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Current and Upcoming Therapies for Ocular Surface Chemical Injuries

Alireza Baradaran-Rafii, MD[1,*], **Medi Eslani, MD**[2,*], **Zeeshan Haq, BS**[2], **Ebrahim Shirzadeh, MD**[1], **Michael J. Huvard, MD**[2], and **Ali R. Djalilian, MD**[2]

[1]Ophthalmic Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[2]Department of Ophthalmology and Visual Sciences, University of Illinois at Chicago, Chicago, Illinois, USA

Abstract

Chemical injuries frequently result in vision loss, disfigurement, and challenging ocular surface complications. Acute interventions are directed at decreasing the extent of the injury, suppressing inflammation, and promoting ocular surface re-epithelialization. Chronically, management involves controlling inflammation along with rehabilitation and reconstruction of the ocular surface. Future therapies aimed at inhibiting neovascularization and promoting ocular surface regeneration should provide more effective treatment options for the management of ocular chemical injuries.

Keywords

chemical burn; cornea; limbal stem cell deficiency; ocular chemical burn; ocular surface; stem cell

I.. Introduction

Ocular chemical injuries are true ophthalmic emergencies that require immediate and intensive intervention to minimize severe complications and profound visual loss.[1] Such injuries, which are most prevalent among young males aged 20- 40, can result in chronic complications and life-long disability. The severity of chemical injury is determined by several factors, including the chemical and physical characteristics of the offending agent (particularly the pH), the specific reactivity with tissues (pK), concentration, volume, temperature, and impact force.[2,3] It is well known that alkaline substances, due to their lipophilicity, penetrate the eye more readily and therefore threaten both ocular surface tissues as well as intraocular structures such as the trabecular meshwork, ciliary body, and

Corresponding Author: Ali R. Djalilian, MD, 1855 W. Taylor St, EEI 3164, Illinois Eye and Ear Infirmary, Department of Ophthalmology and Visual Sciences, University of Illinois at Chicago, Chicago, IL 60612. Tel: 312-996-8936. adjalili@uic.edu.
*Drs. Baradaran-Rafii and Eslani contributed equally to this paper.

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lens. In contrast, acidic substances cause protein coagulation in the epithelium, a process that limits further penetration into the eye.[4–6] Nonetheless, acids may severely damage the ocular surface. With all ocular chemical injuries, swift intervention is crucial to improving the outcome and prognosis.

The purpose of this review is to provide an update on the current medical and surgical management of ocular chemical injuries and to describe future potential therapies.

II. Classification of Ocular Surface Injuries

There are several classification systems of ocular surface injuries that predict prognosis and clinical outcome by grading the severity of the injury.[3,7–8] The Roper-Hall (R-H) classification, first introduced by Ballen[9] in the mid-1960s and later modified by Roper-Hall,[8] grades the severity of injury by the extent of corneal haze and perilimbal ischemia (Table 1). A similar classification proposed by Pfister is based upon the same variables but categorizes the severity of injury as mild, mild-to-moderate, moderate-to-severe, severe, or very severe based upon photographs.[3] In contrast, Dua proposed a classification based on both clock-hour limbal involvement as determined by fluorescein staining and percentage of bulbar conjunctival involvement (Table 2).[7] These clinical findings are then translated into an analog grading scale that should be calculated daily during the acute stage as the extent of injury becomes evident.

The common element in all of these classification schemes is the identification of the amount of limbal involvement at the time of injury. Indeed, studies have shown that the relative proportion of surviving limbal tissue is a major prognostic factor (Figure 1).[4,10–14] However, the Dua grade has been found to have better prognostic predictive value in severe ocular injuries than the R-H system.[7,15] Accordingly, we prefer to use the Dua classification for prognostication of ocular chemical injuries, particularly in the presence of significant limbal stem cell disease. Universal adoption of a single system should be considered, as it will facilitate the comparison of published studies on outcomes.

McCulley[10,16] has categorized the pathophysiology and course of the disease process into four distinct clinical phases: immediate, acute (0 to 7 days), early repair (7 to 21 days), and late repair (after 21 days) phases. For simplicity, we have chosen to classify the management of ocular chemical injuries chronologically into the immediate, acute (<6 weeks), and chronic (>6 weeks) phases.

III. Management of Immediate Phase

The obvious first step in treating an ocular chemical injury is to immediately and thoroughly irrigate the surface to remove the offending agent.[2,14,17–21] Given the correlation between time to irrigation and outcomes, swift irrigation is usually performed at the site of the accident and prior to completion of a thorough assessment of the injury.[22] Accordingly, tap water is appropriately employed as the aqueous solution for irrigation in most pre-hospital settings due to its ubiquitous availability. However, some studies have suggested that it may promote corneal edema due to its hypotonicity relative to the corneal stroma.[4,20,23] For this reason, some have suggested the use of purpose-designed solutions such as lactated ringers

(**LR**) or balanced salt solution (**BSS**).[24] More recently, amphoteric solutions (e.g., Diphoterine®) have been proposed as a preferred option for emergency neutralization.[25–27] These novel neutralizers have been shown to correct the pH more rapidly than other irrigating solutions. Moreover, amphoteric solutions are typically hypertonic and offer non-specific chelation of acids and bases and less exothermic reactivity.[28] However, the choice of aqueous solution is of less prognostic importance than the timing of treatment and any delay in irrigation should be avoided.

Once in the hospital setting, the most effective choice of irrigation solution remains undetermined. In a crossover study of 12 eyes with acute chemical burns, Herr et al found that patient comfort was statistically superior with balanced saline solution plus (**BSSP**) compared to normal saline.29 Of note, all tested solutions produced comparable changes in objective outcomes, including conjunctival pH and degree of injection. However, the potential for bias as a result of accumulated benefit from inadequate washout in the acute setting and the small number of studied patients must be considered. Accordingly, unless immediately available, the preferential use of BSSP should be limited to patients with severe discomfort that precludes appropriate irrigation with other solutions.

In a nonrandomized comparative case series of 66 patients, Merle et al found that 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.[30] However, in-hospital irrigation was delivered, on average, more than 40 minutes later in the group receiving normal saline. In addition, irrespective of injury severity, no significant differences were detected in vision or corneal opacification between the two groups. Given the intergroup discordance in time-to-treatment and lack of difference in functional outcomes, no definitive recommendations can be made on the basis of these findings.

IV. 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 (Figure 2).[31]

A. Anti-inflammatory Therapy

Topical corticosteroids can be critical in controlling acute inflammation and reducing the resulting 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.[32] Topical therapy is started immediately after the chemical injury and continued for at least 7 days.[33,34] Published studies have described intense regimens including prednisolone 0.5% hourly or fluoromethalone 1% bihourly with subsequent tapering. Caution must be exercised after the first week, as corticosteroids can inhibit epithelialization and collagen synthesis and potentially increase the risk of corneal perforation.[35,36] Accordingly, in the setting of severe injury or a nonhealing epithelial defect, topical corticosteroid therapy should be tapered to a low dosage by 2 weeks. Otherwise, if the injury site has epithelialized, topical corticosteroids can be used safely beyond 2 weeks with adjunctive ascorbic acid (topical and systemic) to minimize secondary inflammatory damage to the ocular surface.[33,34] If

necessary, systemic corticosteroids can be considered to augment suppression of inflammation with fewer local side effects. Furthermore, in sufficiently severe injuries where prolonged inflammation is likely to be encountered, a steroid-sparing agent such as mycophenolate mofetil may also be used (discussed in Section V below).

B. Prevention of Stromal Breakdown

Corneal ulceration and melting occur relatively frequently after severe chemical injuries (Figure 3). Reactive inflammatory cells release enzymes such as collagenases and matrix metalloproteinases (**MMP**s), which potentiate corneal thinning.[37] Collagenase inhibitors (e.g., tetracyclines, citrate, cysteine, acetylcysteine, sodium ethylenediamine tetra acetic acid [**EDTA**], penicillamine) and proteinase inhibitors (e.g., aprotinin) have been found to prevent corneal thinning experimentally and/or clinically after chemical injuries.[2,10,37–40]

Tetracyclines are thought to suppress neutrophil-mediated tissue damage through several mechanisms, including the inhibition of neutrophil migration and degranulation, suppression of the synthesis of oxygen radicals, and inhibition of MMPs.[11,41] Similarly, citrate has been shown to prevent polymorphonuclear leukocyte migration into damaged tissue, thus reducing the release of free radicals and proteolytic enzymes.[42,43] However, studies of these treatments are limited to animal experiments and evidence of clinical benefit from human reports remains lacking.[38] While roles for systemic tetracycline and topical citrate as adjunctive treatments have been suggested,[33,44] no well-controlled reports of either treatment in humans with ocular chemical injuries have been published to date.

In contrast to enzyme inhibition, ascorbic acid supplementation directly promotes corneal stromal repair.[42,43,45] Ascorbate, an essential cofactor for wound healing, has been shown in animal studies to acutely decrease in concentration (by as much as two-thirds) in the aqueous following an alkali injury.[46,47] This low level is sustained 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 persistently lowered aqueous concentrations of ascorbate. As mentioned above, ascorbic acid 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.[33,34]

C. Promotion of Re-epithelialization and Repair

In addition to standard therapy, which includes frequent preservative-free lubricants and prophylactic antibiotic drops, a number of measures may be used to further enhance repair of ocular surface tissue in the acute setting.

