

Angular Cheilitis, Part 2: Nutritional, Systemic, and Drug-Related Causes and Treatment

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Angular cheilitis (AC) is associated with a variety of nutritional, systemic, and drug-related factors that may act exclusively or in combination with local factors. Establishing the underlying etiology of AC is required to appropriately focus treatment efforts.

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Angular cheilitis (AC) was described in depth in part 1 of this article with a focus on local etiologic factors.¹ Part 2 reviews the causes of AC that may not be so readily apparent including nutritional, systemic, and drug-related factors. When treatment focused on local etiologies (irritant, allergic, and infectious) has been exhausted, less common causes should be identified to effectively treat what can become a chronic condition.

Nutritional Deficiencies

Angular cheilitis can herald a variety of nutritional deficiencies that can have potentially debilitating effects (Table 1). Identification of these deficiencies followed by nutrient replenishment is critical for these patients. Deficiencies of iron and various B vitamins account for as many as 25% of cases of AC.⁴

Anemia has been associated with AC in as much as 11.3% to 31.8% of patients in several studies.⁵⁻⁸ Although this incidence rate may not be applicable in the United States today, there is still a considerable number of patients with nutritional deficiencies resulting in AC in third world countries.^{5,6,9}

Chronic iron deficiency can cause koilonychia, glossitis, and cheilosis with fissuring. The mechanism for AC in these patients has not been fully elucidated, but it has been suggested that iron deficiency decreases cell-mediated immunity, thereby promoting mucocutaneous candidiasis.¹⁰

Riboflavin (vitamin B₂) deficiency often is accompanied by a mixed vitamin B complex deficiency due to its role in the metabolism of vitamin B₆ and tryptophan, the latter of which is then converted to niacin (vitamin B₃). Generally, riboflavin deficiency will present as redness of the mucous membranes, AC, and magenta-colored glossitis.¹¹ It may also present as oculo-oro-genital syndrome, characterized by the following changes: perlèche or cheilosis, magenta-colored glossitis, interstitial keratitis and corneal vascularization, and scrotal and vulvar lesions.³

Pyridoxine (vitamin B₆) deficiency causes cheilosis; glossitis; and seborrhealike changes around the mouth, eyes, and nose. It often occurs in alcoholics and may occur in patients on medications that impair vitamin B₆ metabolism, which includes cycloserine, isoniazid, hydralazine hydrochloride, oral contraceptives, D-penicillamine, and levodopa (when taken without carbidopa).¹²

Decreased vitamin B₁₂ (cyanocobalamin) levels make patients vulnerable to the development of AC. It commonly is associated with malnutrition, alcoholism, and pernicious anemia. Other causes include terminal ileum resection or disease (common in Crohn disease), postgastrectomy states, chronic pancreatitis, strict vegan diets, and infection with *Diphyllobothrium latum*. Vitamin B₁₂ levels are changed by

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Table 1.

Nutritional Deficiencies Implicated in Angular Cheilitis

Etiology	Diagnostic Test	Treatment
Iron ²	Serum iron, total iron-binding capacity, serum ferritin	50–65 mg elemental iron orally 3–4 times daily (<300 mg daily)
Riboflavin (vitamin B ₂) ³	Elevated RBC glutathione reductase level	5–15 mg daily
Pyridoxine (vitamin B ₆) ³	Pyridoxal 5'-phosphate level	50 mg daily or 100–200 mg daily (this dosing if deficiency is drug related)
Cyanocobalamin (vitamin B ₁₂) ³	CBC (megaloblastic anemia), serum cobalamin level, elevated serum methylmalonic acid level	500 µg in 1 nostril once weekly, then maintenance therapy 25 µg in each nostril daily; or 250 µg orally daily; or 30 µg per day intramuscularly for 5–10 days, then maintenance therapy 100–200 µg intramuscularly monthly
Folic acid ³	CBC (megaloblastic anemia), serum folate	Folic acid 5–15 mg orally daily
Niacin ³	2-pyridone and 2-methyl nicotinamide urinary excretion	Nicotinamide (preferred) or nicotinic acid 100–200 mg
Zinc ³	Serum zinc <70 µg/dL	60 mg elemental zinc orally twice daily

