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Urban legends: recurrent aphthous stomatitis

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Recurrent aphthous stomatitis (RAS) is the most common idiopathic intraoral ulcerative disease in the USA. Aphthae typically occur in apparently healthy individuals, although an association with certain systemic diseases has been reported. Despite the unclear etiopathogenesis, new drug trials are continuously conducted in an attempt to reduce pain and dysfunction. We investigated four controversial topics: (1) Is complex aphthosis a mild form of Behçet's disease (BD)? (2) Is periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome a distinct medical entity? (3) Is RAS associated with other systemic diseases [e.g., celiac disease (CD) and B12 deficiency]? (4) Are there any new RAS treatments? Results from extensive literature searches, including a systematic review of RAS trials, suggested the following: (1) Complex aphthosis is not a mild form of BD in North America or Western Europe; (2) Diagnostic criteria for PFAPA have low specificity and the characteristics of the oral ulcers warrant further studies; (3) Oral ulcers may be associated with CD; however, these ulcers may not be RAS; RAS is rarely associated with B12 deficiency; nevertheless, B12 treatment may be beneficial, via mechanisms that warrant further study; (4) Thirty-three controlled trials published in the past 6 years reported some effectiveness, although potential for bias was high.
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Introduction

In this chapter of the urban legends series on controversial topics in oral medicine, we focused on four questions about recurrent aphthous stomatitis (RAS): (1) Is complex aphthosis a mild form of Behçet's disease (BD)? (2) Is periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome a distinct medical entity? (3) Is RAS associated with other systemic diseases? (focusing here on celiac disease (CD) and vitamin B12 deficiency) (4) Are there any new RAS treatments?

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Is complex aphthosis a mild form of Behçet's disease?

To address this question, one must understand the difference between simple and complex aphthosis. RAS is a disease state characterized by the development of oral aphthae (aphthosis). RAS has two presentation forms and three morphological types. The two forms are simple and complex aphthosis, and the three morphological types are minor, major, and herpetiform aphthous ulcers; though, not everyone agrees that herpetiform ulcers are RAS. All three forms can occur in patients with simple and complex aphthosis. RAS lesions occur in the context of BD. Table 1 presented by Rogers at the International Conference on Behçet's disease (ICBD) in 2003 illustrates the difference between simple, the most common, and complex, the much less common presentation of RAS (Rogers, 2003). The answer to this question in much of Asia and the Middle East would be a qualified yes because many patients who present with recurrent oral ulcerations develop BD, as reported in a prospective series from Korea (Bang *et al*, 1995) or in Anatolia (Turkey), which has the highest prevalence of BD in the world (370 patients per 100 000 inhabitants) (Zouboulis, 2001). On the other hand, the answer to this question would be a definite no in Western Europe or North America (Jorizzo *et al*, 1985; Ghate and Jorizzo, 1999; Mc Carty and Jorizzo, 2003; Rogers, 2003; Jurge *et al*, 2006).

The term complex aphthosis was coined by Jorizzo *et al* (1985) to describe patients suffering three or more almost constantly present oral aphthae, or oral and genital aphthae, in the absence of BD. This construct was used to describe patients referred to professor Jorizzo with a possible diagnosis of BD, when most of them did not have BD. Mc Carty and Jorizzo (2003)

Table 1 Classification of recurrent aphthous stomatitis

Simple aphthosis	*Complex aphthosis*
Common	Uncommon
Episodic	Episodic or continuous
Short-lived lesions	Persistent lesions
Few lesions	Few to many lesions
Three to six episodes per year	Frequent or continuous ulcerations
Prompt healing	Slow healing
Pain	Marked pain
Little disability	Disabling
Limited to oral cavity	May have genital lesions

described 81 patients with possible BD. Of this cohort, 11 (13.6%) had simple aphthosis, 6 (7.4%) did not have aphthosis at all, leaving 64 (79%) patients with complex aphthosis. Ten of the 64 patients with complex aphthosis did have BD (15.6%).

At the 2003 ICBD conference, Rogers described his experience with 244 Mayo patients with complex aphthosis. These patients suffered oral aphthous ulcerations approximately 50% of the time and/or had continuous oral aphthous ulcerations and/or had oral and genital aphthous ulcerations and/or suffered major disability from aphthosis. Patients with simple aphthosis were excluded from this cohort. In addition, 25 patients with complex aphthosis because of BD were excluded from his cohort. Thus, true BD occurred in only 25/269 or 9.3% of these patients with complex aphthosis (Rogers, 2003). The work by Jorizzo and Rogers highlights, therefore, that the vast majority of patients with complex aphthosis neither do not have nor will develop BD. Their disease appears quite distinct in its manifestations, natural history, and prognosis. Hence, this should not be considered an attenuated form of BD, but rather a discrete, more benign entity with similar mucosal manifestations. This can be very reassuring to patients with complex aphthosis.

Jurge *et al* (2006) in their excellent review of RAS in this journal emphasized that, in contradistinction to patients with RAS, patients with BD had a multisystem disease affecting oral, ocular, and anogenital mucosal surfaces as well as vascular, neurological, and rheumatologic systems. Moreover, they emphasized that RAS does not have a notable geographic distribution and does not share the human leukocyte antigen (HLA) associations of BD.

Complex aphthosis can be divided into primary and secondary groups (Mc Carty and Jorizzo, 2003; Rogers, 2003). Primary complex aphthosis has no identifiable underlying cause and remains idiopathic. Causes of secondary complex aphthosis (Mc Carty and Jorizzo, 2003; Rogers, 2003; Jurge *et al*, 2006) include hematinic deficiencies (iron, vitamins B1, B2, B6, B12, folic acid, and zinc), cyclic neutropenia, benign familial neutropenia, primary and secondary immunodeficiencies including HIV disease, MAGIC syndrome, Sweet's syndrome, PFAPA, gluten-sensitive enteropathy, inflammatory bowel disease including ulcerative colitis and Crohn's disease, drug reactions to non-steroidal anti-inflammatory agents (NSAIDs) and nicorandil and, of course, BD.

Evaluation of patients with complex aphthosis depends upon the identification of secondary factors and the exclusion of BD. Managing these secondary factors ('correctable causes') can reduce the severity of the disease. Treatments with anti-inflammatory medications including both systemic corticosteroids and NSAIDs utilizing the therapeutic ladder emphasized by Jorizzo *et al* (1985) (Ghate and Jorizzo, 1999; Mc Carty and Jorizzo, 2003), and affirmed by the study of Lynde *et al* (2009), offer the clinician an opportunity to achieve an excellent level of disease control or even remission in many of these patients with this chronic, disabling condition.

In summary, in Western Europe and North America some patients with complex aphthosis do arguably have a forme fruste of BD, perhaps 10%, while the vast majority have a condition which merits a careful evaluation, seeking 'correctable causes' and is responsive to treatment with an excellent prognosis for control or remission. However, along the 'Silk Road' in the Middle East and much of Asia, complex aphthosis is more likely to signify the subsequent development of full-blown BD.

Is periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome a distinct medical entity?

First described in 1987 (Marshall *et al*, 1987), PFAPA syndrome is a clinical entity characterized by recurrent episodes of fevers without an identifiable source of infection. Despite better understanding of some the basic aspects of the disease, the etiology of PFAPA syndrome is still unknown and the question remains as to whether PFAPA syndrome is or not a distinct medical entity.

