CONTENTS

PART I

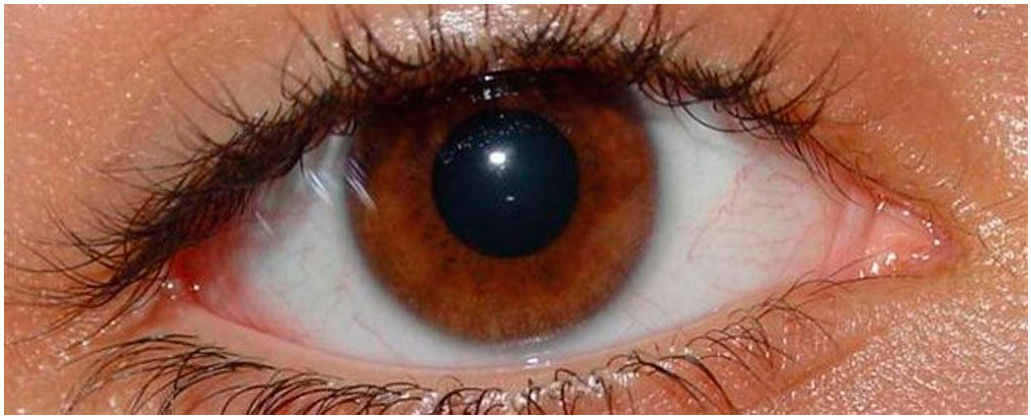
INTRODUCTION

The word cicatrix originates from Latin and it means the scar of a healed wound [6]. Cicatrizing conjunctivitis(CC) constitutes a group of chronic local and systemic disorders that cause conjunctival inflammation and scarring [3-7]. Conjunctival scarring and chronic inflammation lead to persistent ocular discomfort, limbitis, limbal epithelial stem cell deficiency, and ocular surface failure with subsequent blinding keratopathy [3]. Cicatrising conjunctivitis are a rare but sight threatening group of disorders for which early diagnosis and appropriate treatment are essential [3,4]. A systematic approach is required to sift through the clinical history, examination, and laboratory investigations of patients to arrive at the correct diagnosis of the underlying cause. Establishing the etiology is critical, as the therapeutic approach changes based on the cause of conjunctival inflammation [6].

ANATOMY

Ocular surface constitutes the anterior most part of the eyeball that is exposed to the environment. It consists of the conjunctival mucosa that lines the bulbar and palpebral surfaces, the corneoscleral limbus, the corneal epithelium and the tear film. These elements work physiologically along with eyelids and lacrimal functional unit (LFU) to maintain a healthy ocular surface and thus form an "ocular surface system". The ocular surface protects the eye from mechanical, toxic, infectious and immunologic insults and ensures smooth movement of the globe against palpebral mucosa for visual tracking [1].

Fig.1 : Healthy ocular surface



Functional Anatomy

Lids :

The eyelids form the first line of defense against trauma and desiccation. The eyelashes trap dust particles and prevent debris from entering the eye. The lids cover the ocular surface and thus help in conjunctival and corneal epithelial healing. The normal blinking action also helps in tear film redistribution.

The outer surface of the lid can get involved in a variety of systemic dermatological diseases like epithelial diseases (e.g. contact dermatitis), basement membrane diseases (e.g. pemphigus), connective tissue disorders (SLE, scleroderma) and follicular diseases (e.g. folliculitis). As a clinical sequelae, this results in scarring, retraction and trichiases causing exposure keratopathy and mechanical trauma to the surface. The meibomian glands are located within the tarsal plate, and produce oily secretions that form the lipid layer of the tear film, thereby preventing the evaporation of the tears and also acts as surfactant to spread tear film all over the ocular surface. Inflammation of these glands called meibomitis, is a common condition and is often difficult to treat permanently. These glands are also target for chronic inflammatory diseases like acne rosacea and ocular cicatricial pemphigoid [1].

Conjuntiva :

It is the mucosal membrane that extends from mucocutaneous junction of lid margins, upto the fornices and resurfaces the bulbar region and ends at the corneoscleral limbus. The conjunctival folds are more prominent in the fornices and facilitate the movement of globe against the lids and socket. Ocular surface stem cells are spread all over the bulbar conjunctiva, limbus and fornices. This explains conjunctival regeneration in some cases even after sustaining severe ocular surface injuries. The conjunctival mucosa also harbors accessory lacrimal glands and ducts of main lacrimal gland, which pass through it and open onto its surface. They contribute to aqueous component of tear film and may get involved in various conjunctival diseases and dry eye disorders (DED). Globet cells constitute 5-10% of the conjunctival epithelial cells and they contribute to the mucin layer of the tear film which firmly binds to ocular surface and provides base for aqueous layer to rest upon it. The tear film, conjunctiva-associated lymphoid tissue (CALT) and the rich conjunctival vascular supply contribute to the surface immunity [1].

Cornea :

Cornea is an avascular tissue which consists of epithelium, Bowman's layer, stroma, Descemet's layer, Dua's layer and endothelium. Its optical properties have a significant contribution in maintaining vision.

It has approximately 5-7 cells thick stratified squamous epithelium that is devoid of keratinization unlike skin for maintenance of optical clarity. But this makes the surface more prone for dehydration and trauma. Functional corneal innervation provides trophic support to epithelium, mediates blinking process and also reflex tear secretion from main lacrimal gland [1].

Limbus :

Limbus is the junction between sclera and cornea wherein the conjunctival epithelium abruptly ends and corneal epithelium begins; both being significantly different in their phenotypes. The conjunctival mucosa has radial folds at limbus called the 'limbal palisades of Vogt'. These palisades of Vogt and interpalisade rete ridges are nests for limbal stem cells.

Limbal stems cells are involved in maintaining corneal clarity by renewal and regeneration of the corneal epithelium in an organised manner along with prevention of conjunctival overgrowth. They are unique in a way that they are undifferentiated and are capable of indefinite multiplication to form highly differentiated progeny [1].

Characteristic feature of limbal stem cells

- Lack of differentiation
- High proliferative reserve
- Pluripotency
- Slow cell cycle
- Long lifespan
- Asymmetric division
- Require optimal microenvironment for survival – 'niche hypothesis' – proposed by Schofield (1983)

Davanger and Evensen (1971) showed centripetal migration of limbal cells in regeneration of corneal epithelium. In 1983, Thoft and Friend proposed XYZ hypothesis, where X represents basal proliferation, Y represents centripetal migration of stem cells and Z represents loss of superficial cells from surface [1].

Fig.2: Histology of corneoscleral limbus

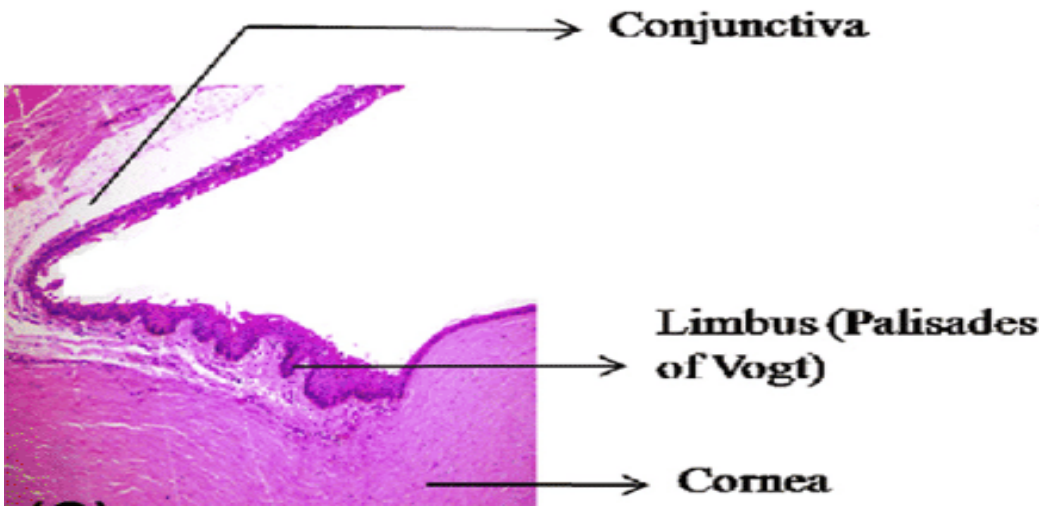
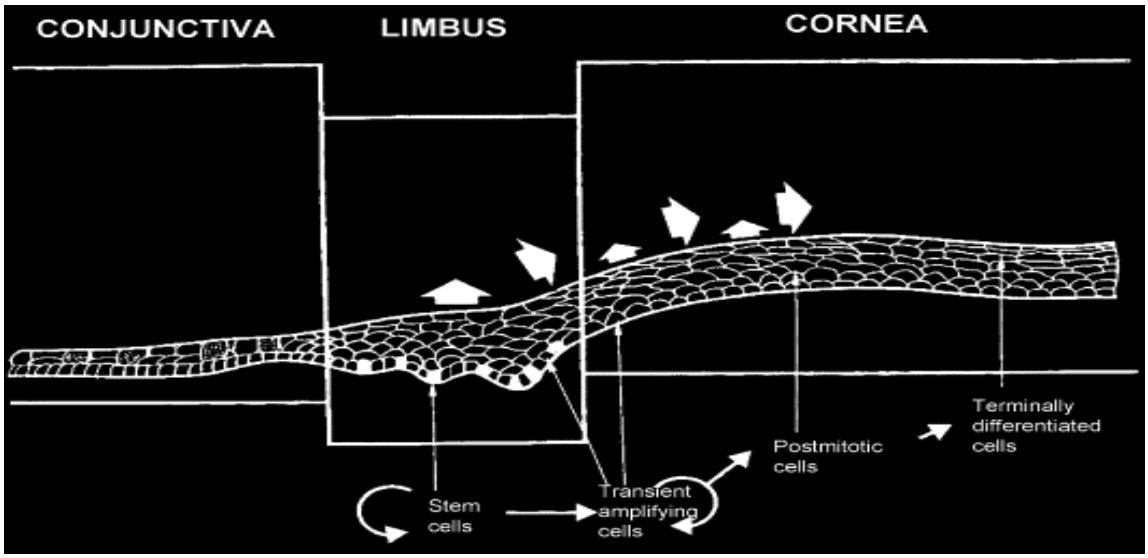


Fig.3: Limbal stem cells differentiate through various stages into corneal epithelial cells



ETIOLOGY

The etiological classification of cicatricial conjunctivitis is varied and can be broadly considered under four groups.

1) **Allergic/Non autoimmune cause** – Stevens-Johnson syndrome, atopic keratoconjunctivits
2) **Autoimmune cause** – Mucous membrane pemphigoid, lupus, scleroderma, lichen planus, Sjogren's syndrome
3) **Infectious origin** – adenovirus, trachoma
4) **Others**- chemical burns, trauma, and medicamentosa

Immune cicatricial conjunctivitis associated with bullous dermatoses:

These are heterogenous group of autoimmune skin disorders distinguished by the presence of bullae or blisters

- Pemphigus vulgaris
- Bullous pemphigoid
- Paraneoplastic pemphigus
- Cicatricial pemphigoid
- Linear IgA bullous dermatosis (LABD)
- Dermatitis herpetiformis
- Bullous systematic lupus erythematosus

The diagnosis of the specific entity is based upon the fluorescent pattern of the antibodies [2].

Table 1 : Conditions which are associated with cicatrising conjunctivitis[7]

Physical
Heat
Ionising radiation
Chemical
Infection
Trachoma
Membranous conjunctivitis (bacterial and viral)
Oculocutaneous disorders
Erythema multiforme
Stevens-Johnson syndrome
Toxic epidermal necrolysis
Mucous membrane pemphigoid
Linear IgA disease
Bullous pemphigoid
Epidermolysis bullosa
Dermatitis herpetiformis
Pemphigus group
Chronic atopic keratoconjunctivitis
Other associated systemic disorders
Rosacea
Sjögren's syndrome
Inflammatory bowel disease
Graft-versus-host disease
Immune complex diseases
Paraneoplastic syndromes
Drug-induced
Systemic
Topical (pseudopemphigoid)

PATHOGENESIS

Initially, there is induction of submucosal inflammation which starts a chain of events leading to hyperproliferation of fibroblasts and new tissue formation. The transition from inflammation to scar tissue seems to be mediated by the same mechanisms as those in wound healing and fibrosing diseases.

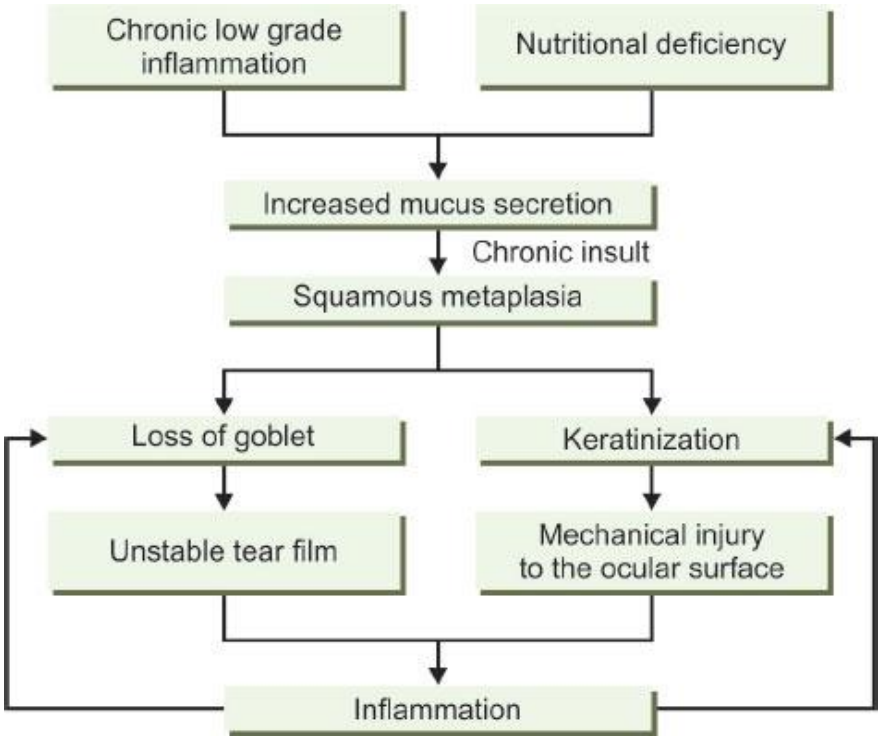
Macrophages are essential for wound healing and they promote the transition from inflammation to new tissue formation by secretion of fibrogenic growth factors. In active disease, the conjunctiva shows significantly increased number of macrophages, indicating a potential cause for the promotion of scar tissue formation.

Cytokines factors like transforming growth factor beta (TGF-β), platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF) and tumour necrosis factor alpha (TNF-α) too have a role in wound healing and fibrosing condition. There is evidence of upregulation of these fibrogenic cytokines in cicatrising conjunctivitis.

The role of T cells in the pathogenesis of cicatrisation is not completely understood. It seems that they are not essential for scar tissue formation, as shown in T cell depletion experiments. The main role of T cells appears to be regulation and perpetuation of the repair process [7].

Studies suggests that it is not primarily the composition of the cellular infiltrate but the differences in the secretory activity of these cells which determine the clinical characteristics of these diseases [16-19].

Fig.4: Vicious cycle involved in ocular surface damage [1]



Ocular surface failure :

Ocular surface failure has been divided into 2 types.

1) Type I failure : characterised by squamous metaplasia where thenon-keratinised corneal epithelium is replaced by keratinised one. It is usually associated with conjunctival squamous metaplasia

2) Type II failure : It is characterised by LSCD where the normal corneal epithelium is replaced by conjunctival epithelium [1]

Table 2 : Ocular surface failure type 1 conditions [1]

- *Malnutrition*:
  - Vitamin A deficiency
- *Oculocutaneous disease:*
  - Cicatricial pemphigoid
  - Bullous pemphigoid
  - Linear IgA disease
  - Dermatitis herpetiformis (Duhring)
  - Epidermolysis bullosa acquisita
  - Stevens-Johnson syndrome/toxic epidermal necrolysis
  - Toxic epidermal necrolysis (Lyell syndrome)
  - Porphyria cutanea tarda
  - Atopic keratoconjunctivitis
  - Acne rosacea
- Drugs (pseudopemphigoid)
- *Miscellaneous conjunctival inflammations:*
  - Sjögren's syndrome
  - Systemic sclerosis (scleroderma)
  - Graft-versus-host disease
  - Inflammatory bowel disease
  - Reiter's syndrome
- *Infectious membranous conjunctivitis:*
  - Viral conjunctivitis
  - Bacterial conjunctivitis
- Ocular surface burns

Table 3 : Ocular surface failure type 2 conditions [1]

- *Primary LSCD:*
  - Aniridia
  - Sclerocornea
  - Multiple endocrine deficiency (MEN)
  - *Ectodermal dysplasia*:
    - Ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome
    - Senter's syndrome or keratitis-ichthyosis-deafness (KID) syndrome
  - Erythrokeratoderma
  - Lacrimo-auriculo-dento-digital (LADD) syndrome
  - Dominantly inherited keratitis
  - Dyskeratosis congenita
  - Epidermolysis bullosa
  - Turner's syndrome
  - Peter's anomaly
  - Xeroderma pigmentosum
- *Secondary LSCD:*
  - *Systemic conditions:*
    - Vitamin A deficiency
    - Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN)
    - Mucous membrane pemphigoid
    - Sjögren's syndrome
    - Graft-versus-host disease (GVHD)
    - Rosacea
    - Systemic chemotherapy (e.g. anticancer drug S-1 for treatment of gastric cancer)
  - Ocular conditions
- *Trauma:*
  - *Chemical:* acid, alkali, others
  - Thermal burns
  - Radiation
- *Ocular diseases:*
  - Postinfectious keratitis
  - Neurotropic keratitis
  - Keratoconjunctivitis sicca
  - Vernal keratoconjunctivitis
  - Ocular surface tumors
  - Pterygium and pseudopterygium
  - Contact lens use
  - Aphakic and pseudophakic bullous keratopathy
- *Iatrogenic:*
  - Multiple ocular surgeries
  - Pterygium excision
  - Cyclocryotherapy
  - Antimetabolites—topical mitomycin C, 5-fluorouracil
  - Toxicity from topical medications [benzalkonium chloride (BAC)]
- Idiopathic

HALLMARK CLINICAL FEATURES OF OCULAR SURFACE DISEASES :

1) Dysfunctional tear syndrome – It is complex of overlapping symptoms of tear film disorder and goblet cell deficiency that includes ocular discomfort, burning, stinging, foreign body sensation, photophobia and blurred vision. There may be variable surface inflammation along with lustreless surface, increased blink rate and decreased tear meniscal height.

2) Conjunctival infections and allergic eye diseases present with discharge, conjunctival injections, papillae and follicles. Chronic cases may involve cornea and cause corneal ulcers like in VKC.

3) Limbal stem cell deficiency (LSCD) – can cause two classes of problems. (i) improper healing due to recurrent epithelial erosions and persistent epithelial defects (PED). (ii) superficial vascularisation and conjunctivalisation of cornea due to breach in LSC barrier. Both classes of patients have variable irregular corneal surface [1].

