ClinicalEvidence

Aphthous ulcers (recurrent)

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ABSTRACT

INTRODUCTION: Most people with recurrent aphthous ulcers develop a few ulcers less than 10 mm in diameter that heal after 7 to 10 days without scarring. The causes are unknown but local physical trauma may trigger ulcers in susceptible people. In 10% of sufferers, lesions are more than 10 mm in diameter and can cause scarring. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of selected topical treatments for recurrent idiopathic aphthous ulcers? We searched: Medline, Embase, The Cochrane Library, and other important databases up to December 2013 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found nine studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: analgesics (local), corticosteroids (topical), tetracycline antibiotic mouthwash, and topical antiseptic agents (chlorhexidine and similar agents).

QUESTIONS

What are the effects of selected topical treatments for recurrent idiopathic aphthous ulcers? 3

INTERVENTIONS

TREATMENT

Likely to be beneficial

Corticosteroids (topical) 5

Topical antiseptic agents (chlorhexidine may be effective; insufficient evidence for other similar agents) 12

Unknown effectiveness

Analgesics (local) 3

Tetracycline antibiotic mouthwash 10

Key points

- Recurrent aphthous ulcers are the most common cause of recurrent oral ulceration in otherwise-healthy individuals.
- Most people with recurrent aphthous ulcers develop a few ulcers less than 10 mm in diameter that heal after 7 to 10 days without scarring.

  In 10% of sufferers, lesions are more than 10 mm in diameter and can cause scarring.

  The majority of aphthous ulcers are idiopathic, although factors such as local physical trauma may trigger ulcers in susceptible people.
- Chlorhexidine mouth rinses may reduce the severity and pain of ulceration, although studies have reported inconclusive results about whether the incidence of new ulcers is reduced.
- Topical corticosteroids may reduce the number of new ulcers, reduce pain, and increase healing of ulcers without causing notable adverse effects.
- We don't know whether local analgesics or tetracycline mouthwash work, as evidence was weak.

Clinical context

GENERAL BACKGROUND

Recurrent aphthous ulcers are the most common cause of recurrent oral ulceration. They are painful and usually occur in recurrent bouts at intervals of a few days to a few months. Up to 66% of young adults give a history consistent with recurrent aphthous ulceration. The frequency of recurrent aphthous ulceration lessens with advancing age.

FOCUS OF THE REVIEW

This update focuses on the evidence base for selected topical treatments used for idiopathic recurrent aphthous ulceration. Topical treatments, in general terms, are safer than systemic interventions and are considered as a first-line treatment for recurrent aphthous ulceration.

COMMENTS ON EVIDENCE

This systematic review highlighted inconclusive evidence-based results with regard to the best topical intervention for recurrent aphthous ulceration. Consideration needs to be given that, in clinical practice, different topical treatments may appear to be effective in individual patients despite the paucity of evidence to substantiate the treatment's efficacy. Hence, the lack of evidence may simply reflect either the absence of studies for certain therapies or inadequate study design and/or implementation combined with the multifactorial nature of recurrent aphthous ulceration.

SEARCH AND APPRAISAL SUMMARY

The updated literature search for this review was carried out from the date of the last search, August 2006 to December 2013. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the review, please see the Methods section. Searching of electronic databases retrieved 153 studies. After deduplication and removal of conference abstracts, 109 records were screened for inclusion in the review. Appraisal of titles and abstracts led to the exclusion of 100 studies and the further review of nine full publications. Of the nine full articles evaluated, two RCTs were added at this update.

ADDITIONAL INFORMATION

In future updates, we would like to consider other topical interventions such as barrier techniques (i.e., inactive preparations that put a lining on ulcers), topical immunosuppressant agents (e.g., tacrolimus), topical calcineurin inhibitors, and homeopathic topical treatments.

DEFINITION

Recurrent aphthous ulcers (RAU) are superficial, rounded, painful mouth ulcers usually occurring in recurrent bouts at intervals of a few days to a few months in otherwise-well people. [1] They are the most common cause of recurrent oral ulceration and may be classified as minor (<10 mm), major (>10 mm) or herpetiform aphthous ulcers.

INCIDENCE/ PREVALENCE

The point prevalence of recurrent aphthous ulcers in Swedish adults has been reported as 2%. [1] Prevalence may be 5% to 10% in some groups of children. Up to 66% of young adults give a history consistent with recurrent aphthous ulceration. Frequency of RAU lessens with advancing age. [2]

AETIOLOGY/ RISK FACTORS

The majority of aphthous ulcers are idiopathic with no known cause identified, although, factors such as local physical trauma may trigger ulcers in susceptible people. Recurrent aphthous ulcers are uncommon on keratinised oral mucosal surfaces or with people who smoke tobacco. [1] [3] Aphthous-like ulcers may develop secondary to systemic diseases such as Behçet's disease, coeliac disease, inflammatory bowel disease, and haematinic deficiencies, or to drugs such as non-steroidal anti-inflammatory drugs (NSAIDS). [1] [3] Only idiopathic RAU are considered in this review.

