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Angular Cheilitis: A Multidisciplinary Approach to Clinical Diagnosis, Nutritional Assessment, Laboratory Evaluation, and Pharmacological Management-An Updated Review.

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Abstract

Background: Angular cheilitis is a common inflammatory disorder affecting the labial commissures and results from interacting infectious, mechanical, nutritional, inflammatory, and systemic factors. Persistent saliva-induced maceration compromises the epithelial barrier and facilitates colonization by organisms such as *Candida albicans* and *Staphylococcus aureus*. The condition is particularly relevant in older adults, denture users, individuals with nutritional deficiencies, immunocompromised patients, and those with systemic diseases.

Aim: This review aims to provide a comprehensive overview of the etiology, epidemiology, pathophysiology, clinical manifestations, diagnostic evaluation, and multidisciplinary management of angular cheilitis, with emphasis on nutritional, laboratory, dental, and pharmacological considerations.

Methods: A narrative review of relevant clinical and biomedical literature was undertaken to synthesize evidence concerning the causes, risk factors, epidemiological characteristics, pathophysiological mechanisms, clinical assessment, diagnostic investigations, and therapeutic approaches for angular cheilitis.

Results: Angular cheilitis commonly develops through persistent commissural maceration associated with saliva exposure, anatomical changes, denture use, xerostomia, mechanical irritation, and impaired epithelial integrity. Infectious involvement, particularly *Candida* and *Staphylococcus*, is frequent. Nutritional deficiencies involving iron, vitamin B12, folate, riboflavin, and zinc may contribute to persistent or recurrent disease. Systemic disorders, including diabetes, Sjögren syndrome, inflammatory bowel disease, and immunodeficiency, may increase susceptibility. Diagnosis is primarily clinical, with microbiological, nutritional, metabolic, immunological, patch-testing, or histopathological investigations selected according to presentation. Management includes barrier protection, antimicrobial therapy, correction of nutritional deficiencies, dental intervention, behavioral modification, and control of underlying systemic disease.

Conclusion: Effective management requires identification and correction of both local and systemic predisposing factors. A multidisciplinary approach can improve treatment response and reduce recurrence.

Keywords: Angular cheilitis, angular stomatitis, cheilosis, *Candida albicans*, nutritional deficiency, oral candidiasis, denture-associated disease, laboratory diagnosis, pharmacological management, multidisciplinary care.

Introduction

Angular cheilitis is a localized inflammatory disorder affecting the labial commissures, or corners of the mouth, and may arise from multiple infectious, inflammatory, mechanical, nutritional, systemic, or pharmacological factors. The condition is characterized clinically by erythema, maceration, scaling, fissuring, crusting, and soreness at one or both oral commissures. The terminology used to describe this disorder includes angular cheilosis, angularstomatitis, commissural stomatitis, rhagades, and *perleche*. The term *cheilitis* originates from the Greek *chilos*, meaning lips, whereas *perleche* is

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derived from the French expression associated with habitual lip licking
. The term *rhagades* refers specifically to painful linear fissures that develop in areas exposed to repeated mechanical movement and moisture, particularly the corners of the mouth and, less commonly, the nasal region [1][2][3]. The anatomical characteristics of the oral commissures contribute substantially to the development of angular cheilitis. The corners of the mouth represent a dynamic transition between facial squamous epithelium and the mucosal surface of the oral cavity. They function as mechanical hinges during speaking, eating, swallowing, facial expression, and other oral movements. Consequently, the commissures are exposed to repetitive tensile forces, friction, saliva, food residues, and changes in local moisture. Persistent moisture and maceration can compromise the integrity of the epithelial barrier and facilitate colonization by microorganisms, while mechanical stress may promote fissuring and prolong local inflammation. These interacting factors explain why angular cheilitis may occur as an isolated local disorder or as a manifestation of broader physiological or pathological disturbances [1][2].

The etiological spectrum of angular cheilitis is heterogeneous. Local contributing factors may include excessive salivation, lip licking, poorly fitting dental prostheses, reduced vertical dimension of occlusion, and accumulation of saliva within the oral commissures. Infectious causes, particularly *Candida* species and *Staphylococcus aureus*, may contribute to persistent or recurrent lesions. Nutritional deficiencies, including deficiencies of iron, folate, vitamin B12, and other micronutrients, may also predispose susceptible individuals to commissural inflammation. Systemic diseases, immune dysfunction, medication-related xerostomia, and age-associated changes may further increase susceptibility. Therefore, evaluation should consider both local precipitating factors and underlying systemic abnormalities rather than treating the visible lesion in isolation [1][2][3]. Angular cheilitis should also be distinguished from other forms of cheilitis, which encompass a broad group of inflammatory disorders with different etiological mechanisms. These include eczematous, contact, drug-induced, infectious, actinic, glandular, granulomatous, exfoliative, plasma cell, and nutritional cheilitis. Although some clinical manifestations may overlap, their diagnostic evaluation and management can differ substantially. Accordingly, the present discussion focuses specifically on angular cheilitis and its multidisciplinary clinical, nutritional, laboratory, and pharmacological considerations rather than on diffuse forms of cheilitis [1][2][3].

