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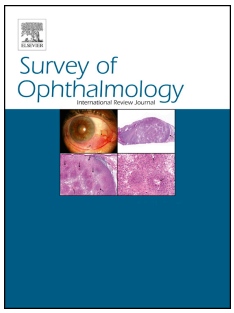

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Title Page

Infectious Crystalline Keratopathy

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Abstract

Infectious crystalline keratopathy (ICK) was first reported by Gorovoy et al in 1983 when they identified bacteria colonizing a cornea after a penetrating keratoplasty. Subsequent cases have elaborated on the organisms responsible and the management outcomes. Patients present with a white or grey branching opacity originating from an epithelial defect, commonly after a penetrating keratoplasty. Local immunosuppression contributes to the quiescent nature and the limited inflammatory response associated with ICK.

Diagnosis of the infective pathogens may be difficult, with a corneal scraping often being too superficial to obtain an adequate specimen. A biofilm is present that advantages microorganism survival, reduces antibiotic bioavailability, and inhibits diagnostic microbial detection. Treatment begins with topical antimicrobials, initially broad spectrum and then targeted to microorganism sensitivity. Adjunctive therapies to enhance the efficacy of treatment include disruption of the microorganism biofilm by laser, intrastromal antibiotics, and keratectomy. In recalcitrant cases, or where corneal scarring ensues, corneal transplantation is required.

Key words

infectious crystalline keratopathy, keratoplasty, biofilm, keratitis

I. Infectious Crystalline Keratopathy

A. INTRODUCTION

Infectious crystalline keratopathy (ICK) has been defined as an indolent infective keratitis with characteristic needle-like branching opacities and an absence of corneal or anterior segment inflammation.[126] Infective microorganisms enter the corneal stroma through an epithelial defect and proliferate.[69, 117] In ICK, the usual immune response is blunted by localized immunosuppression, allowing microorganisms to become a sessile pathogen surrounded by a biofilm, resulting in a discrete keratitis with limited inflammation in the surrounding tissues.[86]

To date, there have been a number of publications exploring the etiology, pathophysiology, and treatment of ICK; however, as ICK is uncommon, these are predominantly case reports or small series. We consolidate the current knowledge of ICK into a format we hope will be useful when managing this condition.

B. HISTORICAL BACKGROUND

ICK has been extensively reported in the literature, with Gorovoy et al[48] being the first to describe a case in 1983. Their patient underwent an uncomplicated right penetrating keratoplasty; however, at six-months post-operatively, a branching, needle-like opacity developed in the peripheral stroma. Ultimately, this required re-grafting, and light microscopic analysis of the excised corneal button showed an intact epithelium with epithelial ingrowth along the suture track and gram-positive cocci in the corneal stroma. They reported the case as "intrastromal non-inflammatory bacterial colonization", preferring this terminology to "infection" as there was no inflammatory reaction to the bacteria.

The term "infectious crystalline keratopathy" was introduced by Meisler et al,[87] who proposed that it linked the clinical characteristics and the underlying etiology. Histology on their three cases revealed that the bacterial colonies predominantly were found in the anterior stroma, and the lack of an inflammatory response was reiterated. All three cases were receiving topical corticosteroids, supporting the hypothesis by Gorovoy et al regarding the role of local immunosuppression in ICK pathogenesis.[87] They cultured *Streptococcus viridans* and identified an increased minimum inhibitory concentration for antibiotic treatment four times greater than the usual treatment level. This was a relevant finding as biofilms resulting in antibiotic resistance were later identified in ICK cases. In a subsequent paper by the same group, they reported two of the cases had developed ICK after *Herpes simplex* keratitis expanding ICK beyond corneal transplants.[88] Reiss et al[106] in 1986, reviewed the previously published seven cases and described a further ICK case. They initiated discussion on the pathophysiology by hypothesizing that the crystalline appearance was intrastromal bacterial accumulation and advised earlier corneal scraping and aggressive antimicrobial treatment.[106]

Terminology previously used in the literature includes "arborescent bacterial keratopathy".[137] Watson et al[137] felt that "infectious crystalline keratopathy" as a term was inappropriate as the process is neither infective nor has actual crystal deposition. They presented two cases, both arising after penetrating keratoplasty while using topical corticosteroids.[137] Interestingly, the first patient developed bilateral ICK two years apart and required repeat penetrating keratoplasties on both occasions.[137]

Nanda et al[93] described a case of "intracorneal bacterial colonization in a crystalline pattern", in which a 78-year-old woman underwent bilateral penetrating keratoplasty and cataract extraction. The left eye was complicated by recurrent episodes of keratitis in a branching pattern that regressed with subconjunctival and topical gentamicin.

The other terminologies failed to be adopted, with subsequent reviews by Reiss et al,[106] Stern[126] and Remeijer et al,[107] along with numerous case reports preferring the term "infectious crystalline keratopathy". In 1993, Stern[126] further described his case and consolidated the knowledge of ICK. He associated the cases with epithelial defects whether caused by surgery or through other mechanisms (such as contact lens, herpetic and acanthamoeba keratitis) while using topical corticosteroids.[126] He pointed out that the crystalline description refers to the clinical appearance as opposed to the deposition of actual crystals and concluded that they were caused by an indolent corneal infection. Early cultures and aggressive medical therapy with fortified antibiotics were recommended, progressing to surgical intervention if these methods proved inadequate.[126]

II. Epidemiology

ICK is an uncommon corneal infection; however, there has been no determination of actual incidence. Sánchez Pérez et al[112] investigated infectious keratitis over a 17-year period (1980 – 1997) in 246 penetrating keratoplasty cases. In this review, only a single case of ICK was identified (0.4%).[112] Bates et al[10] reviewed thirty cases that

developed keratitis after penetrating keratoplasty, five of which had a crystalline appearance. ICK cases tend to be included in infectious keratitis reviews, making true incidence estimates difficult.[10, 30, 118] A dramatic increase in ICK cases was recorded with the increase in number of penetrating keratoplasty operations;[106, 126, 107] however, as lamellar keratoplasty becomes more frequent, this may result in a decrease in the incidence of ICK.[39, 141] The association with acanthamoeba keratitis appears to have a higher prevalence, with Tu et al[133] reporting three cases of ICK in 111 cases of acanthamoeba keratitis (2.7%).

ICK occurs predominantly in the adult population, more commonly unilaterally.[117] There does not appear to be a gender or racial predominance.[117]

III. Clinical Findings

A. CLINICAL PRESENTATION

Cases of ICK may be asymptomatic or present with the symptoms of keratitis: a decrease in visual acuity, photophobia and pain.[23, 102] Conjunctival injection and adjacent inflammation may be less prominent compared with typical microbial keratitis, due to the indolent nature of the organisms and concurrent use of topical corticosteroids.[86] Many cases present with a recent history of epithelial disturbance or an epithelial deficit present at the time of examination.[128] Clinically, ICK has a number of phenotypes. Classically it is characterized by an insidious infiltration of white or grey opacities within the corneal stroma, appearing as stellate or branching fern-like opacities (Figure 1 and 2).[21, 48, 55, 126] Atypically they may develop into amorphous lesions or be associated with satellite lesions that appear to be related to treatment and cessation of topical corticosteroids.[21, 48, 55]

The microbial colonies commonly aggregate in the anterior or mid-stroma, although have also been reported in the posterior corneal stroma.[76, 101] The reason for the predilection in the anterior stroma is unknown; however, it is likely multifactorial. Seeding of bacteria by penetrance through the epithelium and Bowman membrane would favor anterior bacterial colonization.[59] The more advantageous environment and improved oxygen gradient of the anterior stroma was also proposed by Samples et al[110] as a contributing factor and perhaps correlates with the involved microorganisms relatively lower virulence. There are four reported positive cultures from posterior stroma ICK.[53, 89, 103] All were facultative anaerobes, likely more suited to the lower oxygen content of the posterior stroma. ICK can also appear in the form of an annular corneal opacity as occurred in a case related to a contact lens associated epithelial defect.[86] The epithelial defect progressed despite three months of broad-spectrum topical antibiotics and corticosteroids, and a corneal scraping cultured *Streptococcus mitis.*[86]

Endophthalmitis as a complication of ICK was reported in a 19-year-old male with a history of Stevens-Johnson syndrome in childhood.[135] Small crystalline opacities were identified in the corneal stroma after multiple corneal transplants and were associated with anterior chamber material and a significant deterioration in visual acuity. Anterior paracentesis culture grew *Mycobacterium abscessus*; however, despite intravitreal antibiotics, extensive surgeries including a vitrectomy and further grafting, the eye was eventually lost. Endophthalmitis after ICK has also been reported with *Staphylococcus epidermidis*[46] and *Candida tropicalis*.[90, 138]

B. DIFFERENTIAL DIAGNOSES

Conditions mimicking the appearance of ICK are shown in Table 1. In order to differentiate these conditions, a thorough medical history needs to be taken , including the possibility of gout and multiple myeloma.[15, 45, 96] Topical medications should also be recorded as they may cause crystalline deposition in the superficial corneal stroma.[105] A history of an epithelial defect, including surgical procedures, and topical corticosteroids are important in considerations.[126] Ophthalmic examination must exclude corneal dystrophies and infective keratitis.[92, 145] The needle-like branching opacities and an absence of corneal or anterior segment inflammation are important clinical signs for a diagnosis of ICK.[126]

Graft rejection may appear similar to ICK, with immune complex crystals being deposited in the posterior cornea.[81, 91] James et al[59] proposed that the depth of the crystals may assist with differentiation; however, this is not an absolute as ICK has been found at the posterior cornea.[53, 89, 103]

Laboratory investigations will depend on clinical suspicion of other differential diagnoses and may include a complete blood count, blood urea, nitrogen, creatinine and electrolytes, protein electrophoresis, uric acid, and white cell cystine level.[15, 45, 96]

IV. Pathophysiology

A. HISTOPATHOLOGY

Examination of ICK cases revealed consistent distinct features. Microorganisms form dense colonies within the interlamellar spaces, shaped as distended spindles.[21, 46] The colonies dissect the lamellar planes, preserving the structure of adjacent lamella and keratocytes, without necrosis or thinning.[21] Commonly, they are described as confining to a single lamellar plane; however, they can be spread across multiple planes.[128] Where erosion of the lamella occurs, filamentous projections pass through the bacterial colonies.[21] (Figure 3). There are small numbers of inflammatory cells surrounding the microorganism colonies, without inflammatory cells infiltrating the colonies. Polymorphonuclear cells are also in small numbers, despite a thick complement coating of the bacterial colonies, reflecting impairment of phagocytosis.[21] In contrast, other cases of infectious keratitis have a high number of inflammatory cells, including polymorphonuclear cells and lymphocytes, and microorganism cell walls are coated with complement factors. This comparison highlights the importance of the biofilm in the pathogenesis of ICK and its contribution to the impaired phagocytosis.

