PERIPHERAL ULCERATIVE KERATITIS – A PROSPECTIVE STUDY

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CERTIFICATE

This is to certify that this dissertation entitled **"PERIPHERAL ULCERATIVE KERATITIS – A PROSPECTIVE STUDY"** is a bonafide done by **Dr. Naveen keshav.S** under the guidance and supervision in the department of Cornea, Aravind Eye Hospital and Post Graduate Institute of Ophthalmology in Madurai during his residency period from June 2015 to May to 2018.

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DECLARATION

I, **Dr. Naveen Keshav .S** solemnly declare the dissertation titled **"PERIPHERAL ULCERATIVE KERATITIS – A PROSPECTIVE STUDY"** has been prepared by me. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, diploma to any other university board either in India or abroad.

This dissertation is submitted to the **Tamil Nadu Dr. M. G. R. Medical University**, Chennai in partial fulfilment of the rules and regulation for the award of **M. S. Ophthalmology (BRANCH III)** to be held in May 2018.

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PART I

PERIPHERAL ULCERATIVE KERATITIS – A PROSPECTIVE STUDY

PART 1

INTRODUCTION

Peripheral ulcerative keratitis is an ulcerative inflammation of the cornea that is usually associated with a systemic or local autoimmune disease. It is considered as a potentially life threatening disease as it may precede or follow an autoimmune disease[1]. The need for studying the presentation of this peripheral corneal ulceration arises because of its varied aetiology and lack of specific treatment of choice for PUK. Though many studies have been conducted, much remains to be done as the etiopathogenesis is not clearly understood to go about in managing this disease.

Peripheral ulcerative keratitis is a crescent-shaped destructive inflammation of the juxta-limbal corneal stroma with an epithelial defect, stromal degradation and thinning.[1, 2]About 50 % of the non-infectious PUK have association with collagen vascular disease.[3]

Mooren's ulcer being one of the common causes of peripheral ulcerative keratitis has a rapidly progressive course which initially affects the peripheral cornea ,spread circumferentially and later may go on to

involve the central cornea .Mooren's was first described by Bowman in 1849 ,then by Mckenzie in 1854 as "a chronic serpignous ulcer or ulcus rodens". But the name Mooren's was given to this condition following publication of case series reported by Mooren in 1863 and 1867 [4]The reason why peripheral part of the cornea has affection to systemic diseases is attributed to its anatomical and physiological pecularities in comparison with the central cornea as follows:

- Capillaries enter 0.5mm into clear cornea [5]
- Subconjunctival lymphatics accompany the capillaries[5]
- Contains more IgM[6], C1[7], Langerhan's cell[8]

Though the mean age of occurrence of PUK is around 65 years, 2 cases have been reported in children[10, 11]

Early diagnosis and treatment is important because peripheral ulcerative keratitis can be a window to occult potentially lethal systemic disease.

It has been hypothesized that PUK could occur following intra-ocular surgery.[1, 13, 14, 15] Studies have also identified a possibility of an infectious disease like blepharitis could trigger the immune system to develop PUK.[9,16] Conjunctival resection can reduce the chance of perforation only temporarily[17], helping to buy time for a keratoplasty.

Many studies have shown that starting immunosuppression therapy not only treats PUK but also the decreases the mortality due to systemic vasculitis[18]. Hence managing the disease with immunosuppression which is tailored to the individual's response and keeping in mind the adverse effects of it is the need of the hour.

ETIOLOGY [1, 3]

- **OCULAR INFECTIONS** - Streptococcus, Staphylococcus, Herpes zoster, Herpes simplex, Fungal.
- **SYSTEMIC INFECTIONS** - Varicella-zoster, Gonococcal arthritis, Dengue fever, Leishmaniosis
- **NON-INFECTIOUS OCULAR** – Mooren's ulcer, Traumatic, Post-surgical, Sicca syndrome, Metaherpetic, Neuroparalytic, Exposure keratitis, Carcinoma.

NON-INFECTIOUS SYSTEMIC

VASCULITIS	OTHER AUTOIMMUNE DISORDERS	DERMATOLOGIC
Rheumatoid arthritis	Graft-versus-host disease	Rosacea
Granulomatous polyangitis	Progressive systemic sclerosis	Cicatricial pemphigioid
Polyarteritis nodosa		Psoriasis
Relapsing polychondritis		Steven-Johnson's syndrome
Systemic Lupus Erythematosis		
Sjogren's arthritis		
Churg strauss		

OTHERS - Leukaemia, Porphyria

RHEUMATOID ARTHRITIS [3, 5]

Rheumatoid arthritis affects approximately 0.5 to 1 % of the worldwide adult population. Incidence of RA is more between 25 and 55 years of age. It occurs more commonly in the female population. The female: male ratio is 2 to 3:1 probably due to the fact that estrogen stimulates the production of Tumour Necrosis Factor alpha (TNF-alpha). The presenting symptom results from inflammation of joints, tendons, and bursae. Common complaints are early morning small joint stiffness in a symmetric pattern. The overall mortality rate is twice greater than general population. Ischemic heart disease is the most common cause of death followed by infection. There is higher risk for survival with extra-articular involvement.

Extra-articular manifestation occurs during the course of the disease or even prior to onset of arthritis. They occur in approximately 25% of patients. Extra-articular disease has more association with smoking, especially those who are tested positive for serum rheumatoid factor and anti-cyclic citrullinated proteins. A study showed that women had 2.5 times more chance of RA on smoking. Subcutaneous nodules, secondary Sjogren's syndrome, pulmonary nodules, and anaemia are most commonly observed. Secondary Śjogren's is seen in 10 % of patients.

RA is caused by the recognition of a self-antigen has come from the fact that it is an HLA-associated disease with accumulation of HLA-DR4+ individuals. RA has a genetic factor that contributes to its occurrence. It is 2 to 10 times more common in first-degree relative than general population. The HLA-DRB 1 allele share an amino acid sequence at positions70-74 called shared epitope which is associated with production of anti-CCP antibodies. Among the HLA DR-B1 alleles *0401 has a high risk of disease.

The pathophysiology of RA is complex. Genetic predisposition with environmental factors acts as trigger for activation of CD4 + T-cell. The current concept of RA is that inflammation and tissue destruction result from complex cell-to-cell interactions, including antigen-presenting cells, CD4+T cells, macrophage activation with resultant secretion of proinflammatory cytokines, particularly interleukin 1, interleukin 15, and tumour necrosis factor alpha (TNF-alpha). The pivotal role in pathobiology of inflammation is by TNF-alpha. It upgrades the adhesion molecules and influx of leukocytes and activates the fibroblasts. These fibroblasts secrete matrix metalloproteinases (MMP) as well as other proteases that are responsible for breakdown of proteoglycans and collagen, leading to tissue destruction.

The diagnosis of rheumatoid arthritis is based on the EULAR criteria 2010 where it has to satisfy >= 6/10. The diagnosis of RA is clinical, with arthritis in three or more joints (especially the proximal interphalangeal, metacarpophalangeal, or wrist joints), morning stiffness, rheumatoid factor, and autoantibodies to IgG in the serum. Very high titers of IgM rheumatoid factor are typically present during active vasculitis in RA. RF was found to be positive in 75-80% of patients with RA. But Rheumatoid factor may be also found in scleroderma, polyarteritis nodosa, Wegener's granulomatosis, systemic lupus erythematosus, sarcoidosis, and certain infections (e.g. hepatitis B and C).1-5% of normal population are also positive for RF.

Ocular manifestations of RA, includes keratoconjunctivitis sicca, episcleritis, anterior scleritis, marginal corneal furrows, and choroidal lesions and/or retinal vasculitis secondary to posterior scleritis. Corneal melting, in association with rheumatoid arthritis, appeared as a late phenomenon. The mean time between diagnosis of RA and the onset of the corneal melt was 19.6 years. [20]

Scleral involvement includes nodular and diffuse anterior scleritis, as well as potentially severe and blinding conditions, such as necrotizing scleritis, scleromalacia perforans, and posterior scleritis. Among the scleritis patients having RA, the reported incidence of corneal

abnormalities ranges from 49% to 69%.In patients studied by Tauber et al, RA accounted for 34% of non-infectious PUK, and 44% of PUK cases were bilateral[3]

Peripheral inflammatory cell infiltration and vascularization followed by permanent scarring-localized to the site adjacent to scleral inflammation.[21]

Patients with RA and severe PUK typically progress to corneal perforation without vigorous immunosuppressive therapy. Patients with destructive PUK and necrotizing scleritis have a decreased life expectancy because of systemic vasculitis. In 100% of scleral biopsies and 83% of conjunctival biopsies of patients with RA-associated necrotizing scleritis and/or PUK a microangiopathy with fibrinoid necrosis, neutrophil invasion of the vessels, and/or vascular immunodeposits with IgA, IgG, IgM, C3, and C4 was identified.

Although the antigen responsible for the immune complex disease is unknown, one that appears to participate is the patient's own immunoglobulin. The so-called rheumatoid factor is an immunoglobulin M (IgM) antibody formed against the patient's IgG immunoglobulin. Antigen/antibody complexes then form and produce a microvasculitis within the joint synovium. Capillary and arteriolar vasculitis is routinely present, and seems to be responsible for the "arthritis" in these patients.

Activation of the complement system, through both conventional and alternative pathways, results in chemotactic attraction of mononuclear cells and neutrophils. Immune complex phagocytosis and subsequent release of inflammatory cell enzymes result in tissue destruction. This microvasculitis is not restricted to the synovium. Rheumatoid arthritis is a systemic disease in which extra-articular vasculitis is common but is subtle and frequently overlooked. Microvasculitis lesions occur in nerve, pleura, pericardium, muscle, subcutaneous tissue, kidney, heart, and eyes of patients with rheumatoid arthritis. The granulomatous lesions that form in these areas are a direct consequence of the appearance of a small area of microvasculitis. PUK is the sensitive indicator to assess a lethal occult systemic vasculitis. For microvasculitis in RA HLA-DW4 antigen seems to be involved .Mean duration for arthritis patient to develop PUK is 14 years. Only 1 / 17 patients on immunosuppression died that on discontinuation over a 10 years follow up in comparison to 9/17 deaths on conventional therapy for RA with PUK.[18]

MOOREN'S ULCER

By definition, it is an acute, painful ulceration of the cornea up to the sclera, but not involving it, in the absence of any on-going ocular infection or any systemic disease. The presenting complaints of patients with Mooren's ulcer are tearing, redness and photophobia, but pain is

typically the outstanding feature. The patient experiences incapacitating pain and are often well out of proportion to the inflammation.[4]Decreased visual acuity can also be a presenting feature in certain cases that occurs secondary to central corneal involvement, or irregular astigmatism due to peripheral corneal thinning or associated iritis.

Mooren's ulcer, on examination may seem to begin with patchy, peripheral stromal infiltrates that then coalesce, more often in the medial and lateral quadrants than in the superior and inferior ones. In this area develops an epithelial defect and then a shallow furrow. Limbal involvement in Mooren's is contrasting feature in comparison to other forms of PUK, like that seen with rheumatoid arthritis Wegener's granulomatosis or staphylococcal marginal disease. Part of the ulcer may be quiescent while others are active. The end- stage result is typically a scarred, vascularized cornea that may be thinned to less than half of its original thickness. As the end stage of the process approaches, the patient may experience sudden relief from the excruciating pain that has been present throughout the course of the disease. Ulcerative process first spreads circumferentially and then centrally to involve the entire cornea eventually. The anterior one-third to one-half of the stroma is involved, characteristically with a steep, overhanging edge. Healing and

vascularization then follow, with the disease slowly running its course over 4 to 18 months [4].

Features of Mooren's ulcer according to P.G.Watson [21]:

- Crescent-shaped peripheral corneal ulcer which commences slightly central to the corneo-scleral limbus
- Extensive undermining of the central edge of the ulcer
- Stromal yellow/white infiltrates in advance of the ulcer
- Central and circumferential progression of the ulcer leaving a thin vascularised cornea behind
- No scleral involvement
- No detectable systemic disease

There are two clinical types of Mooren's ulcer according to Wood and Kaufman[22]:

Type 1 - Usually unilateral, with mild to moderate symptoms, and generally responds well to medical and surgical therapy. This type occurs in older patients and was called as *typical* or *benign* Mooren's ulcer.

Type2- Bilateral, with relatively more pain and a generally poor response to therapy progressing to perforation in more than 1/3rd of cases. This occurs more commonly in younger patients and came to be known as *atypical* or *malignant Mooren's* ulcer.

The normal vascular architecture at the limbus gets disrupted prior to the appearance of the ulcer at that site. This is followed by appearance of new vessels that sprout from the superficial conjunctival capillaries and extend to the advancing edge of the ulcer. Vessels leak at the advancing tips, in the active stage of the disease. Subsequently vaso-occlusive changes develop. They precede the appearance of destructive corneal changes which once they have occurred are permanent. Those areas that are affected due to destructive corneal changes are subject to new vessel formation.

The limbal capillaries and adjacent episcleral network needs to be carefully observed either clinically, using red free light, or with anterior segment fluorescein angiography can indicate whether the disease is active and progressive or is in a quiescent phase. Disruption of the normal capillary architecture is the earliest indication of disease. During this active phase of the disease the new vessel sprouts are straight and leak at their tips. When the disease becomes quiescent these leaky vessels anastomose with adjacent normal vessels to form a mature arcade. Hence leakage from their tips ceases at this stage.[23]

According to P.G.Watson based on clinical presentation and low – dose anterior segment fluorescein angiographic findings 3 distinct varieties[21] :

1. 1.Unilateral Mooren’s ulceration(UM) – in elderly patients, painful, progressive ulceration with non-perfusion of superficial vascular plexus of the anterior segment
2. Bilateral aggressive Mooren’s ulceration (BAM) – in young patients, progress circumferentially and later central cornea. Angiography shows vascular leakage new vessel into base of ulcer.
3. Bilateral indolent Mooren’s ulceration (BIM) - middle-aged, progressive peripheral guttering with little inflammatory response. No angiography changes except for a new vessel extension into the ulcer Based on the analysis of 287 cases from 20 published series on Mooren's ulcer in 1990 the aforementioned concepts about the epidemiology of Mooren's ulcer did not correlate with the available data. They found that more number of older patients (43%) had bilateral disease, whereas only one-third of patients younger than 35 years had bilateral disease. Whites were more than twice as likely to have bilateral disease as blacks. The analysis also revealed that men had 1.6 times more propensity to develop Mooren's ulcer than women. This could be attributed to the increased incidence of ocular trauma in men (an association with Mooren's ulcer) or cultural practices that discourage female to go to hospital in some countries. Hence this finding may not reflect a true biological tendency for men to develop Mooren’s ulcer.[24.]

Mooren's ulcer has been associated with many entities hence it is important to obtain their causal relationship. A possible relationship between hookworm and Mooren's ulcer was proposed by Kuriakose ET. All 6 cases of Mooren's ulcer seen by him had ancylostomiasis. Regression of ulcer occurred only after administration of tetrachlorethylene. He was the first to suggest that hookworm toxins might have diffused through the perilimbal plexus to cause the disease.[25]

Another study suggested that the progression of the ulcerative keratitis was arrested by local therapy in combination with systemic therapy for the parasitic infection. A causal relationship, suggesting that helminth toxins or antigens deposited in the cornea may lead to antigen-antibody reactions or that infection may cause alteration of the host immune system, allowing the keratitis to occur was proposed. Subsequently, investigators started looking into the validity of this causal relationship with helminthiasis. In a prospective observational case control study by Srinivasan et al involving 15 patients with age and gender matched controls it was found that there appears to be a significant association between hookworm infestation and Mooren's ulcer especially in male patients of older age group.

In 2 patients with bilateral Mooren's ulcers, chronic hepatitis C infection was documented. Both patients had pruritic dermatitis at

presentation .they were also tested positive for serum anti-HCV antibodies. The keratitis in both patients was observed to improve after treatment of the hepatitis with interferon alpha2b. They proposed that molecular mimicry may be involved, with the hepatitis C virus stimulating an autoimmune response to corneal antigens through cross-reacting epitopes. Alternately, they also propose that deposition of immune complexes in the limbal or peripheral corneal tissues may lead to an immune response and the release of proteolytic enzymes. Chronic hepatitis C infection is not a rare disorder. So if a causal relationship is established, then Mooren's ulceration would be expected to be seen more frequently and their line of management would also differ focusing towards monoclonal antibodies.[26]

Other infections that have been associated with Mooren's ulcer are syphilis and tuberculosis. Mooren's ulcer has also been reported following local corneal disease. Specific associations have included physical trauma, foreign bodies, chemical burns, herpes simplex infection, herpes zoster infection, and surgical procedures like penetrating keratoplasty and cataract extraction. These cases may not represent true cases of strictly defined Mooren's ulcer and, if they do, definitive associations and causal relationships have not been identified.

Corneal scrapings for culture will usually establish an infectious origin for ulcerative keratitis. In those cases, there is also a characteristic discharge and a response to antibiotics. Mooren's ulcer could be differentiated from the non-inflammatory corneal degenerations, such as pellucid marginal degeneration or Terrien's, in which the epithelium remains intact and pain is absent. The degenerations in Mooren's ulcer begins generally in the interpalpebral regions, in contrast to the non-inflammatory corneal degenerations which generally begin in the superior and inferior quadrants. Staphylococcal marginal keratitis may be differentiated from Mooren's ulcer by a lack of severe pain, the presence of blepharitis, a lucid zone between the infiltrate and the limbus, and a quick response to topical steroid therapy. The presence of a Mooren's-like ulcer requires an extensive search for occult and potentially lethal systemic diseases. A thorough medical history and examination are mandatory, and also a comprehensive laboratory investigation. Investigations include a complete blood cell count with evaluation of the differential count, platelet count, erythrocyte sedimentation rate, rheumatoid factor, antineutrophil cytoplasmic antibody (ANCA), complement fixation, antinuclear antibodies, circulating immune complexes, liver functions tests, VDRL and fluorescent treponemal antibody absorption (FT A-ABS) tests, blood urea nitrogen and creatinine, serum protein electrophoresis, urinalysis, and a chest X-ray.

Lab testing additional to this may also be required based on the presentation of the patient. Its mandatory to go about with laboratory investigations as only when they fail to prove a disease could a diagnosis of Mooren's ulcer could be made, as it is a diagnosis of exclusion only.[4]

GRANULOMATOSIS WITH POLYANGITIS (WEGENER'S)

It is characterised by the presence of granulomatous inflammation in the upper (92%) or lower (85%) respiratory tract, focal necrotizing glomerulonephritis (77%), and focal necrotizing vasculitis in small vessels (involving both arteries and veins). Its prevalence is 3 per 100,000. Renal disease is associated with mean survival of 5 months.[28]

A limited form of WG has been recognized that spares the kidneys and carries a better prognosis than does the classic syndrome. Ocular involvement does not differ in frequency or severity between classic and limited WG.

