority setting exercise. The first was the 2012 'Systemic interventions for recurrent aphthous stomatitis' review (Chapter 2) with 25 included studies. The second systematic review was from the ongoing review 'Topical interventions for recurrent aphthous stomatitis' (Appendix 6). At the time of data extraction in August 2015, 48 papers had been included. This gave a total of 73 papers for data extraction.

For each of the identified 73 trials, the following data were extracted and entered onto an excel spreadsheet:

- Outcome measurement
- Stated as primary or secondary outcome
- Timing of outcome measurement
- Method or tool of measurement

The final list of outcomes was reviewed by the author team (TW/AMG/JT) and duplicates were removed. The resulting outcomes were discussed and grouped under broader domains of similar outcomes where possible.

Consensus methods (with relevant stakeholders) – trial run

In advance of the formal consensus process at the BSOM annual meeting, a practice-run was carried out at the Northern Oral Medicine Group Meeting (a yearly meeting for oral medicine teams based in Liverpool, Manchester, Leeds and Newcastle). This allowed

the consensus gathering process, using clicker technology, to be trialled ahead of the larger national meeting. Feedback was obtained from participants with regard to ease of use of the clickers for voting. Following the success of the trial process, a roll out to the national meeting was agreed.

Consensus process – final

The British Society of Oral Medicine (BSOM) is the national society for oral medicine in the UK and Ireland (www.bsom.org.uk). There is an annual scientific meeting aimed at improving the knowledge base for clinicians in the practice of oral medicine. The residing President in 2014 Dr Alan Mighell, was aware of the work being carried out in the development of COSRAS and was keen that this important research area was disseminated widely. This gave the COSRAS development team a valuable opportunity to incorporate the opinions of a large number of clinicians involved in the care of RAS patients.

Each of the outcomes identified through either the patient involvement exercise or the appraisal of trials included within the systematic reviews was considered individually by the group. Participants were asked to rate the level of importance of each outcome measure on a scale of 1-9 (1 limited importance, 9 critical importance). Consensus was agreed when greater than 70% agreed and less than 15% disagreed (Williamson et al., 2012).

An information pack (Appendix 7) was given to the participants at the national meeting a day in advance of the consensus process. Box 1 Provides an illustration of how the consensus process was run.

Box 1. Running of the consensus process

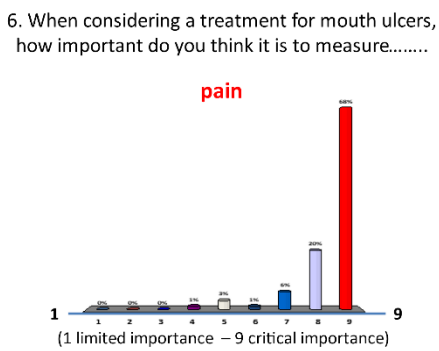
Round 1.

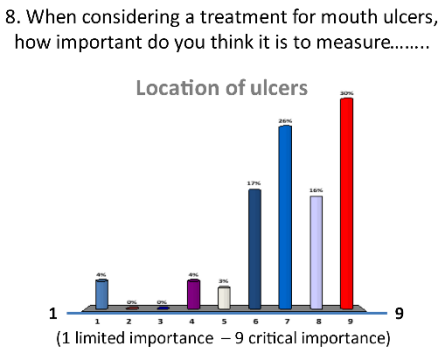
Question posed for each outcome:

'When considering a treatment for mouth ulcers, how important do you think it is to measure….. ?'

The voting process was open and dynamic. The participants were shown the question and given 20 seconds to decide a score. During that time, the participants could see how the group was scoring via a dynamic table. At 15 seconds, a 5 second warning asked participants to place their final score. This allowed individuals to reconsider their score if they wished

Examples of scoring results after Round 1:





Round 2.

All outcomes achieving a score of between 1-3 were discarded. The process was rerun for the remaining outcomes as before.

6.4 Results

Patient Involvement

Following invitation, seven RAS patients volunteered to take part in an interactive meeting to discuss living with RAS and the importance of choices outcome measurements in trial settings. The patients were given free reign with regards to the number of outcomes they wished to be measured. A review of the audio recordings of the patient information meeting revealed a natural unanimous agreement for a total of six essential outcomes that the patients felt should be measured when considering the effects of a treatment for recurrent aphthous stomatitis:

- Size
- Duration
- Frequency
- Number
- Pain
- Diet

All six of the outcome measurements were included in the 22 from systematic review and after consensus these 6 outcomes were within the final 13 outcomes from the COS

Identifying existing knowledge

A total of 313 individual outcomes were identified from the 73 evaluated trials. These outcomes were condensed down to 22 by removing duplication and grouping into relevant domains (e.g. discomfort/soreness/tenderness/pain were grouped as the

overarching domain ‘pain’)

- Presence or absence of an ulcer or ulcers
- Size
- Duration
- Frequency
- Diet
- Pain
- Number of ulcers
- Location of ulcers
- Side effects of treatment
- Quality of life
- Composite score
- Other signs and symptoms (burning, erythema)
- Additional ulcer treatment required
- Improvement
- Blood test
- Vital signs
- Induced /challenged pain
- Tolerability of treatment
- Changes in condition
- Clinical evaluation
- Patient’s overall assessment
- Healing

Consensus process

Participants were asked to select which category best represented their job, as illustrated in Figure 13.

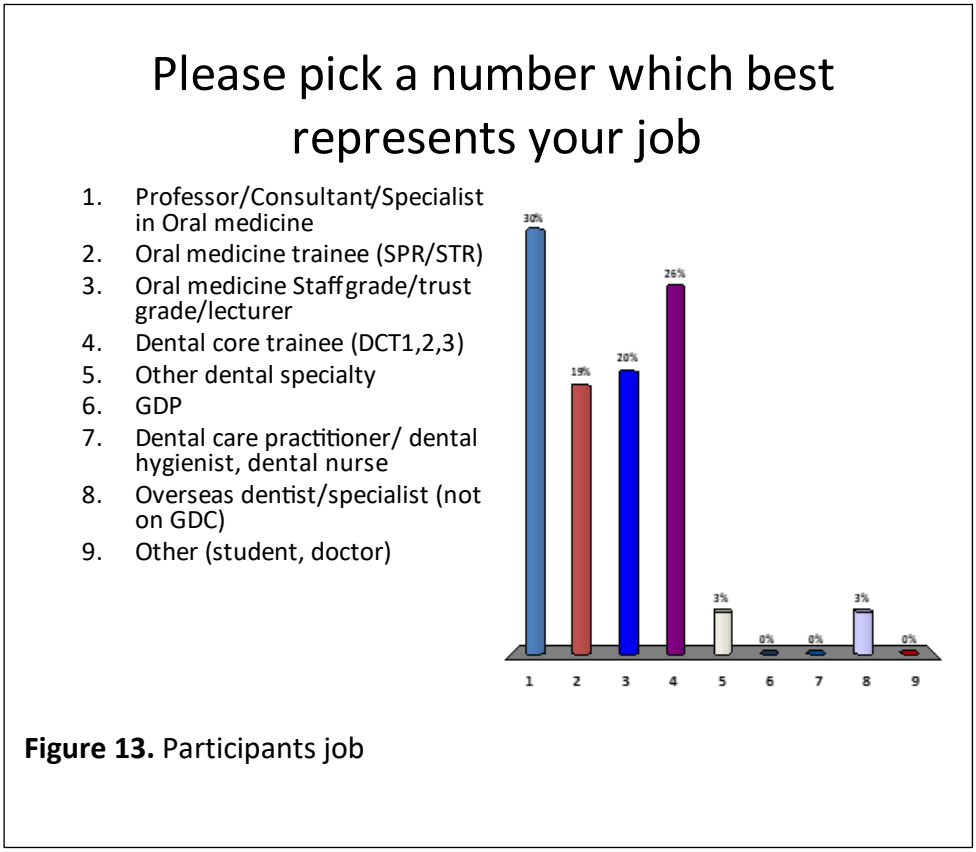
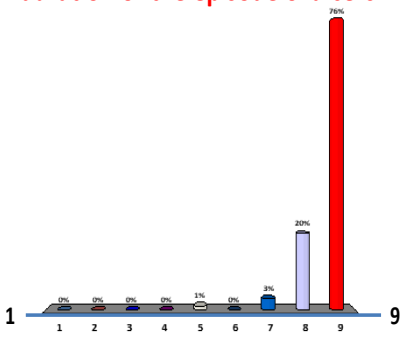
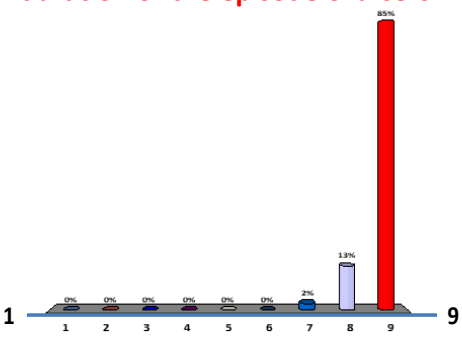
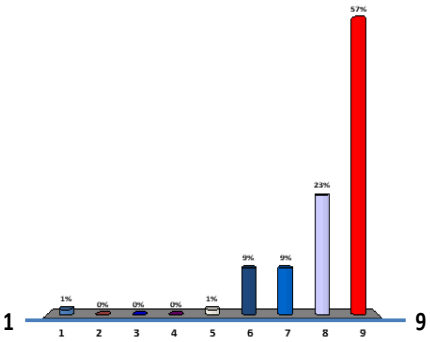
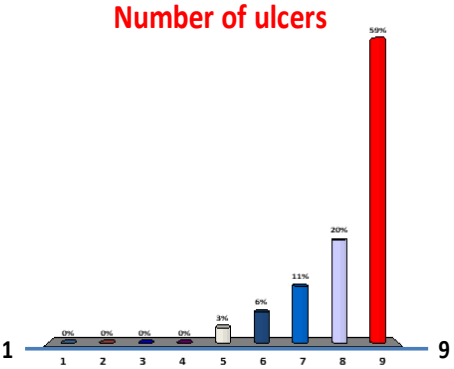
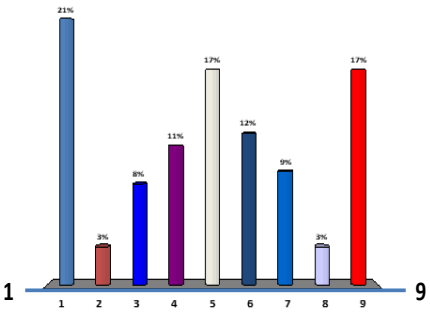
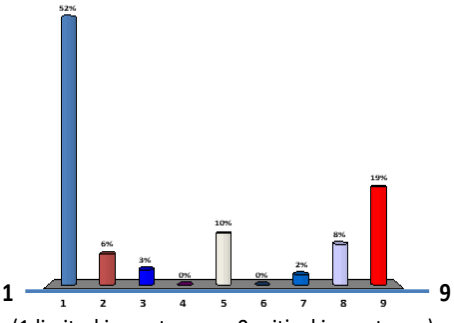


Figure 13. Participants job

Two rounds of consensus gathering were carried out. Figure 14 provides examples of the change in voting between Round 1 and 2 (showing a move towards consensus).

ROUND 1	ROUND 2
3. When considering a treatment for mouth ulcers, how important do you think it is to measure……. **duration of the episode of ulcers**  (1 limited importance – 9 critical importance)	3. When considering a treatment for mouth ulcers how important do you think it is to measure……. **duration of the episode of ulcers**  (1 limited importance – 9 critical importance)
7. When considering a treatment for mouth ulcers how important do you think it is to measure……. **Number of ulcers**  (1 limited importance – 9 critical importance)	7. When considering a treatment for mouth ulcers, how important do you think it is to measure……. **Number of ulcers**  (1 limited importance – 9 critical importance)
11. When considering a treatment for mouth ulcers how important do you think it is to measure……. **Composite score**  (1 limited importance – 9 critical importance)	11. When considering a treatment for mouth ulcers how important do you think it is to measure……. **Composite score**  (1 limited importance – 9 critical importance)

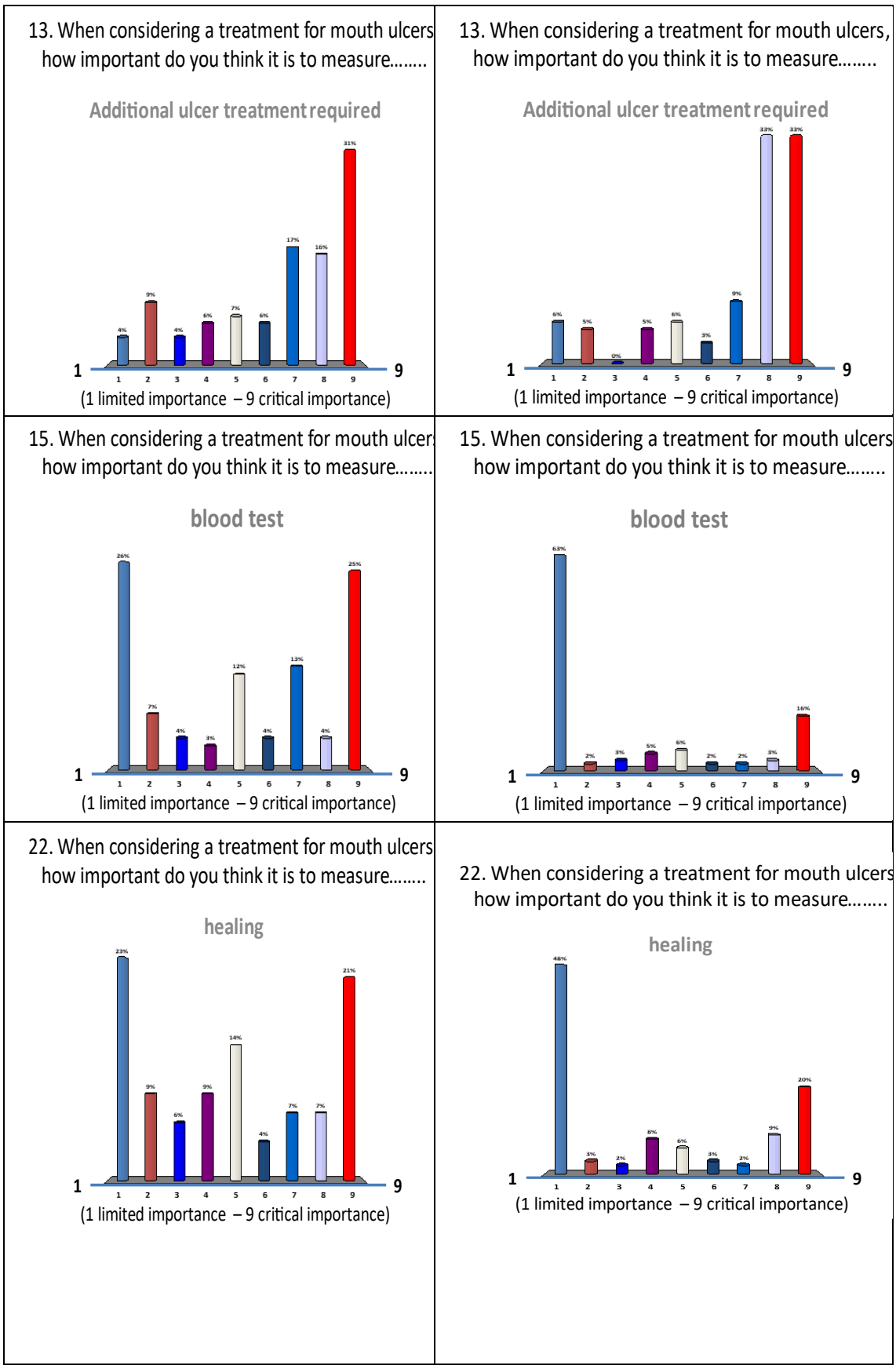


Figure 14. Examples of change in voting between Round 1 and Round 2

Box 2 - showing overall results between voting rounds

Round	**IN**	**UNCLEAR**	**OUT**
Pre -vote	22	0	0
Round 1	12	7	4
Round 2	13	6	4

A final agreement for the inclusion of 13 outcomes was reached. These were agreed as follows.

- Presence or absence of an ulcer or ulcers
- Size
- Duration
- Frequency
- Diet
- Pain
- Number of ulcers
- Location of ulcers
- Side effects of treatment
- Quality of life
- Improvement
- Additional ulcer treatment required
- Tolerability of treatment

All participants were asked to give feedback on the processes and unanimously found it to be a positive experience. Many commented that they were keen for this process to be used for development of outcome sets in other conditions.

It is unclear if the results achieved through the live interactive process would mirror those of a traditional Delphi survey. One of the advantages of the process was that all stakeholders could see how their colleagues were voting in real time – this allowed for instant consensus to be achieved when voting closed

6.5 Discussion

At the time this study was carried out, no other core outcome sets had been developed in the field of Oral Medicine. The area of Core Outcome Set development was in its infancy and no widely agreed standard process for development was available. Guidance was sought from the Comet initiative, the paper by Williamson et al (2012) and large groups such as OMERACT (https://omeract.org). Examples of well-planned projects include the MOMENT (Harman et al.), the GASTROS study (http://gastrosstudy.org) and the ongoing work on Trigeminal neuralgia (Nova et al.).

The methodology used in established Core Outcome Sets can vary, however the three main elements of development are common throughout. These are patient involvement, review of existing literature and consensus process.

Patient involvement

Timing - The patients were involved at an early stage of this project. In the initial patient information meeting the patients were given the opportunity to discuss which outcomes they felt were important to them. By allowing this open approach the patients were not limited to the number of outcomes they suggested and a natural conclusion from the group of seven patients was towards an agreement on six outcomes. Had we presented the patients with a choice of outcome or even presented

them with the 22 outcomes gathered from the systematic review, there is a possibility more outcomes would have been selected by them.

The results show that all six outcomes suggested by the patients were part of the final 13 outcomes. It is reassuring that the patients' voice is heard throughout the process despite the patients not directly participating in the final consensus process. Future projects would likely involve patients throughout the full process.

Location - The patients were taken from only one UK site. It is likely that patients from other areas both nationally and internationally would experience similar symptoms and have the same requirements from treatments. However, future patient involvement should involve more than one geographical area.

Design - Formal qualitative research methods would be an advantage to ensure that all areas of importance to the patients are discussed. It is important to ensure that saturation of responses is reached and ensure that no further information is required from each group.

Personnel - In this study the patient meeting was led by a non-clinical researcher. This was to ensure the clinician would not indirectly lead or guide the patient's voice. Other options would include using a clinician to introduce outcome measures that the patients may not have considered.

Identifying existing knowledge

Using the previously published systematic reviews and the ongoing topical interventions review from the Cochrane collaboration to collate outcome measurement data was a time saving process and avoided the need of developing a separate systematic review specifically for outcome measurements. The methodology of Cochrane systematic reviews is established and respected. It is likely (although not proven) that all possible outcomes were found within the 73 papers (and 313 total outcomes extracted). The option for additional outcomes to be added at any stage minimised the risk of outcomes being missed during the review process.

Consensus Process

Recognised consensus processes include individual questionnaires, individual interviews, focus groups, and Delphi surveys (Williamson et al., 2012, Rosenbaum et al., Kirwan et al., Sanderson et al., Schmitt et al.)

Delphi methodology

The Delphi process is an iterative survey method which aims to gather the opinions of a number of key stakeholders and allow consensus to be reached through a structured process of elimination. The success of the process relies on clear and logical planning to allow the most relevant stakeholders to be involved and for the questions being asked to be relevant to the aims of the research questions.

After the preliminary list of outcomes has been identified, the Delphi technique is the most commonly used method for rating the importance of these outcomes for including in the COS (Williamson et al.).

There is no consensus as to the ideal methodology for Delphi technique use in the development of Core Outcome Sets, however mixed method techniques can often use patient interviews as an adjunct to a systematic review of the literature to identify an initial list of potential outcomes for inclusion in a Delphi consensus survey (Remus et al.).

Delphi process is often carried out as a series of rounds of voting via postal survey or via email. With each round the number of outcomes to vote on is reduced leading to a natural consensus. Attrition of response rates in Delphi technique is a known problem due to the timescales involved (Williamson et al., 2012). Attrition can be minimised by reducing the time between rounds (Trevelyan and Robinson, 2015). Therefore the concept of a live interactive consensus process was introduced to allow a timely agreement on core outcomes, minimising the chance of attrition.

Future work

An option to develop this project further would be to carry out a formal Delphi consensus survey using the data from the patients and systematic reviews. The results and attrition rates could then be compared with the clicker process.

Another option would be to take the clicker process to a bigger audience, perhaps including international stakeholders, to see if a similar group of outcomes would make the final set. During the ongoing Covid pandemic, the use of technology has improved exponentially. There are opportunities to reach a wider audience through international online meetings and the instant consensus clicker technology is now available as a

smartphone app or embedded in technology such as Zoom. This is an area worth exploring further, if not for this project, then for new outcome set developments in other conditions.

The results so far could be separated into potential domains such as

Domain 1 – *Timeline*

- Presence of ulcer
- Duration
- Ulcer free time

Domain 2 -*Ulcer details*

- Size
- Number
- Pain
- QoL
- Additional treatments
- Improvement

Domain 3 -*Treatment effects*

- Side effects
- tolerability of treatment

Working with Domains as opposed to individual outcomes may make further work easier to manage.

If these are accepted as the core outcome domains/ core outcome set, then further research work now needs to be undertaken to explore optimal timing of outcomes and tools of measurement for the outcomes (COSMIN: https://www.cosmin.nl).

