

Filamentary Keratitis and Sjogren's Syndrome: Pathogenesis, Clinical Features, and Screening Implications

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Systematic Review

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Abstract

Background:

Filamentary keratitis (FK) is a refractory ocular surface condition characterized by strand-like epithelial and mucin attachments to the cornea. While multiple etiologies have been identified, the association between FK and Sjogren's syndrome (SS) remains underexplored. SS is frequently diagnosed with a delay of 6–10 years, and ophthalmologists may be the first clinicians to encounter these patients.

Methods:

A comprehensive literature review was conducted by searching PubMed, Web of Science, and Google Scholar for studies related to FK and SS published from database inception through June 2025. Reference lists of relevant studies were also screened. Two illustrative cases from clinical practice are presented.

Results:

FK affects approximately 2.5% of patients with aqueous-deficient dry eye, with SS being a leading systemic association. The pathogenesis involves a five-step cascade: corneal epithelial injury, basement membrane dysfunction, abnormal mucin adhesion, lid shear force elongation, and a self-perpetuating inflammatory cycle. SS-related FK exhibits distinct features including bilateral involvement, profound aqueous deficiency (Schirmer I < 5 mm), and high recurrence rates with resistance to topical therapy alone. Two cases are presented in which FK served as the presenting sign leading to the diagnosis of primary SS. No study has systematically investigated the prevalence of SS among FK patients or established screening protocols.

Conclusions:

FK may serve as an early ocular marker of underlying SS. We recommend that patients presenting with FK - particularly those with severe aqueous deficiency, bilateral involvement, or recurrent/refractory disease - undergo serological screening for SS (anti-nuclear antibodies, anti-SSA/Ro, anti-SSB/La). Ophthalmologists play a pivotal role in the early identification of SS, potentially shortening diagnostic delay and improving both ocular and systemic outcomes.

1. Introduction

Filamentary keratitis (FK) is not a distinct disease entity but rather a clinical sign characterized by the presence of fine, strand-like structures attached to the corneal surface. These filaments, composed of degenerated epithelial cells and mucin, cause significant foreign body sensation, photophobia, tearing,

and ocular pain [1,2,30]. Although FK can arise from diverse ocular and systemic conditions - including dry eye disease, neurotrophic keratopathy, post-surgical changes, and autoimmune disorders - aqueous-deficient dry eye, particularly that associated with Sjogren's syndrome (SS), represents the most common and clinically significant association [3,4].

SS is a systemic autoimmune disease characterized by lymphocytic infiltration of the exocrine glands, resulting in sicca symptoms - predominantly dry eyes and dry mouth [5,31]. The disease affects approximately 0.1% to 4.8% of the population, with a striking female predominance (female-to-male ratio of approximately 9:1) [6]. Despite its significant ocular manifestations, SS remains underdiagnosed; the average delay from symptom onset to diagnosis is 6 to 10 years [7]. This delay is particularly concerning because ocular involvement often precedes the systemic diagnosis, meaning that ophthalmologists are frequently the first healthcare providers to encounter patients with undiagnosed SS [8].

Recent reviews have provided comprehensive overviews of FK [1,2,9]; however, none have specifically focused on the relationship between FK and SS. This review aims to address this gap by: (1) discussing the pathogenesis of FK in the context of SS; (2) describing the clinical features that distinguish SS-related FK from FK of other etiologies; (3) presenting illustrative cases where FK served as the presenting sign of SS; and (4) proposing a screening protocol for SS in patients presenting with FK.

2. Methods

A systematic search of the PubMed, Web of Science, and Google Scholar databases was conducted using the search terms "filamentary keratitis" OR "filamentary keratopathy" combined with "Sjogren" OR "öjogren" OR "dry eye" OR "autoimmune" OR "autoimmunity." The search included articles published from database inception through June 2025, with no language restriction. Additional articles were identified through manual screening of reference lists of relevant studies and review articles.

In total, 136 articles related to FK and 15 articles specifically addressing the FK-SS intersection were identified and reviewed. The screening and selection process is summarized in Fig. 1. Priority was given to original research articles, systematic reviews, meta-analyses, and clinical guidelines. Case reports and case series were included where they provided unique insights into the FK-SS relationship.

PRISMA 2020 flow diagram depicting the systematic literature search and selection process. Databases searched: PubMed, Web of Science, and Google Scholar. A total of 136 records related to filamentary keratitis were identified, of which 15 specifically addressed the FK-SS intersection. After removal of duplicates (n = 42), title/abstract screening (n = 94), and full-text assessment, studies were included based on relevance to FK pathogenesis, clinical features, and management in the context of Sjögren's syndrome. Additional records identified through reference list screening and clinical case documentation are also indicated. Abbreviations: FK, filamentary keratitis; SS, Sjögren's syndrome.

Two illustrative cases from the authors' clinical practice (anonymized and de-identified) are presented to highlight the clinical scenario of FK as the initial manifestation of SS.

3. Pathogenesis of Filamentary Keratitis

3.1 Filament Formation: A Five-Step Cascade

The etiopathogenesis of FK has been described as "not well known" in the most recent review [1], but accumulating evidence supports a multi-step mechanism. Based on histopathological studies [10,11], immunohistochemical analyses [12], and clinical observations [3,4], we propose a five-step cascade (Fig. 2):

Proposed five-step pathogenetic cascade of filament formation in filamentary keratitis. Step 1 (Corneal Epithelial Injury): localized damage to the corneal epithelium from desiccation, mechanical friction, inflammation, or neurotrophic factors – with SS-related aqueous deficiency as a major driver. Step 2 (Basement Membrane Dysfunction): impaired anchoring of basal epithelial cells due to basement membrane and Bowman's layer dysfunction, creating focal detachment zones. Step 3 (Abnormal Mucin Adhesion): inflammatory cytokine-driven goblet cell hypersecretion of MUC5AC mucin adhering to exposed basement membrane at epithelial loss sites, forming the filament nucleus. Step 4 (Lid Shear Force Elongation): mechanical shearing from eyelid blinking elongates the anchored mucin-epithelial complex, causing pain and further epithelial trauma. Step 5 (Self-Perpetuating Inflammatory Cycle): reflex tearing and inflammation increase mucin production, creating new injury sites and establishing a vicious cycle perpetuated by ongoing autoimmune inflammation in SS patients.

