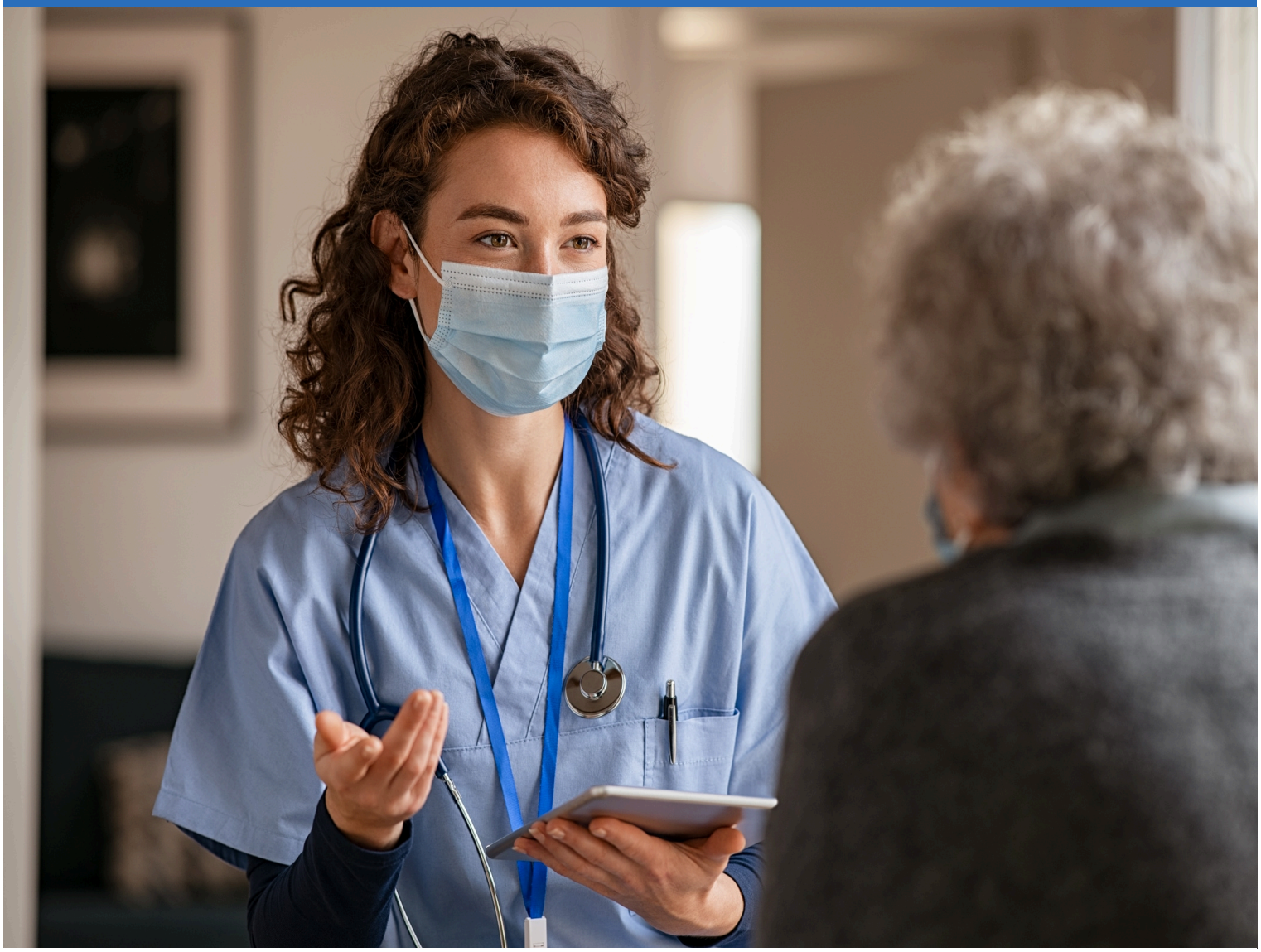
BMJ Best Practice

Angular cheilitis

Straight to the point of care



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Summary

Angular cheilitis is inflammation of the angles of the mouth, characterised by fissures, scaling, erythema, and crusting.

Aetiology is multi-factorial and includes mechanical factors, infectious agents, nutritional deficiencies, or inflammatory dermatological conditions.

Diagnosis is made clinically; however, laboratory tests help to identify aetiology.

Successful therapy is based on identifying and correcting each and all factors of this multi-factorial condition.