Chapter 7 Discussion

7.1 Background to the work

As a clinical trainee in the specialty of oral medicine, I became involved in the early stages of a Cochrane review evaluating the evidence for systemic interventions in recurrent aphthous stomatitis {Brocklehurst, 2012 #87}. This common condition was frequently seen in the clinics, and I wanted to justify my clinical care with the support of high-quality evidence.

It became clear during this systematic review, that there were numerous problems with the evidence base we were reviewing. These issues were wide ranging including trial designs, choice of interventions and controls and variation in outcome measurements and timings. As a result of these issues, there was not enough homogenous data to allow for direct comparison or pooling of information from multiple trials. These issues are exacerbated when we consider that many of the oro-mucosal conditions we manage are uncommon and therefore often trials are low in participant numbers. Without the ability to pool together results from multiple trials, we will continue to struggle to produce high quality evidence base leading to further production of large narrative systematic reviews and no data meta-analysis.

The issues we discovered in the first of the reviews, were not new and had been previously highlighted (Baccaglini et al., 2010).

Following this review, the protocol for the follow-on topical review for RAS was published and work began on screening the search results. The volume of published evidence was vast and to date the review is ongoing with over 80 included papers so far. It is likely the review will be divided up to allow further progressions of this important topic.

Interestingly the methodological issues noted in the systemic review have been found throughout the topical review thus far. Heterogeneity of outcome measures, timing of outcome measures, tools/instruments of outcomes are too varied to group together. It is

unclear at this stage if meta-analyses will be possible. The quality of the studies assessed so far is low.

The next stage of the process was to see if these methodological problems were isolated to the diagnosis of RAS – an episodic oral ulcerative problem in otherwise healthy patients – or if they extended to other oral medicine conditions including oral ulcerative conditions associated with systemic disease (Bechet's) and persistent oral ulcerative conditions with potentially more serious morbidity and mortality (PV/MMP).

To try an improve the future evidence base, the development of a core outcomes set was a suggestion in each review conclusion, for future research. This was the natural direction to take the project forward and start the development process of a COS for RAS.

Further discussion of results

The results of the four systematic reviews give a narrative review of the trials of a range of treatments available for each oral condition. They assess the quality of each trial and give an overview of the up-to-date evidence base. Each review highlights the range of methodological limitations and recognises the problems of heterogeneity of outcome measurements. These reviews have been disseminated widely and have been cited regularly within the body of oral medicine literature. There is a desire from clinicians to better understand the quality of the evidence, however there is also general disappointment at the lack of data driven high quality evidence.

Randomised controlled trials are expensive and time consuming. A brief review of PROSPERO (www.prospero.whatever) shows the vast number of prospective studies registered in the numerous oral medicine mucosal conditions, yet the likelihood is that none of the results of these trial will be able to provide enough new high quality data to affect any real changes to

patient care. Only by improving the quality of the evidence and make it easier to pool the evidence will we improve the situation in the future.

In chapters 2-4, the reviews of treatments are for a variety of oral ulcerative conditions however the aetiology and clinical presentations of these conditions vary both in severity and potential morbidity. Despite these differences, the problems of heterogeneity of outcome measurements are similar throughout.

The core outcome set project is a step towards to improving the future evidence base. It demonstrates a mixed methodology and staged approach to the development of a consensus agreed set of outcomes. This area of research has grown in popularity over the years of this project, and with that growth there has been an increased complexity to the development of the outcomes sets. The simplistic approach of the COSRAS project made it manageable to process and as such the methodology has been used and adapted for further projects in different conditions.

The development of a core outcome set will act as a baseline for further outcome measures work. The COS development is the 'what to measure' part and further consensus is needed for the 'how to measure' aspects.

Strengths of thesis

This thesis forms a body of work undertaken by a clinician hoping to assess and improve the oral medicine evidence base. The aim was to try and change the output of systematic reviews and allow for more pooling of data from shared research. The research project had to evolve and flex to accommodate the (at the time) new area of core outcome set development. It was the early days of interest around core outcome sets for other dental specialties and the first project of its kind in oral medicine. By involving the oral medicine professional community in the UK in the consensus process and by disseminating the published findings widely

throughout the course of the project, it has increased the awareness of this important research area

The work from this thesis has directly led to the ongoing development of two core outcome set development projects by the WWOM in the topics of oral lichen planus and dry mouth. I am the co-section head of the Lichen Planus group and we are using the methodology from this thesis to guide that process.

Limitations of the thesis

The core outcomes set was a new area of research when it was started and was designed to be a more pragmatic approach to gaining consensus from a variety of stakeholders. The technology to support live interactive consensus processes has improved dramatically and the use of virtual platforms has allowed greater access to wider participation.

The major limitation of this project was the patient participation section of the core outcome set development. As the patient's voice was such an essential part of the project, in retrospect we should have formalised the patient participation as a formal focus group and qualitative study. This would have required ethical approval and the support of an experience qualitative researcher. The project was gaining critical momentum at that stage and, with the invitation to carry out the interactive consensus at the national meeting, the decision was made to proceed with the information meeting as planned.

Implications for future research

The discussion section for the COSRAS chapter explores the potential positives and negatives of the study and it acts as a foundation on which to develop the methodology further. The ongoing work by WWOM to develop a core outcome set for Oral Lichen Planus has used the same three stage approach however with the added improvement of a multicentre qualitative

study for the patient participation element to the project. In addition, the patients will be invited to the final consensus meeting which is planned to be a live interactive process at an international conference.

The final core outcome set included 13 individual outcomes however I have suggested these can be divided into domains to allow for further work on both the timings of the outcomes and the tools of measurements. Alternatively, a traditional Delphi process could be undertaken with a variety of stakeholders including patients to see if the 22 original outcomes is reduced to a similar group of 13. The null hypothesis would be that there was no difference in the core set of outcomes from a traditional Delphi compared to a live interactive clicker Delphi.

Final Conclusions

Core Outcome Sets should be developed for Oral medicine conditions to allow future pooling of data which will lead to a higher quality of evidence base to support clinical care of patients. The Comet-initiative continues to encourage work and research in this area and it is important that this type of research is disseminated widely not only to health researchers but to patients and clinicians as well.

FUTURE WORK

Completing this research also opens the opportunities of a future clinical academic role. None of this would have been possible without the continuous support of my PhD supervisors to whom I am indebted.

This thesis pulls together work carried out over 9 years and the output has been recognised as the introduction of core outcome sets in oral medicine.

As a result of this work, I was selected to be a co-section head of a further outcome set project. Following my involvement in the WWOM in 2014, the need for core outcome sets was recognised. The next WWOM is in Memphis in 2022 and for the first time in the history of WWOM – an agreement to develop 2 core outcome sets was made (this decision moves away from the previous solely systematic review approach). It is widely recognised that until we do something about improving the evidence base, continually reviewing literature without an ability to pool data for meta- analyses, is a waste of time. The clinical topics for the WWOM core outcome sets are OLP and dry mouth and these have been registered with the Comet initiative.

My experience of core outcomes set development has allowed me to lead my group in the OLP outcome set development (alongside my co- section head Dr Jairo Robledo). Our group is diverse with international participants (all selected via competitive process) from Columbia, USA, Spain, UK, Ireland, India, and China. To date we have completed the systematic review and have ethical approval for the patient focus groups. The plan is to carry out interactive consensus process live at the American Academy of Oral Medicine meeting in Memphis, May 2022 (following on from the WWOM).

Following completion of the WWOM projects, my next plan is to look at core outcome sets in head and neck cancer. I have recently been invited to join a regional Head and neck cancer research group (GLAHNC – Glasgow Head and neck cancer) and I look forward to developing relationships and participating in further work in this research area.

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Appendices

APPENDIX 1. Systemic interventions for the management of RAS:

Medline (OVID) Search strategy

1. Stomatitis, aphthous/

2. (recur$ or reoccur$ or severe).ti,ab.

3. 1 and 2

4. ((recur$ or reoccur$ or severe) adj10 ((aphthous or apthous or mouth$ or oral$) adj3 (ulcer$ or lesion$ or stomatitis))).ti,ab.

5. (aphthae or aphthae).ti,ab.

6. "canker sore$".ti,ab.

7. "herpetiform ulcer$".ti,ab.

8. "periadenitis mucosa necrotica recurrens".ti,ab.

9. or/3-8

APPENDIX 2. Systemic interventions for the management of RAS: Characteristics of included studies

Bratel 2005

Methods	Location of trial: Göteburg, Sweden Number of centres: 1 Funding: supported by Paramedical A/S Denmark Trial ID: not stated Type of RCT: parallel Power calculation: not stated
Participants	Source of recruitment: Clinic of Oral Medicine, Public Dental Service of Göteburg, Sweden Age: mean 43.2 years (range = 21 to 68) in LongoVital group; mean 40.4 years (range = 21 to 54) in placebo group Gender: 28 females/22 males (16 females/9 males in LongoVital group; 12 females/13 males in placebo group) Inclusion criteria: at least 30 days of ulcers or at least 3 periods of RAS recurrences during phase 1 Exclusion criteria: not stated Number randomised: 50 Number analysed: 50
Interventions	Comparison: LongoVital versus placebo Gr A (n = 25): LongoVital herbal tablets 3 times per day for 6 months Gr B (n = 25): placebo as for Gr A
Outcomes	Ulcer duration, pain, number, size. Blood analyses (CD4+, CD8+ and CD3+ T cells, S-Asat, S-Alat, S-ALP and S-gamma GT) Duration of follow-up: 6 months treatment
Notes	Pre treatment phase 3 months then treatment phase of 6 months. Reported outcomes at 9 months (end of treatment). Data presented as monthly average for pre-treatment and treatment period

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...stratified according to the minimization method..."
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "...double-blind..." Comment: no description in text
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "...double-blind..." Comment: no description in text
Incomplete outcome data (attrition bias)	Low risk	Minimal drop-out. Unlikely to alter estimate of effect
Selective reporting (reporting bias)	Unclear risk	Insufficient information; some confusion regarding timing of outcome assessment
Other bias	Unclear risk	Potential bias with regards to the use of co-interventions

de Abreu 2009

Methods	Location of trial: São Paulo, Brazil Number of centres: 1 Funding: not stated Trial ID: not stated Type of RCT: parallel Power calculation: not stated
Participants	Source of recruitment: Stomatology Outclinic, Federal University of São Paulo, Brazil Age: range = 15 to 60 years; mean 38 years (SD 2.4) in clofazimine group; mean 34 years (SD 2.6) in colchicine group; mean 45 years (SD 3.4) in placebo group Gender: 68% males Inclusion criteria: aphthous stomatitis episodes associated with intense pain (constant pain and difficulty eating and speaking); no response to topical therapies Exclusion criteria: hypersensitivity to clofazimine or colchicine; cardiac, renal, hepatic, hematologic, and gastrointestinal abnormalities or evidence of underlying systemic diseases such as connective tissue

	diseases, malignant neoplasias, and infections (e.g. HIV); pregnant and lactating women; use of medications which may interact with colchicine (e.g. depressors of bone marrow and central nervous system, sympathomimetics, acidifying or alkalizing agents, and NSAIDs) or with clofazimine (e.g. dapsone, rifampicin, estrogens, and vitamin A); use of medications which may cause a beneficial action on the lesions (e.g. corticosteroids, thalidomide, levamisole, pentoxifylline, or any immunomodulatory agent) Number randomised: 66 Number analysed: varies across outcomes and time points
Interventions	Comparison: clofazimine versus colchicine versus placebo Gr A (n = 23): clofazimine 100 mg daily for 30 days, then 100 mg every other day Gr B (n = 23): colchicine 0.5 mg 3 times per day Gr C (n = 20): placebo pill twice per day
Outcomes	Ulcer number, size, duration, pain intensity; time since last episode (frequency); patient satisfaction; physician rated improvement; adverse events Duration of follow-up: 6 months treatment
Notes	80% of the study sample presented with minor clinical form, 12% with major form, and 8% with herpetiform Data presented as percentages. Number analysed per group at each time point due to exclusions from analysis

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description

Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "...partially blind..." Comment: no description in text
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "A physician who was not aware of the drug regimen of the patients also rated their improvement..." However, the trial arms used different drug regimen so incomplete blinding
Incomplete outcome data (attrition bias)	High risk	No intention-to-treat. Imbalance in drop-outs.
Selective reporting (reporting bias)	High risk	No detail regarding lesion size, despite being listed as outcome assessed
Other bias	Unclear risk	No comparison at baseline

De Cree 1978

Methods	Location of trial: Antwerp, Belgium Number of centres: 1 Funding: not stated Trial ID: not stated Type of RCT: parallel Power calculation: not stated
Participants	Source of recruitment: Clinical Research Unit, St Bartholomeus Age: median 25 years (range = 14 to 72) in levamisole group; median 30 years (range = 14 to 74) in placebo group Gender: 13 females/5 males (6 females/3 males in levamisole group; 7 females/2 males in placebo group) Inclusion criteria: history of at least 1 aphthous lesion per month during the preceding year Exclusion criteria: not stated Number randomised: 18 Number analysed: 18
Interventions	Comparison: levamisole versus placebo

	Gr A (n = 9): 50 mg levamisole tablet (patients received coded vial containing 27 tablets and, when a RAS episode began, took 1 tablet 3 times per day for 3 consecutive days, provided at least 2 weeks had elapsed since the previous drug period. Therefore there was enough medication to allow evaluation of 3 treatment episodes per patient. No patient received any concurrent medications Gr B (n = 9): placebo as for Gr A (all tablets identical in appearance)
Outcomes	Median time interval between treatment periods (frequency); median duration of aphthous episodes; pain Duration of follow-up: "Total duration of the study period to cross-over (that is, the median time required for three RAS episodes to occur) was 95 (49 to 46 1) days for the levamisole group and 50 (45 to 75) days for the placebo group"
Notes	Exclusion of participants with systemic disease not explicit

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias)	Low risk	Quote: "...all tablets were identical in appearance..."
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "...double-blind..." Comment: no description in text
Incomplete outcome data (attrition bias)	Unclear risk	Unclear whether there were any drop-outs
Selective reporting (reporting bias)	High risk	Pain not reported
Other bias	Unclear risk	No other apparent biases but poorly reported study

Drinnan 1978

Methods	Location of trial: Buffalo, USA Number of centres: 1 Funding: supported by Janssen R & D, Inc, New Jersey, USA Trial ID: not stated Type of RCT: parallel Power calculation: not stated
Participants	Source of recruitment: patients were either under the care of one of the clinical investigators or were referred by their physicians or dentists to the Department of Oral Medicine of the School of Dentistry at the State University of New York at Buffalo specifically for the study Age: range = 9 to 65 Gender: 19 females/11 males Inclusion criteria: documented history of at least 3 previous episodes of RAS; normally experienced at least 6 episodes during a 12-month period; able to take tablets Exclusion criteria: pregnant; suffering from any chronic debilitating disease; receiving antibiotic or steroid medication; suffered from continuous or persistent oral ulcerations i.e. were "never free" of ulcers Number randomised: 30 Number analysed: 24
Interventions	Comparison: levamisole versus placebo Gr A (n = 11): 150 mg levamisole to be taken daily for 3 days at onset of first prodromal symptoms of an ulcer (total of 450 mg per 3-day period) *, ** Gr B (n = 13): placebo as for Gr A * Dose adjusted to not exceed 2.5 mg/kg per day for those weighing less than 70 kg ** Medication was not to be repeated within 1 week and a second 3-day course was only to be started for a newly developing ulcer
Outcomes	Ulcer number and duration; interval between episodes (frequency); pain; adverse events ¬ Duration of follow-up: follow-up dependant on when patients took medication
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The code for identifying active and placebo tablets, which looked identical, were kept in individually marked containers"
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "...double-blind..." Comment: no description in text
Incomplete outcome data (attrition bias)	High risk	4/15 in active group and 2/15 in placebo group not evaluated
Selective reporting (reporting bias)	High risk	Pain not reported. Standard deviations not reported. Duration of lesions not reported for all visits
Other bias	High risk	Some patients reported continuous ulcers so unable to assess ulcer-free time. The mean number of days between episodes was greater in the placebo group than in the active group

Femiano 2003

Methods	Location of trial: Naples, Italy Number of centres: 1 Funding: not stated Trial ID: not stated Type of RCT: parallel Power calculation: not stated
Participants	Source of recruitment: Stomatology Clinic, School of Medicine and Surgery, II University of Naples, Italy Age: median 32 years; range = 21 to 48

	Gender: 24 females/6 males Inclusion criteria: frequent minor RAS over more than 4 months; at least 3 episodes of aphthae each month; no abnormal findings on investigation; failed to respond to conventional topical therapies (usually corticosteroids) Exclusion criteria: not stated Number randomised: 30 Number analysed: 30
Interventions	Comparison: sulodexide versus prednisone versus placebo Gr A (n = 10): sulodexide ULS 250 orally twice per day for 1 month, then once per day for 1 month Gr B (n = 10): oral prednisone 25 mg in the morning for 1 week, then dose reduction as follows: 20 mg in weeks 2 and 3; 15 mg in weeks 4 and 5; 10 mg in weeks 6 and 7; 5 mg in week 8 Gr C (n = 10): placebo (cellulose starch 100 mg) as for Gr A
Outcomes	Days to pain cessation (patient assessed VAS); days to ulcer epithelialization (patient assessed); number of new aphthae; adverse events (recorded by patient) ¬ Duration of follow-up: 4 months (2 months treatment, 2 months follow-up)
Notes	Reported at ulcer level with no estimate of variability. Also authors report p values for t-tests despite three arm trial. Not clear which comparisons are being referred to with the p value results

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "...double-blind..." Comment: treatment B differs

Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "...double-blind..." Comment: treatment B differs
Incomplete outcome data (attrition bias)	Low risk	Quote: "no drop-outs"
Selective reporting (reporting bias)	High risk	Number of days to pain cessation measured using VAS but pain intensity not reported
Other bias	Unclear risk	Potential imbalance with regard to gender

Femiano 2010

Methods	Location of trial: Naples, Italy Number of centres: 1 Funding: not stated Trial ID: not stated Type of RCT: parallel Power calculation: not stated
Participants	Source of recruitment: Stomatology Clinic, School of Medicine and Surgery, II University of Naples, Italy Age: median 26 years; range = 18 to 48 Gender: 38 females/22 males (10 females/10 males in prednisone group; 12 females/8 males in montelukast group) Inclusion criteria: history of RAS for minimum 6 months with average of 2 outbreaks per month and 2 to 3 aphthae per outbreak; previous reporting in patient's clinical history of oral pain and discomfort during outbreaks; unresponsive to topical betamethasone dipropionate ointment therapy used for 2 weeks or difficulty applying topical ointment Exclusion criteria: altered hematological parameters; gastrointestinal diseases; endocrine system disorders; local oral factors which could favour the appearance of aphthae; other medications taken usually or occasionally (NSAIDS, activators of adenosine triphosphate-sensitive potassium [nicorandil], angiotensin-converting enzyme inhibitors, and antiarrhythmics) Number randomised: 60

	Number analysed: unclear
Interventions	Comparison: prednisone versus montelukast (leukotriene receptor antagonist) versus placebo ¬ Gr A (n = 20): oral prednisone 25 mg per day for 15 days, then 12.5 mg per day for 15 days, then 6.25 mg per day for 15 days, then 6.25 mg on alternate days for 15 days Gr B (n = 20): oral montelukast 10 mg every evening for first month and then on alternate days for the second month Gr C (n = 20): placebo (cellulose) 100 mg every day for first month and then on alternate days for the second month
Outcomes	Number of lesions per month; pain;efficacy on time to resolution; adverse events ¬ Duration of follow-up: 4 months (2 months treatment, 2 months follow-up)
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...random number generator program on a computer..."
Allocation concealment (selection bias)	Low risk	Quote: "...different operator...allocated patients"
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "...an identical white container..." However, the trial arms used different drug regimen so incomplete blinding
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "All patients and all subsequent investigators...did not know the therapy used for each group" However, the trial arms used different drug regimen so incomplete blinding
Incomplete outcome data (attrition bias)	Low risk	No patient drop-out
Selective reporting (reporting bias)	Unclear risk	Important outcomes reported but not for all time points

Other bias	Unclear risk	Imbalance in gender between groups

Graykowski 1978

Methods	Location of trial: Bethesda, USA Number of centres: 1 Funding: not stated Trial ID: not stated Type of RCT: parallel Power calculation: not stated
Participants	Source of recruitment: volunteers referred to the clinical section of the Laboratory of Oral Medicine (National Institute of Dental Research, National Institutes of Health, Bethesda, Maryland, USA) by private practitioners of medicine and dentistry. Age: < 36 years (5 in tetracycline group/8 in placebo group); > 35 years (6 in tetracycline group/6 in placebo group) Gender: 14 females/11 males (4 females/7 males in tetracycline group; 10 females/4 males in placebo group) Inclusion criteria: willing to keep daily ulcer record charts and weekly appointments for 20 weeks; RAS for at least 1 year and not free of ulcers for longer than 2 weeks during the preceding 6 months Exclusion criteria: presence of any other mucous membrane ulcerative disease or a skin disease possibly associated with oral lesions; finding of any physical or mental abnormality by the examining physician which would interfere with or be affected by the study procedures Number randomised: 35 Number analysed: 25
Interventions	Comparison: tetracycline versus placebo ¬ Gr A (n = 11): tetracycline suspension 5 ml teaspoon containing 250 mg tetracycline held in the mouth for 2 minutes and then swallowed, 4 times per day at new ulcer outbreak, and continue for 20 doses (5 days). Also instructed not to take anything orally for 30 minutes following each treatment