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. Of note, silicone hydrogel contact lenses have been found to confer improved corneal health and patient satisfaction among frequent lens wearers and may be preferable.[48] In patients with relatively 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.[49] 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.[11,50–53]

2. Amniotic Membrane Transplantation—An amniotic membrane may be 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.[54–57] Both as a graft and as a patch, amniotic membranes have been shown to promote epithelialization and to reduce inflammation, scarring, and neovascularization.[55,56,58] It works in part by trapping and inducing apoptosis of the post-injury inflammatory infiltrate, which is primarily composed of neutrophils and macrophages.[59]

Animal studies and noncomparative case series have supported the effectiveness of amniotic membrane transplantation (**AMT**) in ocular surface reconstruction after chemical injuries.[60–62] For patients with acute ocular burns, multiple randomized clinical trials have shown that AMT offers better acute pain reduction and earlier epithelialization in patients with mild to moderate grade injuries.[63,64] However, no differences in long-term benefits were detected in these studies and a systematic review of the literature found insufficient evidence for the use of AMT in the setting of acute ocular burns.[65] Nonetheless, AMT is most often employed as an adjunct to medical therapy in patients with severe ocular injuries.[12,56,66–73]

More recently, 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. Using this technique, the amniotic membrane usually lasts days to weeks (typically around 1 week) and its application can be repeated. In a series of chemical injury patients, the use of Prokera appeared to facilitate rapid limbal stem cell recovery and promote epithelial healing.[68] However, future studies with adequate control groups are necessary to further elucidate its clinical benefit.

3. Autologous Serum—Human serum contains many soluble factors that promote healing in various tissues including the cornea.[47,74–79] Autologous serum has been shown to be effective in promoting wound healing in patients with persistent epithelial defects due to a variety of etiologies, including chemical injury.[80] 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.[81,82]

More recent studies have reported the use of platelet rich plasma (**PRP**) as a variation of autologous serum in patients with ocular chemical injuries.[78,83–86] These reports include both topical and subconjunctival injection of PRP and suggest it is a safe and effective adjunct to standard medical treatments. The mechanism of action of autologous PRP is likely the same as that of autologous serum. However, 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 reestablish the limbal blood supply and to promote ocular surface repair.[87] 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.[88] This intervention enables the reconstruction of the conjunctival matrix and limbal vascularity, which prevents anterior segment necrosis, scleral ischemia, melting, and sterile ulceration.[4,89] Most recently, tenonplasty combined with buccal mucosal autograft has also demonstrated benefit for patients with sclerocorneal melt after a chemical injury.[90]

5. Treatment of High Intraocular Pressure—Chemical agents that reach the trabecular meshwork can lead to an elevation in intraocular pressure (**IOP**), a complication that can be easily overlooked. Glaucoma after alkali injury may be immediate (less than a month) or delayed (months).[91,92] Mechanistically, immediate injury may cause tissue damage with subsequent impairment of aqueous humor outflow channels. In the largest study to date, Kuckelkorn et al reviewed 66 cases (90 eyes) of severe chemical injuries and found that early glaucoma occurred in 14 (15.6%) eyes and late glaucoma occurred in 20 (22.2%) eyes.[93]

IV. 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. Much effort has been made to develop more effective surgical interventions for the ocular surface disorders in these patients. 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, followed by management of glaucoma, then ocular surface reconstruction/transplantation, and finally keratoplasty (Figure 4).

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. As a general rule, all eyelid and fornix abnormalities should be corrected before any limbal or corneal surgery is performed.

Symblepharon and ankyloblepharon are best classified as a form of conjunctival deficiency (Figure 5). The surgical approach depends on the severity of the symblepharon.[68,88,94,95]

In both mild and moderate symblephara, multiple observational studies have demonstrated that the fornix can be reconstructed with the help of amniotic membrane transplantation to the denuded surfaces.[68,73,96] Amniotic membrane can be sutured or glued to the surgical site. In addition, antimetabolites such as mitomycin-C (MMC) or 5-fluorouracil can be

simultaneously applied to the subconjunctival forniceal area to decrease the chance of recurrent forniceal shrinkage.[96]

In severe and extensive symblepharon or ankyloblepharon formation, new mucosal tissue must be transplanted. In cases of unilateral injury, an autologous conjunctival graft from the fellow eye can be used to replace destroyed conjunctiva.[97] In bilateral or extensive disease, mucosal membrane grafts (**MMG**s) may be necessary for full fornix reconstruction and restoration of normal lid-globe relationships.[98–100] Recently, cultivated oral mucosal epithelial transplantation (**COMET**) has been reported for ocular surface reconstruction. The advantage of COMET is that the transplanted epithelial sheet contains stem cells that help to reconstruct the corneal surface and maintain the integrity of the ocular surface.[98]

In addition, some authors advocate for the use of nasal mucosa rather than buccal mucosa in order to replenish the mucus-secreting capabilities of the ocular surface.[101] In addition to surgical intervention, the most important element in the success of eyelid and fornix reconstruction is the control of ocular surface inflammation, which drives the cicatricial process. It is generally recommended that surgical intervention be delayed as long as possible in order to avoid surgery on “hot” eyes.[102] In eyes with chronic inflammation, treatment with systemic immunosuppression is advised in preparation for surgery.[103] Oral prednisone on a tapering dose along with mycophenolate may be started several months before surgery; however, severe inflammation may require additional or stronger agents. Moreover, the use of systemic steroids in the perioperative period helps to mitigate postoperative inflammation and improve surgical success rates.[104]

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. However, the development of glaucoma may be partially counteracted by ciliary body necrosis in deeply penetrating alkali injuries.[92] In addition, other 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.

Secondary glaucoma is common following a severe chemical injury, with an estimated incidence of over 20%; however it may go unrecognized since the focus of care is often on the ocular surface.[105] Tsai et al diagnosed glaucoma in more than 50% of eyes in patients with severe ocular surface disease caused by ocular chemical or thermal injuries.[105] Lin et al identified an association between glaucoma and the severity of the ocular chemical injury: 84% of eyes with ocular chemical injuries R-H grade III or higher required long-term glaucoma medication.[92] In addition, glaucoma can occur after therapeutic corneal procedures, with published incidences ranging from 10% to over 50%.[92]

Management of glaucoma secondary to ocular chemical injury is challenging.[92,106,107] While 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. Accordingly, procedural interventions are generally considered earlier in these patients.

Cyclophotocoagulation may also be indicated, particularly in cases with advanced conjunctival shrinkage and scar formation. Despite the prognostic importance of glaucoma in these patients, no prospective studies evaluating the utility of various IOP treatment strategies have been performed to date.

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. In LSCD, 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 (Figure 6A and B). 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.[108]

Treatment depends on the extent of the injury and the involvement of the central cornea. Many patients with central cornea-sparing partial LSCD can be managed with conservative measures, such as nonpreserved lubrication and autologous serum eye drops.[77,109–111] Surgical management of partial LSCD may be considered in cases with central cornea involvement.[111] Sectoral conjunctivalization of the cornea may be effectively managed in select cases with sequential sector conjunctival epitheliectomy (**SSCE**) or AMT that may mitigate or prevent recurrent conjunctival ingrowth.[61,62,68,112,113]

Limbal stem cell transplantation (**LSCT**) may be considered for patients with more extensive corneal conjunctivalization.[103,112,114–120] LSCT is not recommended during active inflammation and should be delayed until ocular surface inflammation has subsided or is well controlled with medications. In addition, all eyelid abnormalities (e.g., entropion, trichiasis, symblepharon) should be addressed before considering LSCT (Figure 7).[103,115,116,121–124]

Limbal stem cells can be harvested from autologous or nonautologous sources.[103,125–129] A conjunctival limbal autograft (**CLAU**) taken from the healthy fellow eye is considered the most effective surgical procedure in patients with total unilateral LSCD. It produces excellent results, often with complete regression of corneal neovascularization such that successful re-epithelialization and functional vision is achieved in 80% to 90% of patients (Figure 8).[130,131] 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.[100,120,132–139] Pooling the results of previous studies, the overall success rate is estimated to be 72% of 720 eyes while 63% had ≥2 lines of improvement in visual acuity at last follow-up compared to baseline.[140]

Living-related conjunctival limbal allograft (**lr-CLAL**) and keratolimbal allograft (**KLAL**) are surgical alternatives in patients with bilateral LSCD.[103,125–129] Lr-CLAL utilizes tissue from one eye (or occasionally both eyes) of a patient's first-degree blood relative, a method that benefits from fresh tissue that has a strong genetic similarity to the patient. Lr-CLAL

also has the advantage of providing viable conjunctival tissue, which may be used in patients with severe conjunctival deficiency. In comparison, KLAL, which utilizes cadaveric tissue, is more accessible and offers more stem cells because of larger clock hours of available graft tissue (Figure 9).