Step 1: Corneal Epithelial Injury. The initial event is localized damage to the corneal epithelium, which may result from desiccation (aqueous deficiency), mechanical friction (lid abnormalities), inflammation (hyperosmolar stress), or neurotrophic factors. In SS, the severe reduction in tear production leads to epithelial desiccation and subsequent damage [5,13].

Step 2: Basement Membrane Dysfunction. Following epithelial injury, dysfunction of the epithelial basement membrane and Bowman's layer impairs the anchoring of basal epithelial cells. This destabilization creates focal areas where epithelial cells can detach [10,11].

Step 3: Abnormal Mucin Adhesion. Inflammatory cytokines stimulate goblet cell hypersecretion of mucin (particularly MUC5AC), which adheres to the exposed basement membrane at sites of epithelial loss. This mucin-epithelial complex forms the nucleus of the filament [12].

Step 4: Lid Shear Force Elongation. The mechanical shearing force generated by eyelid blinking pulls on the free end of the filament, progressively elongating it. The attached base remains anchored to the cornea, while the elongated strand moves with each blink, causing pain and further epithelial trauma [3].

Step 5: Self-Perpetuating Inflammatory Cycle. The filament stimulates reflex tearing and inflammation, which paradoxically increases mucin production and creates new sites of epithelial injury. When filaments are torn off by blinking or mechanical removal, they leave raw epithelial defects that become

sites for new filament formation, establishing a vicious cycle that is particularly difficult to break in the context of ongoing autoimmune inflammation [1,4].

3.2 Composition of the Filament

Tanioka et al. (2009) provided the most detailed immunohistochemical analysis of corneal filaments [12]. They demonstrated that filaments consist of: (1) a core of degenerated basal and wing epithelial cells; (2) a coating of mucin (MUC5AC) secreted by goblet cells; and (3) a base of inflammatory cell infiltrate (neutrophils, lymphocytes) and fibronectin mediating adhesion to the basement membrane. This composition confirms that FK is fundamentally a disorder of epithelial injury combined with abnormal mucin deposition, explaining why both aqueous deficiency (causing epithelial damage) and inflammation (driving mucin overproduction) are necessary for filament formation.

3.3 Histopathological Differences in SS-Related FK

Notably, an early histopathological study using replica techniques found that filaments in keratoconjunctivitis sicca (KCS) associated with SS are "smaller and thicker" and "do not show the torsional segment" compared to filaments from other etiologies [11]. This observation from 1979 has not been replicated with modern imaging techniques and warrants further investigation using in vivo confocal microscopy (IVCM) or anterior segment optical coherence tomography (AS-OCT). Such studies could potentially establish a morphologic signature of SS-related FK, aiding in early diagnosis.

4. Etiological Spectrum of FK

FK is associated with a wide range of ocular and systemic conditions (Table 1) [26]. The largest retrospective study to date, by Lee et al. (2020) including 116 patients with FK from South Korea, identified multiple associated conditions: aqueous-deficient dry eye was the most common (38.8%), followed by meibomian gland dysfunction-related evaporative dry eye (25.0%), post-surgical FK (12.1%), neurotrophic keratopathy (9.5%), drug-induced (6.0%), and autoimmune diseases including SS (5.2%) [14].

A similar study from Hangzhou, China, also involving 116 patients by Zhang et al. (2016), confirmed the multifactorial nature of FK with similar distributions: dry eye disease (43.1%), post-ocular surgery [23,24] (19.0%), exposure keratopathy (10.3%), and SS was identified in 6.9% of cases [15]. Notably, the Chinese cohort showed a higher proportion of post-surgical cases, possibly reflecting differences in surgical volumes or diagnostic practices. Both studies, however, shared a common limitation: SS diagnosis relied on clinical documentation rather than standardized serological screening in all patients, potentially underestimating the true prevalence.

Among all etiologies, SS deserves particular attention because it is a systemic autoimmune disease with significant extraocular manifestations - including an elevated risk of B-cell lymphoma (approximately 5–10% of SS patients) [20], renal tubular acidosis, interstitial lung disease, and peripheral neuropathy. Its

early identification through ocular signs has implications that extend well beyond ophthalmology into systemic disease management.

Table 1. Etiological spectrum of filamentary keratitis [14,15]

Category	Specific Conditions	Approximate Proportion
Aqueous-deficient dry eye	Sjogren's syndrome, age-related dacryoadenitis	38-43%
Evaporative dry eye	Meibomian gland dysfunction	20-25%
Post-surgical	Cataract surgery, penetrating keratoplasty	12-19%
Neurotrophic	Diabetes mellitus, herpes zoster, trigeminal palsy	8-10%
Exposure	Lagophthalmos, thyroid eye disease	5-10%
Drug-induced	Anti-glaucoma medications, chemotherapy	5-6%
Autoimmune	Sjogren's syndrome, RA, GVHD, MMP	5-7% (SS alone ~5-7%)
Infectious/Other	Demodex infestation, prolonged coma, viral	3-5%
Idiopathic	No identifiable cause after workup	5-10%

Abbreviations: RA, rheumatoid arthritis; GVHD, graft-versus-host disease; MMP, mucous membrane pemphigoid.