	Gr B (n = 14): placebo as for Gr A
Outcomes	Ulcer duration, pain, number, size ¬ Duration of follow-up: 12 weeks
Notes	Selection of patients was not based on the severity of their disease Patients were not divided according to the predominant type of ulceration - major or minor Exclusion of participants with systemic disease not explicit Reported at ulcer level

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A pharmacist dispensed the medication according to a series of random numbers prepared by the statistician"
Allocation concealment (selection bias)	Low risk	Quote: "A pharmacist dispensed the medication according to a series of random numbers prepared by the statistician. Numbers were assigned consecutively to the patients at the beginning of the study"
Blinding of participants and personnel (performance bias)	Low risk	Placebo suspension
Blinding of outcome assessment (detection bias)	Unclear risk	No description
Incomplete outcome data (attrition bias)	High risk	10 out of 35 patients dropped out; unclear as to which group they were assigned
Selective reporting (reporting bias)	High risk	Adjusted means only
Other bias	Unclear risk	Analysis at ulcer level with no accounting for cluster

Hamazaki 2006

Methods	Location of trial: Toyamama, Japan Number of centres: 1 (please check as AMG put 2) Funding: Science and Technology Agency of Japan Trial ID: not stated Type of RCT: parallel Power calculation: not stated
Participants	Source of recruitment: internet/newspaper adverts Age: mean 42 years (range = 21 to 70) Gender: 22 females/8 males Inclusion criteria: minor RAS at least once per month Exclusion criteria: allergy and/or autoimmunity Number randomised: 33 Number analysed: 30
Interventions	Comparison: perilla cooking oil versus soybean cooking oil Gr A (n = 17): perilla oil as only cooking oil Gr B (n = 16): soybean oil as only cooking oil Recruited participants were asked to maintain their body weight and physical activity levels
Outcomes	Prevalence of minor RAS, resolution, fatty acid/dietary analysis, adverse effects ¬ Duration of follow-up: 8 months treatment
Notes	Unclear if ulcer or patient level data Summary data for prevalence of aphthae not available, presented as figures only

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description

Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "...double-blind..." Comment: no description in text
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "...double-blind..." Comment: no description in text
Incomplete outcome data (attrition bias)	Low risk	3/30 patients not included in analysis but reasons given and unlikely to alter findings
Selective reporting (reporting bias)	Unclear risk	Not all important outcomes reported
Other bias	Low risk	No other apparent biases

Kolseth 2005

Methods	Location of trial: Oslo, Norway Number of centres: 1 Funding: supported by Paramedical A/S Denmark Trial ID: not stated Type of RCT: parallel Power calculation: not stated
Participants	Source of recruitment: national newspaper and patient register of Faculty of Dentistry, University of Oslo, Norway Age: mean 42 years (range = 16 to 75) Gender: 32 females/20 males Inclusion criteria: minor RAS based on disease history and clinical inspection during a 60-day introduction period (at least 1 attack during this period) Exclusion criteria: no severe physical or psychological illness, or oral disease apart from RAS; patients who had taken LongoVital or any other systemic medication for RAS in the preceding 3 months Number randomised: 60 Number analysed: 52

Interventions	Comparison: LongoVital (vitamin/herbal supplement) versus LongoVital (herbal component alone) versus placebo Gr A (n = 20): LongoVital (vitamin/herbal supplement) - 3 tablets each morning Gr B (n = 20): LongoVital (herbal component alone) - 3 tablets each morning Gr C (n = 20): placebo - 3 tablets each morning
Outcomes	Ulcer-free days, new ulcers, immunological parameters, patient's preference ¬ Duration of follow-up: 8 months (4 months treatment, 4 months follow-up)
Notes	Summary data reported as medians with 95% CI

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The tablets were coated to make them indistinguishable from each other"
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "...double-blind..." Comment: no description in text
Incomplete outcome data (attrition bias)	Unclear risk	2/20, 4/20 and 2/20 patients withdrew from group A, B and C respectively. 4 of the withdrawals in group A and B were due to indigestion
Selective reporting (reporting bias)	High risk	Pain not reported
Other bias	High risk	Use of alleviating drugs, mainly corticosteroids and antiseptic mouthwash. Study was supported by Paramedical A/S, Denmark

Koray 2009

Methods	Location of trial: Turkey Number of centres: 1 Funding: not stated Trial ID: not stated Type of RCT: parallel Power calculation: not stated
Participants	Source of recruitment: not stated Age: mean 42.6 years Gender: not stated Inclusion criteria: not stated Exclusion criteria: presence of any significant local or systemic disease Number randomised: 31 Number analysed: 31
Interventions	Comparison: beta-glucan versus placebo Gr A (n = 21): 10 mg 1.3 to 1.6 beta-glucan twice per day for 20 days Gr B (n = 10): placebo as for Gr A
Outcomes	Ulcer severe score (USS compound scale of number, duration, ulcer-free days, site and pain); lymphocyte proliferation ¬ Duration of follow-up: 20 days treatment
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description

Blinding of participants and personnel (performance bias)	Unclear risk	No description
Blinding of outcome assessment (detection bias)	Unclear risk	No description
Incomplete outcome data (attrition bias)	Low risk	All randomised participants included in analysis
Selective reporting (reporting bias)	Unclear risk	Compound score
Other bias	Unclear risk	Study reported as letter to editor; little information provided

Lalla 2012

Methods	Location of trial: Connecticut, USA Number of centres: 1 Funding: The Patrick and Catherine Weldon Donaghue Medical Research Foundation, NIH General Clinical Research Center and NIH career development grant Trial ID: not stated Type of RCT: parallel Power calculation: sample size of at least 50 participants per group (after accounting for drop-outs) needed to detect at least 65% probability that those receiving multivitamin intervention had a better outcome to those receiving placebo; power = 0.80 at 5% significance level
Participants	Source of recruitment: from general population of Hartford County, Connecticut, via flyers, emails to health center community and advertisements in local newspapers Age: range = 18 to 72 Gender: 104 females/56 males Inclusion criteria: validated history of at least three episodes of idiopathic minor RAS within the previous twelve months Exclusion criteria: smoking, pregnancy, regular use of vitamin supplements or any over the counter or prescription agents for RAS, and a diagnosis of a systemic condition that can cause oral ulceration Number randomised: 160 Number analysed: 160 (analysis on intention-to-treat basis despite 25 drop-outs in Gr A and 21 in Gr B)

Interventions	Comparison: multivitamin versus placebo (lactose powder) Gr A (n = 83): generic multivitamin supplement containing the US reference daily intake of essential vitamins A, B1, B2, B3, B5, B6, B9, B12, C, D, D, E Gr B (n = 77): placebo as for Gr A
Outcomes	Primary: number and duration of RAS episodes during the 1-year study period Secondary: mouth pain and normalcy of diet
Notes	Compliance an issue

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-based pseudorandom number generator"
Allocation concealment (selection bias)	Low risk	Quote: "research pharmacist assigned participants..." and "kept confidential records of study drug assignment..."
Blinding of participants and personnel (performance bias)	Low risk	Identical placebo
Blinding of outcome assessment (detection bias)	Low risk	"research pharmacist assigned participants..." and "kept confidential records of study drug assignment...", "not accessible to study investigators during the study"
Incomplete outcome data (attrition bias)	Low risk	25/83 participants in the intervention group and 21/77 participants in the placebo group dropped-out. Reasons not stated but analysis carried out on intention-to-treat basis
Selective reporting (reporting bias)	Low risk	Important outcomes reported
Other bias	Low risk	No other apparent biases

Lu 2004

Methods	Location of trial: Beijing, China Number of centres: 1 Funding: not stated Trial ID: not stated Type of RCT: parallel Power calculation: not stated
Participants	Source of recruitment: patients attending the China-Japan Friendship Hospital between January 2002 and September 2002 Age: range = 14 to 65 (no mean or SD reported) Gender: 39 females/21 males Inclusion criteria: patients diagnosed with RAS Exclusion criteria: severe RAS; Behçet's disease; anaemia; peptic ulcer; acute infective disease; autoimmune disease; taken analgesics within 24 hours; taken antibiotics within 1 month; taken steroids or immunosuppressants within 3 months Number randomised: 60 Number analysed: 60
Interventions	Comparison: rofecoxib versus tinidazole (control) Gr A (n = 30): oral rofecoxib for 4 days - 50 mg on first day and 25 to 50 mg per day on the following days Gr B (n = 30): oral tinidazole 1 g per day for 3 days
Outcomes	Total effective rate; pain intensity (VAS); ulcer size (diameter); diet scores Duration of follow-up: 4 days treatment
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description

Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "...single-blind..." Comment: no description in text
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "...single-blind..." Comment: no description in text
Incomplete outcome data (attrition bias)	Low risk	All patients included in analysis
Selective reporting (reporting bias)	High risk	Only reported on pain
Other bias	Unclear risk	Length of treatment time differs between groups

Meyer 1977

Methods	Location of trial: Deurne, Belgium Number of centres: 1 Funding: Janssen Pharmaceutica supplied the samples Trial ID: not stated Type of RCT: parallel Power calculation: not stated
Participants	Source of recruitment: not clearly stated Age: median 41 years; range = 14 to 68 Gender: 87 male/37 female Inclusion criteria:Had suffered RAS for years, at least one episode per month Exclusion criteria: not discussed Number randomised: 124 Number analysed: 124
Interventions	Comparison: levamisole versus placebo Gr A (n = 75): 50 mg levamisole Gr B (n = 49): placebo as for Gr A
Outcomes	Number of RAS episodes per month; duration of episodes; number of lesions per episode; pain; changes in diameter of lesions

	¬ Duration of follow-up: end of each month, complete study 4 months
Notes	Exclusion of participants with systemic disease not explicit Cumulative data rather than month/month

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Tablets looked identical and were supplied in identical coded bottles"
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "...double-blind..." Comment: no description in text
Incomplete outcome data (attrition bias)	High risk	9 drop-outs but no discrepancies between groups (levamisole: 4/32; placebo: 5/39); however, no pain data at month 4 for 7/39 in placebo group compared to 2/32 in the active group
Selective reporting (reporting bias)	Low risk	Main outcomes reported
Other bias	High risk	Imbalance in gender and smoking habits between groups at baseline

Miller 1978

Methods	Location of trial: Pennsylvania, USA Number of centres: 1 Funding: grants from Janssen Pharmaceutical Company and National Institutes of Health, National Research Service Award

	Trial ID: 1 T32 DE07036 Type of RCT: parallel Power calculation: not stated
Participants	Source of recruitment: Department of Oral Medicine, University of Pennsylvania, Philadelphia, USA Age: mean 38.7 years Gender: 15 females/5 males Inclusion criteria: severe RAS defined as minimum of 12 episodes per year; previous visual confirmation of oral lesions; no self-referrals; older than 18 years of age Exclusion criteria: evidence of concomitant disease or any condition which may be contributory to the ulcers Number randomised: 32 Number analysed: 20
Interventions	Comparison: levamisole versus placebo Gr A (n = 10): levamisole 150 mg for 11 days followed by 11 day period of no drug intake. This 2-week schedule was continued for duration of treatment (with reduction of dosage as required) Gr B (n = 10): placebo as for Gr A
Outcomes	Mean number of ulcers; duration ¬ Duration of follow-up: minimum 9 week treatment (unclear)
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Third party
Allocation concealment (selection bias)	Low risk	Third party

Blinding of participants and personnel (performance bias)	Low risk	Quote: "...neither of the investigators directly involved in patient management had access to the code book..."
Blinding of outcome assessment (detection bias)	Low risk	Code not known by outcomes assessor
Incomplete outcome data (attrition bias)	High risk	Only subjects who participated for at least 9 weeks were included in the analysis
Selective reporting (reporting bias)	Unclear risk	Pain not reported
Other bias	High risk	Difference in mean number of days in study. Gender imbalance at baseline

Mousavi 2009

Methods	Location of trial: Tehran, Iran Number of centres: 1 Funding: not stated Trial ID: not stated Type of RCT: parallel Power calculation: not stated
Participants	Source of recruitment: patients referred to the Oral Medicine Clinic of Tehran University, Iran, from March 2002 to March 2004 Age: not stated Gender: not stated Inclusion criteria: 18 to 65 years old; presented with 1 to 5 aphthous ulcers of less than 24-hours duration; more than 5 episodes in the preceding year; ulcers diameter was not greater than 6 mm; not suffering from acute or chronic diseases of the oral mucosa Exclusion criteria: concurrent clinical conditions; ulcers as a manifestation of a systemic disease process such as ulcerative colitis, Crohn's disease, Behçet's disease, or serious anaemia; history of alcohol or drug abuse; taking any narcotic analgesics; history of systemic immunosuppressive therapy Number randomised: 100 Number analysed: 100

Interventions	Comparison: homeopathic medicine (individually tailored for each patient) versus placebo (identical sucrose globules) Gr A (n = 50): single dose of homeopathic medicine in 6C dilution, in liquid form, diluted in 100 ml of water. The same dose was repeated after 12 hours Gr B (n = 50): single placebo globule diluted in 100 ml of water and repeated after 12 hours
Outcomes	Ulcer size (clinical measurement); pain (VAS) - both measures converted to an efficacy index (EI) calculated as a percentage of the baseline value and evaluated on a 4-rank scale: Healed: EI = 100% Marked improvement: 70 to 99% Moderate improvement: 30 to 69% No improvement: < 30% ¬Duration of follow-up: intervention on day 1 with follow-up on days 4 and 6
Notes	Individually tailored homeopathic treatments Summary data for pain score and ulcer size presented as figure only

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...computer generated random list..."
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias)	Low risk	Patients-only blinded
Blinding of outcome assessment (detection bias)	High risk	Outcomes assessment carried out by investigators
Incomplete outcome data (attrition bias)	Low risk	No drop-outs
Selective reporting (reporting bias)	Low risk	Main outcomes reported

Other bias	Low risk	No other apparent biases

Olson 1978

Methods	Location of trial: San Francisco, USA Number of centres: 1 Funding: Janssen R & D Inc supplied levamisole Trial ID: not stated Type of RCT: parallel Power calculation: not stated
Participants	Source of recruitment: patients referred to the Oral Medicine Clinic, University of California, San Francisco, USA Age: not stated Gender: 27 females/21 males Inclusion criteria: RAS attacks at least every other month Exclusion criteria: not stated Number randomised: 48 Number analysed: 48
Interventions	Comparison: levamisole versus placebo Gr A (n = 23): single dose of 1 tablet (50 mg per tablet) repeated 3 times per day for 3 days. Dosage was not repeated more often than weekly. New lesion had to be present to re institute therapy. Each patient repeated schedule for the course of 6 episodes of aphthae. Patients took no concurrent medication for their condition Gr B (n = 25): identical placebo as for Gr A
Outcomes	Days between attacks (frequency); duration; pain (self-assessed); investigator's clinical evaluation of patient's subjective treatment response ¬ Duration of follow-up: variable
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias)	Low risk	Quote: "...active and placebo tablets were obviously identical except for the presence or absence of levamisole"
Blinding of outcome assessment (detection bias)	Low risk	Quote: "...codes broken when the patient completed the sixth episode of double-blind medication"
Incomplete outcome data (attrition bias)	Unclear risk	Quote: "...patients who had been on levamisole continued if they had experienced improvement and were dropped from the study if they had not"
Selective reporting (reporting bias)	Low risk	Main outcomes reported
Other bias	High risk	Confusion regarding dropping of patients, plus "most people assessed for 4 of 6 episodes"

Pakfetrat 2010

Methods	Location of trial: Tehran and Mashhad, Iran Number of centres: 2 Funding: not stated Trial ID: not stated Type of RCT: parallel Power calculation: sample size of 17 patients in each group, power = 0.80
Participants	Source of recruitment: oral medicine clinics of 2 universities including Tehran and Mashhad dental schools

	Age: mean 31 years Gender: 22 females/12 males Inclusion criteria: history of RAS (at least 3 episodes per month); unresponsive to conventional topical treatments; no medication taken to treat RAS in 2 weeks prior to beginning of the study; 18 years or over; normal biochemical screening Exclusion criteria: previous medical history of systemic disease; taken medication which may affect the immune system; involvement of other mucous membranes Number randomised: 34 Number analysed: 34
Interventions	Comparison: colchicine versus prednisolone Gr A (n = 17): 0.5 mg colchicine per day for 3 months Gr B (n = 17): 5 mg prednisolone per day for 3 months
Outcomes	Size; number of lesions; recurrence; intensity of pain; burning sensation; side effects ¬ Duration of follow-up: 12 weeks treatment, assessed at 2-week intervals
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "To guarantee blinding a random number was generated for each participant using SPSS software"
Allocation concealment (selection bias)	Low risk	Quote: "Patients were referred to the pharmacist to pick up their assigned medication according to their number"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "All tablets were enclosed in identical sealed dark boxes"

Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "...double-blind..." Comment: no description in text
Incomplete outcome data (attrition bias)	Low risk	All patients included in analysis
Selective reporting (reporting bias)	Low risk	Main outcomes reported
Other bias	Low risk	No other apparent biases

Pourahmad 2010

Methods	Location of trial: Jahrom, Iran Number of centres: 1 Funding: Shifoo Company produced camel thorn distillate (intervention); financial support from Jahrom University of Medical Sciences Trial ID: not stated Type of RCT: parallel Power calculation: not stated
Participants	Source of recruitment: patients presenting to the Internal Medicine Clinic at Jahrom University of Medical Sciences for evaluation and treatment of RAS Age: mean 27.4 years in camel thorn group; mean 31.8 years in placebo group Gender: 44 females/49 males (22 females/27 males in camel thorn group; 22 females/22 males in placebo group) Inclusion criteria: an aphthous lesion on oral mucosa and history of recurrent similar lesions Exclusion criteria: presence of the lesion for more than 3 days prior to presentation; use of medication prior to presentation; Behçet's disease or other autoimmune disorder (or history of); lack of compliance with/discontinuation of study drug; long distance between the patient's home and clinic (which may affect ability to return for follow-up visits); children or very elderly (unlikely to be able reliably report severity of pain); if lesions were suspected to be herpes simplex ulcers Number randomised: 93 Number analysed: 93
Interventions	Comparison: camel thorn distillate versus placebo (distilled water)

	Gr A (n = 49): 40 ml solution 4 times per day until complete resolution of symptoms (drug held in the mouth for 1 minute and then swallowed) Gr B (n = 44): placebo as for Gr A
Outcomes	Size of lesions (diameter); pain intensity (0 to 10 numerical rating scale); time to complete resolution of symptoms (when lesion diameter and pain = 0); side effects ¬ Duration of follow-up: up to 14 days (or complete resolution if sooner)
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	Quote: "...patient was sent to pharmacy to obtain their study drug" Comment: unclear if allocation was concealed
Blinding of participants and personnel (performance bias)	Low risk	Quote: "...solutions were placed in identical containers"
Blinding of outcome assessment (detection bias)	Unclear risk	No description
Incomplete outcome data (attrition bias)	Unclear risk	Insufficient information regarding patients analysed
Selective reporting (reporting bias)	Low risk	Main outcomes reported
Other bias	Low risk	No other apparent biases

Preshaw 2007

Methods	Location of trial: Newcastle, UK

	Number of centres: 1 Funding: not stated Trial ID: not stated Type of RCT: parallel Power calculation: power = 0.85 for 20 participants in each group
Participants	Source of recruitment: patients presenting with long-term history of RAS at the Oral Medicine Clinic at Newcastle Dental Hospital Age: mean 40 years (range = 18 to 64) Gender: 32 females/18 males Inclusion criteria: history of RAS necessitating appointments on oral medicine clinic more than 2 times per year Exclusion criteria: deficiencies in serum ferritin, vitamin B12 and/or folate; pregnant or nursing (lactating) women; known hypersensitivity to tetracyclines; women of child-bearing potential not taking adequate contraceptive precautions; taking clinically significant concomitant drugs; patients with diabetes mellitus, systemic infection, kidney or liver disease; patients requiring prophylactic antibiotic coverage for routine dental therapy Number randomised: 50 Number analysed: 50
Interventions	Comparison: subantimicrobial dose doxycycline versus placebo (identical in appearance) Gr A (n = 25): subantimicrobial dose doxycycline 20 mg twice daily for 90 days Gr B (n = 25): placebo as for Gr A
Outcomes	Number of new ulcers; pain (VAS); additional ulcer treatment ¬ Duration of follow-up: 90 days treatment
Notes	Data presented at 90-day end of treatment and over treatment period

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A predetermined computer generated randomisation schedule"
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Placebo and SDD tablets were identical in appearance"
Blinding of outcome assessment (detection bias)	Low risk	Patient reported outcomes
Incomplete outcome data (attrition bias)	Low risk	All patients included in analysis
Selective reporting (reporting bias)	Low risk	Main outcomes reported
Other bias	High risk	Quote: "All subjects were permitted to use any additional ulcer management therapies at any time during the study" Pharma as co-author

Samet 2007

Methods	Location of trial: Boston, USA Number of centres: 1 Funding: not stated Trial ID: IRB #M10778-101 Type of RCT: parallel Power calculation: not stated (pilot study)
Participants	Source of recruitment: patients presenting for treatment at Harvard School of Dental Medicine clinics, members of the local community, and word-of-mouth referrals, recruited over a 10-month period Age: not stated (at least 18 years old at the time of enrolment) Gender: not stated