Antineutrophil cytoplasmic antibodies (ANCA) toward proteinase 3 (PR3) with the classic "cytoplasmic" immunofluorescence staining pattern (cANCA) have a specificity of approximately 90% in biopsy-proven WG. This c-ANCA is not only a seromarker but also play a role in pathogenesis of this disease. ESR and IgA are elevated with leucocytosis.

Conjunctivitis, corneoscleral ulceration, uveitis, episcleritis, and/or scleritis may be observed in the anterior eye of affected patients. Corneoscleral involvement begins with perilimbal infiltrates, which may ulcerate concentrically to form a ring ulcer that may ultimately perforate. It is important to remember that ulcerative peripheral keratitis is a local manifestation of a systemic vasculitis. Therefore, control of the disease requires systemic rather than local treatment.

The incidence of ocular involvement in WG is 52%. Eye involvement was the presenting feature in 16% of WG patients in one study[18]. The eyes may be affected secondary to contiguous granulomatous paranasal sinus disease, which can cause orbital inflammation, obstruction of the nasolacrimal duct, ocular muscle involvement, or optic neuropathy.

Focal ocular involvement of the peripheral cornea and sclera is caused by a small-vessel vasculitis of the intrascleral portions of the anterior ciliary arteries or perilimbal arteries, or both. Peripheral ulcerative keratitis and necrotizing scleritis may be the initial manifestations of the disease and may indicate a generalized vasculitic process.

Antineutrophil cytoplasmic antibodies appear to also be sensitive and specific for WG-associated vasculitic ocular involvement. Most

patients with WG show serum levels of c-ANCA; however, in limited disease a perinuclear immunofluorescence pattern (p-ANCA) may be prominent. Power et al demonstrated that a relapse of scleritis in WG is, in general, not preceded by a significant rise in ANCA titre, and, therefore, ANCA levels do not correlate with disease activity, as was shown for systemic vasculitis. They suggested, however, that a failure of ANCA titres to return to normal levels may be associated with potential relapse in patients with limited ophthalmic WG. Furthermore, elevated levels of soluble IL-2 receptors may be an indicator of future relapses of WG-associated ocular disease. Peripheral ulcerative keratitis is a common, often bilateral, manifestation of WG. It usually begins as paralimbal infiltrates, which lead to epithelial and stromal necrosis with subsequent furrow-like ulceration. The process may extend concentrically to form a ring ulcer, or it may progress centrally. Scleral inflammation is invariably present, ranging from redness to localized necrotic slough. Several studies from the 1960s and 1970s reported widespread scleral necrosis and peripheral ulceration in patients with WG, which gradually deteriorated without therapy. Koyama et al reported a patient with WG associated with bilateral ocular destruction and replacement of the entire globes by granulomatous tissue. Bullen et al noticed peripheral corneal involvement in 11 of 40 patients, of whom five developed corneal ulceration. Like RA patients, patients with WG have also been reported to

have postoperative PUK with necrotizing scleritis. A striking granulomatous inflammatory reaction was present in patients with peripheral corneal ulcers and in necrotic sclera, lending support to the contention that immune reactions play a major role in WG.Histopathologic examination of eyes with PUK associated with WG revealed an impressive occlusive necrotizing vasculitis of the anterior ciliary arteries, supporting the vasculitic nature of the eye involvement.The immunopathogenesis of WG certainly is complex, as not only a simple type III immune reaction is involved; a type IV immune reaction with granulomatous inflammation as its prominent feature also plays a major role in typical WG lesions.

Peripheral corneal involvement in Wegener's granulomatosis usually consists of an ulcerative keratitis. This process is usually bilateral, is classically associated with an adjacent scleritis, and may be the presenting sign of the disease. The keratitis usually begins as multiple peripheral stromal infiltrates, similar to those seen in staphylococcal hypersensitivity. Eventually, the epithelium and uninvolved stroma overlying these infiltrates ulcerate.

Progression of the ulcerative keratitis is generally circumferential; a 360" peripheral ring ulcer may result. In some cases, the ulcer may extend centrally, with an overhanging central edge similar to that seen in

Mooren's ulcer. Untreated, the central and peripheral ulcerations may perforate.

The histopathologic features of peripheral keratitis in Wegener's granulomatosis include: necrosis of the epithelium and superficial stroma; stroma1infiltration by inflammatory cells; and, occasionally, the presence of epithelioid and giant cells surrounding the ulcer base. This necrotizing granulomatous inflammation may extend into the adjacent sclera and ciliary body. The pathogenesis of peripheral ulcerative keratitis in Wegener's granulomatosis is believed to involve an occlusive vasculitis of the adjacent intrascleral blood vessels.

RELAPSING POLYCHONDRITIS

Relapsing polychondritis is a rare autoimmune disorder characterized by a recurrent inflammation of the cartilaginous tissues throughout the body, particularly the ears and nose. Incidence of relapsing polychondritis is 3.5 per million population per year. Average age of onset is between 32 and 51 years.

Approximately 30% of the cases will have associated rheumatologic disorder, commonly systemic vasculitis followed by rheumatoid arthritis and systemic lupus erythematosis. These disorders

usually antedate the presentation of relapsing polychondritis. About 70% had respiratory symptoms; 61% had nasal involvement. [30]

The clinical diagnosis of relapsing polychondritis is usually obvious by inflammatory episodes involving the typical sites. McAdam et al suggested diagnostic criteria, including recurrent chondritis of both auricles or of the nasal cartilage, polyarthritis, chondritis of the respiratory tract, cochlear or vestibular damage, and ocular inflammation.[31]

The diagnosis of relapsing polychondritis is established when three of the following criteria are met, when one sign is present along with histologic confirmation, or when two anatomically separate locations are involved. There are no specific laboratory tests available to establish the diagnosis of relapsing polychondritis. A biopsy of nasal or auricular cartilage is not mandatory.[32]

Ocular inflammation is common in relapsing polychondritis and has been estimated to occur in up to 60% of patients. It is evident at the time of diagnosis in 19% to 32% of cases. In a study of 112 patients, episcleritis (39%) and scleritis (14%) were the most common ocular findings, followed by lid edema(9%), iritis (9%), retinopathy (9%), muscle paresis (5%), optic neuritis (5%), and peripheral ulcerative keratitis (4%).The presence of scleritis and episcleritis was often

associated with inflammation at other sites, commonly the nose and the joints. [33]

A study reported sclerokeratitis or marginal corneal ulceration in 11% of their patients. A severe form of peripheral ring ulcer was associated with scleromalacia and erythema nodosum. [34] A case of bilateral destructive PUK leading to perforation, endophthalmitis, and ultimately enucleation of both eyes was reported. [35]

SYSTEMIC LUPUS ERYTHEMATOSIS

Systemic lupus erythematosis (SLE) is a multisystem disorder which may affect the articular, cutaneous, renal, hematologic, pulmonary, neurologic, cardiovascular, and ocular systems.

Ocular complications of SLE include scleritis, keratitis, cornea1 furrowing, and retinal vasculitis.

Corneal stromal involvement in SLE is distinctly rare. Bilateral deep interstitial keratitis in a bandshaped pattern has been reported in two SLE patients. Discoid lupus ervthematosis (DLE) is a related collagen vascular disorder that affects only the skin and mucous membrane. As with SLE, superficial punctate keratitis is the major cornea1 complication in DLE. Diagnosis can be made by skin biopsy, and the keratitis resolves well with systemic therapy .[5]

POLYARTERITIS NODOSA

It is a necrotizing vasculitis of small and medium-sized vessels throughout the body. It occurs more frequently in males in the middle decades of life. It is a diagnosis of exclusion. It is a nongranulomatous vasculitis of arteries. The annual incidence of PAN is 2.4/million.[37]

More than 50 % of cases have only weight loss, fever, mononeuritis multiplex (51%), livedo reticularis, fatigue, myalgias/arthralgias (64%) as presentation. 60% have renal involvement which manifest as hypertension, renal insufficiency or haemorrhage. It can occur either as a primary vasculitis or in association with hepatitis B or C or other viral infections. Leukocytes are elevated with predominant neutrophils.

Ocular involvement occurs in approximately 20% of polyarteritis nodosa patients and includes scleritis, choroidal vasculitis, retinal vasculitis, optic atrophy, exudative retinal detachment, papilledema, and keratitis. The keratitis in polyarteritis nodosa is usually peripheral, bilateral, ulcerative, and progressive. It may begin with marginal stromal infiltrates, and eventually the overlying epithelium and anterior stroma ulcerate. This process generally spreads circumferentially, and may also extend Mooren's-like into the central cornea. Frequently, the keratitis is associated with an adjacent necrotizing scleritis. Like Wegener's

granulomatosis, peripheral ulcerative keratitis may be the presenting sign. Orbital pseudotumor, papilledema or papillitis, and extraocular muscle dysfunction have been reported. Involvement of the posterior segment occurs both as a result of the arteritis and secondary to the associated systemic hypertension. Involvement of the anterior ciliary arteries may result in conjunctival, episcleral, and corneal lesions. The histological features are scleral with surrounding granulomatous reaction. [38]

IgG, IgM, and complements were demonstrated in the arteriole wall of a conjunctival lesion in a patient with PAN, indicating an immune complex–mediated vasculitis. [39]

A furrow –like ulceration in paralimbal region with infiltrate and vascularisation morphologically similar to Mooren's ulcer has been observed as the presenting manifestation of PAN.[40]

MICROSCOPIC POLYANGITIS AND CHURG-STRAUSS SYNDROME[3]

Churg-Strauss syndrome is defined by the combination of asthma, peripheral eosinophilia(>1000 cells/microL), and a systemic necrotizing vasculitis. Elevated ESR, fibrinogen seen in 81% cases. Pulmonary infiltrates, mononeuritis multiplex (72%), allergic rhinitis sinusitis (61%),purpura (51%) and cardiac involvement are more common than in other ANCA-associated conditions.

Microscopic polyangiitis is characterized by a small-vessel vasculitis, usually associated with necrotizing glomerulonephritis, respiratory tract lesions, and the absence of granulomatous inflammation. It is rare, with an annual incidence of 3.6/million. [41]

The presence of antineutrophil cytoplasmic antibodies against myeloperoxidase (p-ANCA) has become an important diagnostic tool to establish a diagnosis of MPA or CSS. 75% of patients with MPA are ANCA-positive, with ANCAs directed toward myeloperoxidase in 70% of cases.[39]

Ocular manifestations-

Bilateral PUK associated with MPA that progressed both centrally and circumferentially with undermining of the central edge of the ulcer and corneal perforation similar to Mooren's ulcer. However, involvement of the adjacent sclera clearly distinguishes PUK in PAN, MPA, or CSS from Mooren's ulcer. In CSS, multiple ocular lesions including conjunctival granuloma, episcleritis, peripheral ulcerative keratitis, uveitis, multifocal choroidal ischemia, ischemic optic neuropathy, and cranial nerve palsies have been reported. However, ocular involvement is rare.[5]

PATHOGENESIS

The exact pathophysiologic mechanism of PUK remains unclear, but the same pathogenic mechanism is thought to occur in all forms of PUK. Research suggest that both humoral-mediated and cell-mediated autoimmune processes are involved. Reactions to corneal antigens, circulating immune complex deposition, and hypersensitivity reactions to exogenous antigens are other mechanisms implicated in the pathogenesis of PUK[42]

The peripheral cornea has distinct morphologic and immunologic characteristics that predispose it to immune inflammation. Unlike the avascular central cornea, the limbus and the peripheral cornea receive a portion of their nutrient supply from the capillary arcades, which extend only approximately 0.5 mm into the clear cornea[5]. The vascular architecture of the limbus is suitable for accumulation of IgM[6], the first component of complement cascade C1[7], and other high molecular weight molecules and immune complexes in the limbus and corneal periphery. It was found that IgM was present only in the peripheral cornea and absent in the central cornea. [6]

The pathogenesis of most vasculitic syndromes is not completely understood, one common feature of vasculitis appears to be the involvement of the immune system, as indicated by the presence of circulating autoantibodies. However, the antigen specificity of these antibodies and the pathogenesis of the vessel damage differ among the various vasculitides. Antibodies binding to cell-surface antigens and a subsequent complement-mediated attack have been proposed as one possible mechanism for vascular damage (immune complex–mediated vasculitis). Vasculitis may also be initiated by a process involving leukocyte-mediated cytotoxicity caused by antineutrophil cytoplasmic antibodies (ANCA) directed against neutrophil granule enzymes, mainly antiprotease 3 and antimyeloperoxidase (ANCA-positive, pauci-immune vasculitis).*In vitro* studies showed that ANCA promotes neutrophil activation and endothelial injury [5]

Two types of pathological change have been noted in ulceration of the cornea in rheumatoid arthritis in patients with marginal guttering (Iwamoto et al., 1972).[43]

1. Inflammatory group- marked vascularization in and around the corneal lesion and dilatation of the adjacent conjunctival blood vessels. Often these patients are treated with local steroid eye drops which reduce the inflammation, but the cornea continues to melt

away. Electron microscopy of the cornea shows changes resembling hypersensitivity reactions with accumulation of lymphocytes, neutrophils, and oedema, and fibrinoid necrosis of small blood vessels.

2. The quiescent group - less vascularization and no evidence of inflammation. The electron microscopic appearances show fatty degenerative changes in the stroma.

Vasculitis patients have antibodies to two 66-kDa corneal antigens and that autoantibodies to these antigens are mutually exclusive. It has also been shown that antibodies to BCEA-B are associated with CSS, whereas BCEA-A antibodies are associated with WG and RA [44]

There is a high level of association between anti-BCEA-A antibodies and PUK complications in WG patients(50%). Because PUK is often a presenting problem in WG.

But patients with RA develop PUK much later, 10 to 15 years into the on-going systemic disease. At such a late stage, the anti-BCEA-A antibodies are among a wide spectrum of circulating autoantibodies. They may contribute to the autoimmune reaction in the eye secondary to an advanced systemic disease. The different characteristics of PUK in RA and WG may account for the difference in the frequency of anti-BCEA-A antibodies in these two groups

Anti-BCEA-B antibodies have a 60% association with CSS, but are present in only 13% of patients with WG. This is the first time that a significant association between an antigen and CSS has been shown. It helps to distinguish CSS from WG in the early stages of the disease. To fully understand the relevance of these two new antigens, both in the disease process and as diagnostic tools, longitudinal studies are needed.[45]

Indirect immunofluorescence on bovine corneal sections demonstrated that antibodies bound to epithelial antigens in two distinct patterns: a lattice-like pattern, probably staining intercellular membrane antigens, and a diffuse pattern covering the entire surface of the epithelium. Both patterns were associated with PUK rather than systemic disease whilst the presence of the *lattice pattern* was more associated with the onset of the PUK. [46]

The detection of a lattice pattern by immunofluorescence was related to patients with PUK and particularly with WG (100%). The lattice pattern was present at the onset of disease in all the patients with WG and PUK and in 50% of cases the staining was lost upon remission of the PUK.

Among a number of corneal antigens targeted that were being targeted by immunoblotting of sera to extracts of corneal epithelial

proteins two antigens were found to be of particular importance. They are 54 k-Da and 70kDa antigens. [46]

Antibodies to the 54 kDa antigen, the major corneal-specific antigen, were also detected by enzyme-linked immunosorbent assay (ELISA). The protein has also been identified biochemically as an aldehyde dehydrogenase in bovine and human cornea with both structural and enzymatic roles. Longitudinal studies showed that these antibodies often first occurred after an episode of PUK. This information supports the hypothesis that antibodies to the 54 kDa protein are produced as a response to tissue damage in the cornea brought about by the disease process, and that they do not play any role in the initiation of the condition.

Antibodies to the 70 kDa antigen were related to the Wegener's granulomatosis rather than the PUK .Antibodies directed against the corneal epithelium were found in 91.3% of patients with PUK compared with 36% of patients without PUK. This suggests that the presence of antibodies alone is insufficient to cause corneal disease. Although autoantibodies have been demonstrated in the serum of the patient studied,no *in vivo* fixation of the antibodies was observed. It is therefore unlikely that the autoantibodies are responsible for the eye lesion.

However, it is suggestive that there exists a relation between the occurrence of the antibodies and the disease under study.

As for Mooren's ulcer,[14] CD4/CD8 ratio is significantly higher than normal in the adjacent bulbar conjunctiva. In the inflammatory lesion of Mooren's ulcer, it is thought that cyclosporin A inhibits the function of helper T lymphocytes and stimulates suppressor/cytotoxic T lymphocytes. Therefore, the helper T lymphocytes are more likely to participate in Mooren's ulcer. Infiltration of macrophages was also observed in the conjunctival submucosa. Since infiltration of T lymphocytes and macrophages was observed in the Mooren's ulcer lesion site, it seems that some abnormalities of the immune system are involved in the pathogenesis of the disorder. a recent study has shown that paramyosin that is present in the hookworm that is capable of binding to c (CaGC) inciting a reaction and resulting in Mooren's ulcer. CaGC is a protein released by activated neutrophils and involved in host defence against filarial infections. The identification of binding protein of the helminth Brugia malayi to CaGC and the ability of binding complexes to induce keratitis explains the pathophysiology of development of Mooren's ulcer on hookworm infestation. [48]

ROLE OF MATRIX METALLOPROTEINASE IN PUK [49]

Activated matrix metalloproteinase I (MMP-Ior collagenase I), the enzyme that exhibits specificity for type I collagen, the major component of the corneal extracellular matrix, has long been implicated as a causative agent of PUK. The results of an early investigation indicated that this enzyme is secreted by limbal inflammatory cells and/or conjunctival epithelial cells lying adjacent to the corneal ulcers induced by rheumatoid arthritis. More recently it has been suggested that MMP-I is produced within the stroma of affected corneas, either by the corneal keratocytes themselves or by infiltrating macrophages. There exists uncertainty with respect to the source of this enzyme, its activation mechanism, and whether other proteolytic enzymes are also involved in the initiation or maintenance of the diseased state.

The role of proteolytic enzymes in PUK is primarily on the stimulated production of interstitial collagenase (MMP-1) and/or an apparent reduction in the tissue concentration of its inactivating protein ligand,TIMP-1. Although it has been reported that MMP-1 is an endogenous corneal enzyme, secreted by stromal keratocytes readily hydrolyse type IV and type I collagen denatured by heating at 60°C for 20 minutes, but not native type 1 collagen.