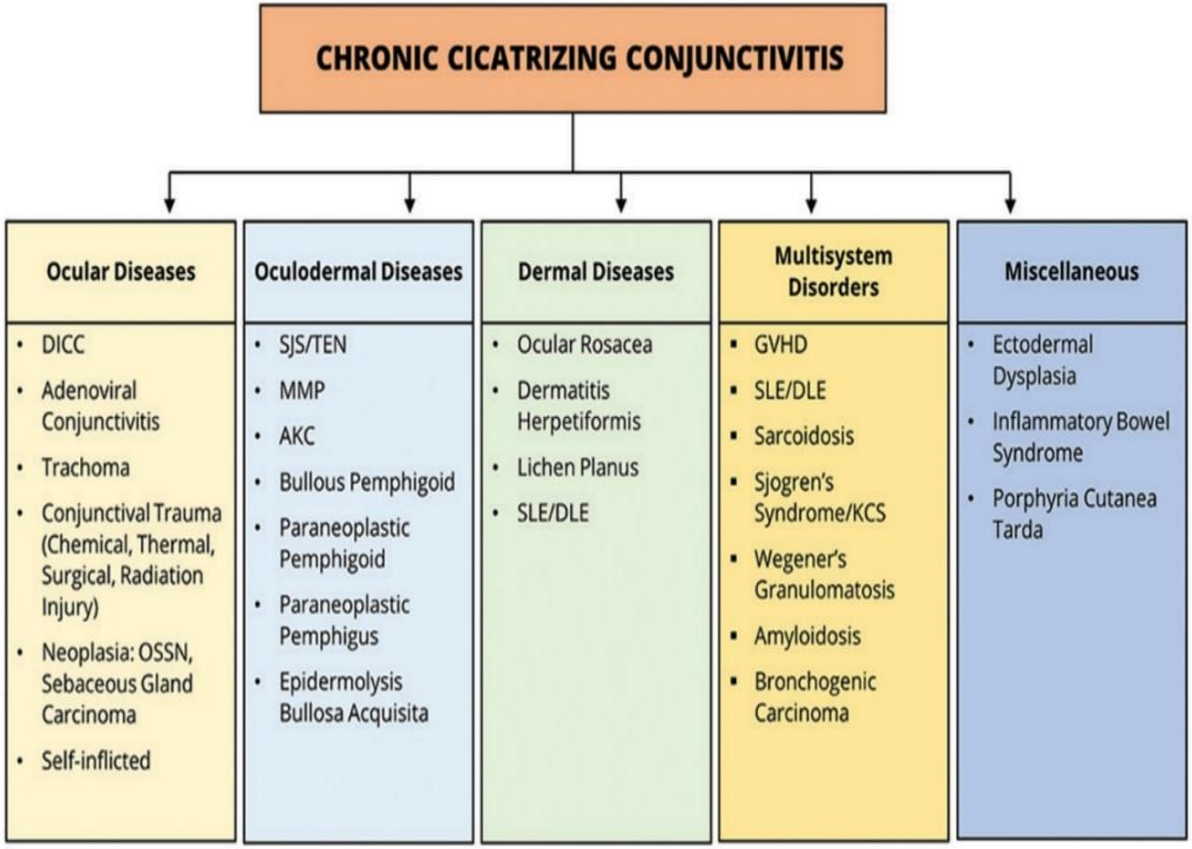
TELL TALE SIGNS OF CCC

The early and subtle signs of CCC may include subconjunctival or caruncluar fibrosis leading to symblepharon formation and forniceal foreshortening. More advanced cases present with dry ocular surface, loss of plica semilunaris, keratinisation of the ocular surface or lid margin, loss of normal architecture of the lid margin and mucocutaneous junction, trichiasis, entropion, ankyloblepharon, and dermalization of ocular surface. In long standing cases, there may be features of LSCD which presents with loss of corneal luster, persistent corneal epithelial defects, or fibrovascular pannus formation [6].

DIFFERENTIAL DIAGNOSIS

- Blinding scarring diseases:
  - Mucous membrane pemphigoid
  - SJS/TEN
  - Drug-induced progressive scarring
- Ocular surface neoplasia:
  - OSSN
  - Sebaceous cell carcinoma
- Ocular disease with no systemic involvement:
  - Adenoviral conjunctivitis
  - Trachoma
  - Atopic conjunctivitis
  - Conjunctival trauma (chemical, thermal, radiation, surgical)
- Systemic diseases (other than MMP and SJS):
  - Ocular Rosacea
  - Bullous pemphigoid
  - Para neoplastic pemphigoid
  - Pemphigus vulgaris
  - Para neoplastic pemphigus
  - Lichen planus
  - Dermatitis herpetiformis
  - SLE
  - Sarcoidosis
  - Graft versus host disease [1]

Fig.5 showing the differential diagnosis of CCC [6]



ESTABLISHING THE DIAGNOSIS

The presence of clinical signs of CCC should prompt the clinician to look for the underlying cause systematically.

Few conditions may present in childhood and may have specific hair, teeth, skin and other mucosal structures like epidermolysis bullosa and ectodermal dysplasia.

Infections like trachoma, adenoviral keratoconjunctivitis and mycoplasma induced rash and mucositis are known to cause nonprogressive conjunctival scarring and can be identified based on history and specific clinical signs.

Insults like ocular surface chemical or thermal burns, ocular surface surgery, and radiotherapy to the head/neck region can be ruled in or out by a detailed history.

History of allogeneic bone marrow transplantation followed by dry eye disease gives clue to the diagnosis of graft-versus-host disease.

History of long term use of any topical medication can cause CCC due to either the drug itself or the preservatives used. This is described as pseudopemphigoid or drug induced cicatrizing conjunctivitis (DICC). This is more common in patients using antiglaucoma medications for prolonged duration. Clinical clues in such cases be involvement of inferior lacrimal puncta (punctual edema, fibrosis or occlusion), periocular skin changes, zipper like scarring and symblepharon in the inferior and medial part of the eye.

Patients with dry eye and dry mouth indicate diagnosis of long standing primary or secondary Sjogren's syndrome which can be further evaluated my systemic examination, serological tests, HLA typing and a salivary gland biopsy if indicated. Patients with long standing ocular allergy like in AKC/VKC present with history of itching and may have conjunctival papillae, whereas rosacea blepharoconjunctivitis has typical skin features. Patients with history of any oral and/or skin ulceration may indicate SJS or OcMMP [6].

ROLE OF CONJUNCTIVAL BIOPSY :

It is indicated in all cases with a clinical suspicion of ocular MMP. This not only confirms the diagnosis but also helps in identifying other causes of CCC like OSSN, sarcoidosis, and AKC. Two biopsies are taken measuring 2-4mm each from the clinically uninvolved parts of the bulbar conjunctiva. Biopsy from forniceal conjunctiva is contraindicated. Also avoid areas that are already scarred or that have other coexistent pathologies like a pinguecula or pterygium. One biopsy is fixed in formalin for histopathology and the other is transferred in an appropriate transport media like Michel's medium for DIF. DIF is said to be positive for MMP if linear deposits of immunoglobulins or complement are found in the basement membrane. The reported rate of biopsy positivity widely varies from 50% to 86%. Simultaneous biopsies from both bulbar and buccal mucosa is recommended nowadays [3-6, 12].

Fig.6: The diagnostic problems in cicatrising conjunctivitis [5]

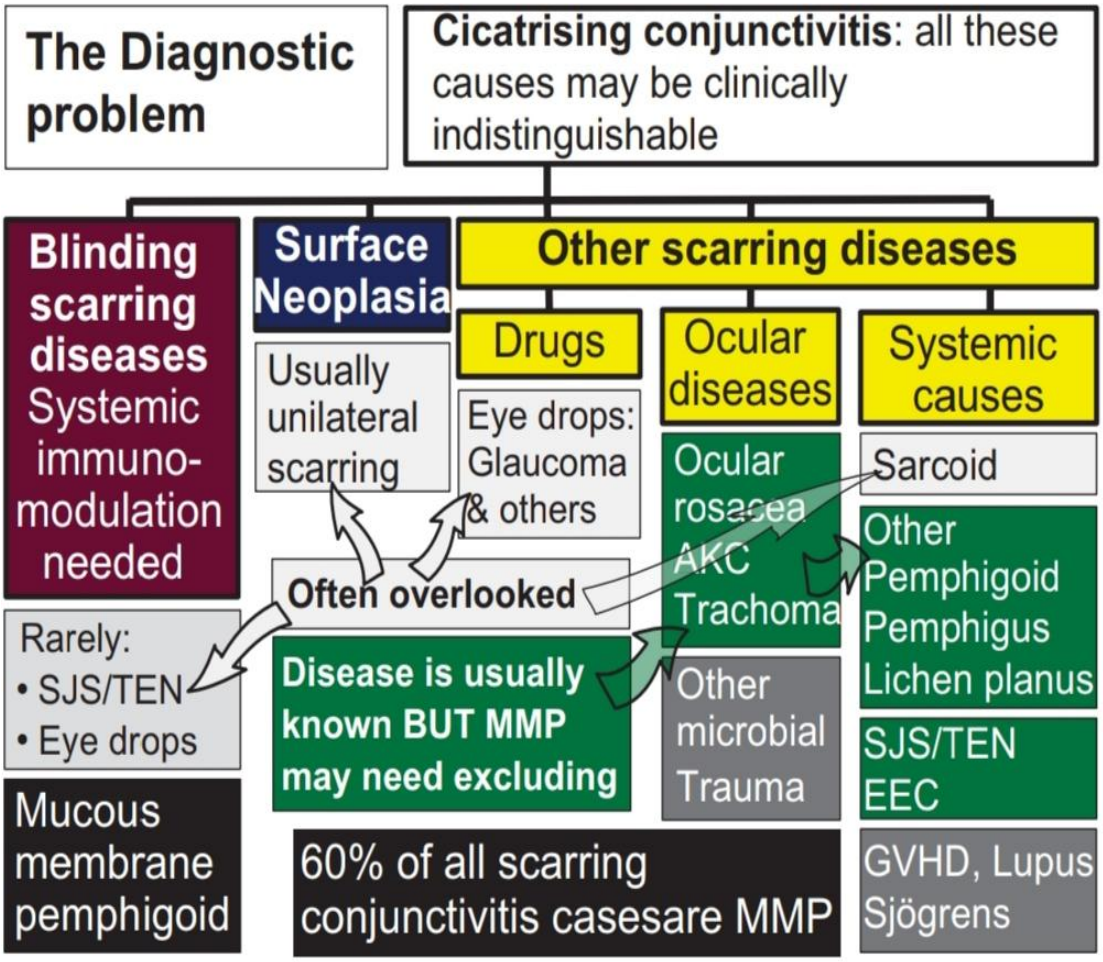


Fig.7: Algorithm to establish the etiological diagnosis of CCC [6]

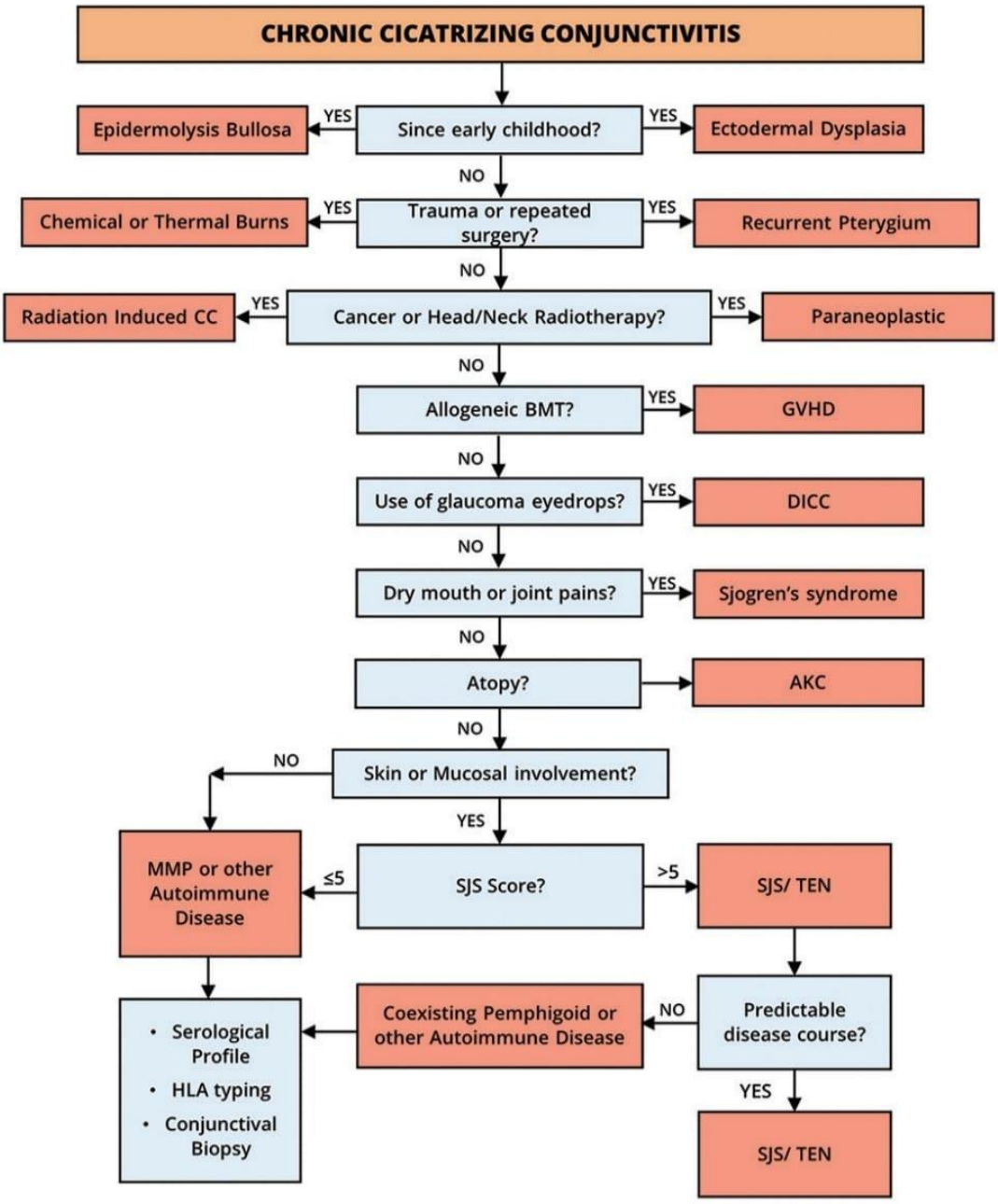
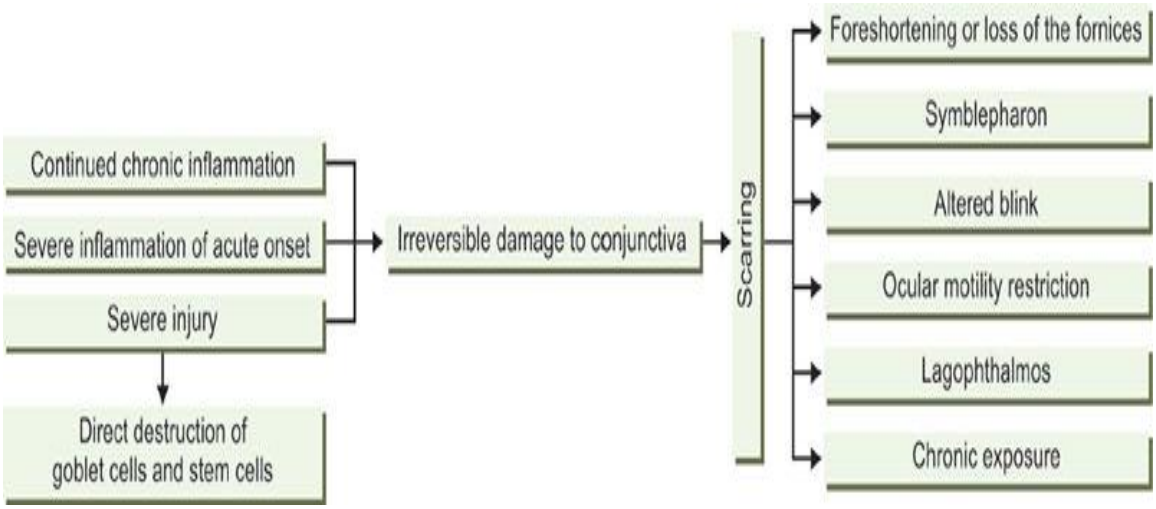


Table 4 : Sequelae of chronic progressive conjunctival cicatrisation [7]

Eyelids and annexe
Obstruction of lacrimal glands and meibomian glands
Blockage of canaliculi and lacrimal puncta
Aberrant eyelash growth
Distortion of the lids
Cicatricial entropion
Ocular surface
Loss of goblet cells and of normal microvillous structure
Tear film alteration
Secondary infection
Trichiasis
Keratopathy

Fig.8: Anatomical changes and long term sequel to ocular surface damage caused by acute and chronic insults [1]



GOALS OF TREATMENT

- To arrest progressive cicatrization,
- Correction of lid abnormalities,
- To prevent complications like keratopathy and corneal perforation,
- Providing symptomatic relief, as well as improving vision [6].

In SJS, several studies have shown that early amniotic membrane grafting can dramatically reduce chronic ocular complications [20, 21].

In acute chemical injuries, urgent and appropriate treatment with irrigation and lavage, intensive topical steroids, and amniotic membrane grafting can go a long way in limiting the conjunctival fibrosis and reduce the need for further reconstructive surgery.

In progressive CCC, due to DICC, withdrawing the offending drug and replacing it with a preservative-free alternative can arrest the progression of cicatrization in most cases. Also, topical steroids can be added and used in tapering doses to control the surface inflammation.

Systemic autoimmune disorders like MMP lead to progressive CCC that, if unchecked, can and usually does lead to blinding complications .

A clinical diagnosis of MMP warrants treatment with systemic Immunomodulatory therapy. A large number of drugs have been used for

this purpose. Severe disease usually requires treatment with intravenous or oral steroids along with cyclophosphamide or rituximab for the control of inflammation. Less severe cases or cases where the inflammation has been adequately controlled can be treated with the maintenance doses of drugs like mycophenolate mofetil, azathioprine, and methotrexate.

Nonprogressive cicatrization due to causes like ocular surface burns and SJS/TEN does not need systemic immunosuppression.

The focus of therapy in these cases should be on optimizing the ocular surface environment. Cases of SJS/TEN often have disturbances of the mucocutaneous junction at the eyelid margins, and may lead to keratinization. If left unaddressed, over months and years this can cause progressive keratopathy which leads to corneal vascularization, opacification, and perforation. Early identification of lid margin changes and the corresponding keratopathy is essential as it provides a window of opportunity for intervention in these cases. It has been shown that measures such as lid margin mucous membrane grafting (MMG) and use of fluid-filled scleral lenses are effective in preventing progressive keratopathy and thus preserve good vision in the long term.

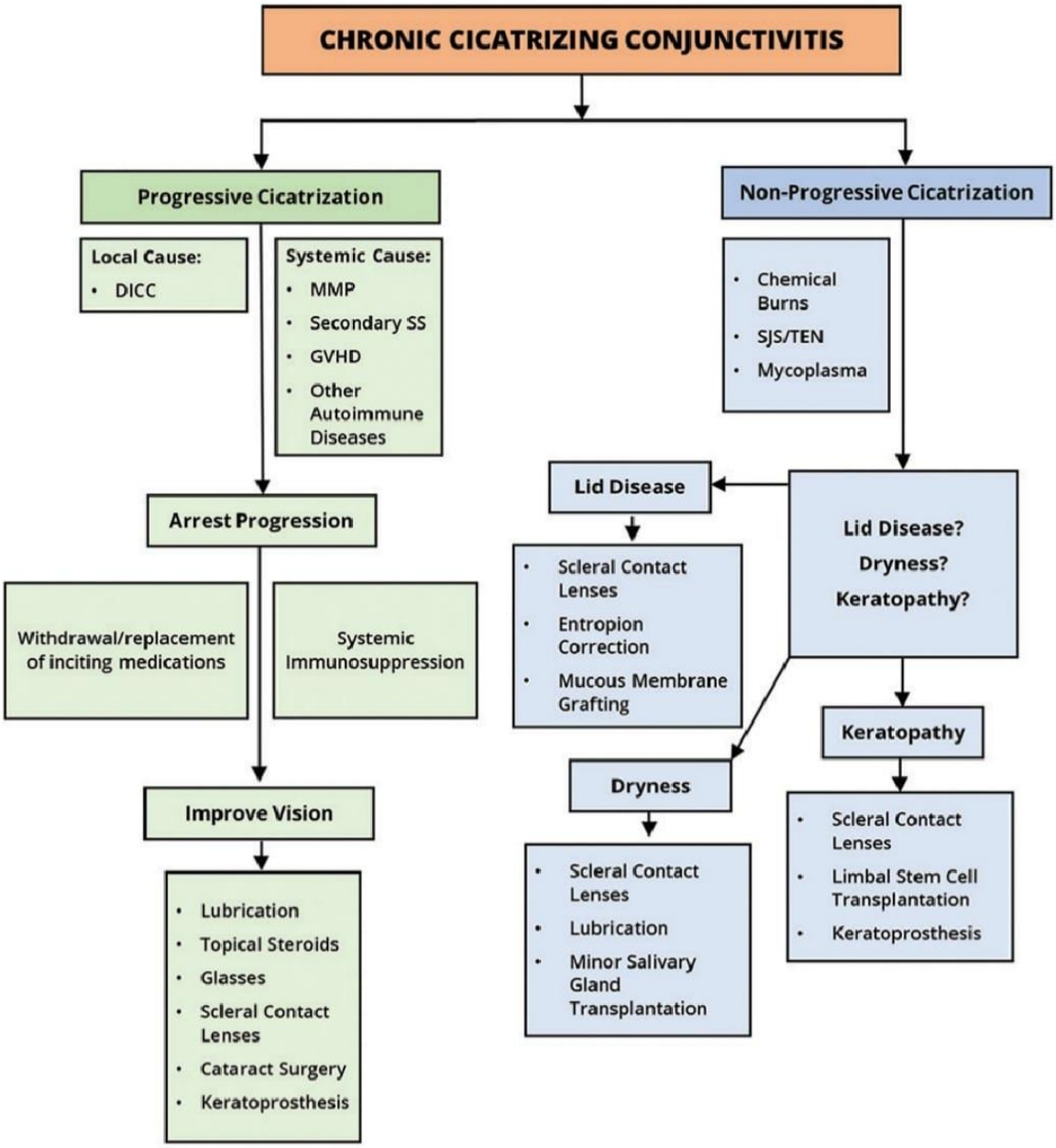
In both progressive and nonprogressive cases of CCC, dry-eye disease may warrant treatment with frequent lubricant medication,

autologous serum as well as the use of fluid-filled scleral lenses. In cases of severe dry eye, transplantation of minor salivary gland to the eye may be helpful.