	Inclusion criteria: at least 18 years old at the time of enrolment; RAS not associated with other conditions (e.g. anaemia, vitamin deficiencies, inflammatory bowel disease, celiac disease, Behçet's disease, Reiter's disease, or HIV-associated immunosuppression) Exclusion criteria: history of allergy to propolis, bee products, or bee sting Number randomised: 19 Number analysed: 19
Interventions	Comparison: bee propolis versus placebo (calcium-based food supplement) Gr A (n = 10): bee propolis 1 capsule (500 mg) per day Gr B (n = 9): placebo as for Gr A Patients asked not to use any other product for the prevention or treatment of aphthous ulcers while participating in this study
Outcomes	Frequency of RAS outbreaks (self-reported); number of new ulcers; duration; subjective severity (1 to 10 scale); patient-reported improvement in quality of life ¬ Duration of follow-up: 6 months treatment (minimum i.e. some were longer)
Notes	Pilot study

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias)	Low risk	Quote: "neither the participants nor the investigators knew the identity of the product distributed"
Blinding of outcome assessment (detection bias)	Low risk	Quote: "neither the participants nor the investigators knew the identity of the product distributed"

Incomplete outcome data (attrition bias)	Unclear risk	Uneven drop-outs; unclear if intention to treat analysis undertaken
Selective reporting (reporting bias)	High risk	Duration and perceived severity of ulcers not reported
Other bias	Low risk	No other apparent biases

Thornhill 2007

Methods	Location of trial: Manchester, UK Number of centres: 1 Funding: Hoechst Marion Roussel provided pentoxifylline and matching placebo tablets Trial ID: NCT00315679 Type of RCT: parallel Power calculation: not stated
Participants	Source of recruitment: posters in offices or surgical areas of general medical and general dental practitioners in the Greater Manchester area, then screened for suitability using standardised telephone questionnaire Age: overall range = 18 to 55 years; overall mean 33 years (SD 10.2); mean 34 years (SD 8.1) in pentoxifylline group (range = 21 to 55); mean 33 years (SD 12.6) in placebo group (range 18 to 53) Gender: 17 females/9 males (9 females/5 males in pentoxifylline group; 8 females/4 males in placebo group) Inclusion criteria: more than 2 ulcers per month for more than 6 months; no current treatment for ulceration or a willingness to stop the current treatment; aged 16 to 65 years; not taking ketorolac, theophylline or antihypertensive medications except diuretics (contraindicated in patients taking pentoxifylline); no underlying systemic conditions which would contraindicate taking pentoxifylline (e.g. pregnancy, hypotension, ischaemic heart disease, allergy to pentoxifylline, etc) Exclusion criteria: see inclusion criteria Number randomised: 26 Number analysed: 26 (intention-to-treat analysis)
Interventions	Comparison: pentoxifylline versus placebo (identical) Gr A (n = 14): 400 mg tablet of pentoxifylline 3 times per day with food for 60 days

	Gr B (n = 12): placebo as for Gr A
Outcomes	Ulcer number; size; number of episodes; pain (10-point scale) ¬ Duration of follow-up: 180 days (60 days treatment and 60 days follow-up)
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer generated random number"
Allocation concealment (selection bias)	Low risk	Third party allocation
Blinding of participants and personnel (performance bias)	Low risk	Quote: "drug and placebo control...identical oblong pink tablets"
Blinding of outcome assessment (detection bias)	Low risk	Quote: "trial number not released by pharmacy until after the study had been completed"
Incomplete outcome data (attrition bias)	Low risk	Intention-to-treat analysis undertaken
Selective reporting (reporting bias)	High risk	Compound score
Other bias	Low risk	No other apparent biases

Van de Heyning 1978

Methods	Location of trial: Turnhout, Belgium Number of centres: not stated/unclear Funding: not stated Trial ID: not stated

	Type of RCT: parallel Power calculation: not stated
Participants	Source of recruitment: not stated Age: mean 33.6 years in levamisole group (range = 20 to 53); mean 32.8 years in placebo group (range = 18 to 45) Gender: 9 females/4 males (5 females/2 males in levamisole group; 4 females/2 males in placebo group) Inclusion criteria: at least 1 aphthous lesion per month in the preceding year Exclusion criteria: not stated Number randomised: 13 Number analysed: 13
Interventions	Comparison: levamisole versus placebo (identical) Gr A (n = 7): levamisole 50 mg 3 times per day for 3 consecutive days, repeated every other week for 2 months (36 tablets given to each participant) Gr B (n = 6): placebo as for Gr A
Outcomes	Ulcer frequency; duration; number; pain (all recorded by patient on a diary card) ¬ Duration of follow-up: 2 months treatment
Notes	Exclusion of participants with systemic disease not explicit

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "...double-blind..." Comment: insufficient description in text

Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "...double-blind..." Comment: insufficient description in text
Incomplete outcome data (attrition bias)	Low risk	No drop-outs
Selective reporting (reporting bias)	Low risk	Main outcomes reported
Other bias	Low risk	No other apparent biases

Volkov 2009

Methods	Location of trial: the Negev, Israel Number of centres: not stated/unclear Funding: Solgar (pharmaceutical company) provided "partial funding" Trial ID: not stated Type of RCT: parallel Power calculation: power = 0.80 for 24 participants in each group (given the assumption of a 'no aphthous ulcers status' of 73% among patients in the intervention group and 30% of those in control group)
Participants	Source of recruitment: personal letters sent by email from 20 family physicians Age: mean 33.1 years (SD 9.57) in vitamin B12 group (range = 21 to 62); mean 29.15 years (SD 6.61) in placebo group (range = 18 to 47) Gender: 29 females/29 males (15 females/16 males in vitamin B12 group; 14 females/13 males in placebo group) Inclusion criteria: older than 18 years; suffering from RAS for at least 1 year (at least 1 outbreak every 2 months) Exclusion criteria: known systemic diseases concurrent with lesions in the mouth (Behçet's disease, rheumatoid arthritis, lupus, AIDS); received treatment with vitamin B12 in any form for the last year; received other concurrent treatment for aphthous ulcers; were pregnant or nursing; had Leber's optic atrophy; suffered from psychosis; or had a known vitamin B12 deficiency Number randomised: 58 Number analysed: 52

Interventions	Comparison: sublingual vitamin B12 versus placebo (same ingredients except for the vitamin B12) Gr A (n = 27): vitamin B12 1000 mcg in a 100 mg tablet once daily before going to sleep for 6 months Gr B (n = 25): placebo as for Gr A
Outcomes	Average duration (days) of an aphthous stomatitis episode; monthly number of aphthous ulcers; severity of pain (patient assessed) according to the Numerous Rating Scale (NRS); side effects Duration of follow-up: 6 months treatment (with monthly follow-up)
Notes	Unclear if mean or median data presented. No variance presented

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...batch numbers generated by a computer program"
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The physicians and the participants were blinded to the group assignment until the study ended", "...types of tablets were the same in shape, size, color, and flavor"
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The physicians and the participants were blinded to the group assignment until the study ended"
Incomplete outcome data (attrition bias)	Low risk	27/31 in the intervention group and 25/27 in the placebo group completed the study, therefore no discrepancies in drop-out between groups
Selective reporting (reporting bias)	Low risk	Main outcomes reported
Other bias	Unclear risk	Quote: "Solgar pharmaceutical company provided partial funding for this study"

Weckx 2009

Methods	Location of trial: São Paulo, Brazil Number of centres: 1 Funding: unknown (translated) Trial ID: unknown (translated) Type of RCT: parallel Power calculation: not stated
Participants	Source of recruitment: patients presenting with recurrent aphthae at the Stomatology Outpatient Sector of the Federal University of São Paulo/Paulista School of Medicine Age: mean 39.1 years in levamisole group (range = 17 to 83); mean 25.9 years in placebo group (range = 12 to 46) Gender: 17 females/7 males (9 females/5 males in levamisole group; 8 females/2 males in placebo group) Inclusion criteria: RAS (minor form) at least episode per month for the past 12 months Exclusion criteria: contraindications to the use of levamisole; pregnant women Number randomised: 28 Number analysed: 24
Interventions	Comparison: levamisole versus placebo Gr A (n = 14): levamisole 150 mg on Mondays, Wednesdays and Fridays in the first 4 weeks, then on alternate weeks from the 5th to 12th week, then every 3 weeks from the 13th to 24th week Gr B (n = 10): placebo as for Gr A
Outcomes	Frequency of episodes per month; number of lesions per episode; duration in days of each episode; pain; adverse effects; medical evaluation ¬ Duration of follow-up: 25 weeks
Notes	Unclear if mean or median vales presented Exclusion of participants with systemic disease not explicit

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly by drawing lots"
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias)	Unclear risk	No description
Blinding of outcome assessment (detection bias)	Unclear risk	No description
Incomplete outcome data (attrition bias)	Unclear risk	4/28 drop-outs; group not specified
Selective reporting (reporting bias)	High risk	Composite value for clinical improvement reported without any definition of composite value
Other bias	Unclear risk	No other apparent biases but poorly reported study

Zissis 1983

Methods	Location of trial: Thessaloniki, Greece Number of centres: not stated Funding: not stated Trial ID: not stated Type of RCT: parallel Power calculation: not stated
Participants	Source of recruitment: not stated (recruited over 6-month period) Age: median 32 years in Gr A; median 25 years in Gr B; median 31 years in Gr C Gender: 20 females/13 males (10 females/3 males in Gr A; 4 females/7 males in Gr B; 6 females/3 males in Gr C) Inclusion criteria: at least 1 episode monthly during past 6 months Exclusion criteria: history of agranulocytosis due to drug intake; pregnant women

	Number randomised: 33 Number analysed: unclear ("Two patients in group A and two patients in group B interrupted their treatment early because of unwanted effects but they were followed-up for the whole 16 week observation period and they were evaluated separately. After stopping their treatment, side effects subsided and from the point of view of disease severity, they returned to their pre-trial condition")
Interventions	Comparison: levamisole versus levamisole plus placebo versus placebo All groups took medication (all identical) for 2 consecutive days per week (given 2 vials numbered 1 and 2 - first day medication taken from vial 1 and the next day from vial 2) Gr A (n = 13): levamisole 50 mg 3 times per day for days 1 and 2 Gr B (n = 11): levamisole 50 mg 3 times per day for day 1 and placebo tablet 3 times per day for day 2 Gr C (n = 9): placebo tablet 3 times per day for days 1 and 2
Outcomes	Duration of ulcers (days); frequency of episodes per month; number of ulcers in each episode; ulcer size; pain (0 to 4 scale); adverse effects ¬ Duration of follow-up: 16 weeks treatment
Notes	Inconsistencies if data presented

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "...double-blind..." Comment: insufficient description in text
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "...double-blind..." Comment: no description in text
Incomplete outcome data (attrition bias)	Low risk	All patients included in analysis

Selective reporting (reporting bias)	High risk	Inconsistencies in presented data in the tables
Other bias	Low risk	No other apparent biases

Footnotes
AIDS = acquired immune deficiency syndrome
CI = confidence interval
HIV = human immunodeficiency virus
NSAIDs = nonsteroidal anti-inflammatory drugs
RAS = recurrent aphthous stomatitis
RCT = randomised controlled trial
SD = standard deviation
VAS = visual analogue scale

APPENDIX 3. Systemic interventions for the management of RAS: data analysis

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Recurrence	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
1.1.1 Colchicine versus prednisolone	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
1.2 Episode duration (days)	4		Mean Difference(IV, Fixed, 95% CI)	No totals
1.2.1 Vitamin B12 versus placebo	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.2.2 Montelukast versus placebo	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.2.3 Prednisone versus placebo	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.2.4 Prednisone versus montelukast	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.2.5 Perilla versus soybean	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.2.6 Multivitamin versus placebo	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.3 Number of new lesions	3		Mean Difference(IV, Fixed, 95% CI)	No totals
1.3.1 Multivitamin versus placebo	1		Mean Difference(IV, Fixed, 95% CI)	No totals

1.3.2 Montelukast versus placebo	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.3.3 Prednisone versus placebo	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.3.4 Prednisone versus montelukast	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.3.5 SDD versus placebo	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.4 Number of new lesions per day	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.4.1 SDD versus placebo	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.5 Number of new lesions per week	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.5.1 Tetracycline versus placebo	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.6 Number of new lesions per month (6 month tx)	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.6.1 LongoVital herbal alone	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.7 Levamisole versus placebo	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
1.7.1 Decrease in frequency of attacks	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals

1.7.2 Decrease in duration of attacks	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
1.7.3 Decrease in number of ulcers	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
1.7.4 Decrease in pain	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
1.8 Number of episodes per month	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.8.1 Vitamin B12 versus placebo	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.9 Ulcer-free status	3		Risk Ratio(M-H, Fixed, 95% CI)	No totals
1.9.1 Vitamin B12 versus placebo	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
1.9.2 Rofexib versus tinidazole	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
1.9.3 Homeopathy versus placebo	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
1.10 Number of days of pain per month (6 month tx)	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.10.1 LongoVital herbal alone	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.11 Mean size of aphthae per month (6 month tx)	1		Mean Difference(IV, Fixed, 95% CI)	No totals

1.11.1 LongoVital herbal alone	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.12 General discomfort per month (6 month tx)	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.12.1 LongoVital herbal alone	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.13 Number of ulcers at completion	2		Mean Difference(IV, Fixed, 95% CI)	No totals
1.13.1 Colchicine versus prednisolone	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.13.2 Subantimicrobial dose doxycycline versus placebo	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.14 Pain (VAS)	5		Mean Difference(IV, Fixed, 95% CI)	No totals
1.14.1 SDD versus placebo	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.14.2 Colchicine versus prednisolone	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.14.3 Vitamin B12 versus placebo	1		Mean Difference(IV, Fixed, 95% CI)	No totals
1.14.4 Montelukast versus placebo	1		Mean Difference(IV, Fixed, 95% CI)	No totals

1.14.5 Multivitamin versus placebo	1		Mean Difference(IV, Fixed, 95% CI)	No totals

APPENDIX 4. Interventions for managing oral ulcers in Behçet's disease: Search strategies

MEDLINE (OVID)

1. Behcet syndrome/
2. (Behcet adj2 (syndrome$ or disease)).ti,ab.
3. ("triple-complex syndrome$" or "triple-complex disease$").ti,ab.
4. or/1-3
5. Stomatitis, aphthous/
6. ((aphthous or apthous or mouth$ or oral$) adj3 (ulcer$ or lesion$ or stomatitis)).ti,ab.~
7. (aphthae or apthae).ti,ab.
8. "canker sore$".ti,ab.
9. "herpetiform ulcer$".ti,ab.
10. "periadenitis mucosa necrotica recurrens".ti,ab.
11. or/5-10
12. 4 and 11

The above subject search was linked with the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials in MEDLINE: sensitivity maximising version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of the *Cochrane Handbook for Systematic Reviews of Interventions,* Version 5.1.0 [updated March 2011] (Higgins 2011).

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. exp animals/ not humans.sh.
11. 9 not 10

The Cochrane Oral Health Group Trials Register

1. (((Behcet* and disease*) or (Behcet* and syndrome*)):ti,ab) AND (INREGISTER)
2. ((("triple-complex syndrome*" or "triple-complex disease*")):ti,ab) AND (INREGISTER)
3. MeSH DESCRIPTOR Behcet Syndrome
4. (#1 or #2 or #3) AND (INREGISTER)

Cochrane Central Register of Controlled Trials (CENTRAL)

#1 [mh "Behcet syndrome"]
#2 (behcet near/2 syndrome*) or (behcet near/2 disease*)
#3 ("triple-complex syndrome*" or "triple-complex disease*")
#4 {or #1-#3}
#5 [mh "Stomatitis, aphthous"]
#6 ((aphthous or apthous or mouth* or oral*) and (ulcer* or lesion* or stomatitis))
#7 (aphthae or apthae)
#8 "canker sore*"
#9 "herpetiform ulcer*"
#10 "periadenitis mucosa necrotica recurrens"
#11 {or #5-#10}
#12 #4 and #11

EMBASE (Ovid)

1. Behcet disease/
2. (Behcet adj2 (syndrome$ or disease)).ti,ab.
3. ("triple-complex syndrome$" or "triple-complex disease$").ti,ab.
4. or/1-3
5. Stomatitis, aphthous/
6. ((aphthous or apthous or mouth$ or oral$) adj3 (ulcer$ or lesion$ or stomatitis)).ti,ab.
7. (aphthae or apthae).ti,ab.
8. "canker sore$".ti,ab.
9. "herpetiform ulcer$".ti,ab.
10. "periadenitis mucosa necrotica recurrens".ti,ab.
11. or/5-10
12. 4 and 11

The above subject search was linked to the Cochrane Oral Health Group filter for identifying RCTs in EMBASE via OVID:

1. random$.ti,ab.
2. factorial$.ti,ab.
3. (crossover$ or cross over$ or cross-over$).ti,ab.
4. placebo$.ti,ab.

5. (doubl$ adj blind$).ti,ab.
6. (singl$ adj blind$).ti,ab.
7. assign$.ti,ab.
8. allocat$.ti,ab.
9. volunteer$.ti,ab.
10. CROSSOVER PROCEDURE.sh.
11. DOUBLE-BLIND PROCEDURE.sh.
12. RANDOMIZED CONTROLLED TRIAL.sh.
13. SINGLE BLIND PROCEDURE.sh.
14. or/1-13
15. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
16. 14 NOT 15

CINAHL (EBSCO)

S1 (MH "Beḫcet's Syndrome")
S2 (behcet N2 syndrome*) or (behcet N2 disease*)
S3 ("triple-complex syndrome*" or "triple-complex disease*")
S4 S1 or S2 or S3
S5 (MH "Stomatitis, Aphthous")
S6 ((aphthous or apthous or mouth* or oral*) and (ulcer* or lesion* or stomatitis))
S7 (aphthae or apthae)
S8 "canker sore*"
S9 "herpetiform ulcer*"
S10 "periadenitis mucosa necrotica recurrens"
S11 S5 or S6 or S7 or S8 or S9 or S10
S12 S4 and S11

The above subject search was linked to the Cochrane Oral Health Group filter for identifying RCTs in CINAHL via EBSCO:

S1 MH Random Assignment or MH Single-blind Studies or MH Double-blind Studies or MH Triple-blind Studies or MH Crossover design or MH Factorial Design
S2 TI ("multicentre study" or "multicenter study" or "multi-centre study" or "multi-center study") or AB ("multicentre study" or "multicenter study" or "multi-centre study" or "multi-center study") or SU ("multicentre study" or "multicenter study" or "multi-centre study" or "multi-center study")
S3 TI random* or AB random*
S4 AB "latin square" or TI "latin square"
S5 TI (crossover or cross-over) or AB (crossover or cross-over) or SU (crossover or cross-over)
S6 MH Placebos
S7 AB (singl* or doubl* or trebl* or tripl*) or TI (singl* or doubl* or trebl* or tripl*)
S8 TI blind* or AB mask* or AB blind* or TI mask*
S9 S7 and S8
S10 TI Placebo* or AB Placebo* or SU Placebo*
S11 MH Clinical Trials
S12 TI (Clinical AND Trial) or AB (Clinical AND Trial) or SU (Clinical AND Trial)
S13 S1 or S2 or S3 or S4 or S5 or S6 or S9 or S10 or S11 or S12

AMED (Ovid)

1. ((behcet and syndrome$) or (behcet and disease$)).ti,ab.
2. ("triple-complex syndrome$" or "triple-complex disease$").ti,ab.
3. or/1-2
4. ((aphthous or apthous or mouth$ or oral$) adj3 (ulcer$ or lesion$ or stomatitis)).ti,ab.
5. (aphthae or apthae).ti,ab.
6. "canker sore$".ti,ab.
7. "herpetiform ulcer$".ti,ab.
8. "periadenitis mucosa necrotica recurrens".ti,ab.
9. or/4-8
10. 3 and 9

US National Institutes of Health Trials Register (ClinicalTrials.gov) and WHO Clinical Trials Registry Platform

Behcet* and oral and ulcer*
Behcet* and mouth and ulcer*
Behcet* and stomatitis

APPENDIX 5. Interventions for managing oral ulcers in Behçet's disease: Characteristics of included studies

Aktulga 1980

Methods	Study design: RCT parallel Trial MD: NS Conducted in: Turkey Number of centres: 1 Recruitment period: NS Sample size calculation undertaken and met: not mentioned
Participants	Source of recruitment: NS Age GrA: 34.2 years ±7.2 Age GrB: 33 years ±12.8 Gender (overall sample): 6F/22M Gender GrA: 5F/9M Gender GrB: 1F/13M Inclusion criteria: well defined Behcet's disease according to the O'Duffy criteria Exclusion criteria: NS Number randomised: 35 Number evaluated: 28
Interventions	**Comparison: colchicine versus placebo** GrA (n = 14): capsules containing colchicine 0.5 mg, lactose 40 mg, amidone, 60 mg taken tds GrB (n = 14): placebo capsules containing phenolphthalein 60 mg, lactose 40 mg tds (decreased to bd if diarrhoea a problem)
Outcomes	Primary outcomes (patients seen monthly): semiquantitative assessment of 0-3 for aphthous stomatitis Carried out monthly for 6 months No reporting of adverse events, quality of life or cost

Funding	Supported in part by Turkish and Technical research council (TAG 386)
Notes	Comparable groups at baseline: no information in study

Risk of bias table

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear	Quote: "were randomised"
Allocation concealment (selection bias)	Low	Quote: "the code was known to a local pharmacist who dispensed the medication according to our instructions"
Blinding of participants and personnel (performance bias)	High	Quote: "identical capsules" Placebo group were informed to decrease dose from 3 times a day to twice daily if diarrhoea a problem
Blinding of outcome assessment (detection bias)	High	Given different instructions provided to the 2 treatment arms, blinding unlikely
Incomplete outcome data (attrition bias)	Unclear	7 dropouts no details given (evenly distributed)
Selective reporting (reporting bias)	Unclear	Insufficient details given for outcome measurements, who was assessing and interassessor calibration
Other bias	Low	None apparent