There are many additional surgical options for bilateral LSCD, including the Cincinnati procedure, which is a combination of lr-CLAL with KLAL.[141] COMET or allogeneic CLET are other surgical options.[142–146] 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.[147] In addition, another variation of LSCT has been described in which a 2 × 2 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.[148]

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.[103,116,122,123] Close collaboration with an organ transplant team is generally required for the optimal management of the immunosuppression regimen and monitoring of its associated side effects.[149]

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).[121,124] 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.[124] Ocular surface reconstruction using different tissue engineering methods is an emerging option that is currently an active area of research.[150–153]

D. Corneal Transplantation

Conventional penetrating keratoplasty (**PK**) or deep anterior lamellar keratoplasty (**DALK**) can be performed for visual rehabilitation in patients with extensive stromal scarring after chemical injury.[154] In cases of partial LSCD with opacification of the central cornea, primary PK or DALK may be adequate; however, 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.[155] 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 (Figure 10).[156] Studies show that 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 nonstaged procedures. Long-term outcomes similarly favor staged procedures; the 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.[102,157,158]

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.[159–164] Currently, the Boston Type 1 keratoprosthesis (**B1-KPro**) is the most widely used device for restoring vision in patients who have failed previous corneal procedures.[159,165] Placement of a keratoprosthesis with or without a shunt may be considered 6 months after inflammation subsides (Figure 11).[106,166] The B1-KPro study group found excellent anatomical retention in patients with ocular chemical injuries: 94% after 1 year and 89% after 2 years.[167]

The ideal candidate for keratoprosthesis implantation must be amenable to long-term risks, the need for life-long regular follow-up, adherence to daily antibiotic prophylaxis, and other chronic maintenance issues.[160,162,163] Reported long-term complications include retroprosthetic membrane formation, IOP elevation and/or glaucoma progression, sterile corneal stromal necrosis or corneal thinning, infectious keratitis, persistent epithelial defect, retinal detachment, sterile uveitis/vitritis, and infectious endophthalmitis.[168–171] Most of these adverse events can be prevented or successfully treated with current postoperative management practices. However, glaucoma is an irreversible process and occurs with greater frequency in patients with chemical injuries. Accordingly, early detection and treatment of elevated IOP are of particular importance in this population. Coupling the baseline incidence of glaucoma in chemical burn patients with the high risk of progression as a result of B1-KPro implantation, we recommend consideration of a LSCT procedure prior to use of a keratoprosthesis in appropriate patients.

The Boston Type 2 keratoprosthesis (**B2-KPro**) and the osteo-odonto-keratoprosthesis (**OOKP**) are last resort options usually reserved for patients with bilateral corneal blindness in the setting of severe dryness and keratinization.[172,173] Indications include severe chemical or physical injury with loss of lids. In patients with a residual tear film, other surgical interventions (e.g., ocular surface reconstruction with stem cell transplant) should be considered prior to B2-KPro or OOKP implantation.[174]

VI. Future Horizons

Most patients with mild-to-moderate chemical injuries can achieve a stable ocular surface and functional visual acuity with current management strategies. However, most severe chemical injuries have an unfavorable prognosis. A substantial number of patients with severe injuries go on to develop significant corneal and limbal stem cell disease, often 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. Therefore, more effective treatments are needed to prevent the most visually disabling sequelae of chemical injuries.

The two upcoming therapeutic strategies described below may potentially improve the outcomes of our treatment in chemical injuries.

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.[175–179] Accordingly, the prevention and reversal of CNV is of utmost importance for improving the visual outcome after a chemical injury. The pathophysiologic mechanism of corneal angiogenesis (hemangiogenesis and lymphangiogenesis) after chemical injury is multifactorial, involving inflammation and production of angiogenic factors, as well as loss of the natural anti-angiogenic milieu. A number of important angiogenic factors, such as basic fibroblast growth factor, vascular endothelial growth factors (**VEGF**s), and transforming growth factor-α and -β, placenta growth factor, IL-1, TNF-α, IL-8, monocyte chemoattractant-1, MMPs, and platelet activating factor have been implicated in corneal neovascularization.[175] In addition, loss of anti-angiogenic factors such as soluble fms-like tyrosine kinase-1, angiostatin, endostatin, restin, neostatin, thrombospondins, pigment epithelium-derived factor, arrestin, canstatin, tumstatin, and angiopoetin-2 likely play an important role in the breakdown of corneal avascular privilege.[175,180]

Numerous agents with anti-angiogenic effects have shown potential benefit in inhibiting corneal neovascularization in experimental models of chemical injury.[181–204] In recent years, the availability of anti-VEGF agents (e.g., bevacizumab, ranibizumab, pegaptanib and aflibercept) and their success in treating retinal vascular disorders has opened the possibility of their clinical use for CNV.[202,205–207] Both topical and subconjunctival bevacizumab and ranibizumab have shown beneficial effects in reducing CNV in various clinical conditions.[203] However, at this time, there are no reports of these agents being used in patients immediately after chemical injury.

While the clinical effects of anti-VEGF therapy in CNV have been modest, there are also several limitations and potential safety concerns with their use in the setting of chemical injury. In particular, inhibiting pleiotrophic cytokines such as VEGF may adversely affect the overall wound healing response. For example, anti-VEGF therapy can potentially increase the likelihood of a corneal melt in the setting of the most severe injuries.[208] Accordingly, more studies are needed to define their role in the management of ocular surface chemical injuries.

B. Stem Cell-based Therapy

In the last decade, there has been intense focus on stem cells for regenerative therapies. Many sources of stem cells, including bone marrow, fat, umbilical cord, dental pulp, hair follicle, and induced pluripotent stem cells, have shown promising results in experimental models of ocular surface injury.[209,210] Among these, mesenchymal stem cells (**MSC**s) hold the most promise for clinical application. Recently, there has been tremendous progress in the use of MSCs for tissue repair and regeneration.[211,212] MSCs are found in most adult tissues, including the cornea and limbus, and play an important role in tissue repair and maintenance. A number of clinical trials aimed at evaluating the safety and efficacy of MSCs

in the promotion of cardiac tissue regeneration, modulation of systemic immune diseases, and healing of soft tissue injuries are currently underway.[211–217] In animal models of chemical injury, MSCs have been shown to accelerate corneal wound healing, attenuate inflammation, and modulate corneal neovascularization.[209,218–227] These effects have been shown to be mediated in part through secreted factors such as TSG-6.[228] Overall, MSC-based therapies are likely to be beneficial for management in both the acute phase after chemical injury to help control inflammation and chronically to help restore a more normal ocular surface environment.

VII. Summary

Chemical injuries can have devastating consequences for the ocular surface and periocular structures. The overall goal of treatment is restoration of normal ocular surface anatomy, a process that begins with immediate treatment, followed by measures to control inflammation, and ultimately reconstructive procedures to restore a normal ocular surface environment. With advancements in regenerative medicine, the clinical outcomes are expected to further improve.

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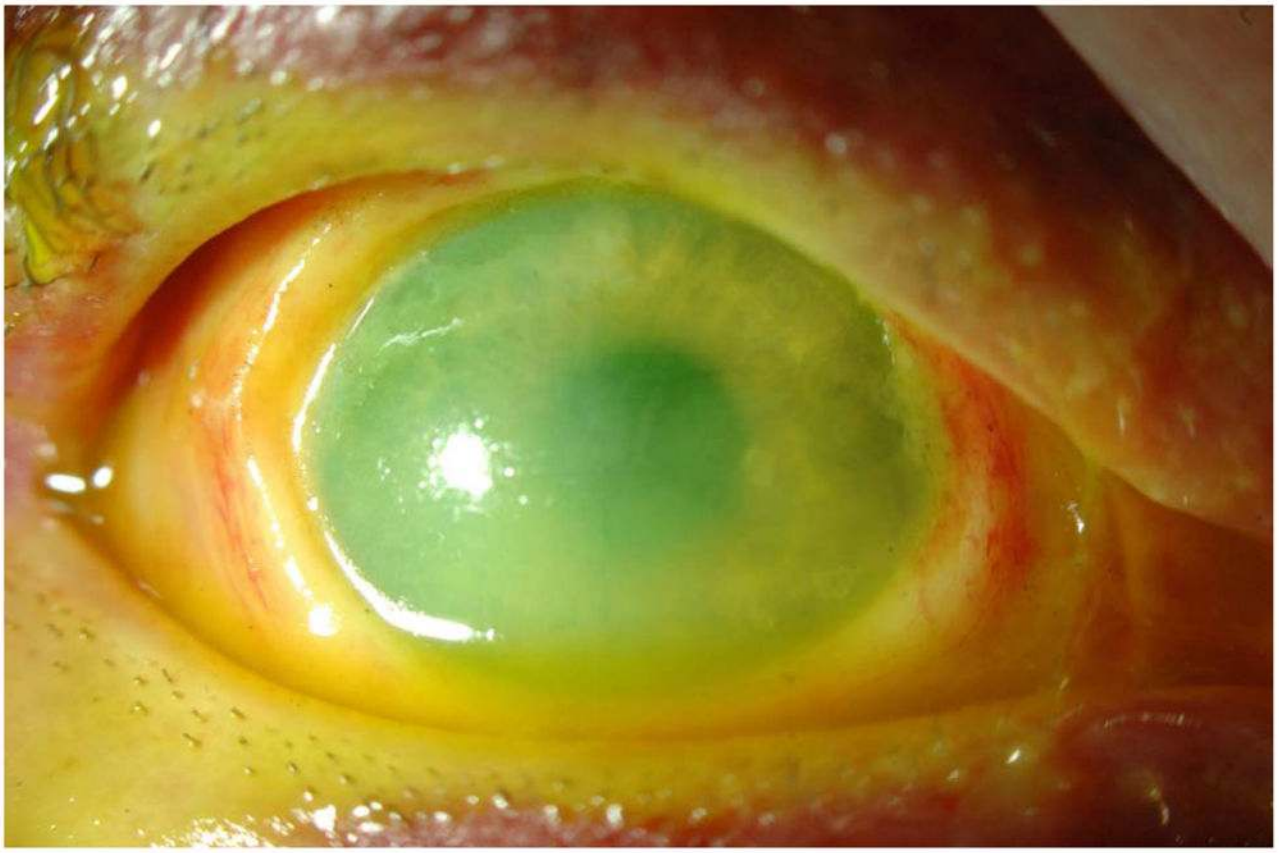