B. CRYSTALLINE APPEARANCE

The nature of the crystalline opacity was originally thought by Reiss[106] to be attributable to the bacterial colonies, where the lamellar planes and crisscrossing cell bodies, represent a path of least resistance for expansion of the colonies. This pattern can be replicated by injection of air into the corneal stroma and appears to be the accepted theory.[137] Electron dense bodies were identified by Samples et al[110] that had needle-like projections. They hypothesized that these may have been responsible for the crystalline appearance; however, given the size of the structures, this was thought to be unlikely.

The crystalline pattern commonly associated with ICK is a fine arborescent white crystalline distribution; however, amorphic collections have also been reported.[128] The characterization of the crystalline pattern does not correlate with a particular organism, although it does appear to correlate with immunosuppression and lamellar alignment.[86, 128]

ICK is recognized as a pauci-inflammatory infection of the eye.[106] In rabbit corneas inoculated with *Streptococcus mitis*, McDonnell et al inoculated five corneas with concurrent immunosuppression, while two others were not immunosuppressed.[86] They showed that inoculation associated with localized immunosuppression produced a crystalline appearance with minimal associated inflammation, while those without immunosuppression developed a poorly defined central opacity with surrounding stromal edema and inflammation.[86] This would suggest that the ICK entity is within the spectrum of infectious keratitis and not a separate condition.

Butler et al[18] investigated the crystalline pattern of ICK by testing the development of the infections in compact cornea tissue versus turgid corneal tissue. It was found that the ICK pattern developed in the compact corneal tissue inoculated with either *Streptococcus viridans* or *Klebsiella oxytoca*, while in the turgid corneal tissue, amorphic, globular bacterial colonies developed.[18] This suggests that the lamellar architecture, contributes to the formation of the ICK clinical pattern.[18] Intralamellar fibrils run parallel, except at lamellar branches.[72] Horizontal branching can occur at all depths through the stroma, while antero-posterior branching only occurs within the anterior stroma.[72] Early reports of ICK commonly described the infiltrate in the anterior to mid stroma; however, posterior stromal infiltration may occur and intraocular spread is possible.[76, 91] The appearance of the crystalline structure would be expected to follow the lamellar pattern and would be different depending on the depth of the opacities. These findings were also mirrored in a review by Sutphin et al[128] who found both of these appearances on confocal microscopy of corneal tissue. Contrasting to earlier reviews, they found that the bacterial colonies occurred across several lamellar planes, with none of their cases showing restriction to a single tissue plane.[128] The findings on confocal microscopy and at the slit lamp did not correlate with the pathogen or treatment undertaken.[128] The use of confocal microscopy to evaluate early ICK cases by this group highlights that there is an expanding role for technology, including anterior segment optical coherence tomography, to assist with the diagnosis of suspected early ICK, particularly in atypical cases.[51, 74, 94]

C. BIOFILM

Classically, a biofilm refers to a community of microbes that are adherent to a surface and held together by an extracellular matrix composed of polysaccharides, proteins, and DNA.[12] The cells are interfaced and phenotypically sessile compared with their planktonic counterparts that can initiate a biofilm when they adhere and recrudesce when they detach from the community.[12]

Eukaryotic life has a multitude of tightly regulated mechanisms within the innate and adaptive immune system to promote symbiotic and inhibit pathogenic reactions.[12, 148] Prosthetic devices lack similar defenses making them an ideal nidus for pathogens and biofilm formation.[147] Examples include ocular infections with punctual plugs,[144] scleral buckles[52] and intraocular lenses.[27] Opportunistic pathogens can initiate biofilms on host tissue despite

local immune responses--notably in patients with cystic fibrosis developing a *Pseudomonas aeruginosa* infection;[121] *Escherichia coli* in uroepithelium;[122, 6] and oral dentition affected by resident microbial flora.[79]

The ability to produce a biofilm within the corneal stroma appears to contribute to the development of ICK and is reported with corneal sutures in early ICK cases.[48, 59] Biofilm production is also found in bacterial colonies within the corneal lamellae without any prosthetic devices.[21, 43]

Hunts et al[58] infected rabbit corneas with *Streptococcus sanguinis* type II, grown either in brain-heart infusion or sucrose enriched brain-heart infusion. They proposed that exopolysaccharide development generated in a greater volume by bacteria from a sucrose-rich environment would contribute to the development of ICK.[58] Within 24 hours the corneas inoculated with bacteria from the sucrose enriched solution, 71% (10 of 14) had developed ICK, while only 25% (3 of 12) developed ICK in the other arm ($p = 0.05$).[58] By 72 hours, all lesions had developed into a suppurative infection with significant inflammation.[58] Examination for mucopolysaccharide showed that, in the ICK lesions, there was an intense staining for exopolysaccharide that prevented inflammatory cell infiltration;[58] however, exopolysaccharide production was greatly reduced in the suppurative lesions, with an increased rate of neutrophilic infiltration causing subsequent streptococcal degeneration and surrounding tissue necrosis.[58] Similar results have been found by histopathological, electron microscopic, and confocal microscopic examination of both ICK and infective keratitis.[21, 43, 77] They confirmed the role of biofilm production in ICK and can be distinguished from infective keratitis by impaired inflammatory response, with less infiltration of lymphocytes, macrophages and polymorphonuclear cells with impaired complement-mediated phagocytosis.[21, 43]

The initial surface adherence between pathogen and lamellar cell wall is attributed to electrostatic interaction.[12] Although unconfirmed, this may contribute to the predominance of some bacterial species over others in the formation of ICK. The lamellar separation creates an environment with surfaces onto which planktonic microbes may aggregate and irreversibly adhere.[36, 95] The graded availability of resources across the biofilm can also reduce bacterial replication, with estimates ranging from a reduction of five to 15 times slower than the planktonic bacteria and may contribute to their indolent nature.[27, 13, 38, 122, 42] The same principle affects microbial treatment, with pathogens near the periphery being more susceptible to antimicrobial agents than those in the center of the colony.[40] Concentrations of 10 - 1000 times that required to have the same effect as on organisms without a biofilm.[29]

Fungal species may also produce biofilms, with Elder et al reporting on a case of a male patient with Stevens-Johnson syndrome causing bilateral ocular surface disease.[36] ICK developed in the penetrating keratoplasty originating from a suture track. Initial corneal scrape results were negative and despite topical therapy, at six months the keratopathy had progressed, requiring a repeat penetrating keratoplasty. Cultures of the excised corneal button were positive for *Candida albicans*. Additional electronic microscope examination demonstrated a coat of polysaccharide-rich glycocalyx.

The variety of microorganisms that are able to cause ICK indicates a common pathogenesis. The underlying principles appear to be the formation of bacterial colonies within the lamellar spaces, resulting in the crystalline appearance.[21, 128] The indolent nature of ICK is likely multifactorial and may be attributable to intrinsic microbial factors and their ability to produce a biofilm, use of topical corticosteroids and whether the environment of the corneal stroma is inimical to pathogen replication.[18, 43, 86]

V. Etiology

ICK does not occur as a primary corneal disease,[117] but arises as a complication following an epithelial defect from a surgical procedure, as well as other non-surgical causes.[126] The microorganism proliferation in ICK is potentiated by localized immunosuppression that contributes to the appearance of ICK.[86]

A. LOCAL IMMUNOSUPPRESSION

The most common form of localized immunosuppression is topical corticosteroids; however, other sources have been shown to contribute to the pathogenesis and need to be considered as predisposing factors for ICK.[53, 86, 123]

Localized immunosuppression in a case where intravitreal and sub-tenon triamcinolone was used has been shown to be associated with ICK development.[53] This case underwent a complicated cataract extraction with anterior vitrectomy and subsequent cystoid macular edema. Repeated intravitreal and sub-tenon triamcinolone injections were administered and ICK developed appearing as a tri-lobed, anterior stromal crystalline infiltrate. Cultures returned positive for *Streptococcus viridans*.

Systemic immunosuppression also provides an environment for the development of ICK. A 51-year-old woman was receiving dexamethasone 4mg three times daily, concurrently with docetaxel and trastuzumab, for

metastatic breast cancer.[124] She misused short wear contact lenses for extended periods and developed an epithelial defect that subsequently lead to the development of a central infiltrate with crystalline projections within the corneal stroma. Burnette et al[17] reported a case of a neonate born with Turner syndrome who died at age 18 days from staphylococcal sepsis and subsequent medical complications. ICK was evident bilaterally on the inferior superficial cornea at autopsy.[17] Microscopic examination revealed a completely absent epithelium and gram-negative rods populating the interlamellar spaces, with minimal inflammatory response or adjacent destruction. There was no record of topical or systemic corticosteroids; however, it is likely immunosuppression was an etiological factor in this patient.[78, 104, 143]

Brooks et al[14] reported a 37-month-old male that underwent corneal grafting with an epikeratophakia procedure for unilateral aphakia. Post-operatively, the graft failed to re-epithelialize, and no topical corticosteroids were used. One week later, the cornea developed a diffuse stromal haze, however was lacking the focal infiltrates of typical ICK. Subsequently, the patient had to be re-grafted, with cultures taken at the graft-host interface demonstrating *Streptococcus viridans* and aerobic diphtheroids. Histopathology identified minimal inflammatory cells that did not infiltrate into the bacterial colonies. They hypothesized that the lyophilized tissue of the graft provided the environment for initial bacterial colony formation.[1] The lack of local immunosuppression, without the typical focal branching patterns makes this an atypical presumed ICK case.

B. SURGICAL

Corneal surgery is a predisposing factor, particularly penetrating keratoplasty (Table 2).[48, 87, 110] The high association is attributable to the presence of both etiological risk factors, with epithelial defects around the surgical incision and suture tracks, as well as local immunosuppression with topical corticosteroids administered to prevent graft rejection post-operatively.[48, 87]

Other ophthalmic surgery has also been associated with the development of ICK. ICK was reported in a 68-year-old woman who underwent bilateral lamellar keratoplasty for corneal perforation.[24] Ten months post-operatively, a filamentous branching opacity was observed subsequent to suture removal in the left eye that resolved after superficial keratectomy and topical antibiotics for two weeks. We have also observed a case of ICK occurring six weeks following an endothelial keratoplasty in a 68-year old woman (Figure 4).[103] Topical antibiotics partially controlled the infection, with a subsequent penetrating keratoplasty undertaken to completely remove the infection. *Enterococcus faecalis* colonies were identified in the graft interface. Post-operative endophthalmitis complicated the procedure requiring a vitrectomy to resolve the infection.

