CLASSIFICATION AND MANAGEMENT OF OCULAR SURFACE INJURIES

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A. Hughes's classification

Mild	Erosion of corneal epithelium. Faint haziness of cornea. No ischemic necrosis of conjunctiva or sclera
Moderately severe	Corneal opacity blurring iris details. Minimal ischemic necrosis of conjunctiva and sclera
Very severe	Blurring of pupillary outline Blanching of conjunctival and scleral vessels

B. Hughes classification of ocular alkali burns

Grade I	Corneal epithelial defect without limbal ischemia
Grade II	Corneal epithelial defect with stromal haze ischemia affecting <1/3rd of limbus
Grade III	Total corneal epithelial defect with stromal haze obscuring iris details ischemia affecting < 1/3 – ½ of limbus
Grade IV	Opaque cornea Obscuring view of iris and pupil Ischemia > ½ of limbus

C. Roper-Hall Classification system

Grade	Prognosis	Cornea	Limbal ischemia
Grade I	Good	Corneal epithelial damage	None
Grade II	Good	Corneal haze, iris details visible	< 1/3
Grade III	Guarded	Total epithelial loss, stromal haze, iris details obscured	1/3-1/2
Grade IV	Poor	Cornea opaque, iris and pupil Obscured	>1/2

D. Dua's classification

Grade	Prognosis	Clinical findings	Conjunctival involvement	Analogue 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%

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Dua grade has been found to have better prognostic predictive value in severe ocular injuries than the R-H system. Dua classification preferred for prognostication of ocular chemical injuries, particularly in the presence of significant limbal stem cell disease.

Management

I Management of Immediate Phase	Irrigation
II. Management of Acute Phase	A. Anti-inflammatory Therapy B. Prevention of Stromal Breakdown C. Promotion of Re-epithelialization and Repair 1. Bandage Contact Lens 2. Amniotic Membrane Transplantation 3. Autologous Serum 4. Tenonplasty 5. Treatment of High Intraocular Pressure
III. Management of Chronic Phase	A. Fornix and Eyelid Reconstruction B. Management of Glaucoma C. Management of Limbal Stem Cell Deficiency D. Corneal Transplantation E. Keratoprosthesis Surgery
IV. Future Horizons	A. Anti-angiogenic Therapy B. Stem Cell-based Therapy