Expression of MMP-8 (a neutrophil collagenase) has been associated with inflammatory conditions and plays a crucial role in wound healing and tissue remodelling. Overexpression of MMP-8 may be involved in the pathogenesis of non-healing chronic ulcerations systemically. Therefore MMP-8 may play a role in triggering or exacerbating a corneal ulceration in cases associated with the use of NSAIDs.

The PUK disease progression correlates with the abnormal production of MMP-2 in corneal stromal tissue and with the appearance of MMP-9 in tear secretions. Both these enzymes exhibit specificity for type IV basement membrane collagen. The MMP-2 is secreted by the corneal keratocytes, the MMP-9 secretory cells have not been identified yet.

Production or overproduction of gelatinase (MMP-2 an MMP-9) correlated with clinical manifestations of PUK progression, we hypothesised that these enzymes, once activated, may initiate perforation by breaching the corneal basement membranes (epithelial cell and Descemet's). By hydrolysing newly synthesised, non-cross-linked interstitial collagens, they could also limit tissue repair and facilitate infiltration of inflammatory cells and their proteolytic enzymes (including the MMP that hydrolyses type 1 collagen) into the corneal stroma.

Corneal perforation is usually a localised event and mostly occurs at a site inflammatory cells could produce adjacent to invasive inflammatory cells in cases of PUK. These enzymes or growth factors that locally stimulate the production of activated corneal gelatinases, including the MMP-9 produced by corneal epithelial cells. Following action of these enzymes on type IV basement membrane collagen and other susceptible components of the corneal matrix, the penetration and diffusion of macrophages and inflammatory cell proteases, including the collagenase that hydrolyses the interstitial (types I and III) collagens, would be facilitated.

CLASSIFICATION

Tauber et al graded corneal ulceration in PUK based on the depth[3] as

- <25% – grade 1
- 25-50% - grade 2
- 50- 75%- grade 3
- 75 – 100% - grade 4

According to Sharma et al, PUK classified as follows[1]:

SEVERITY	DESCRIPTION OF ULCER
MILD	2’ clock hours, superficially upto anterior stroma
MODERATE	2’ - 4’ clock hours, with anterior stromal involvement/ any clock hours with mid stromal involvement
SEVERE	Extends upto Descemet’s membrane/ perforation

TREATMENT OF PUK [50]

The management of PUK depends on the severity of findings within the cornea and the extent of extra-ocular disease. The treatment initiated for the systemic autoimmune disease has been found to have beneficial effects on ocular manifestations. Regardless of the management of corneal disease, results will be disappointing unless aggressive treatment of the systemic disease is considered. The current treatment strategy for PUK with underlying systemic disease is a combination of systemic corticosteroids with a cytotoxic agent during the acute phase of the disease. The exact cytotoxic agent may differ according to the underlying systemic disease.

The primary goal of medical treatment for ocular disease is to reduce inflammation, promote epithelial healing, and to minimize the stromal loss. Though there have been advancements in immune-modulatory and biologic agents, the outcome of PUK depends primarily on the accompanying disease, and timely diagnosis and treatment. This re-emphasis the need for identifying the underlying cause of PUK. Hence a stepladder approach should be considered for the management of PUK starting from diagnosis to local, systemic and surgical treatments.

AIM OF MANAGEMENT OF PUK:

1. Identifying the etiology

2. Facilitating epithelial wound repair

3. Check ulceration and support repair

ESTABLISHMENT OF ETIOLOGY AND PRIMARY THERAPY

- Examine eyelids, corneal sensation and tears-Schirmer's test
- Obtain cultures and scrapings- gram stain, KOH mount
- Debride devitalized tissue
- Initiate antimicrobial therapy
- Initiate anti-inflammatory therapy
- Systemic evaluation (e.g., for collagen-vascular disease)

Total count, Differential count, Erythrocyte sedimentation rate, C-reactive protein, Random blood sugar, Rheumatoid factor, Urine routine, Chest X-Ray, Mantoux test, Anti-nuclear antibody, anti-HCV antibodies, Anticyclic citrullinated peptide antibodies, Complete metabolic panel Sacroiliac joint radiographs, IgE levels, rapid plasma regain, gastrointestinal evaluation fluorescent treponemal antibody absorption(FTA/ABS) assay, Lyme antibody, scleral biopsy. Perform dermatological evaluation (e.g; for acne rosacea, herpes, cutaneous vasculitis, psoriasis,)

Facilitate epithelial wound repair

- Administer tear substitutes, lubricants; punctal occlusion can be done in severely dry eyes
- Eyelid closure (pressure patching, taping, or tarsorrhaphy)
- Therapeutic soft contact lens
- Surgical therapy
- Conjunctival transplantation
- Keratoepithelioplasty

Check ulceration and support repair

- Tissue adhesive
- Glued-on hard contact lens
- Anti-inflammatory agents
- Progestational steroids
- Systemic corticosteroids
- Immunosuppression
- Surgical therapy
- Conjunctival flap
- Conjunctival resection
- Corneoscleral lamellar graft
- Lamellar keratoplasty
- Penetrating keratoplasty

LOCAL TREATMENT

Local bacterial and viral infections that cause PUK are usually relieved with local targeted treatment. Lubricate the ocular surface with preservative-free lubricating agents. This is done as most of the patients with PUK also suffer from tear film abnormalities. These agents are also helpful for removing or diluting harmful inflammatory proteins and mediators on the ocular surface. In patients with marginal ulcerative keratitis without an accompanying systemic disease, eyelid hygiene and topical corticosteroids can be used and tapered according to the clinical response. A topical antibiotic is recommended before corticosteroid use.

Collagenase inhibitors or collagenase synthetase inhibitors, such as topical l% medroxyprogesterone and topical 20% acetylcysteine, may be of limited benefit in reducing additional stromal ulceration. Topical corticosteroids are not appropriate in patients with related systemic disease, because these drugs inhibit new collagen production and thereby increase the risk of perforation. Oral tetracycline derivatives may provide additional benefit in preventing further stromal loss by decreasing protease activity.

In cases of acne rosacea with limbal ulceration, administration of systemic tetracycline (250 mg orally four times daily for 1 month,

followed by tapering doses) may be effective in promoting epithelial closure and may suppress stromal inflammation and collagenolysis.

In patients with abnormalities of eyelid-globe relationships, correction of the anatomical disorder will facilitate epithelial recovery. Correction may include epilation or cryoablation of aberrant lashes in trichiasis and appropriate repair of eyelid ectropion or entropion. The liberal use of artificial tears and ointments may promote epithelial migration in many patients with tear deficiency, exposure, or irregular epithelium. Preparations conatining sensitizing preservatives, like thimerosal must be avoided. Prefer an unpreserved eye drop or ointment. In patients with severe dry-eye conditions, punctal occlusion by thermal or electrical cauterization may augment the effect of tear substitutes.

Eyelid closure can encourage resolution of persistent epithelial defects. In some cases, pressure patching or the use of tape may be sufficient to encourage reepithelialisation.

Fibronectin has been shown to be an integral part of corneal epithelial wound healing. Uncontrolled clinical trials have suggested it may be effective in the treatment of persistent epithelial defects. In alkali-burned rabbit corneas, fibronectin has been shown to improve epithelial cell adhesion. Still, the use of this compound is investigational and will require appropriate clinical trials before its efficacy can be established.

In patients with persistent epithelial defects following chemical burns in whom healthy donor tissue is not available in the fellow eye, lenticules of donor cornea covered by epithelium may be placed at the corneoscleral limbus. The epithelium spreads from the donor lenticule and resurfaces the recipient cornea with functionally normal epithelium.

CHECK ULCERATION AND SUPPORT REPAIR

Management should be aimed at suppressing or at least delay stromal ulceration or perforation until neovascularization can provide serum antiproteases, macroglobulins, and other inhibitors of collagenolytic enzymes or until management strategies such as immunosuppression can reduce the inflammatory response, and healing provides adequate structural reinforcement. Depending on the situation, any one or a combination of the following approaches may be employed during this phase of therapy.

Tissue Adhesives [51]

For limiting ulceration tissue adhesive isobutyl cyanoacrylate is the ideal technique. Many experimental and clinical experiences reinstates that the application of adhesive in any eye with stromal ulceration or impending perforation will prevent further ulceration and support the stroma through the period of neovascularization and repair . Instead of

awaiting perforation and its attendant complications, this proactive measure of early use of tissue adhesive in nearly any case of persistent epithelial defect with progressive stromal ulceration is a boon. The cyanoacrylate glue is easily and quickly applied to the nonperforated cornea at the slit lamp with minimal preparation and complication. The mechanism of action is believed to be through the exclusion of inflammatory cells from the ulcerating stroma. When the glue is applied, a durable bandage contact lens is usually applied to provide comfort and to reduce the risk of glue dislodgment. Prophylactic antibiotics are mandatory. Cycloplegics, lubricants, and steroids can help reduce inflammation and discomfort.

Anti-inflammatory Agents[52]

Topical corticosteroids are advocated in the early therapy. In eyes in which severe inflammation is present but ulceration is progressive, their use can become dangerous. . As corticosteroids can interfere with collagen synthesis, alternatively progestational steroids reduce inflammation, curb collagenase activity with less delay in collagen synthesis.

In severe cases of herpetic stromal keratitis or uveitis, the use of systemic steroids is justified as a means of halting inflammatory process without facilitating further stromal ulceration. Systemic corticosteroids

can also be effective in peripheral ulcerative keratitis associated with relapsing polychondritis, rheumatoid arthritis, and systemic lupus erythematosis. Dosage selection depends on both systemic manifestations and ocular response. Most patients are begun on 60 to 300 mg prednisone per day, followed by tapering of the dose and switching to an alternate-day regimen if possible. In many cases, the combination of systemic steroids with immunosuppression is usually more effective than either modality alone.

Corticosteroids, whether administered topically or systemically, are usually ineffective in peripheral ulcerative keratitis associated with Wegener's granulomatosis or Mooren's ulcer. They may be effective, however, in reducing inflammation while the patient is being immunosuppressed.

Systemic immune modulation

Glucocorticoids

Systemic corticosteroids are the traditional first-line therapy for acute phases of PUK, but alone are often unable to inhibit disease progression or overcome the autoimmune disease. The usual starting dose is 1 mg/kg/day maximum 60 mg/day), followed by a tapering schedule based on clinical response. Pulsed methylprednisolone 1 g/day for 3 consecutive days, followed by oral therapy, might be initiated in patients

with imminent danger of vision loss. Immunosuppressive drugs or biologic agents are administered with or without glucocorticoids in cases refractory to glucocorticoids and when glucocorticoid-associated adverse effects become an issue. Common complications of systemic corticosteroids, such as osteoporosis, exacerbation of hypertension and diabetes, electrolyte imbalance, and gastrointestinal bleeding, may be avoided with initiation of immunosuppressive drugs. Although steroids have a profoundly positive effect on ocular and systemic symptoms, they fail to reduce the high mortality rate in patients with rheumatoid vasculitis[18]. Therefore, the addition of cytotoxic chemotherapy comes up to successfully treat these patients.

Immunosuppressives/immunomodulators

Immunosuppressives used in cases of peripheral ulcerative keratitis with auto-immune etiology include antimetabolites, alkylating agents, T cell inhibitors, and biologic agents. Cyclophosphamide is the most commonly used drug.

Methotrexate, azathioprine, mycophenolate mofetil, and leflunomide are suitable antimetabolite agents. Methotrexate and azathioprine are the two most commonly used antimetabolites in cases unresponsive to oral corticosteroids and with recalcitrant rheumatoid PUK. Oral methotrexate in doses ranging from 7.5–25 mg/week and

azathioprine 1.0–2.5 mg/kg/day have been reported to be effective. Recent studies indicated better inflammatory control and fewer side effects with mycophenolate mofetil (1.0 g twice daily) than with methotrexate or azathioprine. Clinical reports now suggest that leflunomide might be efficacious in the treatment of ocular inflammation. The alkylating agents, cyclophosphamide and chlorambucil, are suggested for use in severe progressive cases and in cases unresponsive to methotrexate or other antimetabolites.

In a retrospective case series, Messmer and Foster reported that cytotoxic immunosuppressive agents are highly effective in patients resistant to systemic corticosteroids[52]. Cyclophosphamide was reported to be the most effective agent in their series; however, methotrexate was reported to be very effective with less potential toxicity and was suggested as a potential first choice for immunosuppression. Cyclophosphamide may be administered orally at doses of 1–2 m/kg/day or as pulsed intravenous therapy every 3–4 weeks under rheumatologic or internal medicine guidance. Data on the use of cyclosporine A in patients with rheumatoid arthritis and severe inflammatory eye disease suggest that cyclosporine could be the initial immunosuppressant treatment of choice in idiopathic cases or in those not associated with systemic vasculitis, particularly if there are no serious concerns about

nephrotoxicity. Hence, cases associated with systemic vasculitis more potent immunosuppressives like cytotoxic (eg, cyclophosphamide) or antimetabolite (eg, methotrexate) therapy is instituted.

Biologic agents

Infliximab is a specific, chimeric monoclonal antibody against pro-inflammatory cytokine tumor necrosis factor alpha (TNF-α). It has been approved for use by the US Food and Drug Administration in 1999. Use of infliximab for ocular inflammation was first reported in 2001 for patients with panuveitis and rheumatoid arthritis-associated scleritis. It is currently indicated for treatment of connective tissue or vasculitic autoimmune diseases, and accompanying PUK, as well as other ocular inflammatory states, such as necrotizing scleritis and uveitis. It is a specific, chimeric monoclonal antibody against proinflammatory cytokine tumor necrosis factor alpha (TNF-α), which stimulates production of the matrix metalloproteinases responsible for corneal stromal lysis in PUK. It binds both soluble and transmembrane TNF-α by blocking its receptor. Cells expressing transmembrane TNF-α bound to infliximab may also be susceptible to complement-mediated lysis, potentially increasing its anti-inflammatory effect. Dosing of infliximab varies from 3 mg/kg intravenously for rheumatoid arthritis to 5 mg/kg intravenously for Crohn's disease, and is administered at weeks 0, 2, and 6, and then every

8 weeks for up to 18 months. Improvement usually occurs 1–2 weeks after the first infusion. Although the optimal frequency and dosing of infliximab for PUK and/or corneal perforation have not yet been established, a dosing regimen similar to that used for rheumatoid arthritis seems reasonable. The maintenance of remission must be weighed against potential adverse events, because the long-term efficacy and safety of biologics for use in ocular inflammation is unknown. Before administering infliximab, opportunistic infections such as tuberculosis must be ruled out, in addition to absolute contraindications such as congestive heart failure. The reported side effects of long-term use include increased risk of opportunistic infections, anaphylaxis, diarrhea, cardiac failure, and resistance. More serious side effects, such as lymphoproliferative disorders, malignancy, hepatotoxicity, and endogenous endophthalmitis, have been reported. Moreover, increased risk of thrombosis was reported, ranging from branch retinal vein occlusion to myocardial infarction and pulmonary embolus; therefore, special care must be taken when using infliximab and other biologic agents. Other biologics, including etanercept (Enbrel) and rituximab (Rituxan), have been used for the treatment of PUK. Etanercept is a human recombinant dimeric fusion protein that mimics the effects of naturally occurring soluble TNF-α receptors. It has been used for the treatment of refractory uveitis, necrotizing scleritis, and keratitis, but is

less efficacious than infliximab for the treatment of ocular inflammation. This may be due to the ability of infliximab to bind to membrane-bound TNF-α, in addition to free-floating cytokines.

In a study by Thomas et al, 3 patients with progressive rheumatoid arthritis associated keratolysis refractory to steroids and immunosuppressives were given infliximab infusion. There was marked reduction in conjunctival injection and epithelial defects healed. Clinical improvement occurred in first week of infusion. They also showed synergistic action with methotrexate administration. Hence, infliximab can be considered as an alternative in cases refractory to corticosteroids and methotrexate.[53]

Rituximab is a chimeric IgG kappa antibody is directed against CD20-α antigen. It has been used to treat refractory PUK associated with Wegener granulomatosis. It has shown to reduce anterior ocular inflammation and corneal perforations. Hence it might be the drug that could halt the progress of PUK associated with Wegener's and also other vasculitic PUK.[54]

Surgical Technique

Surgical intervention is enforced in patients with progressive, destructive corneoscleral inflammatory disease. Aim of the surgical techniques is to reduce inflammation or to reinforce the cornea or sclera. But control of the underlying disorder is pending. Hence, these techniques by themselves are ineffective in providing a lasting cure.[50] A partial conjunctival flap may be successful in reducing limbal inflammation and arresting further ulceration. But ulcer recurs and ultimately results in perforation.

When the defect is more than 2 mm, cyanoacrylate glue may not provide sufficient tectonic support. Loss of scleral and adjacent limbal tissue secondary to rheumatoid arthritis, Wegener's granulomatosis, or periarteritis nodosa can occur. In such cases, a need arises to reinforce the entire area to prevent severe consequences. When both cornea and sclera get involved, lamellar corneoscleral grafting is the modality of therapy. Such grafts are dissected individually from the donor eye and cut to appropriate dimensions to match the patient's eye. The corneal sutures are placed first, and the scleral section is then shaped to match the area of scleral defect. In cases in which only the cornea is involved and the lesion is peripheral, a lamellar keratoplasty is preferred if an appropriate corneal bed for the graft is dissected. When the disease involves a reasonable

portion of the cornea and the limbal region with sufficient necrosis that precludes dissection of an adequate lamellar bed, then a penetrating keratoplasty may be required. But this has the risk of vascularization, rejection, and formation of peripheral anterior synechiae.[50]

Conjunctival resection

It is a minor room procedure done under topical anaesthesia. Isolation and excision of 2 to 4mm strip of conjunctiva adjacent to ulceration. In this process the risk of excising perilimbal strips of conjunctiva are minimal, and the use of this procedure decreased the need for bandage lenses or tissue adhesive. When Tenon's capsule was included in the resection there seems to be no added therapeutic effect.