Cataract surgery has been reported ot be safe and effective in conditions like MMP and SJS/TEN, provided the activity of the disease is controlled before surgery.

In cases of LSCD, one must consider the status of the tear film, eyelids, fornices, conjunctiva and cornea involvement. In cases with wet ocular surface and normal adnexa, allogenic limbal stem-cell transplantation can be tried. Other surgical techniques like simple limbal epithelial transplantation (SLET), which is an inexpensive, single stage technique, that allows for in vivo expansion of limbal epithelial stem cells on the recipient surface can also be done. Good case selection and adequate systemic IMT are keys for achieving successful surgical outcome. Another alternative in these cases is Type 1 Boston Keratoprosthesis. For cases with bilateral LSCD and dry ocular surface, the surgical options for improving vision would be type 2 Boston keratoprosthesis, modified osteo-odonto keratoprosthesis or LVP keratoprosthesis [6].

Fig.9: Algorithm for management of CCC



STEVEN JOHNSON SYNDROME

It is characterised by a severe immunologic dermatobullous condition. It is an acute, self limiting vesicobullous disorder which affects the skin and at least two mucous membranes. Severe necrosis of the body surfaces lead to fatal systemic complications with lifelong comorbidities.

Fig.10 : A case of acute Stevens Johnson syndrome

Spectrum of disease

1)SJS - <10% BSA involved

2)SJS/TEN overlap – 10 %-30% involvement

3)TEN – >30% involvement

Predisposing factors

Idiosyncratic response to systemic drugs has been implicated

Pathophysiology

It is a type IV delayed hypersensitivity reaction mediated by CD8+ cytotoxic T cells and natural killer cells leading to widespread keratinocyte apoptosis and epidermal necrosis. HLA association with certain drugs has also been implicated across different ethnic groups. HLA B*1502 has strong association with carbamazepine induced SJS/TEN in Asian population [1].

Table 5 : Few important drugs implicated in SJS [1]

- *Anticonvulsants*:
  - Phenytoin
  - Phenobarbital
  - Carbamazapine
- *NSAIDs*:
  - Salicylates
  - Ibuprofen
  - Pyrazoline derivatives
- *Antimicrobials*:
  - Beta-lactam antibiotics
  - Macrolides
  - Tetracyclines
  - Quinolones
  - Griseofulvin
  - Nystatin
  - Chloroquine
  - Quinine
  - Nevirapine, Abacavir
- *Sulfa derivatives*:
  - Trimethoprim
  - Sulfasalazine
  - Sulfadiazine
- *Metals*:
  - Arsenic
  - Lithium
  - Mercury
  - Gold
- *Miscellaneous*:
  - Acetazolamide
  - Allopurinol
  - Cimetidine
  - Lamotrigine
  - Indapamide
  - Enalapril, Captopril
  - Calcium-channel blockers
  - Diuretics
  - Vaccinating agents

Clinical course

Ocular involvement is unrelated to systemic illness and it can range anywhere from mild conjunctival hyperemia to total soughing of ocular surface epithelium [1].

Fig.11 : Ocular features of SJS in chronic stage showing keratinisation of upper and lower lid margin, trichiasis, corneal opacification and vascularisation

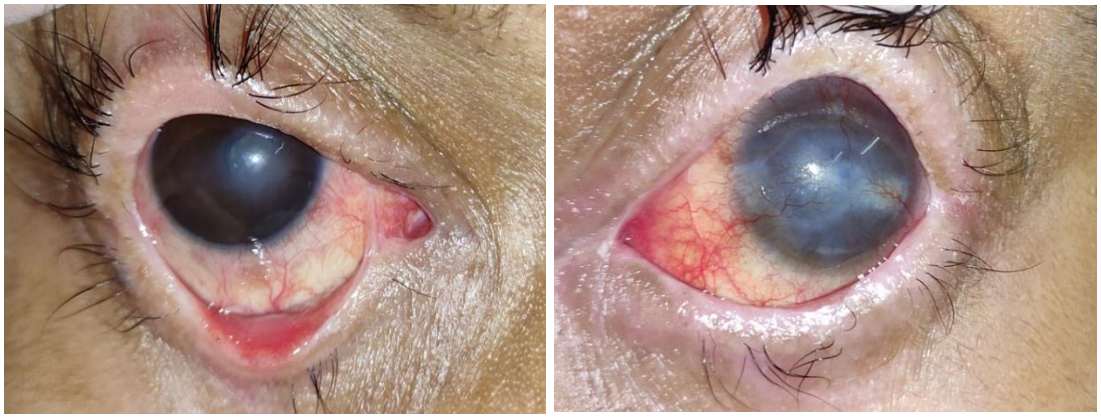


Table 6 : Ophthalmologic grading criteria and treatment recommendation [1]

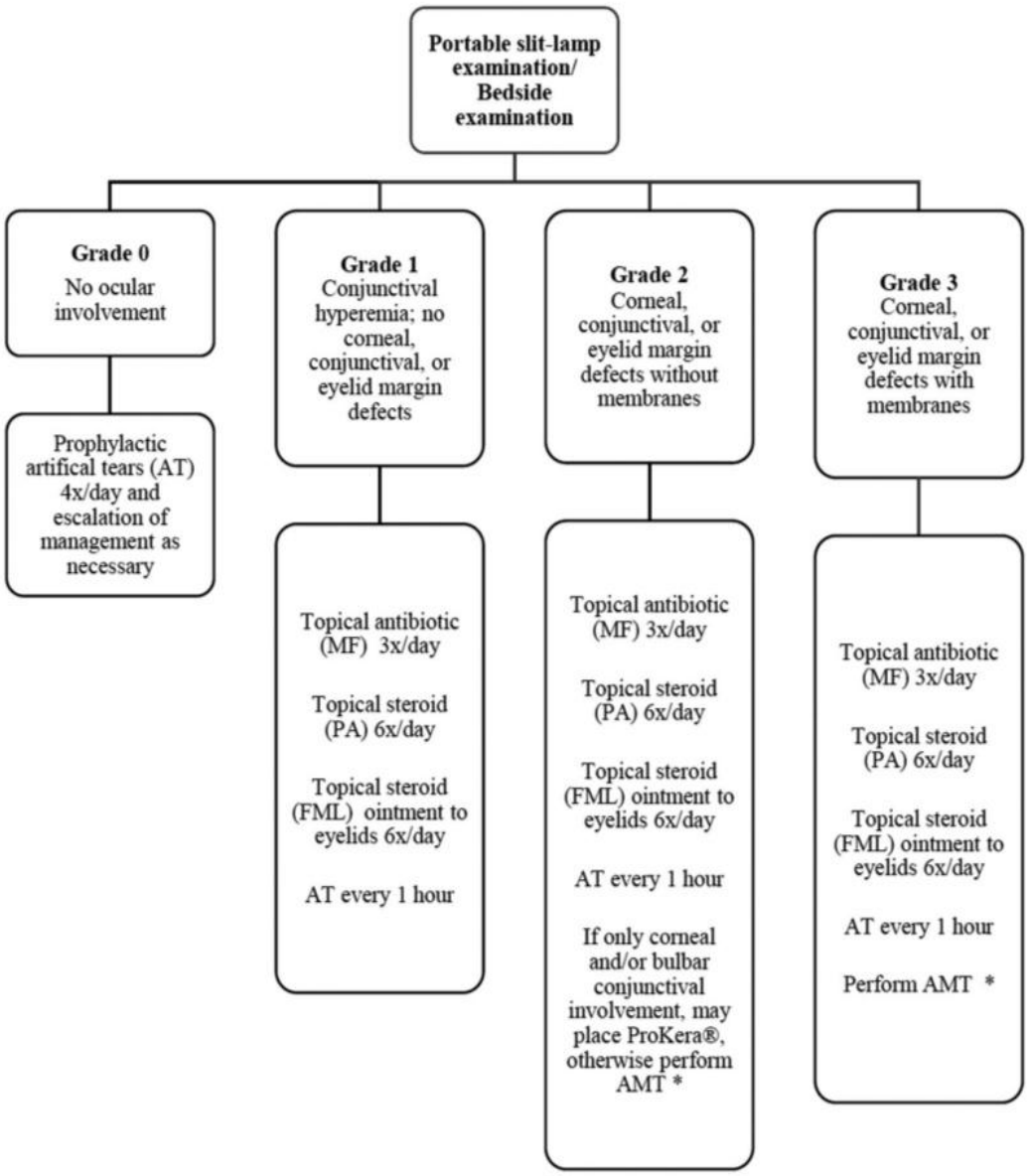
Staining location and treatment recommendations	Severity of eye involvement			
	Mild	Moderate	Severe*	Extremely severe†
Lid margin	No stain	Stain <1/3 of lid margin length	Stain >1/3 of lid margin length on at least 1 lid	Stain >1/3 of lid margin length on more than 1 lid
Cornea	No stain	No stain	Any epithelial defect more than punctate staining	Any epithelial defect more than punctate staining
Conjunctiva (bulbar and palpebral)	Hyperemia, without stain	(+)Stain, <1 cm in greatest diameter	(+)Stain >1 cm	Multiple areas of stain >1 cm
Treatment recommendations	Medical	Medical and close observation	Medical and urgent amniotic membrane transplantation (AMT)	Medical and urgent AMT (may require repeat AMT)

Table 7 : Scoring system for the diagnosis of SJS [8]

Characteristic	Score
Medical history	
Sudden onset of conjunctivitis	+1
Fever or drug intake preceding conjunctivitis	+1
Associated with peeling of skin on pressure	+1
Associated with loss of nails on fingers or toes	+1
Severe morbidity with admission in intensive care unit or burn ward	+1
Associated with mucosal ulcers but not skin rash/blisters/bullae	–1
Recurrent mucosal ulceration or rectal bleeding (melena)	–1
Clinical examination	
Skin discoloration	+1
Disfigured fingernails or toenails	+1
Posterior migration of mucocutaneous junction in the mouth	+1
Lid-margin keratinisation (in at least one eyelid)	+1
Distichiasis (in at least one eyelid)	+1
Total score	

A score of >5 is highly sensitive and specific in diagnosing SJS as the underlying cause of CCC

Fig.12 : Protocol for the management of ocular manifestation in acute SJS [9]



Management of chronic SJS Sequelae

1) **Systemic immunomodulators** – to combat the persistent ocular inflammation. Topical steroids are best avoided in long run vowing to the associated complications.

2) **Scleral contact lens** – Application of PROSE (prosthetic replacement of the ocular surface ecosystem) scleral lenses reduce pain, enhances vision and improves the surface over a period of time. It vaults over the cornea and and protects the surface against blink related microtrauma and provides it with a fluid filled reservoir which hydrates the ocular environment and promotes healing.

3) **Mucous membrane graft** – used to replaces the keratinised surface. It also repairs symblepharon and cicatricial entropion

4) **Keratoprosthesis** (K-Pro) – helps to restore vision in end stage [1] .

Fig.13 : Scleral lens in a patient with SJS

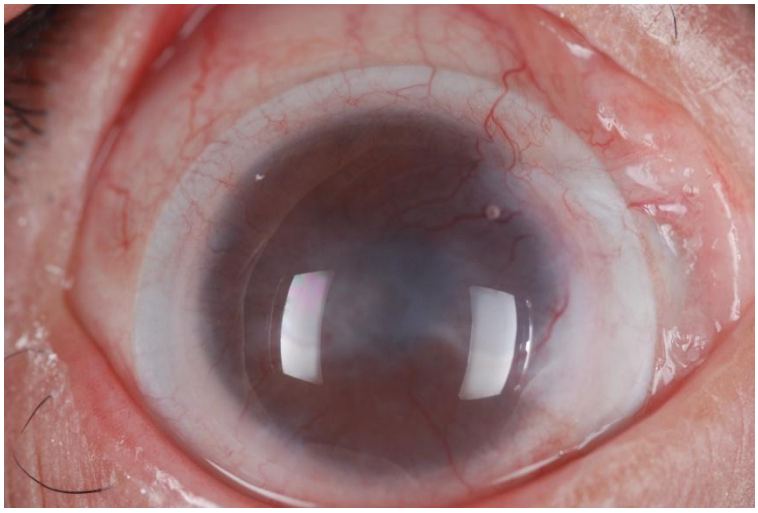


Fig.14 : Mucous membrane grafting in a patient with SJS sequelae

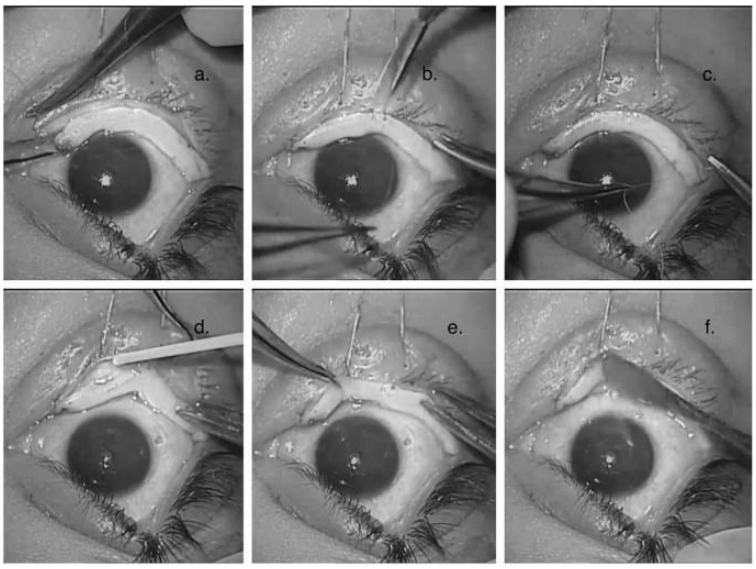


Fig.15 : Boston K-Pro assembly [1]

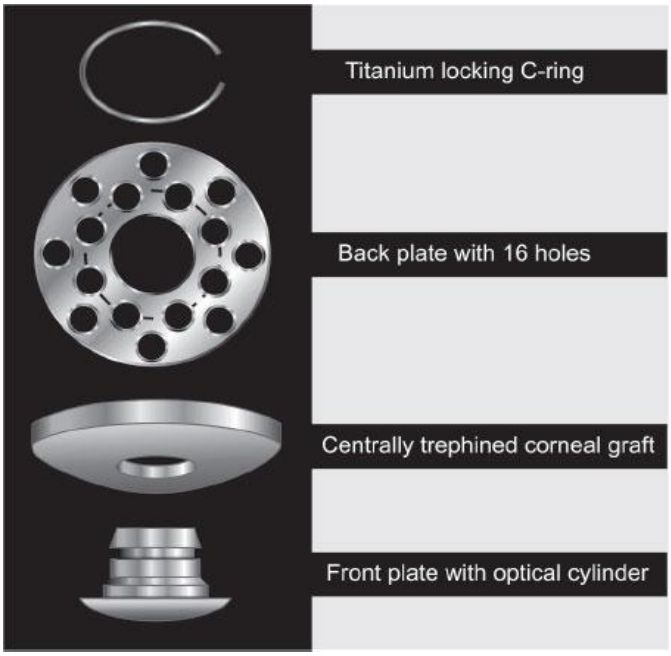


Fig.16 : Auro K-Pro in place in a patient's eye with total LSCD [1]

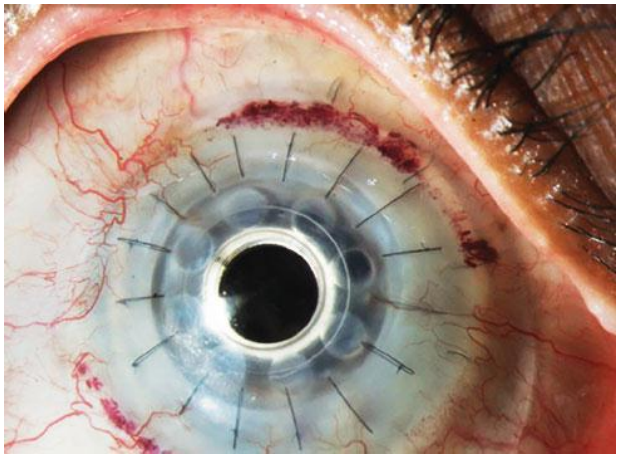


Table 8 : Ocular complications of SJS [1]

Acute	Chronic
• Self-limited conjunctival hyperemia	• Symblepharon formation
• Near total/total ocular surface epithelial sloughing	• Ankyloblepharon formation
• Lid margin de-epithelialization	• Ectropion
• Pseudomembrane/membrane formation	• Entropion
• Early symblepharon formation	• Punctal occlusion
• Fornix foreshortening	• Lid margin keratinization
• Corneal ulceration/perforation	• Meibomian gland atrophy
	• Distichiasis
	• Trichiasis
	• Severe dry eye disease (DED)
	• Limbal stem cell deficiency (LSCD)
	• Persistent epithelial defect (PED)
	• Stromal scarring
	• Corneal perforation

Table 9 : Management of chronic SJS sequelae [1]

Complications	Management
Trichiasis	Hyfrecation, cryotherapy, eyelash bulb extirpation, mucous membrane grafting (MMG) if associated with entropion
Lagophthalmos	Release of cicatrix, tarsorrhaphy
Entropion/Ectropion	Lateral canthoplasty/tarsal strip, anterior lamellar repositioning, posterior lamellar tightening, transconjunctival advancement
Persistent epithelial defect	Lubrication, punctal occlusion, bandage contact lens, tarsorrhaphy, autologous serum tears, amniotic membrane transplantation (AMT), scleral lens, cultivated oral mucosal epithelial transplantation (COMET)
Dry eye	Preservation-free artificial tears, punctal cautery, minor salivary gland transplant
Posterior lid margin keratinization	All-trans-retinoic acid ointment, scleral lens, MMG
Symblephara	Lysis/fornix reconstruction with amnion/MMG
End-stage corneal blindness	MMG, COMET, keratoprosthesis

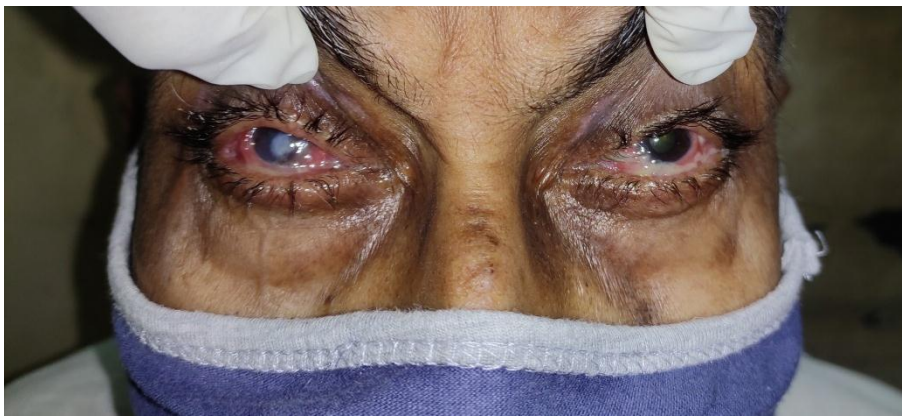
OCULAR CICATRICAL PEMPHIGOID/MUCOUS MEMBRANE PEMPHIGOID

It is a rare autoimmune disease with male preponderance. The average age of incidence is 65years.