Alpsoy 1999

Methods	Study design: RCT (parallel) Trial ID: NS Conducted in: Turkey Number of centres: NS

	Recruitment period: NS Sample size calculation undertaken and met: NS
Participants	Source of recruitment: NS Age (overall sample): 33.4 years (SD 7.61) Age GrA: 33.0 years (SD 9.0) Age GrB: 34.1 years (SD 5.3) Gender (overall sample): 14 F/16 M Gender GrA: 8 F/8 M Gender GrB: 6 F/8 M Inclusion criteria: diagnosed according to the criteria of International Study Group for Behçet's disease Exclusion criteria: active eye disease or organ involvement requiring systemic therapy or received recent systemic therapy for at least 12 weeks and topical therapy for at least 4 weeks prior to the study Number randomised: 40 (20:20) Number evaluated: 30 (16:14)
Interventions	**Comparison: sucralfate suspension versus placebo** GrA (n = 16): 5 mL of sucralfate to use as an oral rinse for 1 to 2 minutes after routine mouth care and before sleep GrB (n = 14): as for sucralfate 3 months treatment; 3 months follow-up
Outcomes	Mean frequency of lesion Healing time Pain (scale of 0 to 3 (0, absent; 1, mild; 2, moderate; and 3, severe)) Adverse events No reporting of quality of life or cost
Funding	NS
Notes	Comparable groups at baseline: yes Treatment for oral and genital lesions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear	Insufficient information
Allocation concealment (selection bias)	Unclear	Insufficient information
Blinding of participants and personnel (performance bias)	Low	Quote: "The clinical investigator (H.E.) and patients were unaware of the specific drugs that the patients were taking during the course of the study" Comment: placebo identical in appearance
Blinding of outcome assessment (detection bias)	Low	Quote: "The clinical investigator (H.E.) and patients were unaware of the specific drugs that the patients were taking during the course of the study"
Incomplete outcome data (attrition bias)	Low	Quote: "The clinical investigator (H.E.) and patients were unaware of the specific drugs that the patients were taking during the course of the study"
Selective reporting (reporting bias)	Low	10 patients (4 sucralfate-treated patients and 6 placebo-treated patients) failed to complete the study. In all patients, medication use was well tolerated, and no patients were withdrawn from the study because of adverse events. High dropout but reasons and numbers similar across groups
Other bias	Low	None apparent

Alpsoy 2002

Methods	Study design: RCT (parallel) Trial ID: NS Conducted in: Turkey Number of centres: NS

	Recruitment period: June 1996 to March 2000 Sample size calculation undertaken and met: NS
Participants	Source of recruitment: NS Age (overall sample): 32.38 (SD 7.94) Age GrA: 32.82 years (SD 8.17) Age GrB: 31.89 years (7.85) Gender (overall sample): 17 F/27 M Gender GrA: 7 F/16 M Gender GrB: 10 F/11 M Inclusion criteria: Behcet's disease as defined by the International Study Group for Behcet's disease Exclusion criteria: those with hepatic, renal, cardiovascular, infectious or other autoimmune disease; those who had received recent systemic therapy for at least 4 weeks; pregnant or lactating women Number randomised (overall and by group): 50 (25:25) Number evaluated (overall and by group): 44 (23:21)
Interventions	**Comparison: interferon alfa-2a versus placebo** GrA (n = 23): interferon alfa-2a, 6×10^6 IU, or placebo subcutaneously 3 times a week GrB (n = 21): as for interferon alfa-2a 3 months treatment; 3 months follow-up
Outcomes	Mean frequency and duration of lesions (patient level) Pain (scale of 0 to 3 (0 indicates absent; 1, mild; 2, moderate; and 3, severe)) Overall response Patients were examined clinically at weekly intervals and were followed up for another 3 months after the treatment Adverse events No reporting of quality of life or cost
Funding	NS
Notes	Comparable groups at baseline: yes

	Co-interventions: subjects were given oral acetaminophen, 1000 mg before injections and 500 mg after 6 hours, during the first month of the therapy. Unclear if for both groups Treatment for treatment of Behcet's disease and not specifically oral ulceration

Risk of bias table

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear	Insufficient information
Allocation concealment (selection bias)	Unclear	Insufficient information
Blinding of participants and personnel (performance bias)	Unclear	Quote: "double-blind" Comment: identical placebo, however, unclear if both groups or just those in treatment group received paracetamol during first month of study
Blinding of outcome assessment (detection bias)	Unclear	Quote: "observed and assessed by an investigator (E.A.) who was blinded to the test medication being used"
Incomplete outcome data (attrition bias)	Low	2/25 in the interferon-alfa 2a and 4/25 in placebo group not included in analysis
Selective reporting (reporting bias)	High	Data not fully reported in text
Other bias	Unclear	Unclear if both groups or just those in treatment group received paracetamol during first month of study, which may affect pain scores

Davies 1988

Methods	Study design: RCT (cross-over) Trial ID: NS Conducted in: UK

	Number of centres: NS Recruitment period: NS Sample size calculation undertaken and met
Participants	Source of recruitment: NS Age (overall sample): mean 43 years (range 18 to 55 years) Gender (overall sample): 15 F/7 M Inclusion criteria: patients with recurrent oral and genital ulceration and other disease features fulfilling the Mason and Barnes diagnostic criteria for Bechet syndrome Exclusion criteria: patients with life-threatening or severe complications such as active uveitis were excluded Number randomised: 22 Number evaluated: 18 Comorbidities: not stated but "All patients had serum creatinine concentrations within the normal range"
Interventions	**Comparison: aciclovir versus placebo** After 1 month of baseline observations patients were randomly assigned to a 3-month period of treatment with acyclovir or placebo and after a further 1 month of 'wash-out' observation, they received 3 months' treatment with acyclovir or placebo GrA (n = 18): active treatment consisted of oral acyclovir 800 mg 5 times daily for 1 week, followed by 400 mg twice daily for 11 weeks GrB (n = 18): matched dummy tablets were used during the period of placebo treatment
Outcomes	Number and severity of oral (and genital) ulcers were recorded. Severity 0 (no symptoms) to 3 (severe discomfort) (Clinical assessment) ‘Other disease features’ were similarly assessed Frequency (number of new ulcers in each treatment period) and severity of oral and genital ulcers and the pattern of other disease features (patient self-assessment) Adverse events No reporting of quality of life or cost.
Funding	"We are grateful to Dr Angela Gilbert and Dr Karen Ditchfield of Burroughs Wellcome for help in devising the trial protocol and for supplying drugs and placebo material"

Notes	Comparable groups at baseline: predominantly female. No difference in disease severity in pretrial 1 month Co-interventions: other drug therapy "Six patients were receiving systemic prednisolone (mean dose of 6 mg daily, range 1.25-12.5 mg). One patient were receiving 150 mg azathioprine daily and a second patient 4.8 g aspirin and 400 mg tolmetin sodium (Tolectin) daily. These drug doses were not changed during the trial"

Risk of bias table

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low	Quote: "The order in which patients received acyclovir or placebo was randomly determined by computer generated code"
Allocation concealment (selection bias)	Unclear	Insufficient information
Blinding of participants and personnel (performance bias)	Low	Quote: "Matched dummy tablets were used during the period of placebo treatment"; "double blind"; matched placebo
Blinding of outcome assessment (detection bias)	Low	Quote: "The patients were assessed by one clinician (U.M.D.) on a blind basis before and after each phase of the trial"
Incomplete outcome data (attrition bias)	Low	2/22 patients dropped out in the first phase of treatment. Both were on active therapy. 1 had unacceptably active disease and the other could not swallow the tablets. 2 other patients kept inadequate records. Total dropout 4/22, 18%
Selective reporting (reporting bias)	Unclear	Frequency of oral ulcers (patient reported 0 not fully reported (missing paired sd). Severity of oral ulcers (patient reported) not reported. Frequency and severity of oral ulcers (clinical assessment) given as P value only (P = 0.45)
Other bias	High	Other systemic interventions were given, unclear as to which group these participants were in Order effects assessed - cross-over trial Quote: "As the order in which the patients received acyclovir or placebo did not influence the outcome, the results have been pooled"

		The order in which patients received treatment or placebo was randomly assigned, however the data or results were not presented separately

Ergun 1997

Methods	Study design: RCT (parallel) Trial ID: NS Conducted in: (country) NS Number of centres: NS Recruitment period: NS Sample size calculation undertaken and met: NS
Participants	Source of recruitment: NS Age (overall sample): mean 36.5 years (range 22 to 54 years SD 6.5 years) Gender (overall sample): 19 F/5 M Inclusion criteria: Beḥcet's syndrome according to the criteria of the International Study Group (ISG), and having had more than 8 ulcers within the previous 8-week period Exclusion criteria: patients with eye, joint or visceral involvement, hepatic, renal, hematological disorders, hypertension, pregnancy, or lactation were excluded Number randomised (overall and by group): 24 (12: 12) Number evaluated (overall and by group): 20 (NS:NS) Comorbidities: NS
Interventions	**Comparison: cyciosporine-A versus placebo** GrA (n = 12): topical cyciosporine-A 70 mg per g of orabase GrB (n = 12): orabase as a placebo 8-week treatment period
Outcomes	Primary outcomes: number, size and healing time Secondary outcomes: side effects or lab abnormalities (4 and 8 weeks) Adverse events No reporting of quality of life or cost

Funding	NS
Notes	Comparable groups at baseline: predominantly female Co-interventions: NS

Risk of bias table

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low riskUnclear riskHigh risk	Quote: ‘"Patients were assigned randomly" Comment: method not stated
Allocation concealment (selection bias)	Unclear	Insufficient information
Blinding of participants and personnel (performance bias)	Unclear	Quote: "orobase as a placebo" Comment: insufficient information
Blinding of outcome assessment (detection bias)	Unclear	Insufficient information
Incomplete outcome data (attrition bias)	Unclear	Time of assessment: 4/24 did not complete the study. Distribution across the 2 groups not given; no reasons given for non-failure to complete
Selective reporting (reporting bias)	High	Incomplete reporting of all outcomes
Other bias	Low	None apparent

Fani 2012

Methods	Study design: RCT (parallel, 2 arms) Trial ID: IRCT201107036920N2 Conducted in: Iran Number of centres: 1

	Recruitment period: NS Sample size calculation undertaken and met: NS
Participants	Source of recruitment: NS Age (overall sample): range = 15 to 65 years Age GrA: 35.47 years (SD 8.85), range = 15 to 57 years Age GrB: 38.77 years (SD 9.4), range = 17 to 65 years Gender (overall sample): 44 F/16 M Gender GrA: 22 F/8 M Gender GrB: 22 F/8 M Inclusion criteria: first visit; not taking any medication for the disease Exclusion criteria: NS Number randomised (overall and by group): 60 (30:30) Number evaluated (overall and by group): 60 (30:30) Comorbidities: NS
Interventions	**Comparison: 0.1% triamcinolone acetonide (TA) ointment versus phenytoin syrup** GrA (n = 30): TA ointment applied to the lesions 3 times per day (advised not to eat or drink for 30 min after application) GrB (n = 30): 2 teaspoons of phenytoin syrup in half a glass of warm water used as a mouthwash for 4-5 min 3 times per day (advised not to eat or drink for 30 min after application) Interventions were taken for 1 week
Outcomes	Positive response (no definition supplied) (outcome recorded at participant level) No reporting of adverse events, quality of life or cost
Funding	NS
Notes	Comparable groups at baseline: yes Co-interventions: no

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear	Quote: "randomly treated" Comment: insufficient information
Allocation concealment (selection bias)	Unclear	Quote: "randomly treated" Comment: insufficient information
Blinding of participants and personnel (performance bias)	High	Interventions were different in appearance and delivery. Participants and personnel would be aware of what intervention each participant received
Blinding of outcome assessment (detection bias)	High	Interventions were different in appearance and delivery. Participants and personnel would be aware of what intervention each participant received
Incomplete outcome data (attrition bias)	Low	No dropouts
Selective reporting (reporting bias)	High	No definition is given for the only outcome 'positive response'. Also, trial protocol states different outcome measures from publication
Other bias	Low	None apparent

Hamuryudan 1991

Methods	Study design: RCT (parallel, 2 arms) Trial ID: NS Conducted in: Turkey Number of centres: presumed to be 1 (but unclear from the letter) Recruitment period: NS Sample size calculation undertaken and met: NS
Participants	Source of recruitment: NS Age (overall sample): NS Age GrA: NS

	Age GrB: NS Gender (overall sample): 37 F/26 M (randomised) Gender GrA: 14 F/16 M (analysed) Gender GrB: 22 F/9 M (analysed) Inclusion criteria: Behcet's disease patients with active oral ulcers Exclusion criteria: receiving systemic drug therapy Number randomised (overall and by group): 63 (31:32) Number evaluated (overall and by group): 61 (30:31) Comorbidities: NS
Interventions	**Comparison: interferon-α-2c hydrogel versus placebo** GrA (n = 31): interferon-α-2c hydrogel (1 x 10^5 U/g) to be applied in a thin layer on any ulcer 3 times per day for 24 weeks. A similar application to upper and lower lip mucosa irrespective of the presence of ulcers GrB (n = 32): placebo hydrogel (same regimen as GrA) All other topical medications were withheld during the study
Outcomes	Number of ulcers (by examiner every 2 weeks) (ulcer level) Type of ulcers (by examiner every 2 weeks) (ulcer level) Number and type of ulcers occurring and healing between visits (by patient) No reporting of adverse events, quality of life or cost.
Funding	Boehinger Ingelheim Zentrale, GmbH, Germany supplied the active intervention
Notes	Comparable groups at baseline: no (gender imbalance although not clear if statistically significant) Co-interventions: no

Risk of bias table

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear	Quote: "randomized double blind trial" Comment: insufficient information

Allocation concealment (selection bias)	Unclear	Quote: "randomized double blind trial" Comment: insufficient information
Blinding of participants and personnel (performance bias)	Unclear	Quote: "double blind" Comment: no information of taste/appearance
Blinding of outcome assessment (detection bias)	Low	Quotes: "double blind" and "seen by the same blind observer every second week"
Incomplete outcome data (attrition bias)	Low	1 dropout per group
Selective reporting (reporting bias)	High	Separate analysis carried out on gender imbalance but data not presented
Other bias	Low	None apparent

Hamuryudan 1998

Methods	Study design: RCT (parallel, 3 arms) Trial ID: NS Conducted in: Turkey Number of centres: 1 Recruitment period: October 1993 to April 1996 Sample size calculation undertaken and met: undertaken but not met
Participants	Source of recruitment: Behcet's Syndrome Research Center at the University of Istanbul Age GrA: 27.8 years (95% CI 25.9 to 29.6) Age GrB: 27.6 years (95% CI 25.7 to 29.4) Age GrC: 26.7 years (95% CI 24.8 to 28.6) Gender: all males Inclusion criteria: males aged 18 to 35; active mucocutaneous disease (occurrence of at least 2 episodes of oral or genital ulceration within 3 months before the study started) Exclusion criteria: moderate or severe eye disease resulting in any decrease in visual acuity; organ involvement requiring immunosuppressive therapy; previous immunosuppressive therapy; clinical neuropathy

	Number randomised (overall and by group): 96 (32:32:32) Number evaluated (overall and by group): 95 (32:32:31) Comorbidities: NS
Interventions	**Comparison: thalidomide (higher dose) versus thalidomide (lower dose) versus placebo** GrA (n = 32): 300 mg thalidomide per day (each patient given 3 bottles containing 100 mg tablets and instructed to take 1 tablet from each; 1 in the morning and 2 in the evening) GrB (n = 32): 100 mg thalidomide per day (each patient given 3 bottles (the morning and 1 evening bottle containing identical placebo tablets and the second evening one containing 100 mg tablets) and instructed to take 1 tablet from each; 1 in the morning and 2 in the evening) GrC (n = 32): identical placebo tablets (1 in the morning and 2 in the evening) 24 weeks of treatment, final follow-up was 4 weeks later (28 weeks). Participants seen every 4 weeks or when they had a problem
Outcomes	Primary outcomes: number of new lesions (ulcer level); complete response, defined as absence of any oral or genital ulcer of any size during the 24-week treatment period Secondary outcomes: changes in the number of mucocutaneous lesions, and response of eye disease to treatment, defined as the absence of uveitis activations and any decrease in visual acuity in either eye No reporting of adverse events, quality of life or cost
Funding	Funding source: Grunenthal GmbH, Aachen, Germany
Notes	Comparable groups at baseline: yes Co-interventions: patients permitted to use topical lidocaine for pain relief when required

Risk of bias table

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low	Quote: "A simple, computer-generated, random-number list was prepared by a person not involved in the trial"
Allocation concealment (selection bias)	Low	Quote: "The code was kept in an opaque, sealed envelope by the senior author of the study and was opened only after all data had been entered into a computer for analysis"

		Comment: the random sequence was adequately concealed
Blinding of participants and personnel (performance bias)	Low	Quote: "double blind" Comment: active and placebo tablets were identical
Blinding of outcome assessment (detection bias)	Low	Quote: "double blind" Comment: active and placebo tablets were identical
Incomplete outcome data (attrition bias)	Low	Only 1 participant was not analysed (due to adverse event); unlikely to influence results
Selective reporting (reporting bias)	High	Data for oral and genital ulcers not reported separately. Graph of number of oral ulcers over time presented but no raw data
Other bias	Low	None apparent

Kilic 2009

Methods	Study design: RCT (parallel, 3 arms) Trial ID: NCT00483184 (protocol available on ClinicalTrials.gov) Conducted in: Turkey Number of centres: 4 Recruitment period: 20 months Sample size calculation undertaken and met: yes but not met
Participants	Source of recruitment: rheumatology or dedicated Behcet's disease outpatient clinics of 4 medical schools Age (overall sample): 37 (SD 9.4), range = 20 to 57 years Age GrA: 36 (SD 9.4), range = 22 to 56 years Age GrB: 36 (SD 8.6), range = 20 to 50 years Age GrC: 37 (SD 10.2), range = 21 to 57 years Gender (overall sample): 59 F/25 M Gender GrA: 19 F/7 M Gender GrB: 20 F/7 M Gender GrC: 20 F/11 M

	Inclusion criteria: aged 18 to 75 years; fulfilling Behcet's disease International Study Group criteria; presence of active oral ulcers within previous year; at least 2 oral ulcers accessible to measurement with a total diameter of ≥ 4 mm Exclusion criteria: having disease features requiring any form of IFN or other immune suppressive medication within 30 days of screening; hypersensitive to IFN-α; pregnant/lactating/childbearing potential and not using a medically acceptable contraceptive method during the study Number randomised (overall and by group): 84 (26:27:31) Number evaluated (overall and by group): 72 (23:22:27) Comorbidities: none noted
Interventions	**Comparison: interferon-α lozenges (2000 IU/day) versus placebo versus interferon-α lozenges (1000 IU/day)** GrA (n = 26): 2 x 500 IU IFN-α lozenges twice daily for 12 weeks GrB (n = 27): 2 placebo lozenges twice daily for 12 weeks GrC (n = 31): 1 x 500 IU IFN-α lozenge plus 1 placebo lozenge twice daily for 12 weeks
Outcomes	Subjects were monitored weekly over an initial 4 weeks of the treatment and then bi-weekly over an additional 8 weeks of treatment. Oral lesions were counted and measured at each study visit Primary outcomes: percentage change in a pt's total ulcer burden (from baseline) Secondary outcomes: oral ulcer initial response at weeks 1-10; time to initial response; oral ulcer sustained response at weeks 3-10; oral ulcer recurrence at weeks 2-12; time to recurrence; patient-reported pain associated with oral lesions; patient-reported general well-being; global disease severity (both patient- and investigator-reported); safety assessment/adverse events No reporting of cost
Funding	Supported by Nobel Ilac San. Ve Tic. A.S., Istanbul, Turkey
Notes	Comparable groups at baseline: yes Co-interventions: no Treatment for oral ulcers associated with Behcet's

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low	Quote: "Using randomly permuted blocks"
Allocation concealment (selection bias)	Low	Quote: "Using randomly permuted blocks" Comment: also active and placebo lozenges prepared by pharma, and bottling and preparation of randomization boxes was carried out remotely by Dilan Laboratories in Canada
Blinding of participants and personnel (performance bias)	Low	Quote: "double blind" Comment: active and placebo lozenges were identical
Blinding of outcome assessment (detection bias)	Low	Quote: "double blind" Comment: active and placebo lozenges were identical
Incomplete outcome data (attrition bias)	Low	14% total attrition (A: 12%, B: 19%, C: 13%) with reasons reported in full, which were similar across groups
Selective reporting (reporting bias)	High	Most outcomes were not presented as stated in methods. Measures of variance not provided
Other bias	Low	None apparent

Koc 1992

Methods	Study design: RCT parallel Trial ID: NS Conducted in: (country) Turkey Number of centres: 1 Recruitment period: NS Sample size calculation undertaken and met: NS
Participants	Source of recruitment: patients with oral aphthous ulceration and a diagnosis of Behcets' attending Hacettepe University Age (overall sample): mean 31 (18-50)