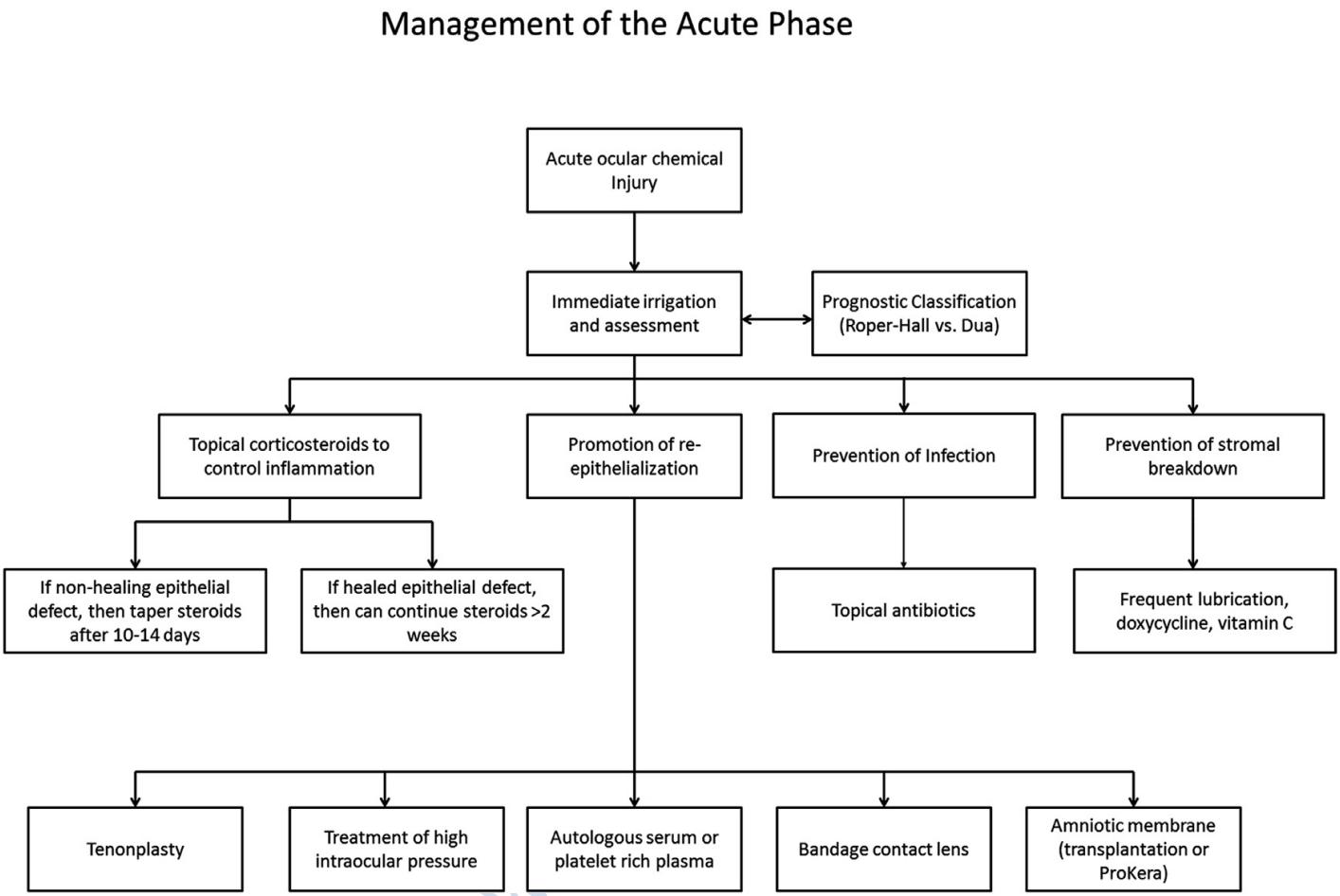
I. Management of immediate phase

- 1st step in treating an ocular chemical injury is to immediately and thoroughly irrigate the surface
- Irrigation is performed at the site of the accident prior to completion of assessment of the injury.
- Tap water is employed as the aqueous solution for irrigation in most pre-hospital settings due to its ubiquitous availability. Some studies have suggested that it may promote corneal edema due to its hypotonicity relative to the corneal stroma.
- Use lactated ringers (LR) or balanced salt solution (BSS), amphoteric solutions (e.g., Diphoterin) have been preferred option for emergency neutralization to correct the pH more rapidly.
- Amphoteric solutions are hypertonic and offer non-specific chelation of acids and bases, less exothermic reactivity.
- Balanced saline solution plus (BSSP) >> normal saline.
- Preferential use of BSSP should be limited to patients with severe discomfort that precludes appropriate irrigation with other solutions.
- The time to re-epithelialization was significantly shorter in R-H grade 1- or 2- patients who received irrigation with Diphoterine compared to normal saline.

Irrigation solution	**Proposed advantages**
Tap water (H2O)	Ubiquitous availability
Phosphate buffer	Correction of pH
Purpose-designed solutions (e.g. NS, LR, BSSP)	Isotonic to stroma Patient comfort (BSSP)
Amphoteric solutions (e.g. Diphoterine)	Hypertonic to stroma Rapid pH correction Non-specific chelation Faster re-epithelialization (mild injuries only)

II. Management of acute phase

The main objectives during the acute phase are to decrease inflammation, avoid further epithelial and stromal breakdown, and foster re-epithelialization



A. Anti-inflammatory Therapy

- Topical corticosteroids- controlling acute inflammation and reducing inflammatory damage to the ocular surface after a chemical injury.
- Corticosteroids reduce inflammatory cell infiltration and stabilize neutrophil cytoplasmic and lysosomal membranes, mitigating the release of matrix-degrading enzymes.
- Topical therapy is started immediately after the chemical injury and continued for at least 7 days. Prednisolone 0.5% hourly or fluoromethalone 1% bihourly with subsequent tapering.
- > 1st week - they can inhibit epithelialization and collagen synthesis and potentially increase the risk of corneal perforation.
- Severe injury / non-healing epithelial defect e/d steroid should be tapered to low dosage by 2 weeks.
- Injury site has epithelialized- can be used safely beyond 2 weeks with adjunctive ascorbic acid (topical and systemic) to minimize secondary inflammatory damage to the ocular surface.
- Systemic corticosteroids - augment suppression of inflammation with fewer local side effects.
- Sufficiently severe injuries- prolonged inflammation is likely use steroid-sparing agent mycophenolate mofetil.