Disease spectrum

OCP is a variant of MMP where in ocular features are predominantly present. There may be other mucous membrane involvement also namely nasal cavity, oropharynx, and the genetalia[1,5,12].

Fig.17 : A case of ocular cicatricial pemphigoid



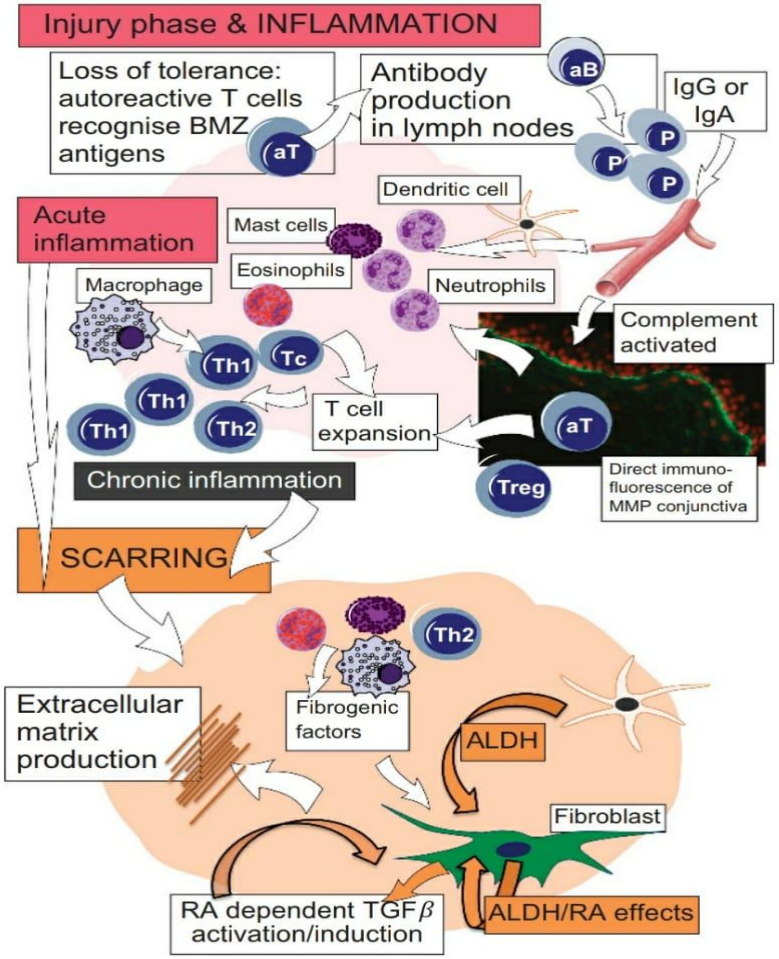
Epidemiology

MMP may affect any race, but it seems to be more common in Caucasians than in Indians and Chinese. Expression of the HLA-DR4, HLA-DQw3 and HLA-DQβ*10301 alleles, which are involved in antigen presentation to T cells, is associated with development of OcMMP [12].

Pathogenesis

OCP is a type II immune reaction characterised by immunoreactants deposition on the epithelial basement membrane inducing a subepidermal split with subsequent blister formation. Specific β -4 integrin subunit antibodies are seen in cases with exclusive ocular mucosa involvement [1].

Fig.18 Summary of pathogenesis of ocular MMP [5]



Clinical features

Initially the findings are unilateral, chronic, recurrent, papillary conjunctivitis that progresses to involve both eyes. There occurs subepithelial fibrosis which progresses to cicatricial conjunctivitis. The inferior fornix is usually affected earlier than the superior one. The other ocular manifestations include entropion, lagopthalmos, symblepharon, surface and lid margin keratinisation, trichiasis, distichiasis , severe dryness corneal erosion, ulceration, vascularisation and perforation [1].

Systemic involvement

Skin involvement is seen in 4-15% of cases involving face, inguinal region, face, scalp and extremities. Oral mucosa is commonly involved and present with desquamative gingivitis. Other features would be epiglottic erosions causing dysphonia and coarse voice, esophageal strictures causing dysphagia and aspiration [1] .

Table 10 : Foster's classification of OCP [1]

Stages	Ocular condition
I	Chronic conjunctivitis with subepithelial fibrosis
II	Forniceal shortening
III	Symblepharon appearance
IV	Ankyloblepharon, frozen globe

Table 11 : Mondino and Brown classification of OCP [1]

Stages	Conjunctival forniceal shortening
I	≤25%
II	25–50%
III	~75%
IV	End-stage diseases: obliterated fornices

Diagnosis

High clinical suspicion is required in diagnosing OCP. Conjunctival biopsy reveals linear IgG, IgA, IgM and or complement deposition on EBM. Negative result does not rule out the disease and may require repeat biopsy [1].

Fig.19 : Proposed revised immunopathological criteria for the diagnosis of OCP [3]

Consensus criteria[a]	1. Direct immunofluorescence – presence of basement membrane zone (BMZ) deposits of IgG, IgA, IgM, and/or C3. • Detection of one or combination of the above linear epithelial BMZ immune deposits establishes the diagnosis of autoimmune MMP. • Patients with clinical manifestations similar or identical to MMP but in whom epithelial BMZ immune deposits have not been demonstrated, these patients may be drug-induced or the pathogenesis of the disease needs to be further elucidated. 2. Indirect immunofluorescence – presence of IgG and IgA autoantibodies binding to skin BMZ on salt split epithelial substrate. • Not all patients with MMP have detectable circulating autoantibodies to the basement membrane zone. The consensus does not consider these findings to be an absolute criterion.
Proposed revised criteria	Patients with a typical ocular phenotype of progressive conjunctival scarring consistent with a clinical diagnosis of ocular mucous membrane pemphigoid PLUS either one of the following: 1. Positive conjunctival direct immunofluorescence or positive direct immunofluorescence from any other site (eg, oral mucosa, skin) that meet the current consensus criteria. *Or* 2. Negative direct immunofluorescence from any site and positive indirect immunofluorescence are diagnosed as having MMP. *Or* 3. Negative immunofluorescence studies (direct or indirect) only when other diseases that may cause this phenotype have been excluded, are diagnosed as presumed OcMMP.

Fig.20 : Immunofluorescence staining of conjunctival biopsy specimen showing IgG positive basement membrane in a case of OCP [1]

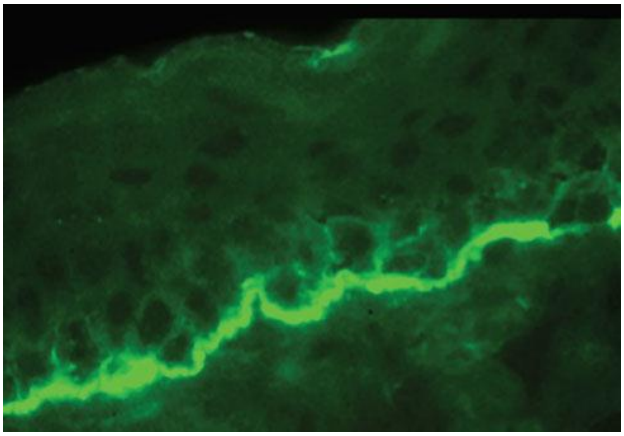


Fig.21 : Epithelial basement membrane structure and immunofluorescent tests [5]

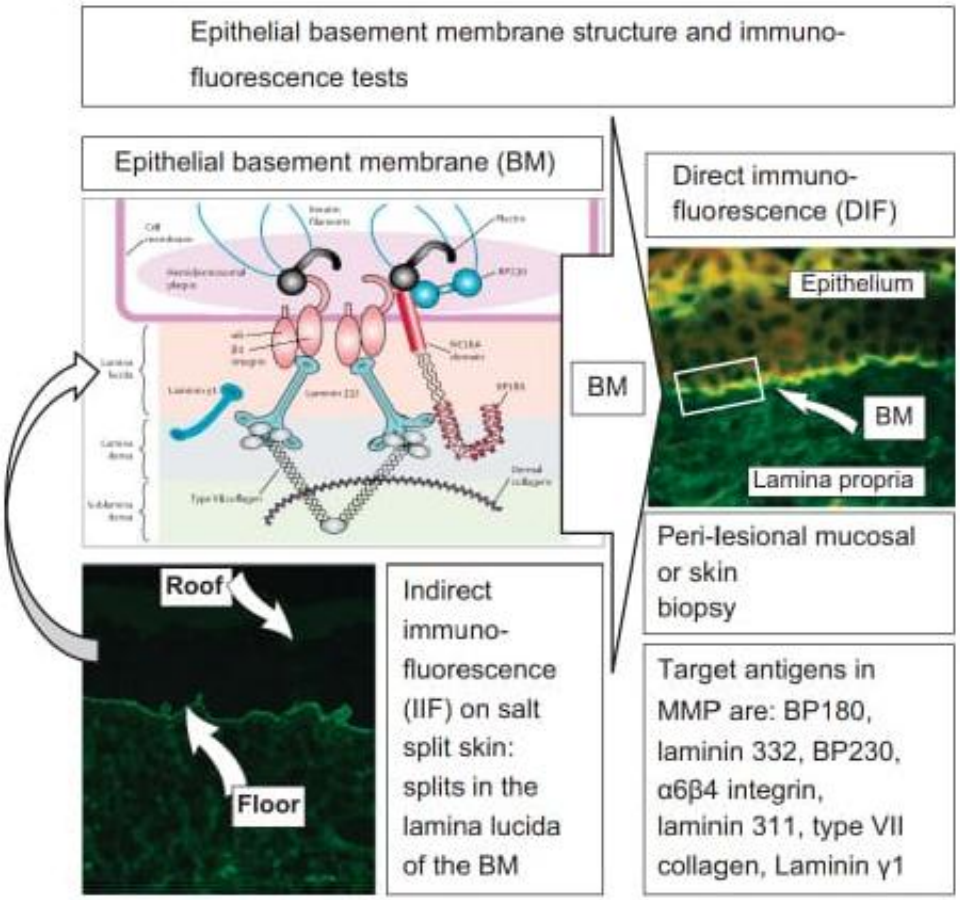
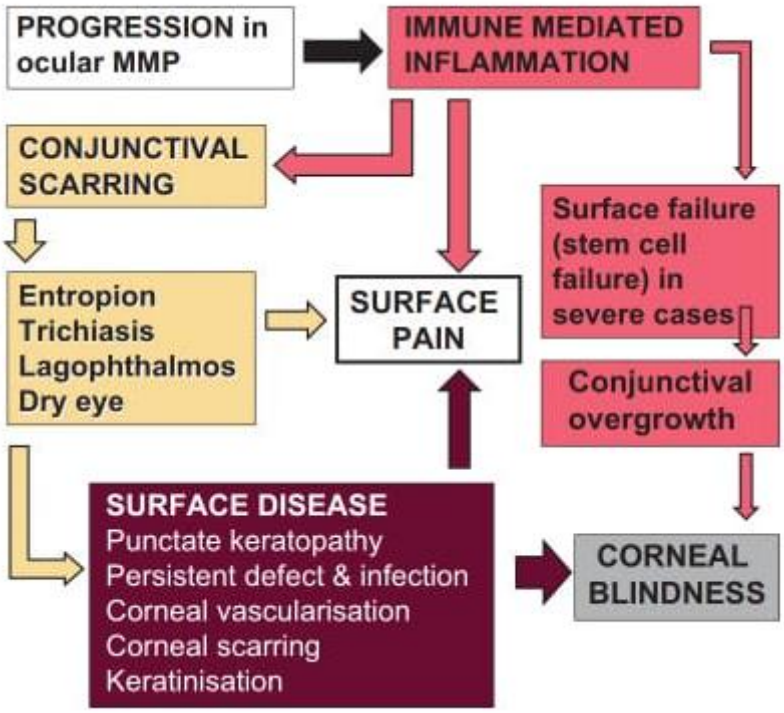


Fig.22 : Factors contributing to progression of disease in OcMMP [5]



Medical Management

Local :

Preservative free lubricants for dry eyes, warm compresses and antibiotics for blepharoconjunctivitis. Topical calcineurin inhibitors used to halt the progression of the disease. Subconjunctival steroids offer short term symptomatic relief. Gas permeable limbal fit corneal or scleral lenses can improve vision and halt progression of sterile corneal ulcer.

Systemic :

Systemic immunosuppressants are effective in controlling OCP. They are started and continued in cross consultation with dermatologist and physician to monitor for systemic disease and adverse drug effects. A step ladder approach is practiced usually. Systemic therapy is usually initiated in stage II OCP as ocular involvement is considered as a high risk for MMP. Oral prednisolone is useful in controlling ocular scarring. Dapsone and methotreaxate are generally first line treatment in initial phase, later mycophenolate mofetil is preferred. For resistant cases, pulsed iv cyclophosphamide is highly efficacious. Another promising combination for late stages is rituximab with iv Ig infusion.

Fig.23 : Immunosuppressants for OcMMP [5]

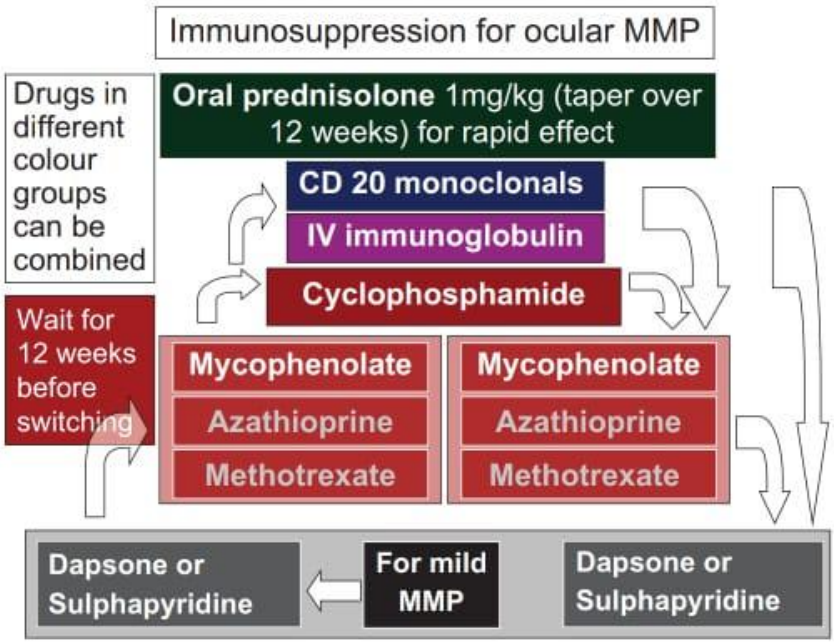
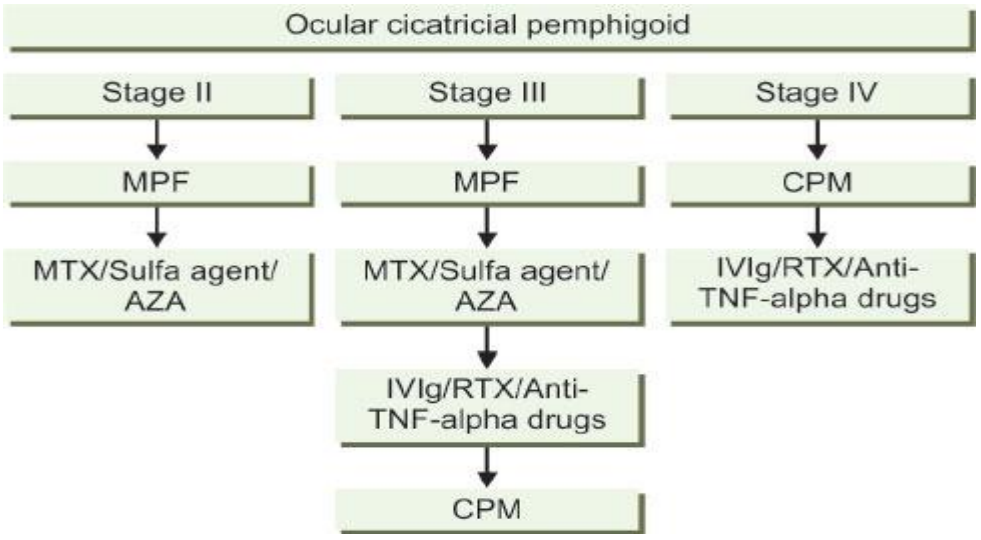


Fig.24 : Stepwise approach to treatment of OCP [1]



Surgical management:

This mainly entails correction of eyelid abnormalities and fornix reconstruction. Amniotic membrane grafting and mucous membrane grafting are most conducive options. Minor salivary gland transplantation (MIST) has been attempted for severe dry eye, though salivary tears has been claimed to lack similar nutritional and visual properties. Penetrating keratoplasty often fail in these cases and should be attempted with caution. Ultimate option for visual rehabilitation remains K-Pro.

Differential diagnosis

I) **Pemphigus vulgaris**

It presents with catarrhal conjunctivitis and early cicatrisation but does not progress to conjunctival scarring and symblepharon. Blisters in PV are flaccid and have a erythematous base, unlike MMP which has tense bullae. The condition can be further differentiated on tissue biopsy

which shows intraepidermal split with diagnostic acantholytic cells. Ocular PV respond well to systemic steroids. Resistant cases may require adjuvant immunosuppressants [1,2].

II) **Dermatitis herpetiformis**

50% of DH have ocular involvement and a similar course to OCP. Patients have a prodrome of pruritis before emergence of cutaneous lesions. The lesions comprise of annular bullae resembling 'string of pearls'. DIF and serology are diagnostic. Most cases respond well to Dapsone and refractory cases respond to IVIg [1].

III) **Pseudopemphigoid/drug induced pemphigoid**

Certain systemic and topical drugs result in vesicobullous condition mimicking MMP. Culpable drugs include topical timolol, brimonidine, pilocarpine, iodide and echothiophate and systemic practolol, phenytoin, amiodarone and vancomycin. Removal of the causative agent and short course of steroids work well [1,6,7].

IV) **Paraneoplastic pemphigus**

It is associated with neoplasia wither benign or malignant; most common being leukemia or lymphoma. Conjunctival involvement, usually bilateral, is common. Erosions predominantly affect the lips and the buccal mucosa, they are painful and persistent and may be located on an erythematous base. Lesions similar to target lesions of erythema multiforme may sometimes occur. DIF shows IgG and C3 deposits in the intercellular spaces and along the basement membrane [1,2,7,12].

V) **Bullous Pemphigoid**

The characteristic feature is presence of large, tense bullae due to the subepidermal location of the blisters. The trunk and extremities are usually involved; mucosal lesions are confined to oral cavity, anus and genitalia. On DIF, there is linear deposits of IgG and C3 along the basement membrane zone [2].

VI) **Linear IgA disease**

It primarily affects the skin causing a rash with spontaneous blistering, but without cutaneous scarring. The skin lesions may look similar to those seen in DH or bullous pemphigoid. However, eye involvement is asymptomatic and the course of the ocular disease seems to be less aggressive. Homogeneous linear deposits of IgA along the dermoepidermal junction in the uninvolved skin and along the sub-epithelial basement membrane of mucous membranes is the characteristic immunofluorescence finding [7].