	Age GrA: 31.1 years Age GrB: 32.5 years Gender (overall sample) : 17/24 Gender GrA male to female ration 1.4 Gender GrB male to female ratio 0.6 Inclusion criteria: Behcet's disease diagnosed by 'international criteria' no reference given Oral ulcers Not taking immunosuppression or cytotoxic therapy Exclusion criteria: NS Number randomised (overall and by group): 41 Number evaluated (overall and by group): 35 Comorbidities: NS
Interventions	**Comparison: sucralfate suspension versus placebo** GrA (n = 24): sucralfate suspension applied to ulcers 4x day with applicator for up to 12 weeks GrB (n = 11): placebo suspension applied to ulcers 4x day with applicator for up to 12 weeks Following 12 weeks treatment, all interventions stopped and patients followed for 12 weeks 'no treatment'
Outcomes	Number of ulcers (NU): sum of oral ulcers observed in 12-week period Number of days with oral ulcers: sum of days with oral ulcers in 12-week period Number of episodes with oral ulcers Mean duration of ulcer episodes Number of painful days Ratio of painful days to days with ulcers Size of oral ulcers No reporting of adverse events, quality of life or costs
Funding	Research grant from Bilim pharmaceutical company
Notes	Comparable groups at baseline: insufficient information Co-interventions: patients taking colchicine were allowed to continue – but no allowance for this made in the results (i.e. we do not know how many patients in each group were also taking colchicine)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear	Quote: "the study was prospective double blind randomized" Comment: insufficient details
Allocation concealment (selection bias)	Unclear	No information on randomisation or concealment
Blinding of participants and personnel (performance bias)	Low	Quote: "prepared by the manufacturer and were similar in taste and colour"
Blinding of outcome assessment (detection bias)	Unclear	No details re blinding of clinicians
Incomplete outcome data (attrition bias)	High	6 dropouts - all from intervention group, insufficient reasons given
Selective reporting (reporting bias)	Unclear	Reports all outcomes however it is unclear how many patients are actually making up the results table (i.e. was it 41 then 35 evaluable then 6 dropouts in intervention, or were the dropouts before – either way it means the arms were not balanced)
Other bias	Low	None apparent

Masuda 1989

Methods	Study design: RCT (parallel) (double masked and double dummy) Trial ID: NS Conducted in: Japan Number of centres: 1 Recruitment period: NS Sample size calculation undertaken and met: NS

Participants	Source of recruitment: NS Age: NS Gender: NS Inclusion criteria: complete or incomplete Behcet's disease, visual acuity 20/40 or less, at least 2 episodes of ocular attack during the 16 weeks before study selection Exclusion criteria: renal or hepatic dysfunction, neurological Behcet's and /or hypertension Number randomised (overall and by group): 96 (47:49) Number evaluated (overall and by group): 92 (46:46) Comorbidities: NS
Interventions	**Comparison: cyclosporin versus colchicine** GrA (n = 47): cyclosporin 10 mg/kg GrB (n = 49): colchicine 1 mg Both given once per day for 16 weeks (if side effects then dose reduced or treatment stopped)
Outcomes	Primary outcomes: ocular; immunological bloods Secondary outcomes: non-ocular complications (oral aphthous, dermal and genital ulceration) were classified into 4 grades 0-3 based on frequency and number of lesions. No information as to what specific oral outcome measures were used, when they were used or whether it was patient-reported or clinician Adverse events No reporting of quality of life or costs
Funding	Supported by the Japan Society for Promotion of Science and the National Eye Institute, Bethesda, USA
Notes	Comparable groups at baseline: not stated regarding baseline oral ulcer history Co-interventions: not stated if any topical measures used in addition Treatment of ocular disease associated with Behcet's

Risk of bias table

Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Unclear	Quote: "randomized" Comment: no information given
Allocation concealment (selection bias)	Unclear	Insufficient information given
Blinding of participants and personnel (performance bias)	Unclear	Quote: "double masked and double dummy" Comment: however no description of appearance/taste of interventions
Blinding of outcome assessment (detection bias)	Unclear	No information given
Incomplete outcome data (attrition bias)	Low	4/97 dropouts; equally balanced
Selective reporting (reporting bias)	High	Outcome data not fully reported
Other bias	Unclear	Not stated if any topical measures used in addition

Mat 2006

Methods	Study design: RCT parallel Trial ID: NS Conducted in: Turkey Number of centres: 1 Recruitment period: February 2001 to March 2002 Sample size calculation undertaken and met: yes, but not met due to dropouts
Participants	Source of recruitment: multidisciplinary Behcet's Syndrome outpatient clinic at the Cerrahpasa Medical Facility Istanbul Age GrA: 31.7 years ± 7 Age GrB: 29.4 years ± 6 Gender (overall sample): 43F/ 43M Gender GrA: 21F/ 21M

	Gender GrB: 22F/ 22M Inclusion criteria: 18 to 45, active genital disease, live in Istanbul Exclusion criteria: previous immunosuppression in last month, previous steroids greater than 5 mg/day, severe organ involvement, or eye disease, or DM, active infection, peptic ulcer, hypertension, pregnancy Number randomised (overall and by group): 86 (42:44) Number evaluated (overall and by group): 72 (34:38) Comorbidities: patients continued their colchicine, low dose aspirin, amitriptyline, acetaminophen. Topical treatment as well as additional systemic drugs such as thalidomide were also permitted for oral and genital lesions. Only systemic immunosuppressives were withheld
Interventions	**Comparison: corticosteroid injections versus placebo** GrA (n = 42): depot corticosteroid intramuscular injections (40 mg methylepred) GrB (n = 44): depot injection as above but with 1 ml saline Injections given every 3 weeks for 27 weeks
Outcomes	Primary outcomes: difference in the mean number of genital ulcers Secondary outcomes: difference in the mean numbers of other mucocutaneous lesions and attacks of arthritis reported as mean number of lesions Adverse events No reporting of quality of life or costs
Funding	Supported by association for the rheumatology section at Cerrahpsa Medical Facility
Notes	Comparable groups at baseline: no detailed baseline ulcer information given Co-interventions: 4 in each arm received colchicine, 3 in each arm amitryptilne, 9 in each arm NSAIDS, 1 in each arm low dose aspirin and 1 in each arm thalidomide

Risk of bias table

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear	Quote: "random number generated by a computer"

		Comment: simple randomisation has resulted in equally balanced groups according to gender and additional medication
Allocation concealment (selection bias)	Low	Quote: "a study nurse, not involved in data collection, kept the randomization list and injected the drug or placebo….the randomization code was not opened until the data had been entered"
Blinding of participants and personnel (performance bias)	Low	Quote: "syringe covered with a label to conceal the milky solution"
Blinding of outcome assessment (detection bias)	Low	Quote: "the physicians involved in patient assessment were blinded to the treatment allocation"
Incomplete outcome data (attrition bias)	Unclear	Presents attrition data but no explanation as to why there were "lost to follow-ups"
Selective reporting (reporting bias)	High	Patients receiving additional therapies not presented separately but as part of the arms Results also presented male/female and this was not a pre-specified outcome
Other bias	Low	None apparent

Matsuda 2003

Methods	Study design: RCT (parallel) Trial ID: NS Conducted in: Japan Number of centres: 6 Recruitment period: August 1994 to December 1996 Sample size calculation undertaken and met: NS
Participants	Source of recruitment: various clinics Age: NS Age GrA: NS Age GrB: NS Gender (overall sample): NS

	Gender GrA: NS Gender GrB: NS Inclusion criteria: Behcet's disease diagnosed using the Japanese criteria (reference given) presence of aphthae for more than 7 days in the month before the study Exclusion criteria: use of any other drugs to treat gastric ulcer or gastritis Number randomised (overall and by group): 35 Number evaluated (overall and by group): 31 Comorbidities: NS
Interventions	**Comparison: rebamipide versus placebo** GrA (n = 19): rebamipide 300 mg tablet to be taken 3x day after meals GrB (n = 16): placebo tablet to be taken 3x day after meals Treatment period: 6 months
Outcomes	Primary outcomes: aphthae count (patient reported on daily basis); pain score (patient reported on daily basis); monthly aphthae count; total monthly pain scores; global evaluation of above rated by investigator at the end of the study on 6-point scale Secondary outcomes: monthly bloods Adverse events No reporting of quality of life or costs
Funding	Pharma funded (Otsuka pharmaceutical company)
Notes	Comparable groups at baseline: states yes Co-interventions: yes, patients remained on existing treatment including immunosuppression and steroids

Risk of bias table

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear	Quotes: "the study controller created a random allocation list" and "patients were randomly assigned" Comment: insufficient evidence of randomisation

Allocation concealment (selection bias)	Unclear	No information given
Blinding of participants and personnel (performance bias)	Unclear	Quote: "placebo tablets which were 'indistinguishable from the active" Comment: no other details given
Blinding of outcome assessment (detection bias)	Unclear	Insufficient details
Incomplete outcome data (attrition bias)	Low	2 from each group and reasons stated
Selective reporting (reporting bias)	High	Does not report the individual outcome measures – groups them together in the observer global score (subjective?)
Other bias	Low	None apparent

Melikoglu 2005

Methods	Study design: RCT parallel Trial ID: NS Conducted in: Turkey Number of centres: 1 Recruitment period: NS Sample size calculation undertaken and met: NS
Participants	Source of recruitment: Behcet's syndrome research centre Cerrahpsa Medical Faculty, Istanbul Age GrA: 28.5 years ±5.3 Age GrB: 30.8 years ±6.2 Gender: all male Inclusion criteria: males, age 18 to 45, presence of at least 1 of a list of criteria including oral ulcers, genital ulcers, nodular lesions, swollen joints, positive pathergy and MSU test Exclusion criteria: serious organ involvement e.g. eye and cns and major arterial disease, systemic or local infection in yb, previous use of study drug 4 weeks prior, abnormal bloods (specifically stated)

	Number randomised (overall and by group): 40 (20:20) Number evaluated (overall and by group): 38 (19:19) Comorbidities: NS
Interventions	**Comparison: etanercept versus placebo** GrA (n = 19): etanercept 25 mg dissolved in 1 ml distilled water subcutaneous twice weekly GrB (n = 19): placebo 25 mg vial dissolved in 1 ml distilled water and delivered as above.
Outcomes	Primary outcomes: amount of suppression of pathergy and MSU tests Secondary outcomes: differences between the mean number of mucocutaneous lesions and swollen joints between the study arms at each weekly visit; mean number of oral ulcers Adverse events No reporting of quality of life or costs
Funding	NS
Notes	Comparable groups at baseline: yes all baseline data presented Co-interventions: additional drugs used prednisolone, indomethacin, paracetamol, ornidazole, azathioprine, naproxen, topoca cs Treatment for Behcet’s disease

Risk of bias table

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low	Quote: "equal number of cards mixed drawn and placed sequentially on a list"
Allocation concealment (selection bias)	Unclear	Quote: "code was opened only after data had been entered into computer" Comment: states that vials were distributed to patients by a study nurse who was not blinded
Blinding of participants and personnel (performance bias)	Unclear	Quote: "characteristics of the study drug and placebo were identical and the clinical assessors and patients were blinded to the preparation being administered" Comment: unclear how robust blinding mechanisms was as one patient withdrew following discovery they were on placebo

Blinding of outcome assessment (detection bias)	Unclear	Unclear how robust blinding mechanisms was as one patient withdrew following discovery they were on placebo
Incomplete outcome data (attrition bias)	Low	2/40 dropouts, equally distributed
Selective reporting (reporting bias)	High	Includes results for all patients even those on additional treatments. States "separate analysis done" "our findings remain robust" "agree" but separate analysis not presented
Other bias	Low	None apparent

Yurdakul 2001

Methods	Study design: RCT, double-blind, placebo-controlled study Trial ID: NS Conducted in: Turkey Number of centres: 1 Recruitment period: "Consecutive patients attending the center were recruited into the study between November 1991 and December 1995. The recruitment period was 24 months" Sample size calculation undertaken and met: NS
Participants	Source of recruitment: "'multidisciplinary Beḥcet's Syndrome Research Center at the Cerrahpasa Medical School" Inclusion criteria: patients fulfilled the criteria for the diagnosis of Beḥçet's syndrome and be consecutive patients (male or female); be 18-35 years of age; have active disease; have a disease duration of 2 years; and live at reasonable travelling distance from centre Active disease was defined as the minimum presence of oral or genital ulceration or erythema nodosum occurring at least 3 times within the preceding 6 months Exclusion criteria: patients who had received immunosuppressive agents, steroids or colchicine within the preceding 6 months; had organ involvement requiring immunosuppression; had eye disease, especially with retinal involvement during the recruitment period Number randomised: 116 (58:58)

	Number evaluated monthly: 84 by study end
Interventions	**Comparison: colchicine versus placebo** GrA (n = 58): 0.5 mg colchicine tablets. Dose adjusted per weight in kg GrB (n = 58): placebo tablets that were identical to the active drug in appearance and taste
Outcomes	Primary outcomes: oral ulceration; genital ulcers; erythema nodosum; follicular lesions; arthritis Secondary outcomes: adverse events No reporting of quality of life or costs
Funding	NS
Notes	Comparable groups at baseline: yes Co-interventions: placebo group given various additional treatments thalidomide, pulsed methylpred, systemic prednisolone and NSAID; "the patients were permitted to use treatment for oral and genital ulceration and acetaminophen or NSAID for joint disease, if needed"

Risk of bias table

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low	Quote: "equal numbers of cards that were assigned to either the active drug or the placebo arm were mixed, drawn, and placed sequentially on a list by a secretary not involved in running the trial"
Allocation concealment (selection bias)	Low	Quote: "The code was kept in a sealed envelope by one of the authors (HY) and was opened only after all data had been entered into the computer for analysis. The allocation to the study and the dispensing of the medications were done by a research assistant"
Blinding of participants and personnel (performance bias)	Low	Quote: "At each visit, the patients received a bottle containing either 0.5 mg colchicine or placebo tablets that were identical to the active drug in appearance and taste"
Blinding of outcome assessment (detection bias)	Low	Quote: "All participating physicians were blinded to the patients’ allocation to the study arms"

Incomplete outcome data (attrition bias)	Low	Quotes: "One hundred twenty consecutive patients were eligible for the study. Four women declined to participate" and "Eighty-four patients (72%; 45 male, 39 female) completed the 24-month study (Figure 1)" Dropouts equal in both sides; reasons given for dropouts 2 year trial – not unreasonable dropout considering length of trial
Selective reporting (reporting bias)	Low	Author provided addition raw ulcer data
Other bias	Low	None apparent

Footnotes; bd = twice per day; CI = confidence interval; min = minute; NS = not specified; RAS = recurrent aphthous stomatitis; RCT = randomised controlled trial; SD = standard deviation; tds = 3 times per day.

APPENDIX 6. Topical interventions for recurrent aphthous stomatitis (mouth ulcers)

Cochrane Database of Systematic Reviews

Topical interventions for recurrent aphthous stomatitis (mouth ulcers) (Protocol)

Taylor J, Brocklehurst P, Glenny AM, Walsh T, Tickle M, Lewis MA, Riley P, Yates JM, Pemberton MN

Taylor J, Brocklehurst P, Glenny AM, Walsh T, Tickle M, Lewis MA, Riley P, Yates JM, Pemberton MN.
Topical interventions for recurrent aphthous stomatitis (mouth ulcers).
Cochrane Database of Systematic Reviews 2013, Issue 12. Art. No.: CD010881.
DOI: 10.1002/14651858.CD010881.

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[Intervention Protocol]

Topical interventions for recurrent aphthous stomatitis (mouth ulcers)

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

The objectives of this review are to determine the clinical effectiveness and safety of topical interventions in the reduction of pain associated with recurrent aphthous stomatitis, a reduction in episode duration, a reduction in episode frequency and improved quality of life.

BACKGROUND

Description of the condition

Recurrent aphthous stomatitis (RAS) is the most common form of oral ulceration with a prevalence in the general population ranging between 5% and 60% (Jurge 2006). It is characterised by recurrent oral mucosal ulceration in an otherwise healthy individual (Porter 1998). The peak age of onset is between 10 and 19 years of age (Ship 2000), and it can persist into adulthood and throughout the patient's lifespan, with no age, gender or cultural preference (Ship 2000).

According to Bagan 1991, there are three recognised forms of RAS.

1. Minor aphthae - typically round and less than 10 mm in diameter. These are generally pale in colour with an erythematous border and commonly affect non-keratinised mucosa including the labial and buccal mucosa, the borders of the tongue, and the floor of the mouth. Minor aphthae can occur in isolation but multiple presentations are also common. Healing is spontaneous and usually takes 7 to 10 days. Episodes of ulceration are usually followed by an ulcer-free period lasting a few days to several weeks before the next episode occurs (Thornhill 2007). Minor aphthae account for 80% of patients with RAS (Thornhill 2007).
2. Major aphthae are similar to minor aphthae but are larger, usually exceeding 10mm in diameter and deeper. Consequently healing can take longer (20 to 30 days) and may result in scarring (Bagan 1991).
3. Herpetiform ulcers are less than 1 mm in diameter and often occur in multiples from 1 to 100. There is a tendency for adjacent ulcers to merge to form a large affected area. Healing takes place within 15 days and can result in scarring (Bagan 1991).

The aetiopathogenesis of RAS is multifactorial (Jurge 2006). Some patients have a genetic predisposition, with at least 40% of patients having a positive family history (Sircus 1957). In a review of the literature, Jurge 2006 suggests that a bacterial or viral aetiology is unlikely and that the immunopathogenesis of the disease is most likely to involve a cell-mediated immune response mechanism involving the generation of T-cells, interleukins and tumour necrosis factor (TNF) (Natah 1998; Sun 2000). However, a lymphocyte-mediated mechanism in addition to immune complexes have also been proposed (Jurge 2006), and cross-reactivity between streptococci and the oral mucosa has been demonstrated (Lehner 1991). Local factors can predispose patients to RAS and physical trauma can initiate ulcers in susceptible people (Wray 1981), but RAS is uncommon in patients who smoke tobacco (Salonen 1990). Reduced iron storage has also been reported in 37% of patients (Porter 1993), and psychological illness has also been postulated but this has not been substantiated (Miller 1977).

Patients with systemic diseases are also prone to oral ulceration but these manifestations may be secondary to their medical condition and so they should be considered separately. These can include, but are not limited to, coeliac disease, vitamin B12 deficiency, iron deficiency anaemia, human immunodeficiency virus infection/acquired immunodeficiency syndrome (HIV/AIDS), cyclic neutropenia, Reiter's syndrome, Behçet's Disease (Baccaglini 2011).

For clarity, if there is no associated systemic disease, this will be described as 'RAS'. When the ulceration may be associated with an underlying systemic disease, then this will be described as 'RAS type ulceration'.

Description of the intervention

Treatment is primarily aimed at pain relief and the promotion of healing to reduce the duration of the disease or reduce the rate of recurrence. A variety of topical and systemic therapies have been utilised (Porter 1998), but few studies have demonstrated efficacy. Empirically, effective treatments include the use of corticosteroids, immunosuppressants and topical barriers (Eisen 2001). Mycophenolate mofetil, pentoxyphylline, colchicine, dapsone and thalidomide have also been used but with some caution due to the potential for adverse effects. The cause of RAS is not known therefore the aims of treatment are primarily pain relief and the reduction of inflammation (Scully 2006).Topical interventions can include mouthrinses, pastes, gels, sprays, injections, laser and locally dissolving tablets. Many treatments are available for patients to buy without prescription.

How the intervention might work

As the aetiopathogenesis of aphthous ulceration is not fully understood, the precise mode of action of topical interventions is unclear. Topical interventions range from inert barriers to active treatments. Providing a barrier for the ulcer (for example a mucoadhesive paste) should allow the breach in the mucosa to temporarily be protected and therefore noxious stimulants are less likely to sensitise nerve endings. This in theory should provide pain relief. The addition of active compounds to the barrier can potentially give an immunomodulatory effect. Due to the nature of the mucosal layer, there is great variability in the penetration of active compounds through the mucosal barrier, and as such there is great variability as to the efficacy of such topical treatments.

Why it is important to do this review

All three clinical types of RAS are associated with varying degrees of morbidity, including pain and difficulties in function. RAS is a chronic episodic oral mucosal condition which can impact upon the experiences of daily life, such as physical health and functioning (Riordain 2011). Given, its high prevalence, the prevention of RAS or the reduction of the pain or longevity of the disease are important goals in oral medicine. This review will focus on the use of topical interventions in the management of RAS and complements the Cochrane systematic review of systemic interventions for the management of RAS by the same author team (Brocklehurst 2012).

OBJECTIVES

The objectives of this review are to determine the clinical effectiveness and safety of topical interventions in the reduction of pain associated with recurrent aphthous stomatitis, a reduction in episode duration, a reduction in episode frequency and improved quality of life.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) investigating the effects of topical interventions for the management of recurrent aphthous ulcers. We will also include RCTs of a cross-over design, provided that the trial included a suitable washout period and no carry-over effects were evident. Split-mouth studies will also be included if it is apparent that there is no risk of contamination of the intervention from one part of the mouth to another. This will be more likely for the topical interventions which are a physical barrier.

Types of participants

Participants with a previous or current history of recurrent aphthous stomatitis (RAS), diagnosed either clinically or histopathologically. We will exclude participants with the following conditions:

- Behçet's disease;
- Reiter's syndrome;
- recurrent erythema multiforme or any viral infection.

In addition, we will exclude patients with coeliac disease, Crohn's disease, ulcerative colitis, anaemia and haematinic deficiency (vitamin B12, folic acid and iron), when sufficient detail is provided in the trial. This will ensure that patients entering into a trial are for primary lesions, not lesions that are secondary to a medical condition. We will also exclude participants taking medications associated with oral ulceration e.g. nicorandil, diclofenac.