The diagnosis is established on the basis of clinical criteria that require the presence of a recurrent fever of early onset (<5 years) with a clockwork periodicity (usual interval <4 weeks) and ≥ 1 of the 3 associated symptoms (aphthosis, cervical adenitis, and pharyngitis), in the absence of upper respiratory tract infections and cyclic neutropenia (Marshall *et al*, 1989). The primary complaint is the periodic fever rather than the stomatitis. There is a level of uncertainty about the pattern of intraoral ulcers in PFAPA, but they are generally described as few to several, non-clustered, small (<5 mm), shallow ulcers that heal over 5–10 days (Long, 1999). However, it has been suggested that those ulcers could just mimic typical aphthae and the term aphthous-like ulcers has been consequentially used (Femiano *et al*, 2008). In 1999, the diagnostic criteria were partially modified to exclude leukocytosis and elevated sedimentation rate as these frequently accompany febrile illnesses and do not add specificity for the diagnosis (Thomas *et al*, 1999).

By definition, the diagnosis of PFAPA syndrome requires exclusion of other monogenic periodic fevers, which are hereditary conditions and include familial mediterranean fever (FMF), the spectrum of mevalonate kinase deficiencies (MKD) (such as hyper-Ig-D syndrome and mevalonate aciduria), and tumor necrosis

factor-associated periodic syndrome (TRAPS) among others (Scully *et al*, 2008), each characterized by a specific genetic mutation involving the mediterranean fever (*MEFV*), mevalonate kinase (*MVK*), and tumor necrosis factor receptor superfamily, member 1A (*TNFRSF1A*) gene, respectively. However, genetic tests have been only sporadically used to support the PFAPA diagnosis despite the fact that current PFAPA syndrome diagnostic criteria have very low specificity.

Several Authors have indeed expressed concern about the diagnostic accuracy of the revised criteria (Lierl, 2007; Hofer, 2008; Brown *et al*, 2010). When comparing the clinical manifestations of published PFAPA cohorts (Table 2), the heterogeneity is evident, particularly regarding the presence of aphthae sometimes just reported in a minority of the cases. This is possibly because of selective referral patterns as most of the cohorts are seen by pediatric, ENT, or rheumatologic groups.

A relevant number of patients with monogenic periodic fevers also meet the diagnostic criteria for PFAPA syndrome (Gattorno *et al*, 2008). In a preliminary experience, 83% of patients with MKD, 57% of patients with TRAPS, and 8% of patients with FMF satisfied the criteria for PFAPA syndrome, which shows that the criteria have limited utility in differentiating PFAPA syndrome from monogenic periodic fevers. Importantly, oral aphthosis was found to be independently associated with a positive genetic test result indirectly suggesting the possible lack of specificity of this clinical feature for PFAPA diagnosis (Gattorno *et al*, 2008).

Moreover, a recent large multicenter multinational study employing genetic tests to distinguish PFAPA from other inherited periodic fevers clearly confirmed that PFAPA syndrome criteria are not able to distinguish genetically positive patients (i.e., patients likely without PFAPA but with a PFAPA-like phenotype) from genetically negative patients (the likely PFAPA affected). In this case–control study of 210 children that met the clinical criteria for PFAPA syndrome, 38% were genetically positive for either MKD, FMF, TRAPS, or displayed low penetrance or incomplete mutations, and 62% had negative genetic testing profiles (Gattorno *et al*, 2009). Among the genetically positive individuals, the frequency of diarrhea, vomiting, abdominal pain, rash, and arthralgias was higher, whereas exudative pharyngitis was more common in genetically negative patients. Cardinal features of the PFAPA syndrome, such as oral aphthosis and enlargement of cervical lymph nodes, were observed with similar frequencies in genetically negative patients and in subjects positive for MKD and FMF.

The authors then applied the Gaslini diagnostic score (Gattorno *et al*, 2008), which takes into account several clinical features to predict the likelihood that a patient would have positive genetic markers. This score identified 91% of the genetically positive individuals and those at risk for carrying genes associated with monogenic periodic fevers. The authors concluded that low-risk patients can be diagnosed as having PFAPA syndrome without genetic testing; conversely, those at high-risk should be diagnosed with PFAPA syndrome only in light of negative genetic markers as they would likely evolve into monogenic periodic fevers (Gattorno *et al*, 2009).

Periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome may not be as sporadic as initially thought. With the aid of a European registry encompassing 14 rheumatologic centers in eight countries, Cochard *et al* noted that many PFAPA patients had a positive family history (FH+) of periodic fever. The authors recruited 84 PFAPA patients and 47 healthy children and found 45% of PFAPA patients FH+ for recurrent fever, with the affected family member being a sibling or parent in 76% of the cases. The recurrent fever was indeed PFAPA in 26% of FH+. All healthy children had a negative FH of PFAPA or recurrent fever (Cochard *et al*, 2010). However, in a previously cited large study (Gattorno *et al*, 2008), only 14% of PFAPA patients were FH+.

Table 2 Distribution of main clinical manifestations associated with fever episodes in different cohorts of patients with periodic fever, aphthous stomatitis, pharyngitis, and adenitis

		Symptoms (%)					
Author, year	N	*Fever*	*Pharyngitis*	*Cervical adenopathy*	*Aphthous stomatitis*	*Headache*	*Abdominal pain*
Marshall *et al*, 1987	12	100	75	67	75	NA	NA
Thomas *et al*, 1999	66	100	65	77	67	65	45
Padeh *et al*, 1999	28	100	100	100	68	18	18
Galanakis *et al*, 2002	15	100	100	87	33	NA	NA
Tasher *et al*, 2006	54	NA	96	61	39	46	65
Renko *et al*, 2007	35	100	29	21	21	NA	NA
Padeh *et al*, 2008	15	100	100	100	40	20	20
Pignataro *et al*, 2009	18	100	100	89	89	33	44
Gattorno *et al*, 2009	130	100	84	84	58	41	53
Garavello *et al*, 2009	39	100	97	85	59	NA	NA
Kovacs *et al*, 2010	14	100	93	86	21	NA	NA
De Cunto *et al*, 2010	12	100	100	83	67	NA	42
Brown *et al*, 2010	10	100	100	90	90	NA	40
Feder and Salazar, 2010	105	100	85	62	38	44	41
Dagan *et al*, 2010	57	100	NA	44	33	NA	35

NA, not available.

In addition to genetic testing, the measure of procalcitonin has been recently proposed as a marker for PFAPA syndrome, the hypothesis being that elevated procalcitonin levels would rule out PFAPA syndrome as procalcitonin is reported to be a sensitive marker for systemic bacterial infection, which by definition should be absent in PFAPA (Yoshihara *et al*, 2007).

Lastly, the mainstay of treatment for PFAPA syndrome is the systemic administration of corticosteroids, just one or two doses of either prednisone or prednisolone (1–2 mg kg^{-1} per dose) normally result in rapid resolution of fever and the associated symptoms (Thomas *et al*, 1999). Early studies have also examined the therapeutic use of cimetidine and found that it was efficacious in both treating the condition and inducing the remission (Feder, 1992). In recent years, however, a role for tonsillectomy for treatment of this syndrome has been suggested (Wong *et al*, 2008; Garavello *et al*, 2009). Nonetheless, as prednisone is an effective, inexpensive, and relatively safe medication and as patients typically outgrow the condition by age 10–11 without further recurrence or sequelae, the role of tonsillectomy is still a matter of controversy (Leong *et al*, 2006; Hofer, 2008).