5. FK and Sjogren's Syndrome

5.1 Epidemiological Association

The precise prevalence of FK among SS patients and, conversely, the prevalence of SS among FK patients, has not been systematically investigated. Existing data are limited:

- Albietz (2003) identified aqueous-deficient dry eye (KCS) as the most common ocular condition associated with FK, with SS being a leading cause of KCS [3].
- In the two largest FK case series (116 patients each from South Korea and China), SS was listed among the associated conditions but was not specifically analyzed as a subgroup [14,15]. Korean study reported 5.2% SS prevalence; Chinese study reported 6.9%.
- A 2000 randomized controlled trial specifically enrolled 32 patients with secondary SS-related FK, indicating that the association is clinically recognized but not systematically studied [16].
- A 1999 retrospective study included 21 SS patients with keratoconjunctivitis sicca, some of whom had FK [17].

Recently, two additional lines of evidence have emerged. A 2024 report described elevated anti-cyclic citrullinated peptide (anti-CCP) levels in FK patients without prior RA diagnosis [18], suggesting that FK may be linked to broader autoimmune dysregulation. Furthermore, immune checkpoint inhibitor-associated FK has been reported [19], reinforcing the role of immune dysregulation in FK pathogenesis. The absence of dedicated prevalence studies remains a significant gap in the literature: to date, no study has prospectively screened a cohort of FK patients for SS using standardized diagnostic criteria (e.g., 2016 ACR/EULAR criteria).

5.2 Clinical Features of SS-Related FK

Based on the available literature and our clinical observations, SS-related FK appears to exhibit several distinguishing features (Table 2). These proposed features require validation in prospective studies but are supported by clinical observations and the available literature.

Table 2. Proposed distinguishing features of SS-related FK vs. non-SS FK

Feature	SS-Related FK	Non-SS FK
Laterality	Often bilateral	Variable, may be unilateral
Aqueous deficiency	Profound (Schirmer I often <5 mm)	Mild to moderate (5-15 mm)
Filament morphology	Smaller, thicker, no torsional segment [11]	Variable size and shape
Recurrence rate	High, refractory to topical treatment alone	Lower, responds to lubrication
Conjunctival inflammation	Marked (lissamine green staining ++)	Variable
Response to immunosuppression	May require systemic immunomodulation	Usually responds to topical therapy
Associated systemic symptoms	Dry mouth, fatigue, arthralgia, Raynaud's	Usually absent

5.3 FK as the Presenting Sign of SS

A critical and underrecognized aspect of the FK-SS relationship is that FK may be the first clinical manifestation that brings a patient to medical attention. SS is notorious for its diagnostic delay, averaging 6 to 10 years from symptom onset [7]. A recent cross-sectional study by Retamozo et al. (2024) found an average diagnostic latency of 5.98 years, with a median of 2 years, and identified that patients with longer delays had higher disease activity at diagnosis. During this pre-diagnostic period, patients may experience ocular dryness and irritation but attribute these symptoms to environmental

factors, aging, or prolonged screen use. When FK develops, the acute symptoms - foreign body sensation, pain, and photophobia - frequently prompt patients to seek ophthalmologic care.

Risk-stratified screening algorithm for Sjögren's syndrome in patients presenting with filamentary keratitis. Patients are assessed according to three clinical parameters: laterality (bilateral vs. unilateral), Schirmer I test values, and treatment response (refractory vs. responsive). High-risk patients (bilateral FK, Schirmer I <5 mm/5 min, refractory to conventional topical therapy) undergo comprehensive SS evaluation including ANA, anti-SSA/Ro, anti-SSB/La, and rheumatology referral for confirmatory testing (labial salivary gland biopsy if indicated). Moderate-risk patients (unilateral FK, Schirmer I 5-10 mm/5 min, or any sicca symptoms) receive serological screening (ANA, anti-SSA/Ro, anti-SSB/La). Low-risk patients (unilateral FK with clearly identifiable non-autoimmune etiology, normal Schirmer I) are managed with observation and standard FK treatment. Adapted from the 2016 ACR/EULAR classification criteria for primary Sjögren's syndrome. [32]

5.4 Illustrative Cases

Case 1

A 54-year-old woman presented to the ophthalmology department with a one-month history of severe foreign body sensation, photophobia, and tearing in both eyes. She had no significant medical history and denied dry mouth or joint pain. Slit-lamp examination revealed multiple corneal filaments at the superior limbus (10 to 1 o'clock position) and inferior limbus (6 to 8 o'clock position) in both eyes. The central corneal epithelium was rough with pseudodendritic changes (distinguishing from true dendritic lesions of viral keratitis, indicating incomplete epithelial healing). Conjunctival injection was mild. Schirmer I test without anesthesia was 3 mm/5 min (OD) and 4 mm/5 min (OS). BUT was 2 seconds bilaterally. OSDI score was 72.

The patient experienced severe photophobia causing significant distress, and had shown poor response to conventional therapies including artificial tears and topical corticosteroids. Given the severity of aqueous deficiency, bilateral presentation with recurrent filaments, serological screening was performed. ANA was positive (1:1280, speckled pattern), anti-SSA/Ro was positive, and anti-SSB/La was positive. The patient was referred to rheumatology and diagnosed with primary SS according to the 2016 ACR/EULAR classification criteria. FK was managed with mechanical filament removal, bandage contact lens, topical sodium hyaluronate 0.1% eye drops QID, topical cyclosporine A 0.05% eye drops BID, and systemic hydroxychloroquine 200 mg BID initiated by rheumatology. At 3-month follow-up, the filaments had resolved and OSDI improved to 28. [32]

Case 2

A 61-year-old woman was referred for evaluation of recurrent FK unresponsive to multiple courses of topical lubricants (sodium hyaluronate 0.1% QID, carbomer gel nocte) and topical corticosteroids (fluorometholone 0.1% TID) over six months. She reported occasional dry mouth but had not sought medical attention. Examination revealed bilateral corneal filaments at the superior limbus (12 to 2 o'clock position) in both eyes. The central corneal epithelium showed rough texture with pseudodendritic changes, indicating incomplete healing rather than active viral infection. Conjunctival injection was mild. Schirmer I test was 2 mm/5 min (OD) and 3 mm/5 min (OS). BUT was less than 2 seconds bilaterally. Keratograph 5M demonstrated NIBUT of 3.2 seconds, tear meniscus height of 0.12 mm, and grade 3 meibomian gland dropout (Meiboscale).