Figure 1.
Eye after combined chemical and thermal injury to the lids and ocular surface due to an explosion of a pyrotechnic device. There is total corneal epithelial defect and 360°limbal ischemia (Roper-Hall grade IV and Dua's grade VI).

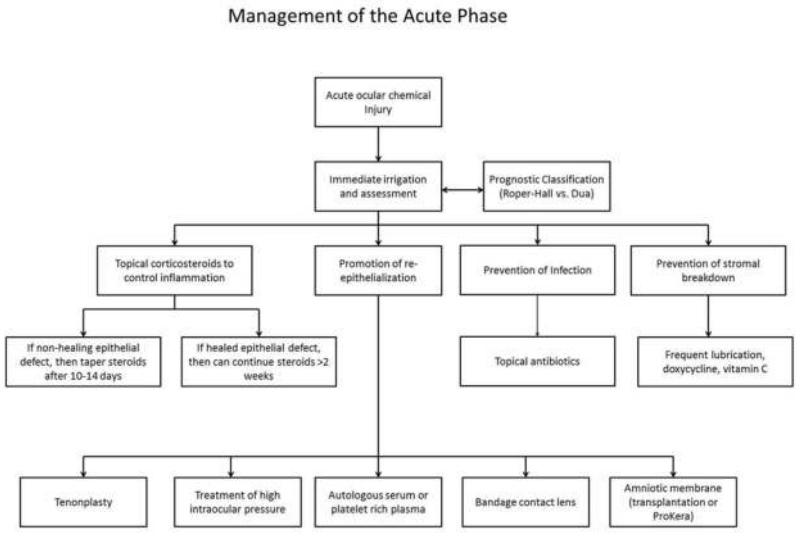


Figure 2.
Algorithm for the management of acute phase after chemical burn.

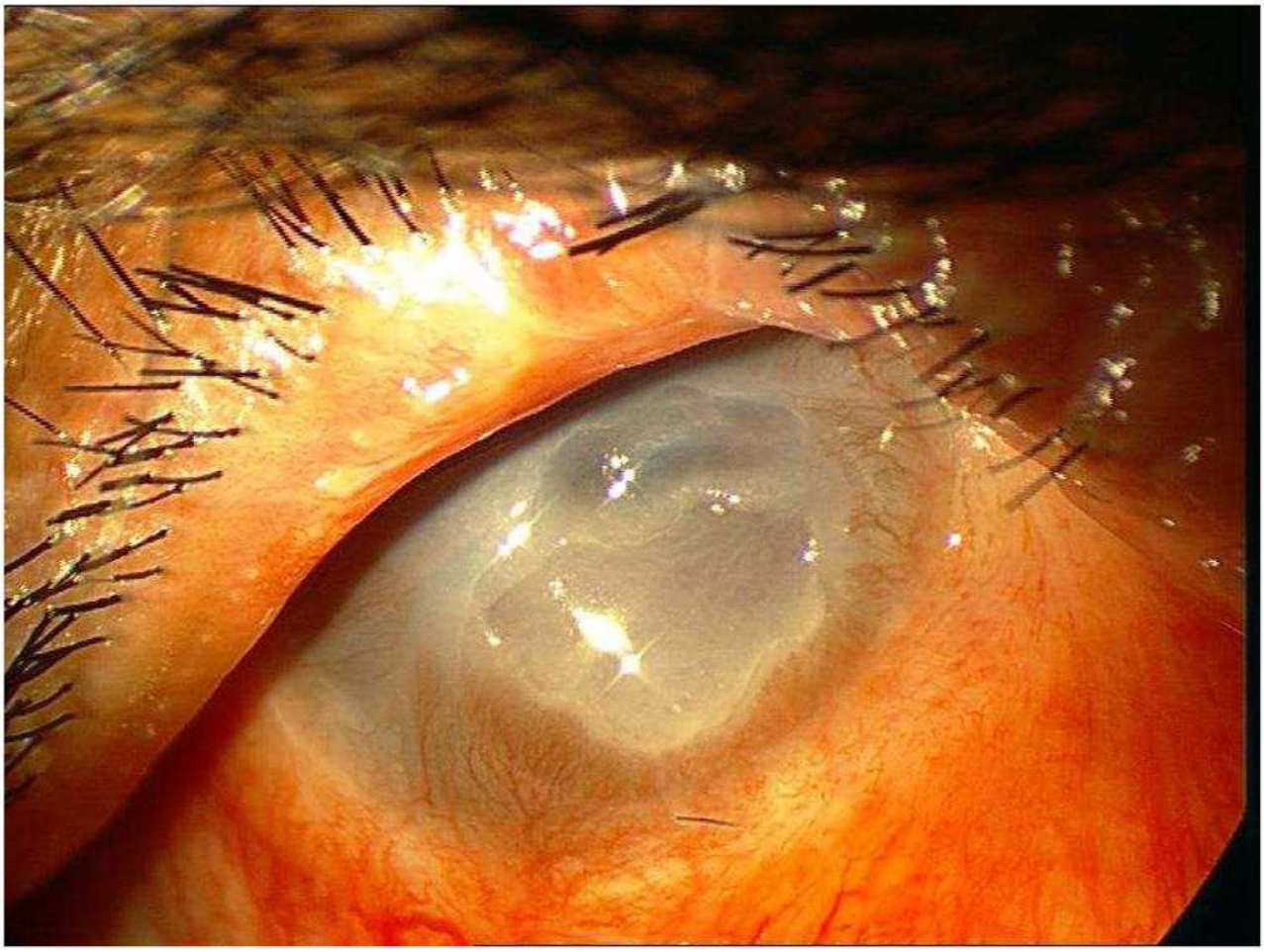


Figure 3.
Severe corneal thinning after severe chemical burn.

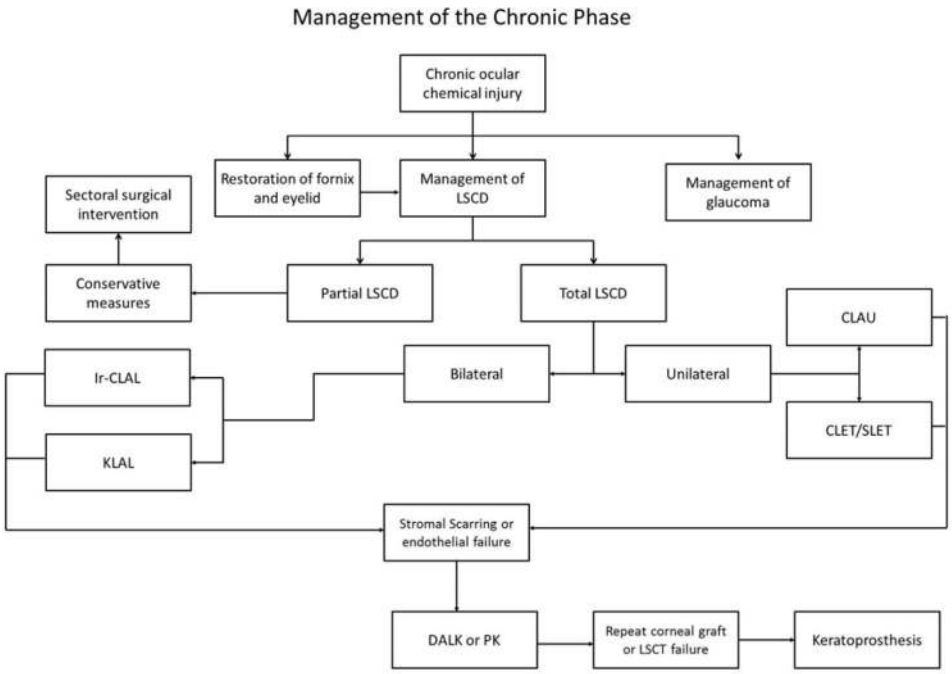


Figure 4.
Algorithm for the management of chronic phase after chemical burn.