Types of interventions

Active treatment will include any preventive, palliative or curative interventions administered topically (i.e. where the primary mode of action is topical, acknowledging that some of the topical interventions may also have systemic effect). Controls will be either no active treatment or the administration of a placebo, but head to head trials of different interventions will also be included, if identified.

Types of outcome measures

Primary outcomes

Primary outcome measures assessed will be:

1. pain associated with RAS;
2. episode duration associated with RAS;
3. episode frequency associated with RAS;
4. safety of the intervention including adverse effects.

Secondary outcomes

Any patient reported outcomes that measure improvements in the patients' quality of life and reduction in morbidity (e.g. function).

Search methods for identification of studies

For the identification of studies included or considered for this review, we will develop detailed search strategies for each database searched. These were based on the search strategy developed for MEDLINE (OVID) but revised appropriately for each database (Appendix 1). We will combine this search strategy with the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials in MEDLINE: sensitivity maximising version as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will link the search of EMBASE to the Cochrane Oral Health Group filter for identifying RCTs.

Electronic searches

The following electronic databases will be searched:

- the Cochrane Oral Health Group's Trials Register (to present);
- the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, current issue);
- MEDLINE via OVID (1946 to present);
- EMBASE via OVID (1980 to present);
- CINAHL via EBSCO (1980 to present);
- AMED via OVID (1985 to present).

Searching other resources

Unpublished trials

We will screen the bibliographies of included papers and relevant review articles will be checked for studies not identified by the search strategies above. We will search the US National Institutes of Health Trials Register (http://clinicaltrials.gov/) for ongoing trials.

Language

Any non-English trials that are identified will be translated through The Cochrane Collaboration.

Data collection and analysis

Selection of studies

Three review authors (Paul Brocklehurst (PB), Anne-Marie Glenny (AMG) and Jennifer Taylor (JT)) will independently screen the titles and abstracts obtained from the initial electronic searches. Reports from the studies that fulfil the inclusion criteria will be obtained. When there are insufficient data in the study title to determine whether a study fulfils the inclusion criteria, the full report will be obtained and assessed independently by the same review authors. Disagreement will be resolved by discussion.

Data extraction and management

At least two review authors (JT, AMG, Tanya Walsh (TW), PB, Philip Riley (PR), Julian Yates (JY)) will independently extract data from each included study using a tool developed for the review. All studies meeting the inclusion criteria will undergo data extraction and an assessment of risk of bias will be made using a pre-standardised data extraction form. Studies rejected at this and subsequent stages will be recorded in the table of excluded studies. Differences will be resolved by discussion. If a single publication reports two or more separate studies, then the data from each study will be extracted separately. If the findings of a single study are spread across two or more publications, then the publications will be extracted as one. For each study with more than one control or comparison group for the intervention, the results will be extracted for each intervention arm.

For each trial the following data will be recorded.

1. Year of publication, country of origin and source of study funding.
2. Details of the participants including demographic characteristics and criteria for inclusion.
3. Details on the type of intervention and comparisons.
4. Details on the study design.
5. Details on the outcomes reported, including method and timings of assessments, and adverse outcomes.

Assessment of risk of bias in included studies

All review authors will assess the risk of bias in included studies using The Cochrane Collaboration's tool for assessing risk of bias. The domains that will be assessed for each included study will be:

1. sequence generation;
2. allocation concealment;
3. blinding;
4. completeness of outcome data;
5. selective outcome reporting;
6. risk of other potential sources of bias.

We will tabulate a description of the above domains for each included trial, along with a judgement of on the risk of bias (low, high or unclear), based on the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011):

1. low risk of bias (adequate concealment of the allocation (e.g. sequentially numbered, sealed, opaque envelopes or centralised or pharmacy-controlled randomisation));
2. unclear risk of bias (unclear about whether the allocation was adequately concealed (e.g. where the method of concealment is not described or not described in sufficient detail to allow a definite judgement));
3. high risk of bias (inadequate allocation concealment (e.g. open random number lists or quasi-randomisation such as alternate days, date of birth, or case record number)).

We will provide a summary assessment of the risk of bias for the primary outcome across the studies (Higgins 2011). For each study, we will assess according to the following rationale:

1. low risk when there is a low risk of bias across all six key domains;
2. unclear risk of bias when there is an unclear risk of bias in one or more of the six key domains;
3. high risk of bias when there is a high risk of bias in one or more of the six key domains.

Measures of treatment effect

For dichotomous outcomes (e.g. pain or adverse effects: yes/no), we will express the estimate of effect of an intervention as risk ratios (RRs) together with 95% confidence intervals (CIs). For continuous outcomes (e.g. pain on a visual analogue scale), we will use mean differences (MDs) and 95% CIs to summarise the data; in the event that different studies measure outcomes using different scales, we will express the estimate of effect of an intervention as standardised mean differences (SMDs) and 95% CIs.

Unit of analysis issues

Where cluster randomised trials are included, we will undertake data analysis, whenever feasible, at the same level as the randomisation, or at the individual level accounting for the clustering.

Analysis of cross-over studies should take into account the two-period nature of the data using, for example, a paired t-test. We will enter log RRs or MDs/SMDs and standard errors into Review Manager software (Review Manager 2013), using the generic inverse variance method (Higgins 2011).

Dealing with missing data

We will contact trial authors for missing data if the report was published from the year 2000 or onwards. We consider it unfeasible to obtain data for trials published prior to this cut-off date. We will use methods as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* to estimate missing standard deviations (Higgins 2011).

Assessment of heterogeneity

We will assess the significance of any discrepancies in the estimates of the treatment effects from the different trials by means of Cochran's test for heterogeneity; heterogeneity will be considered significant if P value < 0.1 (Higgins 2011). We will also use the I^2 statistic, which describes the percentage total variation across studies that is due to heterogeneity rather than chance, to quantify heterogeneity with I^2 over 50% being considered substantial heterogeneity (Higgins 2011).

Assessment of reporting biases

If there are a sufficient number of trials (more than 10) included in any meta-analysis, we will assess publication bias according to the recommendations on testing for funnel plot asymmetry as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Data synthesis

We will perform meta-analysis of studies assessing the same comparisons and outcomes. We will combine RRs for dichotomous outcomes, and MDs (or SMDs if different scales are used) for continuous outcomes, using a random-effects model where there are four or more studies, or a fixed-effect model if there are less than four studies. We will include data from cross-over studies in any meta-analysis using the generic inverse variance method described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), combining them with parallel studies using the methods described in Elbourne 2002. We will present data from studies not included in meta-analyses in an additional table.

Subgroup analysis and investigation of heterogeneity

As appropriate, we will pursue subgroup analysis according to the three classifications of RAS highlighted above: minor, major and herpetiform.

Sensitivity analysis

If the number of studies allows, we will undertake a sensitivity analysis for each intervention and outcome limiting the analysis to studies at overall low risk of bias.

Presentation of main results

We will develop a 'Summary of findings' table for the main outcomes of this review using the GRADEPro software (GRADEpro 2008). We will assess the quality of the body of evidence with reference to the overall risk of bias of the included studies, the directness of the evidence, the inconsistency of the results, the precision of the estimates, the risk of publication bias and the magnitude of the effect. We will categorise quality of the body of evidence of each of the main outcomes as high, moderate, low or very low.

ACKNOWLEDGEMENTS

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APPENDICES

Appendix 1. MEDLINE (OVID) search strategy

1. Stomatitis, aphthous/
2. (recur$ or reoccur$ or severe).ti,ab.
3. 1 and 2
4. ((recur$ or reoccur$ or severe) adj10 ((aphthous or apthous or mouth$ or oral$) adj3 (ulcer$ or lesion$ or stomatitis))).ti,ab.
5. (aphthae or apthae).ti,ab.
6. "canker sore$".ti,ab.
7. "herpetiform ulcer$".ti,ab.
8. "periadenitis mucosa necrotica recurrens".ti,ab.
9. or/3-8

CONTRIBUTIONS OF AUTHORS

Development of protocol based on the latest Cochrane guidance: Jennifer Taylor (JT), Philip Riley (PR), Paul Brocklehurst (PB), Mike Lewis (ML), Mike Pemberton (MP), Anne-Marie Glenny (AMG), Tanya Walsh (TW), Martin Tickle (MT).

Identification of studies: JT, PB, AMG.

Data extraction: JT, PB, AMG, TW, Julian Yates (JY), PR.

Assessment of risk of bias: JT, PB, AMG, TW, JY, PR.

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There are no financial conflicts of interest and the review authors declare that they do not have any associations with any parties who may have vested interests in the results of this review.

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APPENDIX 7. Summary of the Chan et al. (2002) consensus treatment guidelines

Supplementary Table I. Summary of treatment recommendations from the First International Consensus on mucous membrane pemphigoid (MMP)*

Risk class	*Criteria (site, severity, rapidity)*	*Treatment*
High	Ocular, genital or esophageal and/or laryngeal lesions; OR Rapidly progressive disease	**SEVERE disease:** **Prednisone** (0.5−1.5 mg/kg/day) plus cyclophosphamide (1−2 mg/kg/day) OR alternative therapies: **Azathioprine** (1−2 mg/kg/day) *(Check thiopurine methyltransferase (TPMT) level before starting. Monitor activity: low level predicts efficacy and potentially severe myelosuppression/adverse events.)* OR **Mycophenolate mofetil** (1−2 g/day in divided doses) **MILD Disease:** **Dapsone** (50−200 mg/day) *(Check glucose-6-phosphate dehydrogenase (G6PD) level: Deficiency. Increases risk of hemolytic anemia.)* OR **Sulfamethoxypyridazine** (0.5−1 g/day) or **sulfapyridine** (0.25−1 g/day) *(Not universally available.)* *(Must improve ≤3 months or begin prednisolone + immunosuppressive agent.)*
Low	Oral mucosa only Or Oral mucosa + Skin	Moderate to high-dose topical corticosteroid If additional control needed: Add dapsone (50−200 mg/day) or other sulfa drug OR Low dose systemic corticosteroid Tetracycline (1-2 g/d) and nicotinamide (2-2.5 g/d) Consider adjuvants if further control needed: Azathioprine (1-2 mg/kg/day) Mycophenolate mofetil (1-2 g/d in divided doses)

*Chan LS, Ahmed AR, Anhalt GJ, et al. The first international consensus on mucous membrane pemphigoid: definition, diagnostic criteria, pathogenic factors, medical treatment, and prognostic indicators. Arch Dermatol. 2002;138:370-379.

Supplementary Table II. Mucous membrane pemphigoid (MMP) interventions

Intervention/ co-intervention	*Study type and number*	*Levels of evidence*	*Summary*	*References*
Azathioprine	**MMP**		**Letko, 2004** – Ocular MMP cohort, high risk of bias, variable treatments with insufficient details, outcome measures used had questionable validity	**MMP**
	CR-1	3		**CR**
	Ocular			(Kennedy, Devillez, et al., 2010)
	Cohort-1	2–		**Ocular**
	CS-1	3	**Thorne, 2008** – ocular MMP series, oral cyclophosphamide and oral prednisolone with variable adjuvants including azathioprine (see cyclophosphamide)	**Cohort**
	CR-1	3		(Lebeau, Mainetti, et al., 2004)
				CS
				(Thorne, Woreta, et al., 2008)
				CR
				Galdos and Etxebarria, 2008
Colchicine	**MMP**		**Chaidemenos, 2011** – series of 15 patients with MMP – treated with prednisone 40 mg/day and adjuvants including colchicine 1 mg/day – complete remission on colchicine in 5 of/12	**MMP**
	CS-1	3		**CS**
				(Chaidemenos, Sidiropoulos, et al., 2011)
Corticosteroids – IV	**MMP**		**El-Darouti 2011** – RCT of ocular MMP in 30 participants – comparing pulsed CYP IV/IV methylprednisolone (standard) versus standard plus IV pentoxyfylline (see cyclophosphamide)	**MMP**
	CR-1	3		**CR**
	Ocular			(Schumann, Schmidt, et al., 2009)
	RCT-1	1–		**Ocular**
	CS-1	3		**RCT**
			Suelves, 2013 – ocular MMP series treated with pulsed IV CYP and IV methylprednisolone (see cyclophosphamide)	(El Darouti, Fakhry Khattab, et al., 2011)
				CS
				(Suelves, Arcinue, et al., 2013)
Corticosteroids – oral	**MMP**		**El-Darouti, 2011** – RCT of ocular MMP in 30 participants – comparing pulsed CYP IV/IV methylprednisolone (standard) versus standard plus IV pentoxyfylline. Oral prednisolone used as adjuvant in both arms (see cyclophosphamide)	**MMP**
	CS-5	3		**CS**
	CR-5	3		(Segura, Iranzo, et al., 2007; Chaidemenos, Sidiropoulos, et al., 2011; Doycheva, Deuter, et al., 2011; Lourari, Herve, et al., 2011; Staines and Hampton, 2012)
	Ocular			
	RCT-1	1–		
	Cohort-1	2–		
	CS-1	3	**Letko, 2004** – ocular MMP cohort, high risk of bias, variable treatments with insufficient details, outcome measures used had questionable validity	**CR**
	CR-1	3		(Gunther, Wozel, et al., 2004; Wozniak, Waszczykowska, et al., 2006; Taverna, Lerner, et al., 2007; Yu, Chong, et al., 2007; Schumann, Schmidt, et al., 2009)
	Pediatric			
	CR-1	3	**Kharfi, 2010** – a case of a 20-month-old boy with MMP – treated successfully with systemic steroids followed by disease free maintenance on dapsone and topical (ocular) cyclosporine and oral prednisone	**Ocular**
				RCT
				(El Darouti, Fakhry Khattab, et al., 2011)
				Cohort
				(Letko, Miserocchi, et al., 2004)
				CS
				(Thorne, Woreta, et al., 2008)
				CR
				(Galdos and Etxebarria, 2008)
				Pediatric
				CR
				(Kharfi, Khaled, et al., 2010)
Corticosteroids –topical	**MMP**		**Canizares, 2006** – series of 3 patients with oral and ocular disease treated with etanercept 25 mg, topical clobetasol and nystatin	**MMP**
	CS-3	3		**CS**
	CR-1	3		(Canizares, Smith, et al., 2006; Carrozzo, Arduino, et al., 2009; Le Roux-Villet, Prost-Squarcioni, et al., 2011)
			Carrozzo, 2009 – open-label uncontrolled series of 9 MMP patients using minocycline – 5 with adjuvant topical clobetasol (see minocycline)	**Ocular**
				CR
				(Galdos and Etxebarria, 2008)
			Le Roux-Villet, 2011 – series of 25 MMP (10 with ocular disease) patients treated with 1–2 cycles rituximab and adjuvants, including dapsone and/or sulfasalazine and topical corticosteroids (see rituximab)	

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Supplementary Table II. Continued

Intervention/ co-intervention	*Study type and number*	*Levels of evidence*	*Summary*	*References*
Cyclophosphamide	**MMP**		**El-Darouti, 2011** – RCT of ocular MMP in 30 participants – comparing pulsed CYP IV/methylprednisolone IV (standard) versus standard plus IV pentoxyfylline. Study suggests no significant clinical benefit of standard therapy and pentoxyfylline over standard therapy alone. No drug discontinuation was needed in either arm due to adverse effects.	**MMP**
	CS-3	3		**CS**
	CR-2	3		(Segura, Iranzo, et al., 2007; Chaidemenos, Sidiropoulos, et al., 2011; Munyangango, Le Roux-Villet, et al., 2013)
	Ocular			**CR**
	RCT-1	1–		(Wozniak, Waszczykowska, et al., 2006; Yu, Chong, et al., 2007)
	Cohort-1	2–		**Ocular**
	CS-2	3		**RCT**
	CR-1	3		(El Darouti, Fakhry Khattab, et al., 2011)
			Letko, 2004 – ocular MMP cohort, high risk of bias, variable treatments with insufficient details, outcome measures used had questionable validity	**Cohort**
				(Letko, Miserocchi, et al., 2004)
			Segura, 2007 – series of 4 patients with MMP, treated with IVIg monotherapy of with adjuvant IS (including CYP) – (see IVIg)	**CS**
				(Thorne, Woreta, et al., 2008; Suelves, Arcinue, et al., 2013)
			Chaidemenos, 2011 – series of 15 patients with MMP – treated with prednisone 40 mg/day and adjuvants including oral CYP– complete remission in 1 of 4 using oral CYP	**CR**
				(Galdos and Etxebarria, 2008)
			Munyangango, 2013 – series of 13 MMP patients treated with oral CYP and adjuvants in 10 of 13 (dapsone/ sulfasalazine) - 7 of 13 achieved complete remission (3 of 5 ocular disease patients). 2 of 13 stopped CYP due to lymphopenia	
			Suleves, 2013 – ocular MMP series treated with pulsed IV CYP and IV methylprednisolone – complete remission in 54 of 65. 12 of 54 required to stop therapy due to adverse effects – 3 of 54 developed malignancy – the most common adverse effects were nausea (29%) and transient lymphopenia (26%)	
			Thorne, 2008 - ocular MMP series, oral cyclophosphamide and oral prednisolone with variable adjuvants, including azathioprine, dapsone, MMF – 58 of 70 patients achieved complete control. Adverse events included hematuria, infection (34 of 70), malignancy (8 of 70 – including 1 bladder carcinoma)	
Cyclosporine – topical	**Ocular**		**Doycheva, 2011** - series of 10 patients with ocular MMP treated with MMF 1 g twice daily as well as prednisolone and cyclosporine A 2% eye drops. 11 of 17 eyes with active inflammation at commencement of therapy showed a reduction in ocular inflammation. Prevention of cicatrization was prevented in 9 eyes of 7 patients.	**Ocular**
	CS-1	3		**CS**
	Pediatric			(Doycheva, Deuter, et al., 2011)
	CR-1	3		**Pediatric**
				CR
				(Kharfi, Khaled, et al., 2010)
			Kharfi, 2010 – a case of a 20-month-old boy with MMP – treated successfully with systemic steroids followed by disease-free maintenance on dapsone and topical (ocular) cyclosporine and oral prednisone	
Dapsone	**MMP**		**Chaidemenos, 2011** – series of 15 patients with MMP – treated with prednisone	**MMP**
	CS-3	3		**CS**

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Supplementary Table II. Continued

Intervention/ co-intervention	*Study type and number*	*Levels of evidence*	*Summary*	*References*
	CR-2	3	40 mg/day and adjuvants including dapsone – complete remission in 3 of 10 using dapsone	(Chaidemenos, Sidiropoulos, et al., 2011; Staines and Hampton, 2012; Munyangango, Le Roux-Villet, et al., 2013)
	Ocular			
	Cohort-1	2–	**Staines, 2012** – series of 6 patients with MMP treated with combination of MMF, dapsone and oral prednisolone – all had complete oral disease control on therapy at 18 months follow-up	**CR** (Yu, Chong, et al., 2007; Gurcan and Ahmed, 2009)
	CS-1	3		**Ocular**
	CR-1	3		**Cohort** (Letko, Miserocchi, et al., 2004)
	Pediatric			**CS** (Thorne, Woreta, et al., 2008)
	CR-2	3	**Munyangango, 2013** –series of 13 MMP patients treated with oral CYP and adjuvants in 10 of 13 (dapsone/ sulfasalazine) – (see cyclophosphamide)	**CR** (Prey, Robert, et al., 2007)
			Letko, 2004 – ocular MMP cohort, high risk of bias, variable treatments with insufficient details, outcome measures used had questionable validity	**Pediatric**
				CR (Schoeffler, Roth, et al., 2004; Kharfi, Khaled, et al., 2010)
			Thorne, 2008 – ocular MMP series, oral cyclophosphamide and oral prednisolone with variable adjuvants including azathioprine, dapsone, MMF – (see cyclophosphamide)	
			Kharfi, 2010 – a case of a 20-month-old boy with MMP – treated successfully with systemic steroids followed by disease-free maintenance on dapsone and topical (ocular) cyclosporine and oral prednisone	
			Schoeffler, 2004 – a 9-year-old girl with vulval MMP. No clinical response was obtained after 4 weeks of topical clobetasol propionate cream – dapsone was then started – complete healing was obtained in 1 month, with persistent remission after tapering dapsone to a dosage as low as 25 mg on alternate days over 1 year. There was no recurrence after discontinuation of the treatment. Adverse events were not discussed.	
Etanercept	**MMP**		**Canizares, 2006** – series of 3 patients with oral and ocular disease treated with etanercept 25 mg and topical clobetasol and nystatin – 2 of 3 gained partial control and 1 of 3 complete control of disease	**MMP**
	CS-1	3		**CS** (Canizares, Smith, et al., 2006)
	CR-2	3		**CR** Kennedy, Devillez, et al., 2010
				Ocular
				CR (Canizares, Smith, et al., 2006; Prey, Robert, et al., 2007; Kennedy, Devillez, et al., 2010)
IVIg	**MMP**		**Canizares, 2006** – series of 3 MMP patients treated with etanercept – 1 case was treated with IVIg unsuccessfully before etanercept – headaches and hypertension were reported with the IVIg therapy	**MMP**
	CS-2	3		**CS** (Canizares, Smith, et al., 2006; Segura, Iranzo, et al., 2007)
	CR-3	3		**CR** (Wozniak, Waszczykowska, et al., 2006; Yu, Chong, et al., 2007; Gurcan and Ahmed, 2009)
	Ocular			
	Cohort-1	2–		
	CS-1	3	**Segura, 2007** – series of 4 patients with MMP, treated with IVIg monotherapy of with adjuvant IS. 1 of 4 with oral disease had complete remission after 8 cycles of monotherapy, 2 of 4 had partial remission (1 on monotherapy; 1 with oral prednisolone and oral CYP) – these 2 cases had to discontinue therapy due to	**Ocular**
	CR-1	3		**Cohort** (Letko, Miserocchi, et al., 2004)
				CS (Sami, Letko, et al., 2004)