Corneal cross-linking has been shown to have low rates of complications in patients over 18-years of age; however, in younger patients outcomes may be less favorable.[72, 19, 20] Steinwender and coworkers,[125] in a series of 133 patients, identified a case of ICK occurring three weeks after a cross-linking procedure in a 16-year-old. They suspected that the inoculation may have occurred shortly after the procedure prior to the epithelium completely healing.

Laser in situ keratomileusis (LASIK) has also been linked with the development of ICK. Alvarenga et al[5] presented three cases of ICK complicating LASIK procedures, all caused by *Mycobacterium chelonae*. First signs of ICK commenced 15 – 20 days after the procedure despite all patients being on tobramycin and dexamethasone. Two of the cases did not resolve until the flap was excised despite intensive topical and oral antibiotics. The third case required two penetrating keratoplasties and a further lamellar keratoplasty. These cases demonstrate the potentially aggressive nature of ICK. Verma et al[136] also reported on a case of ICK after LASIK, with the initial symptoms starting three weeks after the operation. Anterior chamber inflammation was evident in this case.[136] Corneal flap scraping was undertaken and topical vancomycin 5% added to the tobramycin.[136] Progression of the infection occurred with flap melting, and a penetrating keratoplasty was consequently performed. Cultures showed growth of an Alternaria species, prompting the addition of natamycin 5% to the treatment regime, without any further signs of recurrence. Del Valle et al[32] reported a case of Achromobacter causing ICK, four months after a LASIK procedure. Initially this was treated with fortified vancomycin and amikacin, however ultimately required a penetrating keratoplasty to remove the infection.

Pterygium excision is an uncommon predisposing risk factor for ICK, with a case in a 65-year-old woman.[112] A large dense crystalline aggregate was present over the previous surgical site, reported to have insidiously developed over the year following the pterygium removal. Penetrating keratoplasty was performed, identifying *Streptococcus viridans* as the responsible pathogen and with concurrent topical antibiotics the infection completely resolved.

ICK originating from a phacoemulsification incision, with branching midstromal opacities was reported by Ferrer et al.[41] A corneal biopsy revealed no evidence of inflammatory cells.[41] They used polymerase chain reactions to identify *Candida parapsilosis* and *Staphylococcus aureus* as the causative agents.[41] A similar case described by

Servat et al[114] had a *Mycobacterium chelonae/Mycobacterium abscessus* complex causing ICK and eventually corneal perforation.

Trabeculectomy operations have been reported to be associated with ICK, Patitsas et al[99] cultured *Streptococcus viridans* in a patient who previously underwent a trabeculectomy with 5-fluorouracil. Apel et al[8] reported a similar case in a non-insulin dependent diabetic woman in which a variant of streptococcus was isolated in corneal cultures. The crystalline deposits resolved with topical therapy. 5-fluoroacil exposure was proposed in the pathogenesis of the first case while in the second case where 5-fluorouracil was not used, the diabetes may have been a contributing factor.

C. NON SURGICAL

Topical anesthetic abuse can cause epithelial damage, progressing from a punctate keratitis to complete epithelial loss.[142, 99] ICK related to this has been reported, with Kintner et al[69] describing two cases. In the first case, the topical anesthetic abuse had been persistent for three months with multiple stromal infiltrates. Initial cultures were negative, with a corneal biopsy performed two weeks later being positive for *Streptococcus viridans*. Six months later, the crystalline infiltrate had resolved, however the patient ultimately required a penetrating keratoplasty.[69] The second case had a shorter onset, presenting three days after a fingernail abrasion on the cornea. One month later, there was a rapid deterioration in visual acuity and a crystalline infiltrate was noted, with *Streptococcus viridans* identified on corneal biopsy.[69] They hypothesized that the topical anesthetic drops may alter the immunologic response of the cornea, as there was no record of topical corticosteroids in the second case.[69] The infiltrate in this patient changed rapidly from a branching ICK pattern to a suppurative confluent pattern consistent with infective keratitis, reflecting the increase in virulence of the bacteria and lack of immunosuppression .

D. ACANTHAMOEBA

Acanthamoeba keratitis has also been associated with numerous ICK cases. Davis et al[31] reported two cases of ICK complicating acanthamoeba keratitis both of which were initially presumed to be herpes simplex keratitis for three and twelve months respectively. In both cases, an annular stromal ICK developed after prolonged topical corticosteroid use. Acanthamoeba and alpha-hemolytic Streptococcus were identified in the corneal buttons following penetrating keratoplasty. This was complicated by recurrent infection in both cases.

In a separate review by Mathers et al,[83] they identified a case in a 62-year-old male, who developed acanthamoeba keratitis after wearing contact lenses whilst swimming and required penetrating keratoplasty.[83] This was complicated by *Streptococcal viridans* ICK.[83] Fortified antibiotics did not resolve the infection that required subsequent re-grafting. Tu et al[133] presented three cases where acanthamoeba keratitis was complicated by ICK as early as one week after diagnosis. They reported that all cases of ICK occurred subsequent to treatment targeting acanthamoeba, which led them to hypothesize that an endosymbiont relationship was present between the organisms causing ICK and acanthamoeba. This temporal relationship is in alignment with the case reports discussed in the earlier literature.[25, 83]

In ICK complicating acanthamoeba keratitis, the microorganisms responsible for ICK must have the property of being resistant to acanthamoeba.[68, 11] An amoeba-resistant microorganism is able to enter and multiply within its host.[68, 11] Expulsion would occur through vesicle release, or upon treatment, lysis of the acanthamoeba cyst, resulting in release of the internalized microorganisms.[68, 11] The lysis of acanthamoeba would result in rapid infection in the deep stroma where the acanthamoeba had been residing. This appearance also occurred in the cases identified by Tu et al,[133] supporting the hypothesis. Concomitant ICK presented with advanced disease and has been associated with significant stromal loss and subsequent scarring.[133, 25, 30, 83]

E. ORGANISMS

When ICK is suspected, the etiological pathogen can be determined through culturing of the infiltrate. Superficial corneal scrapings are often unsuccessful, as they may not reach the depth of the lesions and a corneal biopsy may be required to confirm the diagnosis.[61, 23] There is future potential for fine needle aspiration and polymerase chain reaction techniques to play a role in pathogen recognition and would avoid the need for more invasive corneal biopsy techniques.[51, 4]

A review of all the patients diagnosed with ICK at Cullen Eye Institute between 1978 and 1995 revealed 18 cases.[65] Of these, 10 cases had gram-positive cocci, five had gram-negative rods and three had positive cultures for fungi. There was no significant difference in the rates of predisposing factors, the clinical appearance or the final visual outcome.

There is a significant predilection for streptococci as the causative pathogen in the ICK cases.[87, 93, 106] The reason for this predominance is unknown as they are primarily found in the upper airway; however, their ability to produce mucopolysaccharides as a biofilm is considered to be an important factor.[58, 97] Further research is needed to elucidate the strong association with Streptococci and the other gram-positive bacteria including staphylococc*al*, gemella, and enterococcal species in ICK. [64, 130, 37, 34]

Table 3 shows the microorganisms cultured in the literature to date. The number of causative pathogens has considerably broadened since first being described and reflects the necessity for early investigation to direct appropriate microbial treatment.[126] Low virulent microorganisms are commonly associated with ICK, however more virulent bacteria have been reported more recently.[43] More than one causative organism may be present, and if deterioration continues despite treatment, other organism sensitivities should be considered.[62]

VI. Treatment

A. MEDICAL THERAPY

It is important to remember the pathophysiology of ICK when considering treatment options. First line management of ICK is topical broad-spectrum anti-microbial therapy that is then tailored according to sensitivities.[106] Topical antibiotics may be fortified, to improve bioavailability across the biofilm surrounding the bacterial colonies.[87] Antibiotic penetration is good across the cornea; however, will be reduced in the context of the biofilm surrounding the microorganisms in ICK.[66] Cessation of topical corticosteroids has been proposed and is thought to change the underlying infective process to a more suppurative mechanism.[66] This switch back to a labile pathogen thereby reduces the biofilm production and hence improves the bioavailability of the topical antibiotics.[66, 117]

Early and aggressive topical therapy may be sufficient to resolve the infection, as well as prevent vascularization and scar formation.[106] Where initial topical therapy is insufficient, alternative treatment modalities need to be considered, particularly those that target the biofilm. The use of intrastromal antibiotics is showing potential in the management of ICK and is thought to provide a higher concentration of antibiotics and contribute to biofilm disruption.[64, 2] Intrastromal cefuroxime was used with adjuvant corneal debridement in a patient who developed *Streptococcus parasanguinis* ICK.[64] Khan et al had a patient who had been placed on two weeks of topical levofloxacin without resolution. Cefuroxime was selected based on bacterial sensitivities, its availability as a preservative free solution, and because it was less toxic than vancomycin. Over the period of two months after the intrastromal injection, the ICK clinically resolved. Agahan et al[2] reported a patient who developed ICK two years after a re-suture for wound dehiscence of a penetrating keratoplasty. Intrastromal moxifloxacin was injected with concurrent topical moxifloxacin and prednisolone. After three days, the border of the corneal opacities had become more diffuse, with eventual resolution of the keratitis.

B. LASER

Laser to disrupt the microbial biofilm with concurrent topical antibiotics has been used in the management of ICK. Earliest cases used excimer laser, initially in animal models and then later on human corneas, with good effect.[35, 49, 113] Eiferman et al[35] used a 193nm argon fluoride excimer laser and performed a 25µm myopic ablation followed by a 25µm hyperopic ablation with a maximum diameter of 5.8 mm at 112mJ/cm^2 and were able to remove an infection without recurrence.

The use of Nd:YAG laser has also been effective in cases resistant to topical therapy. Three separate cases have described the use of Nd:Yag as an adjuvant therapy in ICK.[82, 28] Two of the cases resolved after one session; one received 30 shots of 3.1mJ and the other 30 applications of 3.2mJ.[82, 28] The third case complicated by immunosuppression underwent an initial session of 86 shots at 2.5-3 mJ (total energy 226mJ), and required a repeat treatment (total energy 525mJ) of photodisruption at six weeks due to recurrent ICK.[82] After the second treatment this patient had resolution at two months with a BCVA of 20/20.[82]

We have used adjuvant Nd:Yag in a 91-year-old woman with ICK treated with topical moxifloxacin (Figure 5a and b). Three sessions were undertaken: 1st 168 applications of 0.5mJ, 2nd 200 applications of 0.5mJ and 3rd 68 applications of 3mJ for a total energy of 388mJ, with the ICK resolving without recurrence.