PROGNOSIS

Minor recurrent aphthous ulcers typically involve non-keratinised oral mucosa, are less than 10 mm in diameter, and persist over a 7 to 10 day period. Spontaneous healing without scarring is generally followed by a variable ulcer-free period and recurrence of the ulceration. [4] The minor variant accounts for 80% of patients with RAU. [5] Major recurrent aphthous may involve both keratinised and non-keratinised oral mucosa, may exceed 10 mm in diameter, may persist for 20 to 30 days, and heal with scarring. [4] Herpetiform ulcers present as multiple (ranging from 1–100) pinpoint ulcers involving either keratinised or non-keratinised mucosa with the potential for these ulcers to merge into a larger area of ulceration. [4] Most of the trials in this review have focused on the treatment of minor aphthous ulceration.

AIMS OF INTERVENTION

To reduce the severity of the episode and the incidence, duration, and pain of ulceration with minimal adverse effects.

OUTCOMES

Ulcer severity includes Ulcer Day Index (the sum of the number of ulcers each day over a period, usually 4–8 weeks, which indicates the severity of the episode and reflects the mean prevalence and duration of ulcers), number of ulcer-free days during a specified period, duration of ulceration (mean duration of individual ulcers, which is difficult to determine because of uncertainty in detecting the point of complete resolution), size of ulcer, severity of pain (symptom score based on subjective pain severity recorded in categories on a questionnaire [e.g., from 0–3, ranging from no pain to severe pain] or on a 10 cm visual analogue scale); **incidence of new ulcers** number of new ulcers appearing within a specified period, usually 4 to 8 weeks; **adverse effects**. The diameter of lesions is a proxy measure of the clinical severity of an episode of ulceration.

METHODS

BMJ Clinical Evidence search and appraisal December 2013. The following databases were used to identify studies for this review: Medline 1966 to December 2013, Embase 1980 to December 2013, and The Cochrane Library, issue 11, 2013. Additional searches were carried in the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) database. We also searched for retractions of studies included in this review. Titles and abstracts identified by the initial search, run by an information specialist, were first assessed against predefined criteria by an evidence scanner. Full texts of potentially relevant studies were then assessed against predefined criteria by an evidence analyst. Studies selected for inclusion were discussed with an expert contributor. All data relevant to the review were then extracted by an evidence analyst. Study design

criteria for inclusion in this review were published RCTs and systematic reviews, at least single-blinded, and containing more than 20 individuals (or 10 in a crossover trial), of whom more than 80% were followed up. There was no minimum follow-up. We included RCTs and systematic reviews of RCTs where harms of an included intervention were assessed, applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the review as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 19). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of selected topical treatments for recurrent idiopathic aphthous ulcers?**

OPTION **ANALGESICS (LOCAL)**

- For GRADE evaluation of interventions for Aphthous ulcers (recurrent), see table, p 19 .
- We don't know whether local analgesics work, as few well planned studies were found

Benefits and harms

Benzydamine hydrochloride mouthwash compared with placebo:

We found no systematic review but identified one small crossover RCT comparing benzydamine hydrochloride mouthwash, chlorhexidine, and placebo. [6]

Ulcer severity

Benzydamine hydrochloride mouthwash compared with placebo Benzydamine hydrochloride mouthwash may be no more effective than placebo at reducing the number of ulcers or at reducing pain in people with recurrent aphthous ulcers; however, the evidence was limited (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer severity					
[6] RCT **Crossover design** **3-armed trial**	18 people	**Number of ulcers , 12 weeks** with benzydamine hydrochloride mouthwash with placebo Absolute results not reported The third arm evaluated chlorhexidine See Further information on studies for details on user preference	Reported as not significant P value not reported	⟷	Not significant
[6] RCT **Crossover design** **3-armed trial**	18 people	**Mean ulcer size , 12 weeks** with benzydamine hydrochloride mouthwash with placebo Absolute results not reported The third arm evaluated chlorhexidine See Further information on studies for details on user preference	Reported as not significant P value not reported	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain relief					
[6] RCT **Crossover design** **3-armed trial**	18 people	**Pain intensity score , 12 weeks** with benzydamine hydrochloride mouthwash with placebo Absolute results not reported The third arm evaluated chlorhexidine See Further information on studies for details on user preference	Reported as not significant P value not reported	⟷	Not significant

Occurrence of new ulcers

No data from the following reference on this outcome. [6]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[6] RCT **Crossover design** **3-armed trial**	18 people	**Adverse effects , 12 weeks** with benzydamine hydrochloride mouthwash with placebo The RCT reported that stinging was reported by 9 people with benzydamine hydrochloride mouthwash and 9 people with placebo The third arm evaluated chlorhexidine See Further information on studies for details on user preference			

Further information on studies

[6] The RCT found that 8/18 (44%) people stated a preference of benzydamine hydrochloride because of its transient topical analgesic effect.