In conclusion, it seems that the question that needs to be addressed is not 'Is PFAPA syndrome a distinct medical entity?,' but rather, 'How to differentiate PFAPA from other similar diseases causing recurring fever?'. In that regard, the importance of oral aphthous ulcers in PFAPA is still questionable and further specific studies are clearly warranted to better describe oral ulcerations in PFAPA patients and at large to set up specific and reliable diagnostic criteria.

Is RAS associated with other systemic diseases?

A number of systemic conditions have been associated with RAS. These include CD, vitamin B12 deficiency, iron deficiency anemia, HIV/AIDS, cyclic neutropenia, Reiter's syndrome etc. However, it is controversial whether the oral ulcerations associated with these systemic conditions are truly RAS or just oral ulcers similar to RAS. Here, we address this question by examining the literature on two conditions commonly associated with RAS: CD and vitamin B12 deficiency. It is worth noting that the answer to this question may not be all or none, i.e., some systemic conditions may truly be associated with RAS while others with non-RAS oral ulceration.

Celiac disease

An association between RAS and CD has been extensively studied in the literature. Studies examining the presence of CD in patients with RAS (Table 3) provide a

Table 3 Studies of celiac disease (CD) in recurrent aphthous stomatitis (RAS) patients

Author, year	*Number of RAS patients with CD/total patients with RAS (%)*	*Comments*
Ferguson *et al*, 1975	7/35 (20)	CD diagnosed based on jejunal biopsies
Wray *et al*, 1975	5/130 (4)	
Ferguson *et al*, 1976	8/33 (24)	CD diagnosed based on jejunal biopsies. Use of a gluten-free diet resulted in complete remission of RAS in these eight patients
Wray *et al*, 1978	20/330 (6)	Extension of above study. CD was present in 6 of 10 patients who had iron deficiency, 12 of 15 patients with folic acid deficiency, and 2 of 11 patients with vitamin B12 deficiency
Rose *et al*, 1978	1/26 (4)	CD diagnosed based on jejunal biopsies. A gluten-free diet did not result in any change in this patient's mouth ulcers
Ferguson *et al*, 1980	2/50 (4)	
Veloso and Saleiro, 1987	4/24 (17)	In the four patients with RAS and biopsy-proven CD, RAS resolved completely upon gluten withdrawal. 0 of 19 non-RAS controls had CD, based on jejunal biopsy
O'Farrelly *et al*, 1991	4/10 (40)	Of 10 RAS patients with normal intestinal biopsies, four patients had increased levels of antibodies to gliadin. In three of these four patients, RAS resolved on a gluten-free diet and recurred on re-challenge
Jokinen *et al*, 1998	9/27 (33)	Of 27 patients suffering from 'recurrent oral ulcerations,' six had antigliadin antibodies and three were diagnosed with CD by biopsy
Biel *et al*, 2000	1/1 (100)	Case report. A 51-year-old woman with a 30-year history of painful refractory RAS was diagnosed with CD by duodenal biopsy. Treatment with a gluten-free diet resulted in complete resolution of RAS lesions and no recurrences in a 3 year follow-up
Nowak *et al*, 2002	1/20 (5)	Diagnosis based on anti-endomysial antibodies in the one patient
Aydemir *et al*, 2004	2/41 (5)	The two patients with CD had positive duodenal biopsy and were both positive for antibodies to gliadin and endomysium. None of 49 (0%) controls were diagnosed with CD
Olszewska *et al*, 2006	2/42 (5)	Two patients with RAS were diagnosed with CD based on anti-endomysial antibodies and duodenal biopsies *vs* 0 of 42 controls (not statistically significant) In the two patients with both RAS and CD, a gluten-free diet resulted in complete resolution of RAS lesions
da Silva *et al*, 2008	1/1 (100)	Case report. CD was confirmed by small intestine biopsy and circulating antigliadin and anti-endomysium antibodies in a woman with frequent RAS episodes. Topical dexamethasone rinse was effective in resolving RAS lesions; the patient was then put on a gluten-free diet

wide range of prevalence of CD in patients with RAS (ranging from 4% to 40%). Case reports were excluded when examining prevalence ranges but are included in the tables for completeness of the literature review. Similarly, studies examining the prevalence of RAS in patients with CD (Table 4) indicate that the number of patients with CD who have RAS ranges from 3% to 61%, excluding case reports. This can be compared against an approximately 37% lifetime prevalence of RAS in the general population (Kleinman *et al*, 1994). A few controlled studies suggested a higher prevalence of recurrent oral ulcers in patients with CD than in comparable control groups. Interestingly, in some cases, oral ulcers can be the first sign of CD. Several authors have reported cases where patients presenting with recurrent oral ulceration were subsequently diagnosed with CD (Veloso and Saleiro, 1987; Jokinen *et al*, 1998; Olszewska *et al*, 2006; da Silva *et al*, 2008). The features of oral ulcers associated with CD have been described as being characteristic of minor RAS, with an average size of 5 mm and a typical mucosal distribution (Ferguson *et al*, 1980). Another study described the oral ulcers in patients with CD as purpuric, papular, or erosive in nature, often surrounded by erythematous margins (Lahteenoja *et al*, 1998). Most of the studies reporting associations between RAS and CD did not report any well-defined criteria for RAS diagnosis, while the diagnosis of CD was usually well supported by biopsy and/or antibody tests.

Table 4 Studies of recurrent aphthous stomatitis (RAS) in patients with celiac disease (CD)