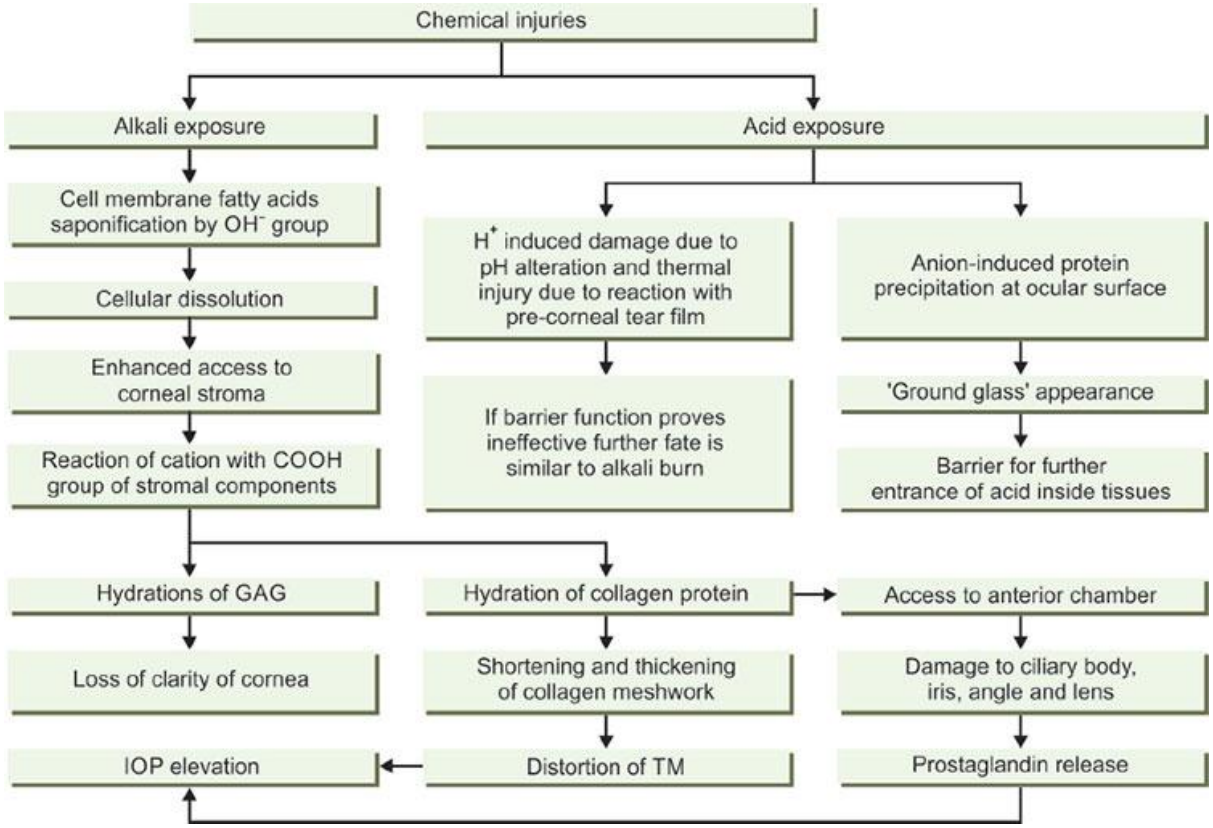
VII) **Other causes of CC**

OCULAR SURFACE CHEMICAL BURNS

Chemical injury is one the major causes of ocular surface disease. They constitute for 7.7-18% of all ocular traumas. In developing countries, the incidence of chemical injury ranges from 1.25% to 4.4%. They are more common in young males of age 16-45yrs.

The severity of the injury depends on various factors including nature of the chemical (acid or alkali), concentration of solution, amount of chemical exposed , duration of exposure and surface area of contact and the associated thermal reaction. Usually , alkali injuries are more grievous than acid ones [1].

Fig.25 :Mechanism of acid and alkali injury [1]



Clinical features

Chemical injury is an ocular emergency and the patient presents with severe pain, burning sensation, lacrimation, blepharospasm and loss of vision. Examination may reveal associated foreign body apart from chemical itself, periorbital edema, erythema, charred skin, with loss of eyebrows and lashes. Ocular surface findings include conjunctival congestion, chemosis, variable limbal ischemia, conjunctival and corneal epithelial defects, corneal haze, corneal edema, sterile corneal ulceration or a perforation. In late phase, dry eye features and LSCD start to appear and end in formation of large thick pannus. Other features would be lagopthalmos, ectropion, entropion, trichiasis and symblepharon formation .

Evaluation and grading

Roper-Hall in 1965, classified chemical injuries based on limbal ischemia and cornea opacification. In 2001, Dua stated a classification based on conjunctival loss (bulbar and forniceal) along with limbal involvement.

Table 12 : Roper-Hall classification [1]

Grade	Prognosis	Cornea	Conjunctiva/limbus
I	Good	Corneal epithelial damage	No limbal ischemia
II	Good	Corneal haze, iris details visible	<1/3 limbal ischemia
III	Guarded	Total epithelial loss, stromal haze, iris details obscured	1/3–½ limbal ischemia
IV	Poor	Cornea opaque, iris and pupil obscured	>½ limbal ischemia

Table 13 : Dua's classification [1]

Grade	Prognosis	Clinical findings	Conjunctival involvement	Analog scale*
I	Very good	0 clock hours of limbal involvement	0%	0/0%
II	Good	<3 clock hours of limbal involvement	<30%	0.1–3/1–29.9%
III	Good	>3–6 clock hours of limbal involvement	>30–50%	3.1–6/31–50%
IV	Good to guarded	>6–9 clock hours of limbal involvement	>50–75%	6.1–9/51–75%
V	Guarded to poor	>9–<12 clock hours of limbal involvement	>75–<100%	9.1–11.9/75.1–99.9%
VI	Very poor	Total limbus (12 clock hours) involved	Total conjunctiva (100%) involved	12/100%

*The analog scale records accurately the limbal involvement in clock hours of affected limbus/percentage of conjunctival involvement. While calculating percentage of conjunctival involvement, only involvement of bulbar conjunctiva, up to and including the conjunctival fornices is considered.

Clinical course

McCulley divided the course of post chemical injury period into 4 phases.

Table 14: Clinical phases after ocular burns by McCulley [1]

Phases	Duration
Immediate	Within few hours
Acute phase	0–7 days
Early reparative phase	7–21 days
Late reparative phase	>21 days

Management

Acute phase management :

Ocular surface to be thoroughly irrigated with double eversion of lids exposing the fornices. Irrigation should be done with atleast 1L of irrigant for atleast 15 minutes. Normal saline can be used for irrigation , but BSS has been shown to be more effective. After irrigation, a thorough clinical examination is done. For early re-epithelisation, frequent lubricants in the form of eye drops and gels are started. Potent corticosteroids like prednisolone acetate1% are started on hourly for atleast 10days, this helps in reducing inflammation and promotes healing. After this period, if epithelialisation is complete, steroids can be continued further. If there is incomplete epithelialisation and stromal

thinning, the steroids have to be tapered as they interfere with collagen synthesis. Topical ascorbate, citrate and oral vitamin C and tetracyclines have all shown to bear a positive effect on collagen synthesis.

Amniotic membrane grafting should be done at the earliest to fasten the recovery for large epithelial defects. It helps in epithelialisation of corneal and conjunctival surface, enhances healing, reduced inflammation and prevents infection. Tarsorrhaphy is an adjunct procedure to AMG which aids in healing. Tenoplasty becomes essential in severe limbal ischemia cases (Dua's grade V,VI).

Chronic phase management:

In the chronic phase, corneal tissue heals with scarring and conjunctivalisation, especially in higher grades. It is essential to address any eyelid problems before attempting for any kind of limbal stem cell transplant. Sometimes penetrating or lamellar keratoplasty can be attempted after successful LSCT. K-pro is reserved for patients with repeated failed keratoplasty or unsuccessful LSCT procedure.

Table 15 : Intervention in different situations in chemical injuries [1]

Condition		Intervention
Corneal epithelial defect	Small	Bandage contact lens (BCL)
	Large	Amniotic membrane grafting (AMG)
Corneal and conjunctival epithelial defect		Prosthetic replacement of the ocular surface ecosystem (PROSE) lens Amniotic membrane patch graft
Epithelial defect with dead necrotic tissue		Surgical debridement along with AMG/tarsorrhaphy/contact lens placement
Epithelial defect with significant limbal stem cell loss and limbal ischemia		Preferred AMG and/or tenoplasty along with conjunctival advancement/tarsorrhaphy
Significant limbal stem cell loss along with severe conjunctival loss	In acute phase	High-risk attempt of limbal stem cell transplantation (LSCT) procedures along with conjunctival transplantation/tenoplasty under immunosuppression cover
Anticipated symblepharon		Regular swipe of fornices with glass rod Symblepharon-amniotic membrane ring complex placement Sutured amniotic membrane
Progressive corneal thinning		Multilayer amniotic membrane Tissue adhesive + BCL
Small corneal perforation Impending perforation	Small	Tissue adhesive + BCL/AMG
Severe corneal thinning Large descemetocele Large corneal perforation Impending perforation		Tectonic keratoplasty
Limbal stem cell deficiency (LSCD)	Unilateral	Conjunctival limbal autograft (CLAU or CLAG), simple limbal epithelial transplantation (SLET)
	Bilateral	SLET-allograft/cultivated limbal epithelial transplantation (CLET)-allograft/keratolimbal allograft (KLAL)/combined conjunctival and keratolimbal allograft (C-KLAL)
Successful LSCT with stromal scarring		Lamellar keratoplasty (LK)/deep anterior lamellar keratoplasty (DALK)/penetrating keratoplasty (PK)
Multiple failed LSCT/keratoplasty	Satisfactory counseling	Boston K-PRO/LVPEI K-PRO (only in one eye)
Symblepharon		Symblepharon release + AMG + CLAG
Obliterated fornix	Unilateral	Reconstruction with bulbar conjunctival transplantation and AMG
Conjunctival scarring Cicatricial entropion	Bilateral	Reconstruction with tarsoconjunctival advancement and AMG Reconstruction with mucous membrane grafting (MMG) and AMG

LSCD

The diagnosis of LSCD has been made based on medical history and clinical signs, which are not specific to LSCD. Slit lamp biomicroscopy has been the most commonly used method to make the diagnosis of LSCD. Examination under cobalt blue light using fluorescein staining is essential to detect the subtle signs.

Mild stage : Epithelial opacity, epithelial staining, loss of palisades of Vogt.

Moderate stage :Vortex keratopathy, superficial vascularisation and peripheral pannus

Severe stage :Recurrent/persistent epithelial defects, stromal neovascularisation, stromal scarring and opacity [13].

Fig.26 : Characteristic clinical features of LSCD [1]

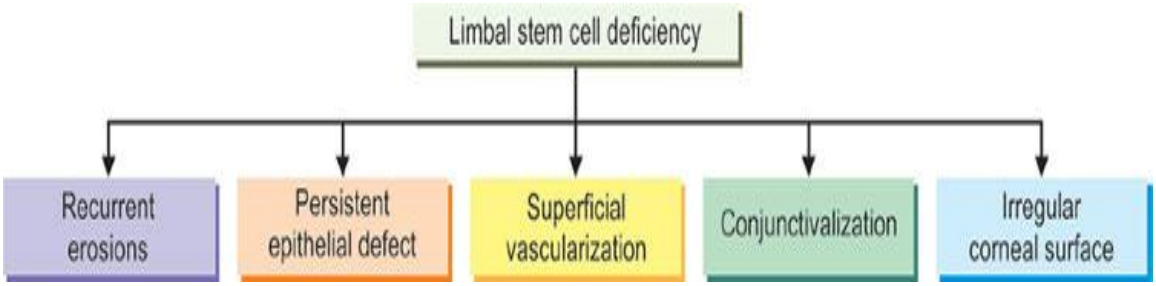
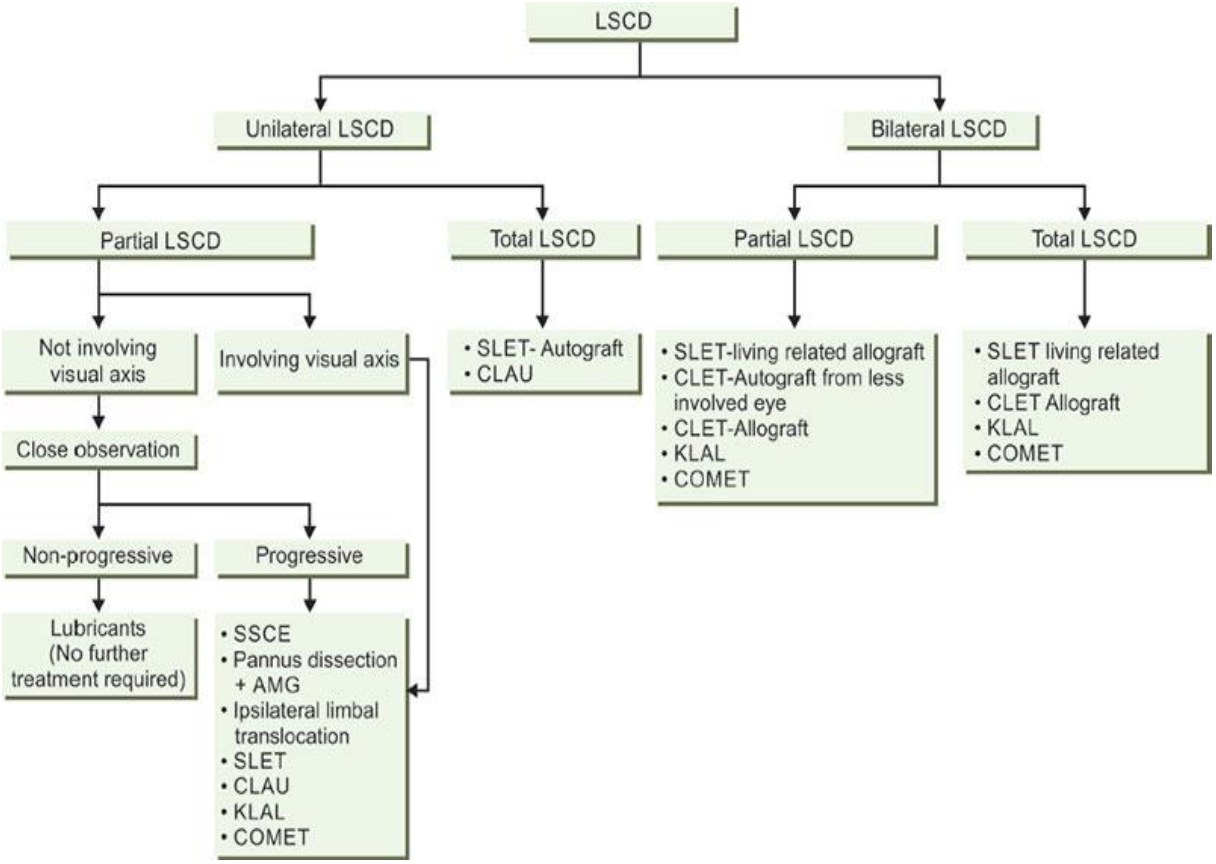


Fig.27 Management of LSCD in ocular surface disorder[1]



REVIEW OF LITERATURE

1) A study by CF Radford et al titled "Incidence, presenting feature, and diagnosis of cicatrising conjunctivitis in United Kingdom" is a prospective study wherein clinical data of newly diagnosed cases of CC were reported through the British Ophthalmological Surveillance Unit (BOSU) at diagnosis and at 12 months follow-up during the year 2008. The aim of this study was to establish the incidence of CC within the United Kingdom, to assess the patients' clinical features at the time of diagnosis and at 12months follow up, and to map the distribution of patients as a first step in planning of a network of collaborating specialist clinics within the UK. Newly diagnosed CC, defined as conjunctival inflammation associated with scarring were included in the study. Patients with history of trachoma, an acute infectious membranous conjunctivitis or ocular trauma were excluded. A total of 124 cases of CC were reported via BOSU. Out of 124 cases, only 82 were eligible cases, of which 50 were diagnosed as OcMMP, 16 were SJS/TEN and 16 were due to other causes of CC. The overall minimum incidence of CC in UK was calculated as 1.3 per million, and that of OcMMP, SJS and other CC was 0.8, 0.2 and 0.2 per million respectively. At diagnosis, 39% of eyes had moderate/severe conjunctival

inflammation, 62% had symblepharon formation. Although 52% of patients were started on immunosuppression, at follow up there was an increase in the number of symblepharon, despite control of inflammation. To conclude these data highlight the need for developing patient access to specialist with expertise in CC [3].

2) "The 2016 Bowman Lecture Conjunctival curses : scarring conjunctivitis 30years on" by JK Dart is a review that contains two sections. The first section summarises 35 conditions causing CC, both common and infrequent. It gives guidelines for making a diagnosis and the use of diagnostic tests. The second section deals with the clinical characteristics, demographics and clinical signs of ocular mucous membrane pemphigoid, which is the commonest cause of CC in most developed countries. It gives a revised hypothesis of the autoimmune mechanisms causing inflammation in OcMMP. It also summarises the role of aldehyde dehydrogenase (ALDH) and retinoic acid (RA) in the initiation and perpetuation of profibrotic activity in MMP fibroblasts, and the potential for antifibrotic therapy using ALDH inhibition. The rationale for the use of systemic immunomodulatory therapy for patients with active OcMMP is discussed. Finally, the areas for research and innovation in the next decade including the need for better diagnostics,

markers of disease activity, potential for biological and topical therapies for both inflammation and scarring are reviewed [5].

3) "Incidence, clinical features and diagnosis of cicatrising conjunctivitis in Australia and New Zealand" by Samantha Bobba and colleagues is a prospective surveillance study done over 17 months via the Australian and New Zealand Ophthalmic Surveillance Unit (ANZOSU) from December 2011 and April 2013, with a 12 month follow up period. The aim of the study was to determine the incidence, clinical features and management of cicatrising conjunctivitis in Australia and New Zealand. Recently diagnosed cases of CC were included in the study. Patients with history of trachoma, trauma or an acute infectious membranous conjunctivitis were excluded. A total of 56 cases of CC were reported to the ANZOSU, of which data were available for only 35 cases. The most common etiologies were ocular mucous membrane pemphigoid (51%), Stevens-Johnson Syndrome (8.6%) and Graft versus host disease (8.6%). The minimum incidence of cicatrising conjunctivitis in Australia and New Zealand was 1.5 per million. The mean age of patients was 74years. Most of the data of this study was comparable to the data from the Radford study of United Kingdom. Thus this is the first study to record the incidence of CC

in Australia and New Zealand and the second worldwide. It also provides novel data on demographics and management of CC [4].

4) A review article titled "Chronic Progressive Conjunctival Cicatrisation" by Wolfgang Bernauer and colleagues was published in 1993. The aim of this article was the demonstrate the spectrum of conditions that are included under the term 'chronic progressive cicatrising conjunctivitis'. It discusses the mechanisms of conjunctival scar tissue formation and describes the sequelae and therapeutic options for this potentially blinding condition. This entity is found in association with some mucocutaneous disorders (cicatricial pemphigoid, linear IgA disease), as part of paraneoplastic syndrome and in long term treatment with certain systemic or topical medications (pseudo-pemphigoid). Recent studies indicate that macrophages may play a pivotal role in the cicatricial process. They mediate the transition from inflammation to scar tissue by secretion of fibrogenic cytokines. The sequelae of chronic progressive conjunctival cicatrisation include obstruction of lacrimal and meibomian glands, alteration of tear film, trichiasis, keratopathy and blindness. This article also has discussed about the present and future options for treatment of chronic conjunctival cicatrisation [7].

5) In October 2020, Jayesh Vazirani et al published a review article titled “Chronic cicatrizing conjunctivitis: A review of the differential diagnosis and an algorithmic approach to management”. The aim of this review article is to put together all the relevant information on chronic cicatrising conjunctivitis in one place for the benefit of cornea and ocular surface specialists, general ophthalmologists and ophthalmology residents. This article reviews the clinical features of chronic cicatrising conjunctivitis and describes the diagnostic and treatment algorithms to help simplify the complexities in the diagnosis and management of the same [6].