Endothelial damage as a complication of the Nd:YAG laser treatment is thought to be unlikely, given that ICK is predominantly anterior in the corneal stroma.[28] Endothelial damage would be dependent on the power and number of shots used and also the distance from the target to the endothelium.[63, 80] Femtosecond LASER modalities may allow for precise excision of bacterial colonies in ICK, with sparing of unaffected tissue, and have been used as novel treatment in a multi-resistant keratitis case.[115]

C. SURGERY

Surgical excision of the infiltrated tissue may be required in cases of recalcitrant keratitis.[23, 117] Sharma et al[117] reported that more than 50% of ICK cases required a penetrating keratoplasty to control the infection. The result after the penetrating keratoplasty is mostly good; however, a recurrence of ICK or keratitis with the same or different pathogens may occur, so continuation of intensive topical antibiotics and close follow-up is needed post-keratoplasty.[130]

The corneal specimen can be divided into halves for histopathological and microbiological examination. The underlying principle of surgical management is to clear completely the involved cornea while sparing as much normal tissue as is feasible.[7, 116] There are no studies comparing the success of lamellar versus penetrating keratoplasty in ICK cases; however, it would seem that for superficial to midstromal lesions, it may be possible to perform a deep anterior lamellar dissection. Deeper lesions, however, necessitate penetrating keratoplasty to remove the infection.[55, 117] In the case of ICK after a Descemet stripping endothelial keratoplasty, a penetrating keratoplasty was required.[103] This was similar to the other cases of posterior ICK who also ultimately underwent a penetrating keratoplasty.[76, 91]

As a majority of ICK occurs in existing keratoplasties, management often involves trephination of the graft-host interface.[23, 117] If the ICK involves the host corneal rim, a larger graft and/or eccentrically positioned graft may be required.[9, 116] There may be a role for intraoperative anterior segment optical coherence tomography (OCT), to assist with lamellar corneal transplantation for ICK, ensuring that the infiltrates are completely excised.[51, 70, 94]

D. TREATMENT OUTCOMES

In the published literature, bacterial (including atypical) ICK is the most common, accounting for 98 cases (73.7%), with 12 cases of fungal (9%) and 6 cases of acanthamoebal ICK (4.5%). (Table 4). There were 17 cases (12.8%) where the microorganism responsible was not specified. There is a publication bias with these numbers, where authors will be less likely to publish already described organisms and cases where the treatment outcome has been unsuccessful. Topical treatment was used in all cases of atypical, fungal, and acanthamoeba ICK; however, in bacterial ICK and where an organism was not specified, there are some cases where the topical treatment was not recorded.

Acanthamoeba causing ICK is associated with poorer final outcomes and have the highest rate of penetrating keratoplasty (66.7%) Fungal and mycobacterial cases of ICK appear to have better resolution with treatment, although 50% of the fungal cases underwent a penetrating keratoplasty compared with 28.6% of the mycobacterial cases. In bacterial cases, 35.8% underwent a penetrating keratoplasty while the rate was 17.6% where an organism was not specified.

All of the cases resolved in the atypical and fungal ICK. This was lower in the bacterial ICK (83.5%), no specified organism (82.4%), and acanthamoeba (66.7%) ICK cases. There were three cases with recurrent infection and also graft rejection or persistent edema. One patient died unrelated to the ICK, and another developed a phthisical eye. Two patients were lost to follow up, and ten cases did not record the outcome of the case.

VII. Conclusion

Our understanding of ICK has been expanding. The predetermining factors, pathophysiology, and the role of biofilm have been well-documented; however, more research is needed. Presentation and diagnosis may still be delayed, resulting in more advanced disease with poorer outcomes. We hope our review will educate clinicians so that they identify pathology sooner and improve patient education in regards to risk factors. Improved delivery of antimicrobials to the site of ICK should increase the efficacy of medical treatment. The increasing use of lamellar corneal surgery and the reduced need for prolonged steroids should reduce the incidence of ICK; however, there will remain indications for penetrating keratoplasty, and the risks for ICK will continue.

Statement of Literature Search

Research Question
What is the current evidence base for infectious crystalline keratopathy?

Aims:
1. Identify all articles discussing infectious crystalline keratopathy
    - Investigate the current pathophysiology and histopathology from the current evidence base
    - Identify features for the diagnosis of infectious crystalline keratopathy

- Investigate all pathogens and predisposing factors
- Investigate all treatment options in regards to infectious crystalline keratopathy

Literature Review

On the 10 August 2016, a literature review was undertaken to answer the aims addressed by the research question.

Search Structure:

1. Infectious AND crystalline AND ('keratopathy'/exp OR keratopathy)
2. arborescent AND bacterial AND keratopathy AND ([Embase]/lim OR [Medline]/lim)
3. #1 or #2
4. ([Embase]/lim OR [Medline]/lim)
5. Language: (All)
6. Time span (<1966 – 2013)

A review of all of the identified abstracts was undertaken. A total of 93 unique abstracts were identified for inclusion in the literature review. 85 Articles were written in English, 8 articles were excluded because they were not relevant to the research question, leaving 77 articles as the final number for the literature review.

All articles were read and the references were cross-matched to identify 11 further articles that had not been recorded in the initial search and were included in the literature review. At final conclusion 88 articles were included in the literature review on infectious crystalline keratopathy.

Disclosure

The authors whose names are listed on this article certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

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Figures

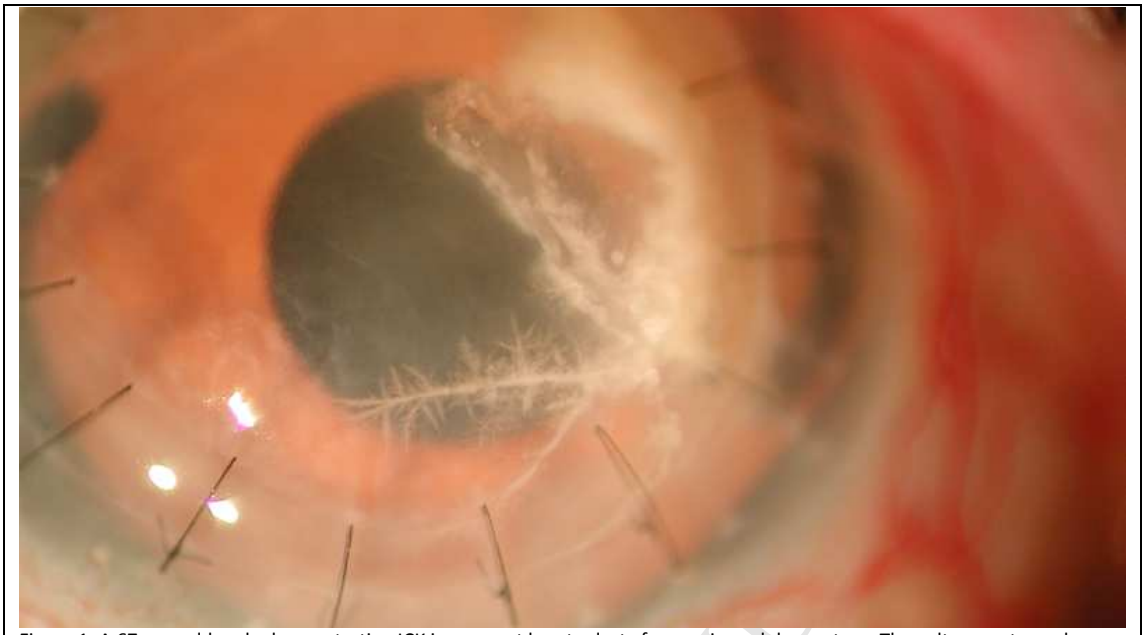

Figure 1. A 67 year old male demonstrating ICK in a repeat keratoplasty for previous globe rupture. The cultures returned positive for *Serratia liquefaciens*. The ICK settled on intensive topical and oral ciprofloxacin.

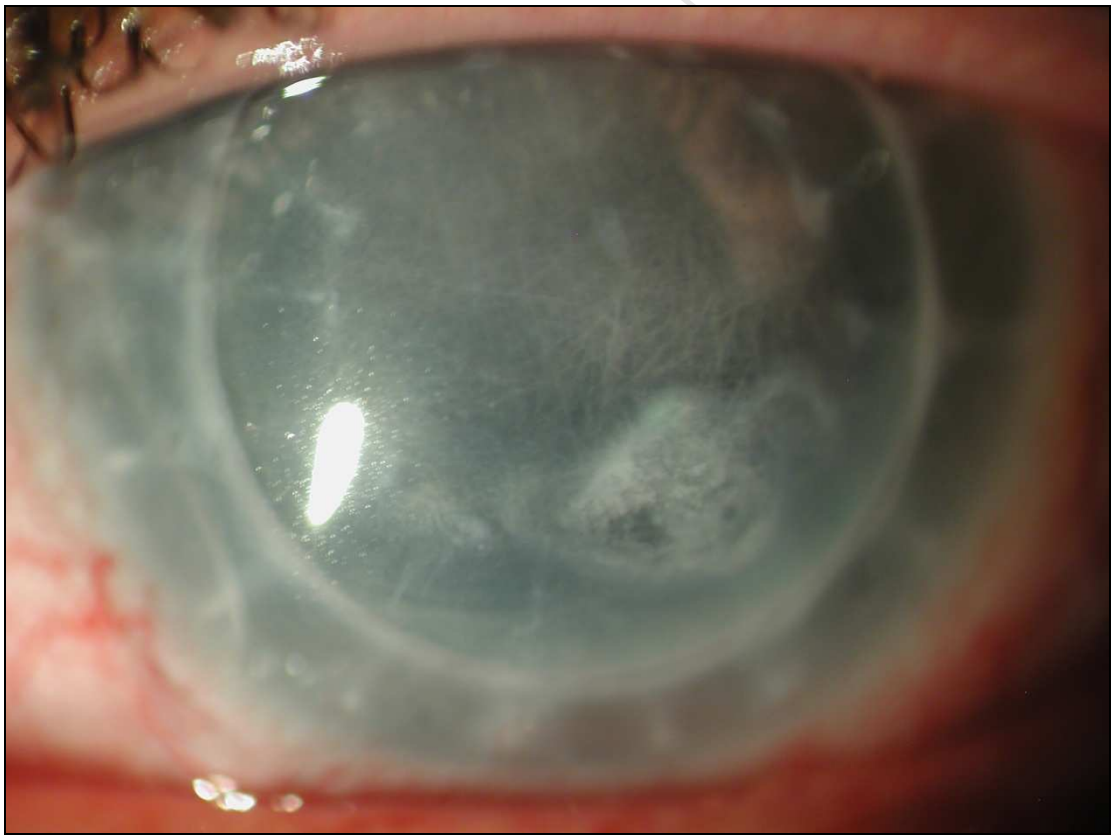

Figure 2. A 19 year old male with ICK after a penetrating keratoplasty for corneal scarring due a penetrating eye injury. A repeat penetrating keratoplasty was undertaken. Cultures returned positive for *Streptococcal sanguinis*.