Author, year	*Number of CD patients with RAS/total patients with CD (%)*	*Comments*
Stevens, 1980	88/144 (61)	
Andersson-Wenckert *et al*, 1984	6/17 (35)	'Recurrent oral ulcerations' were reported by 6 of 17 children with CD and 5 of 19 controls
Majorana *et al*, 1992	19/113 (17)	In the 19 patients with both CD and RAS, a significant association was found between DRw10 and DQw1 HLA antigens and the two diseases
Meini *et al*, 1993	20/113 (18)	Follow-up to the above series by Majorana *et al* (1929). In all 20 cases, a marked improvement in RAS was noted within 1 year of starting a gluten-free diet. Re-challenge with a gluten-containing diet resulted in relapse of RAS in 9 of 10 cases
Corazza *et al*, 1993	36/226 (16)	Chart review of 226 patients diagnosed with CD revealed that 1 of 22 patients with CD (4.5%) were diagnosed with RAS in 1972–1977; 8 of 63 (12.7%) in 1978–1973; and 27 of 141 (19.1%) in 1984–1989
Srinivasan *et al*, 1998	1/1 (100)	Case report of a 14-year-old boy with a history of oral ulcers since the age of 3 years with increased gliadin antibody levels and normal duodenal biopsy. Use of a gluten-free diet caused resolution of the oral ulcers and re-challenge with a regular diet resulted in recurrence. The patient presented again at age 20 with severe oral ulcers on a regular diet, a duodenal biopsy confirmed CD. Once again, a gluten-free diet resulted in resolution of the oral ulcers
Lahteenoja *et al*, 1998	4/128 (3)	Presence of RAS was found in 4 of 128 patients with CD on a gluten-free diet compared to 0 of 30 healthy controls ($P = 0.327$) and 0 of eight patients with newly diagnosed (untreated) CD
Sedghizadeh *et al*, 2002	25/61 (41)	Presence or history of RAS in 25 of 61 (41%) patients with CD *vs* 17 of 62 (27%) age- and gender-matched healthy controls ($P = 0.11$)
de Freitas *et al*, 2002	15/48 (31)	Reviewed records for 48 adult patients with CD and found a history of oral aphthae in 15
Sood *et al*, 2003	19/96 (20)	RAS history based on medical records
Bucci *et al*, 2006	24/72 (33)	Found RAS to be present in 24 of 72 (33.3%) patients with CD and 38 of 162 (23.4%) healthy controls ($P > 0.05$).Among the 24 patients with both RAS and CD, in five patients RAS resolved with a gluten-free diet, in one patient it improved, and in 10 patients RAS persisted even with a gluten-free diet. The remaining eight patients continued gluten intake and RAS persisted in all of them
Procaccini *et al*, 2007	18/50 (36)	Reported that history, records, or clinical signs of RAS were present in 18 of 50 (36%) patients with CD *vs* 6 of 50 (12%) age- and gender-matched controls ($P = 0.009$)
Campisi *et al*, 2007	37/197 (19)	Screened 197 patients with CD and found the clinical presence (34 patients) or history (three patients) of RAS in a total of 37 cases. In comparison, RAS was found in 3 of 413 healthy controls ($P < 0.0001$). After a year on a gluten-free diet, 33 of the 37 cases reported complete resolution of RAS. The other four cases had persistently elevated serum antibodies to tissue transglutaminase, indicating non-compliance with a gluten-free diet
Campisi *et al*, 2007	61/269 (23)	Extended their previous series and found the presence or history of 'aphthous-like ulcers' was present in 61 of 269 (22.7%) CD patients *vs* 41 of 575 (7.1%) healthy controls ($P < 0.0001$). Fifty-three of the 61 patients presented for a 1 year follow-up. Of the 53 patients, 46 adhered strictly to a gluten-free diet: 33 of them reported complete remission of RAS, 4 reported improvement and the remaining 9 reported no change; 7 of the 53 patients did not comply with the gluten-free diet; 6 of them reported no change
Cheng *et al*, 2010	28/67 (42)	History of RAS in 42.4% of 67 CD patients *vs* 23.2% of 69 controls ($P = 0.02$)

Thus, the literature reviewed does support an association between oral ulcers and CD; however, these oral ulcers may not be RAS. Multiple reports of a proportion of CD-associated oral ulcers responding to a gluten-free diet support this conclusion. The oral ulcers that are a manifestation of CD would respond to a gluten-free diet, while classical RAS would not.

Vitamin B12 deficiency

A large number of studies have examined the prevalence of vitamin B12 deficiency in patients with RAS (Table 5). Collectively, these studies indicate that 0–42% of patients with RAS may have a deficiency of vitamin B12 (excluding case reports). This variation may be attributable to geographic and temporal variations in diet and food supplementation. A study compared the dietary intake of 100 patients with RAS to age- and gender-matched nutrient intake data from 9033 subjects from the US National Health and Nutrition Examination Survey (NHANES). Interestingly, patients with RAS were found to have significantly lower daily intake of vitamin B12 as compared to controls ($P < 0.0002$) (Kozlak *et al*, 2010).

A number of case reports indicate that some cases of RAS in patients with vitamin B12 deficiency are successfully treated with vitamin B12 supplementation. Further, treatment with vitamin B12 may be of benefit even in the absence of vitamin B12 deficiency. Submucous injection of vitamin B12 and hydrocortisone, in 22 RAS cases, resulted in reduced frequency, more rapid healing, and diminution of lesions in 36% of cases (Biedowa and Knychalska-Karwan, 1983). A randomized, double-blind, placebo-controlled trial examined the use of once daily sublingual vitamin B12 for RAS (Volkov *et al*, 2009). After 6 months of treatment, 20 of 31 (74.1%) patients with RAS in the active intervention group were free of ulceration, as compared to 8 of 27 (32%) patients with RAS in the placebo group ($P < 0.01$). This significant response to vitamin B12 was independent of initial blood B12 level. It has been pointed out that this trial had some shortcomings; however, the findings support further investigation to

Table 5 Studies of vitamin B12 deficiency in patients with recurrent aphthous stomatitis (RAS)

Author, year	*Number of RAS patients with B12 deficiency/total patients with RAS (%)*	*Comments*
Walker, 1973	4/4 (100)	Case series. In all four cases, complete resolution of RAS was achieved by vitamin B12 supplementation
Nally and Blake, 1975	15/36 (42)	Therapy with vitamin B12 resulted in complete resolution of RAS in 77% of cases
Wray *et al*, 1975	5/130 (14)	5 of the patients with RAS were deficient in vitamin B12, while only 1 of 130 age- and sex-matched controls was B12 deficient (because of latent Addisonian pernicious anemia). When treated with 1000 μg hydroxocobalamin IM followed by 1000 μg every 2 months, four of the five patients with RAS were promptly relieved of symptoms and remained disease-free for at least 1 year, and the 5th subject showed marked improvement
Challacombe *et al*, 1977	3/193 (2)	Reported B12 deficiency in 3 of 193 patients with RAS, 0 of 80 patients with other oral ulcers, 4 of 204 patients with non-ulcerative oral diseases, and 0 of 100 healthy controls ($P > 0.05$)
Wray *et al*, 1978	11/330 (3)	Extension of previous series to 330 patients with RAS, of which 11 were deficient in vitamin B12. Three of these 11 patients were also deficient in iron, 1 in folate, and 1 in both iron and folate, in addition to B12. Of the 11 patients with RAS deficiency in vitamin B12, 8 had Addisonian pernicious anemia, 2 had celiac disease (CD) and 1 had Crohn's disease
Olson *et al*, 1982	0/90 (0)	Screened 90 patients with RAS and 23 healthy controls. There were no cases of B12 eficiency in either group
Tyldesley, 1983	4/102 (4)	Patients had 'recurrent oral ulceration,' not specifically stated to be RAS
Rogers and Hutton, 1986	0/102 (0)	Patients with a history of malabsorption syndromes or inflammatory bowel disease were excluded. Although several patients were deficient in iron and/or folate, none were B12 deficient
Field *et al*, 1987	0/100 (0)	All subjects were children
Porter *et al*, 1988	Not reported/69 (3)	Low levels of serum vitamin B12 occurred in 3.2% of both patients with RAS and disease control subjects
Palopoli and Waxman, 1990	1/1 (100)	Case report of a patient with pernicious anemia and frequent RAS recurrences for 4.5 years, which completely resolved with vitamin B12 therapy
Weusten and van de Wiel, 1998	3/3 (100)	Case reports. The causes of B12 deficiency were pernicious anemia in one case, CD in one case, and unknown in one case. In all three cases, restoration of B12 levels to normal was accompanied by complete resolution of RAS lesions
Piskin *et al*, 2002	8/35 (23)	8 of 35 patients with RAS had B12 deficiency *vs* 0 of 26 healthy controls ($P < 0.05$). Mean B12 levels were significantly lower in the RAS group ($P = 0.005$)
Thongprasom *et al*, 2002	0/23 (0)	Serum B12 levels were normal in 23 patients with RAS and 19 controls
Volkov *et al*, 2005	3/3 (100)	Case reports. All three patients had complete resolution of RAS on replacement therapy with vitamin B12
Koybasi *et al*, 2006	12/34 (35)	Twelve of 34 patients with RAS had deficient serum B12 levels *vs* 0 of 32 controls. B12 levels were associated with occurrence of RAS lesions ($P = 0.028$)

confirm the effectiveness of vitamin B12 in the treatment of RAS (Carrozzo, 2009). Thus, although RAS may only rarely be associated with low blood levels of vitamin B12; treatment with vitamin B12 may nevertheless be of benefit in RAS, via mechanisms that warrant further study.