B. Prevention of Stromal Breakdown

- Corneal ulceration and melting occur after severe chemical injuries.

- Reactive inflammatory cells release enzymes- collagenases and MMPs, potentiating corneal thinning.

Collagenase inhibitors	Tetracyclines, Citrate, Cysteine, Acetylcysteine, Sodium Ethylenediamine Tetra Acetic Acid [EDTA], Penicillamine
Proteinase inhibitors	Aprotinin

- Collagenase and proteinase inhibitors- prevent corneal thinning experimentally and/or clinically after chemical injuries.
- Tetracyclines - suppress neutrophil mediated tissue damage through several: inhibition of neutrophil migration and degranulation, suppression of the synthesis of oxygen radicals, and inhibition of MMPs.
- Citrate- prevents PMN leukocyte migration into damaged tissue, thus reducing the release of free radicals and proteolytic enzymes.
- Ascorbic acid supplementation directly promotes corneal stromal repair. Ascorbate, essential cofactor for wound healing, decreases in concentration (by as much as two-thirds) in the aqueous following an alkali injury for 3 days in a moderate injury, but persists for at least 30 days in a severe injury. Collagen synthesis is impaired as a result of lowered aqueous concentrations of ascorbate. It may play a beneficial role as an adjunct by restoring a favorable wound healing equilibrium in patients with ocular chemical injuries that are receiving corticosteroid therapy.

C. Promotion of Re-epithelialization and Repair

Standard therapy- frequent preservative-free lubricants and prophylactic antibiotic drops.

1. Bandage Contact Lens

- Therapeutic bandage contact lenses protect a compromised ocular surface and promote epithelialization through improvement in the spreading of tear fluid over the ocular surface.
- Silicone hydrogel contact lenses - improved corneal health and patient satisfaction among frequent lens wearers and may be preferable.
- Severe pain and photophobia- large diameter gas-permeable scleral contact lenses can establish a fluid-filled pre-corneal vault, providing even greater protection to the cornea from desiccation and friction from the eyelids during blinking.
- The Prosthetic Replacement of Ocular Surface Ecosystem (PROSE; originally called the Boston Scleral Lens) has been reported to be successful in multiple studies examining its utility in patients with thermal burns and a variety of other ocular surface diseases.

2. Amniotic Membrane Transplantation

- Used as a permanent surgical graft to provide a basement membrane for epithelialization or as a patch where it acts as a biological bandage contact lens.
- Promotes epithelialization and reduces inflammation, scarring, and neovascularization.
- It works by trapping and inducing apoptosis of the post-injury inflammatory infiltrate, which is primarily composed of neutrophils and macrophages.
- Acute ocular burns- AMT offers better acute pain reduction and earlier epithelialization in patients with mild to moderate grade injuries.
- AMT has been applied to the cornea using a carrier with the amniotic membrane secured to a flexible plastic ring (ProKera, Bio-Tissue, Inc., Miami, FL). The ring-amniotic membrane complex is placed onto the ocular surface without any need for suturing or gluing in the office or at the bedside. Amniotic

membrane lasts days-weeks (around 1 week) and its application can be repeated. In a series of chemical injury patients, Prokera facilitated rapid limbal stem cell recovery and promoted epithelial healing.