The fact that complete healing of rheumatoid corneal ulcerations occurred within a few days after conjunctival resection suggests a cause and effect relationship. The early use of this technique for rheumatoid stromal ulcers is advocated, especially when the area of ulceration is extensive, when the stromal loss is progressive, and when stromal reserve is minimal. Early conjunctival resection can shorten the hospital stay, and in more severe cases could prevent perforation. On the basis of successful treatment in patients of peripheral rheumatoid corneal ulcerations, conjunctival resection has an importance in the management of this condition.[55]

Amniotic membrane transplant (AMT)

An amniotic membrane can be used as a patch or graft to decrease inflammation and to promote re-epithelization. The biologic properties of amniotic membrane are responsible for decreasing inflammation .Expression of Fas ligand and human leucocyte antigen-G reduce inflammation and activate suppressor T cell mechanisms. Besides, they produce a variety of anti-angiogenic factors, protease inhibitors, growth factors, anti-inflammatory factors and immune molecules to facilitate healing of corneal ulcer. The AM stromal matrix was found to suppress the expression of certain inflammatory cytokines that originate from the ocular surface epithelia, including interleukin-1alpha and interleukin-1beta interleukin-2, interleukin-8, interferon-gamma, and tumor necrosis factor-alpha. This procedure has been used as a temporizing measure only by controlling inflammation to gain time before penetration keratoplasty or lamellar keratoplasty. AMT can also prevent the harmful effects of corneal ulcer aggravation by topical corticosteroids.[56, 57.]

Treatment of PUK in Rheumatoid arthrits

- Systemic steroid – acute stage
- Increase methotrexate dose if patient is already on it
- If ineffective → Mycophenolate
- If ineffective → Anti-tumor necrosis factor

- Improved visual and anatomical outcomes
- All immunosuppressive side effects were reversible
- Hence judicious use of immunospressive therapy for PUK is mandated

Treatment of Mooren's ulcer[59]

The improvement in the treatment of Mooren's ulcer from the study emphasizes on the following principles:

1. Removal of corneal ulcer and infiltrate
2. Excise conjunctiva and episclera adjacent to corneal ulcer with LKP
3. Fresh lamellar graft with scleral rim
4. Good host –graft junction
5. Topical steroids and 1% cyclosporin-A

REVIEW OF LITERATURE

Sharma et al[1]

In this prospective study, 76 eyes of 65 patients were recruited. 68% of them belong to north India. 73% belong to low socio-economic state. 37% were habitual smokers. Nearly 2/3rd of them belong rural population. 17 % had bilateral disease. Mooren's ulcer (31.5%) was the most common etiology followed by collagen vascular diseases (19.7%) and infections (19.7%). PUK occurred following intra-ocular surgery at same site in 10 cases (13.15%).

The most common intra-ocular complication was complicated cataract (12/24 cases). Extra ocular association with PUK was most frequently meibomitis (17/31). Rheumatoid factor was positive in 15 of the 20 patients in whom serology was done.

They classified the eyes based on the severity of corneal involvement. Mild cases healed by 8 ± 2 days. Moderate cases healed by 17 ± 5 days. For severe cases the healing time was 34 ± 12 days.

2/3rd of cases were treated with topical cyclosporine and steroids. 47% had severe disease of which nearly half required surgical intervention (12 cases underwent penetrating keratoplasty; 5 cases of

patch grafts). The remaining cases were on oral or topical immunosuppressive.

Perforation occurred in 22% (17 eyes). Anatomical integrity was achieved in 83.3%. 6 eyes went for phthisis, 4 following surgical management. Recurrence was observed in 3 eyes. The delay between occurrences of the initial symptom to presentation to a tertiary eye care correlated with disease severity.

Cartwright et al [9]

A retrospective analysis over a 10 year period of 70 patients with PUK requiring systemic immunosuppression was done. 57 % were female and 21% had bilateral disease. Mean age was 65 years. Mean length of follow up was 4.6 years. 34% had blepahritis association. 16% developed corneal perforation most of whom had RA (64 %). It was found that 87% of patients had a systemic association most commonly RA (66%) followed by psoriasis or psoriatic arthritis (6%), acne rosacea (6%) and granulomatosis with polyangitis.

All patients were given systemic steroids (22% intravenous and remaining oral). Topical steroids was given in 31% of patients at presentation but later stopped. For 36% of patients steroids were continued and not tapered. In 51% of patients disease control was

achieved with a single drug. 40% required a second drug to manage the disease progression, most commonly methotrexate (67%) followed by mycophenolate (21%).gastrointestinal upset was the most common side effect. 5 of 11 perforated eyes were treated with cyanoacrylate glue but they underwent corneal transplant eventually. 82% of the eyes with transplant had clear cornea at last follow up. Approximately 11% of eyes developed glaucoma or ocular hypertension.

Thus aggressive systemic anti-inflammatory therapy improved the visual and anatomical outcomes, and also decrease occurrence of perforations. Hence, this study mandates the need for management of PUK with immunosuppressants.

Watson PG et al[21]

Low dose fluorescein angiographic studies of the anterior segment in various etiologies of peripheral corneal ulcer by P.G.Watson revealed that each etiology had a specific angiographic pattern. In Mooren's ulceration, there is characteristic leakage from the deep vascular network derived from the long posterior ciliary circulation. In unilateral Mooren's there is poor or absent perfusion of the superficial network. Vascularisation of the ulcer is from deep vessels. In bilateral aggressive Mooren's ulcer, superficial network is normal but the deep vessels supply

the ulcer with leakage. In bilateral indolent Mooren's ulcer, there is an only vasodilated deep vessel that supplies the ulcer.

In rheumatoid arthritis, one of the common causes of peripheral ulcerative keratitis, angiography is suggestive of vaso-occlusion of capillaries and venular circulation of the episcleral and in severe cases involving the conjunctival circulation also. Venular non-perfusion and disruption of limbal arcades is seen in limbal vasculature. Base of the gutter shows fine new vessels entering it.

In cases of systemic vasculitis such as Wegener's granulomatosis and periarteritis nodosa the guttering and angiographic changes are different. There is characteristic immediate and intense leakage from the tips of the limbal arcade, from which develop new leaky vessel loops.

Based on these angiographic evidences it is made clear that the inflammatory response is mediated through the deeper vessels directed to corneal stroma.

Chen et al[50]

From 1960 to 1996, 550 consecutive cases of Mooren's ulcer were seen in Zhongshan Ophthalmic Center, Guanghzou, China. The clinical features of Mooren's ulcer outcomes of lamellar keratoplasty (LKP) surgery were analysed retrospectively.

Based on age group, it was found that 113 (20.6%) of cases belonged to younger group(<35 years) and 453(79.4%) in older age group. Male to female sex ratio was 1:0.74.

70% of cases were unilateral, 30% are bilateral of which 68.5% belonged to the older age group contrary to the observation made by Wood and Kaufman.

45% of cases involved half the limbus and 21% involved the entire limbus.in that 70% of the ulcers involved the medial or lateral quadrant of the limbus. Depth of the ulceration involved 1/3rd to 1/2 of the corneal stroma.

Out of 715 eyes 95 eyes got perforated**.** In that 62 eyes (65.3%) were bilateral and 33 eyes (34.7%) unilateral. According to age, older group (56.8%) had more perforations than the younger group (43.2%). Based on location limbal cornea (48 eyes) was more affected than peripheral (32 eyes) and central corneas (15 eyes)

Mild anterior uveitis with fine dusty keratic preciptate local posterior synechiae developed in 42 eyes (6.8%). Complicated cataract developed in 14 eyes (2.3%)

Treatment protocol for mooren was subdivided into three eras 1.1960 to 1975 - Topical resection the corneal ulcer and on failure LKP

was done.the final cure rate was 72.4% 2.1976 to 1989 – Topical resection of corneal ulcer + episclera + conjunctiva adjacent to ulcer with LKP in failed cases had cure rate of 89.6% 3.1990 to 2006 – same as in 1976-89 with topical 1% cyclosporine A had a cure rate of 95.6% Recurrence occurred in nearly 25.6% of the cases (141/550).It was more common in older age group (95 cases). First recurrence occurred at the same location. Multiple recurrence occurred at different location also.63.1% were bilateral cases.

The improvement in the treatment of Mooren's ulcer from the study emphasizes on the following principles:

1. Removal of corneal ulcer and infiltrate
2. Excise conjunctiva and episclera adjacent to corneal ulcer with LKP
3. Fresh lamellar graft with scleral rim
4. Good host –graft junction
5. Topical steroids and 1% cyclosporine-A.

Tauber et al[3]

An analysis of the management of 47 patients (61 eyes) with peripheral ulcerative keratitis (PUK) to establish guidelines for systemic chemotherapy was made. 25 patients (53%) had systemic disease. Of these, 25% were newly diagnosed after participating in the study. Their

mean follow up was 20 months. 14 patients (30%) had bilateral PUK. Average degree of ocular inflammation was grade 2. Mean corneal ulceration at presentation was grade 2 (25-50% depth). 7 out of 15 cases of grade 1 ulcer (47%) had rheumatoid arthritis. 9 out of 15 cases (60%) of Mooren's ulcer was more commonly associated with >50% depth ulcers (grade 3or4). Of the 17 patients with scleritis 12 had necrotising scleritis (70.5%) rheumatoid arthritis (58%) being the most common etiology. 7 patients had uveitis (14.8%).

20 of the 38 patients who underwent biopsies had (52.6%) active vasculitis 20 had mast cell involvement. 8 patients had granulomas. 10 of the 14 patients with necrotising scleritis had active vasculitis. High tire of rheumatoid factor correlates with diagnosis of rheumatoid arthritis in all patients tested. Circulating immune complexes were identified in 9 out of 10 patients with vasculitis. There was no worsening of the vision during course of study in patients with vasculitis, but in cases of Mooren's ulcer final visual outcome showed loss of 2 Snellen lines. This study emphasizes the need for thorough historical review of systems and evaluation of biopsied tissues.

Thomas et al[45]

Three patients with progressive rheumatoid arthritis associated keratolysis refractory to steroids and immunosuppressives were given

infliximab infusion. There was marked reduction in conjunctival injection and epithelial defects healed. Clinical improvement occurred in first week of infusion. They also showed synergistic action with methotrexate administration. Hence, infliximab can be considered as an alternative in cases refractory to corticosteroids and methotrexate.

Ngan et al [47]

In this study by Ngan et al of 18 eyes of 14 patients with Mooren's ulcer, amniotic membrane graft was done with complete epithelialization of defect in mean time of 12.4 days. In 10 eyes vision improved to 6/12 or better. Thus amniotic membrane graft can be an alternative when systemic immunosuppressive drugs cannot be given.

Jia et al [49]

Reported 12 patients with peripheral ulcerative keratitis who underwent amniotic membrane transplant after anterior chamber wash with hyaluronate and put on topical corticosteroids. Corneal ulcers healed at 1 to 2 weeks, stromal edema decreased within a month and graft fused by 7 to 10 days. They found that corticosteroid prevented recurrence and also lighten scar and improve corneal transparency. Thus a combined approach is essential to provide a conducive environment for subsequent keratoplasty.

Raizman MB[51]

In this study by Raizman et al 17 eyes of 14 patients with PUK had underwent tectonic keratoplasty. Immunosuppressive drugs were administered in all but 2 cases. Of this 8 of 17 eyes had improved visual acuity and 6 eyes had visual acuity more than 6/60 or better.

Sainz et al[52]

In this review by Sainz et al of 47 cases of scleritis associated with peripheral keratopathy, 24 patients (34 eyes) had PUK. There was equal distribution among male to female with sex ratio 1:1.10 of the 24 cases of PUK were bilateral. Relative risk analysis had found that in comparison of patients with only scleritis and those with scleritis and peripheral keratopathy, patients with peripheral keratopathy were 5.3 times more likely to develop necrotising disease and 4.8 times to have undergone ocular surgery previously at that site. They had 3.4times more likely chance to have Wegener's granulomatosis and 3.7 times more likely to have an infectious disease.

PUK had more frequent association with necrotising scleritis (16 cases, 66.7 %) and previous ocular surgery (14 patients, 58.3%). PUK also had more association to impending corneal perforation (24 patients, 100%). Results showed that every cases of PUK had associated systemic

disease (24 cases, 100%). Rheumatoid arthritis, Wegener's granulomatosis and infectious disease were more associated with scleritis with peripheral keratopathy than with scleritis alone.

The reason behind increased incidence of PUK following ocular surgery could be attributed to the immune-complex mediated vasculitic damage at the site of surgical trauma. 90% (9patients) had underlying autoimmune disease that was treated with immunosuppressives.

O'Donoghue et al [13]

In this study by E O'Donoghue et al of 53 eyes of 42 patients with scleritis following ocular surgery they found that necrosis was 4 times more likely to occur in comparison to scleritis in non-operated patients. 75% developed disease after multiple ocular surgical procedures within a mean period of 9 months of which 40% had association with a pre-existing medical disorder. For single ocular surgical procedures the mean interval was 9.6 years and had 90 % association with pre-existing medical disorder. Totally 63% had underlying medical disorder of which connective tissue disease was the commonest. 70% were females re-instating the fact that causative factor could be autoimmune.

A delayed type of hypersensitivity response is observed on histology. CD4+T-cells are sensitised to altered or exposed antigens that

immune privilege following surgical trauma or due to temporary ischemia post-surgery. Squint surgery and buckle for retinal detachment causes ischemia that could lead on to this condition. During cataract surgery, limbal approach has more incidence than corneal approach, as it causes more vascular disruption.

Another theory is that triggering factor for immune response could be at other places that could manifest in the eye after a long period of time. Immune complex formed elsewhere in the body gets deposited in deep episcleral vessels by surgical procedures. This could be the possible explanation for single surgical procedure to develop scleritis after a prolonged period. Alternate theory could be molecular mimicry of ocular antigen with tissue antigen or a microbial antigen (ankylosing spondylitis and kleibseilla)

Akpek et al[14]

He reported a previously healthy 80 year old male who underwent clear corneal cataract extraction following which he developed PUK 1 week later. On systemic evaluation patient was found to have active rheumatoid arthritis

Burkholder BM et al[15]

In 2016, Burkholder et al reported a case of PUK developing following femtosecond assisted LASIK in a 29 year old Filipino female. Patient had stromal opacification in the flap and peripherally on day followed by diffuse lamellar keratitis the next day. The patient on probing gave a 7year history of renal biopsy for proeteinuria. Patient was later diagnosed to have membranous glomerulonephropathy

Keenan et al [53]

In this case report, a 28 year old woman with hypothyroidism and hyperlipidaemia presented with peripheral corneal thinning, superficial vessels, tiny epithelial defect and nil positive laboratory findings suggestive of PUK. Patient was put in a diagnostic dilemma between Fuchs superficial marginal keratitis and Terrien's marginal degeneration. 5 years later patient ws positive for p-ANCA and skin biopsy showed leukocytoclastic vasculitis revealing diagnosis as PUK. This emphasizes the importance of long term continued laboratory monitoring for a case of ocular inflammation with unknown etiology

Pokharel A et al [16]

There has been a report of PUK following acute bacterial conjunctivitis which indicates that infection could trigger development of PUK in an otherwise normal cornea.

PART II

PART 2

AIMS AND OBJECTIVE

To determine the demographic characteristics, etiology, clinical features and management outcomes of peripheral ulcerative keratitis presenting to the cornea department of Aravind Eye Hospital and Postgraduate institute of Ophthalmology, Madurai.

MATERIALS AND METHODS

STUDY PROTOCOL

- Design: Prospective, observational study.
- Study population: Patients coming to out-patient department, Aravind Eye Hospital, Madurai.
- Sampling technique: A hospital based consecutive sample of cases with peripheral ulcerative keratitis during the study period.
- Sample size: All patients presenting with features of peripheral ulcerative keratitis during the study period.
- Study period: 18 months.
    - ❖ Case recruitment: 1 year (from 01/01/2016 to 31/12/2016)
    - ❖ Follow-up: 6 months (from 1/1/2017 to 30/6/2017)

INCLUSION CRITERIA

- Ulcer within 2mm from the limbus with epithelial defect and stromal thinning or degradation.
- Patient who is willing to give consent and come for follow up visits.

EXCLUSION CRITERIA

- Demarcation by grey line from central cornea with intact epithelium (Terrien's marginal degeneration)
- Central corneal ulcer with a peripheral component

METHODOLOGY

Approval from Institutional Review Board was obtained and patient selection was based on the inclusion and exclusion criteria.

We included 68 consecutive cases diagnosed as peripheral ulcerative keratitis who presented to the cornea department, Aravind eye hospital, Madurai over a period of 12 months.

Any crescent shaped destructive inflammation within 2 mm of limbus along with epithelial defect, with stromal inflammation, degradation or thinning matching the inclusion criteria were included in the study.

Patient details such as age, gender, address were collected. An exhaustive history of symptoms, duration of illness, systemic association and treatment were recorded. Ocular history includes redness, irritation photophobia and pain. A meticulous history of joint swelling, joint pain, oral ulcer, nasal discharge is taken to rule out systemic associations.

Recording of best corrected visual acuity (BCVA) using Snellen's visual acuity chart at 6 metres distance was done. A careful ocular examination using slit lamp was done.

The area of epithelial defect, stromal thinning, ulcer depth, infiltration and vascularisations were measured in clock hours. Based on the severity, PUK was classified as mentioned in Sharma et al as mild, moderate and severe form. Mild disease had an extent of 2 clock hours' with superficial corneal involvement upto anterior stroma. Moderate PUK had two to four clock hours' involvement with depth upto the mid-stroma. When the depth of ulcer was upto the descemet's membrane or when there was perforation regardless of the clock hour involvement cases were grouped under the severe form.

Patients were carefully examined for scleritis and anterior chamber inflammation at presentation and during subsequent follow up. Associated eye findings such as meibomitis, squamous blepharitis, Climatic droplet keratopathy and pterygium were recorded. Intra-ocular pressure was recorded at presentation and during follow up. Corneal scraping was done and sent for smear Grams'stain and potassium hydroxide wet mount. Culture was done in blood agar and Sabourauds' dextrose agar (SDA) to rule out infective etiology.

Systemic examination includes respiratory system exam, joint examination, to look for any skin lesion to rule out collagen vascular disease. A meticulous history taking helps in identifying the etiology and plan the blood investigations accordingly. Routine blood investigations include Total count, differential count, Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Rheumatoid factor (RF) and Mantoux test. Anti-nuclear antibody was used to confirm collagen vascular diseases like rheumatoid arthritis and Granulomatosis polyangitis.

Based on the etiology and the severity of the disease, cases are managed surgically or medically according to the clinician's judgement. Cases with impending or actual perforation and treatment failure with medication were managed surgically.

During the initial visit and in follow-up patient is checked for visual acuity intraocular pressure and slit lamp examination. The epithelial defect, ulcer depth, stromal thinning and infiltration are monitored serially. Patient is undergone Fundus 90 D examination when the etiology is non-infectious was a routine.

Healing ulcer is defined by as a non-progressive ulcer with filling of crater not stained by fluorescein. Recurrence is defined as reappearance of the ulcer after a period of quiescence of 3 months after stopping medication.