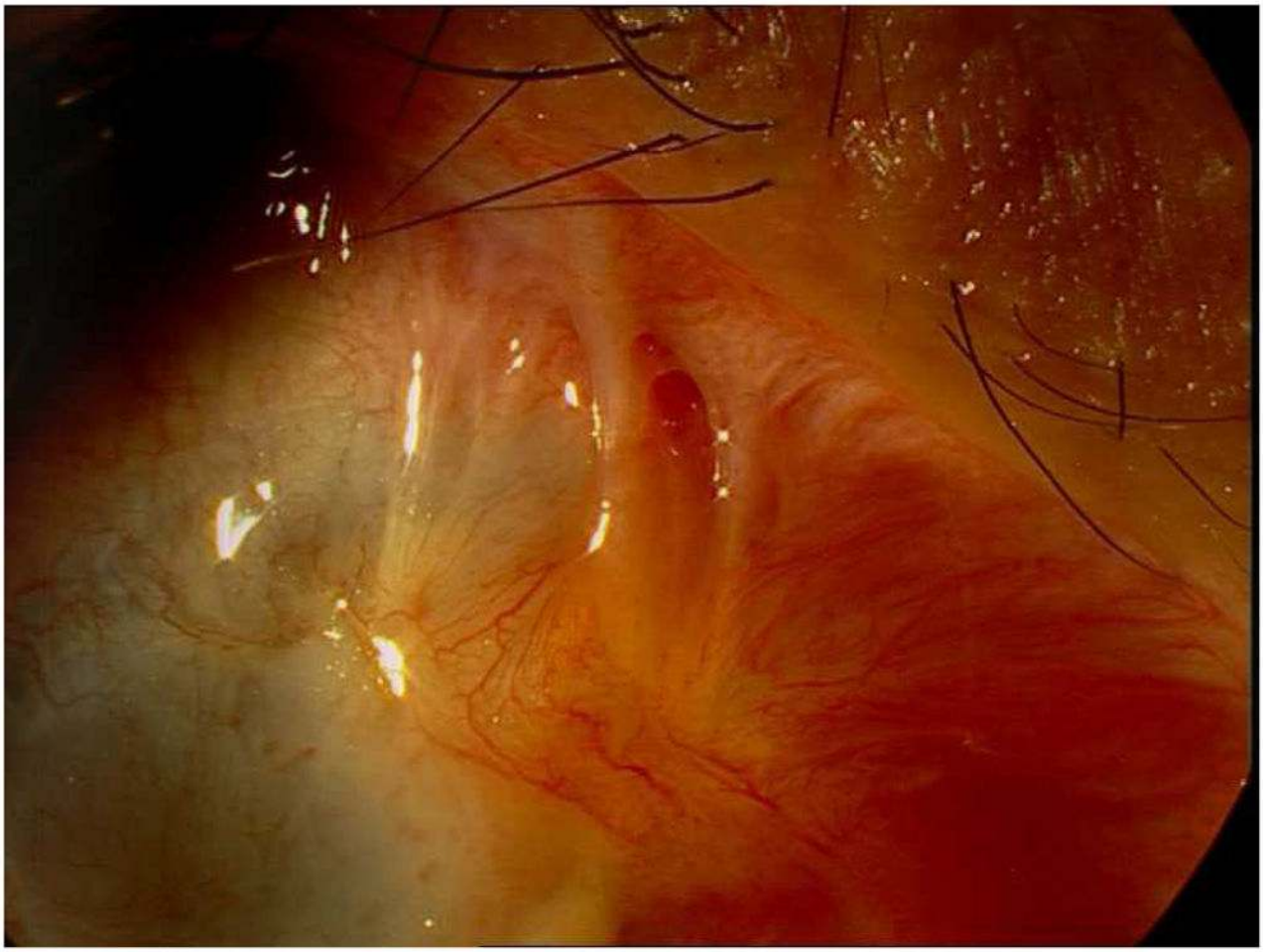
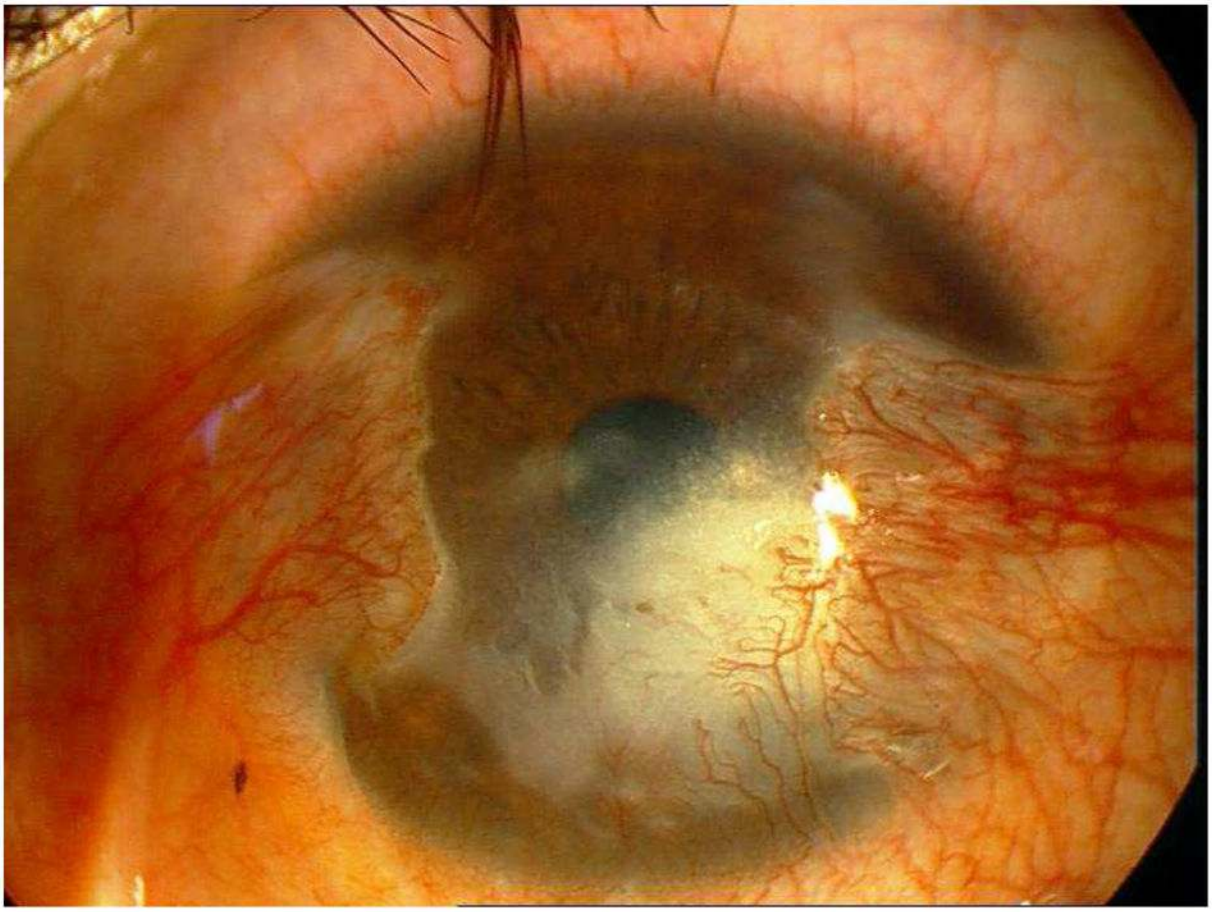


Figure 5.
Symblepharon: Severe symblepharon formation.