Are there any new RAS treatments?

Introduction

Recurrent aphthous stomatitis is a widespread disease affecting over 100 million Americans. New treatments are tested each year in an attempt to reduce its associated pain and dysfunction. The diversity and multitude of published studies of RAS treatments are staggering. In this section, we answered the question 'Are there any new RAS treatments?' by conducting a systematic review of RAS trials published in the past 6 years.

Methods

We searched PubMed using the keyword 'Aphth*,' limiting the search to human clinical trials published in any language from May 15, 2005 to the date of submission, May 30, 2011. We also searched the Cochrane Central Register of Controlled Trials (CENTRAL/CCRCT; http://onlinelibrary.wiley.com/o/cochrane/cochrane_clcentral_articles_fs.html) using the keyword 'Aphth*' in 'All text,' with '2005–2011' as date range. We excluded letters, abstracts of meetings, and full-text studies without a comparison to a control group or not targeted at RAS. We also excluded vitamin B12 trials, covered above. The remaining trials were thoroughly reviewed and assigned an Oxford Centre for Evidence-based Medicine (OCEBM) level of evidence (Richards, 2009) by a single reviewer (L.B.).

Results

From 76 unique studies, we excluded 33 (Figure 1): 11 studies that did not test RAS treatments (Arvola *et al*, 2006; Sunitha and Shanmugam, 2006; Akman *et al*, 2007; Yoshihara *et al*, 2007; van der Hilst *et al*, 2008; Yao *et al*, 2008; Lebranchu *et al*, 2009; Chams-Davatchi *et al*, 2010; Davatchi *et al*, 2010; Erkalp *et al*, 2010; Perico *et al*, 2010), 11 studies without a statistical comparison to a control arm (Kaufman *et al*, 2005; Sharquie and Hayani, 2005; Akhionbare and Ojehanon, 2007; Sharma *et al*, 2007; Karaca *et al*, 2008; Lee *et al*, 2008; Nanke *et al*, 2008; Mimura *et al*, 2009; Ciancio *et al*, 2010; Hello *et al*, 2010; Yasui *et al*, 2010), and eleven other studies (Moezzi *et al*, 2005; Brignone *et al*, 2007; Chuang and Langone, 2007; Passarini *et al*, 2007; Renko *et al*, 2007; Burgess, 2009; Garavello *et al*, 2009; Koray *et al*, 2009; Pignatello *et al*, 2009; Volkov *et al*, 2009 Budde *et al*, 2011).

Of the remaining 43 trials, 10 did not report significant differences in effectiveness between treatment arms (Table 6), and 33 reported significant effects of various topical or local (23 studies, Table 7) and systemic (10 studies, Table 8) treatments. All trials were conducted in patients with idiopathic RAS with no known systemic diseases associated with RAS, except for two studies of BD patients (Arabaci *et al*, 2009; Davatchi *et al*, 2009). The types of ulcers included in individual trials (based on size, number, frequency of occurrence, or response to prior treatment) varied and were not always reported.

Doxycycline, minocycline, amlexanox, triamcinolone acetonide in Orabase, colchicine, and laser therapy were tested more than once, although not always as the same formulation or in the same patient group.

Four studies were in general agreement that synthetic tetracyclines may be useful for RAS. Low-dose

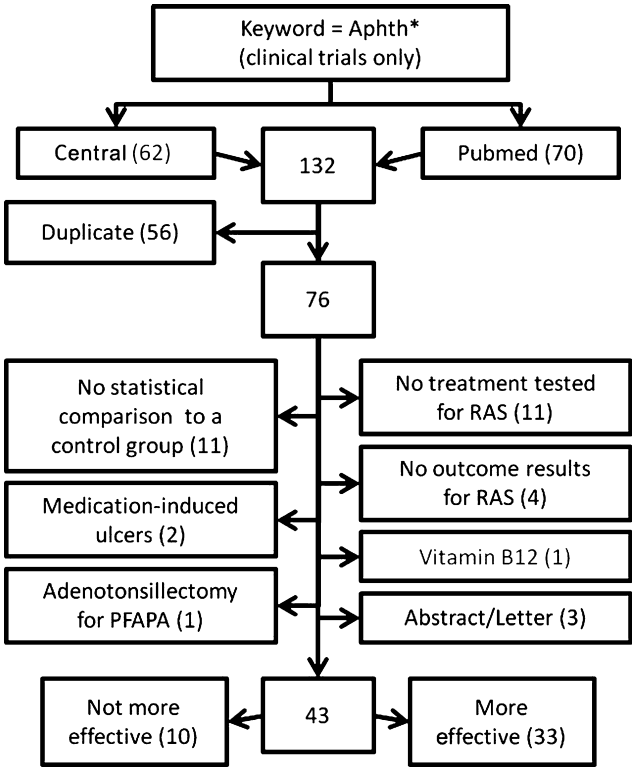

Figure 1 Study selection process for systematic review of recurrent aphthous stomatitis (RAS) treatments. Number of studies is indicated in parentheses

Table 6 Clinical trials for recurrent aphthous stomatitis (RAS) reporting no difference in effectiveness between the two treatment arms

Author, year	*Active treatment*	*Control*
Kolseth *et al*, 2005	Norwegian LongoVital	Placebo
Bratel *et al*, 2005	Swedish LongoVital	Placebo
Arikan *et al*, 2006	Cryotherapy	Hydrogel with cellulose
Nolan *et al*, 2006	Hyaluronic acid gel	Placebo gel
Hamazaki *et al*, 2006	Perilla oil	Soybean oil
Rodriguez *et al*, 2007[a]	Amlexanox paste	Clobetasol paste
Ersoy *et al*, 2007[b]	H. Pylori eradication	No eradication
Weckx *et al*, 2009	Levamisole	Placebo
Moghadamnia *et al*, 2009	Licorice patch	Patch only
Pakfetrat *et al*, 2010[a]	Prednisolone	Colchicine

[a]Trial compared two active treatment arms.
[b]Trial enrolled only patients with Behçet's disease.