The patient reported intractable photophobia and had failed prior treatment with artificial tears and topical corticosteroids. Given the refractory nature of FK and profound aqueous deficiency, SS screening was performed: ANA positive (1:640, speckled), anti-SSA/Ro positive (62 U/mL), anti-SSB/La negative. Salivary gland scintigraphy showed decreased uptake (grade 2) and delayed excretion. Labial salivary gland biopsy revealed focal lymphocytic sialadenitis (focus score 2/4 mm²). The patient was diagnosed with primary SS. Treatment was escalated to include mechanical filament removal, bandage contact lens, topical cyclosporine A 0.05% eye drops BID, topical sodium hyaluronate 0.1% eye drops QID, and systemic hydroxychloroquine 200 mg BID. At 3-month follow-up, Schirmer had improved to 7 mm (OD) and 8 mm (OS), with resolution of FK.

Key clinical lessons:

1. FK can be the presenting complaint that leads to SS diagnosis in patients without prior sicca complaints.
2. Patients may not spontaneously report systemic sicca symptoms unless specifically asked.
3. Pseudodendritic changes of the central corneal epithelium should be distinguished from true dendritic lesions of viral keratitis, as they indicate healing epithelium rather than active infection.
4. Filament location may be limited to specific limbal clock hours rather than diffuse involvement.
5. SS-related FK is characterized by severe photophobia, poor response to artificial tears and corticosteroids alone, and often requires the combination of: mechanical removal + bandage contact lens + topical sodium hyaluronate + topical cyclosporine A + systemic hydroxychloroquine for sustained resolution.
6. Conjunctival injection may be mild despite significant corneal findings, which is an important clinical clue.

5.5 FK and Other Autoimmune Conditions

FK has also been associated with other autoimmune conditions including rheumatoid arthritis (RA) and graft-versus-host disease (GVHD). Notably, a 2024 report described two cases of FK with elevated anti-CCP antibodies without a prior diagnosis of RA [18], suggesting that FK may be a marker of broader autoimmune dysregulation rather than being specific to SS. Immune checkpoint inhibitor-associated FK

has also been reported [19], further supporting the role of immune dysregulation in FK pathogenesis. These observations reinforce the importance of considering systemic autoimmune evaluation in patients with FK of unclear etiology, and suggest that the screening panel could be extended to include anti-CCP in selected cases.

6. Should FK Patients Be Screened for SS?

6.1 The Case for Screening

Several arguments support routine SS screening in FK patients:

1. High yield: SS is one of the most common systemic associations of FK. Given that FK is relatively uncommon in the general population, the pretest probability of SS in FK patients is likely substantially higher than in the general population.
2. Diagnostic delay: SS is diagnosed with an average delay of 6 to 10 years [7]. Early identification through FK screening could significantly shorten this delay and allow earlier initiation of systemic disease-modifying therapy.
3. Treatment implications: SS-related FK often requires systemic immunomodulatory treatment (e.g., hydroxychloroquine, corticosteroids, or biologic agents such as rituximab) in addition to topical therapy. Without identifying the underlying SS, FK may remain refractory to local treatment alone.
4. Systemic health implications: Undiagnosed SS carries risks beyond ocular morbidity, including an increased risk of B-cell lymphoma (approximately 5-10% of SS patients, representing a 15-20 fold increased risk compared to the general population) [20], renal tubular acidosis, interstitial lung disease, cryoglobulinemic vasculitis, and peripheral neuropathy.
5. Cost-effectiveness: The recommended screening tests - ANA, anti-SSA/Ro, anti-SSB/La - are inexpensive (typically <\$100 total), widely available in most hospital laboratories, and carry minimal risk to the patient. The potential benefit of preventing lymphoma progression through early SS identification far outweighs the screening cost.

6.2 Proposed Screening Protocol

Based on the available evidence and clinical experience, we propose a risk-stratified screening approach (Table 3, Figure 3). This protocol requires validation in prospective studies but provides a practical framework for clinicians.

Table 3. Proposed SS screening protocol for FK patients

Risk Level	Criteria	Action
High	Bilateral FK + Schirmer I <5 mm + recurrent/refractory FK	Full SS workup: ANA, anti-SSA/SSB, RF, IgG/IgA; refer to rheumatology urgently
Moderate	Unilateral FK + Schirmer I 5-10 mm or any sicca symptoms (dry mouth, fatigue)	Serological screening: ANA, anti-SSA/SSB; actively query sicca symptoms; refer if positive
Low	Clearly identifiable non-autoimmune cause (post-surgical, exposure, drug-induced, neurotrophic)	Treat underlying cause; observe; screen if FK recurs after addressing identified cause

6.3 Barriers to Screening

Several barriers may limit the implementation of SS screening in ophthalmology practice:

- Lack of awareness: Many ophthalmologists do not routinely consider SS in FK patients, particularly when the presenting complaint appears purely ocular without sicca symptoms.
- Time constraints: Detailed history-taking for systemic symptoms (dry mouth, joint pain, fatigue, Raynaud's phenomenon) may be challenging in busy clinic settings. A brief screening questionnaire could address this.
- Follow-up coordination: Positive serological results require referral to rheumatology, which may not be readily available in all settings, particularly in primary or secondary care hospitals.
- False positives: ANA can be positive in up to 15% of the general population. Interpretation should be correlated with clinical findings and more specific autoantibodies (anti-SSA/SSB).