Definition

Angular cheilitis is inflammation of the angles of the mouth, characterised by fissures, scaling, erythema, and crusting.[1] The cause is usually multi-factorial, due either to a primary infection or to a non-infectious entity such as mechanical irritation, nutritional deficiency, or other dermatological condition.[2]

Angular cheilitis

From the collection of Dr Wanda C. Gonsalves; patient consent obtained

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THEORY

Epidemiology

Prevalence is 7 per 1000, and the condition is seen most often in older people.[4] The incidence is increased about 3-fold in denture wearers and almost two-fold in men.[5] Nutritional deficiencies account for approximately 25% of all cases of angular cheilitis. There is an association with anaemia in 11.3% to 31.8% of patients with angular cheilitis.[6]The prevalence of angular cheilitis in patients with HIV infection is between 5.6% to 28.9%.[6] In a study of patients with HIV infection in Brazil, the incidence of angular cheilitis was 13.9%.[7] Of HIV-infected patients, 10% may have an opportunistic infection with *Candida albicans,* which can present as angular cheilitis.[8] Angular cheilitis was detected in 7.8% of patients with Crohn's disease and 5% of patients with ulcerative colitis.[9]

Aetiology

The condition is multi-factorial in origin and can be broadly grouped according to one, or a combination of several different factors. Unilateral lesions are usually induced by trauma and are short-lived, whereas bilateral lesions often represent an infectious cause or underlying disease process.[3]

- Infective agents: *Candida albicans* and *Staphylococcus aureus* are often isolated alone or in combination.[3] [10] [11] *C albicans* is often isolated in patients wearing dentures, or in people with diabetes. Angular cheilitis associated with candidiasis may be a manifestation of an underlying immunological deficiency such as HIV, diabetes mellitus, or chronic granulomatous disease. In outbreaks of acute pustular and fissured cheilitis occurring in children, staphylococci and streptococci have been isolated.[12]
- Mechanical factors: maceration of the commissural epithelium is often the primary cause of non-infectious cheilitis, brought on by dental trauma, flossing, excessive salivation, drooling, habitual licking, and ill-fitting dentures.[2] [11] [13] The ageing process leads to resultant anatomical changes, including loss of vertical dimension between mandible and maxilla and overhanging skin folds. These changes can lead to angular cheilitis.[14] In Down's syndrome, prognathism (jaw protrusion) and hyper-salivation may lead to cheilitis.[15] Xerostomia (dry mouth), isolated or as part of Sjogren's syndrome, can lead to cheilitis as well.[11] In children, lip-licking and thumb-sucking behaviour can also be causative.
- Nutritional deficiencies: deficiencies of riboflavin, niacin, folate, iron, vitamin B12, and zinc, and general protein malnutrition, show evidence of causation.[2] [11] Angular cheilitis may be the manifestation of any systemic disorder that predisposes a patient to malnutrition, such as inflammatory bowel disease, eating disorders, or a history of total parenteral nutrition.[16] [17]
- Drug-related side effects: some medications can lead to angular cheilitis. It is a common side effect of treatment with isotretinoin, and the antiretroviral medication indinavir.[6] Sorafenib (multikinase inhibitor) has been reported to produce angular cheilitis.[6]

Pathophysiology

Maceration due to various aetiological factors leads to a disrupted epidermal barrier and provides an ideal environment for fungal and bacterial organisms.[2] Edentulous patients experience bone resorption of the mandible, and this also results in sagging of the facial tissue and excessive folds at the commissures. Saliva accumulation and moisture trapping provide an ideal environment for secondary opportunistic infection.

Classification

Clinical classification[3]

- A single rhagad (painful fissure)
- A single deeper and longer rhagad following a skin fold
- Several rhagades radiating from the corners of the mouth
- Erythema of the skin adjacent to the corners of the mouth without rhagades.

Case history

Case history #1

A 73-year-old man presents with redness confined to the corners of his mouth. He wears dentures. Examination reveals fissuring and crusting at the angles of the mouth, with palatal erythema. Laboratory investigations for zinc, iron, folate, riboflavin, niacin, and vitamin B12 are normal, and a fungal culture from the angle of the mouth shows growth of *Candida albicans* .

Other presentations

The more severe forms usually have multiple furrows or fissures radiating from the angle of the mouth.

Approach

Diagnosis is usually made via history and physical examination alone; however, supporting laboratory studies may help identify contributing aetiologies, especially when refractory to empirical treatment. Laboratory testing and additional work-up are usually performed only after treatment failure.