PART II

Study title **: A CROSS SECTIONAL STUDY ON CICATRISING CONJUNCTIVITIS IN A TERTIARY CARE CENTRE**

Aims and objectives : To study the etiology, clinical features, diagnosis and management of cicatrising conjunctivitis

Primary objective : To find the common causes and clinical presentation of cicatrising conjunctivitis

Secondary objective : To establish the diagnosis and management of cicatrising conjunctivitis

Study centre : Department of cornea,

Regional Institute of Ophthalmology and Govt ophthalmic hospital, Chennai 600 008

Study design : Cross sectional study

Study period : October 2020-November 2021

Sample size : 25 (convenient sample size as the disease entity is rare)

MATERIALS AND METHODOLOGY

1) All patients presenting to the cornea clinic with history and clinical features suggestive of cicatrising conjunctivitis were enrolled in the study after getting an informed consent.

2) A detailed history was taken which included history of any predisposing factors like ocular trauma, surgery, skin or mucous membrane lesions, dermatological/rheumatological diseases, drug intake/topical medication, ocular infection/allergy.

3) History taking was followed by a through systemic and ocular examination. Ocular examination involved recording of visual acuity, intraocular pressure, preliminary torch light examination, detailed slit lamp examination, Schirmer's test, TBUT test and a fluorescent staining wherever needed.

4) Complete workup like relevant blood investigations, or a conjunctival biopsy for histopathology/immunofluorescence, if indicated, was done to rule out any systemic cause of the disease and to establish the diagnosis.

5) All patients were initiated on appropriate treatment which included both conservative and surgical forms.

6) The data thus collected was analysed to study the various causes, clinical features and management of cicatrising conjunctivitis.

Inclusion criteria :

All patients with clinical features suggestive of cicatrising conjunctivitis like

- caruncular or subconjunctival fibrosis
- forniceal foreshortening
- symblepharon formation.
- dry ocular surface
- loss of plica semilunaris
- keratin deposits on the ocular surface or lid margin
- loss of the normal architecture of the lid margin and mucocutaneous junction
- entropion
- trichiasis
- distichiasis
- ankyloblepharon
- dermalization of the ocular surface

were included in the study

Exclusion criteria : Patients with

- history of trachoma
- Acute infectious membranous conjunctivitis

were excluded from the study

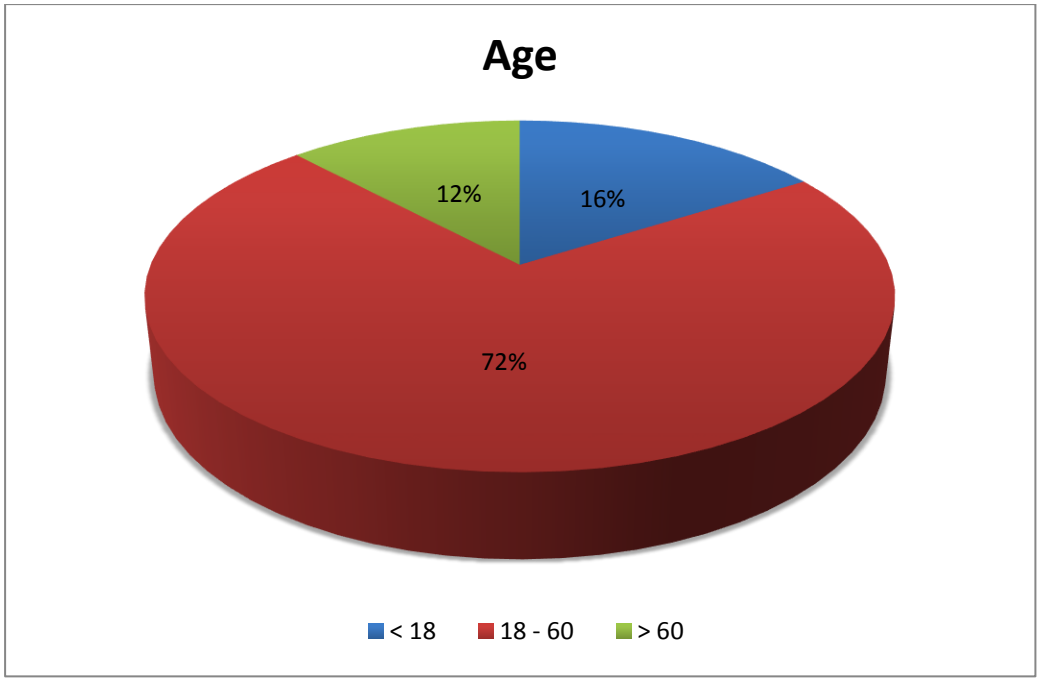
OBSERVATION AND ANALYSIS

1) AGE

Table 1 : Age distribution (n=25)

Age group (in years)	Number	Percentage (%)
<18	4	16
18-60	18	72
>60	3	12
Total	25	100

Fig.1 : Pie chart showing age distribution

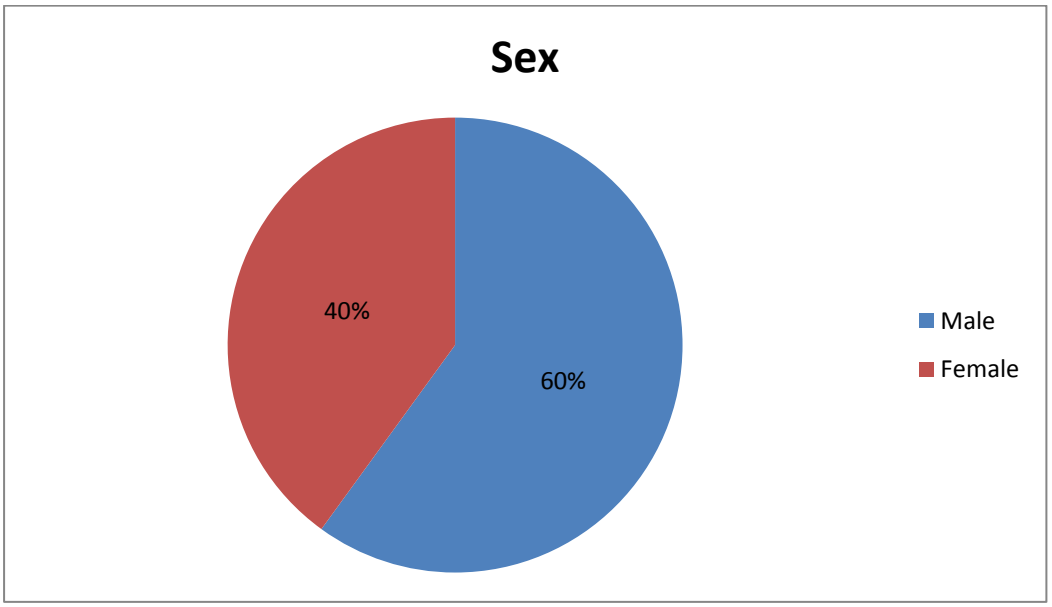


2) **SEX**

Table 2 : Sex distribution (n=25)

Variable	Frequency	Percentage (%)
Male	15	60
Female	10	40
Total	25	100

Fig.2 Pie chart showing sex distribution

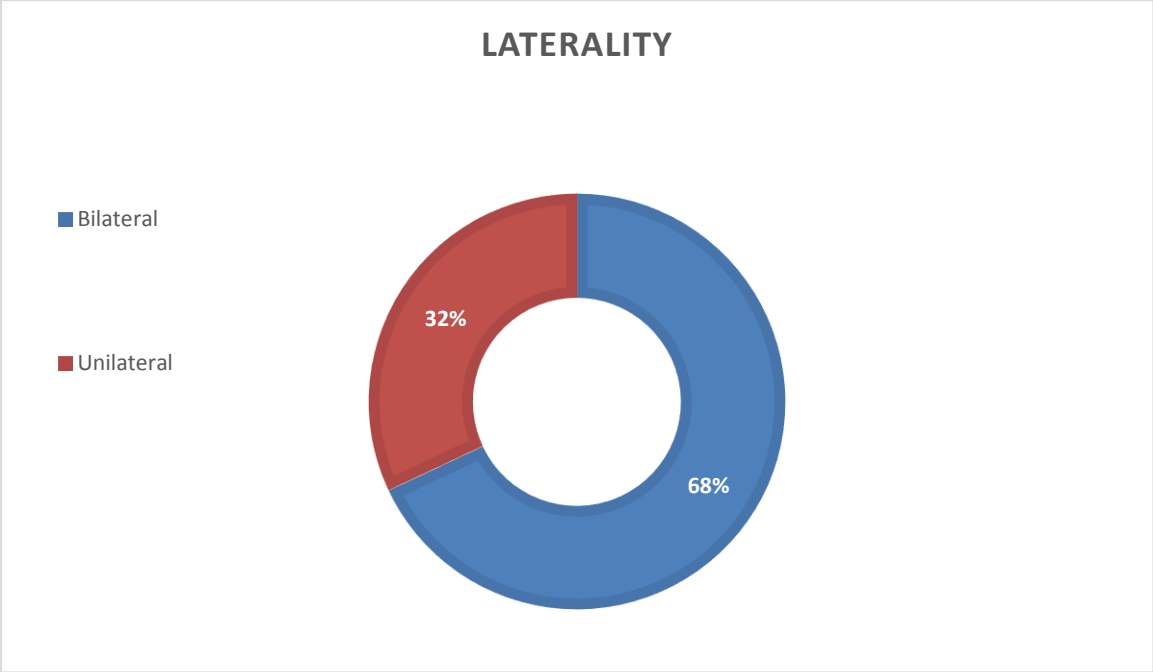


3. LATERALITY

Table 3 : Distribution according to laterality of eye (n=25)

Laterality	Frequency	Percentage (%)
Unilateral	8	32
Bilateral	17	68
Total	25	100

Fig.3: Doughnut chart showing laterality of involvement



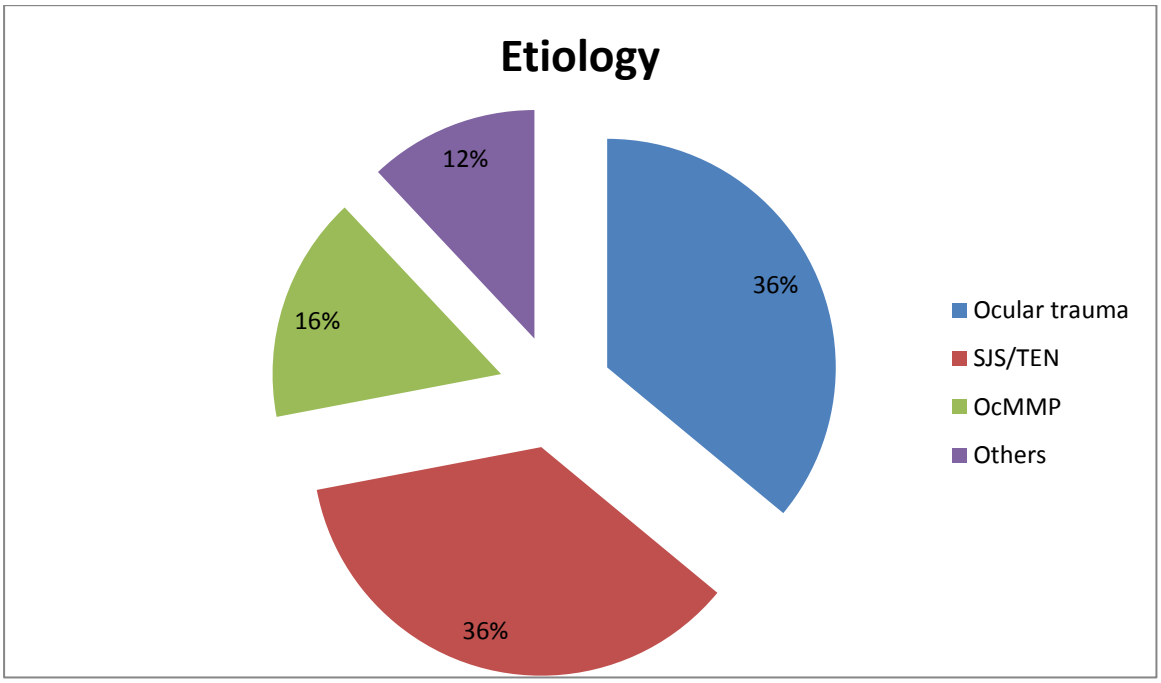
4.Etiology

Table 4 : Distribution of the causes of cicatrising conjunctivitis (n=25)

Causes	No. of patients	Percentage (%)
Ocular trauma	9	36
SJS/TEN	9	36
OcMMP	4	16
Other*	3	12
Total	25	100

(*includes other causes like atopic keratoconjunctivitis, OSSN, Sjogren's syndrome)

Fig.4 Pie chart showing distribution of the various causes of CC



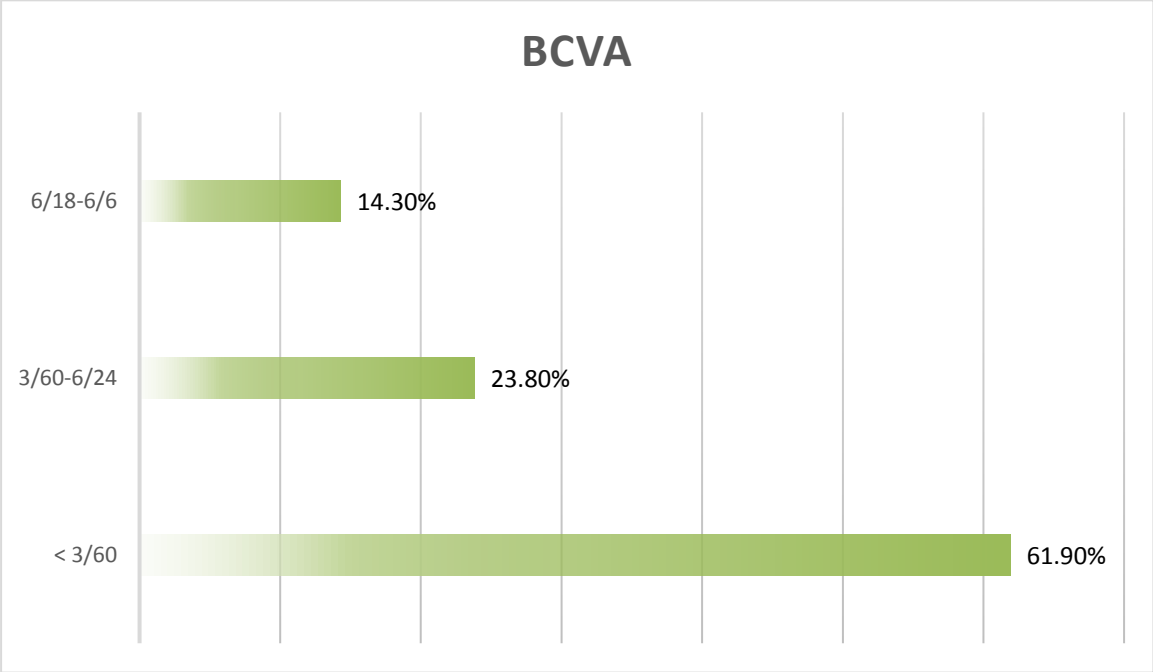
5. VISUAL ACUITY

Table 5 : Distribution of BCVA (best corrected visual acuity) (n=42)*

Visual acuity	Frequency	Percentage (%)
<3/60	26	61.9
3/60 - 6/24	10	23.8
6/18 – 6/6	6	14.3
Total	42	100

*Total number of eyes affected out of 50

Fig.5 Bar diagram showing distribution of visual acuity among patients

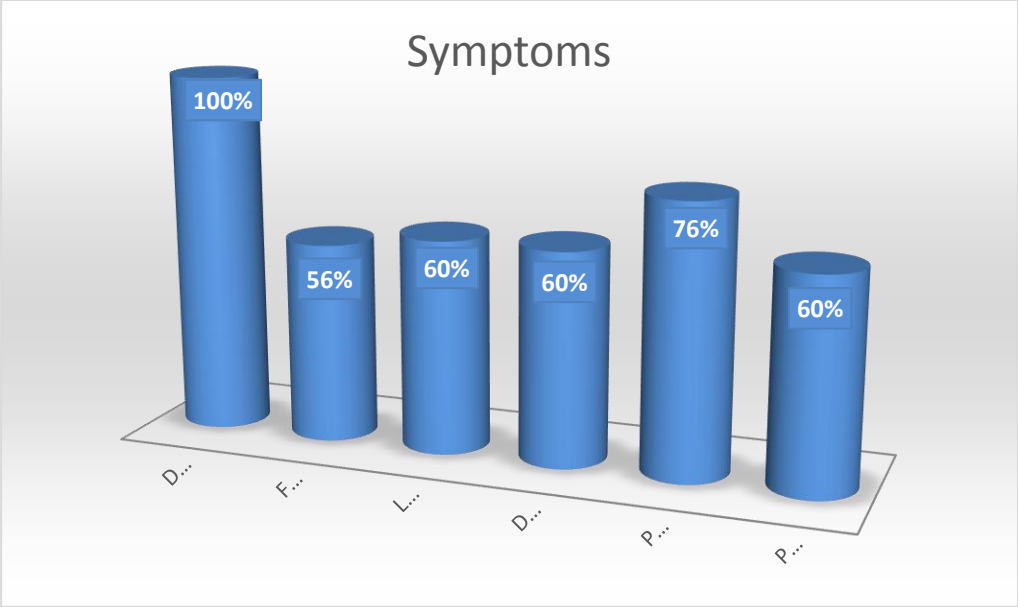


6.SYMPTOMATOLOGY

Table 6: Distribution of the various symptoms of the patient (n=25)

Symptoms	No. of Patients	Percentage (%)
Defective vision	25	100
Foreign body sensation	14	56
Lacrimation	15	60
Discharge	15	60
Photophobia	19	76
Pain	15	60

Fig.6 Bar diagram showing the distribution of the symptoms



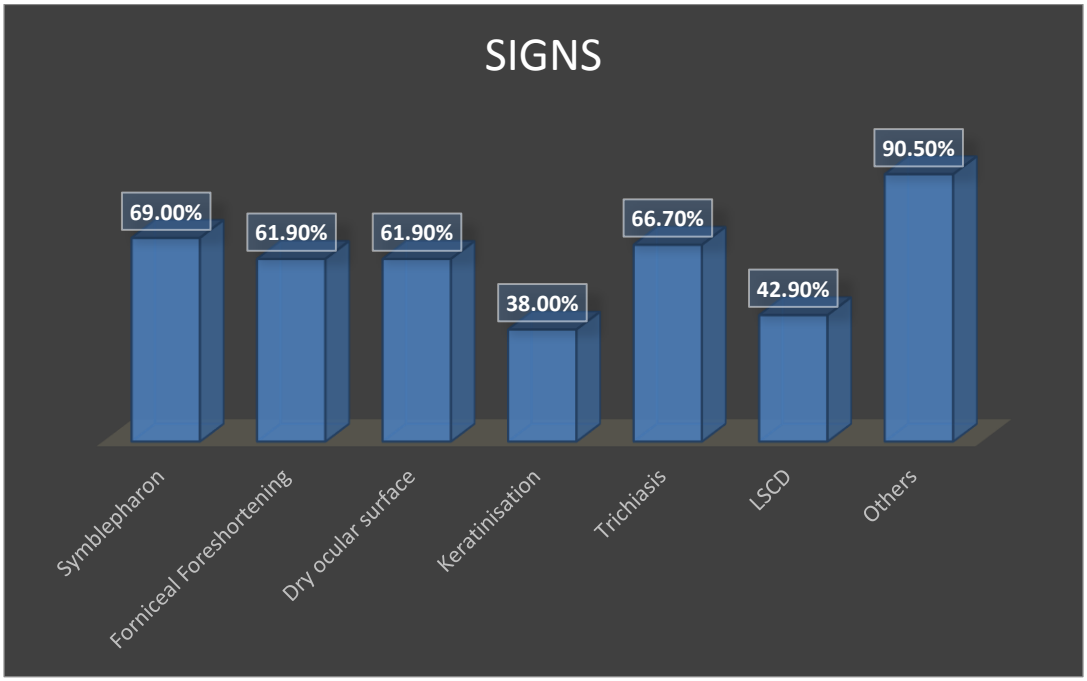
7.SIGNS

Table 7 : Distribution of the ocular signs (n=42)