Comment: We found no other good studies of the efficacy of local analgesic agents for the treatment of aphthous ulceration.

Clinical guide
Analgesics, such as benzydamine hydrochloride, may potentially exert their topical effect on recurrent aphthous ulceration as both an anti-inflammatory and an analgesic agent. Analgesic mouthwashes are available as over-the-counter medicines and patients often use these in the first instance, before

seeking medical advice. There is a lack of evidence of their efficacy; however, they may provide some variable symptomatic relief to some patients.

OPTION CORTICOSTEROIDS (TOPICAL)

- For GRADE evaluation of interventions for Aphthous ulcers (recurrent), see table, p 19 .
- Topical corticosteroids may reduce the number of new ulcers, reduce pain, and increase healing of ulcers without causing notable adverse effects.

Benefits and harms

Topical corticosteroids versus placebo:

We found no systematic review, but found 10 RCTs that reported clinical outcomes in people with recurrent aphthous ulcers. [7] [8] [9] [10] [11] [12] [13] [14] [15] [16]

Ulcer severity

Topical corticosteroids compared with placebo Topical corticosteroids may be more effective than placebo at improving pain relief from ulcers, duration of ulcers, and ulcer size but we don't know whether topical corticosteroids are more effective at reducing the the sum of the number of ulcers each day over a set period (Ulcer Day Index) in people with recurrent aphthous ulcers (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Size of ulcer					
[15] RCT	240 people with minor recurrent aphthous ulcers	**Mean reduction in size of ulcers (mm^2) , day 6** 7.17 with dexamethasone ointment 4.35 with placebo	P=0.000	○○○	dexamethasone ointment
Ulcer Day Index					
[7] RCT **Crossover design**	17 people with recurrent aphthous ulcers	**Ulcer Day Index , 8 weeks** 26.3 with topical corticosteroids 65.9 with placebo Given as tablet allowed to dissolve in region of ulceration The RCT found larger effect sizes than other reported RCTs	P <0.01	○○○	topical corticosteroids
[9] RCT **Crossover design**	26 people with recurrent aphthous ulcers	**Ulcer Day Index , 8 weeks** 58.3 with topical corticosteroids 71.3 with placebo See Further information on studies for details on user preference	Reported as not significant P value not reported	⟷	Not significant
[10] RCT **Crossover design**	25 people with recurrent aphthous ulcers	**Ulcer Day Index , 4 weeks** 24.0 with topical corticosteroids 30.7 with placebo See Further information on studies for details of trial protocol	Reported as not significant P value not reported	⟷	Not significant
[12] RCT **Crossover design**	20 people with recurrent aphthous ulcers	**Ulcer Day Index , 6 weeks** 48.3 with topical corticosteroids 70.6 with placebo See Further information on studies for details on user preference	P <0.05	○○○	topical corticosteroids

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer duration					
[15] RCT	240 people with minor recurrent aphthous ulcers	**Mean duration of ulcers** 6 days with dexamethasone ointment 7 days with placebo	P = 0.000	○○○	dexamethasone ointment
[16] RCT **3-armed trial**	150 people with recurrent aphthous stomatitis	**Duration of ulcers** 3.5 days with triamcinolone ointment 6.8 days with placebo Third arm evaluated myrtle	P <0.01	○○○	triamcinolone ointment
[8] RCT **Crossover design**	50 people with recurrent aphthous ulcers	**Mean number of days of ulcer duration , until complete healing** 6.00 with topical corticosteroids 6.00 with placebo	Reported as not significant P value not reported	⟷	Not significant
[9] RCT **Crossover design**	26 people with recurrent aphthous ulcers	**Mean number of days of ulcer duration , 8 weeks** 8.07 with topical corticosteroids 8.94 with placebo See Further information on studies for details on user preference	Reported as not significant P value not reported	⟷	Not significant
[12] RCT **Crossover design**	20 people with recurrent aphthous ulcers	**Mean number of days of ulcer duration , 6 weeks** 4.93 with topical corticosteroids 7.83 with placebo See Further information on studies for details on user preference	P <0.001	○○○	topical corticosteroids
[14] RCT **Crossover design**	19 people with recurrent aphthous ulcers	**Mean number of days of ulcer duration , 12 weeks** 5.93 with topical corticosteroids 5.92 with placebo	Reported as not significant P value not reported	⟷	Not significant
[11] RCT **Crossover design**	63 people with recurrent aphthous ulcers	**Proportion of people with ulcer duration <6 days , until complete healing** 23/33 (70%) with topical corticosteroids 14/30 (47%) with placebo See Further information on studies for details on user preference	P <0.05	○○○	topical corticosteroids
[13] RCT **Crossover design**	15 people with recurrent aphthous ulcers	**Proportion of people with the total number of ulcer days reduced , 4 weeks** 13/15 (87%) with topical corticosteroids (aerosol spray) Not reported with placebo	P <0.001	○○○	topical corticosteroids
Pain relief					
[15] RCT	240 people with minor recurrent aphthous ulcers	**Mean reduction in pain scores , day 6** 5.62 with dexamethasone ointment 4.94 with placebo	P = 0.001	○○○	dexamethasone ointment