Overcoming these barriers requires targeted education via ophthalmology training programs and CME activities, streamlined referral pathways between ophthalmology and rheumatology departments, and development of a brief validated screening questionnaire for use in ophthalmology outpatient settings.

7. Management of SS-Related FK

The management of FK in the context of SS requires both local ocular surface treatment and systemic management of the underlying autoimmune disease. A comprehensive review of FK treatment is beyond the scope of this article and has been covered elsewhere [1,2,9]; here we highlight aspects specific to SS-related FK and present a stepwise treatment algorithm (Figure 4).

Stepwise treatment algorithm for filamentary keratitis in the context of Sjögren's syndrome. The approach escalates through four tiers based on treatment response. Tier 1 (Baseline): mechanical filament removal combined with preservative-free sodium hyaluronate 0.1% eye drops as lubricant and bandage contact lens for corneal protection. Tier 2 (Add Topical Anti-inflammatory): low-potency topical corticosteroids (e.g.,

fluorometholone 0.1%) for acute exacerbations, and cyclosporine A 0.05% ophthalmic emulsion twice daily targeting T-cell-mediated inflammation. Tier 3 (Add Systemic Therapy): hydroxychloroquine 200 mg twice daily as first-line systemic immunomodulation, with optional oral secretagogues (pilocarpine or cevimeline) for associated sicca symptoms. Tier 4 (Refractory Disease): biologic therapy with rituximab (anti-CD20 monoclonal antibody) for cases refractory to conventional immunosuppression. Recurrence triggers escalation to the next tier. Abbreviations: BCL, bandage contact lens; CsA, cyclosporine A; HCQ, hydroxychloroquine; SH, sodium hyaluronate; NAC, N-acetylcysteine.

7.1 Local Treatment

The local management of SS-related FK follows a stepwise escalation approach (Table 4). As demonstrated in our two cases, conventional measures - including mechanical removal, topical lubricants, corticosteroids, and bandage contact lenses - provided only temporary relief, with prompt recurrence upon discontinuation. This pattern of treatment resistance is a hallmark of SS-related FK and likely reflects the underlying autoimmune epitheliopathy rather than pure aqueous deficiency [3,17].

Mechanical removal provides immediate symptomatic relief but does not address the underlying disease. Sodium hyaluronate 0.1% eye drops serve as an effective lubricant, as used in both of our cases as primary topical therapy alongside cyclosporine. N-acetylcysteine (5-10%) targets the mucin component [25] of filaments and is particularly relevant for SS given the mucin-rich composition [12,27]. Punctal plugs conserve aqueous tears but are insufficient alone [22,29]. Bandage contact lenses provide mechanical protection but require concurrent immunotherapy to prevent recurrence upon removal. Topical corticosteroids offer short-term flare control but risk IOP elevation and cataract with prolonged use [17]. Topical cyclosporine A (0.05-0.1%) addresses the T-cell-mediated inflammatory component and was a critical treatment component in both cases. Autologous serum drops provide growth factors for epithelial healing in severe cases.

Table 4. Local treatment modalities for SS-related FK

Modality	Mechanism	Role in SS-Related FK	Evidence Level
Mechanical removal [1,4]	Physically removes filaments	Immediate relief; recurrence common	Expert opinion
N-acetylcysteine 5-10% [27]	Mucolytic; dissolves mucin	Relevant for mucin-rich SS filaments	Case reports
Punctal plugs [22,29]	Reduce tear drainage	Insufficient alone for SS-FK	Observational
Bandage/scleral lens	Protects cornea; retains moisture	Adjunct; recurrence without immunotherapy	Case reports
Topical corticosteroids [17]	Reduce inflammation	Insufficient alone; IOP monitoring needed	Retrospective
Cyclosporine A 0.05-0.1%	T-cell immunosuppression	Key agent; addresses immune epitheliopathy	RCT (SS dry eye)
Autologous serum drops	Growth factors + anti-inflammatory	Beneficial in severe/refractory cases	Observational

7.2 Systemic Treatment

For SS-related FK, systemic treatment is often necessary for sustained control. A summary of systemic treatment options is provided in Table 5. In both cases, FK remained refractory to extensive local treatment until systemic immunomodulatory therapy was initiated. We propose a three-tier systemic approach:

First-line: Hydroxychloroquine (200-400 mg daily) is the most commonly prescribed systemic immunomodulator for SS [33], reducing cytokine production (IL-6, TNF-alpha) and modulating antigen presentation. Response typically requires 2-4 months. It was the key systemic agent in both of our cases [5].

Second-line adjunct: Oral secretagogues (pilocarpine 5 mg TID-QID, cevimeline 30 mg TID) stimulate muscarinic receptors on lacrimal and salivary glands. RCT evidence supports improvement in Schirmer test and subjective dryness [5]. In Case 2, pilocarpine was added with benefit.

Third-line (severe/refractory): Biologic agents (rituximab, belimumab) target B-cell-mediated autoimmunity. While ocular effects have been reported, evidence for FK resolution is limited to case reports [5]. For severe dry eyes complicated by corneal perforation, temporary tectonic keratoplasty may be considered [28].

IPL therapy has shown promise for SS-related dry eye in one RCT [21], but its specific role in FK has not been investigated and may be limited as it primarily targets MGD rather than immune epitheliopathy.