Signs	No. of Eyes	Percentage (%)
Symblepharon	29	69
Forniceal Foreshortening	26	61.9
Dry ocular surface	26	61.9
Keratinisation	16	38
Trichiasis	28	66.7
LSCD	18	42.9
Others*	38	90.5

(* includes others signs like conjunctival inflammation, persistent epithelial defects, corneal opacities, corneal neovascularisation)

Fig.7 Bar diagram showing distribution of the ocular signs

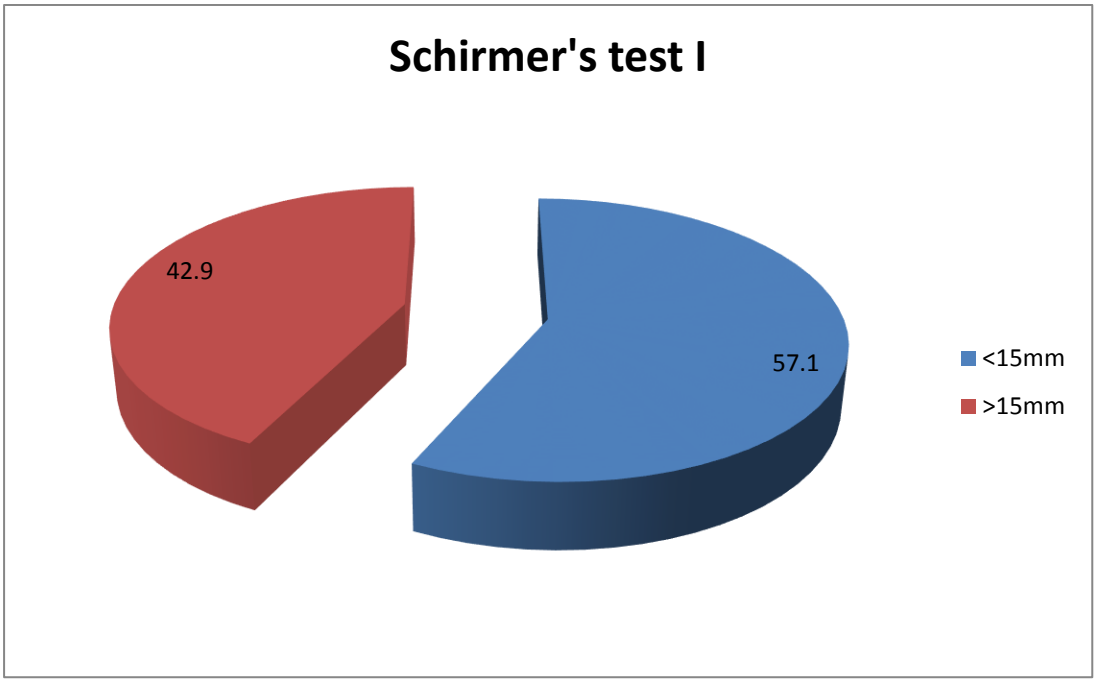


8.SCHIRMER'S TEST

Table 8 : Distribution of Schirmer's test in the affected eyes (n=42)

Schirmer's test I	Frequency	Percentage (%)
< 15 mm	24	57.1
> 15 mm	18	42.9
Total	42	100

Fig.8 Bar diagram showing the distribution of Schirmer's test I



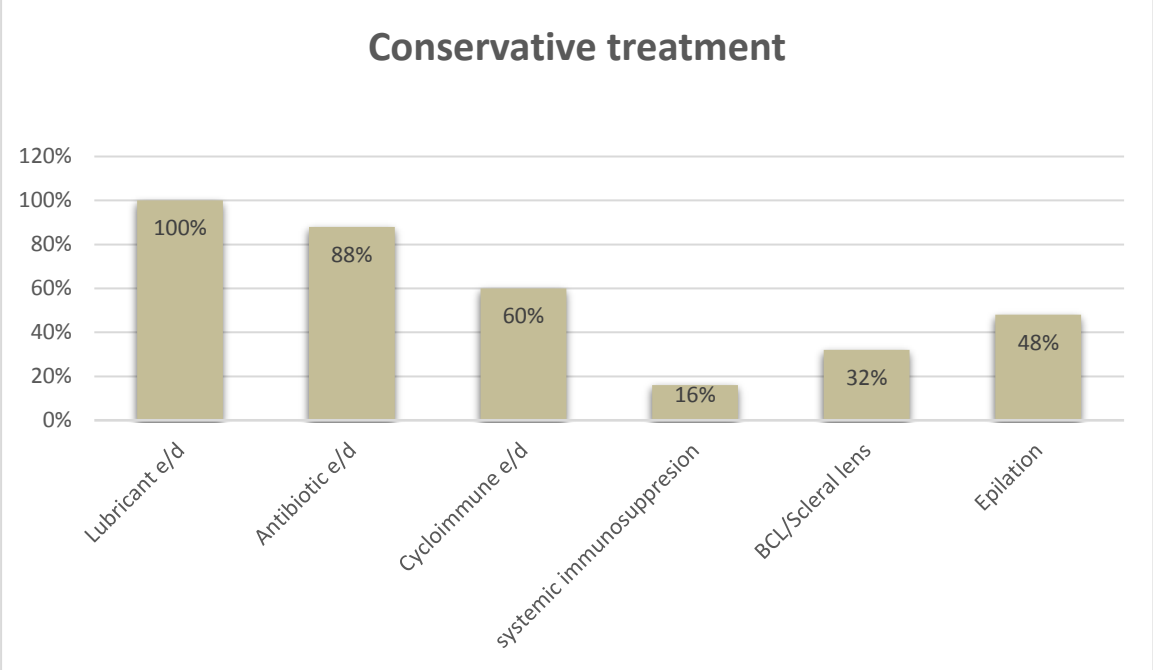
9.CONSERVATIVE TREATMENT

Table 9 : Distribution of conservative treatment modalities (n=25)

Variables	No. of patients	Percentage (%)
Topical lubricants	25	100
Topical antibiotics	22	88
Topical immunosuppression *	15	60
Systemic immunosuppression*	4	16
Scleral lens/Bandage contact lens	8	32
Epilation	12	48

(*includes topical immunosuppressive drugs like prednisolone, flurometholone, cyclosporine e/d and systemic immunosuppressive drugs like oral prednisolone, methotrexate, aziathioprine, cyclophosphamide)

Fig.9 Bar diagram showing distribution of conservative management



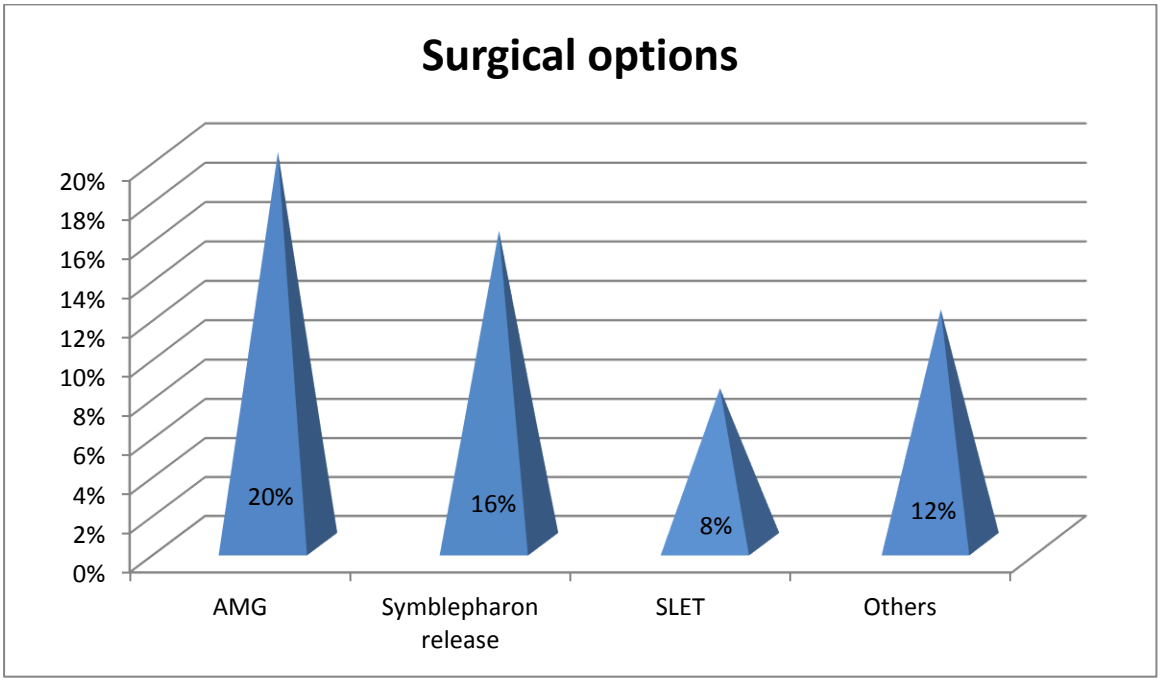
10.SURGICAL MANAGEMENT

Table 10 : Distribution of surgical modalities of treatment (n=25)

Surgical options	No. of Patients	Percentage(%)
AMG	5	20
symblepharon release	4	16
SLET	2	8
Others*	3	12

(*includes miscellaneous procedures like punctual occlusion, tarsorrhapy)

Fig.10 Bar diagram showing the distribution of various surgical procedures



RESULTS

A total of 25 cases of cicatrising conjunctivitis were studied.

1) Age :

Of the 25 cases, 18 (72%) cases were under the age group of 18-60years, 4 (16%) cases were under 18yrs of age and 3 (12%) were above 60yrs of age. The mean age was found to be 40.5yrs (table 1).

2) Sex :

From the Fig.2, it is seen that there is male predominance with 15 (60%) out of 25 patients being male and the remaining 10 (40%) were female.

3) Laterality :

Table 3 shows that about 17 (68%) patients had both eyes affected and remaining 8 (32%) patients had one eye affected.

4) Non-ocular involvement :

Out of the 25 patients, 13 (52%) patients had systemic involvement also apart from ocular findings in the form of skin or mucous membrane affection.

5) Etiology :

The most common causes of CC was found to be ocular trauma and SJS/TEN with 9 (36%) patients affected each. Ocular trauma can be of mechanical, physical or chemical type. It was seen that out of the 9 patients affected with ocular trauma, 1 patient had mechanical trauma, 1 had firecracker injury, the remaining 7 patients had chemical injury. Another common cause of CC apart from trauma and SJS is Ocular cicatricial pemphigoid with 4 (16%) patients affected. The remaining 3 (12%) were affected by miscellaneous causes like Atopic keratoconjunctivitis, OSSN and Sjogren's syndrome each. The patient with OSSN had a coexisting Lichen planus (table 4).

6) BCVA :

All patients underwent a visual acuity examination, both uncorrected and best corrected visual acuity using the Snellen's chart. Out of the 50 eyes studied, 42 were affected and remaining 8 were normal. Among the 42 affected eyes, 26 (61.9%) eyes had a visual acuity of <3/60, 10 (23.8%) eyes had visual acuity ranging from 3/60 to 6/24 and the remaining 6 (14.3%) eyes had BCVA in the range of 6/18 to 6/6 (table 5).

7) Symptoms :

It was seen that almost all patients (100%) had defective vision, 19(76%) patients had photophobia, lacrimation, discharge and pain were present in 15 (60%) of them. About 14 (56%) patients had foreign body sensation in addition (table 6).

8) Signs :

Signs like conjunctival inflammation, PEDs, corneal ulceration, vascularisation and opacities were more common and was seen in about 38 (90.5%) eyes. The next common finding was symblepharon formation which was seen in 29 (69%). About 28 (66.7%) eyes had trichiasis, 26 (61.9%) eyes had forniceal foreshortening and dry ocular surface. Limbal stem cell deficiency was found in 18 (42.9%) eyes and 16 (38%) eyes had keratinisation of the ocular surface (table 7).

9) Schirmer's test I :

Schirmer's test was done in all patients wherein a Whatmann filter paper no.49 was placed in the lower fornix at the junction of lateral one third and medial two third for 5minutes. The wetting of the filter was noted. <15mm was taken as dry eye and >15mm was considered to be normal. So, out of the 42 affected eyes, 24 (57.1%) had Schirmer's <15mm and remaining 18 (42.9%) had Schirmer's >15mm (table 8).

10) Conjunctival biopsy :

Out of the 25 patients, conjunctival biopsy was taken for 4 (16%) patients and sent for histopathology and immunohistopathology studies. Out of those 4 patients, 3 patients had positive results for MMP and 1 had negative results.

11) Conservative management :

Patients were treated with topical medication in the form of lubricant e/d, antibiotic e/d, steroid e/d and cycloplegic e/d wherever needed. The commonly used topical immunosuppression was 1% prednisolone e/d, low dose steroids like 0.5% lotepred e/d, 0.1%fluoromethalone e/d and 0.05%cyclosporine e/d, in the frequency of four to six times per day and gradually tapered. Systemic immunosuppression like oral prednisolone, methotrexate, azathioprine and cyclophosphamide was started for severe cases with progressive cicatrisation. Scleral lens or Bandage contact lens were used in selected cases to reduce the ocular discomfort and to protect the ocular surface from further damage. Spectacles were also prescribed for the patients as per their requirements. Also, the misdirected eyelashes were epilated to protect the corneal. All 25 (100%) patients were given lubricant e/d, 22 (88%) patients were given antibiotic e/d and 15 (60%) patients received topical immunosuppressives. Systemic immunosuppression was started for 4 (16%) patients. BCL/Scleral lenses

were used for 8 (32%) patients. Epilation was done for about 12 (48%) patients (table 9).

12) Surgical Management :

Out of 25 patients, 5 (20%) patients underwent amniotic membrane grafting, 4 (16%) underwent symblepharon release, 2 (8%) underwent Simple limbal epithelial transplantation(SLET) / Conjunctival limbal autograft (CLAU) and 3 (12%) underwent other procedures like punctual occlusion/tarsorhapy (table 10).

DISCUSSION

The aim of this study was to analyse the various causes, clinical presentation, diagnosis and management of cicatrising conjunctivitis. This is quite a rare disease and very few studies have been done in the past. From the review of literature, it is seen that there are only 2 large studies which give the incidence of cicatrising conjunctivitis and there is no reliable data on the incidence of cicatrising conjunctivitis in India. This shows the rarity of the condition and hence this study [6]. The mean age affected in my study is 40.5yrs. In a study by Samantha Bobba et al in 2011-2013, the mean age was 74years [4]. This difference can be attributed to the fact that ocular trauma as a cause of cicatrising conjunctivitis was excluded in their study. The major cause of cicatrising conjunctivitis in their study was Ocular MMP, which is more common in the elderly age group, followed by SJS and GVHD. The common etiologies of CC in my study were ocular trauma especially chemical injury and SJS/TEN, followed by ocular cicatricial pemphigoid and then the other causes like AKC, OSSN and Sjogren's syndrome. This is in contrast with the other studies namely the one by Samantha Bobba et al and CF Radford et al which shows the common etiology of CC to be OcMMP followed by the other causes [3,4]. Hence it is SJS which is the leading cause of CC followed by OCP in Asian countries, unlike the

Western countries where OCP is the first leading cause [3,4,12]. It was seen that almost all patients had blurred vision as the main symptom. Others symptoms were photophobia, lacrimation , pain, discharge and foreign body sensation. The common sign was conjunctival inflammation, corneal vascularisation, opacities and corneal epithelial defects, followed by symblepharon formation, trichiasis, forniceal foreshortening and dry ocular surface. This was a way similar to the CF Radford et al study where conjunctival inflammation and symblepharon formation where the common signs [3]. Development of corneal opacities and vascularisation at the time of presentation and follow up indicates chronicity of the condition. Hence, it is important to advice the patients for regular follow up in view of chronic sequelae and drug toxicity. Majority of the patients had BCVA<3/60. The key points in management is thorough history and examination to rule out systemic involvement and early diagnosis followed by appropriate treatment. All our patients were adequately managed with topical and systemic therapy according to their presentation. Patients were evaluated in each visit to look for progression of the disease and if progression was noted, the necessary interventions were done to prevent further ocular surface damage.

Fig.13 showing the HPE and immunofluorescence pattern

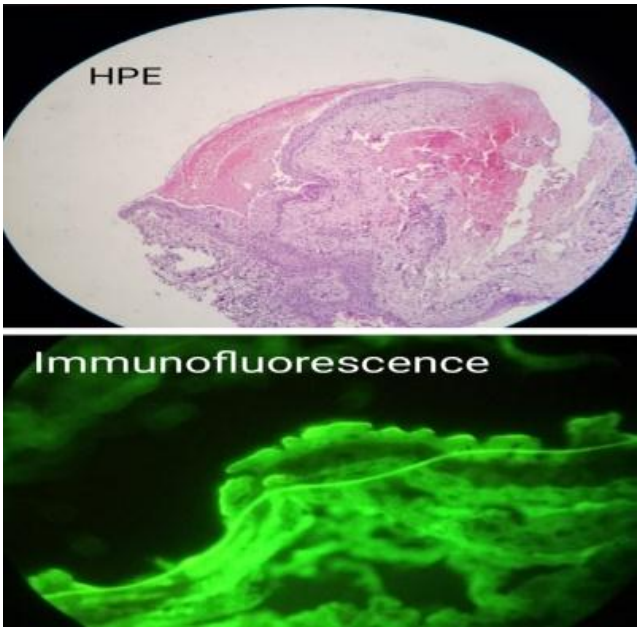


Fig.14 showing the various surgical procedures done for CC

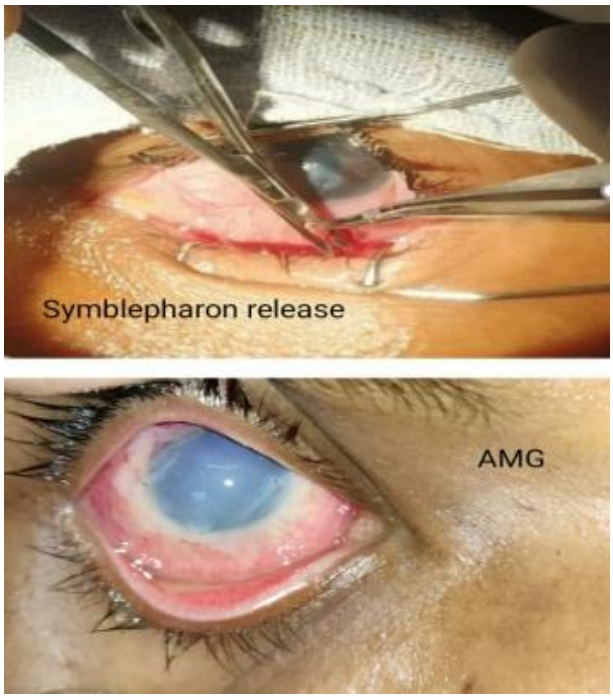


Fig.11 showing the various etiologies of CCC and their presentation

Fig.12 showing a case of OCP at presentation, at 6months and at 1year follow up indicating the disease progression and blinding nature