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[16] RCT **3-armed trial**	150 people with recurrent aphthous stomatitis	**Mean time of pain elimination (days)** 2.64 with triamcinolone ointment 5.90 with placebo Third arm evaluated myrtle	P <0.01	○○○	triamcinolone ointment
[11] RCT **Crossover design**	63 people with recurrent aphthous ulcers	**Proportion of people with pain relief , until complete healing** 29/33 (88%) with topical corticosteroids 18/30 (60%) with placebo See Further information on studies for details on user preference	P <0.01	○○○	topical corticosteroids
[12] RCT **Crossover design**	20 people with recurrent aphthous ulcers	**Average pain severity score during ulcer days , 6 weeks** 2.77 with topical corticosteroids 3.54 with placebo See Further information on studies for details on user preference	Reported as not significant P value not reported	⟷	Not significant
[13] RCT **Crossover design**	15 people with recurrent aphthous ulcers	**Proportion of people with reduced pain severity , 4 weeks** 11/15 (73%) with topical corticosteroids (aerosol spray) Not reported with placebo	P <0.05	○○○	topical corticosteroids
[14] RCT **Crossover design**	19 people with recurrent aphthous ulcers	**Decrease in pain score with time** with topical corticosteroids with placebo Both groups had a decrease in the pain score, but the rate of decrease in pain score was significantly faster with topical corticosteroids compared with placebo It was not clear whether the effect of the crossover sequence had been allowed for	P <0.0001	○○○	topical corticosteroids

Occurrence of new ulcers

Topical corticosteroids compared with placebo Topical corticosteroids may be more effective than placebo at reducing the occurrence of new ulcers in people with recurrent aphthous ulcers (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Occurrence of new ulcers					
[16] RCT **3-armed trial**	150 people with recurrent aphthous stomatitis	**Recurrence , 4 weeks** 19/50 (38%) with triamcinolone ointment 43/50 (86%) with placebo Third arm compared myrtle	P <0.001	○○○	triamcinolone ointment
[7] RCT **Crossover design**	17 people with recurrent aphthous ulcers	**Number of new ulcers/week , 8 weeks** 0.51 with topical corticosteroids 1.15 with placebo	P <0.05	○○○	topical corticosteroids

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Given as tablet and allowed to dissolve in region of ulceration The RCT found larger effect sizes than other reported RCTs			
[9] RCT **Crossover design**	26 people with recurrent aphthous ulcers	**Number of new ulcers/week , 8 weeks** 0.84 with topical corticosteroids 0.94 with placebo See Further information on studies for details on user preference	Reported as not significant P value not reported	⟷	Not significant
[10] RCT **Crossover design**	31 people with recurrent aphthous ulcers	**Number of new ulcers/week , 4 weeks** 0.73 with topical corticosteroids 0.82 with placebo See Further information on studies for details of trial protocol	Reported as not significant P value not reported	⟷	Not significant
[10] RCT **Crossover design**	20 people with recurrent aphthous ulcers	**Number of new ulcers/week , 6 weeks** 1.27 with topical corticosteroids 1.92 with placebo See Further information on studies for details of trial protocol	Reported as not significant P value not reported	⟷	Not significant
[13] RCT **Crossover design**	15 people with recurrent aphthous ulcers	**Effect on reducing frequency of ulcer recurrence during follow-up , 26 weeks** No effect with topical corticosteroids No effect with placebo	Significance not assessed		