3. Autologous Serum

- Human serum contains many soluble factors that promote healing in various tissues including the cornea.
- **Autologous serum** has been shown to be effective in promoting wound healing in patients with persistent epithelial defects due to chemical injury.
- **Umbilical cord serum** has likewise been shown to be very effective in accelerating epithelial healing in acute chemical injuries in both animal models and human studies; however, difficulty associated with acquiring such serum is an important barrier to treatment.
- Use of **platelet rich plasma (PRP)** as a variation of autologous serum in patients with ocular chemical injuries. These reports include both topical and subconjunctival injection of PRP and suggest it is a safe and effective adjunct to standard medical treatments. MOA of autologous PRP is likely the same as that of autologous serum. It has a higher concentration of growth factors and platelets, which may lead to faster healing.

4. Tenonplasty

- Tenonplasty is an intervention that may be utilized in severe injuries that cause loss of limbal vascularity and subsequent anterior segment necrosis.
- The intent of the procedure is to re-establish the limbal blood supply and to promote ocular surface repair.
- After debridement of necrotic tissue, tenonplasty involves the advancement of viable vascular Tenon's layer tissue up to the limbus that is then secured to the sclera.
- Tenonplasty may be combined with AMT with or without lamellar corneal patch grafting.
- This intervention enables the reconstruction of the conjunctival matrix and limbal vascularity, which prevents anterior segment necrosis, scleral ischemia, melting, and sterile ulceration.
- Most recently, tenonplasty combined with buccal mucosal autograft has also demonstrated benefit for patients with sclerocorneal melt after a chemical injury.

5. Treatment of High Intraocular Pressure

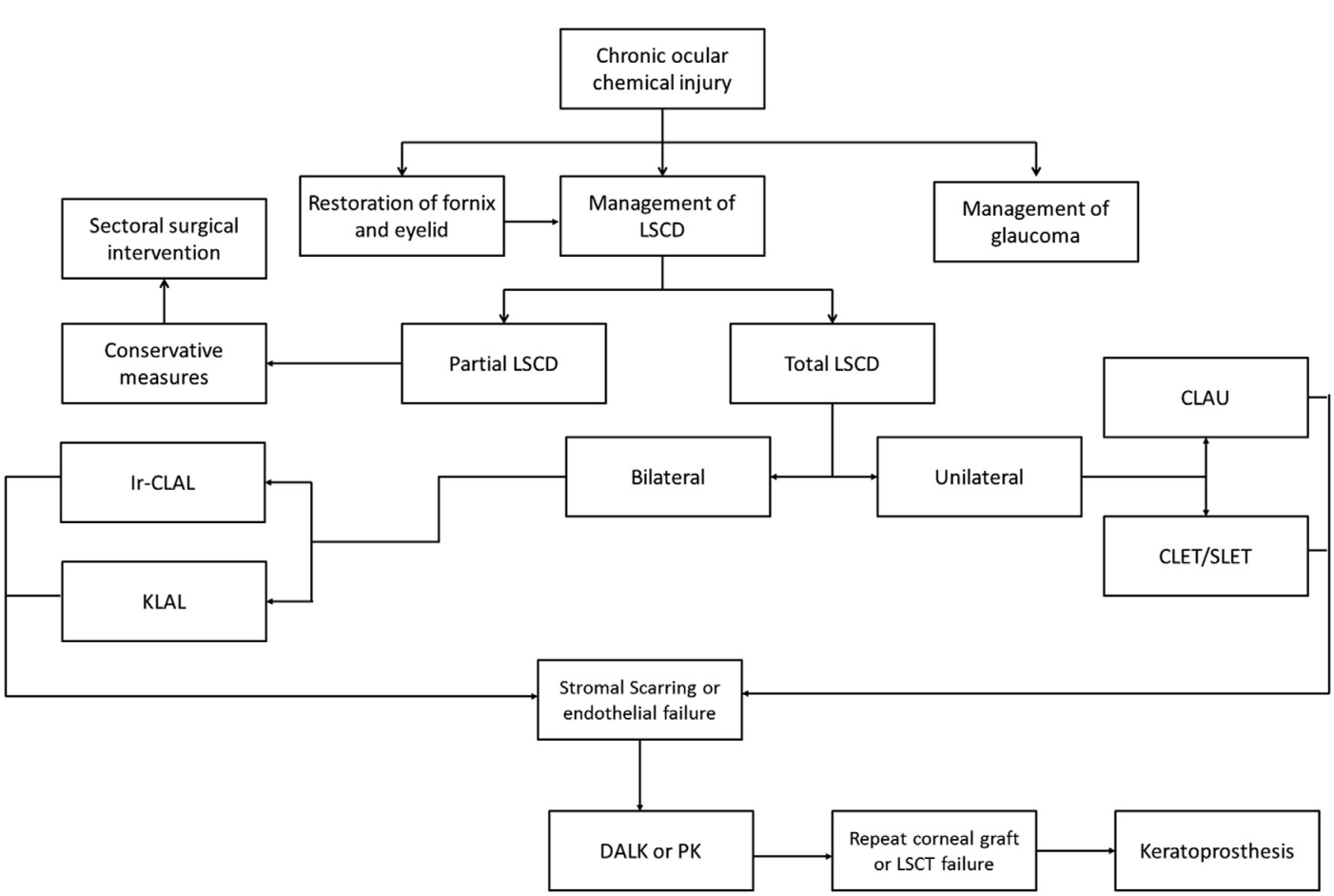
- Chemical agents that reach the trabecular meshwork can lead to an elevated IOP.
- Glaucoma after alkali injury may be immediate (less than a month) or delayed (months).
- Mechanistically, immediate injury may cause tissue damage with subsequent impairment of aqueous humor outflow channels.