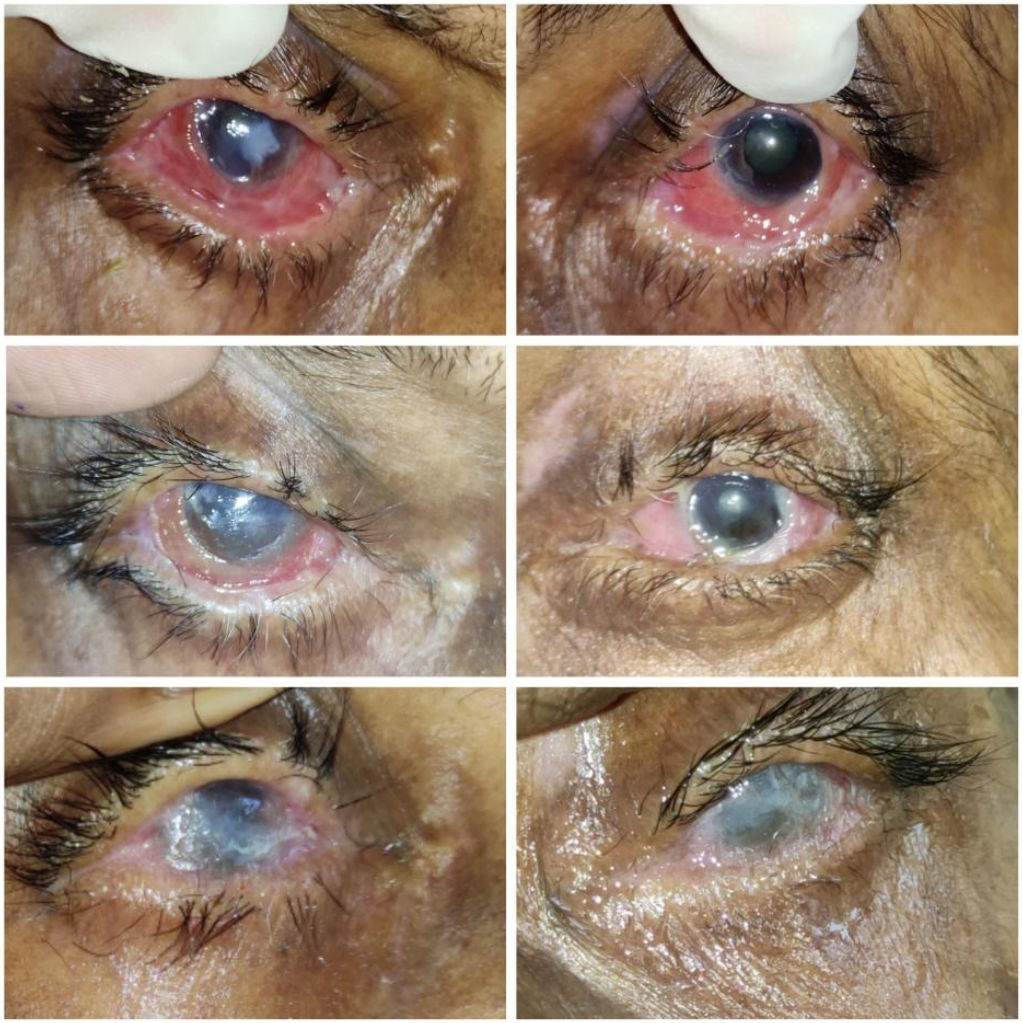


Fig.13 showing the HPE and immunofluorescence pattern

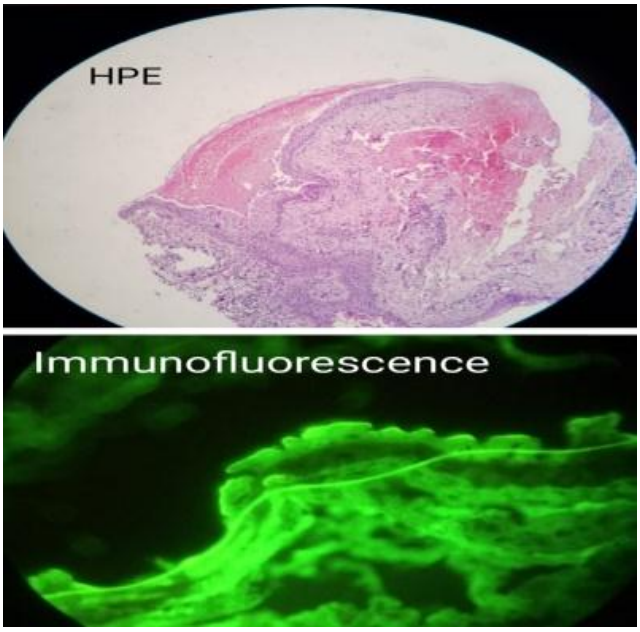
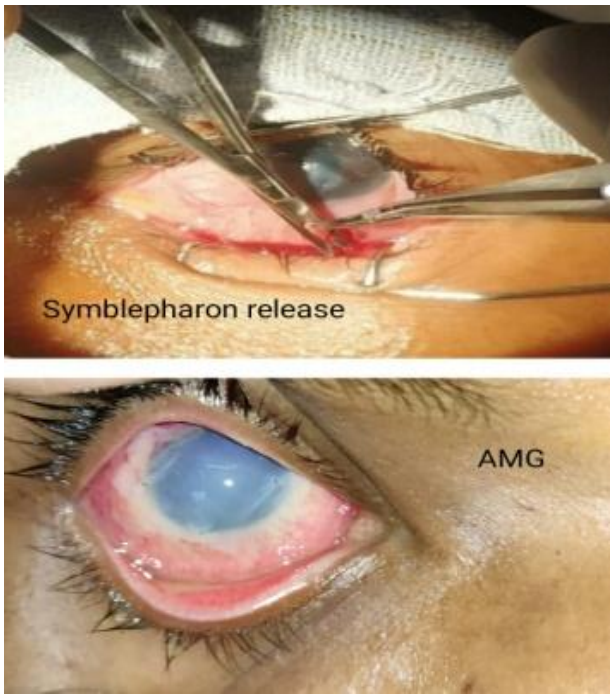


Fig.14 showing the various surgical procedures done for CC



SUMMARY

1) The most commonly affected age group was 18-60yrs, with mean age of 40.5yrs.
2) Male predominance was noted.
3) Majority had bilateral involvement and BCVA <3/60.
4) Common symptoms were blurred vision, photophobia, lacrimation, pain, discharge and foreign body sensation in decreasing order of frequency.
5) Common signs were conjunctival inflammation, corneal epithelial defect, opacity, vascularisation; symblepharon, trichiasis, forniceal foreshortening, dry ocular surface, LSCD and keratinisation in the decreasing order of frequency.
6) Majority had Schirmer's test<15mm indicating dry eye
7) Commonly used medications were topical lubricants, antibiotics, and steroids.
8) Only 16% of patients needed systemic immunosuppression
9) 32% of patients needed BCL/scleral lenses.
10) AMG was the most common surgical procedure done, followed by symblepharon release and SLET.

CONCLUSION

- Cicatrizing conjunctivitis is not a homogenous entity, but a group of local or systemic disorders that cause conjunctival scarring and can potentially lead to blinding sequelae.
- This study aims at sensitizing the need to carefully look for signs of cicatrization in all patients presenting with chronic ocular surface inflammation like in the case of dry eyes, chronic red eyes, allergy or LSCD.
- Hence following an algorithmic approach helps in diagnosis. Early diagnosis and intervention thus prevents vision threatening complications [6].

PART III

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PROFORMA

NAME: Hospital OP no:

AGE: yrs SEX: M F

ADDRESS: Phone No:

CHIEF COMPLAINTS:

- Defective vision
- Watering
- Ocular irritation / discomfort
- Dryness
- Redness

HISTORY OF PRESENT ILLNESS:

1.ONSET OF SYMPTOMS (SUDDEN / GRADUAL) :

2. DURATION AND PROGRESSION:

3. PRE DISPOSING FACTORS/ RISK FACTORS:

- History of ocular trauma
- History of skin or mucous membrane lesions
- History of drug intake
- History of ocular infection/allergy

4.ASSOCIATED SYSTEMIC DISORDERS (joints/connective tissue /skin or mucous membrane disorders):

5.ASSOCIATED OCULAR DISORDERS:

(congenital/Developmental/Genetic/allergic disorders):

6.PAST HISTORY:

- Diabetes mellitus
- Hypertension
- Skin / rheumatological/ pulmonology diseases
- Ocular trauma
- Ocular surgeries

7.FAMILY HISTORY:

8.TREATMENT HISTORY:

9.GENERAL PHYSICAL EXAMINATION:

10) OCULAR EXAMINATION:

RIGHT EYE	OCULAR EXAMINATION	LEFT EYE
	LIDS, LASHES AND ADNEXA	
	PALPEBRAL CONJUNCTIVA	
	BULBAR CONJUNCTIVA	
	CORNEA	
	ANTERIOR CHAMBER	
	IRIS	
	PUPIL	
	LENS	
	VISUAL ACUITY (WITH/W/OGLASSES)	
	INTRAOCULAR PRESSURE	
	EXTRAOCULAR MOVEMENTS	

11) OTHER SYSTEM INVOLVEMENT::

- CVS
- RS
- CNS
- ABDOMEN

12) INVESTIGATIONS:

- Schirmer's test
- Tear film break up test
- Fluorescent staining
- Conjunctival smear
- Conjunctival biopsy
- Histopathology/immunofluorescence
- Blood investigations

13) DIAGNOSIS:

INFORMED CONSENT FORM 1

STUDY TITLE:

"A CROSS SECTIONAL STUDY ON CICATRISING CONJUNCTIVITIS IN A TERTIARY CARE CENTRE"

Name of the Participant:

Name of the Principal Investigator – Dr JAYASHANKARY.S

Name of the Institution: Regional Institute of Ophthalmology,
Government Ophthalmic hospital,
Madras medical college, Chennai -8.

I _____ have read the information in this form (or it has been read to me). I am free to ask any have read the information in this form (or it has been read to me). I am free to ask any questions and they have been answered. I am over 18 years of age and exercising my free power of choice, hereby give my consent to be included as a participant in "A CROSS SECTIONAL STUDY ON CICATRISING CONJUNCTIVITIS IN A TERTIARY CARE CENTRE".

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.

I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to regulatory authorities, Govt. agencies, and Ethics Committee. I understand that they are publicly presented.

(1) I have read and understood this consent form and the information provided to me.

(2) I have had the consent document explained to me.

(3) I have been explained about the nature of the study.

(4) I have been explained about my rights and responsibilities by the investigator.

(5) I have informed the investigator of all the treatments I am taking or have taken in the past including any native (alternative) treatments.

(6) I have been advised about the risks associated with my participation in the study.

(7) I agree to cooperate with the investigator and I will inform him/her immediately if I suffer unusual symptoms.

(8) I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in the hospital.

9) I am also aware that the investigators may terminate my participation in the study at any time, for any reason, without my consent.

(10) I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Government agencies, and ethics committee. I understand that they may inspect my original records.

(11) I understand that my identity will be kept confidential if my data are publicly presented.

(12) I have had my questions answered to my satisfaction.

(13) I consent voluntarily to participate as a participant in this study.

(14) I am aware, that if I have any questions during this study, I should contact the investigators. By signing this consent from, I attest that the information given in this document has been clearly explained to me and understood by me.

(15) I will be given a copy of this consent document.

Name and signature / thumb impression of the participant (or legal representative if participant incompetent):

Name: _____

Signature/Left thumb impression: _____

Date: _____

Name of the witness

Name: _____
Signature:_____

Date: _____

Address and contact number of the witness: _____

Name and signature of the Investigator or his representative obtaining consent:

Name: _____
Signature_____

Date: _____

INFORMED CONSENT FORM 2

Study title

"**A CROSS SECTIONAL STUDY ON CICATRISING CONJUNCTIVITIS IN A TERTIARY CARE CENTRE**"

Name of the Participant: _____

Name of the Participant's LAR(Legally Acceptable Representative): _____

Name of the Principal (Co-Investigator): DR.JAYASHANKARY.S

I _____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am the legally acceptable representative of my child and exercising my free power of choice, hereby give my consent to my child be included as a participant in "**A CROSS SECTIONAL STUDY ON CICATRISING CONJUNCTIVITIS IN A TERTIARY CARE CENTRE**".

- I understand that the participation of my child in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without the medical care or legal rights being affected
- I hereby give permission to the investigators to release the information obtained from my child as result of participation in this study to regulatory authorities, Govt. agencies, and Ethics Committee. I understand that they are publicly presented.
- I have understood that my child's identity will be kept confidential if the data are publicly presented.
- I have had my questions answered to my satisfaction.
- I agree to take part in this study.
- I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document

_____	_____	_____
Signature of LAR	Name of LAR	Date(dd/mm/yyyy)
_____	_____	_____
Signature of the Investigator	Investigator Name	Date (dd/mm/yyyy)
_____	_____	_____
Signature of the witness	Witness Name	Date (dd/mm/yyyy)

ABBREVIATIONS

CC	-	Cicatrising conjunctivitis
CCC	-	Chronic cicatrising conjunctivitis
SJS	-	Steven Johnson's syndrome
TEN	-	Toxic epidermal necrosis
MMP	-	Mucous membrane pemphigoid
OcMMP	-	Ocular mucous membrane pemphigoid
OCP	-	Ocular cicatricial pemphigoid
AKC	-	Atopic keratoconjunctivitis
VKC	-	Vernal keratoconjunctivitis
OSSN	-	Ocular surface squamous neoplasia
DED	-	Dry eye disease
LSCD	-	limbal stem cell deficiency
SLE	-	Systemic lupus erythematosus
DICC	-	Drug induced cicatrising conjunctivitis
PED	-	Persistent epithelial defect
EBM	-	Epithelial basement membrane
DH	-	dermatitis herpetiformis
GVHD	-	Graft versus host disease
K-Pro	-	Keratoprosthesis
IMT	-	Immunomodulator therapy
DIF	-	Direct immunofluorescence
TBUT	-	Tear film break up test
MMG	-	Mucous membrane graft
BSS	-	Balanced salt solution
HLA	-	Human leukocyte antigen

Key to master chart

M – Male

F – Female

HM – Hand moments

CFCF – Counting fingers close to Face

PL – Perception of light

RE – Right Eye

LE – Light Eye

BE – Both Eye

BCVA – Best corrected visual acuity

AMG - Amniotic Membrane Grafting

SLET - Simple Limbal Epithelial Transplant

MASTER CHART

s.no	name	age	sex	etiology	visual acuity		eye involvement	symtoms							signs								tests		conservative treatment						surgical treatment			
					Re	le		non ocular involvement	defective vision	FB sensation	lacrimation	discharge	photophobia	pain	symblepharon	forniceal foreshortening	dry ocular surface	keratinisation	trichiasis	LSCD	others	schirmer's	conjunctival biopsy	lubricants	antibiotics	cycloimmune	systemic immunosuppresion	scleral lens/BCL	epilation	AMG	symblepharon realease	SLET	Ohers
1	abdul rahim	62	m	OCP	HM	CFCF	BE	NO	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	BE < 15mm	YES	YES	YES	YES	YES	NO	YES	NO	NO	NO	YES
2	vellaisamy	55	m	OCP	CFCF	1/2/60	BE	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	NO	YES	NO	YES	BE > 15mm	YES	YES	YES	YES	YES	NO	YES	NO	NO	NO	NO
3	nikitha	12	f	SJS	1/2/60	1/60	BE	YES	YES	YES	NO	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	BE < 15mm	NO	YES	YES	YES	NO	NO	YES	NO	NO	NO	NO
4	sumathi	42	f	SJS	HM	1/60	BE	YES	YES	NO	NO	YES	YES	NO	YES	YES	YES	NO	YES	NO	YES	BE > 15mm	NO	YES	YES	YES	NO	NO	YES	NO	NO	NO	NO
5	anthony	47	m	chemical injury	HM	PL	BE	NO	YES	NO	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	BE < 15mm	NO	YES	YES	YES	NO	NO	NO	YES	NO	YES	NO
6	jaishankar	45	m	firecracker injury	CFCF	6/9	RE	NO	YES	NO	YES	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES	RE < 15mm	NO	YES	NO	NO	NO	YES	YES	NO	NO	NO	YES
7	suganya	11	f	chemical injury	HM	6/6	RE	NO	YES	NO	YES	YES	YES	NO	YES	NO	YES	NO	YES	YES	YES	RE < 15mm	NO	YES	NO	NO	NO	NO	NO	NO	NO	YES	NO
8	suresh babu	35	m	SJS	4/60	6/24	BE	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	NO	YES	BE < 15mm	NO	YES	YES	YES	NO	NO	YES	YES	NO	NO	NO
9	rohith	12	m	SJS	6/12	PL	BE	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	NO	YES	NO	NO	BE < 15mm	NO	YES	YES	YES	YES	NO	NO	NO	YES	NO	NO
10	vasantha	68	f	blepharoconjunctivitis	2/60	6/12	RE	NO	YES	YES	YES	NO	NO	NO	NO	NO	YES	YES	YES	NO	YES	RE < 15mm	NO	YES	YES	NO	NO	YES	YES	NO	YES	NO	NO
11	chitra	40	f	SJS	2/60	HM	BE	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	BE < 15mm	NO	YES	YES	YES	YES	YES	YES	YES	YES	NO	YES
12	udaya kumar	46	m	ocular trauma	HM	6/9	RE	NO	YES	NO	NO	NO	NO	NO	YES	YES	YES	YES	NO	YES	YES	RE < 15mm	NO	YES	YES	NO	NO	YES	NO	NO	NO	NO	NO
13	devaki	37	f	OSSN	6/9	6/18	BE	YES	YES	YES	YES	NO	YES	YES	NO	NO	NO	NO	NO	NO	YES	BE > 15mm	NO	YES	YES	YES	NO	NO	NO	YES	NO	NO	NO
14	samundeswari	43	f	SJS	6/18	6/12	BE	YES	YES	YES	NO	NO	YES	YES	NO	NO	NO	NO	NO	NO	YES	BE > 15mm	NO	YES	YES	YES	NO	NO	NO	NO	NO	NO	NO
15	santha	65	f	sjogren	HM	6/24	BE	YES	YES	YES	NO	NO	NO	NO	NO	NO	YES	NO	NO	NO	YES	BE < 15mm	NO	YES	YES	YES	NO	NO	NO	NO	NO	NO	NO
16	abdul latif	58	m	SJS	4/60	2/60	BE	YES	YES	NO	NO	YES	YES	YES	NO	NO	NO	NO	NO	NO	YES	BE > 15mm	NO	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO
17	panner	20	m	chemical injury	6/6	4/60	LE	NO	YES	YES	YES	NO	YES	YES	NO	NO	NO	NO	NO	YES	NO	LE <15mm	NO	YES	YES	NO	NO	YES	NO	YES	NO	NO	NO
18	malar	46	f	chemical injury	5/60	6/9	RE	NO	YES	NO	YES	YES	YES	NO	NO	NO	NO	NO	NO	YES	NO	RE > 15mm	NO	YES	YES	NO	NO	YES	NO	NO	NO	NO	NO
19	rajarathinam	48	m	chemical injury	PL	6/9	RE	NO	YES	YES	YES	NO	NO	NO	YES	YES	YES	YES	YES	YES	YES	RE < 15mm	NO	YES	NO	NO	NO	NO	NO	NO	YES	NO	NO
20	chinnathambi	53	m	SJS	2/60	5/60	BE	YES	YES	NO	YES	YES	YES	YES	YES	YES	NO	NO	YES	NO	YES	BE > 15mm	NO	YES	YES	YES	NO	YES	YES	NO	NO	NO	NO
21	prabhakaran	48	m	OCP	HM	1/60	BE	NO	YES	NO	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	BE < 15mm	YES	YES	YES	YES	NO	NO	YES	NO	NO	NO	NO
22	rajesh	22	m	chemical injury	6/60	6/36	BE	NO	YES	NO	NO	NO	NO	NO	YES	YES	NO	NO	YES	NO	YES	BE > 15mm	NO	YES	YES	NO	NO	NO	YES	NO	NO	NO	NO
23	shabana	16	f	SJS	6/36	6/18	BE	YES	YES	YES	YES	YES	YES	YES	NO	NO	NO	NO	NO	NO	YES	BE > 15mm	NO	YES	YES	YES	NO	YES	NO	NO	NO	NO	NO
24	sekar	32	m	chemical injury	6/6	2/60	LE	NO	YES	NO	NO	NO	NO	NO	YES	YES	NO	NO	NO	NO	YES	LE > 15mm	NO	YES	YES	NO	NO	NO	NO	NO	NO	NO	NO
25	munnusamy	50	m	OCP	1/60	HM	BE	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	BE < 15mm	YES	YES	YES	YES	NO	NO	YES	NO	NO	NO	NO