Etiology

Angular cheilitis is a multifactorial inflammatory disorder in which local anatomical changes, moisture accumulation, microbial colonization, nutritional abnormalities, immune dysfunction, systemic disease, and repeated mechanical or chemical injury may interact to produce inflammation and fissuring at the labial commissures. Although infection is identified in a substantial proportion of cases, the development of angular cheilitis generally reflects a combination of predisposing factors rather than a single causative mechanism. Understanding these factors is important for appropriate diagnosis because persistent or recurrent lesions may represent an underlying nutritional, systemic, immunological, or malignant disorder rather than an isolated local infection. Maceration caused by persistent exposure of the oral commissures to saliva represents one of the most important predisposing mechanisms in angular cheilitis. The corners of the mouth are exposed to repeated moisture, friction, movement, and mechanical tension. When saliva remains pooled within the commissural folds, prolonged hydration of the stratum corneum weakens the epithelial barrier and increases susceptibility to fissuring, irritation, and microbial colonization. Anatomical and structural changes that increase saliva retention can therefore create an environment favorable for the development of angular cheilitis [1].

Age-related reduction in skin elasticity and turgor may increase the depth of the commissural folds and promote saliva accumulation. Similar changes may occur with smoking or rapid weight loss, both of which can alter the soft-tissue architecture surrounding the mouth. Loss of facial volume can deepen the folds at the oral commissures and increase local moisture retention. Dental abnormalities are also important. Severe tooth wear, complete or partial edentulism, and poorly fitting dentures may reduce the vertical dimension of the lower third of the face. This reduction produces relative overclosure of the mouth and allows the upper lip to overlap the lower lip more extensively, thereby creating a moist environment at the corners of the mouth. Retrognathic malocclusion may produce a similar anatomical effect. Deepened perioral furrows, sometimes described as marionette lines, can additionally function as sites for saliva accumulation and repeated mechanical irritation [1]. Conditions associated with enlargement of the lips can further increase commissural maceration. Orofacial granulomatosis, for example, may produce persistent lip enlargement and structural changes that favor moisture retention. Angular cheilitis has been reported in approximately 20% of affected patients, although *Candida* is not consistently isolated from these lesions, indicating that mechanical and inflammatory mechanisms may be more important than primary fungal infection in some patients. Individuals with Down syndrome may also have an increased prevalence of angular cheilitis, reported at approximately 25%. In this population, macroglossia, tongue protrusion, and associated drooling can

increase chronic exposure of the commissures to saliva and contribute to epithelial maceration [2].

Atopic and Contact Dermatitis

Atopic disease and allergic or irritant contact dermatitis represent important noninfectious causes of angular cheilitis. Contact reactions may account for a substantial proportion of angular and generalized cheilitis, with allergic or irritant contact dermatitis reported in up to 22% of angular cheilitis cases and approximately 25% to 34% of generalized cheilitis cases [3][4]. These reactions can result from direct exposure to substances applied to the lips, oral cavity, or surrounding skin. Potential allergens and irritants are numerous because the oral and perioral regions are routinely exposed to multiple personal-care and dental products. Nickel exposure may occur in individuals wearing orthodontic appliances. Flavoring agents and preservatives in foods can provoke contact reactions, particularly when exposure is repeated. Toothpaste and mouthwash may contain multiple substances capable of producing irritation or allergic responses. Lip balms and cosmetic preparations can also contribute, particularly when they contain preservatives, sodium lauryl sulfate, emollients, colophony, or cocamidopropyl betaine. Expired lip products may contain degraded components that further increase the potential for irritation. Other reported exposures include acne preparations and chewing gum [3][4]. Contact dermatitis may clinically resemble infectious angular cheilitis, particularly when erythema, scaling, fissuring, and burning are present. Failure to respond to appropriate antifungal or antibacterial therapy should therefore prompt consideration of a contact etiology. Patch testing can be useful when allergic contact dermatitis is suspected and may help identify the responsible allergen [5]. Identification and avoidance of the offending exposure are essential components of management because continued exposure may maintain inflammation despite appropriate symptomatic or antimicrobial treatment.

Immune Deficiencies

Defects in cellular or humoral immunity can predispose individuals to angular cheilitis, frequently through increased susceptibility to oral candidiasis. In immunocompromised patients, *Candida* can proliferate within the oral cavity and extend into the commissural regions, particularly when local maceration is already present. Consequently, angular cheilitis may sometimes serve as an external manifestation of impaired host defense. Several conditions have been associated with increased susceptibility, including HIV/AIDS, thymic aplasia, severe combined immunodeficiency, DiGeorge syndrome, hereditary myeloperoxidase deficiency, and Chediak-Higashi syndrome. Chronic exposure to systemic or inhaled corticosteroids may also suppress local or systemic immune responses and increase the risk of fungal overgrowth. Hematological disorders and malignancies may similarly impair host defense, particularly when associated with neutropenia or broader immune dysfunction. Acute leukemia and agranulocytosis are examples of conditions in which compromised immune surveillance may increase susceptibility to opportunistic infection. The presence of persistent, severe, recurrent, or treatment-resistant angular cheilitis should therefore be interpreted in the context of the patient's overall immune status. Recurrent candidal lesions, extensive oral involvement, unexplained infections, or other signs of immunodeficiency may justify further clinical and laboratory evaluation. In such circumstances, treatment of the commissural lesion alone may provide only temporary improvement if the underlying immune abnormality remains unrecognized.