Patients were started on topical antibiotic and steroid combination or plain topical steroids when infectious etiology is ruled out. Commonly used steroid is prednisolone acetate 1%. On resolution the topical steroids are tapered over a period of two to three weeks and then stopped.

In infected cases a rigorous course of antibacterials are prescribed based on culture and sensitivity. Commonly used antibacterial for gram positive cocci is 5% cefazolin sodium and gram negative organism 1.3% tobramycin sulphate is given. Antifungal used routinely is Natamycin 5%, Dosing based on the severity of the ulcer.

In severe cases of impending perforation oral Doxycycline 100mg BD is preferred. Oral steroid can be given in severe cases when it is a non-infective etiology. In cases of collagen vascular diseases like rheumatoid arthritis and granulomatosis polyangitis where the systemic manifestations should also be addressed immunosuppressant were started on consultation with rheumatologist or treating physician. Immunosuppressant can be started if symptoms are severe enough, not responding to oral steroids and in sight threatening conditions. Oral methotrexate 2.5mg once weekly and oral cyclophosphamide 100mg OD has been given in concordance with the rheumatologist. Patients are given tacrolimus eye ointment HS in cases with ocular hypertension on topical steroids previously.

Surgical management includes conjunctival resection tissue adhesives and patch grafts. Conjunctival resection is done for about 2mm from the edge of the peripheral ulcer and 4 mm behind the corneoscleral limbus parallel to the ulcer. Bleeder vessels are then cauterised. For small perforation tissue adhesives like cyanoacrylate glue is applied and then a soft bandage contact lens is placed.

Patch grafts can be circular or crescent shaped depending on the perforation size of the ulcer. Donor cornea from the eye bank is taken and cut into a shape to fit the perforated ulcer and then sutured with 10-O nylon interrupted sutures.

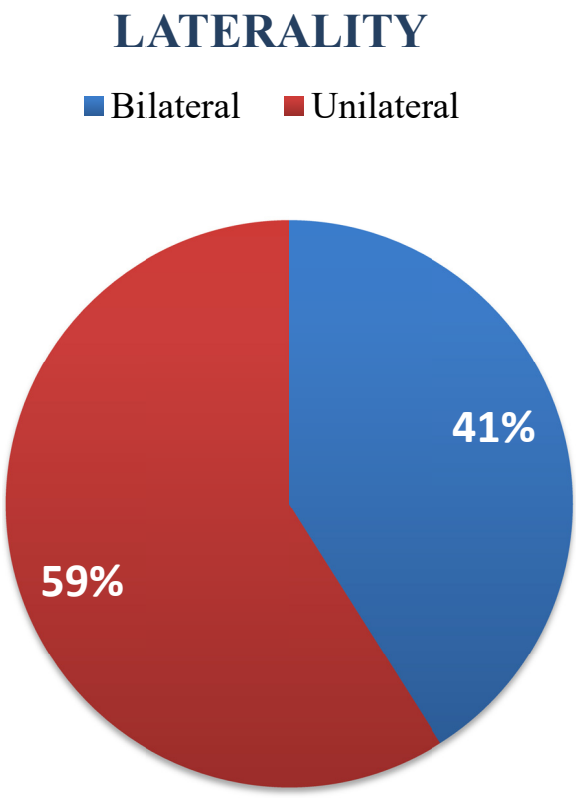
STATISTICAL ANALYSIS

For continuous and categorical variables Mean (SD) and frequency (Percentage) were used respectively. Kruskal-wallis test was done to identify statistical siginificant difference in healing between the grades of PUK. Statistical significance of LogMAR pre and post-treatment visual acuity was assessed using sign rank test. . A p-value of less than 0.05 was considered to be of statistical significance. Statistical analysis was done with the help of statistics software STATA 11.1.

RESULTS

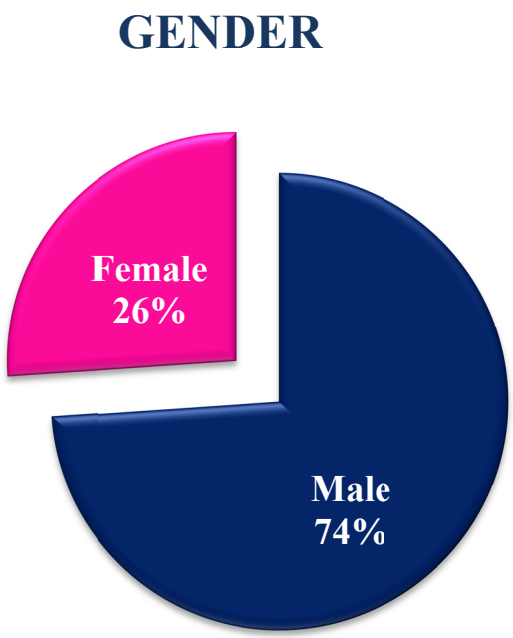
In this prospective study, 98 eyes of 69 patients were recruited. Out of these patients, 5 cases lost to follow up. Henceforth 93 eyes were included for end-point of observation.

GRAPH-1.LATERALITY



Of these patients, 29 cases were bilateral 40 cases had unilateral disease.

GRAPH-2.GENDER DISTRIBUTION



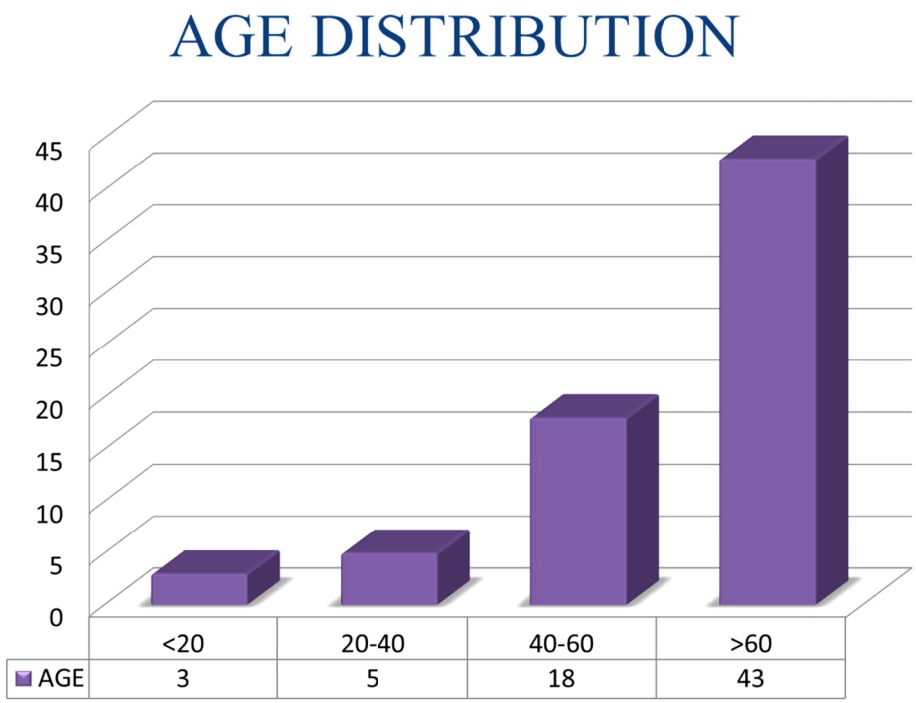
Males were more commonly affected with PUK than females. The male is to female ratio is 3:1

TABLE.1 GENDER DISTRIBUTION IN EACH GRADE OF SEVERITY

Grade	n (%)		Total
	Male	Female	
Mild	5 (23.81)	16 (76.19)	21 (100)
Moderate	21 (77.78)	6 (22.22)	27 (100)
Severe	14 (66.67)	7 (33.33)	21 (100)

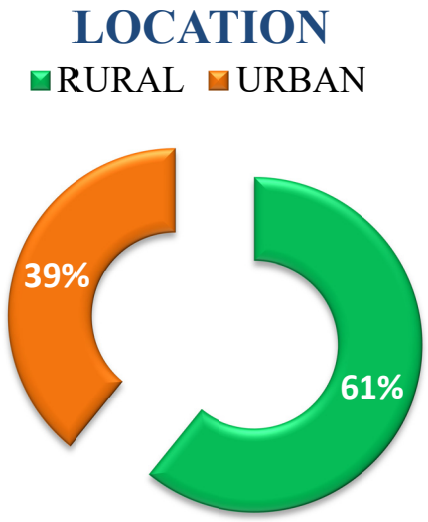
This shows that female had lesser incidence of PUK and also presented with a milder form than men.

GRAPH-3. AGE DISTRIBUTION OF PATIENTS WITH PUK



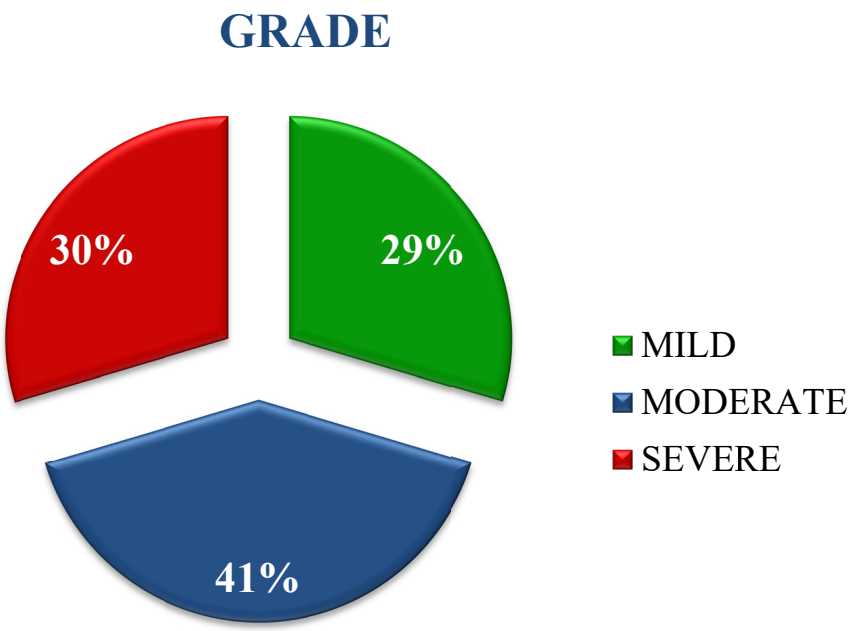
The mean age of presentation is 60.1 ±17years.

GRAPH-4. LOCATION- RURAL AND URBAN DISTRIBUTION OF PATIENTS



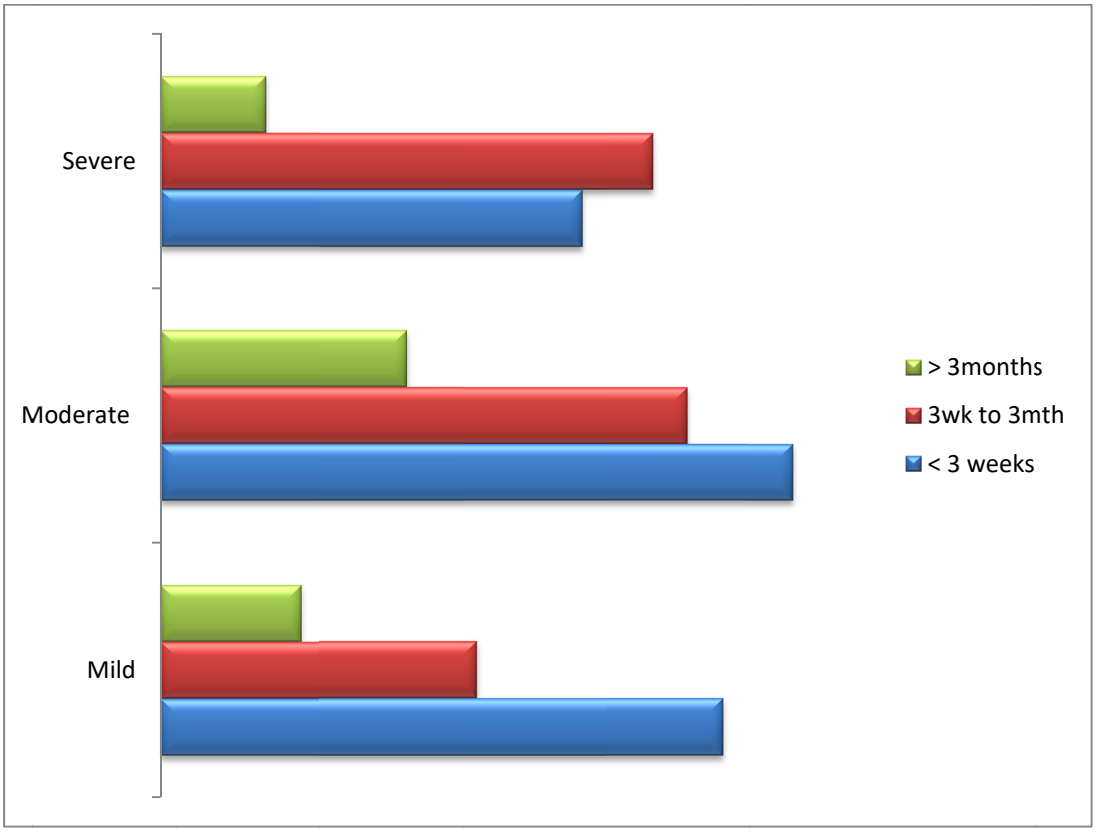
It was found that 24.6% were habitual smokers. Nearly 61% of them belonged to the rural population, and the remaining being urban.

GRAPH-5. CLASSIFICATION OF PUK BASED ON SEVERITY



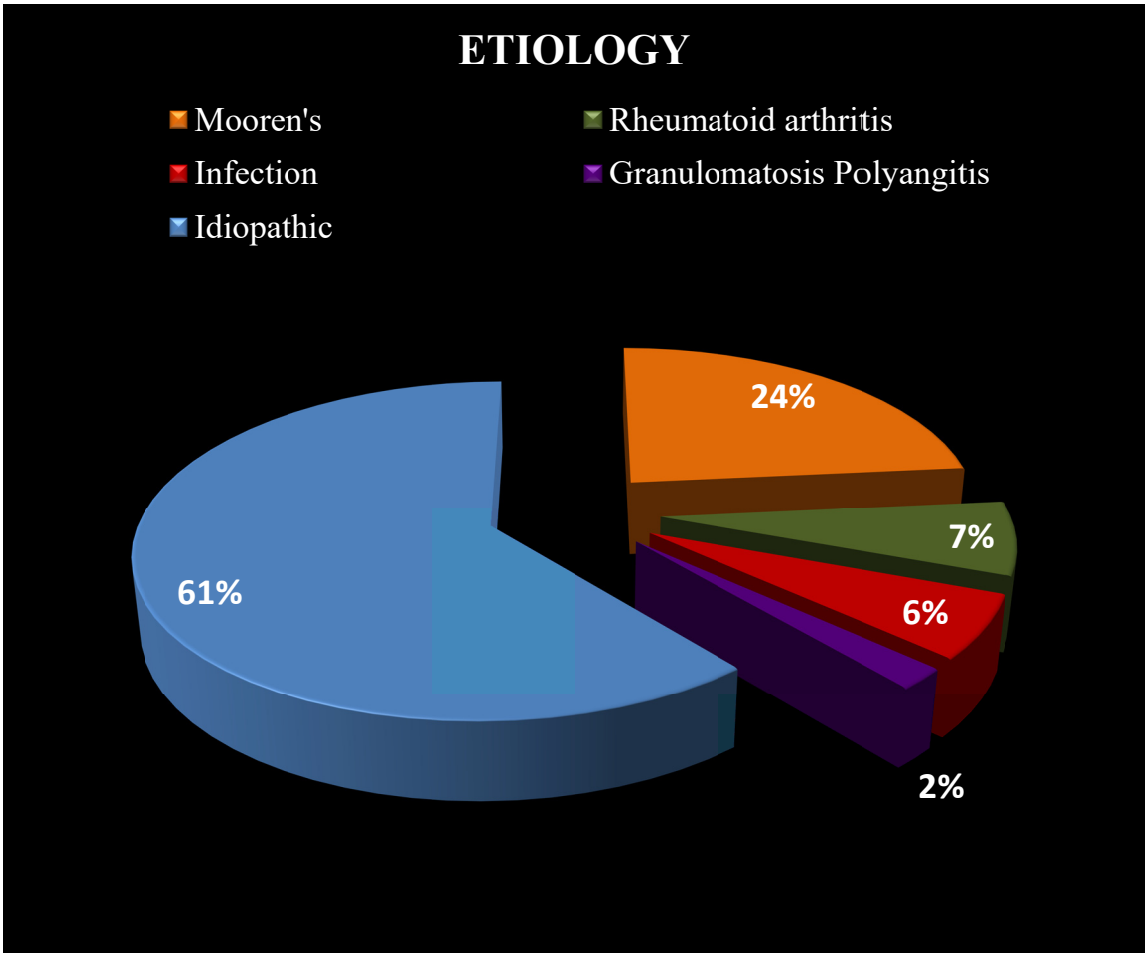
Most common presentation of severity to tertiary eye care centre was of moderate severity. It was found that 40 cases had a moderate grade of PUK. Mild and severe cases had equal incidence of presentation.

GRAPH-6. TIME OF PRESENTATION



The above results shows that patients with severe form of disease had a slightly later presentation. This could be because the disease progressed to a severe form by the time when they reached the tertiary eye care centre. Mild and moderate form of the disease did have a more prompt presentation and hence did not progress to a severe form.

GRAPH-7. ETIOLOGICAL CLASSIFICATION



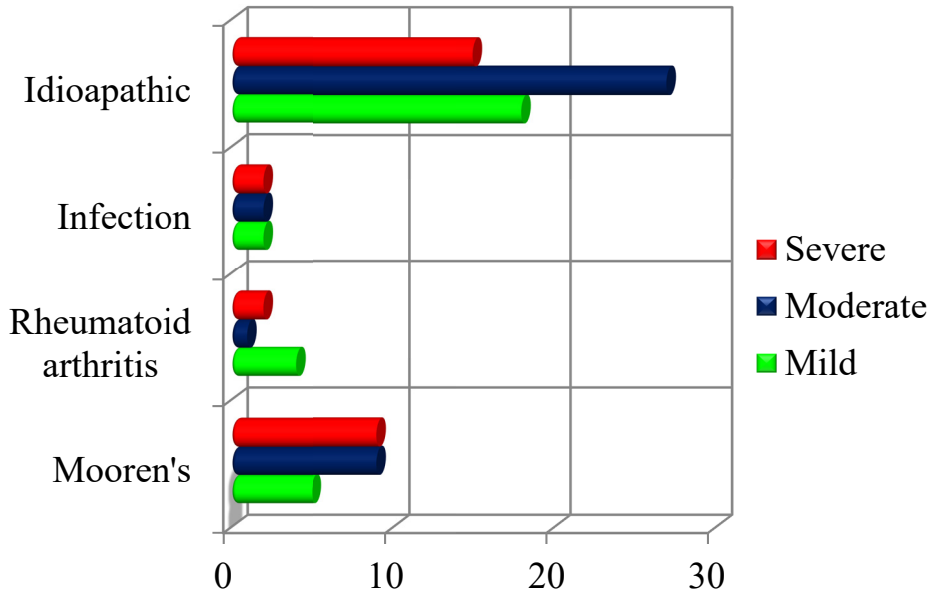
Mooren's ulcer (23.5%) was found to be the common etiology followed by Rheumatoid arthritis (7%), infection (6%) and granulomatosis polyangitis (2%).PUK occurred following intraocular surgeries at the same site in 12.2% of eyes.