Table 7 Controlled trials reporting effectiveness of active topical or local treatment for recurrent aphthous stomatitis (RAS)[a]

Author, year	*Therapy and regimen*	*Treatment arms (n)*[b]	*Mean age*[c]	*Trial duration*	*Outcome/adverse events (AE)*	*OCEBM quality rating – sources of bias*
de Armas *et al*, 2005	Liquid R. Mangle (RMABE; RM) *vs* placebo (water and RMABE excipients), QD	RM (17) PL (15)	39–41	18 days	Faster healing (including pain and erythema) with RM ($P < 0.0001$). No AE	2B – single (patient) blind (or unblinded, if PL tasted/looked differently), randomization method unknown
Murray *et al*, 2005	Amlexanox 5% paste QID at prodromal (PR) *vs* onset (ON) of ulcerative stage and *vs* no treatment (NT)	NT/PR (17)[d] NT/ON (29)[d]	37	10 days	Mean maximum ulcer size was 84% lower in PR and 59% lower in ON *vs* NT ($P < 0.05$). Nine mild AE	2B – open label, only 81% of randomized patients entered the treatment phase, possible period effect (NT preceded PR/ON)
Alidaee *et al*, 2005	Cauterization with silver nitrate (CX) *vs* placebo (melted sugar on a wire) once	CX (52-5) PL (45-7)	25–26	7 days	Less pain with CX starting at day 1 ($P < 0.001$), but no difference in ulcer healing. No AE	2B – patient and examiner blind only, PL may have tasted differently, 12% total attrition, per protocol analysis
Murray *et al*, 2006	Amlexanox 2 mg patch *vs* vehicle patch, QID	AX (26-0) PL (26-0)	32–40	4 days	Smaller thermographically active area at day 4 with AX ($P< 0.05$), but similar size and erythema. Mostly mild 74 AE in both arms	2B – patches had different color, PL arm younger, 15% of participants had missing data
Sharquie *et al*, 2006	Lactic acid 5% mouthwash (LA) *vs* placebo (distilled water) TID	LA (40-4) PL (40-6)	30	7 days	Less ulcers and pain at day 3 and 7 with LA ($P < 0.05$). Two mild AE (irritation) in LA arm	2B – patient blind (or unblinded, if water placebo tasted differently), 12.5% attrition, non-randomized, per protocol analysis
Liu *et al*, 2006	Amlexanox 2 mg adhesive tablet *vs* vehicle tablet QID for 5 days	AX (107-3) PL (108-0)	34	6 days	Smaller size and less pain at days 4 and 6 with AX ($P < 0.001$). One mild AE in each arm	2B – unknown if PL tasted differently, non-parallel design, per protocol analysis, unknown how compliance was monitored, center effects unknown[e]
Amanlou *et al*, 2007	S. Khuzistanica extract (SE) *vs* S. Khuzistanica essential oil (SO) *vs* placebo (ethanol/water), five drops QID	SE (20)[d] SO (20)[d] PL (20)[d]	28	7 days	Faster healing with SE and SO *vs* PL ($P < 0.001$). Two mild AE in SO arm	2B – unknown if placebo looked/tasted the same as SE/SO, 8% total attrition, randomization method unknown, baseline data incomplete, per protocol analysis
Gorsky *et al*, 2007	Minocycline 0.2% (MN) *vs* Tetracycline 0.25% rinse (TE), 5 ml QID	MN (16)/TE (17)[d]	39	10 days then cross over	Lower pain starting at day 2 with MN ($P < 0.05$). No AE	2B – blinding unknown, no PL, only self-reports, per protocol analysis, 48% total attrition
Gorsky *et al*, 2008	Minocycline rinse 0.2% (MN) *vs* placebo, 5 ml QID	MN (18)[d] PL (15)[d]	37–38	10 days	Less pain starting at day 2 with MN ($P < 0.05$). No AE	2B – 39% total attrition, unknown who was blinded, only self-reports, PL may have tasted differently, per protocol analysis
Shemer *et al*, 2008	Patch with citrus oils and Mg salts (PA) QD *vs* Benzocaine 20% with benzoin tincture oral solution (BZ) TID	PA (26-3) BZ (22-4)	41–48	10 days	Less pain at 12 and 24 h, and faster pain relief with PA ($P < 0.05$). Less local AE with PA	2B – open label, per protocol analysis, only self-reported outcomes, inconsistent statistical results, 15% attrition
Motallebnejad *et al*, 2008	Hypericum mouthwash 0.5% in water QID (HY) *vs* placebo (pure water) QID *vs* no treatment (NT)	NT/HY/PL (30)[d] Three episodes/patient	25	7 days then cross over	Less pain at day 2–7 with HY *vs* PL/NT ($P < 0.05$), but no difference in ulcer size. AE unknown	2B – unknown if water placebo looked/tasted the same as HY; NT phase before HY and PL, crossover design and timing unclear, randomization unclear
Martin *et al*, 2008	Licorice patch (16 h day^{-1}; LP) *vs* star anise patch (AP) *vs* no treatment (NT)	LP (23) AP (23) NT (23)	Not stated (≥18)	8–10 days	Smaller size after 7 days and less pain after 3 days with LP *vs* NT ($P < 0.05$). *P*-value for LP *vs* AP unknown. No AE	2B – examiner blind only (or unblinded, because NT recruited later), randomization method not described, incomplete baseline results. No inactive placebo used
Al-Na'mah *et al*, 2009	Dexamucobase 0.1 g per 100 g (DM) *vs* Triamcinolone acetonide in Orabase (TR) QID	DM (53)[d] TR (37)[d]	28–30	14 days	Faster healing with DM ($P < 0.001$). Mild AE in both arms	2B – open label, no randomization, attrition unknown

Table 7 (*Continued*)