Nutritional Deficiencies

Nutritional deficiency represents an important predisposing factor, particularly among individuals with increased nutritional requirements, impaired absorption, restricted diets, or chronic systemic disease. Although severe nutritional deficiencies are less common in populations with adequate food availability, clinically relevant deficiencies remain important in selected patient groups. Older adults, individuals with celiac disease, socially disadvantaged populations, patients with certain mental health conditions, strict vegans, and exclusively breastfed infants who do not receive appropriate supplementation may be particularly vulnerable. Patients who have undergone bariatric surgery or ileal resection may also develop deficiencies because of impaired digestion or absorption. Several gastrointestinal and systemic disorders may further increase susceptibility. Chronic gastritis, chronic pancreatitis, Crohn disease, and pernicious anemia can interfere with nutrient absorption or utilization and may consequently contribute to mucocutaneous manifestations, including angular cheilitis [6]. Nutritional deficiencies are estimated to be associated with up to 25% of angular cheilitis cases in some clinical populations. Particularly relevant deficiencies include vitamin B12, folate, and riboflavin, as well as iron and zinc deficiency. General protein-energy malnutrition may also compromise epithelial integrity and tissue repair [7][8]. Iron deficiency can impair epithelial turnover and tissue integrity, while deficiencies in B vitamins may interfere with cellular metabolism and maintenance of healthy epithelial surfaces. Vitamin B12 and folate deficiencies may additionally produce hematological abnormalities that provide further clinical clues to an underlying nutritional disorder. Zinc deficiency can impair immune function and wound healing. Protein deficiency may reduce the capacity for tissue regeneration and increase susceptibility to infection. Consequently, recurrent or

unexplained angular cheilitis should not automatically be attributed to local infection, particularly when accompanied by pallor, fatigue, glossitis, weight loss, gastrointestinal symptoms, restricted dietary intake, or other signs suggestive of nutritional deficiency [7][8].

Manifestations of Systemic Diseases

Angular cheilitis may occur as an oral manifestation of systemic diseases, particularly disorders that affect salivary gland function, immune regulation, nutritional status, or gastrointestinal health. Sjögren syndrome provides an important example because xerostomia and reduced salivary flow are characteristic features of the disease. A systematic review by Serrano et al involving 2,426 patients with Sjögren syndrome identified angular cheilitis as the most common oral lesion, followed by atrophic glossitis and oral candidiasis. Reported prevalence varied considerably between studies, ranging from 2% to 81%, although the largest patient populations demonstrated frequencies generally within the range of 20% to 40% [9]. Sjögren syndrome is characterized by lymphocytic infiltration and progressive destruction of the salivary glands, resulting in xerostomia and hyposalivation. Reduced salivary flow can compromise lubrication, mucosal protection, tissue repair, and local antimicrobial defense. Interestingly, the relationship between salivary flow and candidiasis in Sjögren syndrome may differ from that observed in other forms of angular cheilitis. Adequate saliva contains immunological components, including secretory immunoglobulin A, which contributes to mucosal defense by interfering with *Candida* adhesion and facilitating microbial clearance. Therefore, disruption of normal salivary function can alter the local oral ecosystem and increase susceptibility to mucosal infection and commissural inflammation [9]. Denture use may further increase the risk among patients with Sjögren syndrome. Dental prostheses can provide surfaces on which *Candida* organisms adhere and persist, increasing the oral fungal burden and facilitating recurrent oral candidiasis and angular cheilitis. Proper denture hygiene and assessment of prosthetic fit are therefore relevant when evaluating these patients [9]. Inflammatory bowel diseases, particularly Crohn disease, can also contribute to angular cheilitis through several mechanisms. Malabsorption and reduced nutritional intake may produce deficiencies of iron, folate, vitamin B12, zinc, and other nutrients. Chronic systemic inflammation may additionally interfere with tissue repair and immune regulation. Accordingly, angular cheilitis in a patient with gastrointestinal symptoms should be considered within the broader clinical context rather than treated solely as a superficial oral lesion.

Infectious Etiology

Infectious mechanisms account for a substantial proportion of angular cheilitis cases. Microorganisms can be isolated from approximately 50% to 80% of affected lesions, although isolation of an organism does not necessarily establish that it is the sole cause of the disease [10]. The commissures are particularly susceptible to infection because persistent moisture and maceration disrupt the epithelial barrier and create favorable conditions for microbial growth. Fungal and bacterial organisms may subsequently colonize the damaged tissue, frequently producing mixed infections. The risk of infection is increased by factors that elevate the local microbial burden or impair host defense. Poor oral hygiene, oral candidiasis, periodontal disease, dental caries, and poor dentition can increase microbial colonization of the oral cavity and perioral skin. Denture use can additionally create microbial reservoirs, particularly when prostheses are poorly cleaned or worn continuously. Diabetes mellitus is another important risk factor because hyperglycemia can promote *Candida* proliferation and enhance fungal adherence to mucosal surfaces [11]. Immunosuppression associated with corticosteroid therapy, chemotherapy, HIV/AIDS, or other disorders can further impair the ability to control microbial growth. Prolonged antibiotic therapy may disrupt the normal bacterial flora of the oral cavity and permit excessive proliferation of *Candida* species.