Abbreviations: RBC, red blood cell; CBC, complete blood cell count.

cholestyramine, colestipol, *p*-aminosalicylic acid, and potassium chloride.¹²

A single case study of patients with glossitis and/or cheilosis refractory to other vitamin B nutrients demonstrated the effectiveness of treatment with calcium pantothenate, a source of vitamin B₅ (pantothenic acid or pantothenate).¹³

Folate deficiency often presents with vitamin B₁₂ deficiency and is characterized by stomatitis, glossitis, and megaloblastic anemia. Folate supplementation is affected by methotrexate, phenytoin, phenobarbital, primidone, oral contraceptives, and triamterene.¹² Chronic alcoholism, tropical and celiac sprues, pancreatic diseases, malnutrition, and other malabsorption syndromes can produce multinutrient deficiencies leading to folate, vitamin B₁₂, and iron deficiencies, which can lead to AC.

Pellagra, the deficiency of niacin (vitamin B₃) and protein, causing the 3 *d*'s (dermatitis, diarrhea, and

dementia), can result in glossitis or cheilitis and has been found to be a more frequent cause of AC than riboflavin deficiency.¹⁴

The final vitamin B deficiency associated with AC is biotin (vitamin B_w or vitamin H). Patients may present with AC along with other symptoms such as dry eyes and alopecia.¹⁵

In addition to vitamin deficiencies, mineral deficiency can cause AC. Lack of the essential mineral zinc is characterized by the triad of diarrhea; alopecia; and dermatitis manifesting as eczematous and erosive changes around the mouth as well as the acral and genital areas. Angular cheilitis, glossitis, and pustular paronychia also are seen. In fact, AC is a common early sign of acrodermatitis enteropathica and heralds relapse in these patients.³ Angular cheilitis can be caused by an autosomal recessive hereditary deficiency known as acrodermatitis enteropathica. It may be seen in association with cystic fibrosis, breastfed

preterm infants, high-cereal diets, and in 3% of alcohol abusers (n=693).^{3,16}

Systemic Disease

A number of systemic diseases are associated with AC (Table 2). Angular cheilitis is very common in Down syndrome, with a reported incidence of 25% (n=77) in one study. Associated factors may include lip licking, picking, and *Candida albicans* infection.²³

Xerostomia accounts for as much as 5% of AC cases.⁴ Conditions that predispose patients to xerostomia include dehydration; salivary gland infection, obstruction, and neoplasms; radiation to the mouth; chemotherapy; diabetes mellitus; neuropathies; Sjögren syndrome; and nutritional deficiencies, and it is a side effect of more than 300 medications.¹² It also is associated with normal aging due to salivary gland and duct atrophy and obstruction, predisposing elderly patients to a decreased sense of taste, a burning sensation of the mouth, an increase in dental caries, and AC.^{24,25} Without adequate saliva, it is difficult to maintain oral hygiene, exacerbating the local infections associated with AC.

Angular cheilitis also is seen in various forms of malnutrition and in patients on total parenteral nutrition.¹⁵ For example, patients with anorexia nervosa often present with AC and angular stomatitis (60%), which are sometimes related to riboflavin and other vitamin deficiencies.²⁶

Many autoimmune diseases are associated with AC. Nearly 50% of patients with Sjögren syndrome develop skin manifestations, which usually include xerostomia, xerosis, eyelid dermatitis, pruritus, and cutaneous vasculitis.²⁷ Four percent of patients (n=73) with systemic lupus erythematosus report cheilitis, most commonly the classic discoid lupus erythematosus.²⁸