History

The first step is a thorough history, with emphasis on identifying medical history, such as:

- Chronic skin conditions
- Inflammatory bowel disease
- Medicines causing xerostomia and immunosuppression
- Diabetes mellitus
- Denture history
- Oral care
- Eating disorders
- History of total parenteral nutrition
- History of acid reflux
- Diarrhoea.

It is also important to identify any rash as pruritic or non-pruritic. The patient's age and sex are important to note, as older men are more prone to angular cheilitis.

Oral examination

The second step is a thorough oral examination, checking for any sign of erythema, candidiasis, xerostomia, or abnormal mucosal changes such as palatal erosions. A dental referral is recommended to assess the patient's oral care, teeth, gums, mouth closure, and the lips and tongue.[21]

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Characteristic painful red fissures may be identified at the corner of the mouth. The 4 possible clinical patterns are:[3]

- A single rhagad (painful fissure)
- A single deeper and longer rhagad following a skin fold
- Several rhagades radiating from the corners of the mouth
- Erythema of the skin adjacent to the corners of the mouth without rhagades.

If the examination reveals palatal erythema, then denture-induced stomatitis is usually due to candidiasis.[2] [13] If dental caries are apparent, an eating disorder is a possible aetiology. An underlying nutritional deficiency may often be revealed via examination of the tongue.[2] [13] The tongue examination may show the following:

- Aphthous ulcers or a pale de-papillated tongue in iron deficiency with or without anaemia
- A de-papillated glossy red tongue in folate or niacin deficiency
- A red atrophic tongue in vitamin B12 deficiency
- A reddish-purple de-papillated tongue in riboflavin deficiency.

Riboflavin deficiency also produces smooth, shiny red lips, associated with angular cheilitis; this combination has been called cheilosis.

Angular cheilitis accompanied by alopecia, diarrhoea, and oral ulcerations suggests a zinc deficiency.

An eczematous dermatitis may extend down onto the cheek or chin, as in infective eczematoid reaction, or as a reaction to topical medicines. Severe pruritus would indicate allergic contact dermatitis.

Laboratory evaluation and dental assessment

Laboratory testing and additional work-up are usually performed only after treatment failure. Bacteriological and mycological cultures are recommended, including sampling the mucosal surfaces covered by dentures (i.e., oral mucosa), and the nares, to identify staphylococcal colonisation. Blood samples for FBC, fasting blood glucose, folate, iron, zinc, riboflavin, niacin, and vitamin B12 are indicated to exclude deficiency syndromes.

Angular cheilitis associated with candidiasis resistant to therapy may prompt investigation for an underlying immunological deficiency, such as HIV. Patch testing may be indicated in patients with recalcitrant disease in order to avoid potential allergens, and for recalcitrant, unilateral disease, tissue biopsy is recommended to exclude malignancy.

History and exam

Key diagnostic factors

presence of risk factors (common)

- Key risk factors include age over 75 years, male gender, presence of dentures, immune deficiency, Down's syndrome, xerostomia, diabetes, and chronic inflammatory skin disease.

dentures with palatal erythema (common)

- Suggests denture stomatitis and possible candidiasis.[2] [13]

oral candidiasis (common)

- Suggests *Candida albicans* as the aetiology.[2]

Other diagnostic factors

pruritus (common)

- If severe, indicates allergic contact dermatitis.

painful red fissures (common)

- Appear at corner of mouth as either a single fissure, a single deeper and longer fissure following a skin fold, several fissures radiating from the corners of the mouth, or erythema of the skin adjacent to the corners of the mouth without fissures.

eczematous dermatitis of lower face (common)

- Suggests a staphylococcal infection as the aetiology.
- May also be medicine reaction.

specific medicines (uncommon)

- Some medicines may induce xerostomia or angular cheilitis.
- Sorafenib (multikinase inhibitor) has been reported to produce angular cheilitis.[6]

history of inflammatory bowel disease (uncommon)

- GI symptoms may occur, such as diarrhoea, constipation, or bloody stool.

history of acid reflux (uncommon)

- There may be a history of acid reflux.

history of total parenteral nutrition (uncommon)

- May be associated with malnutrition.

history of eating disorders (uncommon)

- With dental caries, an eating disorder is a possible aetiology.

alopecia (uncommon)

- Fissures with alopecia, diarrhoea, and oral ulcerations suggest a zinc deficiency.[2]

diarrhoea/constipation (uncommon)

- May occur secondary to inflammatory bowel disease or zinc deficiency.[2]
- Fissures with alopecia, diarrhoea, and oral ulcerations suggest a zinc deficiency.