Mooren's ulcer was the most common etiology in this study. Male were more commonly affected than females. Most of the perforations in this study occurred in Mooren's ulcer (6 out of 23 eyes).

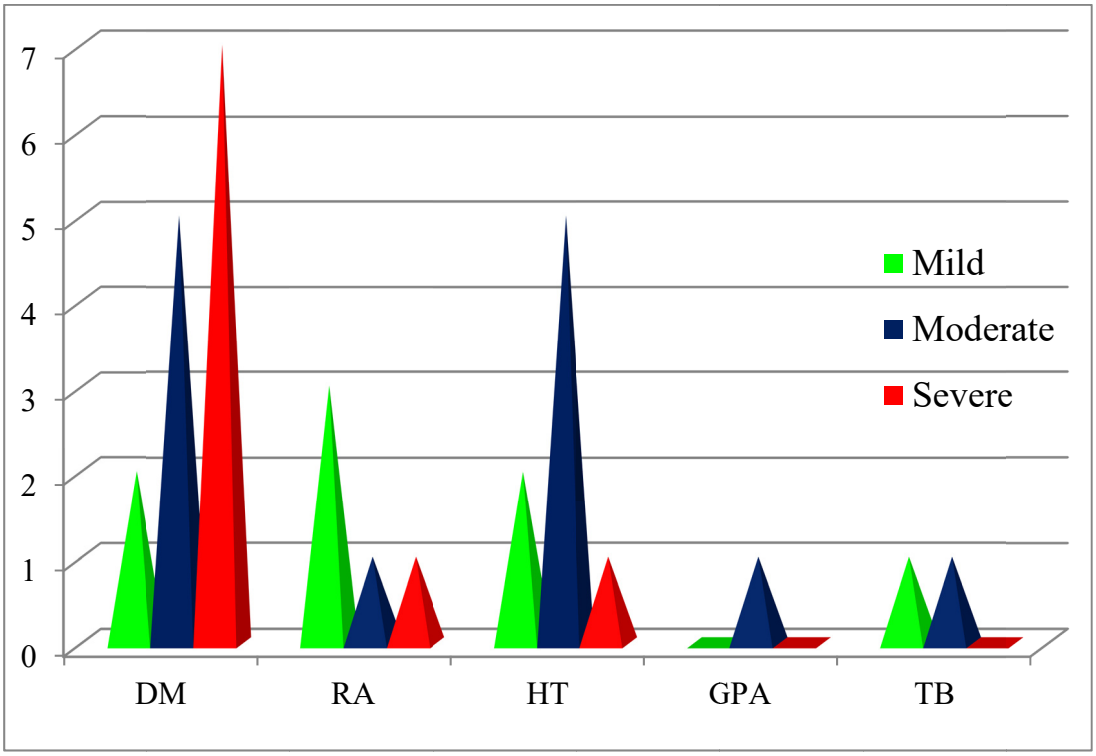
Systemic collagen vascular diseases are the second most common cause of PUK. Among them, rheumatoid arthritis is the most common cause amounting to 7% of the total. Serological evaluation done in these patients showed positivity for rheumatoid factor in 40% of the cases. ESR was elevated in all these cases. Only 1 patient was started with methotrexate for the arthritis by the rheumatologist though the ulcer did not warrant the need for an immunosuppressant

Granulomatosis polyangitis was found to be the etiology in one of these cases. In this patient the ocular finding was the presenting feature. Following this patient developed ulcer in the finger and was later diagnosed by the physician as granulomatosis polyangitis.According to classification based on severity, 29 eyes had mild, 40 eyes had moderate and 29 eyes had severe form of the disease. It was found that females (76%) had milder form of the disease. Most common cause of severe form of disease is Mooren’s ulcer (31.03%).

GRAPH-8. COMPARISON OF ETIOLOGY WITH CLINICAL CLASSIFICATION



GRAPH-9 CO-EXISTING SYSTEMIC CONDITION IN EACH GRADE OF PUK



Regarding the systemic history it was found that diabetes mellitus was present in 21.74% of cases. Rheumatoid arthritis was seen in 7.25% of the cases. One case had Granulomatosis polyangitis (GPA). Diabetes mellitus was seen more commonly in association with severe form (33.3%).

TABLE-2.ASSOCIATED EYE CONDITIONS

Associated Eye Findings	**n (%)**			
	Mild	**Moderate**	**Severe**	**Total**
Meibomitis	2 (6.90)	-	2 (6.90)	4
Squamous blepharitis	2 (6.90)	-	3 (10.34)	5
CDK	1 (3.45)	9 (22.50)	3 (10.34)	13
Pterygium	1 (3.45)	2 (5.00)	1 (3.45)	4
None	23 (79.31)	29 (72.50)	20 (68.97)	72
Total	29 (100)	40 (100)	29 (100)	98(100)

Climatic droplet keratopathy was the most common associated eye finding (13.2%) followed by blepharitis (5%) meibomitis (4%) and pterygium (4%).

Corneal scraping was done in cases suspicious of infectious etiology. Culture showed positivity for gram positive cocci in 4 cases, gram negative bacilli in 1 case and aspergillus flavus in 1 case.

Twelve cases that had undergone intraocular surgery previously had developed ulcer at the same site. Cataract surgery done in 7 eyes had ulcer developing at the same site of incision. Four cases of pterygium with conjunctival auto-graft had developed ulcer at the same site of excision. One case had undergone vitreo-retinal surgery for retinal detachment had developed PUK.

Twenty nine eyes had mild form of PUK and were all treated with topical steroid and antibiotic combination. Mean time for healing of mild PUK is 10.76 days. All cases had anatomical success during the course of the study. No case had treatment failure to medication. There were no cases that had recurrence.

Moderate severity of PUK was seen in 40eyes (41%). All patients were started on topical steroids and antibiotics combination. Mean time for healing was 18.3 days. One case was started on oral Methotrexate for the associated systemic disease (Rheumatoid arthritis). Treatment failure to topical and oral steroids was observed in 5cases (12.5%), of which 1 case was started on oral cyclophosphamide and in 1 case bandage contact lens was applied as the disease progressed to severe form despite

treatment. Conjunctival resection was done in 3 eyes. Anatomical success was achieved in 100% of the cases in this group.

Severe form of PUK was observed in 29 eyes (29.5%). Topical steroid with antibiotic cover was given to all patients. The mean time for healing was 47.8 days. Tacrolimus 0.03% eye ointment was given to one patient not responding with topical prednisolone acetate1%. Oral steroid was started in one patient that had gone for severe progression with topical medication only. Conjunctival resection was done in 4 cases. Perforation occurred in 8 eyes. One case of Mooren's ulcer had gone for perforation and was managed with a patch graft. One of these patients had developed into phthisis despite maximal therapy. Anatomical success of 96.56% (28out of 29) was achieved by the end of study period.

TABLE-3.MODES OF MANAGEMENT

Management	**n (%)**		
	Mild	**Moderate**	**Severe**
Topical steroid +Antibiotic only	28 (96.55)	34 (85)	22 (75.86)
Bandage contact lens	-	1 (2.50)	1 (3.45)
Methotrexate	1 (3.45)	1 (2.50)	-
Cyclophosphamide	-	1 (2.50)	-
Tacrolimus	-	-	1 (3.45)
Patch Graft	-	-	1 (3.45)
Conjunctival resection	-	3 (7.50)	4 (13.79)
Total	29 (100)	40 (100)	29 (100)

Most of these patients were successfully managed with topical steroid and antibiotics in the mild (96.55%) and moderate (85%) form of disease. Medical management only was given in all mild cases and they healed successfully. The severe form of disease required more of surgical management in comparison to the other forms.

COMPLICATIONS

Complicated cataract 49% (20/42 eyes) was the most common complication observed. Anterior uveitis was seen in 12% (5/42eyes) and glaucoma developed in 7% in the course of treatment.

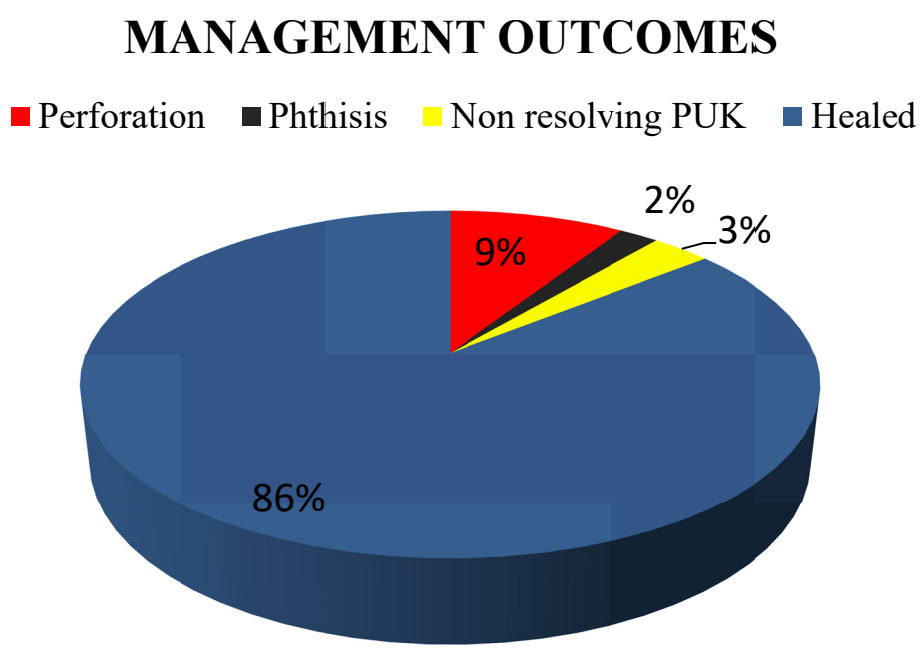
Perforation occurred in 9 eyes (9.2%). Mooren's ulcer was the most commonly involved etiology leading to perforation (66.7%). It was found that 8 of these eyes had severe form of the disease. Perforation occurred in 2 eyes which had a recurrence. Two eyes with perforation had developed phthisis.

Nodular scleritis was seen in 3% of the cases. One patient had extra-pulmonary tuberculosis and developed bilateral nodular scleritis. A case of granulomatosis polyangitis also developed nodular scleritis.

Anterior uveitis developed in 5% of the eyes with PUK. One case was suspected to be of herpetic etiology and started on oral acyclovir. 2 eyes had Mooren's ulcer as the cause of PUK.

Six eyes were found to have raise in intraocular pressure following instillation of topical and/or oral steroid. Most of these patients were managed with anti- glaucoma medication.

GRAPH-10. OUTCOMES OF MANAGEMENT



Anatomical integrity was maintained throughout the study with complete healing at the end of the study in 86% of the cases. It was nearly 100% in mild and moderate cases of PUK.

There was only one recurrence during the course of study in 4 eyes. All of these cases had Mooren's ulcer as the etiology. Of these, 2 cases had a severe form of PUK.

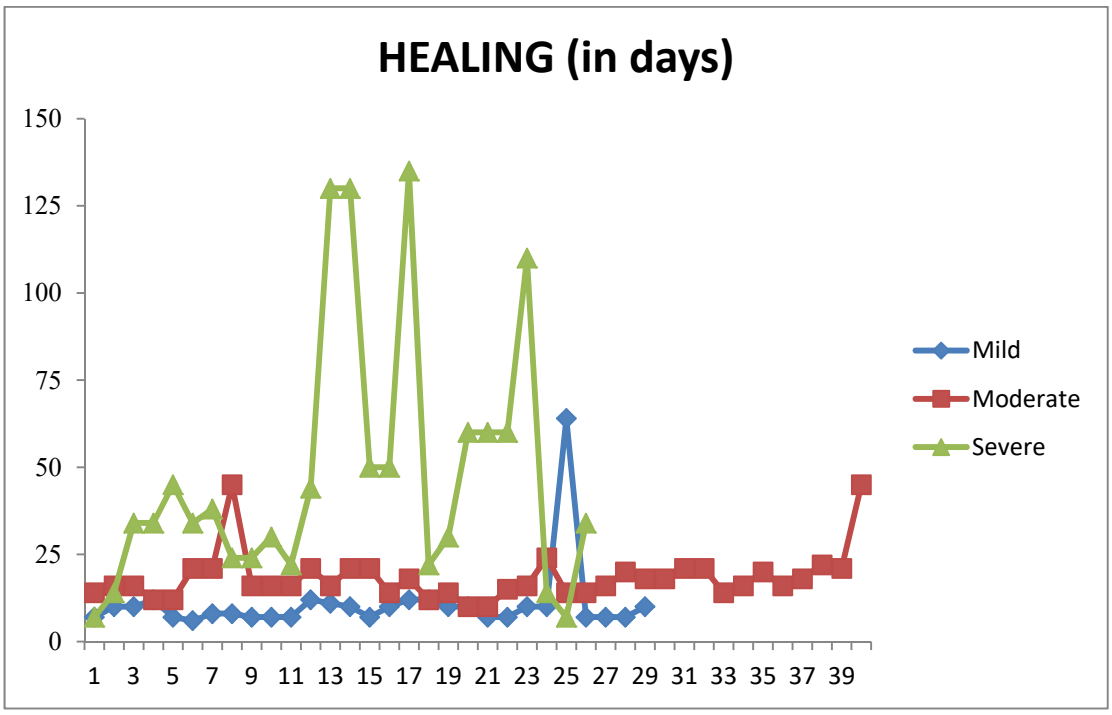
TABLE-4. HEALING TIME IN EACH GRADE OF SEVERITY

Healing	N	Mean (SD)	Min – Max	P value*
Mild	29	10.76 (10.42)	6 – 64	0.0001
Moderate	40	18.27 (7.10)	10 -45	
Severe	26	47.77 (37.44)	7 – 135	

*Kruskal Wallis test

The above P value <0.01 says that there is a statistical significant difference in healing between the three grades.

GRAPH-11. TRENDLINE SHOWING HEALING TIME IN EACH GRADE OF PUK



This linear graph shows the healing trend in each grade of severity. Though there are a few cases of milder disease requiring longer

time to heal, a majority of the patients followed the expected healing trend for their severity.

Three cases failed to heal despite maximal therapy during the period of study.

TABLE-5. COMPARSION OF THE INTIAL AND FINAL VISUAL ACUITY BETWEEN EACH GRADE OF PUK

LogMar VA	Grade	Mean (SD)	Min – Max	P Value [S]
Initial	Mild	0.65 (0.72)	0 – 3.2	0.038
Final		0.52 (0.66)	0 – 3.2	
Initial	Moderate	0.74 (0.62)	0 – 2.9	< 0.001
Final		0.58 (0.57)	0 – 2.9	
Initial	Severe	1.22 (0.91)	0 – 2.9	0.029
Final		0.94 (0.76)	0 – 2.9	

S- Sign rank test

The above p values 0.038 for mild, <0.001 for moderate and 0.029 for severe grades says that there is a statistical significant difference between the Pre-op and Post-op VA in the groups.

The Visual outcomes were studied by comparison of initial pre-treatment BCVA with that of the final post-treatment BCVA. The results were obtained using sign rank test. It shows that moderate grade of PUK had showed marked improvement in visual acuity.

DISCUSSION

We present an observational, prospective study of 98 eyes of 69 patients who were diagnosed as a case of peripheral ulcerative keratitis. We had aimed at understanding the demography, clinical features, etiology and the outcomes of management in these patients who were recruited over a period of 1 year and followed up for 6 months.

Demographic pattern resembled that of studies done previously. It was found that most of these patients were found to be older than 60 years of age (Mean age=60.1)

TABLE-6 DEMOGRAPHIC AND ETIOLOGIC ANALYSIS

	OUR STUDY	**Sharma et al[1]**	**Cartwright et a[19]**	**Tauber et al[3]**	**Chen et al[50]**
No. OF EYES	98	76	85	61	715
Mean Age (years)	60.1	45.5	65	65	48.4
Gender	Male 74%	Male 60%	Female 57%	Male 53%	Male 58%
Bilateral	41%	14.4%	21%	30%	30%
Etiology (Most common)	Mooren's (23.5%)	Mooren's (31.5%)	Rheumatoid arthritis (34%)	Rheumatoid arthritis (66%)	Mooren's

In our study we have observed that there has been a significant delay from appearance of symptom to presentation in tertiary eye care centre. This is seen more commonly with severe cases where the patients find a reason to go to a tertiary eye care only when the symptoms worsened. Such a situation has occurred probably due to irregular follow up and treatment when the symptoms were apparently less severe during the initial stage of the disease. There could be a delay in referral to the tertiary eye care as they were referred only when unresponsive to topical therapy[1]. Hence presentation of the disease at the earliest can help in managing the condition better.

The most common etiology for PUK in our study is Mooren's ulcer (23.5%) similar to another study done in India by Sharma et al (31.5%) [1] and Chen et al[50]. It was found that most of these patients were male 86.7% (13/15) similar to previous studies. But in many other studies rheumatoid arthritis had been the most common etiology.[9]

Rheumatoid arthritis (7%) was found to be the second most common cause of PUK in this study and the most common cause of collagen vascular disease. All these patients had developed arthritis few years before the onset of eye disease. One of these patients was on methotrexate for the systemic condition even though the ocular condition did not demand the need for an immunosuppressant[9]. Probably the

immunosuppressant taken for the systemic condition could have prevented the ulcer to take increase in severity. Therefore collaboration with the rheumatologist to evaluate the systemic condition is mandated in the management of these patients.

Granulomatosis polyangitis (GPA) was diagnosed in one patient in whom the initial presentation was peripheral ulcerative keratitis. The patient showed positivity to c-ANCA and was referred to rheumatologist. This case resembles PUK in GPA as shown in previous studies where ocular finding was the initial presentation[18]. This implies that the eye is indeed a window to look for systemic diseases. Hence it is not only important to identify PUK but also important to confirm the etiology.