Inflammatory bowel diseases may manifest AC as part of the clinical presentation. Patients with Crohn disease (n=77) have oral involvement in 10% to 20% of cases, which can include fissures, mucosal tags, aphthous ulcers, glossitis, lip edema, and gingivitis; AC is found in 7.8% of these patients. Similarly, patients with ulcerative colitis (n=121) can present with aphthous ulcers and pyostomatitis vegetans, as well as AC, which is found in 5% of these patients.²⁹ Orophacial granulomatosis is a nonspecific granulomatous inflammation characterized by painless, nonpruritic, firm edema of the face and lips; oral ulceration; mucosal tags; and gingival overgrowth. Angular cheilitis occurs in 18% of patients (n=60) with this disease.³⁰ Angular cheilitis also may develop as a subset known as cheilitis granulomatosa, which presents with labial swelling only, or it may be part of the Melkersson-Rosenthal syndrome.³¹

Glucagonomas are rare pancreatic neuroendocrine tumors that are correlated with necrolytic migratory erythema, weight loss, diabetes mellitus, anemia, cheilitis, venous thrombosis, and neuropsychiatric symptoms. Angular cheilitis has been described in association with other mucous membrane involvement.³¹

Angular cheilitis often is the presenting sign in Plummer-Vinson syndrome, which is seen mostly in white middle-aged females and is characterized by the triad of postcricoid dysphagia, upper esophageal webs, and iron deficiency anemia.³² The etiology of AC in Plummer-Vinson syndrome is iron deficiency anemia.

Uremic stomatitis initially may present as AC prior to mucosal dissemination. In uremia, ammonia by-products from increased salivary uremia and the action of bacterial urease become irritants at the commissures.³³

Systemic infectious diseases also are implicated in AC. In human immunodeficiency virus (HIV) patients, the prevalence of AC is 5.6% to 28.9% and it is the most common oral symptom of HIV in children.³⁴⁻³⁶ This relationship is thought to be due to oropharyngeal candidiasis, which is estimated to affect more than 90% of HIV patients at some point of their disease.^{37,38} Another infectious cause, secondary syphilis, often presents with split papules at the corners of the mouth as well as pityriasis rosea-like papulosquamous rashes of the trunk, scaled patches on the palms and soles, condyloma latum in the perianal area, and mucous patches of the oral mucosa (Figure 1). All of these lesions harbor active treponeme organisms and are infectious.³⁹

Drug-Related Side Effects

The use of certain drugs, both for therapeutic and recreational use, may lead to AC. The most common side effect occurring in almost all patients on isotretinoin is AC and cheilitis, which often are the earliest presenting signs of toxicity and measures of patient compliance (Figure 2). In addition, there is a tendency for *Staphylococcus aureus* colonization to occur secondary to isotretinoin use, which may dictate AC treatment.⁴⁰ Indinavir, the antiretroviral drug commonly used in the treatment of HIV/AIDS, shows retinoidlike side effects, with between 57.1% (n=84) to 76.19% (n=20) of patients developing AC.^{41,42}

Angular cheilitis has been reported in association with the hand-foot skin reaction, a distinct side effect of the antineoplastic kinase inhibitor-targeted agent sorafenib.⁴³

Drugs of abuse can produce or compound an AC. Cocaine users frequently smack their lips, while methamphetamine and heroin addicts show xerotic cheilitis.⁴⁴ Hallucinogens can produce xerostomia, which predisposes patients to AC.²

Table 2.