Specific Infectious Organisms

Among infectious agents, *Candida* species, particularly *Candida albicans*, represent the most frequently identified fungal organisms in angular cheilitis. *C. albicans* is a normal commensal organism in the oral cavity and can be detected in approximately 40% to 60% of healthy individuals. Its presence in an angular lesion therefore does not necessarily indicate pathogenic infection. *C. albicans* has been reported in approximately 93% of angular cheilitis cases, but it functions as the sole pathogen in only a proportion of these lesions, estimated at approximately 20% to 50%. This distinction is clinically important because colonization and invasive infection are not synonymous. Poor oral hygiene, denture use, xerostomia, diabetes, immunosuppression, and prolonged antibiotic exposure can increase the oral burden of *Candida*. Under favorable conditions, the organism can transition from a relatively harmless commensal yeast to a pathogenic form capable of tissue invasion. Hyphal transformation is particularly relevant to pathogenicity. Histological or microbiological assessment can help distinguish colonization from clinically significant infection when the diagnosis is uncertain. Diabetes is particularly important because persistent hyperglycemia can alter local host defense and increase the availability of glucose that supports fungal proliferation. *Candida* may initially colonize the moist and macerated commissure and subsequently facilitate or coexist with bacterial infection. In infants, angular cheilitis frequently occurs in association with oral candidiasis or thrush. In such cases, treatment directed only at the commissural lesion may be inadequate if oral candidiasis remains untreated, because the oral cavity

can serve as a continuing reservoir for reinfection. *Staphylococcus aureus* is another important pathogen and may function as the sole causative organism in approximately 20% of cases. The anterior nares are a common reservoir for *S. aureus*, making nasal carriage relevant in patients with recurrent staphylococcal angular cheilitis. When a causal relationship is established, consideration of the nasal reservoir may be important in preventing recurrence. Beta-hemolytic streptococci have also been identified in approximately 8% to 15% of cases and may occur as part of mixed microbial populations. Because both *S. aureus* and streptococci may colonize the anterior nares, persistent recurrence may require assessment of potential reservoirs rather than repeated treatment of the commissural lesion alone. Polymicrobial infection is common, and *C. albicans* and *S. aureus* may coexist in approximately 60% to 75% of affected patients. This finding reinforces the concept that angular cheilitis often results from interactions between local barrier disruption and multiple microorganisms rather than from a single pathogen. The distinction between colonization and clinically relevant infection remains essential when interpreting microbiological results.

Recurrent Mechanical, Chemical, and Thermal Injury

Repeated mechanical, chemical, or thermal injury can disrupt the epithelial barrier and predispose the commissures to inflammation. Activities that repeatedly stretch, abrade, wet, or irritate the corners of the mouth may create microscopic epithelial damage and facilitate subsequent microbial colonization. Mechanical injury can also perpetuate an existing lesion by preventing normal healing. Xerostomia contributes to a smaller but clinically important proportion of angular cheilitis cases, estimated at approximately 5%. Reduced salivary secretion may occur following head and neck radiation therapy, in Sjögren syndrome, or as an adverse effect of medications. Drugs associated with xerostomia and xeroderma include isotretinoin, acitretin, indinavir, sorafenib, anticholinergic medications, and certain anticancer agents. Hypervitaminosis A may produce mucocutaneous dryness and contribute to epithelial vulnerability. Environmental conditions such as dry heat and cold exposure can additionally increase lip dryness, cracking, and barrier disruption. Repetitive behaviors may have a particularly important role because they produce repeated cycles of moisture exposure and drying. Excessive lip licking is a common example. Although intended to relieve dryness, repeated licking increases salivary exposure and may ultimately worsen maceration and inflammation. Such behavior may be described as habit-induced or factitious cheilitis and has sometimes been distinguished from classic angular cheilitis. Other behaviors include thumb-sucking, prolonged use of lollipops, excessive drooling, hypersialia, and aggressive dental flossing [12]. Smoking may also contribute through repeated thermal and chemical exposure and through its adverse effects on oral and perioral tissues. Acute mechanical stress can occasionally precipitate commissural injury. Procedures that require prolonged or forceful opening of the mouth, including certain surgical procedures such as tonsillectomy, may temporarily stretch and traumatize the labial commissures. In susceptible individuals, this mechanical injury may provide a portal for secondary infection or prolong pre-existing inflammation [12].

Idiopathic and Recurrent Angular Cheilitis

In some patients, no single underlying cause can be established despite appropriate clinical evaluation. Such cases are often classified as idiopathic angular cheilitis. However, the designation should be used cautiously because the absence of an immediately identifiable cause does not exclude an underlying predisposing condition. Given the importance of salivary maceration and microbial colonization, initial management may reasonably address these mechanisms, particularly when clinical findings are consistent with fungal or bacterial involvement. Persistent or recurrent lesions warrant a broader diagnostic approach. Continued recurrence despite appropriate antimicrobial therapy should prompt reassessment of oral hygiene, denture fit, salivary function, dietary status, medication exposure, contact allergens, diabetes, immunosuppression, and other systemic conditions. Long-term protection of the commissures with appropriate emollient therapy may be useful when excessive moisture, dryness, or mechanical irritation contributes to recurrence. Nevertheless, recurrent disease should not be managed indefinitely with empiric antimicrobial treatment without reconsidering the diagnosis and underlying cause. Nutritional deficiency should receive particular consideration in otherwise unexplained or recurrent cases. Evaluation may be appropriate when clinical findings or patient history suggest iron, vitamin B12, folate, riboflavin, zinc, or protein deficiency. Similarly, persistent unilateral lesions that fail to respond to appropriate treatment require careful reassessment because chronic inflammatory or infectious explanations may not adequately account for the clinical presentation. Malignancy represents an uncommon but important alternative diagnosis, particularly when a lesion is unilateral, indurated, persistent, ulcerated, or refractory to appropriate therapy. A rare systemic cause of angular cheilitis is glucagonoma, a pancreatic neuroendocrine tumor associated with a characteristic constellation that may include dermatitis, diabetes mellitus, weight loss, anemia, and angular cheilitis. Although this diagnosis is uncommon, the association illustrates the broader principle that persistent angular cheilitis can occasionally represent a manifestation of systemic