bloody stool (uncommon)

- May occur secondary to inflammatory bowel disease.

aphthous ulcers (uncommon)

- Indicates iron deficiency with or without anaemia.
- Fissures with alopecia, diarrhoea, and oral ulcerations suggest a zinc deficiency.

pale, de-papillated atrophic tongue (uncommon)

- Suggestive of iron deficiency.[2]

red, glossy, de-papillated tongue (uncommon)

- Suggestive of folate or niacin deficiency.[2]

red atrophic tongue (uncommon)

- Suggestive of vitamin B12 deficiency.[2]

reddish-purple de-papillated tongue (uncommon)

- Suggestive of riboflavin deficiency.[2]

smooth, shiny red lips (uncommon)

- Suggestive of riboflavin deficiency.[2]

dental caries (uncommon)

- An eating disorder is a possible aetiology if dental caries are seen on examination.

palatal erosions (uncommon)

- Abnormal mucosal changes such as palatal erosions may be seen on examination.

Risk factors

Strong

age over 75 years

- More common in older people.[5]

male sex

- There is a 2-fold increase in men.[5]

dentures

- The odds increase 3-fold in denture users.[5]
- Poor denture hygiene may cause mucosal injury or infection via dentures.

immune deficiency

- Frequently present in patients with HIV; 10% may have localised candidiasis.[8]
- Immunosuppressive medicine (e.g., chemotherapy) also increases risk.

Down's syndrome

- Seen in 25% of patients with trisomy 21.[15]

xerostomia

- Either as isolated xerostomia or as part of Sjogren's syndrome.[11]

chronic inflammatory skin disease

- Atopic dermatitis, peri-oral dermatitis, and allergic contact dermatitis at the commissures can cause angular cheilitis.[13] [18]
- An eczematous dermatitis may appear on the cheek or chin, as in infective eczematoid reaction, or as a reaction to topical medicines.

diabetes mellitus

- More common in people with insulin-dependent diabetes.[19]
- In people with diabetes, angular cheilitis is more commonly associated with *Candida albicans* .[19]

Weak

Crohn's disease

- Crohn's disease or orofacial granulomatosis may be found in a very small minority of patients with angular cheilitis.[9] [13]

Investigations

1st test to order

Test	Result
clinical diagnosis • Diagnosis is usually made via history and physical examination alone; however, supporting laboratory studies may help identify contributing aetiologies, especially when refractory to empirical treatment.	**laboratory testing is usually performed only after treatment failure**

Other tests to consider

Test	Result
fungal culture • Sample to include mucosal surfaces covered by dentures.[21] • May be positive if infectious aetiology.	**positive for *Candida albicans***
bacterial culture • Samples include mucosal surfaces covered by dentures (i.e., oral mucosa), and the nares, to identify staphylococcal colonisation.[21] • May be positive if infectious aetiology.	**positive for *Staphylococcus aureus***
FBC • Helpful to exclude deficiency syndromes as contributing factor, and to guide treatment.[21] • May be low if nutritional deficiency is aetiology.	**decreased Hb if nutritional deficiency**
serum iron panel • The panel should include iron, TIBC, iron saturation, and ferritin levels.[21] • May be low if nutritional deficiency is aetiology.	**decreased iron, iron saturation, and ferritin; increased TIBC**
serum vitamin B12 • Helpful to exclude B12 deficiency as contributing factor, and to guide treatment.[21] • May be low if nutritional deficiency is aetiology.	**decreased if nutritional deficiency**
serum folate • Helpful to exclude folate deficiency as contributing factor, and to guide treatment.[21] • May be low if nutritional deficiency is aetiology.	**decreased if nutritional deficiency**
serum zinc • Helpful to exclude zinc deficiency as contributing factor, and to guide treatment.[21] • May be low if nutritional deficiency is aetiology.	**decreased if nutritional deficiency**
fasting plasma glucose • May be elevated in diabetes, producing an immunosuppressed state.[21]	**elevated if diabetes**
HbA1c • May be elevated in diabetes, producing an immunosuppressed state.[21]	**elevated if diabetes**
HIV test • In immunosuppressed patients, annular cheilitis appears readily. • In recurrent or recalcitrant cases, consider test.[21]	**may be positive**
biopsy • Utilised to rule out malignancy, especially if chronic unilateral lesion.	**may be dysplastic or cancerous cells**
patch testing • May be indicated in patients with recalcitrant disease in order to help with the avoidance of allergens.	**positive reactions if allergic aetiology**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Herpes simplex infection	• May occur at the corners of the mouth; however, the infection is usually unilateral. • These lesions start as macules and, over a few days, become vesicular and then pustular, finally forming a crust and healing.[13] [22]	• PCR for HSV is positive.