Systemic Causes of Angular Cheilitis

Etiology	Diagnostic Test	Treatment
Down syndrome	History and physical examination	Multidisciplinary treatment
Xerostomia ¹⁷	History and physical examination	Salivary aids, cholinergic agents, sipping water, chewing sugar-free gum/hard candy
Eating disorders	History and physical examination, <i>DSM-IV</i> criteria	Multidisciplinary treatment
Sjögren syndrome ¹⁷	Schirmer test, ANA, anti-Ro/SS-A and anti-La/SS-B tests, antisalivary duct antibodies	Artificial tears, pilocarpine 5 mg orally 3 times daily, cevimeline 30 mg orally 3 times daily, hydroxychloroquine 200 mg orally daily
Systemic lupus erythematosus ¹⁸	ANA, anti-double-stranded DNA, anti-Smith, antiphospholipid antibodies, ESR, CRP	Prednisone, NSAIDs, hydroxychloroquine
Inflammatory bowel disease (Crohn disease and ulcerative colitis) ¹⁹	Anti-ASCA (Crohn disease), p-ANCA (ulcerative colitis), abdominal radiograph, upper GI barium study, barium enema, upper endoscopy, colonoscopy, biopsy	Sulfasalazine, steroids, immunosuppressive agents, 5-amino-salicylic acid, low-roughage diet, increased iron, decreased lactose, antidiarrheal agents, surgery
Glucagonoma ²⁰	Fasting plasma glucagon >1000 ng/L, mildly abnormal OGTT, hypocholesterolemia, hypoaminoacidemia (alanine, glycine, serine)	Zinc, amino acid, interferon alfa, fatty acid, octreotide, chemotherapy, surgical resection, hepatic artery embolization
Plummer-Vinson syndrome	Classic triad of dysphagia, iron deficiency anemia, esophageal webs	50–65 mg elemental iron orally 3–4 times daily (<300 mg daily)
Secondary syphilis/split papules ²¹	VDRL, RPR, TPPA, FTA-ABS, TPHA (Europe)	Penicillin G benzathine 2.4 million units intramuscularly once or tetracycline hydrochloride (500 mg orally 4 times daily) or doxycycline (100 mg orally twice daily) for 2 weeks (if penicillin allergic)
Diabetes mellitus ²²	Symptoms of diabetes plus random blood glucose concentration 11.1 mmol/L (200 mg/dL), fasting plasma glucose 7.0 mmol/L (126 mg/dL), 2-hour plasma glucose 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test	Diet modification, insulin secretagogues, insulin sensitizers, α -D-glucosidase inhibitors, peptide analogues, insulin

Abbreviations: *DSM-IV*, *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition); ANA, antinuclear antibody; SS-A, Sjögren syndrome antigen A; SS-B, Sjögren syndrome antigen B; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; NSAIDs, non-steroidal anti-inflammatory drugs; ASCA, anti-*Saccharomyces cerevisiae* antibody; p-ANCA, perinuclear antineutrophil cytoplasmic autoantibody; GI, gastrointestinal tract; OGTT, oral glucose tolerance test; RPR, rapid plasma reagin; TPPA, *Treponema pallidum* particle agglutination test; FTA-ABS, fluorescent treponemal antibody absorption test; TPHA, *Treponema pallidum* hemagglutination test.



Figure 1. A 32-year-old patient with split papules at the corners of the mouth associated with a pityriasis rosea-like papulosquamous rash. Fluorescent treponemal antibodies were positive, confirming the diagnosis of secondary syphilis. The patient responded to 2.4 million units of penicillin G benzathine administered intramuscularly.



Figure 2. An 18-year-old patient with severe nodulocystic acne vulgaris was treated with 1 mg/kg of isotretinoin for 6 weeks when dryness, fissuring, and tenderness developed at the corners of the mouth. Treatment with petrolatum white 6 times daily controlled these symptoms, which resolved 10 weeks later when isotretinoin was discontinued.

Diagnostic Approach and Management

Patients with AC may report an acute or insidious onset and a relapsing and remitting pattern. When common treatments have failed—antifungals, antibiotics, and avoidance of allergens and irritants, as well as efforts to enhance compliance with topical antifungals and barrier creams—investigation of a covert systemic condition should be undertaken. Oftentimes it is possible to identify a nutritional deficiency, systemic process, or aggravating medication as the etiology. Treatment of these underlying systemic factors is

important and may lead to more effective control of this common condition.

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