No data from the following reference on this outcome. [8] [11] [12] [14] [15]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[15] RCT	240 people with minor recurrent aphthous ulcers	**Adverse effects** 4/120 with dexamethasone ointment 8/120 with placebo	1 subject in the control group dropped out of the study because of a systemic rash; the remaining 11 cases reported slight rash around the mouth, a burning sensation in the larynx, or a pain at the site of medication application		
[7] RCT **Crossover design**	17 people with recurrent aphthous ulcers	**Adverse effects , 8 weeks** with topical corticosteroids with placebo Given as tablet and allowed to dissolve in region of ulceration No adverse effects were reported in either group			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[10] RCT **Crossover design**	31 people with recurrent aphthous ulcers	**Adverse effects , 4 weeks** with topical corticosteroids with placebo One case of adrenal suppression occurred in one person using betamethasone disodium phosphate See Further information on studies for details of trial protocol			
[11] RCT **Crossover design**	63 people with recurrent aphthous ulcers	**Adverse effects , until complete wound healing** with topical corticosteroids with placebo No adverse effects were reported in either group See Further information on studies for details on user preference			
[12] RCT **Crossover design**	20 people with recurrent aphthous ulcers	**Adverse effects , 6 weeks** with topical corticosteroids with placebo No adverse effects were reported in either group See Further information on studies for details on user preference			
[13] RCT **Crossover design**	15 people with recurrent aphthous ulcers	**Adverse effects , 4 weeks** with topical corticosteroids (aerosol spray) with placebo No adverse effects were reported in either group			
[8] RCT	50 people with recurrent aphthous ulcers	**Adverse effects** with topical corticosteroids with placebo No adverse effects were reported in either group			

No data from the following reference on this outcome. [9] [14] [16]

Further information on studies

[9] The crossover RCT found that some users preferred topical corticosteroids over control preparations; however, no significance data were presented (proportion of people receiving both forms of treatment preferring active treatment at 8 weeks: 13/26 [50%])

[10] Each person received one treatment for 4 weeks, a blank month, then another treatment with another drug. The trial compared an inert base, two local steroids and two other preparations. The figures given here are those during treatment with local steroids and with the inert base.

[11] The crossover RCT found that more users preferred topical corticosteroids than control preparations; however, no significance data were presented (proportion of people receiving both forms of treatment preferring active treatment at complete wound healing: 10/13 [77%])

[12] The crossover RCT found that more users preferred topical corticosteroids than control preparations; however, no significance data were presented (proportion of people receiving both forms of treatment preferring active treatment at 6 weeks: 18/20 [90%])

[16] Method of randomisation was not reported.

Comment: A study of adrenal function found no evidence that corticosteroids (given as tablets allowed to dissolve in the mouth) caused adrenal suppression. [17]

The RCTs differed in many ways: selection of people, type of topical corticosteroid and formulation used, control preparation used (although this was usually a base without topical steroid), duration of treatment, reported outcomes, and design (double or single blind, parallel group or crossover, presence and length of washout period). Withdrawal rates were high. Most people in the trials had more severe ulceration than the average person with recurrent aphthous ulceration.

Clinical guide

Corticosteroids presumably exert their topical effect by suppressing the local inflammatory response; hence, potentially reducing severity and duration of the recurrent aphthous ulceration. In general terms, topical corticosteroid treatments may be applied as a mouthwash, as a spray with asthma-based inhalers (often used on an off-label basis as a delivery device), or as a paste where the corticosteroid preparation is combined with an adhesive base to aid mucosal adherence and optimise contact time. While some licensed corticosteroid preparations, such as hydrocortisone oromucosal tablets, a beclomethasone diproprionate inhaler, and betamethasone soluble tablets dissolved in water and used as a mouthwash are listed in drug formularies for use under the indication of oral ulceration, off-label use of alternative topical corticosteroid preparations is often required in the management of more recalcitrant cases of recurrent aphthous ulceration. Corticosteroid preparations are considered first-line treatment for recurrent aphthous ulceration in specialist oral medicine practice. Despite the use of topical corticosteroids over several years for this indication, there is a lack of high-quality evidence of their efficacy. Long-standing concerns of systemic absorption and adrenal suppression with repeated use of oral topical corticosteroid medications have rarely been documented. Topical corticosteroid treatment of recurrent aphthous ulceration is considered safe and is effective, and is often preferable to achieving ulcer control with systemic treatments.

OPTION TETRACYCLINE ANTIBIOTIC MOUTHWASH

- For GRADE evaluation of interventions for Aphthous ulcers (recurrent), see table, p 19 .
- We don't know whether tetracycline mouthwash works, as the evidence was weak and limited to two small RCTs.

Benefits and harms

Tetracycline antibiotic mouthwash versus placebo:

We found no systematic review, but found two small RCTs comparing different topical tetracycline preparations versus inactive control preparations. [18] [19]

Ulcer severity

Tetracycline antibiotic mouthwash compared with placebo Tetracycline antibiotic mouthwash may be more effective than placebo at reducing the number of days with ulcers and at reducing pain in people with aphthous stomatitis; however, evidence was limited (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer severity					
[19] RCT **Crossover design** **4-armed trial**	57 people in total with aphthous stomatitis	**Ulcer days** with tetracycline antibiotic mouthwash with placebo Absolute results not reported The third and fourth arms evaluated an enzyme-containing dentrifice and a placebo dentrifice;	P <0.05 See Further information on studies for details of methodological issues	○○○	tetracycline antibiotic mouthwash