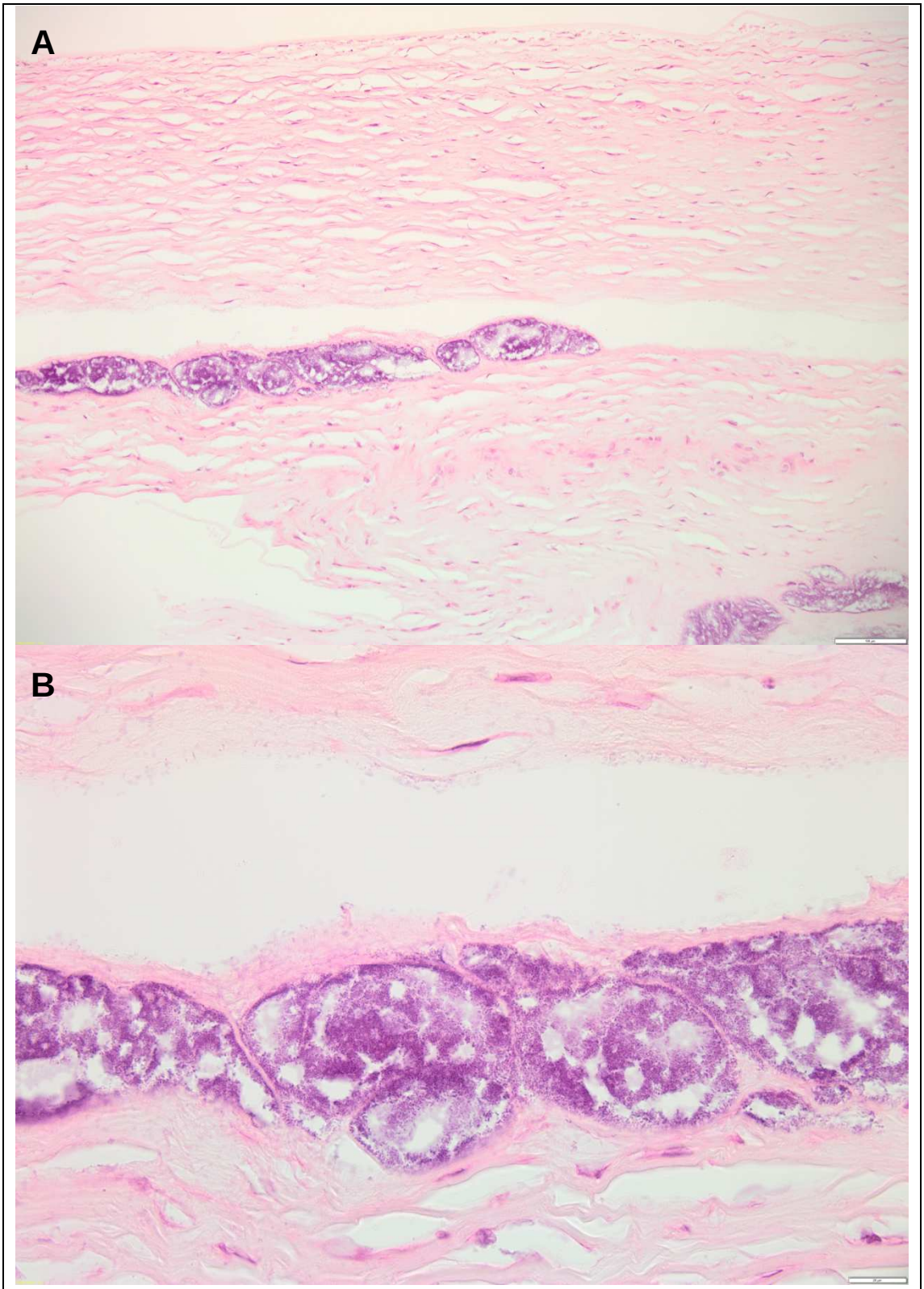

Figure 3a and b. Gram-positive cocci colonies in the interlamellar spaces of a corneal button, with minimal associated surrounding inflammatory reaction. (Hematoxylin and eosin stain, original magnification 300X)

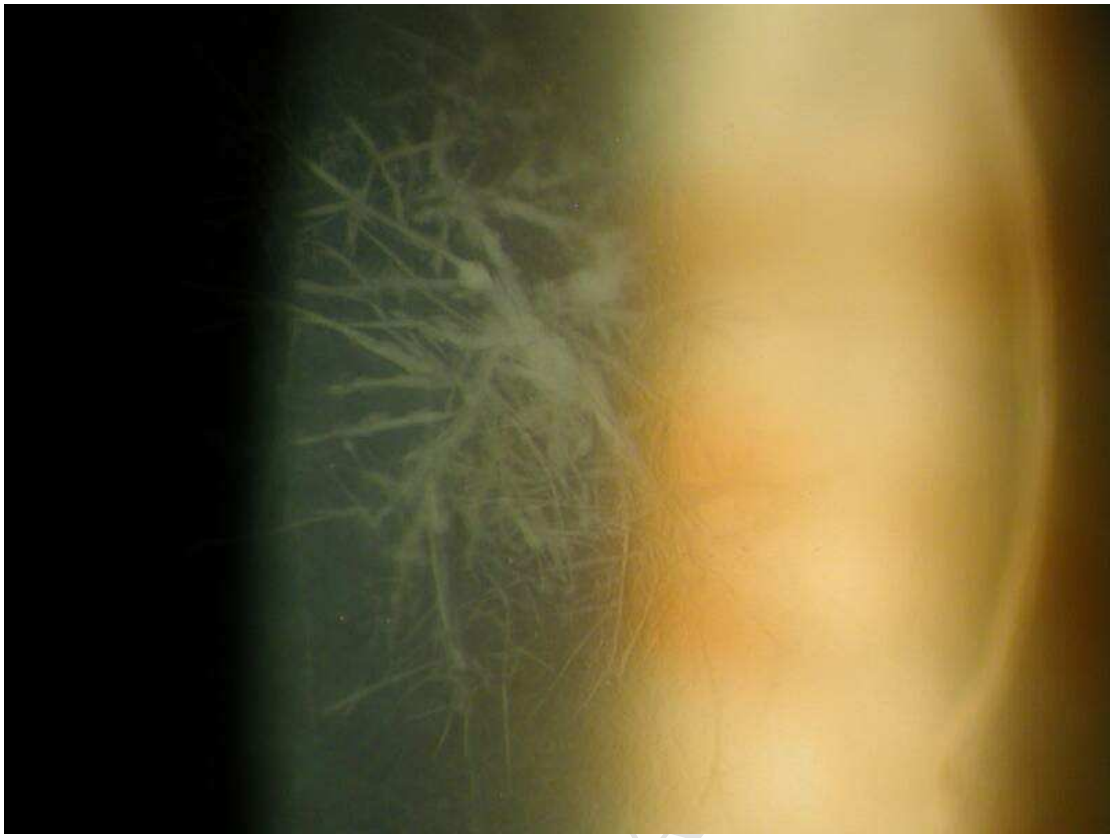

Figure 4. A 68 year old female with ICK occurring six weeks following an endothelial keratoplasty. Topical antibiotics partially controlled the infection, with a subsequent penetrating keratoplasty undertaken to completely remove the infection.