Therapeutic aim	Treatment	Suggested regimen
Reduction of Inflammation	Corticosteroids	Intense therapy 7 days with subsequent taper
Stromal Breakdown Prophylaxis	Tetracyclines	Tetracycline 250 mg PO QID. Doxycycline 100mg PO bid
	Citric acid	Topical Citrate 10% hourly or bihourly
	Ascorbic acid	Ascorbate 0.5 to 2 g QID PO þ topical Ascorbate 10% hourly/ 2 hourly
Promotion of Epithelial Repair	BCL	Daily wear of soft BCL or PROSE scleral lens (in severe cases)
	AMT	Perform within 1 week of injury
	Autologous serum	Topical platelet-rich plasma 10x QD
	Tenonplasty	As needed upon recognition of scleral pathology
	Treatment of high IOP	Topical agents-procedural intervention (e.g. paracentesis)

III. Management of chronic phase

- Management of chronic ocular disease after a chemical injury can pose major therapeutic challenges and requires a multidisciplinary approach involving cornea, oculoplastic, and glaucoma specialists.
- The goal of these surgical interventions is to restore normal ocular surface anatomy and visual function.
- The typical order for surgical intervention is:

Correction of eyelid abnormalities →management of glaucoma→ocular surface reconstruction/ transplantation→ finally keratoplasty



A. Fornix and Eyelid Reconstruction

- Ocular surface exposure due to loss of eyelid tissue, contractures, and/or symblephara is a major contributing factor to corneal complications including ulceration and perforation.
- Significant exposure due to severe eyelid injury may occasionally necessitate corneal coverage by a mucous membrane graft or even skin graft to prevent corneal perforation.
- All eyelid and fornix abnormalities should be corrected before any limbal or corneal surgery is performed.
- **In mild and moderate symblephara**, fornix can be reconstructed with the help of AMT to the denuded surfaces. Amniotic membrane can be sutured or glued to the surgical site. Antimetabolites such as MMC or 5-fluorouracil can be simultaneously applied to the subconjunctival forniceal area to decrease the chance of recurrent forniceal shrinkage.
- **In severe and extensive symblepharon or ankyloblepharon** formation, new mucosal tissue must be transplanted.

B. Management of Glaucoma

- Ocular chemical injuries can lead to significant loss of vision not just from direct injury to the ocular surface but also from glaucoma.
- Secondary chronic inflammation may lead to synechiae and angle closure.
- Development of glaucoma may be partially counteracted by ciliary body necrosis in deeply penetrating alkali injuries.
- Factors such as damage to the trabecular meshwork, severe uveitis, long-term steroid use, phacomorphic or phacolytic mechanisms, and contraction of the sclera may also contribute to chronic glaucoma in these patients.
- Medical therapy is the standard initial treatment, the chronicity of the disease and detrimental effects of eye drops on the ocular surface are a cause for concern.
- Procedural interventions are generally considered earlier in these patients.
- Cyclophotocoagulation may also be indicated, particularly in cases with advanced conjunctival shrinkage and scar formation.