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Supplementary Table II. Continued

Intervention/ co-intervention	*Study type and number*	*Levels of evidence*	*Summary*	*References*
			adverse effects of IVIg. 1 of 4 was a nonresponder despite adjuvant IS therapy **Letko, 2004** – ocular MMP cohort, high risk of bias, variable treatments with insufficient details, outcome measures used had questionable validity **Sami, 2004** – series of 10 MMP patients with refractory ocular disease treated with IVIg monotherapy. All 10 patients initially demonstrated signs of clinical improvement with IVIg therapy. The total number of IVIg cycles ranged from 20 to 42 (mean, 32), and the total duration of IVIg therapy ranged from 25 to 43 months (mean, 35). 8 of 10 patients who completed the protocol had an improvement in their visual acuity and did not have further progression of subepithelial conjunctival fibrosis. 2 of 10 patients dropped out of the protocol and lost vision – the reasons for dropout were unclear	**CR** (Galdos and Etxebarria, 2008)
Low level laser therapy	**MMP** CS-1	3	**Cafaro, 2012** – series of 3 MMP patients treated with LLLT. 3 patients with MMP – all patients had complete resolution of oral lesions in less than a mean of 10 treatment sessions. Single observer, blinding not stated	**MMP** (Cafaro, Broccoletti, et al., 2012)
Methotrexate	**Ocular** Cohort-1	3	**Letko, 2004** – ocular MMP cohort, high risk of bias, variable treatments with insufficient details, outcome measures used had questionable validity	**Ocular** (Lebeau, Mainetti, et al., 2004)
Minocycline	**MMP** CS-1 **Ocular** CR-1	3 3	**Carrozzo, 2009** – open label, uncontrolled series of 9 MMP patients using minocycline (5 with adjuvant topical clobetasol) – complete remission in 3 of 9, 2 of 9 no response – 5 of 9 patients discontinued minocycline due to adverse effects	**MMP** **CS** (Carrozzo, Arduino, et al., 2009) **Ocular** **CR** (Galdos and Etxebarria, 2008)
Mycophenolate mofetil	**MMP** CS-2 CR-1 **Ocular** CS-2	3 3 3	**Chaidemenos, 2011** – series of 15 patients with MMP – treated with prednisone 40 mg/day and adjuvants including MMF– complete remission in 0 of 1 using MMF **Staines, 2012** – series of 6 patients with MMP treated with combination of MMF, dapsone and oral prednisolone – all had complete oral disease control on therapy at 18 months follow-up **Thorne, 2008** – ocular MMP series, oral cyclophosphamide and oral prednisolone with variable adjuvants, including azathioprine, dapsone, MMF (see cyclophosphamide) **Doycheva, 2011** – series of 10 patients with ocular MMP treated with MMF 1 g twice daily as well as prednisolone and cyclosporine A 2% eye drops. 11 of 17 eyes with active inflammation at commencement of therapy showed a reduction in ocular inflammation. Prevention of cicatrization in 9 eyes of 7 patients.	**MMP** **CS** (Chaidemenos, Sidiropoulos, et al., 2011; Staines and Hampton, 2012) **CR** (Taverna, Lerner, et al., 2007) **Ocular** **CS** (Thorne, Woreta, et al., 2008; Doycheva, Deuter, et al., 2011)

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Supplementary Table II. Continued

Intervention/ co-intervention	*Study type and number*	*Levels of evidence*	*Summary*	*References*
Mycophenolic acid	**MMP** CS-1	 3	**Marzano, 2006** – MMP series of 2 participants (1 with Brunsting-Perry variant) with a high risk of bias – treated with MPA and adjuvant oral steroids – partial remission 1 of 2, complete remission in 1 of 2	**MMP** **CS** (Marzano, Dassoni, et al., 2006)
Pentoxyfylline	**Ocular** RCT-1	 1–	**El Darouti, 2011** – RCT of ocular MMP in 30 participants – comparing pulsed CYP IV/methylprednisolone IV (standard) versus standard plus IV pentoxyfylline. Study suggests no significant clinical benefit of standard therapy and pentoxyfylline over standard therapy alone. No drug discontinuation was needed in either arm due to adverse effects.	**Ocular** **RCT** (El Darouti, Fakhry Khattab, et al., 2011)
Rituximab	**MMP** CS-2 CR-2	 3 3	**Le Roux-Villet, 2011** – series of 25 MMP (10 with ocular disease) patients treated with 1–2 cycles rituximab and adjuvants, including dapsone and/or sulfasalazine and topical corticosteroids – 17 of 25 in complete remission at 12 weeks after 1 cycle; 9 of 10 ocular patients were clear of disease after mean of 10 weeks. 10 of 25 relapse at mean of 4(range 1–16) months. 2 of 25 died (also on IS medications) **Lourari, 2011** – series of 6 MMP patients treated with rituximab with unspecified adjuvant IS – 4 of 6 complete remission on therapy	**MMP** **CS** (Le Roux-Villet, Prost-Squarcioni, et al., 2011; Lourari, Herve, et al., 2011) **CR** (Taverna, Lerner, et al., 2007; Schumann, Schmidt, et al., 2009)
Sulfasalazine	**MMP** CS-2	 3	**Le Roux-Villet, 2011** – series of 25 MMP (10 with ocular disease) patients treated with 1–2 cycles rituximab and adjuvants, including dapsone and/or sulfasalazine and topical (see rituximab) **Munyangango, 2013** – series of 13 MMP patients treated with oral CYP and adjuvants in 10 of 13 (dapsone/ sulfasalazine) – (see cyclophosphamide)	**MMP** **CS** (Munyangango, Le Roux-Villet, et al., 2013) (Le Roux-Villet, Prost-Squarcioni, et al., 2011)
Tacrolimus - topical	**MMP** CS-1 CR-3 **Pediatric** CR-1	 3 3 3	**Assmann, 2004** – series of 2 refractory oral MMP patients treated with topical tacrolimus – complete remission was achieved - adverse effects were not discussed **Lebeau, 2004** – case of an 8-year-old with vulval MMP – responded to topical tacrolimus	**MMP** **CS** (Assmann, Becker, et al., 2004) **CR** (Gunther, Wozel, et al., 2004; Suresh, Martinez Calixto, et al., 2006; Lee, Blazek, et al., 2011) **Pediatric** **CR** (Lebeau, Mainetti, et al., 2004)

Note: Modified from 2002. See the full publication for additional details. Site, severity and rapidity of progression determine risk status and medications.

MMP, mucous membrane pemphigoid; ocular, ocular only *MMP* study; pediatric, pediatric only *MMP* study; *RCT*, randomized controlled trial; *CCT*, controlled clinical trial; cohort, cohort study; *CS*, case series; *CR*, case report; *CYP*, cyclophosphamide; *CYP IV*, pulsed *IV* cyclophosphamide; *IS*, immunosuppressant; *IV*, intravenous; *IVIg*, intravenous immunoglobulin; *LLLT*, low level laser therapy; *MMF*, mycophenolate mofetil.

Levels of Evidence (SIGN 2008)

1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

1+ Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias

APPENDIX 8. COS Participant information pack

Core Outcome Set for Recurrent Aphthous Stomatitis (COSRAS)

J Taylor, M. N. Pemberton

Core outcome sets (COS)

Core outcome sets are an agreed minimum set of outcome domains to be measured and reported in all trials of a particular treatment or condition (Williamson, 2012)

Recurrent Aphthous Stomatitis (RAS)

RAS is the most frequent form of episodic oral ulceration in otherwise healthy individuals. There are wide varieties of treatments available but the evidence base to guide clinicians in their decision making is poor. This is due to a number of methodological issues in oral medicine trials including heterogeneity of the outcomes measured.

A set of clinically relevant outcome measures needs to be developed (Brocklehurst, 2012).

How to develop a core outcome set for RAS

- *Stakeholder involvement*
- *Identifying existing knowledge*
- *Consensus methods*

Stakeholder involvement

RAS patients were involved in the process from the initial stages. We acquired a small grant from RfPB (Research for patient benefit) and held a patient information meeting in July 2014. Seven long-term RAS patients attending University Dental Hospital of Manchester oral medicine clinic were invited to take part. These patients had previously been treated with a wide variety of interventions over many years with varying degrees of clinical benefit. A non-clinical researcher facilitated the meeting and patients were invited to discuss a variety topics related to 'living with RAS'. They were asked to develop a list of outcome measures they felt were most important to them as a patient. No limit was given to the number of outcomes they could suggest. They agreed on 6 essential outcomes.

- *Size*
- *Duration*
- *Frequency*
- *Number*
- *Pain*
- *Diet*

Identifying existing knowledge

A systematic review of 73 interventional RAS randomised controlled trials was carried out.

313 individual outcomes were identified. These outcomes were condensed down to 22 by removing duplication and grouping into relevant domains (e.g. discomfort/soreness/tenderness/pain was grouped as pain)

- *Presence or absence of an ulcer or ulcers*
- *Size*
- *Duration*
- *Frequency*
- *Diet*
- *Pain*
- *Number of ulcers*
- *Location of ulcers*
- *Side effects of treatment*
- *Quality of life*
- *Composite score*
- *Other signs and symptoms (burning, erythema)*
- *Additional ulcer treatment required*
- *Improvement*
- *Blood test*
- *Vital signs*
- *Induced /challenged pain*
- *Tolerability of treatment*
- *Changes in condition*
- *Clinical evaluation*
- *Patient's overall assessment*
- *healing*

Consensus methods

Previous studies have used Delphi method to gain consensus (a quantitative option which establishes a convergence of opinion. These are typically carried out as large scale questionnaires over 2 or more rounds with the results of previous rounds revealed to everyone in subsequent rounds)

There are a number of disadvantages to the use of the Delphi method including high attrition rates, expense and time to complete.

In November 2014, we trialled an interactive adapted Delphi method within a group of relevant stakeholders (Northern oral medicine group). We used turning point clicker technology

It was agreed that the process was easy to follow and could be used in future development of core outcome sets in oral medicine.

BSOM 2015

BSOM is keen to support research which aims to improve the quality of our clinical practice in oral medicine. As part of this we hope you will be happy to take part in this interactive process.

We will repeat the interactive clicker process during the morning session on Friday29th May.

Following a brief introduction, you will be asked to vote on the importance of various outcomes on a scale of 1-9 (1 limited importance - 9 critical importance)

If you feel the outcome measure is essential to assess the efficacy of a treatment for RAS, and should be retained in a core outcomes set (must be measured in all future trials) then vote high.

*If you think the outcome is important but does **not** need to be measured in every trial (or it could be measured in addition to the core outcome set when) then vote middle or low*

Most of these outcomes will be easy to understand, however, if an outcome appears vague or you are not quite sure, then you may consider that outcome as of less importance to keep in a core outcome set. (i.e. vote low or middle)

Remember trials will not be limited to the core outcome set. You can still measure as many outcomes as you like in a trial, as long as all trials measure the same group of core outcomes.

Please consider the list of outcomes on the previous page. If you have any essential additional outcomes that you believe should be measured then you will be given an opportunity to add them prior to the clicker session.

Many thanks for your involvement.

(We are grateful to the School of Dentistry, University of Manchester for the use of the clickers and for IT support. Please note the clicker handsets do not work in any other setting and we would be grateful if they could be returned following the session.)

APPENDIX 8. Summary of publications

Brocklehurst P, Tickle M, Glenny AM, Lewis MA, Pemberton MN, Taylor J, Walsh T, Riley P, Yates JM. Systemic interventions for recurrent aphthous stomatitis (mouth ulcers). Cochrane Database of Systematic Reviews 2012, Issue 9. Art. No.: CD005411
Citations to date: 101

Abstract

Recurrent aphthous stomatitis (RAS) is the most frequent form of oral ulceration, characterised by recurrent oral mucosal ulceration in an otherwise healthy individual. At its worst RAS can cause significant difficulties in eating and drinking. Treatment is primarily aimed at pain relief and the promotion of healing to reduce the duration of the disease or reduce the rate of recurrence. A variety of topical and systemic therapies have been utilised. To determine the clinical effect of systemic interventions in the reduction of pain associated with RAS, a reduction in episode duration or frequency. We undertook electronic searches of: Cochrane Oral Health Group and PaPaS Trials Registers (to 6 June 2012); CENTRAL via The Cochrane Library (to Issue 4, 2012); MEDLINE via OVID (1950 to 6 June 2012); EMBASE via OVID (1980 to 6 June 2012); CINAHL via EBSCO (1980 to 6 June 2012); and AMED via PubMed (1950 to 6 June 2012). We searched reference lists from relevant articles and contacted the authors of eligible trials to identify further trials and obtain additional information. We included randomised controlled trials (RCTs) in which the primary outcome measures assess a reduction of pain associated with RAS, a reduction in episode duration or a reduction in episode frequency. Trials were not restricted by outcome alone. We also included RCTs of a cross-over design. Two review authors independently extracted data in duplicate. We contacted trial authors for details of randomisation, blindness and withdrawals. We carried out risk of bias assessment on six domains. We followed The Cochrane Collaboration statistical guidelines and risk ratio (RR) values were to be calculated using fixed-effect models (if two or three trials in each meta-analysis) or random-effects models (if four or more trials in each meta-analysis). A total of 25 trials were included, 22 of which were placebo controlled and eight made head-to-head comparisons (five trials had more than two treatment arms). Twenty-one different interventions were assessed. The interventions were grouped into two categories: immunomodulatory/anti-inflammatory and uncertain. Only one study was assessed as being at low risk of bias. There was insufficient evidence to support or refute the use of any intervention. No single treatment was found to be effective and therefore the results remain inconclusive in regard to the best systemic intervention for RAS. This is likely to reflect the poor methodological rigour of trials, and lack of studies for certain drugs, rather than the true effect of the intervention. It is also recognised that in clinical practice, individual drugs appear to work for individual patients and so the interventions are likely to be complex

in nature. In addition, it is acknowledged that systemic interventions are often reserved for those patients who have been unresponsive to topical treatments, and therefore may represent a select group of patients.

Taylor J, Brocklehurst P, Walsh T, Riley P, Glenny A-M, Gorodkin R, Pemberton MN. Interventions for the management of oral ulcers in Behçet's disease. Cochrane Database of Systematic Reviews 2014, Issue 3. Art. No.: CD011018. DOI: 10.1002/14651858.CD011018

Citations to date: 29

Abstract

Background: Behçet's disease is a chronic inflammatory vasculitis that can affect multiple systems. Mucocutaneous involvement is common, as is the involvement of many other systems such as the central nervous system and skin. Behçet's disease can cause significant morbidity, such as loss of sight, and can be life threatening. The frequency of oral ulceration in Behçet's disease is thought to be 97% to 100%. The presence of mouth ulcers can cause difficulties in eating, drinking, and speaking leading to a reduction in quality of life. There is no cure for Behçet's disease and therefore treatment of the oral ulcers that are associated with Behçet's disease is palliative. Objectives: To determine the clinical effectiveness and safety of interventions on the pain, episode duration, and episode frequency of oral ulcers and on quality of life for patients with recurrent aphthous stomatitis (RAS)-type ulceration associated with Behçet's disease. Search methods: We undertook electronic searches of the Cochrane Oral Health Group Trials Register (to 4 October 2013); the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2013, Issue 9); MEDLINE via Ovid (1946 to 4 October 2013); EMBASE via Ovid (1980 to 4 October 2013); CINAHL via EBSCO (1980 to 4 October 2013); and AMED via Ovid (1985 to 4 October 2013). We searched the US National Institutes of Health trials register (http://clinicaltrials.gov) and the World Health Organization (WHO) Clinical Trials Registry Platform for ongoing trials. There were no restrictions on language or date of publication in the searches of the electronic databases. We contacted authors when necessary to obtain additional information. Selection criteria: We included randomised controlled trials (RCTs) that looked at pre-specified oral outcome measures to assess the efficacy of interventions for mouth ulcers in Behçet's disease. The oral outcome measures included pain, episode duration, episode frequency, safety, and quality of life. Trials were not restricted by outcomes alone. Data collection and analysis: All studies meeting the inclusion criteria underwent data extraction and an assessment of risk of bias, independently by two review authors and using a pre-standardised data extraction form. We used standard methodological procedures expected by The Cochrane Collaboration. Main results: A total of 15 trials (n = 888 randomised participants) were included, 13 were placebo controlled and three were head to head (two trials had more than two treatment arms). Eleven of the trials were conducted in Turkey, two in Japan, one in Iran and one in the UK. Most trials used the International Study Group criteria for Behçet's disease. Eleven different interventions were assessed. The interventions were grouped into two categories, topical and systemic. Only one study was assessed as

being at low risk of bias. It was not possible to carry out a meta-analysis. The quality of the evidence ranged from moderate to very low and there was insufficient evidence to support or refute the use of any included intervention with regard to pain, episode duration, or episode frequency associated with oral ulcers, or safety of the interventions. Authors' conclusions: Due to the heterogeneity of trials including trial design, choice of intervention, choice and timing of outcome measures, it was not possible to carry out a meta-analysis. Several interventions show promise and future trials should be planned and reported according to the CONSORT guidelines. Whilst the primary aim of many trials for Behçet's disease is not necessarily reduction of oral ulceration, reporting of oral ulcers in these studies should be standardised and pre-specified in the methodology. The use of a core outcome set for oral ulcer trials would be beneficial.

Taylor J, McMillan R, Shephard MK, Setterfield J, Ahmed R, Carrozzo M, Grando S, Mignogna M, Kuten-Shorrer M, Musbah TM, Elia A, McGowan R, Kerr AR, Greenberg M, Hodgson T, Sirois D, World Workshop on Oral Medicine VI: A Systematic Review of the Treatment of Mucous Membrane Pemphigoid, Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology (2015), doi: 10.1016/j.oooo.2015.01.024

Citations to date: 55

Abstract

To determine the efficacy and safety of interventions for mucous membrane pemphigoid (MMP). We conducted a systematic review from 2003 to 2013 according to the Cochrane Collaboration methodology. Randomized controlled trials (RCTs) or controlled clinical trials and observational studies were included, with diagnosis confirmed by clinical, histopathologic, and immunofluorescence criteria. The primary outcome was lesion remission or healing; several relevant secondary outcomes were also included. In the final analysis, 1 RCT and 32 observational studies were included. The one included RCT with a high risk of bias in multiple domains found limited evidence that pentoxifylline, combined with corticosteroid and cyclophosphamide, was more effective than standard therapy (corticosteroid + cyclophosphamide alone) for ocular MMP. We summarize here the outcomes from 32 observational studies examining 242 patients across 19 unique treatments. Interventions that show promise include rituximab and intravenous immunoglobulin. This systematic review is the most recent since 2003-2009. There is still lack of high-quality research providing evidence-based MMP treatments.

McMillan R, Taylor J, Shephard M, Ahmed R, Carrozzo M, Setterfield J, Grando S, Mignogna M, Kuten-Shorrer M, Musbah T, Elia A, McGowan R, Kerr AR, Greenberg MS, Hodgson T, Sirois D, World Workshop on Oral Medicine VI: A Systematic Review of the Treatment of Mucocutaneous Pemphigus Vulgaris, Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology (2015) doi: 10.1016/j.oooo.2015.01.022.

Citations to date: 37

Abstract

To determine the efficacy and safety of interventions for pemphigus vulgaris (PV). We conducted a systematic review from 2003 to 2013 according to the Cochrane Collaboration methodology. Randomized controlled trials (RCTs) or controlled clinical trials (CCTs) and observational studies were conducted along with diagnosis confirmed by clinical, histopathologic, and immunofluorescence criteria. Primary outcomes were disease remission and mortality; several relevant secondary outcomes were also included. Fourteen RCTs or CCTs and 110 observational studies were included in the final analyses. RCTs or CCTs demonstrated considerable heterogeneity in outcome measures, and all had a high risk of bias for at least 1 of 8 domains. Of the studies, 96.8% (120) described the use of oral corticosteroids. Azathioprine and mycophenolate-mofetil were the most commonly cited treatments. An increasing number of studies described biologic therapies (rituximab, intravenous immunoglobulin [IVIg]). Evidence supporting recent comprehensive treatment guidelines was reviewed. We found persisting wide variations in treatment practice and inadequate quality of research supporting optimal PV treatment.

Taylor, J., Walsh, T., Worthington, H., Brocklehurst, P., Pemberton M., Glenny AM. Cochrane and the COMET initiative: developing the evidence base in oral medicine. British Dental Journal 223, 729–732 (2017).

Citations to date: 7

Abstract

All clinicians in medicine and dentistry aim to deliver evidence-based practice; however, it is widely recognised that the current evidence base for interventions in oral medicine, as with many other specialties, is of a low quality. The highest level of evidence is considered to be the systematic review and meta-analysis. The Cochrane Collaboration and the Cochrane Oral Health group produce high quality systematic reviews, however, despite the large number of trials carried out for treatments in oral medicine, the results are often not able to be utilised to guide clinical care due to the various methodological limitations of the trials including the heterogeneity of outcome measures used. To improve the strength of the evidence base this will need to change. The Comet initiative aims to support the development of core outcome sets which are used to allow homogeneity of outcome measures in trials and therefore will allow pooling of data for meta-analysis in future systematic reviews. This paper explores the complexities involved in producing evidence for oral medicine interventions and introduces an approach for developing core outcome sets in oral medicine.