disease. Accordingly, unexplained, recurrent, atypical, or treatment-resistant lesions should be evaluated within the context of the patient's nutritional, metabolic, immunological, gastrointestinal, dental, and pharmacological history. Overall, the etiology of angular cheilitis is best understood as a dynamic interaction between local barrier disruption and systemic susceptibility. Salivary maceration, anatomical changes, infection, nutritional deficiency, immune dysfunction, xerostomia, contact exposure, and mechanical trauma may act independently or simultaneously. This multifactorial nature explains why successful management often requires more than treatment of the visible lesion. Identification and correction of the underlying predisposing factor are essential for reducing recurrence and for recognizing patients in whom angular cheilitis represents an early clinical indicator of a broader systemic disorder [12].

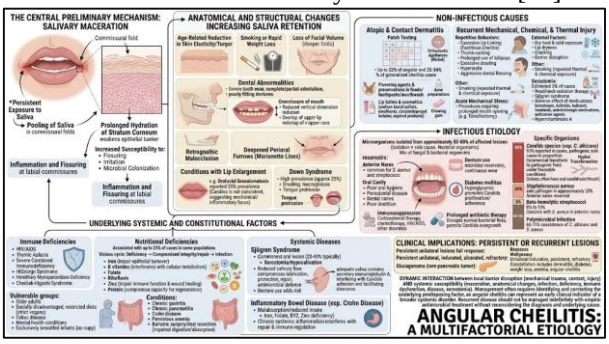

Figure 1: Angular Cheilitis Etiology.

Epidemiology

Angular cheilitis is a relatively common inflammatory disorder of the oral commissures, although its reported prevalence varies considerably according to age, population characteristics, oral health status, denture use, nutritional status, and underlying systemic disease. In the general American population, the prevalence has been estimated at approximately 0.7%. The condition is considerably more frequent in selected populations with local or systemic predisposing factors. Angular cheilitis is regarded as one of the most common infectious conditions affecting the lips, with both fungal and bacterial organisms frequently identified in affected lesions. Its age distribution demonstrates a broadly bimodal pattern, with increased occurrence during childhood and a second rise among adults, particularly between approximately 30 and 60 years of age [13]. Older adults constitute an important high-risk population. The prevalence in this group has been reported at approximately 11%, reflecting the combined effects of age-related changes in skin elasticity, facial anatomy, dentition, salivary function, nutritional status, immune competence, and medication exposure. Dental status is particularly relevant because denture use substantially increases susceptibility. Denture wearers may experience approximately three times the incidence observed in individuals without dentures, with reported prevalence reaching as high as 28%. Poorly fitting prostheses can reduce the vertical dimension of occlusion, deepen commissural folds, and promote saliva pooling. Dentures may also provide reservoirs for *Candida* and other microorganisms, thereby increasing the risk of recurrent infection [13]. Sex-related differences have also been described, with men reported to develop angular cheilitis approximately twice as frequently as women. However, this difference should be interpreted cautiously because it may reflect differences in denture use, oral health, smoking, comorbid conditions, and other exposures rather than an intrinsic biological difference between sexes [13]. The epidemiology of angular cheilitis becomes particularly important in populations with impaired immunity or chronic systemic disease. Individuals with HIV infection have an increased risk of oral candidiasis, and oral thrush may occur with or without accompanying angular cheilitis. Patients with inflammatory bowel disease also demonstrate increased susceptibility. Angular cheilitis has been reported in approximately 7.8% of individuals with Crohn disease and 5% of those with ulcerative colitis at some stage of their illness. The increased frequency in these patients may reflect nutritional deficiencies, malabsorption, chronic inflammation, immunological abnormalities, and medication-related effects. In orofacial granulomatosis, a less common inflammatory disorder associated with lip enlargement and altered oral anatomy, the reported incidence of angular cheilitis may reach approximately 20% [13].

Pathophysiology

The pathophysiology of angular cheilitis involves a complex interaction between mechanical, chemical, microbial, and host-related factors, with persistent moisture and maceration of the labial commissures representing a central initiating mechanism. The oral commissures are particularly vulnerable because their anatomical configuration allows saliva to accumulate within skin folds. Continuous exposure to saliva causes excessive hydration of the stratum corneum and progressively compromises the protective epithelial barrier. Once this barrier is disrupted, the tissue becomes more susceptible to mechanical trauma, irritant inflammation, microbial colonization, and secondary infection. Saliva is essential for normal oral physiology, providing lubrication, facilitating digestion, maintaining mucosal integrity, and contributing to antimicrobial defense. However, prolonged contact with saliva at the external labial commissures can become damaging. Salivary enzymes and other biochemical components may irritate macerated skin when exposure is persistent. Repeated wetting and drying can further weaken the epidermal barrier and produce erythema, scaling, fissuring, and superficial erosions. The resulting inflammatory response may resemble contact dermatitis or an eczematous reaction, with local release of inflammatory mediators contributing to redness, discomfort, burning, and tissue vulnerability.