Approach

Treatment is often challenging and may be lengthy. Successful therapy is based on identifying and correcting each and all factors of this multi-factorial condition. Treatment should be based on the suspected cause rather than used in an algorithmic manner. For all patients, nutritional deficiency identification and treatment is optimal.[2]

Infectious aetiology

First-line therapies include topical miconazole after meals and at bedtime to treat *Candida albicans* .[2] Miconazole may be used to treat mixed fungal and bacterial infections, as it has gram-positive bacteriostatic action as well. Oral fluconazole is a useful second-line alternative. Miconazole is absorbed systemically and may potentiate the action of warfarin, phenytoin, and sulfonylureas; thus, topical nystatin or amphotericin-B are first-line therapies in patients taking these drugs.[13] [23] [24] However, topical amphotericin-B products are not currently available in some countries.

Chronic corticosteroid inhaler therapy may also predispose the patient to *Candida albicans* infection, due to immune suppression. Rinsing of the mouth after inhaler treatment will help eliminate intraoral accumulation of corticosteroid.[25]

Topical mupirocin or a polymyxin-containing preparation are valuable in treating staphylococcal colonisation.[2] [13] [24] In the case of staphylococcal colonisation of the nares, this should also be eradicated.

Patients whose angular cheilitis resists treatment require systemic antifungal therapy (e.g., fluconazole) and amphotericin-B lozenges, if available.[26] Second-line therapy includes the use of dermal fillers in the commissures.[27] [28] Prosthodontic evaluation and construction is an option for older patients who suffer from chronic drooling and angular cheilitis.[29] Also described is a method to incorporate a cannula into the denture prosthesis to channel the saliva towards the oropharyngeal area for older and disabled patients.[29]

Non-infectious aetiology

For all patients, nutritional deficiencies should be identified and corrected.[2]

Depending on patch test results, avoidance of the specific identified allergen is recommended.

Identification of chronic reservoirs of infection, such as dentures, is vital. Dentures are recommended to be removed at night and cleansed well before re-insertion in the morning. At night, the dentures may be stored in hypochlorite or chlorhexidine.

Recommendation is to reduce mechanical stress, including a dental referral for identification and correction of poorly fitting dentures. New dentures may restore facial contours, increasing the vertical dimension of the jaws and face.[22]

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute (summary)		
infectious aetiology		
no concurrent use of warfarin, phenytoin, or sulfonylureas	1st	topical miconazole
	adjunct	topical antibacterial
	2nd	oral fluconazole
	adjunct	topical antibacterial
concurrent use of warfarin, phenytoin, or sulfonylureas	1st	topical nystatin
	adjunct	topical antibacterial
non-infectious aetiology		
	1st	supportive management

Ongoing (summary)		
recalcitrant disease		
	1st	oral fluconazole
	2nd	dermal fillers
	3rd	prosthodontic evaluation and construction

MANAGEMENT

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

infectious aetiology

no concurrent use of warfarin, phenytoin, or sulfonylureas

1st **topical miconazole**

Primary options

» miconazole topical: children and adults: (2%) apply to the affected area(s) twice daily for 7-14 days

» Topical miconazole is used to treat *Candida* after meals and at bedtime.[2]

» It is also effective against mixed infections because it has gram-positive bacteriostatic action.

» Miconazole is absorbed and may potentiate the action of warfarin, phenytoin, and sulfonylureas; thus, topical nystatin or amphotericin-B lozenges should therefore be tried first in patients taking these drugs.[13] [23] [24]

» Patients on chronic corticosteroid inhaler therapy are recommended to rinse the mouth after inhaler treatment, to reduce the risk of recurrent *Candida* infection.[10]

adjunct **topical antibacterial**

Treatment recommended for SOME patients in selected patient group

Primary options

» mupirocin topical: children and adults: (2%) apply to the affected area(s) four times daily for 7-14 days

» Topical mupirocin or a polymyxin-containing preparation are valuable in treating staphylococcal colonisation.[2] [13] [24]

» In the case of staphylococcal colonisation of the nares, this should also be eradicated.