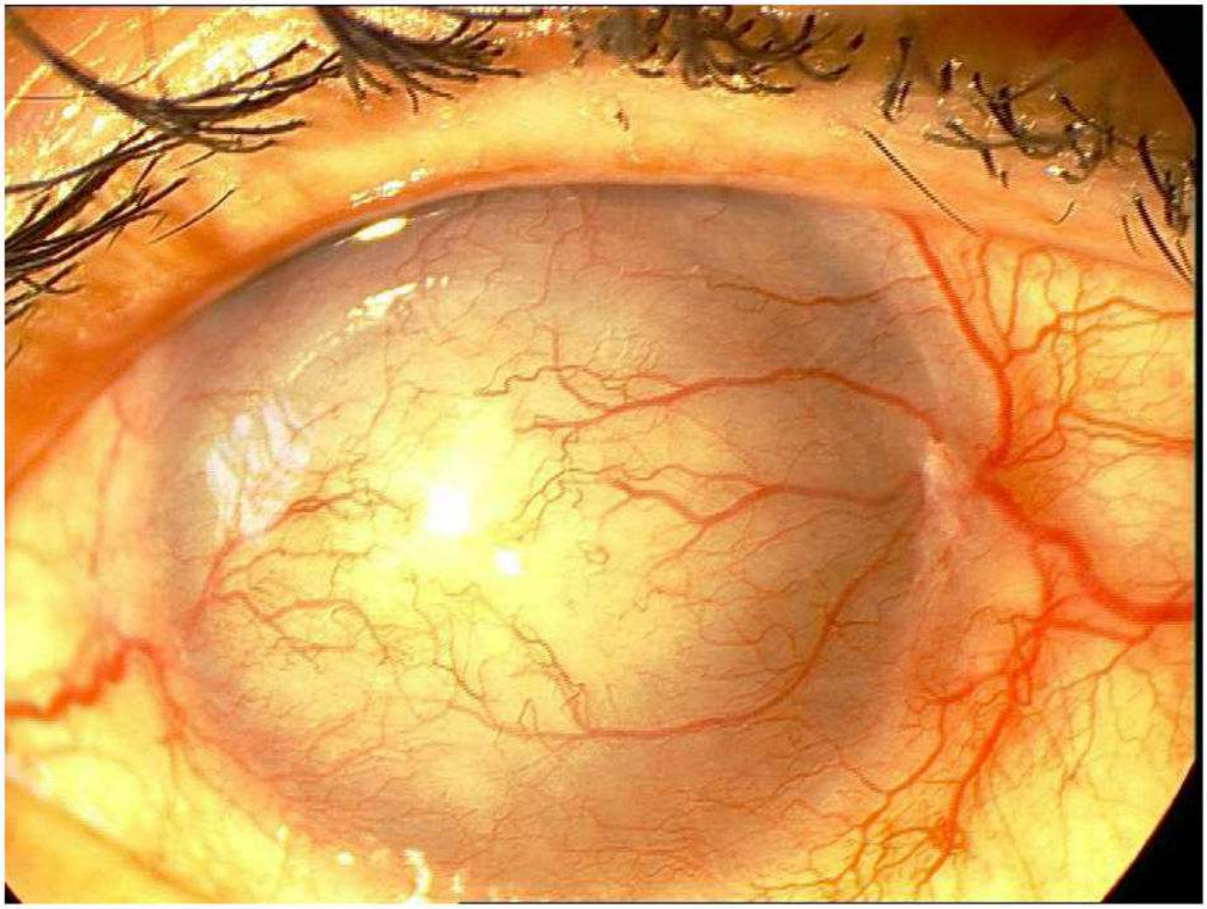


Figure 6.

A: Nasal and temporal pseudopterigia in a case with partial limbal stem cell deficiency due to severe alkaline chemical burn. B: Total LSCD in a case with severe chemical burn.

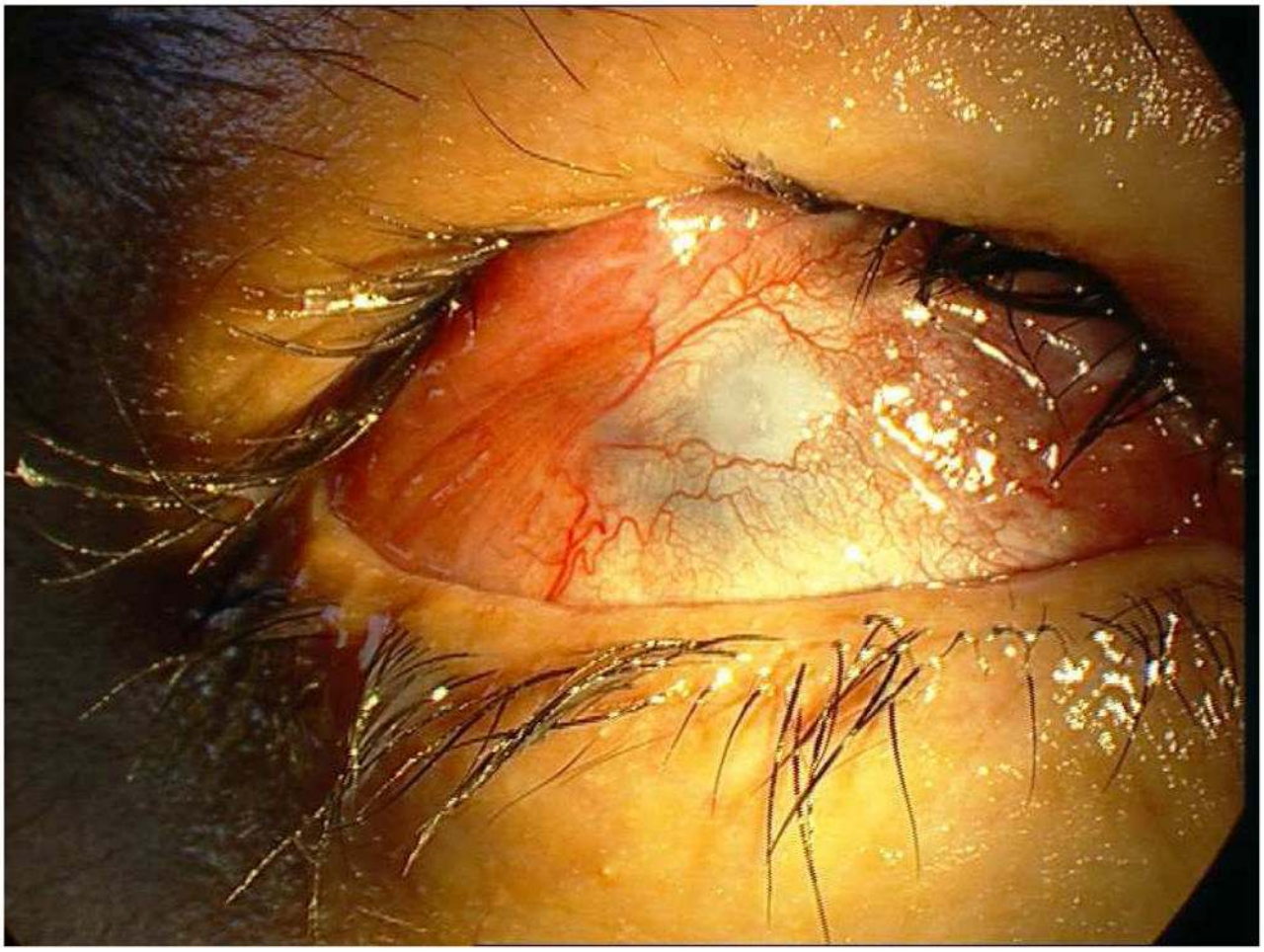


Figure 7.
Upper lid entropion and trichiasis in a case with total LSCD due to severe alkaline chemical burn.

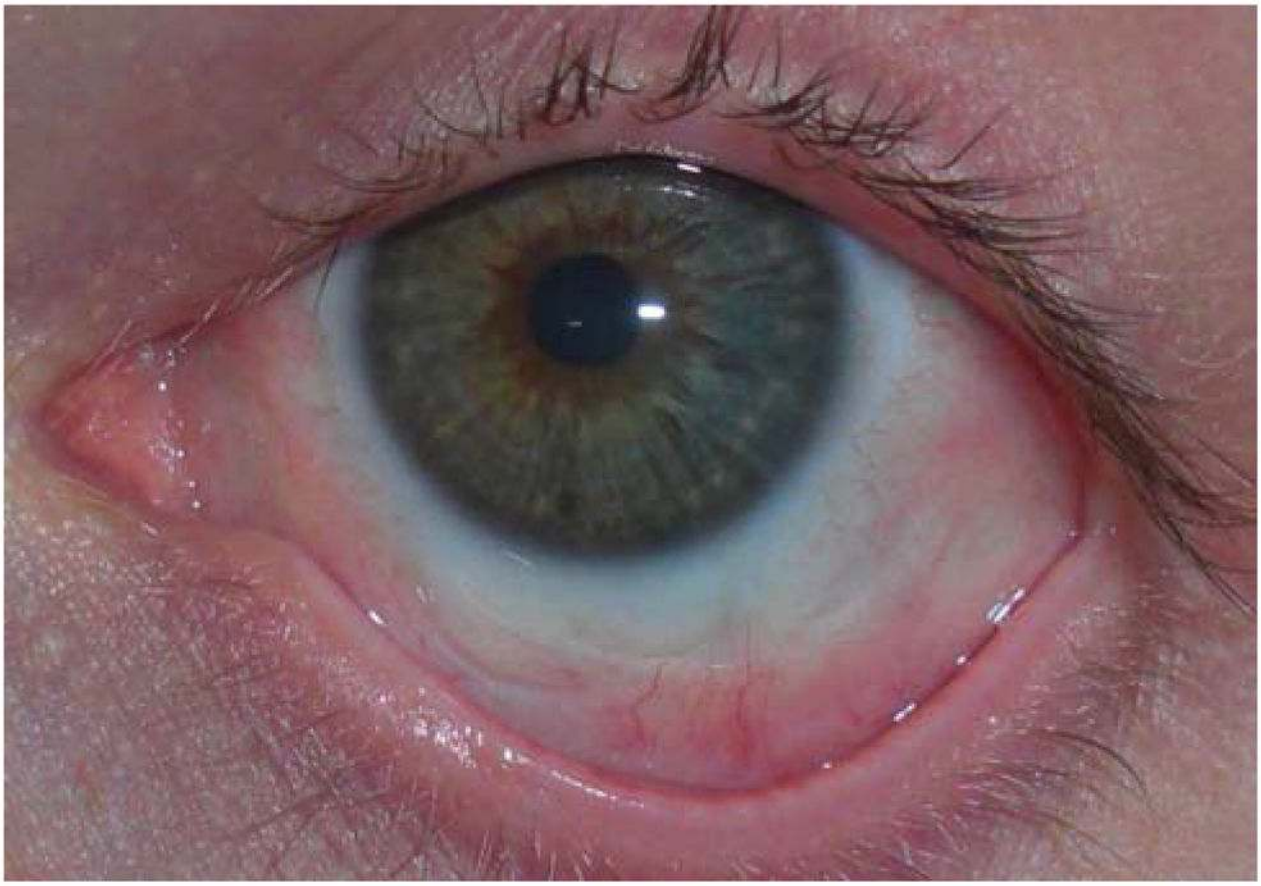


Figure 8.
Patient with total LSCD after chemical burn who was successfully treated with CLAU (2 years after surgery).