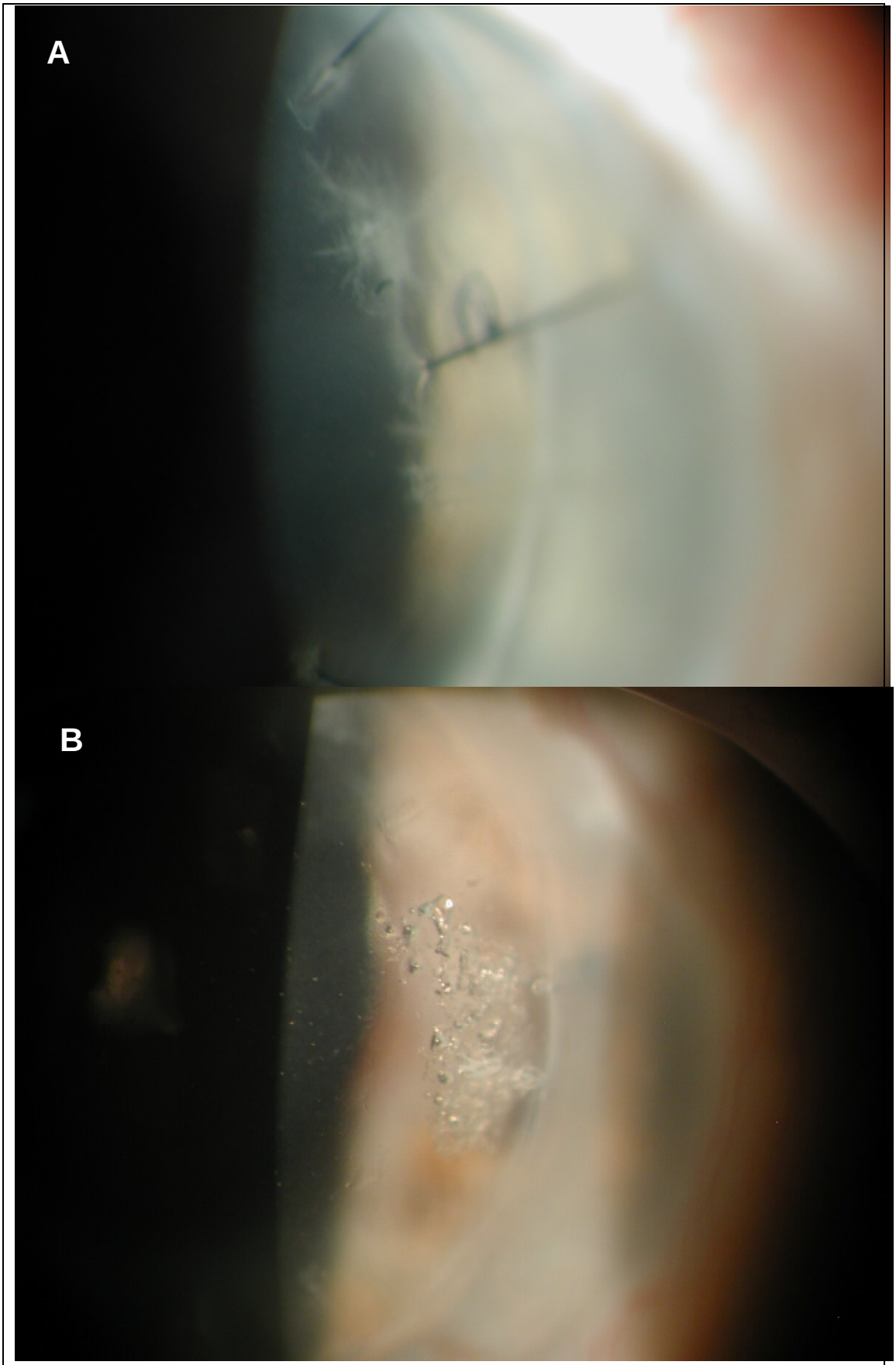

Figure 5A and B. A 91 year old female who had previously had two penetrating keratoplasties, developed ICK. Topical moxifloxacin six times a day and dexamethasone 0.1% three times daily were commenced. Adjuvant Nd:YAG laser was applied to the crystals over three sessions (168 x 0.5mJ, 200 x 0.5mJ, 68x 3mJ) for a total energy of 388mJ. The infection resolved without recurrence.

Table 1: Differential diagnoses of ICK

Differential diagnoses	Crystal pattern
Graft rejection	Graft rejection may appear similar to ICK, with immune complex crystals being deposited in the posterior cornea.
Schnyder corneal dystrophy	Rare autosomal dominant dystrophy resulting in corneal cholesterol deposition in 54% of those affected.
Bietti corneoretinal dystrophy	Bietti corneoretinal dystrophy results in bilateral small yellow crystalline deposits in the superficial peripheral cornea and the retina.
Multiple myeloma	Bilateral circular immunoglobulin distribution as an annular centripetal crystalline opacity with perilimbal sparing.
Monoclonal gammopathy of indeterminate significance	Corneal opacities appear as small polymorphic deposits, with a diffuse stromal haze. They are deposited through all of the corneal layers, and are lustrous superficially and dull elsewhere.
Gout and Hyperuricaemia	Intracellular deposition of uric acid crystals into the epithelial cells and superficial stroma, appears as fine, brown, needle-like refractile crystals in the cornea.
Cystinosis	Rare autosomal recessive condition resulting in intracellular deposition of cysteine. Bilaterally highly refractile needle like opacities, start in infancy with anterior peripheral deposition and progress posteriorly and centripetally.
Lipid keratopathy	A disturbance of cholesterol and sphingomyelin metabolism in the cornea results in a yellow perilimbal pan-stromal infiltrate that can progress centripetally, and is often associated with stromal vessels.
Topical medications	Fluoroquinolone deposition results in small punctate crystals in the interpalpebral and inferior cornea. Clofazime can cause a linear fine brownish red line on the superficial inferior cornea, or deposit as multiple polychromatic opacities in the peripheral cornea. Gold salts can cause small punctate gold opacities in the superficial central cornea.

Table 2. The etiology, management and outcomes of Infectious Crystalline Keratopathy

Author	Patient demographics	Organism	Topical antibiotic (unless otherwise specified)	Significant History	Treatment procedure	Outcome
Gorovoy et al[48] 1983	69, Female	Gram positive cocci	1. Chloramphenicol 0.5% 2. Sulfacetamide 10%	PK	PK	Resolved
Meisler et al[87] 1984	83, Male	Not identified	1. Fortified gentamicin 1.4% and bacitracin 400 units/g 2. Bacitracin/ neomycin/ polymyxin B 400 units/3.5 mg/10,000 units / g	PK		Resolved
	67, Male	Alpha-hemolytic streptococcus	1. Fortified gentamicin 1.4% and natamycin 5% 2. Cefamandole 1g BD and intravenous methicillin 1g QID 3. Fortified gentamicin 1.4% and penicillin G 333,000 IU/mL	Herpetic keratitis	Anterior keratectomy	Resolved
	44, Male	*Streptococcus viridans*	Bacitracin 400 units/g	PK	Keratectomy	Persistent edema
Samples et al[110] 1985	73, Male	Not identified	Miconazole nitrate 1%, cefazolin 5% and natamycin 5%	PK	PK	Resolved
Eiferman et al[34] 1985	83, Female	Peptostreptococcus	Unspecified	PK	PK	Resolved
Reiss et al[106] 1986	57, Female	*Streptococcus viridans*	Cefazolin 5%	PK	PK	Resolved
Dunn et al[33] 1986	31, Male	Gram positive cocci	Unspecified	PK	PK	Resolved
Nanda et al[93] 1986	78, Female	Beta-hemolytic Streptococci	Subconjunctival and topical gentamicin 0.3%	PK	PK, vitrectomy and lensectomy	Resolved
Davis et al[31] 1987	28, Female	Acanthamoeba and *Streptococcus viridans*	Dibrompropamidine 0.15% and paromomycin 2.5%	Acanthamoeba keratitis	PK	Recurred
	27, Male	Acanthamoeba and *Streptococcus viridans*	1. Miconazole 1%, natamycin 5%, neomycin sulfate 0.35% and oral ketoconazole 200mg BD	Acanthamoeba keratitis	PK x 2	Resolved
Groden et al[50] 1987	26, Male	*Haemophilus aphrophilus*	Cefazolin 5% and erythromycin 0.5%	PK		Resolved
Kincaid et al[67] 1987	70, Female	not identified	Chloramphenicol 0.5% and tobramycin 0.3%	PK	PK	Resolved
Mathers et al[83] 1987	62, Male	Acanthamoeba and *Streptococcus viridans*	Fortified cefazolin 5% and gentamicin 1.4%	PK and Acanthamoeba keratitis	PK	
Remeijer et al[107] 1987	54, Male	*Staphylococcus epidermidis*	1. Chloramphenicol 0.4%, neosporin 0.5% 2. Chloramphenicol 0.4%, neosporine 0.5% and trimethoprim 0.1%	PK	PK	Resolved
	68, Male	*Streptococcus viridans*	Chloramphenicol 0.4%	Herpetic keratitis		Resolved
	66, Female	Not identified	Cefazolin 5% and chloramphenicol 0.4%	PK	Keratectomy	Resolved
	79, Male	*Staphylococcus epidermidis* and *Streptococcus viridans*	Unspecified	PK	PK	Resolved
	63, Female	Not identified	Unspecified			Graft rejection, persistent edema
	70, Female	*Streptococcus viridans*		Herpetic keratitis		
	53, Male	*Staphylococcus epidermidis*		PK		Resolved
James et al[59] 1988	32, Male	Not identified	1. Penicillin 5,000 units/ml 2. Subconjunctival and topical gentamicin 0.3% and penicillin 5,000 units/ml	PK		Resolved
Watson et al[137] 1988	31, Female	Streptococcus		PK	PK	Resolved
		Gram positive cocci	1. Chloramphenicol 2. Penicillin 5,000 units/ml	PK	PK	Resolved
	65, Male	*Streptococcal viridans*	1. Chloramphenicol 2. Penicillin 5,000 units/ml	PK		Resolved
Weisenthal et al[138] 1988	85, Female	Alternaria	1. Amphotericin B 0.1% 2. Natamycin 5%	PK	PK	Resolved
	75, Female	*Candida tropicalis*	1. Cefazolin 5% 2. Amphotericin B 0.15% with oral ketoconazole 200mg BD	PK	PK	Resolved
Zabel et al[146] 1988	60, Female	*Streptococcus viridans*	1. Cefazolin 5% 2. Erythromycin 1% and vancomycin 5% with intravenous Penicillin G 3,000,000 units 6 hourly	Herpetic neurotrophic keratitis	Corneal biopsy	Resolved with scarring
Townshend et al[131] 1989	85, Female	*Streptococcus viridans*	Cefazolin 5%	PK		Resolved
Zabel et al[145] 1989	86, Female	*Acinetobacter calcoaceticus*	1. Penicillin G 100,000 IU/mL, tobramycin 1.5% and cefazolin 5% 2. Tobramycin 0.3%	PK		Resolved
Kintner et al[69] 1990	29, Female	*Streptococcus viridans*	1. Tobramycin sulfate 0.3% 2. Penicillin G sodium 333,000 units/ml	Anesthetic abuse	1. Corneal biopsy 2. PK	Resolved
	26, Female	*Streptococcus viridans*	1. Bacitracin ointment 500 units/mL 2. Gentamicin sulfate 1.4% and cefazolin sodium 3.2% 3. Penicillin G 333, 000 units/ml and erythromycin lactobionate 1%	Anesthetic abuse for abrasion	1. Corneal biopsy	Resolved
Burnette et al[17] 1990	17 day old, Female	Gram negative rods		Staphylococcus sepsis, No epithelium		Deceased
Lubniewski et al[76] 1990	75, Female	*Staphylococcus epidermidis*	Vancomycin 2.5%, neomycin/polymyxin B 1.75 mg/10,000 units/ mL	PK	PK, lensectomy and vitrectomy	Resolved
	83, Female	*Staphylococcus epidermidis*	Intravitreal vancomycin 0.1mg and gentamicin 0.2mg with vancomycin 3.3% and tobramycin 1.5%	PK	PK	Resolved
Pararajasegaram et al[101] 1990	48, Female	Gram positive cocci	Chloramphenicol 0.5%	PK	PK	Resolved