C. Management of Limbal Stem Cell Deficiency

- **Limbal stem cells deficiency (LSCD)** is one of the most visually significant long-term sequelae of severe chemical injury.
- Healthy limbal stem cells act as a barrier against invasion of the cornea by conjunctival tissue.
- Conjunctival tissue migrates toward the central cornea, a process called conjunctivalization, the hallmark of LSCD.
- Depending on the extent of the disease, LSCD is classified as either partial or total.
- Clinical findings of LSCD include a loss of the palisades of Vogt, opaque epithelium, whorl-like epithelial staining, recurrent and/or persistent epithelial defects, superficial neovascularization, and ultimately corneal melting (from non-healing defect) or stromal scarring and neovascularization.

- Treatment depends on the extent of the injury and the involvement of the central cornea.

Cornea-sparing partial LSCD	Conservative measures, such as non-preserved lubrication and autologous serum eye drops.
Central cornea involving partial LSCD	Surgical management
Sectoral conjunctivalization of the cornea	Sequential sector conjunctival epitheliectomy (SSCE) or AMT that may mitigate or prevent recurrent conjunctival ingrowth

- Limbal stem cell transplantation (LSCT) may be considered for patients with more extensive corneal conjunctivalization.
- LSCT is not recommended during active inflammation and should be delayed until ocular surface inflammation has subsided or is well controlled with medications.
- Eyelid abnormalities (e.g., entropion, trichiasis, symblepharon) should be addressed before considering LSCT
- Limbal stem cells can be harvested from autologous or non-autologous sources.

CLAU	-A conjunctival limbal autograft (CLAU) taken from the healthy fellow eye is considered the most effective surgical procedure in patients with total unilateral LSCD. -Excellent results, with complete regression of corneal neovascularization with successful re-epithelialization and functional vision is achieved in 80% to 90% of patients
CLET	Cultivated limbal epithelial transplantation (CLET) is a suitable alternative in cases of total unilateral LSCD or in cases of bilateral LSCD when the damage is more severe in one eye. the overall success rate is estimated to be 72%.

Lr-CLAL	Living-related conjunctival limbal allograft (lr-CLAL)- bilateral LSCD. Utilizes tissue from one eye (or occasionally both eyes) of a patient's 1st -degree blood relative, benefits from fresh tissue that has a strong genetic similarity to the patient. It has advantage of providing viable conjunctival tissue may be used in patients with severe conjunctival deficiency.
KLAL	KLAL, which utilizes cadaveric tissue, is more accessible and offers more stem cells because of larger clock hours of available graft tissue
Cincinnati procedure	for bilateral LSCD, a combination of lr-CLAL with KLAL
EVCAU	Transplantation of autologous conjunctival epithelial cells cultivated ex vivo(EVCAU) on a denuded human amniotic membrane graft has also been used in patients with total LSCD
SLET	2X2 mm strip of donor limbal tissue from the healthy eye is divided into 8-10 small pieces and is evenly distributed over an amniotic membrane placed on the cornea
COMET	Cultured oral mucosal epithelial tramsplant.
Allogeneic CLET	

- For patients receiving LSCT from an allogeneic source, systemic immunosuppression consisting of steroids (short-term), tacrolimus (or cyclosporine), and Mycophenolate (or azathioprine) is necessary to prevent limbal allograft rejection.
- LSCT, with or without corneal transplantation, is an effective procedure for anatomical and visual rehabilitation of eyes with total LSCD.
- Complications primarily arise from immunologic rejection, chronic ocular surface exposure, and graft-related complications (thickness, position, and alignment).
- These complications may ultimately lead to ocular surface epithelial breakdown (including persistent epithelial defect), thinning, and progressive corneal conjunctivalization.
- Good tear film status, full correction of adnexal abnormalities, proper handling and dissection of limbal grafts, and adequate immunosuppression are the most important factors in preventing complications.