Author, year	*Therapy and regimen*	*Treatment arms (n)*[b]	*Mean age*[c]	*Trial duration*	*Outcome/adverse events (AE)*	*OCEBM quality rating – sources of bias*
Meng *et al*, 2009	Amlexanox 5% pellicle *vs* placebo pellicle, QID for 5 days	AX (109-1) PL (107-2)	30	6 days	Smaller size and less pain at days 4 and 6 with AX ($P < 0.04$). No AE	2B – unknown if PL tasted/looked differently, larger baseline ulcer size in PL arm, per protocol analysis, unknown how compliance was monitored, center effects unknown[e]
Zand *et al*, 2009	CO_2 laser (LS) *vs* placebo (inactive laser) once	LS/PL (15) 2 RAS/patient	38	4 days	Less pain with LS starting immediately until 96 h ($P < 0.001$)	2B – attempted to blind patient, attrition unknown, only self-reports
Arabaci *et al*, 2009[f]	Nd:YAG Laser(LS) once *vs* Triamcinolone acetonide 0.1% in Orabase (TR) TID	LS (14-0) TR (14-0)	30	7 days	Less exudation with LS ($P < 0.001$), but similar erythema. Less pain immediately and at days 4 and 7 with LS ($P < 0.001$). No AE	2B – unblinded
Tezel *et al*, 2009	Nd:YAG Laser(LS) once *vs* Triamcinolone acetonide 0.1% in Orabase (TR) TID	LS (10-0) TR (10-0)	32	7 days	Less exudation with LS ($P < 0.05$) at the end, but similar erythema. Less pain immediately and at days 4 and 7 with LS ($P < 0.05$). No AE	2B – unblinded
Skulason *et al*, 2009	Doxycycline gel 1.5 mg g^{-1} QID (DX) *vs* placebo (PL)	DX (28-3) PL (28-4)	Not stated (allowed range 18–65)	3 days	Shorter duration with DX ($P < 0.005$, 1-sided). Four AE (transient burning/pain)	2B – unknown if PL tasted/looked differently, 12.5% attrition, per protocol analysis, incomplete baseline results, only self-reports (diaries)
Porter *et al*, 2009	HybenX cauterization (once; HX) *vs* salicept patches as needed (SL)	HX (32-8) SL (31-2)	Not stated (median 23–27)	8 days	Less pain with HX at days 1–2 ($P < 0.02$), but no difference in ulcer healing. Nine AE, likely unrelated	2B – examiner blind only, randomization method unknown, multiple comparisons, per protocol analysis, 16% attrition with more HX patients withdrawn for developing new RAS, significantly different baseline pain levels
Yang and Jang, 2009	Botulinum toxin A (BT) *vs* placebo (saline) injection	BT (35-2) PL (35-2)	26–29	6 days (6-month f/u)	Less pain with BT at 6 days ($P < 0.001$) and no recurrence at 6 months in the same location (*vs* 5 recurrences in PL). No AE	2B – patient blind only, 6% attrition, per protocol analysis
Babaee *et al*, 2010	Myrtle oral paste 5% (MT) *vs* placebo paste, QID	MT/PL (45-5)	30	6 days then cross over	Less pain ($P < 0.05$) and smaller size ($P < 0.001$) with MT. No AE	2B – unknown if PL tasted/looked differently, period and center effects unknown, compliance unknown, 11% attrition[e]
Zhou *et al*, 2010	Penicillin G potassium troche 50 mg QID (PN) *vs* placebo QID (PL) *vs* no treatment (NT)	PN (88-2) PL (90-2) NT (85-1)	36	4 days plus 2 days follow-up	>50% smaller size and less pain in PN *vs* PL/NT at day 3 ($P < 0.001$) and 4–6. Two mild AE in each PN/PL arm	2B – unknown if PL had same color. Randomization method, compliance and center effects unknown. Ulcer selection not random, no sample size justification, per protocol analysis[e]
Hamdy and Ibrahem, 2010	Quercetin cream (QC) *vs* Benzydamine hydrochloride (BZ) rinse TID	QC (20)[d] BZ (20)[d]	25	10 days	Smaller size ($P < 0.004$) and less pain ($P < 0.01$) at day 10 with QC. AE unknown	2B – randomization method, dosage, and attrition unknown, unblinded, no placebo, compliance unknown

[a]All clinical trials were single center, and they were based on a randomized, double-blind, placebo-controlled, parallel arm design including intent-to-treat (ITT) analysis of at least one objective outcome (i.e., confirmed by examination) unless otherwise specified. Trials that did not report presence or absence of attrition also did not mention ITT analysis.
[b]Numbers in parenthesis indicate initial sample size minus number lost to follow-up, if known.
[c]In years. All trials included patients of both genders with idiopathic RAS unless otherwise specified.
[d]Assumed to be the final sample size after attrition (attrition was either not reported or was not reported by each arm).
[e]Multicenter study.
[f]Patients with Behçet's disease.

Table 8 Controlled trials reporting effectiveness of systemic treatments for recurrent aphthous stomatitis (RAS)[a]

Author, year	*Therapy and regimen*	*Treatment arms (n)*[b]	*Mean age*[c]	*Trial duration*	*Outcome/adverse events (AE)*	*OCEBM quality rating – sources of bias*
Thornhill *et al*, 2007	Pentoxifylline (400 mg TID; PX) *vs* Placebo TID	PX (14-3) PL (12-4)	33–34	2 months (plus 2 pre/post)	Reduced ulcer size with PX ($P = 0.05$) but minimal benefits seen for other parameters. AE in both arms	2B – 27% total attrition, small sample size, only self-reported outcomes (diaries)
Preshaw *et al*, 2007	Doxycycline (20 mg BID; DX) *vs* placebo BID	DX (25)[d] PL (25)[d]	37–43	3-month	More days with no new RAS with DX ($P = 0.04$). Other parameters tended to improve, though, not significantly. AE unknown	2B – attrition and compliance unknown, only self-reported outcomes (diaries)
Samet *et al*, 2007	Bee propolis (500 mg QD; BP) *vs* Placebo (calcium-based supplement QD; PL)	BP (10-0) PL (9-2)	Not stated (≥18)	6–13 months	Higher % of patients on BP with ≥50% reduction in # of outbreaks ($P = 0.06$) and improved quality of life (QoL; $P = 0.03$). AE unknown.	2B – only self-reports, PL may not be inert, small sample, incomplete baseline results, 10.5% attrition, randomization method unknown, QoL data collection not standardized
Yazdanpanah *et al*, 2008	Poliovirus vaccine (four drops at baseline; PV) *vs* Placebo (PL)	PV (20)[d] PL (28)[d]	29–30	3 months	Fewer symptoms with PV ($P < 0.01$). No AE	2B – PL and blinding not described, attrition unknown, only self-reported outcomes, some PV contained antibiotics
Sharquie *et al*, 2008	Zinc sulfate (150 mg BID; ZN) *vs* Dapsone (50 mg BID; DP) *vs* Placebo (glucose, 250 mg BID)	ZN (15)[d] DP (15)[d] PL (15)[d]	31	3 months	Significantly smaller size and fewer manifestations with ZN or DP *vs* PL at weeks 4–12. No AE	2B – PL may not be inert, no randomization reported, small sample, multiple comparisons, attrition unknown
Davatchi *et al*, 2009[e]	Colchicine (1 mg QD; CO) *vs* Placebo (PL)	CO/PL (169)	32	4 months, then cross over	Fewer ulcers with CO ($P < 0.005$). AE in both groups, with increased liver enzymes in two patients on CO	2B – unclear design (sample size, attrition, PL description, randomization method) and statistics
de Abreu *et al*, 2009	Clofazimine (100 mg QD for 30 days, then QOD; CL) *vs* Colchicine (0.5 mg QID) *vs* Placebo BID	CL (23)[d] CO (23)[d] PL (20)[d]	34–45	6 months	Improved number and duration, but not size, with CL *vs* CO/PL ($P < 0.05$). CO not better than PL. Gastrointestinal (CO) and cutaneous (CL) AE	2B – incomplete blinding, PL regimen different from CO/CL, attrition unknown, PL older
Mousavi *et al*, 2009	Homeopathic (multiple treatments; HM) *vs* Placebo (PL)	HM (50-0) PL (50-0)	38	6 days	Less pain and smaller size at day 4 and 6 with HM ($P < 0.05$). No dropouts because of AE	2B – single (patient) blind, PL may have tasted differently, individual treatment effectiveness unknown, short trial
Femiano *et al*, 2010	Prednisone (0–25 mg; PN) *vs* Montelukast (0–10 mg, MK) *vs* Cellulose placebo (0–100 mg, PL) QD	PN (20-0) MK (20-0) PL (20-0)	27	2 months plus 2 months follow-up	Fewer RAS with PN/MK *vs* PL at 1–4 months ($P < 0.01$). Less time to healing and pain free with PN *vs* MK and PN/MK *vs* PL ($P < 0.0001$). Two mild AE in each MK/PL arm, 6 AE with PN	2B – PN regimen different than MK/PL, initial sample size unclear, full blinding unclear, unknown if PL pill different from MK/PN, more females in PL arm, inconsistencies in results
Pourahmad *et al*, 2010	Camel thorn distillate (CT) *vs* distilled water (PL), rinse + swallow QID	CT (49)[d] PL (44)[d]	27–32	14 days	Less time to pain resolution in CT arm. Less size and pain with CT at days 3–7 ($P < 0.001$) and 10 ($P < 0.02$). AE unknown	2B – randomization method, dosage and attrition unknown, PL arm had larger RAS at baseline, PL may have tasted/looked differently