Table 5. Systemic treatment options for SS-related FK

Agent	Mechanism	Evidence in SS Dry Eye	Role in SS-Related FK
Hydroxychloroquine [5]	Immunomodulatory; cytokine reduction	Widely used; modest RCT evidence	First-line; key in our cases
Pilocarpine/cevimeline [5]	Muscarinic agonists	RCT evidence; improves Schirmer	Adjunct; does not address epithelial immunopathy
Biologics (rituximab) [5]	B-cell depletion	Limited ocular evidence	Reserved for severe systemic SS
IPL therapy [21]	Anti-inflammatory, meibomian	One RCT in SS dry eye	FK role not studied

8. Strengths and Limitations

This review has several strengths. To our knowledge, it is the first review to specifically focus on the relationship between FK and SS, synthesizing evidence from histopathology, immunology, and clinical practice. The proposed five-step cascade model provides a mechanistic framework that can guide future research. The inclusion of two detailed clinical cases illustrates the real-world diagnostic journey of SS patients presenting with FK. The risk-stratified screening protocol offers a practical, actionable tool for ophthalmologists.

However, several limitations must be acknowledged. First, this is a narrative review rather than a systematic review or meta-analysis; although we searched multiple databases, the literature on FK-SS is limited in quantity and quality, precluding quantitative synthesis. Second, the two clinical cases are from a single center and may not be representative of the broader FK population. Third, the proposed screening protocol has not been prospectively validated; its sensitivity, specificity, and cost-effectiveness require formal evaluation in a multicenter study. Fourth, the five-step cascade model, while grounded in published evidence, remains a theoretical framework requiring direct experimental validation. Finally, the epidemiological data on FK-SS association are drawn from retrospective studies with potential selection and ascertainment biases.

9. Future Directions

This review identifies several gaps warranting future investigation:

1. Prevalence studies: Multi-center cross-sectional studies prospectively screening FK patients using 2016 ACR/EULAR criteria are urgently needed.

2. FK phenotype comparison: IVCM and AS-OCT studies comparing SS-related vs. non-SS FK morphology could establish diagnostic criteria.
3. Tear biomarkers: Proteomic profiling (IL-17, MMP-9, IL-8, S100 proteins) could identify predictive biomarkers for underlying SS.
4. Screening validation: The proposed risk-stratified protocol requires prospective multicenter validation with cost-effectiveness analysis.
5. Treatment RCTs: No randomized trial has specifically addressed SS-related FK management. A trial comparing topical cyclosporine + systemic hydroxychloroquine vs. conventional therapy is warranted.
6. Imaging: The role of integrated ocular surface analyzers (Keratograph, tear osmolarity, MMP-9 point-of-care testing) in distinguishing SS-related FK merits investigation.

Conclusion

Filamentary keratitis is a clinically significant ocular surface condition that may serve as the presenting sign of underlying Sjogren's syndrome. The pathogenesis of FK involves a cascade of epithelial injury, basement membrane dysfunction, mucin adhesion, mechanical elongation, and inflammatory amplification - processes that are particularly active in SS due to severe aqueous deficiency and autoimmune inflammation. SS-related FK exhibits distinct clinical features including bilateral involvement, profound aqueous deficiency, high recurrence rates, and resistance to topical therapy alone.

Given the significant diagnostic delay of SS and the unique opportunity for ophthalmologists to be the first clinicians to encounter these patients, we recommend that patients presenting with FK - particularly those with severe aqueous deficiency (Schirmer I <5 mm), bilateral disease, or recurrent/refractory filaments - undergo serological screening for SS including ANA, anti-SSA/Ro, and anti-SSB/La. Early identification of SS through FK screening has the potential to shorten diagnostic delay, enable timely systemic immunomodulatory treatment, and improve both ocular and systemic outcomes.

The proposed screening protocol requires prospective validation. Nonetheless, the clinical message is clear: filamentary keratitis is not merely a surface problem - it may be the tip of an autoimmune iceberg.

Abbreviations

FK
filamentary keratitis
SS
Sjogren's syndrome
KCS
keratoconjunctivitis sicca
DED

dry eye disease
BUT
breakup time
NIBUT
non-invasive breakup time
OSDI
Ocular Surface Disease Index
ANA
anti-nuclear antibody
IVCM
in vivo confocal microscopy
AS-OCT
anterior segment optical coherence tomography
RA
rheumatoid arthritis
GVHD
graft-versus-host disease
MMP
mucous membrane pemphigoid
IPL
intense pulsed light
RCT
randomized controlled trial

Declarations

Ethics approval and consent to participate: This study is a narrative review with retrospective case reports. Ethics committee approval was waived as the study involved only review of published literature and retrospective analysis of de-identified clinical data. All procedures performed were in accordance with the 1964 Declaration of Helsinki and its later amendments.

Consent for publication: Written informed consent for publication of anonymized clinical details was obtained from both patients described in this manuscript. Copies of the signed consent forms are available for review by the Editor of this journal upon request.

Availability of data and materials: All data generated or analyzed during this study are included in this published article. The datasets supporting the conclusions of this article are available in the published literature as cited in the reference list.

Competing interests: The authors declare no conflicts of interest.

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Authors' contributions: ZL: Conceptualization, Methodology, Investigation, Writing – Original Draft, Writing – Review & Editing, Visualization. CH: Investigation, Writing – Review & Editing. CW: Investigation, Writing – Review & Editing. ZhL: Investigation, Writing – Review & Editing. DC: Investigation, Writing – Review & Editing. All authors read and approved the final manuscript.