D. Corneal Transplantation

- PK or DALK -for visual rehabilitation in patients with extensive stromal scarring.
- Partial LSCD with opacification of the central cornea- primary PK or DALK ,keratoplasty can aggravate a compromised ocular surface with a borderline stem cell reserve in some cases.
- In total LSCD with complete vascularization and opacification of the cornea, corneal transplantation should be preceded by LSCT; otherwise, corneal transplantation will fail.
- Staged procedures are preferred over a combined approach, and it is recommended to wait at least 3 months for the surface to stabilize after LSCT before proceeding with keratoplasty
- Staged procedures offer significantly greater transplant survival; approximately 80% of grafts performed at least 6 weeks after LSCT survive past 1 year compared to only 25% of non-staged procedures. Median graft survival time after a staged procedure has been reported to be 4 years compared with 1 year for concurrent LSCT and PK.
- Given the risk of immunologic graft rejection, DALK may be preferred over PK whenever possible.
- The use of systemic immunosuppression can reduce the risk of endothelial graft rejection in very high risk cases.

E. Keratoprosthesis Surgery

- Surgical placement of an artificial cornea is an effective means of managing repeat corneal graft failure or corneal limbal stem cell failure in patients with unilateral or bilateral chemical injury.

Procedure	Indications	complications	Remarks
Boston Type 1 keratoprosthesis	With/without a shunt-6 months after inflammation subside. Need for lifelong regular follow-up, adherence to daily antibiotic prophylaxis.	Retroprosthetic membrane Glaucoma Sterile corneal stromal necrosis Corneal thinning infectious Keratitis Persistent epithelial defect Retinal detachment sterile uveitis/vitritis endophthalmitis	LSCT procedure prior to use of a Keratoprosthesis.
Boston Type 2 keratoprosthesis osteo-odonto-keratoprosthesis	Bilateral corneal blindness Dryness Keratinization Severe chemical or physical injury with loss of lids.		In pt with residual tear film-ocular surface reconstruction with stem cell transplant should be considered prior to B2-KPro or OOKP implantation

IV. Future horizons

- A substantial number of patients with severe injuries develop significant corneal and limbal stem cell
- disease, complicated by neovascularization, melts, and perforations.
- Furthermore, extensive conjunctival scarring and symblepharon formation often progress in the months following the injury, thus requiring major reconstructive surgical procedures.

A. Anti-angiogenic Therapy

- Corneal neovascularization (CNV) is one of the major complications of ocular chemical injuries.
- CNV leads to loss of corneal transparency and immune privilege.
- Prevention and reversal of CNV is important for improving the visual outcome after a chemical injury.

Increase in angiogenic factors	Loss of anti-angiogenic
Fibroblast growth factor Vascular endothelial growth factors (vegfs) Transforming growth factor-a and –b Placenta growth factor IL-1 TNF-a IL-8 Monocyte chemoattractant-1 MMPs Platelet activating factor	Fms-like tyrosine kinase-1 Angiostatin Endostatin Restin Neostatin Thrombospondins Pigment epithelium-derived factor Arrestin Canstatin Tumstatin Angiopoetin-2
Implicated in corneal neovascularization	Breakdown of corneal avascular privilege.

- Availability of anti-VEGF agents (e.g., bevacizumab, ranibizumab, pegaptanib and aflibercept) has opened the possibility of their clinical use for CNV.
- Both topical and subconjunctival bevacizumab and ranibizumab have shown beneficial effects in reducing CNV in various clinical conditions.

- Inhibiting pleiotrophic cytokines such as VEGF may adversely affect the overall wound healing response. Anti-VEGF therapy can potentially increase the likelihood of a corneal melt in the setting of the most severe injuries.

B. Stem Cell-based Therapy

- Progress in the use of mesenchymal stem cells for tissue repair and regeneration.
- MSCs are found in cornea and limbus, and play an important role in tissue repair and maintenance.
- In animal models of chemical injury, MSCs have been shown to accelerate corneal wound healing, attenuate inflammation, and modulate corneal neovascularization.
- These effects have been shown to be mediated in part through secreted factors such as TSG-6.
- MSC-based therapies are may be beneficial for management in acute phase after chemical injury to help control inflammation and chronically to help restore a more normal ocular surface environment.