In our study it was found that PUK had occurred following intraocular surgery in the same site in 12.2% of the eyes. This was probably due to the corneal tissue disruption during the intraocular surgery that becomes an inciting factor to produce an inflammatory response. In a study by Srinivasan et al[26] 37 % of cases had previous intraocular surgery and 27.6% had ocular trauma at the same location. But in our study there was no case with previous history of ocular trauma as the inciting factor for PUK.

TABLE-7.COMPARISON BETWEEN STUDIES OF PUK AT SAME SITE OF PREVIOUS INTRA-OCULAR SURGERY

SAME SITE	Our study	Chen et al	Sharma et al
Previous intra-ocular surgery	12.25%	2.3%	13.15%
Ocular Trauma	0	6%	4%

Scleritis was a complication that was observed in only 3% of the cases. Nodular scleritis was the most common presentation. Tauber et al stated that patients with Rheumatoid arthritis and PUK developed necrotising scleritis (70%) over a period of 14 years[9]. In our study, tuberculosis and GPA were the common diseases to develop scleritis. No case with rheumatoid arthritis had any form of scleritis in our study. Foster et al stated that mortality rate of patients of RA with necrotising scleritis with or without PUK reduced from close to 52 % to 5% when started on cytotoxic immunosuppressant therapy[18]. This explains the need for a regular follow up of these patients of PUK with RA as it is not just sight threatening, but life threatening.

TABLE-8 COMPLICATIONS

COMPLICATIONS	OUR STUDY	CHEN et al	SHARMA et al
Complicated cataract	20.4%	2.5 %	15.8%
Anterior uveitis	5%	7.6%	-
Ocular hypertension	6.1%	-	-

Glaucoma developed in four eyes during the course of treatment. However the cause effect relationship could not be made out as the disease per se is mostly in older individuals and the incidence of glaucoma is more common in old age. However transient rise in intraocular pressure while prescribing steroids was observed in 6 eyes and where treated with IOP lowering drugs until the steroids were tapered. In one patient oral steroid where replaced with immunosuppressant as the IOP could not be controlled despite maximal medical therapy

The percentage of recurrence observed during the course of study stands at a meagre 4.1%. This may attributed to the shorter follow up period of the study. Hence it could not be compared with Chen et al where the rate of recurrence was 25.6%[50]. However the rate of recurrence in this study was comparable with that of Sharma et al 5.3%[1]. Mooren's ulcer was the most common etiology to have recurrence

(100%) in our study which goes in accordance with previous literature where it was the most common etiology[1,50].

Anatomical integrity was maintained in all cases of mild and moderate severity similar to the observation by Sharma et al[1]. In severe cases, in our study the anatomical success was 96.56% as opposed to 83.33% in Sharma et al. The anatomical integrity was maintained with a preservation rate of 97.96% in comparison to Chen et al 99.7%[50]

It was found that the milder form of disease had better vision at presentation and it remained the same during the course of study. Whereas the severe form of disease had poorer vision to present with and the primary objective in such situations was globe preservation. In our study, only patients in the moderate form of disease had an improvement in vision from the time of presentation.

TABLE-9 COMPARISON OF VISUAL ACUITY BETWEEN EACH GRADE OF VISUAL ACUITY

	p-value for pre and post treatment Visual acuity	
GRADE	OUR STUDY	SHARMA et al
Mild	0.038	0.085
Moderate	<0.001	0.160
Severe	0.029	0.001

The above table shows that our study shows significant visual acuity improvement in moderate cases differing from the previous studies where severe cases had improved visual outcomes[1].

The duration of treatment in PUK is influenced by the state of ulcer healing and the systemic vasculitis, if present. Hence management has to be tailor made to each case and the decision making in medical or surgical management relies on clinician's experience. A collaborative approach by involving the rheumatologist in decision -making, can help serve the patient better

TABLE-9. COMPARSION OF OUTCOMES OF MEDICAL MANAGEMENT ONLY.

MEDICAL MANAGEMENT ONLY	OUR STUDY	SHARMA et al
Mild	100%	100%
Moderate	92.5%	100%
Severe	82.76%	50%

The above table shows that more cases of severe category were managed medically in our study in comparison to Sharma et al where nearly 50% of them required surgical treatment[1].

TABLE-10. COMPARISON OF OUTCOMES OF SURGICAL MANAGEMENT

SURGICAL MANAGEMENT	OUR STUDY	SHARMA et al
Mild	0	0
Moderate	7.5%	0
Severe	17.24%	50%

Conjunctival resection was the most commonly done surgery in our study as it aims at removing the collagenase and blocking the access of cytokines, thereby interrupting the local autoimmunity. Patch grafting was done in cases of perforation to maintain the anatomical integrity. Bandage contact lens was placed in case of impending perforation and was given medical therapy in few cases that did not lead to perforation at a later date.

The major limitation in this study was shorter duration of follow up. Hence recurrence could not be assessed and the systemic findings did not manifest during the course of the study.

CONCLUSION

Peripheral ulcerative keratitis requires a complete evaluation of the ocular and the systemic condition and a battery of investigations to arrive at the etiology, based on which the treatment is initiated. Keeping in mind the association of PUK with lethal vasculitic diseases like rheumatoid arthritis and granulomatosis polyangitis, collaboration with a rheumatologist is mandatory in such situations. Topical steroids had been effective mild to moderate grades of PUK. But in severe cases there has been a need to start on immunosuppressant or go for a surgical approach to achieve anatomical integrity and preserve vision. There has been a delay in patient reaching the tertiary care centre more in severe cases. Hence, earlier the referral to a tertiary centre, better the management outcomes.

ANNEXURES

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ABBREVIATIONS

1.	PUK	Peripheral ulcerative keratitis
2.	RA	Rheumatoid arthritis
3.	GPA	Granulomatosis polyangitis
4.	RF	Rheumatoid factor
5.	ANA	Anti-nuclear antibodies
6.	ANCA	Anti-neutrophil cytoplasmic antibodies
7.	ESR	Erythrocyte Sedimentation Rate
8.	CRP	C-Reactive Protein
9.	TC	Total Count
10.	DC	Differential Count
11.	MTX	Methotrexate
12.	CP	Cyclophosphamide
13.	AC	Anterior chamber
14.	CR	Conjunctival resection
15.	DM	Diabetes mellitus
16.	HT	Hypertension
17.	TB	Tuberculosis
18.	BCL	Bandage contact lens
19.	MU	Moorens Ulcer
20.	SDA	Sabouraud’s Dextrose Agar

21.	CDK	Climatic Droplet Keratopathy
22.	VA	Visual Acuity
23.	BCVA	Best Corrected Visual Acuity
24.	CD	Cluster of Differentiation
25.	TNF	Tumor Necrosis Factor
26.	MMF	Mycophenolate mofetil
27.	HCV	Hepatitis C virus
28.	FTA/ABS	Fluorescent treponemal antibody absorption
29.	CXR	Chest X-ray
30.	MMP	Matrix Metalloproteinase
31.	CaGC	Calgranulin C
32.	ELISA	Enzyme-linked immunosorbent assay

PROFORMA

TITLE- DEMOGRAPHIC PROFILE CLINICAL FEATURES AND TREATMENT OUTCOMES OF PERIPHERAL ULCERATIVE KERATITIS

Serial Number: ☐☐☐

M R Number: ☐☐☐☐☐☐☐

Name:

Age: ☐☐ Gender ☐ 1. Male 2. Female

Address:

Area: ☐ 1.Rural 2.Urban

Phone number:

A. Systemic History

1. Joint swelling ☐ 1. Small joint 2. Large joint 3. None

If yes, duration ☐ 1. <6 weeks 2. >/= 6 weeks

Pain ☐ 1.Yes 2.No

2. Oral ulcers ☐ 1.Yes 2.No

If yes, Pain ☐ 1.Yes 2.No

3. Nasal discharge ☐ 1.Purulent 2. Bloody 3. None

4. Skin lesions ☐ 1. Rosacea 2. Herpes 3. Others _____

5. Systemic Medication ☐ 1. Yes 2. No

If yes, specify _____

B. Personal history: ☐ 1. Smoker 2. Alcoholic 3. None

C. Ocular history:

Affected eye: ☐ 1. Right eye 2. Left eye 3. Both eyes

SYMPTOMS: 1= Yes 2= No

Irritation ☐

Redness ☐

Photophobia ☐

Defective vision ☐

Pain ☐

Others:

Duration of symptoms: ☐ 1. < 2wks 2. < 3months 3. > 3months

Ocular trauma ☐ 1.Yes 2.No

If yes, specify _____

Previous Surgery excision ☐ 1. Cataract surgery 2. Vitreoretinal surgery 3. Pterygium

4. Others _____ 5. None

Previous eye disease ☐ 1. Cataract 2. Glaucoma 3. Others _____ 4. None

Ocular medications Duration Dosage

OCULAR EXAMINATION

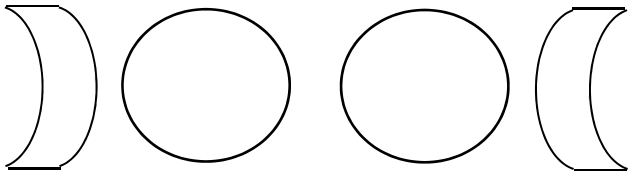
	RIGHT EYE	**LEFT EYE**
Visual acuity		
Intra-ocular pressure		

LIDS 1= Yes , 2= No	**RIGHT EYE**	**LEFT EYE**
Meibomitis		
Squamous blepharitis		
Entropion		
Trichiasis		
Others		

CONJUNCTIVA		
Congestion 1. Diffuse		
2. Circumcorneal		
3. None		
Concretions 1. Yes 2. No		
Others		

SCLERA		
Scleritis 1. Diffuse		
2. Nodular		
3. Necrotising		
4.None		
Episcleritis 1. Yes 2. No		
Others		

CORNEA



Epithelial defect (in clock hours)		
Infiltration (in clock hours)		
Thinning (in clock hours)		
Depth 1. <25% 2. 25-50% 3. 51-75% 4. 76-100%		
Vascularisation (in clock hours)		
Perforation 1. Yes 2. No		
Others		

ANTERIOR CHAMBER		
Cells 1) 0 2) 0.5+ 3) 1+ 4) 2+ 5) 3+ 6) 4+		
Flare 1) 0 2) 1+ 3)2+ 4) 3+ 5) 4+		
Others		

IRIS		
PUPIL		
Size		
Reaction to Light		

LENS	1= Yes, 2= No	
Clear		
Immature		
Mature		
Complicated cataract		
Intra-ocular lens		
FUNDUS		
1. Normal 2. Evidence of diabetic retinopathy 3. Others		

Investigations

1. Corneal smear - Gram's stain ☐ 1. Gram negative cocci 2. Gram positive cocci

3. Gram negative bacilli 4.Gram positive bacilli

- 10% KOH stain ☐ 1.Fungal hyphae present 2. Fungal hyphae absent

2. Culture ☐ 1. No growth 2. Growth

Bacteria - Blood agar ☐ 1.Yes 2.No

Fungi- Potato dextrose agar ☐ 1.Yes 2.No

Acanthamoeba- Non-nutrient agar ☐ 1.Yes 2.No

3. Schirmer's test I ☐ 1. <10 mm 2. >10mm

4. Routine investigations – 1= Normal, 2= Abnormal

Total count ☐

Differential count ☐

ESR ☐

CRP ☐

RBS ☐

5. Rheumatoid factor ☐ 1. Negative 2. Low positive 3. High positive

6. Urine routine RBC ☐ 1.Yes 2. No

Pus cells ☐ 1.Yes 2. No

7. Chest X-Ray ☐ 1. Normal 2. Cavities 3. Nodular infiltrates 4. Others

8. Mantoux test ☐ 1. Positive 2. Negative

9.Anti-nuclear antibody ☐ 1. Positive 2. Negative

10.Conjunctival biopsy

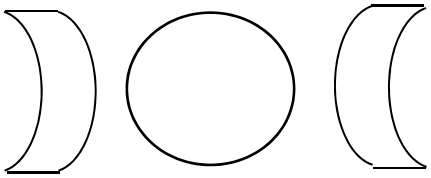
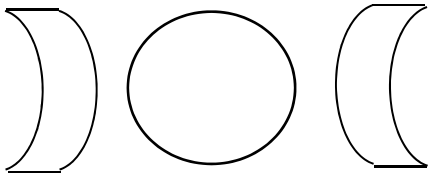
Management

A.MEDICAL	1= Yes, 2=No	Dosage	Duration
a) Topical corticosteroid	☐		
b) Topical antibiotics	☐		
c) Cyclosporine-A	☐		
d) Oral corticosteroid	☐		
e) Others	☐		

Change of drug, if any

B. SURGICAL	1= Yes, 2=No	Date of surgery
1. Conjunctival resection	☐	
2. Patch graft	☐	
3. Amniotic membrane graft	☐	
4. Glue	☐	
5. Others	☐	
6. None	☐	

Follow up

Date		
Lids		
Conjunctiva		
Sclera		
Cornea		
Epithelial defect		
Infiltrate		
Thinning		
Depth		
Vascularisation		
Grade		
Anterior chamber		
Iris		
Pupil		
Lens		
Fundus		
Visual acuity		
Iop		
Perforation		
Drug prescribed		
Next visit		

Informed Consent form to participate in a clinical study

Study Title-

DEMOGRAPHIC PROFILE, CLINICAL FEATURES AND MANAGEMENT OUTCOMES OF PERIPHERAL ULCERATIVE KERATITIS

Protocol Number:

Subject's Name: _____Subject's Initials: _____

Subject ID No: _____

Date of Birth / Age: _____

		Please put initial in the box (Subject)
(i)	I confirm that I have understood the information about the study, procedures and treatments for the above study and have had the opportunity to ask questions and I received satisfactory answers to all of my questions. I have been given a copy of the informed consent form to take home	[ ]
(ii)	I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. However, this is may not be possible for certain surgical procedures	[ ]
(iii)	I understand that the Investigator of the study to access my health records for the research purpose. However, I understand that my identity will not be revealed in any information released to third parties or published.	[ ]
(iv)	I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s)	[ ]
(v)	I agree to take part in the above study.	[ ]

Signature (or Thumb impression) of the Subject:

_____

Date: _____/_____/_____

Subject's Name:

_____

Signature (or Thumb impression) of Legally Acceptable Representative (LAR):

_____ Date: _____

Signature of the Investigator: _____Date: _____/_____/_____

Investigator's Name: _____

Signature of the Witness _____ Date:_____/_____/_____

Name of the Witness: _____

ARAVIND MEDICAL RESEARCH FOUNDATION
Institutional Ethics Committee
(REGISTRATION NO. ECR/182/INST/TN/2013 DATED 20.04.2013)

12th December 2015

To
Naveen Keshav S
MS Resident
Aravind Eye Hospital
Madurai

Dear Dr. Naveen Keshav,

Thesis Title: Peripheral Ulcerative Keratitis- A Prospective Study

IRB Code: IRB201500224

Thank you for submitting your thesis and seeking the approval from the ethics committee. The documents provided by you for consideration which include the thesis protocol and informed consent forms were reviewed for the research methodology and scientific content. The Ethical committee did not find any correction and has recommended the thesis to go ahead in the present form.

Thanking you

Yours Sincerely,

S. Lalitha

Dr.Lalitha Prajna
Member Secretary
Institutional Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
ARAVIND MEDICAL RESEARCH FOUNDATION
No.1, Anna Nagar, Madurai-625 020