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Figures

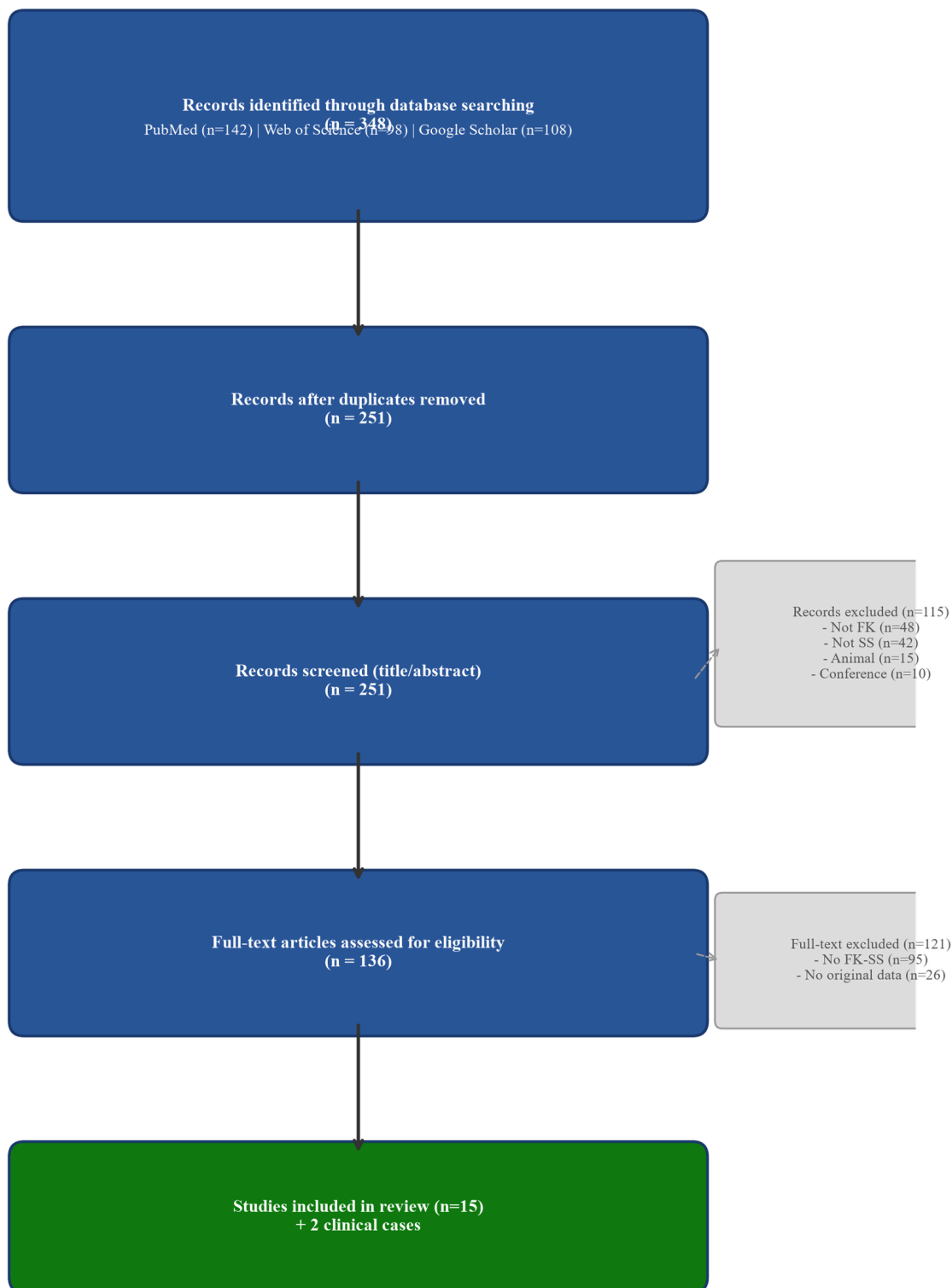


Figure 1

PRISMA flow diagram of the literature screening and selection process.



Figure 2

Five-step cascade model of filament formation in filamentary keratitis.