Sutton et al[129] 1990	76, Female	Gram positive cocci	Penicillin 100,000 units/mL and cephalothin 5% with intravenous penicillin 1g and cephalothin 1g QID	PK	PK	Resolved
Kincaid et al[66] 1991	75, Female	Gram positive cocci	Tobramycin 0.3% and chloramphenicol 0.5%	PK and corneal relaxing incisions	PK	Resolved
Ormerod et al[97] 1991	84, Female	*Streptococcus viridans*	1. Gentamicin 1.4% and cefazolin 1.3% 2. Tobramycin 1.4% and vancomycin 2.5%	PK	Corneal biopsy, cryotherapy, PK	Resolved
	68, Female	*Streptococcus viridans*	Gentamicin 1.4% and cefazolin 1.3%	Contact lens use	PK	Resolved
	81, Female	*Streptococcus viridans*	1. Miconazole 1% 2. Amphotericin B 0.15% 3. Cefazolin 1.3%	Extracapsular cataract extraction	Corneal Biopsy	Resolved
Patitsas et al[99] 1991	55, Female	*Streptococcus viridans*	Cefazolin 5%	Glaucoma filtering surgery	Corneal biopsy	Resolved
Wilhelmus et al[140] 1991	74, Female	*Candida albicans* and *Staphylococcus haemolyticus*	Amphotericin B 0.15% and cefazolin 5%, with oral ketoconazole 200mg BD	PK	PK	Resolved
	59, Male	*Candida albicans* and *Staphylococcus epidermidis*	Cefazolin 5% and amphotericin B 0.15% with oral ketoconazole 200mg BD	Keratoconjunctivitis sicca, radiotherapy and contact lens use		Resolved
Brooks et al[14] 1992	28 month old, Male	*Streptococcal viridans* and aerobic diphtheroids	1. Subconjunctival gentamicin and cefuroxime with fortified topical cefazolin 5% and gentamicin 1.4% 2. Fortified vancomycin 5%	Epikeratophakia	Graft excised	Resolved
Eiferman et al[35] 1992	68, Female	Not identified	Fortified vancomycin 5%	Contact lens use	Excimer LASER ablation	Resolved
Kaufmann et al[62] 1992	87, Female	*Streptococcus viridans*	1. Chloramphenicol 0.5% 2. Penicillin 100,000 units/mL	PK	PK	Resolved
McDonnell et al[86] 1992	41, Male	*Streptococcus mitis*	1. Cefazolin 5% 2. Penicillin 5,000 units/ml and erythromycin ointment 0.5%	Contact lens use	Corneal biopsy	Resolved
Lam et al[73] 1993	65, Male	*Enterococcus faecalis*	Fortified vancomycin 5%	Multiple penetrating keratoplasties	PK	Resolved
	88, Female	Enterococcus	Fortified vancomycin 5%	PK	PK	Resolved
Horsburgh et al[54] 1994	37, Male	*Streptococcus viridans*	Cefazolin 5%, gentamicin sulfate 1.5% and IV cephalothin 2 mg TDS and gentamicin 80mg TDS	PK		Resolved
	74, Female	1. *Hemolytic Streptococcus* 2. *Staphylococcus haemolyticus* and *Staphylococcus epidermidis*	1. Fortified gentamicin 1.5% and oral cephalosporin 500mg QID 2. Fortified gentamicin sulfate 1.5%, cephalothin 5% with oral amoxicillin 1g TDS and probenecid 500mg TDS	PK	Keratectomy and PK x 2	Resolved
Apel et al[8] 1995	73, Female	Streptococcus	1. Fortified cefazolin 5%, gentamicin 1.4% and neomycin/polymyxin B 1.75 mg/10,000 units/ mL 2. Vancomycin 3.3% and gramicidin/polymyxin B 0.025mg/ 10,000 units/ mL	Trabeculectomy		Resolved
Elder et al[36] 1996	45, Male	*Candida albicans*	1. Cefuroxime 5% and penicillin 5,000 units/ml 2. Clotrimazole 1%	PK		Resolved
Rhem et al[108] 1996	66, Male	*Candida parapsilosis*	Amphotericin B 0.15% and oral ketoconazole 200mg BD	PK	PK	Resolved
Morrison et al[91] 1997	90, Female	Gram positive cocci		PK	PK	Resolved
Sutphin et al[128] 1997	88, Female	*Staphylococcus epidermidis*	Vancomycin 2.5%	Ocular cicatricial pemphigoid	PK	Resolved
	81, Male	Gram positive cocci	Cefazolin 5%, vancomycin 2.5% and sulfacetamide 2%	Ocular cicatricial pemphigoid		Resolved
	95, Female	Not Identified	Cefazolin 5%	PK		Resolved
	69, Female	Not Identified	Sulfacetamide 2%, cefazolin 5%	PK		Resolved
	80, Female	*Staphylococcus aureus* and Corynebacterium	Cefazolin 5%, ofloxacin 0.3% and tobramycin 0.3%	Trabeculectomy, herpes zoster ophthalmicus		Resolved
	85, Male	Diphtheroids	Tobramycin 0.3% and cefazolin 5%	Herpetic keratitis		Resolved
	87, Male	*Staphylococcus epidermidis*	Sulfacetamide 2%	Contact lens use		Resolved
	72, Female	Coagulase negative Staphylococcus	Cefazolin 5% and vancomycin 2.5%	PK		Resolved
	63, Female	Not identified	Tobramycin 0.3% and ofloxacin 0.3%	PK		Resolved
	56, Female	Bacillus unspecified	Cefazolin 5%, ofloxacin 0.3% and tobramycin 0.3%	PK and keratitis		Resolved
	83, Female	Micrococcus unspecified and Coagulase negative Staphylococcus	Cefazolin 5%, tobramycin 0.3% and ofloxacin 0.3%	PK		Resolved
	90, Female	*Streptococcus sanguinis*	Cefazolin 5%	Acanthamoeba keratitis	PK	Resolved
	34, Female	Diphtheroids and Coagulase negative Staphylococcus	Cefazolin 5% and ofloxacin 0.3%	Neurotrophic ulcer		Resolved
	58, Male	Bacillus unspecified and Coagulase negative Staphylococcus	Cefazolin 5%, ofloxacin 0.3%, polymyxin B 10,000 units/mL and trimethoprim 0.1%	Alkali injury, PK		Phthisis bulbi
	27, Female	*Staphylococcus epidermidis* and *Propionibacterium acnes*	Cefazolin 5% and ofloxacin 0.3%	Neurotrophic ulcer		Resolved
	74, Female	*Streptococcus viridans*	Cefazolin 5%	PK		Resolved
Ainbinder et al[3] 1998	75, Male	*Candida guilliermondii*	1. Amphotericin B 0.15% 2. Topical fluconazole 0.2% and oral fluconazole 150 mg daily	PK	1. Lamellar biopsy 2. PK	Resolved
Matsumoto et al[85] 1998	64, Female	Candida unspecified	Sulbenicillin 50mg/bottle, cefmenoxime 0.5%, ofloxacin 0.3% and intravenous cefamandole 1g BD and flomoxef 1g BD	PK, astigmatic keratotomies	PK	Resolved

Daneshvar et al[28] 1999	52, Female	*Streptococcus viridans*	Fortified cefazolin 5%	Herpetic keratitis	Nd:YAG Laser 3.2 mJ x 30	Resolved
Uy et al[135] 1999	19, male	*Mycobacterium abscessus*	1. Intracameral amikacin 400µg x 2, topical amikacin 5%, oral azithromycin 1g BD and intravenous amikacin 300mg TDS	PK x 7	PK x 2	Resolved
Chua et al[24] 2000	68, Female	Not identified	Ciprofloxacin 0.3% and penicillin 5,000 units/ml with gentamicin ointment 0.3%	Lamellar corneal graft	Keratectomy	Resolved
Fulcher et al[43] 2001	63, Female	*Streptococcus viridans*	Penicillin 5,000units/ml	Herpetic keratitis	Keratectomy	Resolved
	92, Female			Corneal abscess	Evisceration	
	82, Female	Not identified	Fortified vancomycin 5%	Recurrent corneal ulceration	PK	Resolved
Sridhar et al[124] 2001	51, Female	*Streptococcus anginosus* and *Staphylococcus aureus*	Cefazolin 5%, tobramycin 1.4%	Systemic immunosuppression, superficial punctate keratopathy		Resolved
Sridhar et al[123] 2001	36, Male	*Staphylococcus epidermidis* and Corynebacterium	Ciprofloxacin hydrochloride 0.3%			Lost to follow up
	63, Male	*Pseudomonas aeruginosa*	Ciprofloxacin hydrochloride 0.3%			Persistent infection
Alvarenga et al[5] 2002	30, Male	*Mycobacterium chelonae*	Tobramycin 1.4%, Ofloxacin 0.3% and oral clarithromycin 500mg BD	LASIK	Flap excision	Resolved
	32, Female	*Mycobacterium chelonae*	1. Tobramycin 0.3% 2. Amikacin 5% 3. Amikacin 5% and clarithromycin 1% and ofloxacin 0.3%	LASIK	PK x 2 and lamellar keratoplasty	Resolved
	23, Male	*Mycobacterium chelonae*	1. Sulfacetamide 1.5% and ofloxacin 0.3% 2. Clarithromycin 1%, ofloxacin 0.3% and tobramycin 0.3%	LASIK	Flap excision	Resolved
Georgiou et al[47] 2002	81, Female	Coccal microorganisms	1. Ofloxacin 0.3% and penicillin 5,000 units/ml	PK	Keratectomy	Resolved
Touzeau et al[130] 2003	63, Male	1. *Streptococcus viridans* 2. *Candida albicans*	1. Fortified amikacin 5% and vancomycin 5% and rifamycin 10,000 IU/mL 2. Amphotericin B 0.15%	PK	PK	Resolved
Christakopoulos et al[21] 2003	73, Female	Gram positive cocci		PK		
	70, Female	Gram positive cocci				
	56, Male	Gram positive cocci				
	82, Female	Gram positive cocci		PK		Lost to follow up
	78, Female	Gram positive cocci		PK		
Gartaganis et al[46] 2004	73, Female	*Staphylococcus epidermidis*	1. Tobramycin 0.3% 2. Vancomycin 3.3% and tobramycin 1.5%	Corneal ulcer while using contact lens	PK	Resolved
Umapathy et al[134] 2005	44, Female	*Mycobacterium chelonae*	Amikacin 0.5% and amphotericin B 0.1%	Contact lens use		Resolved
	80, Female	*Mycobacterium chelonae*	1. Ciprofloxacin 0.3% and amikacin 2.5% 2. Ciprofloxacin 0.3%, amikacin 2.5%, moxifloxacin 0.5% and oral clarithromycin 250 mg BD	PK		Resolved
Servat et al[114] 2005	74, Male	1. *Staphylococcus epidermidis* 2. *Mycobacterium chelonae* and *Mycobacterium abscessus*	1. Vancomycin 5% and levofloxacin 0.5% 2. Vancomycin 5%, levofloxacin 0.5% and oral doxycycline 100 mg BD, with oral clarithromycin 500mg BD	Phacoemulsification	Corneal biopsy	Resolved
Verma et al[136] 2005	29, Female	Alternaria	1. Vancomycin sulfate 5% and tobramycin sulfate 1.4% 2. Ciprofloxacin hydrochloride 0.3% and natamycin 5%	LASIK	1. Flap revision 2. PK	Resolved
Osakabe et al[98] 2006	72, Female	Streptococcus	Cefmenoxime 0.5%, fluconazole 0.2% and micafungin 0.1%	PK	PK	Resolved
Hollander et al[53] 2006	75, Male	*Streptococcus viridans*	1. Fortified vancomycin 5% 2. Moxifloxacin 0.5%	Multiple ocular surgeries with subsequent edema	PK	Resolved
El Mallah et al[37] 2006	65, Female	*Gemella haemolysans*	1. Chlorhexidine 0.02% and dibrompropamidine 0.15% 2. Chlorhexidine 0.02% dibrompropamidine 0.15% and gatifloxacin 0.5% 3. Vancomycin 2.5%	Acanthamoeba keratitis/ PK		Resolved
Ferrer et al[41] 2006	63, Male	*Candida parapsilosis* and *Staphylococcus aureus*	Amphotericin B 1% and cefazolin 5%	Phacoemulsification		Resolved
Chen et al[22] 2007	70, Female	*Serratia marcescens*	Tobramycin 1.5% and vancomycin 2.5%.	PK	PK	Resolved
Connell et al[26] 2007	50, Male	*Haemophilus influenzae*	1. Penicillin 5,000 units/ml 2. Cefuroxime 1% and ticarcillin 0.5% 3. Ofloxacin 0.3%	PK x 2	PK	Resolved
Kailasanathan et al[61] 2007	51, Female	*Gemella haemolysans*	1. Cefuroxime 5%, ofloxacin 0.3% and acyclovir 400mg QID 2. Vancomycin 0.5% 3. Cefuroxime 5% and ofloxacin 0.3%	PK x 2 for herpetic keratitis	Corneal biopsy	Resolved
Del Valle et al[32] 2009	52, Male	Achromobacter species	1. Amikacin 0.4% and vancomycin 1.5%. 2. Ceftazidime 5%	LASIK	PK	Resolved
Masselos et al[82] 2009	36, Female	Not identified	1. Cephalothin 5% and gentamicin 0.9% 2.Vancomycin 5% and chloramphenicol 0.5%	Corneal ulcer while using contact lens	Nd:YAG 3.1mJ x 30	Resolved
	55, Male	Coagulase negative Staphylococcus	1. Cephalothin 5% and tobramycin 0.3%	Herpetic keratitis, chronic myeloid leukemia	Nd:YAG x 2, 525mJ total	Resolved
Tu et al[133] 2009	32, Male	Acanthamoeba and *Streptococcus oralis*	1. Propamidine isethionate 0.1% and Chlorhexidine gluconate 0.02% 2. Fortified vancomycin 1.5% and gatifloxacin 0.5%	Acanthamoeba keratitis	PK	Resolved
	38, Male	Acanthamoeba and *Streptococcus oralis*	1. Propamidine isethionate 0.1%, Chlorhexidine gluconate	Acanthamoeba keratitis		Resolved