[a]All clinical trials were single center, and they were based on a randomized, double-blind, placebo-controlled, parallel arm design including intent-to-treat (ITT) analysis of at least one objective outcome (i.e., confirmed by examination) unless otherwise specified. Trials that did not report presence or absence of attrition also did not mention ITT analysis.
[b]Numbers in parenthesis indicate initial sample size minus number lost to follow-up, if known.
[c]In years. All trials included both genders and were conducted in patients with idiopathic RAS unless otherwise specified.
[d]Assumed to be the final sample size after attrition (attrition was either not reported or was not reported by each arm).
[e]Patients with Behçet's disease.

doxycycline seemed effective, particularly as a topical gel (Preshaw *et al*, 2007; Skulason *et al*, 2009). Minocycline rinses (0.2%) also seemed safe and more effective than either placebo or tetracycline rinses (Gorsky *et al*, 2007, 2008).

Four studies tested various formulations of topical amlexanox (paste, disk, pellicle, or tablet) and reported improvement of some outcomes, especially for treatment initiated during the prodromal phase. A fifth study reported similar responses to 5% amlexanox and 0.05% clobetasol pastes (Rodriguez *et al*, 2007).

Systemic colchicine produced inconsistent results. The drug appeared to be effective in BD-related oral ulcers, but not in otherwise healthy patients with frequent RAS unresponsive to topical treatments (de Abreu *et al*, 2009; Davatchi *et al*, 2009).

Two unblinded studies by the same team showed greater pain reduction with Nd:YAG laser *vs* triamcinolone acetonide in Orabase (Arabaci *et al*, 2009; Tezel *et al*, 2009).

Various compounds and plant extracts with anti-inflammatory, analgesic, or antiseptic properties showed some effectiveness as topical treatments (de Armas *et al*, 2005; Amanlou *et al*, 2007; Martin *et al*, 2008; Motallebnejad *et al*, 2008; Babaee *et al*, 2010). However, most trials were not fully blinded.

Overall, different types of systemic and topical treatments were reported to be effective in regard to at least one of the outcomes studied. However, the quality of evidence of these trials was low (OCEBM rating 2B), because of moderate to high potential for bias (Tables 7–8). We did not find systematic reviews of randomized clinical trials published in the past 6 years (OCEBM rating 1A).

Discussion

The most commonly studied treatments in the past 6 years were doxycycline, minocycline, amlexanox, colchicine, triamcinolone acetonide in Orabase, and laser therapy.

Low-dose synthetic tetracyclines (doxycycline and minocycline), particularly as gel or rinse, appeared to reduce RAS pain and duration, possibly through local inhibition of collagenases or immunomodulatory effects. However, long-term adverse events (AE) in the general population are unknown and may include bacterial resistance, fungal overgrowth, and fetal harm.

Amlexanox showed some effectiveness short-term, particularly when used during the prodromal phase. Its exact mechanism of action on RAS is unknown, although it is an anti-inflammatory drug. The number of AE reported during amlexanox trials varied by research team (ranging from 0 to 74), suggesting possible differences in reporting standards.

Systemic colchicine lacked effectiveness in frequent idiopathic RAS and was associated with gastrointestinal AE. More severe AE have also been reported in the literature. We could not find double-blind, randomized, placebo-controlled trials of colchicine for idiopathic RAS before 2005. Thus, this drug should be used with caution until further evidence.

Lasers or chemical cauterization may provide fairly rapid pain relief, attributed to disruption of local nerve endings or reduction in inflammatory mediators. However, some of these therapies require repeated dental visits, which are not feasible long-term or for frequent RAS.

Triamcinolone acetonide in Orabase was used in three trials as the active control and was less effective than Nd:YAG laser (for immediate pain relief) or dexamucobase (for accelerating healing).

Other topical therapies were tested with some success. However, incomplete blinding because of differences in taste, texture, or appearance between products was likely.

When selecting treatments, the patient's clinical status and preferences should be considered, such as potential fetal harm in pregnant women and accidental ingestion in children. Most studies were conducted in adults, limiting generalizability to all ages. This is a consideration, because RAS is common in teenagers and differences in compliance in younger patients can alter drug's effectiveness.

Although statistical significance was achieved in many studies, results may have been affected by underlying study bias. Studies testing multiple outcomes were more susceptible to false positive results.

Most trials reported generally mild or no AE. However, these studies were also short and small. Thus, less common AE or AE from long-term use cannot be excluded. Safety could not be assumed for studies failing to report presence or absence of AE.

Our review included studies published in the past 6 years and listed in two major databases. Gray literature, additional databases, or earlier studies were not included. Thus, this is not an exhaustive review of all RAS trials. For example, topical and systemic corticosteroids, widely used in practice for RAS treatment, were infrequently studied in recent trials, although positive effects of prednisone were noted in one study (Femiano *et al*, 2010). A single reviewer performed the review, which may have resulted in more selection and rating bias than in the case of multiple reviewers.

When rating the evidence, assessment of potential bias was often limited by lack of study details. For example, diagnostic criteria for RAS were universally not specified or incompletely specified. It was sometimes unclear how outcome data were measured.

Studies rarely described the randomization method or allocation concealment strategy. Postrandomization loss to follow-up was often unclear or, if attrition had occurred, intent-to-treat analyses were not always conducted. The degree of item non-response (e.g., incomplete data collection from a patient) was almost universally never reported. Measurement of treatment compliance was almost never described.

A number of studies reported the use of a placebo, although not all studies actually used a placebo in its strict definition or fully described potential differences with the active drug. Strong placebo effects were frequent in patients with RAS. Thus, studies of treatment effectiveness based solely on before and after

differences in RAS outcome without a control group provide a very low level of evidence and were excluded from this review.

Conclusions

Until RAS etiology is discovered, treatment options will remain few and only partially effective. Recent trials have focused primarily on local and topical treatments. These therapies in general carry lower risks of systemic adverse effects and should be considered as the first line of treatment. Improved design, analysis, and standardized reporting of clinical trials are needed to maximize study quality, disclose potential sources of bias, and ensure complete assessment of product safety and effectiveness. Thus, future research should focus on identifying RAS etiology, developing standardized diagnostic criteria for RAS, and improving the design and reporting of clinical trials. Trials should be carefully planned by clinician–statistician teams and reported using universal guidelines, such as the Consolidated Standards of Reporting Trials (CONSORT; http://www.consort-statement.org/).

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Author contributions

L. Baccaglini and M. Carrozzo led the review team. R.V. Lalla, A.J. Bruce, J.C. Sartori-Valinotti, M.C. Latortue, R.S. Rogers, M. Carrozzo and L. Baccaglini reviewed the literature, wrote sections of the manuscript, revised and reviewed the full manuscript and approved the submitted version.

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