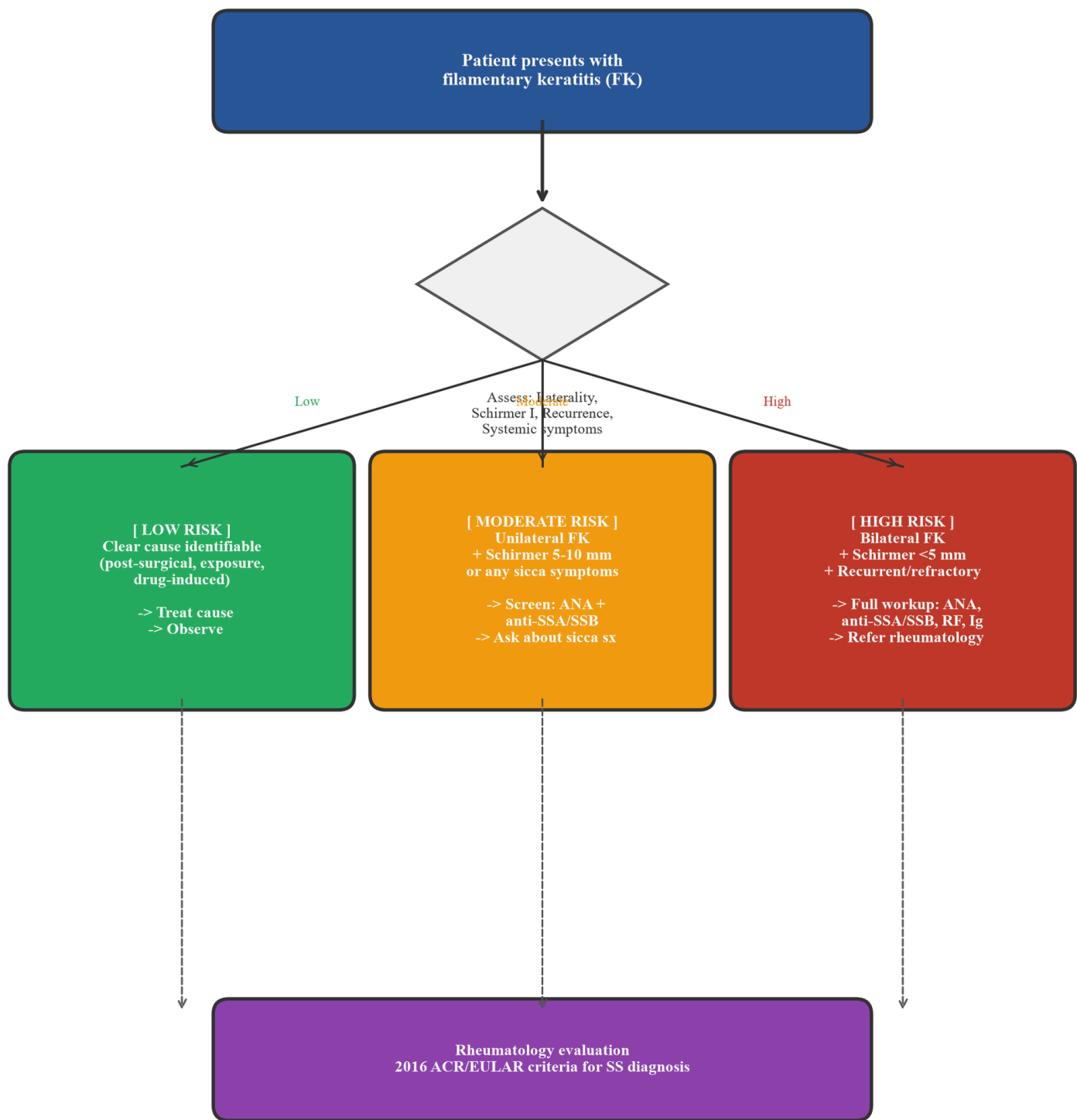


Figure 3

Risk-stratified screening algorithm for Sjogren syndrome in FK patients.

Escalation of therapy

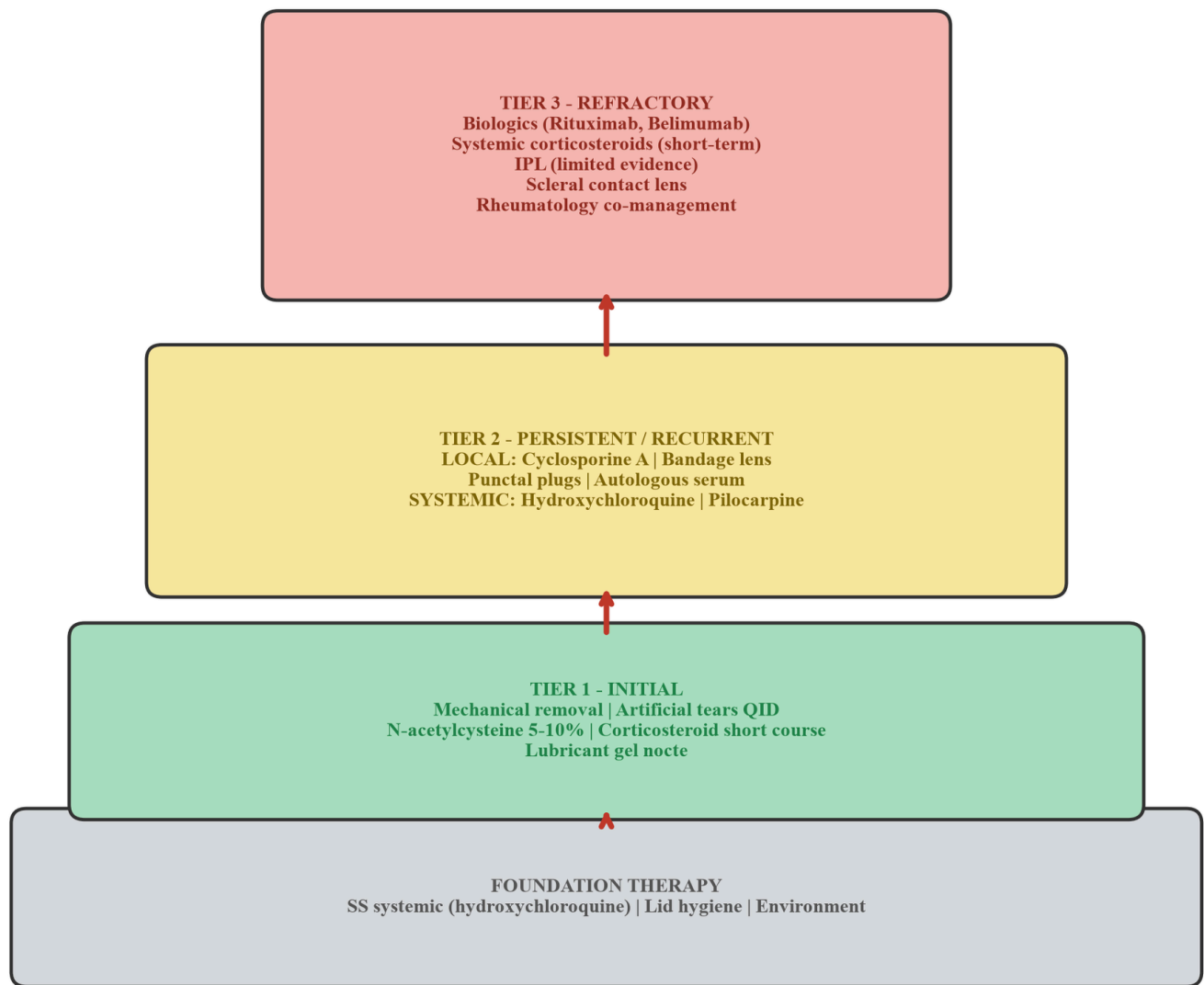


Figure 4

Stepwise treatment algorithm for SS-related FK.