Once the stratum corneum has been compromised, microorganisms that normally colonize the oral cavity and surrounding skin can gain access to damaged tissue. *Candida albicans* is particularly important because it commonly exists as a commensal organism within the oral cavity. Under favorable conditions, including persistent moisture, maceration, altered local immunity, diabetes, antibiotic exposure, denture use, or nutritional deficiency, *Candida* can proliferate and transition toward a pathogenic phenotype. Fungal invasion may further damage the epithelium and sustain local inflammation [13].

Bacterial organisms can subsequently participate in the inflammatory process. *Staphylococcus aureus* and beta-hemolytic *Streptococcus* species may colonize the damaged commissural tissue, either independently or together with *Candida*. Consequently, many cases represent polymicrobial disease rather than infection caused by a single organism. The interaction between fungal and bacterial colonization can intensify local tissue injury, delay epithelial repair, and contribute to persistent or recurrent lesions. Several mechanisms can promote this pathological sequence. Anatomical changes that increase saliva retention, such as reduced facial skin turgor, loss of vertical dimension due to tooth loss or denture-related changes, deep commissural folds, and lip enlargement, increase local moisture exposure. Conversely, xerostomia can also increase susceptibility by impairing lubrication, mucosal defense, and tissue repair. Repetitive lip licking, drooling, thumb-sucking, smoking, and mechanical trauma may further disrupt the epithelial barrier. Systemic conditions such as diabetes, immune deficiency, Sjögren syndrome, inflammatory bowel disease, and nutritional deficiencies can additionally interfere with host defense or wound healing. The final clinical lesion therefore develops through a multifactorial process in which epithelial barrier failure, inflammation, microbial colonization, and impaired repair reinforce one another. Persistent maceration initiates tissue damage, barrier disruption facilitates microbial invasion, infection amplifies inflammation, and systemic or local factors may prevent adequate healing. This pathophysiological model explains why antimicrobial therapy alone may be insufficient in recurrent disease. Successful management requires identification and correction of the factors responsible for saliva retention, epithelial injury, microbial overgrowth, impaired immunity, nutritional deficiency, or defective tissue repair [13].

History and Physical

Evaluation of angular cheilitis begins with a comprehensive clinical history directed toward identifying local, dental, nutritional, infectious, medication-related, and systemic predisposing factors. The clinician should determine the duration, recurrence, progression, and laterality of the lesions and ask about previous dental procedures, tooth loss, orthodontic treatment, and denture use. The adequacy and fit of dental prostheses should be specifically assessed because alterations in the vertical dimension of occlusion can promote saliva pooling at the oral commissures. Patients may report little or no pain, particularly during the early stages. When symptoms are present, they commonly include dryness, itching, soreness, irritation, burning, or mild tenderness. These sensations are usually localized to the affected commissures and may become more noticeable during mouth opening, eating, speaking, or other movements that stretch the fissured tissue. Severe lesions may interfere with eating and occasionally contribute to inadequate nutritional intake, although angular cheilitis itself is rarely the primary cause of clinically significant malnutrition. The history should therefore explore symptoms suggesting an underlying systemic disorder. Chronic diarrhea, abdominal pain, weight loss, or hematochezia may suggest inflammatory bowel disease, particularly Crohn disease. Persistent oral or ocular dryness should raise consideration of Sjögren syndrome. When oral thrush is present, the clinician should assess potential predisposing factors, including diabetes mellitus, recent or prolonged antibiotic exposure, proton pump inhibitor therapy, corticosteroid use, immunosuppression, and possible HIV infection [14].

Physical Examination

Physical examination typically demonstrates erythematous, edematous, and sometimes tender lesions at one or both labial commissures. Lesions are often triangular and initially appear as mild pink erythema with relatively normal or slightly chapped surrounding lips. Progressive moisture exposure produces maceration and superficial erosion, sometimes creating gray-white areas surrounded by erythematous tissue. More established lesions may become eczematous, fissured, scaly, or crusted. Severe fissures may bleed, while chronic lesions may develop exudation, crusting, or granulation tissue. Bacterial infection may produce pustules or honey-colored exudates. Angular cheilitis is usually bilateral and relatively symmetrical, although asymmetric salivary pooling, mechanical trauma, or dental abnormalities may produce unilateral disease. An unexplained unilateral lesion should therefore receive additional evaluation. The examination should extend beyond the commissures to include the lips, oral mucosa, tongue, gingiva, teeth, and dental prostheses. Clinicians should specifically evaluate for oral candidiasis, including pseudomembranous plaques, erythematous or atrophic lesions, chronic hyperplastic lesions, denture stomatitis, median rhomboid glossitis, and keratinized lesions with secondary *Candida* infection. Other mucosal disorders, including leukoplakia, lichen planus, and lupus erythematosus, should also be considered in the differential diagnosis [14].