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		this comparison is not of interest in this review and the data are not reported 30 people in this analysis			
Pain relief					
[18] Quasi-randomised RCT	31 people in total with aphthous stomatitis	**Mean pain** with tetracycline antibiotic mouthwash with placebo Absolute results reported graphically Application of treatment or control made by a clinician using a spatula	P <0.05 See Further information on studies for details of methodological issues	○○○	tetracycline antibiotic mouthwash
[19] RCT **4-armed trial**	57 people in total with aphthous stomatitis	**Mean pain** with tetracycline antibiotic mouthwash with placebo Absolute results not reported The third and fourth arms evaluated an enzyme-containing dentrifice and a placebo dentrifice; this comparison is not of interest in this review and the data are not reported 30 people in this analysis	P <0.05 See Further information on studies for details of methodological issues	○○○	tetracycline antibiotic mouthwash

Occurrence of new ulcers

No data from the following reference on this outcome. [18] [19]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[19] RCT **Crossover design** **4-armed trial**	57 people in total with aphthous stomatitis	**Adverse effects** with tetracycline antibiotic mouthwash with placebo The third and fourth arms evaluated an enzyme-containing dentrifice and a placebo dentrifice; this comparison is not of interest in this review and the data are not reported 30 people in this analysis The RCT reported that “no side effects were encountered”	See Further information on studies for details of methodological issues		

No data from the following reference on this outcome. [18]

Further information on studies

[18] The RCT was single blind. Allocation was made by alternate allocation, with every second subject being in the experimental group and all others being in the control group. In addition, the application of treatment or control was made by a clinician using a spatula, and was made only once during the aphthous ulcer episode. Unlike a conventional mouthwash, this would, therefore, not have any potential effect on non-lesional mucosa.

[19] The method of randomisation was not described, and outcomes were assessed by people being asked to record, on pretyped forms, days when pain and/or ulcers were present (further details of forms and timing of final assessment not reported).

Comment: There is limited evidence that topical tetracyclines lessen the signs or symptoms of aphthous ulceration.

Clinical guide
Tetracyclines may potentially exert their topical effect on recurrent aphthous ulceration as an immunomodulatory and anti-microbial agent. Tetracycline mouthwashes have long been used as topical treatments for recurrent aphthous ulceration; however, there is a lack of evidence of their efficacy. One should avoid prescribing tetracyclines, even for topical use in children and pregnant and lactating mothers due to risk of staining and/or malformation of the developing dentition consequent to systemic absorption or inadvertent swallowing.

OPTION TOPICAL ANTISEPTIC AGENTS (CHLORHEXIDINE AND SIMILAR AGENTS)

- For GRADE evaluation of interventions for Aphthous ulcers (recurrent), see table, p 19 .
- Chlorhexidine mouth rinses may reduce the severity and pain of ulceration, although studies have reported inconclusive results about whether the incidence of new ulcers is reduced.
- There was insufficient evidence for any other topical antiseptic agents.

Benefits and harms

Chlorhexidine versus placebo:

We found no systematic review but found three RCTs comparing chlorhexidine gluconate with inactive control preparations. [20] [21] [22]

Ulcer severity

Chlorhexidine compared with placebo Chlorhexidine gel and mouthwash may be more effective than placebo at reducing the severity of ulceration (as assessed using the Ulcer Day Index), and chlorhexidine gel may be more effective at reducing the duration of ulceration and at reducing pain (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer Day Index					
[21] RCT **Crossover design**	12 people	**Ulcer Day Index , 5 weeks** 9.5 with 0.2% chlorhexidine gel 17.0 with control preparation	P <0.05 See Further information on studies for details of methodological issues	○○○	0.2% chlorhexidine gel
[22] RCT **Crossover design**	38 people	**Ulcer Day Index , 6 weeks** 42.8 with 0.2% chlorhexidine mouthwash 52.3 with control preparation	P <0.05	○○○	0.2% chlorhexidine mouthwash

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer free days					
[22] RCT **Crossover design**	38 people	**Number of ulcer-free days , 6 weeks** 22.9 with 0.2% chlorhexidine mouthwash 17.5 with control preparation	P <0.02	○○○	0.2% chlorhexidine mouthwash
Ulcer duration					
[20] RCT **Crossover design**	20 people	**Mean number of days of ulcer duration , 5 weeks** 4.8 with 1% chlorhexidine gel 7.80 with control preparation	P <0.01	○○○	1% chlorhexidine gel
[22] RCT **Crossover design**	38 people	**Mean number of days of ulcer duration , 6 weeks** 5.02 with 0.2% chlorhexidine mouthwash 5.78 with control preparation	Reported as not significant P value not reported	⟷	Not significant
Pain relief					
[20] RCT **Crossover design**	20 people	**Mean pain severity score , 5 weeks** 0.93 with 1% chlorhexidine gel 1.22 with control preparation	P <0.05	○○○	1% chlorhexidine gel
[21] RCT **Crossover design**	12 people	**Mean total pain severity score , 5 weeks** About 24 with 0.2% chlorhexidine gel About 49 with control preparation Absolute results reported graphically	P <0.05 See Further information on studies for details of methodological issues	○○○	0.2% chlorhexidine gel
[22] RCT **Crossover design**	38 people	**Mean total pain severity score , 6 weeks** 16.31 with 0.2% chlorhexidine mouthwash 16.35 with control preparation	Reported as not significant P value not reported	⟷	Not significant