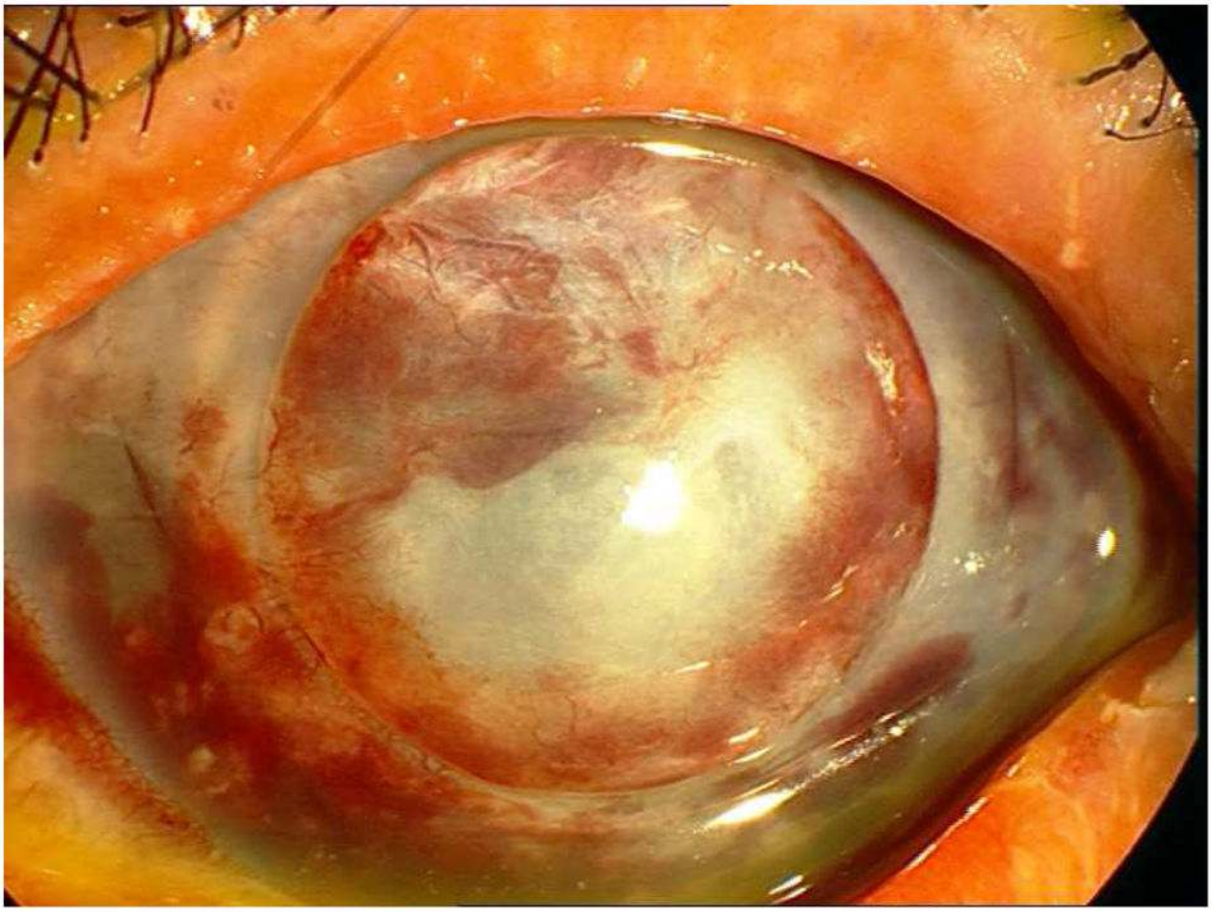


Figure 9.
Keratolimbal allograft surgery in a case with total limbal stem cell deficiency due to acidic chemical burn.

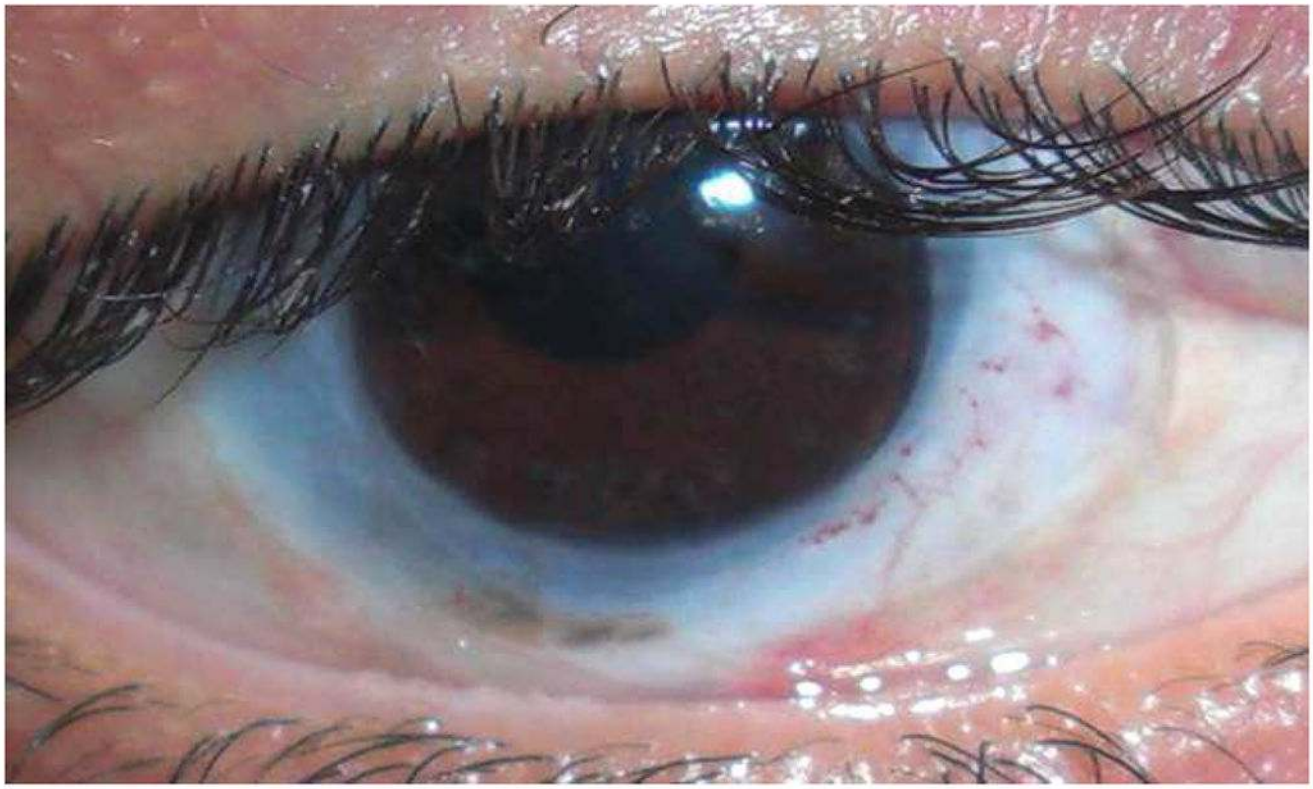


Figure 10.
Patient with total LSCD after chemical burn who underwent KLAL and PKP with systemic immunosuppression (18 months after surgery).