2nd **oral fluconazole**

Primary options

» fluconazole: children: 6 mg/kg orally as a single dose on day 1, followed by 3 mg/kg/day for 13 days; adults: 200 mg orally as a

Acute

single dose on day 1, followed by 100 mg once daily for 13 days

» Second-line therapies include fluconazole and amphotericin-B lozenges.[26] However, the lozenges are not currently available in some countries.

adjunct **topical antibacterial**

Treatment recommended for SOME patients in selected patient group

Primary options

» mupirocin topical: children and adults: (2%) apply to the affected area(s) four times daily for 7-14 days

» Topical mupirocin or a polymyxin-containing preparation are valuable in treating staphylococcal colonisation.[2] [13] [24]

» In the case of staphylococcal colonisation of the nares, this should also be eradicated.

concurrent use of warfarin, phenytoin, or sulfonylureas

1st **topical nystatin**

Primary options

» nystatin topical: children and adults: (100,000 units/g) apply to the affected area(s) twice daily until healing is complete

» Miconazole is absorbed systemically and may potentiate the action of warfarin, phenytoin, and sulfonylureas; thus, topical nystatin or amphotericin-B are first-line therapies in patients taking these drugs.[13] [23] [24] However, topical amphotericin-B products are not currently available in some countries.

adjunct **topical antibacterial**

Treatment recommended for SOME patients in selected patient group

Primary options

» mupirocin topical: children and adults: (2%) apply to the affected area(s) four times daily for 7-14 days

» Topical mupirocin or a polymyxin-containing preparation are valuable in treating staphylococcal colonisation.[2] [13] [24]

» In the case of staphylococcal colonisation of the nares, this should also be eradicated.

non-infectious aetiology

MANAGEMENT

Acute

1st **supportive management**

» Supportive care includes management of dentures, which should be removed from the mouth at night and cleansed well before re-insertion in the morning. They can be stored in hypochlorite or chlorhexidine. Improvement in denture fit or new dentures may be necessary.[22]

» For all patients, nutritional deficiencies are to be identified and corrected.[2]

» Depending on patch test results, avoidance of the specific identified allergen is recommended.

Ongoing

recalcitrant disease

1st **oral fluconazole**

Primary options

» fluconazole: children: 6 mg/kg orally as a single dose on day 1, followed by 3 mg/kg/day for 13 days; adults: 200 mg orally as a single dose on day 1, followed by 100 mg once daily for 13 days

» First-line therapy includes systemic antifungal therapy with fluconazole.[26]

» Amphotericin-B lozenges are often used with fluconazole; however, they are not currently available in some countries.

2nd **dermal fillers**

» Options include the use of dermal fillers in the commissures.[27] [28]

3rd **prosthodontic evaluation and construction**

» Prosthodontic evaluation and construction is an option for older patients who suffer from chronic drooling and angular cheilitis.[29]

» For older and disabled patients, a cannula may be incorporated into the denture prosthesis to channel the saliva towards the oropharyngeal area.[29]

Primary prevention

Good oral hygiene and proper fitting of dentures reduce the incidence of angular cheilitis. A decrease in angular cheilitis was noted in patients aged 60 years and older who chewed gum containing xylitol or chlorhexidine acetate and xylitol.[20]

Secondary prevention

Xylitol gum or petroleum jelly are recommended for use in the lip folds to prevent maceration.[20]

Patient discussions

Patients should be educated as to the importance of treating all causes for clinical improvement. In addition, education is important about the need for frequent re-application of topical antifungal or antibacterial agents to the corners of the mouth.

Patients must avoid trauma to the angles of the mouth, and attention should be drawn to the avoidance of thumb sucking or dummy use in young children and constant lip licking in older individuals.[31]

Those who have poorly-fitting dentures, due to weight loss or other causes, are recommended for dental referral for correction and information regarding good oral hygiene. In the case of a nutritional deficiency, patients require information as to the importance of supplements or improved diet.

Complications

Complications	Timeframe	Likelihood
acquired linear anetoderma	**long term**	**low**
The paucity of elastic fibres in the dermis may be secondary to preceding inflammation. Laser re-surfacing is an option to improve the cosmetic appearance.[30]		

Prognosis

Relapses may occur and treatment may need to be prolonged. It is more often due to poor medicine compliance, failure to remove and clean dentures appropriately, or inability to resolve the underlying factors.[22]

For non-responders, additional testing by a dermatologist should be considered.

Key articles

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Images

Figure 1: Angular cheilitis

From the collection of Dr Wanda C. Gonsalves; patient consent obtained

Figure 2: Angular cheilitis

From the collection of Dr Wanda C. Gonsalves; patient consent obtained

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This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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