Occurrence of new ulcers

Chlorhexidine compared with placebo We don't know whether chlorhexidine gel and chlorhexidine mouthwash are more effective than placebo at reducing the occurrence of new lesions in people with recurrent aphthous ulceration (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Occurrence of new ulcers					
[20] RCT **Crossover design**	20 people	**Number of new ulcers/week , 5 weeks** 1.04 with 1% chlorhexidine gel 1.4 with control preparation	Reported as not significant P value not reported	⟷	Not significant
[21] RCT **Crossover design**	12 people	**Number of new ulcers/week , 5 weeks** 0.60 with 0.2% chlorhexidine gel 1.02 with control preparation	P <0.05 See Further information on studies for details of methodological issues	○○○	0.2% chlorhexidine gel

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[22] RCT **Crossover design**	38 people	**Number of new ulcers/week , 6 weeks** 1.26 with 0.2% chlorhexidine mouthwash 1.38 with control preparation	Reported as not significant P value not reported	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[21] RCT **Crossover design**	12 people	**Adverse effects , 5 weeks** with 0.2% chlorhexidine gel with control preparation Chlorhexidine had a bitter taste and was associated with brown staining of teeth and tongue, and with nausea	See Further information on studies for details of methodological issues		

No data from the following reference on this outcome. [20] [22]

Hexetidine compared with placebo:

We found no systematic review but found one RCT comparing 0.1% hexetidine mouthwash with an inactive control preparation. [23]

Ulcer severity

Hexetidine compared with placebo Hexetidine may be no more effective than placebo at reducing the severity or duration of ulceration, or at reducing pain from ulcers in people with recurrent aphthous ulceration (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer Day Index					
[23] RCT **Crossover design**	37 people	**Ulcer Day Index , 6 weeks** 79.7 with 0.1% hexetidine mouthwash 65.7 with control preparation See Further information on studies for details on user preference	Reported as not significant P value not reported	⟷	Not significant
Ulcer duration					
[23] RCT **Crossover design**	37 people	**Mean number of days of ulcer duration** 6.64 with 0.1% hexetidine mouthwash 6.80 with control preparation See Further information on studies for details on user preference	Reported as not significant P value not reported	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain relief					
[23] RCT **Crossover design**	37 people	**Mean total pain severity score , 6 weeks** 16.9 with 0.1% hexetidine mouthwash 17.8 with control preparation See Further information on studies for details on user preference	Reported as not significant P value not reported	⟷	Not significant

Occurrence of new ulcers

Hexetidine compared with placebo Hexetidine may be no more effective than placebo at reducing the occurrence of new ulcers in people with recurrent aphthous ulceration (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Occurrence of new ulcers					
[23] RCT **Crossover design**	37 people	**Number of new ulcers/week** 1.48 with 0.1% hexetidine mouthwash 1.39 with control preparation See Further information on studies for details on user preference	Reported as not significant P value not reported	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[23] RCT **Crossover design**	37 people	**Adverse effects , 6 weeks** 1/37 (3%) with 0.1% hexetidine mouthwash 0/37 (0%) with control preparation One case of severe gum inflammation with 0.1% hexetidine mouthwash See Further information on studies for details on user preference	Significance not assessed		

Proprietary antibacterial rinse compared with control:

We found no systematic review but found one RCT comparing a proprietary antibacterial rinse (that is, a commercially available mouth wash with a fixed, reproducible set of ingredients) with a hydroalcoholic control. [24]

Ulcer severity

Proprietary antibacterial rinse compared with control A proprietary antibacterial rinse may be no more effective at reducing the duration of or pain from ulcers in people with recurrent aphthous ulceration compared with a hydroalcoholic control (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ulcer duration					
[24] RCT	96 people	**Median fall in days of ulcer duration from start to end of trial , 24 weeks** 2.19 with proprietary antibacterial rinse 1.94 with hydroalcoholic control	Reported as not significant P value not reported See Further information on studies for details of methodological issues	⟷	Not significant
Pain relief					
[24] RCT	96 people	**Pain severity** with proprietary antibacterial rinse with hydroalcoholic control	Reported as not significant P value not reported See Further information on studies for details of methodological issues	⟷	Not significant