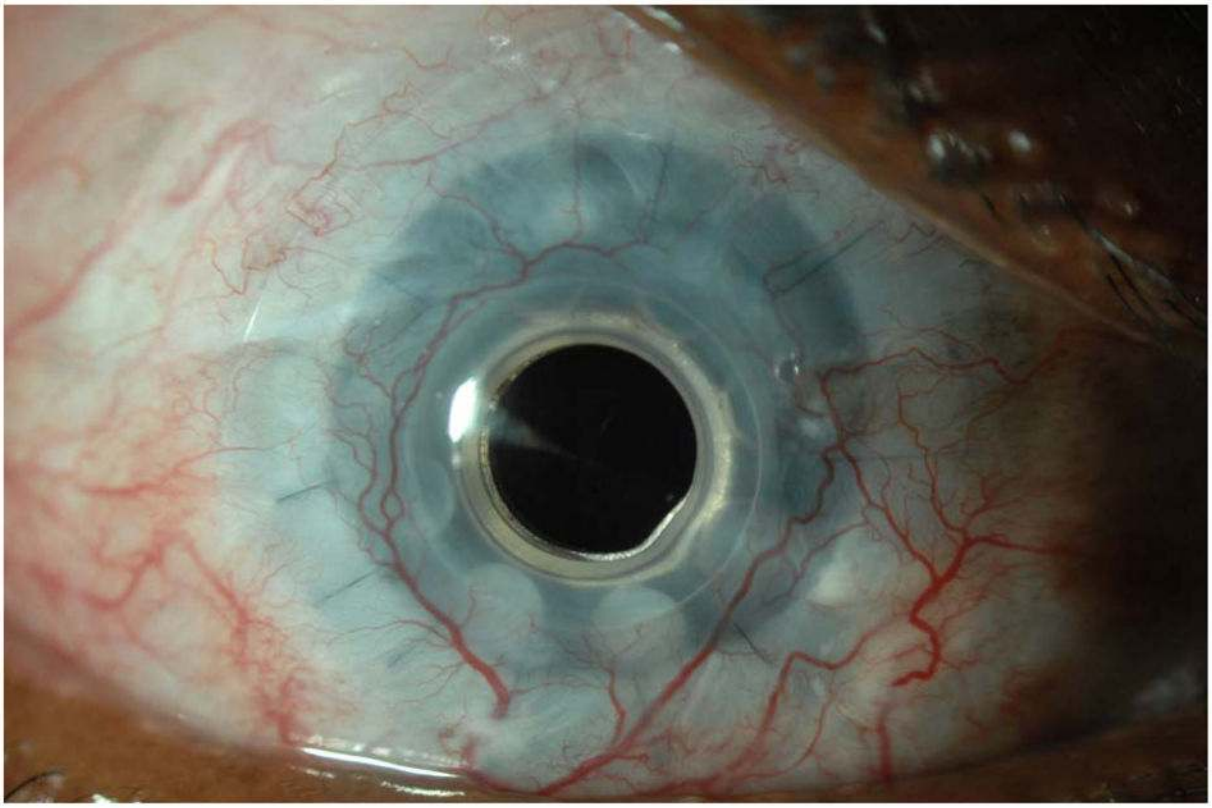


Figure 11.
Boston Type I keratoprosthesis in a patient with LSCD due to chemical injury (Courtesy of Dr. Maria S. Cortina, University of Illinois at Chicago).

Table 1

Roper-Hall classification of the severity of ocular surface burns.

Grade	Prognosis	Cornea	Limbal Ischemia
I	Good	Corneal epithelial damage	None
II	Good	Corneal haze, iris details visible	$<\frac{1}{3}$
III	Guarded	Total epithelial loss, stromal haze, iris details obscured	$\frac{1}{3}\ to\ \frac{1}{2}$
IV	Poor	Cornea opaque, iris and pupil obscured	$>\frac{1}{2}$

Table 2

Dua's classification of the severity of ocular surface burns.

Grade	Prognosis	Limbal Involvement (clock hours)	Conjunctival Involvement (%)*	Analogue Scale**
I	Very good	0	0	$\frac{0}{0}$
II	Good	≤3	≤30	$\frac{0.1\ to\ 3}{1\ to\ 29.9}$
III	Good	>3 to 6	>30 to 50	$\frac{3.1\ to\ 6}{31\ to\ 50}$
IV	Good to guarded	>6 to 9	>50 to 75	$\frac{6.1\ to\ 9}{51\ to\ 75}$
V	Guarded to poor	>9 to <12	>75 to <100	$\frac{9.1\ to\ 11.9}{75.1\ to\ 99.9}$
VI	Very poor	12 (Total limbus)	100 (Total conjunctiva)	$\frac{12}{100}$

*Refers only to bulbar conjunctiva (up to and including conjunctival fornices).

**The analog scale is calculated through division of limbal involvement by conjunctival involvement.

Table 3

Irrigation solutions for the immediate phase management of ocular chemical injuries.

Irrigation Solution*	Proposed Advantages	Grade of Available Evidence**	Evidence-based Recommendations
Tap water (H_2O)	Ubiquitous availability	C	The choice of most effective solution is equivocal. Published reports are limited to in vivo experiments in animal models and, at best, small observational studies with significant limitations. Given the importance of prompt and continuous treatment, the most immediately available and sufficiently abundant solution should be utilized.
Phosphate buffer	Correction of pH	D	
Purpose-designed solutions (e.g. NS, LR, BSSP)	Isotonic to stroma Patient comfort (BSSP)	C	
Amphoteric solutions (e.g. Diphoterine®)	Hypertonic to stroma Rapid pH correction Non-specific chelation Faster re-epithelialization (mild injuries only)	C	

NS = normal saline; LR = lactated ringers; BSSP = balanced saline solution plus *Rinsing with an aqueous solution should be initiated immediately and continued until confirmation of adequate neutralization of the tear film pH by a health care professional.

** The grades of evidence are based upon the rating scale (A to D) put forth by the Oxford Centre for Evidence-based Medicine.

Table 4

Therapies for the acute phase management of ocular chemical injuries.

Therapeutic Aim	Treatment	Grade of Available Evidence*	Evidence-based Recommendations	Suggested Regimen
Reduction of Inflammation	Corticosteroids	C	Retrospective cohort studies suggest benefit with topical treatment in non-severe injuries.	Intense therapy ≥7 days with subsequent taper
Stromal Breakdown Prophylaxis	Tetracyclines	D	Literature is limited to animal studies and expert opinion.	Tetracycline 250 mg PO QID
	Citric acid	C	A single cohort study suggests a role as an adjunct in moderate injuries.	Topical Citrate 10% hourly or bihourly
	Ascorbic acid	C	Retrospective cohort studies suggest benefit as an adjunct to corticosteroids.	Ascorbate 0.5 to 2 g QID PO + topical Ascorbate 10% hourly or bihourly
Promotion of Epithelial Repair	Bandage contact lens (BCL)	C	Retrospective cohort studies suggest benefit but are limited to non-chemical injuries.	Daily wear of soft BCL or PROSE scleral lens (in severe cases)
	Amniotic membrane transplantation	C	Multiple case series suggest benefit in severe injuries.	Perform within 1 week of injury
	Autologous serum	C	A randomized controlled trial suggested benefit in non-mild injuries.	Topical platelet-rich plasma 10x QD
	Tenonplasty	C	Observational studies suggest benefit in patients with scleral ischemia or melt.	As needed upon recognition of scleral pathology Topical agents ±
	Treatment of high intraocular pressure	D	Extrapolation from cohort studies suggests benefit in all patients.	procedural intervention (e.g. paracentesis)

*The grades of evidence are based upon the rating scale (A to D) put forth by the Oxford Centre for Evidence-based Medicine.

Table 5

Therapies for the chronic phase management of ocular chemical injuries.

Pathology	Treatment	Grade of Available Evidence*	Evidence-based Recommendations
Fornix and Eyelid Disease	AMT + anti-metabolite (e.g. MMC, 5-FU)	C	Multiple interventional case series suggest benefit in patients with mild to moderate disease.
	MMG	C	Small interventional case series suggest benefit in patients with severe disease.
Glaucoma	Standard algorithm	C	Observational results suggest benefit. CPC may be of particular utility given the complication profile associated with tube placement in patients with chemical injury.
Limbal Stem Cell Deficiency	Pharmacotherapy ± sectoral surgical intervention	C	Multiple case series suggest reversibility of partial LSCD with conservative measures. In patients with involvement of the central cornea, sectoral procedures (e.g. partial LSCT) have also demonstrated benefit.
	CLAU, CLET	C	Multiple interventional case series demonstrate high rates of visual recovery in patients with unilateral total LSCD.
	KLAL, lr-CLAL	C	Multiple interventional case series suggest benefit in patients with bilateral total LSCD. Long-term results are favorable if adequate immunosuppression is used.
	Keratoprosthesis	C	Multiple interventional case series suggest benefit as salvage therapy after failed LSCT.
Corneal Opacification	PK, DALK	C	Multiple case series suggest benefit for visual rehabilitation. A staged approach with antecedent LSCT is advised in patients with total LSCD.
	Keratoprosthesis	C	Multiple interventional case series suggest benefit as salvage therapy after failed corneal transplantation.

AMT = amniotic membrane transplantation; MMC = mitomycin-C; 5-FU = 5-fluorouracil; MMG = mucous membrane graft; CPC = cyclophotocoagulation; LSCD = limbal stem cell deficiency; LSCT = limbal stem cell transplantation; CLAU = conjunctival limbal autograft; CLET = cultivated limbal epithelial transplantation; KLAL = keratolimbal allograft; lr-CLAL = living-related conjunctival limbal allograft; PK = penetrating keratoplasty; DALK = deep anterior lamellar keratoplasty

*The grades of evidence are based upon the rating scale (A to D) put forth by the Oxford Centre for Evidence-based Medicine.