Syndromic and Nutritional Presentations

The clinical examination should also consider whether angular cheilitis represents a manifestation of nutritional deficiency. Riboflavin deficiency may produce angular cheilitis, cheilosis, magenta-colored glossitis, stomatitis, photosensitivity, and pharyngitis. Niacin deficiency may present with the classical combination of dermatitis, diarrhea, cognitive manifestations, glossitis, and angular cheilitis. Although uncommon, deficiencies of vitamins B5 and B6 may also produce commissural inflammation accompanied by glossitis, dermatitis, anemia, neuropathy, oral ulceration, or other systemic manifestations. Folate and vitamin B12 deficiencies may cause megaloblastic anemia, glossitis, peripheral neuropathy, cognitive abnormalities, and angular cheilitis. Iron deficiency commonly manifests with microcytic anemia, glossitis, angular cheilitis, brittle or spoon-shaped nails, and hair loss. Dysphagia accompanying iron deficiency may suggest Plummer-Vinson syndrome. Zinc deficiency may present with angular cheilitis, alopecia, diarrhea, dermatitis, and oral ulceration, particularly in disorders associated with impaired zinc absorption. Recognition of these associated manifestations is important because treatment of the commissural lesion without correction of the underlying nutritional abnormality may result in persistent or recurrent disease [14].

Evaluation

The diagnosis of angular cheilitis is primarily clinical and is generally established through the characteristic appearance and distribution of the lesions together with an appropriate medical, dental, nutritional, and medication history. In uncomplicated cases, extensive laboratory investigation is not routinely necessary. However, diagnostic testing becomes increasingly important when the lesion is persistent, recurrent, atypical, severe, unilateral, associated with systemic manifestations, or unresponsive to appropriate initial treatment. Because fungal and bacterial infections represent important causes, microbiological testing may be considered when an infectious etiology is suspected or when empirical therapy fails. Initial evaluation should establish whether the lesion is predominantly inflammatory, infectious, mechanical, nutritional, allergic, or multifactorial. When candidiasis is suspected, samples obtained from the affected commissure can be examined microscopically or cultured. Bacterial culture with antimicrobial susceptibility testing may be appropriate when purulent discharge, recurrent infection, or suspected *Staphylococcus aureus* or streptococcal infection is present. Laboratory evaluation for systemic disease should be guided by the clinical presentation rather than performed indiscriminately. Failure to improve after approximately 2 to 3 weeks of appropriate initial antifungal or antibacterial treatment should prompt reassessment of the diagnosis and investigation for underlying conditions. A useful laboratory assessment may include complete blood count with hemoglobin and mean corpuscular volume, iron studies including ferritin, folate, vitamin B12, relevant B-vitamin assessment, serum zinc, and fasting blood glucose. Additional testing should be selected according to clinical findings, dietary history, gastrointestinal symptoms, medication exposure, and suspected systemic disease [12][13][14].

Candidal Angular Cheilitis

When *Candida* infection is suspected, microscopic examination of lesion scrapings can provide supportive evidence. Periodic acid-Schiff staining highlights fungal structures and may demonstrate yeast or hyphal forms. Potassium hydroxide preparations can similarly demonstrate yeast and hyphae, while Gram staining may identify fungal structures as strongly staining organisms. The distinction between colonization and clinically significant infection is important because *Candida* commonly exists as part of the normal oral flora. Additional microbiological methods may be used when species identification or confirmation is necessary. These include fungal culture on Sabouraud dextrose agar, cornmeal agar, or chromogenic media such as CHROM agar. The germ tube test can assist in identifying *C. albicans* and related species, while chlamydospore formation and biochemical assays may provide additional differentiation. More specialized approaches, including strain typing, morphotyping, resistance profiling, and immunodiagnostic techniques, are generally reserved for selected clinical or research settings rather than routine evaluation [14].

Etiology-Specific Investigations

Investigation should be tailored to the suspected underlying cause. For bacterial disease, culture and antimicrobial susceptibility testing can guide targeted treatment. Patients with extensive or recurrent oral candidiasis should be assessed for predisposing conditions such as diabetes mellitus and immunodeficiency. Glucose testing may include fasting or random blood glucose and glycated hemoglobin, while HIV testing should be considered when clinically appropriate. When nutritional deficiency is suspected, assessment may include serum folate, vitamin B12, homocysteine or methylmalonic acid when additional clarification is required, iron studies including ferritin, serum zinc, and selected biochemical indicators of riboflavin status. Dietary history and evaluation for malabsorption are particularly important in patients with gastrointestinal disease, restrictive diets, previous bariatric surgery, or unexplained recurrent lesions. Patch testing is appropriate when allergic contact dermatitis is suspected, particularly when symptoms persist despite antimicrobial treatment or follow exposure to dental, cosmetic, or oral-care products. Finally, persistent, indurated, ulcerated, atypical, or treatment-resistant lesions require consideration of neoplasia and other disorders that may mimic angular cheilitis. In such circumstances, biopsy provides

definitive histopathological assessment and should not be delayed when clinical features raise concern for malignancy [13][14].