Occurrence of new ulcers

Proprietary antibacterial rinse compared with control A proprietary antibacterial rinse may be no more effective at reducing the occurrence of new ulcers in people with recurrent aphthous ulceration compared with a hydroalcoholic control (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Occurrence of new ulcers					
[24] RCT	96 people	**Number of new ulcers/week** 0.09 with proprietary antibacterial rinse 0.13 with hydroalcoholic control	Reported as not significant P value not reported See Further information on studies for details of methodological issues	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [24]

Further information on studies

[21] The crossover RCT did not specify whether reported results took account of the effect of confounding factors, such as inadequate washout period, and different loss to follow-up in the two treatment periods (data were available from only 12/26 people who were recruited).

[23] The crossover RCT found no significant difference in user preference between 0.1% hexetidine mouthwash and control mouthwash, but found that many more people preferred the treatment received second.

[24] The parallel group RCT had fewer withdrawals than the crossover RCTs: 106 people with recurrent aphthous ulceration were recruited, and 96 completed the study. Analysis was not by intention to treat, and the method of randomisation was not reported. People recruited to the trials might not be typical of the average person with recurrent aphthous ulceration.

Comment: Four of the RCTs used a crossover design and reported high withdrawal rates. A consistent observation was that outcomes improved during the course of the trials irrespective of the treatment received.

Clinical guide
Antiseptics, such as chlorhexidene, may potentially exert an antimicrobial effect and prevent secondary infection. Antiseptic mouthwashes or gels are available as over-the-counter medicines and general medical and dental practitioners often prescribe such medicines as first-line treatment for recurrent aphthous ulceration. There is a lack of evidence of their efficacy; however, they may provide some variable symptomatic relief to some patients. Prolonged use of chlorhexidine may result in reversible dental staining.

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Corticosteroids (topical) Two RCTs added. [15] [16] Categorisation changed from 'unknown effectiveness' to 'likely to be beneficial'.

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GRADE **Evaluation of interventions for Aphthous ulcers (recurrent).**

Important outcomes			Occurrence of new ulcers, Ulcer severity						
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of selected topical treatments for recurrent idiopathic aphthous ulcers?									
1 (18) [6]	Ulcer severity	Benzydamine hydrochloride mouthwash compared with placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
13 (685) [7] [8] [9] [10] [11] [12] [13] [14] [15] [16]	Ulcer severity	Topical corticosteroids versus placebo	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and uncertainty about methodology
5 (217) [7] [9] [10] [13] [15]	Occurrence of new ulcers	Topical corticosteroids versus placebo	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and uncertainty about methodology
1 (30) [19]	Ulcer severity	Tetracycline antibiotic mouthwash versus placebo	4	–3	0	–2	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and uncertainty about randomisation; directness points deducted for uncertainty of reporting outcomes and single application of treatment in 1 RCT
3 (70) [20] [21] [22]	Ulcer severity	Chlorhexidine versus placebo	4	–3	–1	–1	0	Very low	Quality points deducted for sparse data, poor follow-up, and incomplete reporting of results; consistency point deducted for conflicting results; directness point deducted for uncertainty about benefit of treatment
3 (70) [20] [21] [22]	Occurrence of new ulcers	Chlorhexidine versus placebo	4	–3	–1	–1	0	Very low	Quality points deducted for sparse data, poor follow-up, and incomplete reporting of results; consistency point deducted for conflicting results; directness point deducted for uncertainty about benefit of treatment
1 (37) [23]	Ulcer severity	Hexetidine compared with placebo	4	–3	0	–1	0	Very low	Quality points deducted for sparse data, poor follow-up, and incomplete reporting of results; directness point deducted for uncertainty about benefit of treatment
1 (37) [23]	Occurrence of new ulcers	Hexetidine compared with placebo	4	–3	0	–1	0	Very low	Quality points deducted for sparse data, poor follow-up, and incomplete reporting of results; directness point deducted for uncertainty about benefit of treatment
1 (96) [24]	Ulcer severity	Proprietary antibacterial rinse compared with control	4	–3	0	–2	0	Very low	Quality points deducted for poor follow-up, incomplete reporting of results, no intention-to-treat analysis, and uncertainty about method of randomisation; directness point deducted for uncertainty about disease severity in population and benefit from treatment

Important outcomes			Occurrence of new ulcers, Ulcer severity						
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (96) [24]	Occurrence of new ulcers	Proprietary antibacterial rinse compared with control	4	–3	0	–2	0	Very low	Quality points deducted for poor follow-up, incomplete reporting of results, no intention-to-treat analysis, and uncertainty about method of randomisation; directness points deducted for uncertainty about disease severity in population and benefit from treatment

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.