			0.02% and oral voriconazole 200mg BD 2. Vancomycin 1.5% Q2H added			
	21, …	Acanthamoeba and *Staphylococcus aureus*	1. Cefazolin 5% and gentamicin 1.4% 2. Propamidine isethionate 0.1%, Chlorhexidine gluconate 0.02% and vancomycin 1.5%.	Acanthamoeba keratitis.		Resolved
Abry et al[1] 2010	83, Female	*Abiotrophia defectiva*	1. Ciprofloxacin 0.3% and vancomycin 5%	PK	PK	Resolved
Garcia-Delpech et al[44] 2010	23, Female	*Fusarium solani*	1. Tobramycin 0.3% and amphotericin B 0.15% 2. Tobramycin 0.3% and voriconazole 1%	Corneal cross linking	Corneal Grafting	Resolved
Jeganathan et al[60] 2010	52, Male	*Abiotrophia adiacens*	1. Vancomycin 5% and tobramycin 1.4% 2. Ciprofloxacin 0.3%	PK x 3		Resolved
Khan et al[64] 2010	84, Female	1. *Streptococcus mitis* 2. *Streptococcus parasanguinis*	1. Levofloxacin 0.5% 2. Intrastromal cefuroxime 0.025% and topical levofloxacin 0.5%	Ocular mucous membrane pemphigoid	Keratectomy. intrastromal antibiotics.	Resolved
Shtein et al[119] 2011	75, Female	Actinomyces	1. Fortified cefazolin 5% and gentamicin 1.5%	PK	PK x 2	Resolved
Chou et al[23] 2012	80, Female	*Klebsiella oxytoca* and Staphylococcus	Moxifloxacin 0.3% and fortified tobramycin 1.4%	PK		Resolved
Huerva et al[56] 2012	76, Female	*Enterococcus faecalis*	Fortified vancomycin 5%	Cataract extraction		
Sánchez Ferreiro et al[111] 2012	65, Female	*Streptococcus viridans*	Unspecified	Pterygium excision	PK	Persistent infection
Burke et al[16] 2013	40, Male	Gram positive cocci	1. Cefuroxime 1%, gentamicin 0.3% and oral aciclovir 400 mg QID 2. Cefuroxime 1% and ofloxacin 0.3%	PK	Multiple Intrastromal Cefuroxime 0.01% and keratectomy	
Paulus et al[102] 2013	78, Male	*Abiotrophia defectiva*	Moxifloxacin 0.5%, vancomycin 2.5% and natamycin 5% and oral ciprofloxacin 750mg BD	PK		Resolved
Mesiwala et al[89] 2014	76, Male	Group A-hemolytic strep	Ciprofloxacin ointment 0.3%	PK x 2	PK	Resolved
Huerva et al[57] 2015	15, Female	*Pseudomonas fluorescens*	Fortified vancomycin 5% and ceftazidime 5%, with intravenous vancomycin 500mg QID and ceftazidime 1g TDS	Contact lens use		Resolved
Agahan et al[2] 2016	44, Male	Gram Positive Bacilli	Intrastromal and topical moxifloxacin 0.5%	PK	Intrastromal antibiotics	Resolved
Steinwender et al[125] 2016	16, …			Corneal cross linking		
Stock et al[127] 2016	40, Male	*Cladosporium sphaerospermum*	1. Moxifloxacin 0.5%, natamycin 5% and oral fluconazole 150mg 2. Vancomycin 5% and moxifloxacin 0.5% 3. Moxifloxacin 0.5%, natamycin 5% and fluconazole 150mg daily	PK	PK	Resolved
This Article Case 1	67, Male	*Serratia liquefaciens*	Topical ciprofloxacin 0.3% and oral ciprofloxacin	Globe rupture, vitrectomy and PK x 2	PK	Resolved
Case 2	19, Male	*Streptococcus sanguinis*	Ceftazidime 5%	PEI and PK	PK	Resolved
Case 3	68, Female	*Enterococcus faecalis*	Ciprofloxacin 0.3% with oral ciprofloxacin 750 mg BD	DSEK	PK, vitrectomy	Resolved
Case 4	91, Female	Staphylococcus	Moxifloxacin 0.5%	PK x 2	Nd:YAG	Resolved

Table 3. Causative microorganisms in Infectious crystalline keratopathy

Gram positive:
Staphylococcus epidermidis[46] other coagulase negative staphylococcus[82]
Streptococcus mitis[66, 40] / *pneumoniae*[84] /*viridans*[130, 53] / *pyogenes*[89] / *sanguinis*[109] / *parasanguinis*[64]
Abiotrophia defectiva[102, 1] / *adiacens*[60]
Enterococcus faecalis[56, 73]
Actinomyces[119]
Gemella haemolysans[37, 61]
Peptostreptococcus[34]

Gram Negative:
Haemophilus influenzae[26] / aphrophilus[50]
Pseudomonas aeruginosa[124] / *fluorescens*[57]
Serratia marcescens[22] / *liquefaciens*[Case 1]
Klebsiella oxytoca[23]
Stenotrophomonas maltophilia[65]
Enterobacter aerogenes[65]
Citrobacter koseri[65]
Acinetobacter iwoffii[65] / *calcoaceticus*[145]
Achromobacter[32]

Atypical:
Mycobacterium abscessus[135] / *chelonae*[134]

Fungal:
Candida albicans[36, 140] / *tropicalis*[65] / *guilliermondii*[3] / *parapsilosis*[108, 130]
Alternaria[136]
Furarium solani[44]

Acanthamoeba
Acanthamoeba and *Streptococcus oralis*[133]
Acanthamoeba and *Staphylococcus aureus*[133]
Acanthamoeba and *Gemella haemolysans*[37]

Non acanthamoeba co-infections
Nocardia species and *Mycobacterium chelonae*[5]
Streptococcus anginosus and *Staphylococcu aureus*[124]
Staphylococcus epidermidis and *Corynebacterium*[124]
Candida parapsilosis and *Staphylococcus aureus*[41]
Mycobacterium chelonae and *Mycobacterium abscessus*[114]

Table 4. Outcomes of Infectious Crystalline Keratopathy according to Organism

Organism	Sex M:F	Mean age (yrs) M:F	Age range (yrs) M:F	Topical treatment n (%)	Other adjuvant treatment n (%)	Therapeutic penetrating keratoplasty n (%)	Resolved Infection n (%)
Bacteria (n=91)	36:54*	56:68	2-87: 0.05-91	75 (82.4)	Nd:YAG – 3 (3.3) Oral antibiotics – 4 (4.4) Intravenous antibiotics – 3 (3.3) Intrastromal antibiotics - 3 (3.3)	33 (35.8)	76 (83.5)
Mycobacterium (n=7)	4:3	36:52	19-74: 32-80	7 (100)	Oral antibiotics – 4 (57.1)	2 (28.6)	7 (100.0)
Fungus (n=12)	6:6	58:58	40-75: 23-85	12 (100)	Oral antibiotics – 6 (50)	6 (50)	12 (100)
Acanthamoeba (n=6)	4:1*	39:28	27-62: 28	6 (100)	Oral antibiotics – 2 (33.3)	4 (66.7)	4 (66.7)
Not Specified (n=17)	3:13	62:69	32-83: 36-95	13 (76.5)	Nd:Yag – 1 (5.8) Excimer – 1 (5.8)	3 (17.6)	14 (82.4)