Treatment / Management

Management of angular cheilitis should be directed toward the underlying cause while simultaneously restoring the integrity of the labial commissures and preventing recurrent maceration. Because saliva exposure and local barrier disruption are major contributing factors, protection of the affected area with petrolatum, emollients, or an appropriate lip barrier is a fundamental intervention and may be sufficient in mild idiopathic cases [15]. Patients should also be advised to avoid lip licking, smoking, and other behaviors that increase moisture, friction, or chemical irritation. Clinical reassessment after approximately 2 weeks is important to determine whether the lesion is resolving and whether additional investigation is required. When candidal infection is suspected or confirmed, topical antifungal therapy is generally appropriate for localized disease. Common options include nystatin, clotrimazole, ketoconazole, or miconazole, with treatment usually continued for approximately 1 to 2 weeks. Combination preparations containing an antifungal and a mild corticosteroid may be considered when substantial inflammatory or eczematous features accompany infection. Gentian violet may be used in selected pediatric cases, although its staining properties can limit acceptability. More extensive or refractory oral candidiasis may require systemic antifungal therapy. Fluconazole has strong evidence for efficacy, while other systemic azoles or echinocandins may be reserved for selected severe, resistant, or immunocompromised cases [16]. Drug interactions and hepatic considerations should be reviewed when systemic azoles are prescribed.

Bacterial angular cheilitis requires appropriate topical antiseptic or antibacterial treatment. Mupirocin or fusidic acid may be used for suspected staphylococcal infection, while bacterial culture and susceptibility testing are particularly useful in recurrent, extensive, or treatment-resistant disease. When nasal carriage contributes to recurrent infection, treatment of the anterior nares may be considered. Systemic antibiotics are generally unnecessary unless infection is extensive or fails to respond to appropriate topical therapy. Topical corticosteroids may be useful for noninfectious inflammatory angular cheilitis or as short-term adjuncts to antimicrobial treatment. Hydrocortisone or desonide can reduce inflammation, discomfort, and tissue irritation, but corticosteroids should not be used indiscriminately when untreated fungal or bacterial infection is present. Correction of nutritional deficiencies is essential when iron, vitamin B12, folate, riboflavin, zinc, or other nutritional abnormalities contribute to disease. Similarly, optimal management of diabetes, HIV infection, Sjögren syndrome, inflammatory bowel disease, and other systemic conditions can reduce recurrence. Dental management is particularly important for patients with poorly fitting dentures, altered occlusion, or reduced vertical facial dimension. Dentures should be appropriately refitted and thoroughly cleaned because they can serve as reservoirs for *Candida*. In selected patients, correction of commissural anatomy through dental procedures or specialist soft-tissue interventions may reduce persistent saliva pooling.

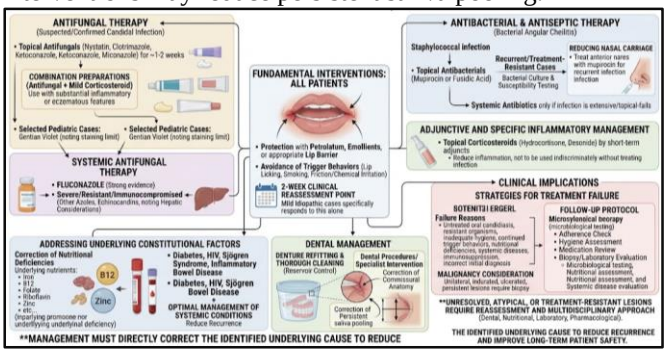

Figure 2: Treatment and management of angular cheilitis.

Treatment failure should prompt reassessment rather than repeated empirical therapy. Persistent disease may result from untreated oral candidiasis, resistant organisms, inadequate hygiene, poorly fitting dentures, continued lip licking or smoking, nutritional deficiencies, immunosuppression, systemic inflammatory disease, or an incorrect initial diagnosis [17]. Recurrent or atypical lesions may require microbiological testing, nutritional assessment, evaluation for systemic disease, or biopsy when malignancy is suspected. Follow-up should therefore assess lesion resolution, adherence, oral and denture hygiene, medication exposure, and correction of underlying risk factors. A multidisciplinary approach involving dental, nutritional, laboratory, and pharmacological assessment is particularly valuable in persistent or recurrent angular cheilitis.

Conclusion:

Angular cheilitis is a multifactorial inflammatory disorder in which local commissural maceration, microbial infection, nutritional deficiency, anatomical abnormalities, mechanical irritation, and systemic disease may interact. Persistent saliva exposure compromises the epithelial barrier and creates favorable conditions for *Candida*, *Staphylococcus*, and other microorganisms. Recognition of associated nutritional deficiencies, particularly involving iron, vitamin B12, folate, riboflavin, and zinc, is important in recurrent or unexplained cases. Clinical diagnosis remains the primary approach, while microbiological, laboratory, nutritional, allergy, and histopathological investigations should be guided by the patient's presentation and response to treatment. Management

should combine barrier protection with appropriate antifungal or antibacterial therapy when infection is present, together with nutritional replacement, dental correction, behavioral modification, and optimal control of underlying systemic conditions. Persistent, unilateral, atypical, or treatment-resistant lesions require further investigation to exclude immunodeficiency, inflammatory disease, nutritional disorders, or malignancy. Coordinated involvement of dental professionals, pharmacists, nutritionists, laboratory specialists, and other healthcare providers can facilitate accurate diagnosis, individualized treatment, and prevention of recurrence. Early identification of contributing factors is therefore central to achieving sustained clinical resolution.

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