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Locality = 1.urban 2.Rural

Etiology 1.Mooren's 2.RA 3. Infection 4.idiopathic 5.GPA

Systemic positive 0.None 1.DM 2.RA 3. HT 4.TB 5.GPA

Smoker 1. Y 0.no

Duration 1.<2wk 2.<3mth 3.>3mth

Previous Sx=1.cataract Sx 2.VR Sx 3.Pterygium excision 4.Trab 0.None

Ass. Eye cond= 1.Cataract 2.Glaucoma 3.uveitis 0. None

Recurrence 1.Yes 0.No

Scleritis 1.Yes 0.No

Ass. Finding1.meibomitis 2.Sq blepharitis 3.CDK 4.Pterygium 0.None

Depth of Thinning 1.<25% 2.25-50% 3.50-75% 4.>75%

Grade 1.Mild 2.Moderate 3.Severe

Perforation 1.Yes 0.No

Steroid topical 1.Yes 0.No

Topical AB(antibiotic) 1.Yes 2.No

AB+ Steroid topical 1.Yes 0.No

Oral steroid 1.Y 0.No

Oral AB 1. Y 0.N

CR (conjunctival resection) 1.Y 2.No

OTHERS= 1.BCL 2.Mtx 3. CP 4.Tacrolimus 5.Patch Graft 0.None

Recurrence 1.Y 0.No

Complication 1.Glaucoma 2.ant uveitis 3. Phthisis 4.perforation5.Scleritis

S No.	MR no.	DATE	EYE	NAME	AGE	Sex	Ph No.	Locality	Etiology	systemic +	Smoker	wk 2.	Previous S.	Eye co	VA	Final Va	ecurrenc	Scleritis	s. Findi	(in cloc	filtratio	hinning	cularisah	of Thi	Grade	erforatio	SR high	roid topi	pical Ateroid	tal steroi	oral AB	CR	P 4.	Tac	Healin (days)	Complication
1	2E+06	02-12-15	RE	Jeelan	66	M	1E+10	2	1	0	0	2	0	0	No PL	No PL	0	0	1	-	-		4	4	1	1	0	1	0	0	1	1	0	0	2	7	0
	2E+06	02-12-15	LE						1			2	1	0	3/60	6/60	1	0	0	-	-		3	-		4	3	1		0	0	0	0	0	0	0	7	4
2	2E+06	16-12-15	RE	Pandiar	60	F	8.9E+09	2	1	4	0	2	0	0	6/24	6/18	0	0	0		6	2	6	-		4	1	0	0	0	0	0	0	0	0	10	0
	2E+06	16-12-15	LE						1			2	0	0	6/18	6/18	0	0	0		8	2	7	-		4	1	0		0	0	0	0	0	0	0	10	0
3	3E+06	18-12-15	RE	Manick	63	M	9.8E+09	1	1	0	1	1	0	1	FCF	5/60	1	0	0		3	2	3	-		4	1	0	0	1	1	1	0	1	0	0	12	0
4	4E+06	21-12-15	LE	Chellan	75	F	9.9E+09	2	2	1.2.3		0	2	1	6/24	6/18	0	0	0	-		8		-		3	1	0	1	0	0	1	0	1	0	0	7	0
5	4E+06	22-12-15	RE	Raman	33	M	9.8E+09	1	1	0	1	2	0	0	6/6p	6/6	0	0	0	-	-		3	3	1	1	0	0	0	0	1	0	0	0	0	6	0
6	4E+06	23-12-15	RE	Rajeshv	17	F	9.9E+09	1	2	2	0	1	0	0	6/6	6/6	0	0	0	-	-		3	3	1	1	0	1,2		0	0	1	0	0	0	8	0
	4E+06	23-12-15	LE						2			1	0	0	6/6	6/6	0	0	0	-	-		3	3	1	1	0			0	0	0	0	0	0	8	0
7	2E+06	25-12-15	RE	Marimu	70	M	Nil	1	2	0	0	2	0	0	5/60	6/60	0	0	1	7		4	12	4	4	1	0	1	0	0	0	0	0	0	0	7	0
8	2E+06	01-01-16	RE	Bhanud	65	M	7.5E+09	2	1	0	1	2	0	0	PL +		0	0	2	-	-		2	-		4	3	1	0	0	0	1	0	0	1	0	14	3
9	1E+06	07-01-16	RE	Soora R	77	M	9.8E+09	2	3	0	0	3	1	0	6/9p	6/6	0	0	2		3	1	5	-		3	1	0	0	0	1	0	0	0	0	7	0
	1E+06	07-01-16	LE						3			3	1	0	6/6	6/6	0	0	0	-	-		4	4	2	1	0		0	0	0	0	0	0	0	7	0
10	4E+06	11-01-16	LE	Palania	57	F	1E+10	2	4	0	0	2	4	2	6/60	6/60	0	0	0		3	-		3	-		2	2	0	0	0	1	1	0	0	0	14	2
11	3E+06	12-01-16	RE	Kamak	47	F	9.6E+09	1	4	4	0	1	1	0	6/6p	6/6	0	1	0	-	-		4	4	2	2	0	1	0	0	1	0	0	0	0	16	5
	3E+06	12-01-16	LE						4			1	1	0	6/6p	6/6	0	1	0		3	3	4	-		1	2	0		0	0	1	0	0	0	0	16	5
12	2E+06	20-01-16	RE	Erulaye	65	F	Nil	2	4	0	0	2	0	0	6/18p	6/12	0	0	3	1	-		4	-		3	2	0	0	0	1	1	0	0	0	12	0
	2E+06	20-01-16	LE						4			2	0	0	6/24	6/18	0	0	3	-	-		2	-		1	2	0		0	1	1	0	0	0	0	12	0
13	2E+06	21-01-16	RE	Munisa	72	M	9.9E+09	2	4	3	1	2	0	0	5/60	6/60	0	0	0	-	-		2	2	2	2	0	0	0	1	1	0	0	0	0	21	0
	2E+06	21-01-16	LE						4			2	0	0	5/60	6/60	0	0	0	-	-		2	2	3	2	0		0	1	1	0	0	0	0	21	0
14	2E+06	23-01-16	RE	Amirth	60	M	Nil	2	1	0	1	1	0	0	6/36	612	1	0	0		5	-		5	-		4	2	1	0	0	1	1	0	0	0	45	4
	2E+06	23-01-16	LE						1			1	0	0	6/24	6/9	0	0	0	-	-		3	3	3	2	0		0	1	1	0	0	0	0	16	0
15	4E+06	25-01-16	RE	Nallan	58	M	8.1E+09	1	3	0	1	3	0	0	6/36	6/24	0	0	0	-	-		12	-		3	2	0	0	0	0	0	0	0	1	0	16	0
	4E+06	25-01-16	LE						3			3	0	0	1/60	6/60	0	0	0	-	-		12	-		3	2	0		0	0	1	1	0	1	0	16	0
16	2E+06	27-01-16	RE	Thanga	51	M	8.8E+09	2	4	1	0	2	0	0	6/9	6/9	0	0	0	3	-		1	2	0	0	0	0	1	1	0	0	0	0	0	21	0
17	2E+06	01-02-16	RE	Chinna	67	M	9.9E+09	2	4	0	0	2	0	0	6/9	6/9	0	0	0	-			5	-		3	3	0	0	0	1	1	0	0	0	0	34	0
18	2E+06	03-02-16	RE	Rakku	69	F	7.7E+09	2	4	0	0	2	1	0	6/24p	6/24	0	0	0		4	2	2	-		3	3	0	1	0	0	1	0	0	0	0	34	0
	2E+06	03-02-16	LE						4			2	0	0	HM	HM	0	0	0		2	2	2	-	2	3	3	0		0	0	0	0	0	0	0	45	0
19	2E+06	16-02-16	LE	Vellais	70	M	Nil	1	4	0	0	1	1	0	6/36p	6/18	0	0	1	1		3	5	-		3	3	0	0	0	1	1	0	0	0	34	0
20	4E+06	18-02-16	LE	Vasantl	41	F	8.1E+09	1	4	0	0	1	0	0	6/9p	6/9	0	0	1	-		1	3	3	3	3	0	0	0	1	1	0	0	0	0	38	0
21	2E+06	23-02-16	LE	Ravana	69	M	Nil	1	4	1	0	1	1	0	6/36p	6/36	0	0	3	-	-		4	4	3	3	0	0	0	0	1	0	0	0	0	24	0
	2E+06	23-02-16	RE						4			1	0	0	5/60	6/60	0	0	3	-	-		2	3	3	3	0		0	0	1	0	0	0	0	24	0
22	4E+06	27-02-16	RE	Pappa M	48	F	Nil	2	4	0	0	1	1	0	6/18	6/18	0	0	3	-	-		2	4	3	3	0	0	0	0	1	0	0	0	0	30	0
23	2E+06	25-04-16	RE	Mandhu	88	M		2	4	1	1	2	1	0	2/60	5/60	0	0	0		4			3	3	3	3	0	0	0	0	1	0	0	0	0	22	0
24	2E+06	10-05-16	LE	Arumu	59	M	nil	2	4	1	0	1	0	0	6/18	6/12	0	0	0		2	2		3	2	1	0	0	0	0	1	0	0	0	0	12	0
25	4E+06	04-06-16	LE	Nandhi	15	F	8.9E+09	1	4	0	0	1	0	0	6/36	6/9	0	0	2			5	10	4	3	3	1	0	0	1	1	0	0	0	0	44	4
26	4E+06	11-06-16	RE	Madasa	67	M	8.3E+09	1	4	0	0	2	0	1,3	6/18	6/18	0	0	0		3	3	3		1	1	0	0	0	1	1	0	1	0	0	11	2
	4E+06	11-06-16	LE						4			2	0		1 6/36	6/36	0	0	0		3	3	3		3	2	0		0	1	1	0	1	0	0	16	0
27	4E+06	20-06-16	RE	Kandas	75	M	9.7E+09	2	1	0	1	1	1.3		0 5/60	4/60	1	0	0		9	4	9		4	3	0	0	0	0	1	1	1	0	0	130	0
	4E+06	20-06-16	LE						1			1	1.3		0 HM	1/60	0	0	0		12	3	12		4	3	0		0	0	0	0	0	0	0	130	0
28	2E+06	30-06-16	LE	Nallusa	70	M		1	1	0	0	1	1		1 6/9p	6/6	0	0	0	4	5		4		2	2	0	0	0	0	1	1	0	0	0	21	0
	2E+06	30-06-16	RE						1			1	0		0 6/12	6/6	0	0	0		3		4		2	2	0		0	0	0	0	0	0	0	21	0
29	4E+06	01-07-16	RE	Pandiya	81	M	9.4E+09	1	1	0	0	3	0		1 PL +	PL+	0	0	0			2	5	5	3	2	0	0	0	1	1	0	1	0	0	14	4
30	4E+06	02-07-16	LE	Thanga	55	M	9.8E+09	1	3	1	0	2	0		3 3/60	3/60	0	0	0		12				3	3	0	0	0	1	0	1	0	0	1	0	50	2
31	4E+06	09-07-16	LE	Subbaia	65	M	9.8E+09	1	1	0	0	1	0		1 6/60	6/36	0	0	0		2	2	2		4	2	0	0	0	1	1	0	1	0	0	18	0

32	4E+06	13-07-16 RE	Ramaia	70 M	9.4E+09	2	1	1	1	3 1	3 6/24	6/36	0	0 0		10	4	10	3	3	3	0	0	1	1	0	0	1 1	0	NH	2
	4E+06	13-07-16 LE					1			3 1	3 6/24	5/60	0	0	4	10	6	10	2	3	3	0		0	0	0	0	0 0	0	NH	2
33	4E+06	18-07-16 RE	Karupp	85 F	9.2E+09	2	3	1	0	1 1	0 PL +	PL-	0	0 2		3	4	5		4	3	1	0	0	1	0	0	1 0	0	NH	4
	4E+06	18-07-16 LE					1			1 1	0 6/24	6/24	0	0 0				4		2	2	0		0	0	0	0	0 0	0	12	0
34	4E+06	29-07-16 RE	Vipin k	29 M	9.9E+09	1	2	2	0	2 0	0 6/18p	6/36	0	0 0				5		4	3	0 1,2		0	0	1	0	0 1	0	50	0
35	4E+06	30-07-16 RE	Rathina	60 F	7.7E+09	1	1	1	0	2 0	0 5/60	6/60	0	0 0				6		4	3	1	1	0	0	1	0	0 0	5	135	4
	4E+06	30-07-16 LE					1			2 0	0 6/24p	6/24	0	0 0				4		3	2	0		0	0	1	0	0 0	0	14	0
36	4E+06	03-08-16 RE	Subbula	41 F	9.7E+09	1	5	5	0	2 0	0 6/60	6/12	0	1 0			3	5		1	2	0 cANCA		0	0	0	0	0 0	0	10	5
	4E+06	03-08-16 LE					5			1 0	0 6/24	6/9	0	0 0			12	3		3	3	0		0	1	1	0	0 0	0	22	0
37	4E+06	24-08-16 RE	Ananth	45 M	9.8E+09	1	4	0	0	2 1	1 HM +		0	0 0				2		3	3	0	1	0	1	1	0	0 0	0	30	0
38	4E+06	03-09-16 RE	Chinnal	60 M	9.8E+09	2	4	0	0	1 0	1 6/18	6/12	0	0 0				3		1	1	0	0	0	1	1	0	1 0	0	10	0
	4E+06	03-09-16 LE					4			1 0	0 6/18p	6/18	0	0 0			3	6		2	2	0		0	1	1	0	0 0	0	10	0
39	4E+06	07-09-16 RE	Ajith ku	17 M	8.8E+09	1	1	0	0	1 0	0 6/6	6/6	0	0 0		2		2		3	2	0	0	0	1	1	0	0 0	0	15	0
40	4E+06	09-09-16 RE	Chellai	64 M	1E+10	1	4	0	0	2 0	1 6/36	6/24	0	0 0		4	2		5	2	2	0	0	0	1	1	0	0 0	0	16	0
41	4E+06	26-09-16 LE	Chinna	65 M	9.6E+09	2	4	3	0	2 1	1 6/6		0	0 0				6	5	4	2	0	0	0	0	1	0	0 0	1	24	0
42	4E+06	28-06-16 RE	Muthus	90 M	7.7E+09	1	4	3	0	1 1	0 6/9	6/6	0	0	3	3		3		2	2	0	0	0	1	1	0	0 0	0	14	0
	4E+06	28-06-16 LE					4			1 1	0 3/60	6/36	0	0	3	3	3	6		1	2	0		0	0	0	0	0 0	0	14	0
43	4E+06	26-02-16 RE	Ponnala	48 F		1	4	3	0	1 1	0 6/12	6/12	0	0 0		2	2	4		2	1	0	0	0	0	0	0	0 0	0	7	0
44	4E+06	08-09-16 RE	Govind	83 M	1E+10	1	4	0	0	2 1.2	2 6/18	6/12	0	0 0		2	2			1	1	0	0	0	0	0	0	0 0	0	10	0
	4E+06	08-09-16 LE					4			2 1	2 6/18	6/12	0	0 0		3	4			2	2	0		0	0	0	0	0 0	0	16	0
45	4E+06	28-09-16 RE	Meena	30 F	7.7E+09	1	2	2	0	1 0	0 6/6	6/6	0	0 0		4	2	4		3	2	0	1	0	0	1	1	0 1	2	20	0
	4E+06	28-09-16 LE					2			1 0	0 6/6	6/6	0	0 0		4	2	4		4	3	0		0	0	1	0	0 0	0	60	0
46	4E+06	29-11-16 RE	Moham	43 M	9.8E+09	1	4	0	1	1 0	0 6/6	6/9	0	0 0				3	3	1	1	0	0	0	1	1	0	0 0	0	12	0
47	4E+06	03-11-16 RE	Arockiy	65 M	NA	1	4	2	1	1 1	0 6/12	6/12	0	0	4	2		2		1	1	0	0	0	0	1	0	0 0	0	12	0
48	4E+06	09-12-16 LE	Irulappa	55 M	8.5E+09	2	4	0	0	1 1	1 5/60	5/60	0	0	3			4		3	2	0	0	0	1	1	0	0 0	0	18	0
49	4E+06	08-09-16 RE	Periyas	75 M	nil	2	4	0	0	1 0	1 2/60	2/60	0	0	3	3		3		2	2	0	0	0	1	1	0	1 0	0	18	0
50	4E+06	17-10-16 RE	Lakshm	66 M	9.2E+09	1	4	1.3	0	2 1	0 6/36	6/18	0	0 0		3		3		4	3	0	0	0	0	1	0	0 0	0	60	0
	4E+06	17-10-16 LE					4			2 1	0 6/60	6/24	0	0 0		4		4		4	3	0		0	0	1	0	0 1	0	60	0
51	4E+06	30-09-16 RE	Thenm	37 F	9.6E+09	1	4	3	0	3 0	3 6/12p	6/9	0	0 0				5		4	3	1	0	0	1	1	0	1 0	0	110	4
52	4E+06	11-01-16 LE	John fe	45 M	9.6E+09	1	4	1	1	3 1	0 1/60	2/60	0	0 0			5	9	9	3	2	0	0	0	0	1	0	0 0	3	21	0
	4E+06	11-01-16 RE					4			3 1	0 6/6p	6/6	0	0 0				4	4	2	2	0		0	0	0	0	0 0	0	21	0
53	2E+06	29-08-16 LE	Sannasi	64 M	NA	2	4	0	0	1 1	0 2/60		0	0 0		2		2		1	1	0	0	0	0	1	0	0 0	0	10	0
54	2E+06	22-09-16 LE	Marimu	66 M	NA	2	4	0	1	2 1	1 6/60	6/60	0	0 0			4	4		3	2	0	0	0	1	1	0	0 0	0	14	0
55	2E+06	19-10-16 LE	Samaya	65 M		2	4	0	1	2 0	0 6/24	6/24	0	0	4	3		3	3	2	2	0	0	0	0	1	0	0 0	0	16	0
56	2E+06	06-09-16 LE	Kuppar	81 M	NA	2	4	0	0	2 1	0 6/18	6/18	0	0 0		6		3		2	2	0	0	0	1	1	0	0 0	0	20	0
57	2E+06	29-08-16 LE	Dasan	61 M	NA	2	4	0	0	1 1	0 4/60		0	0 0		2		2		1	1	0	0	0	1	1	0	0 0	0	10	0
58	2E+06	22-08-16 RE	Ponnus	81 M		2	4	0	0	3 1	1 6/18p	6/12	0	0	3	6		3		2	2	0	0	0	1	1	0	0 0	0	16	0
	2E+06	LE					4			3 1	1 6/36p	6/24	0	0 0				3	3	1	1	0		0	1	1	0	0 0	0	7	0
59	2E+06	15-08-16 RE	Solaiya	63 F		2	4	1.3	0	3 1	1.2 6/24	6/12	0	0	3	4		2		2	2	0	0	0	0	1	0	0 0	0	18	1
	2E+06	LE					4			3 1	1.2 6/36	3/60	0	0	3	3		2		2	1	0		0	0	1	0	0 0	0	7	1
60	2E+06	14-07-16 RE	Krishna	78 M	NA	1	4	0	1	1 1	0 6/6p	6/6	0	0 0		2		3		1	1	0	0	0	0	1	0	0 0	0	10	0
	2E+06	LE					4			1 1	0 6/6p	6/6	0	0 0		2		3		1	1	0		0	0	1	0	0 0	0	10	0
61	2E+06	26-11-16 RE	Arumug	71 F	NA	2	4	0	0	2 1	1 6/24	6/36	0	0 2			3	3	3	3	1	0	0	0	1	1	0	0 0	0	64	0
62	2E+06	22-11-16 RE	Alagu	56 M	NA	2	4	1	0	1 1	0 3/60	6/36	0	0 0		10		10	7	2	2	0	0	0	0	1	0	0 0	0	22	0
	2E+06	LE					4			1 1	0 6/12p	6/9	0	0 0		7		7	7	1	1	0		0	0	0	0	0 0	0	7	0
63	2E+06	29-11-16 RE	Rangas	71 M	NA	1	4	0	0	1 0	1 5/60	6/60	0	0 0		4		4	4	1	1	0	0	0	0	0	0	0 0	0	7	0
	2E+06	LE					4			1 0	1 6/60	6/60	0	0 0		3		4	4	1	1	0		0	0	0	0	0 0	0	7	0
64	4E+06	03-09-16 LE	Muthai	85 M		1	4	1.3	0	1 1	1 1/60	6/60	0	0 0		6		6		3	2	0	0	0	0	1	0	0 0	0	21	0
65	4E+06	15-09-16 RE	Ramesh	51 M		1	4	0	0	1 1	0 6/9	6/6	0	0 0		4		4	4	3	2	0	0	0	1	1	0	1 0	0	45	0
66	4E+06	19-09-16 LE	Sivakur	25 M		1	1	0	1	2 1	1 5/60	6/60	0	0 0		3	2	3	6	4	3	1	0	0	0	1	1	0 0	1	14	4
67	4E+06	02-09-16 RE	Vellimu	56 M		2	4	0	0	1 1	0 6/24p	6/12	0	0 0		1		1		2	1	0	0	0	0	0	0	0 0	0	10	0
68	4E+06	01-11-16 RE	Ramaki	47 M		1	4	0	0	1 0	1.2 HM	HM	0	0 0		6		6	6	4	3	0	0	0	1	1	0	0 0	0	7	1
69	4E+06	08-11-16 RE	Karuna	75 M		2	1	1	1	2 1	0 HM	6/60	0	0 0		12		12		4	3	1	0	0	0	1	0	0 0	4	34	4