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Current and Upcoming Therapies for Ocular Surface Chemical Injuries

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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

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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 Ballen⁹ 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 (MMPs), 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 (MMGs) 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 LSCT, including the Cincinnati procedure, which is a combination of Ir-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 LSCT.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 LSCT. 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 LSCT 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 LSCT 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 (VEGFs), 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 angiopoietin-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 (MSCs) 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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References

1. Eslani M, Baradaran-Rafii A, Movahedan A, Djalilian AR. The ocular surface chemical burns. *J Ophthalmol*. 2014; 2014:196827. [PubMed: 25105018]
2. Wagoner MD. Chemical injuries of the eye: current concepts in pathophysiology and therapy. *Surv Ophthalmol*. 1997; 41:275–313. [PubMed: 9104767]
3. Pfister R. Chemical injuries of the eye. *Ophthalmology*. 1983; 90:1246–53. [PubMed: 6657201]
4. Schrage NF, Langefeld S, Zschocke J, et al. Eye burns: an emergency and continuing problem. *Burns*. 2000; 26:689–99. [PubMed: 11024601]
5. McCulley JP. Ocular hydrofluoric acid burns: animal model, mechanism of injury and therapy. *Trans Am Ophthalmol Soc*. 1990; 88:649–84. [PubMed: 2095035]
6. Kirkpatrick JJ, Enion DS, Burd DA. Hydrofluoric acid burns: a review. *Burns*. 1995; 21:483–93. [PubMed: 8540973]
7. Dua HS, King AJ, Joseph A. A new classification of ocular surface burns. *Br J Ophthalmol*. 2001; 85:1379–83. [PubMed: 11673310]
8. Roper-Hall MJ. Thermal and chemical burns. *Trans Ophthalmol Soc U K*. 1965; 85:631–53. [PubMed: 5227208]
9. Ballen PH. Treatment of chemical burns of the eye. *Eye Ear Nose Throat Mon*. 1964; 43:57–61.
10. Singh P, Tyagi M, Kumar Y, et al. Ocular chemical injuries and their management. *Oman J Ophthalmol*. 2013; 6:83–6. [PubMed: 24082664]
11. Lin A, Patel N, Yoo D, et al. Management of ocular conditions in the burn unit: thermal and chemical burns and Stevens-Johnson syndrome/toxic epidermal necrolysis. *J Burn Care Res*. 2011; 32:547–60. [PubMed: 21799437]
12. Fish R, Davidson RS. Management of ocular thermal and chemical injuries, including amniotic membrane therapy. *Curr Opin Ophthalmol*. 2010; 21:317–21. [PubMed: 20467317]
13. Kosoko A, Vu Q, Kosoko-Lasaki O. Chemical ocular burns: a case review. *Am J ClinMed*. 2009; 6:41–69.

14. Spector J, Fernandez WG. Chemical, thermal, and biological ocular exposures. *Emerg Med Clin North Am.* 2008; 26:125–36. [PubMed: 18249260]
15. Gupta N, Kalaivani M, Tandon R. Comparison of prognostic value of Roper Hall and Dua classification systems in acute ocular burns. *Br J Ophthalmol.* 2011; 95:194–8. [PubMed: 20805137]
16. McCulley, JP. Chemical injuries. In: Smolin, G.; Thoft, R., editors. *The Cornea: Scientific Foundation and Clinical Practice.* Boston, MA: Little, Brown and Co; 1987.
17. Rodrigues Z. Irrigation of the eye after alkaline and acidic burns. *Emerg Nurse.* 2009; 17:26–9.
18. Gerard M, Merle H, Chiambaretta F, et al. An amphoteric rinse used in the emergency treatment of a serious ocular burn. *Burns.* 2002; 28:670–3. [PubMed: 12417163]
19. Salzman M, O'Malley RN. Updates on the evaluation and management of caustic exposures. *Emerg Med Clin North Am.* 2007; 25:459–76. [PubMed: 17482028]
20. Paterson CA, Pfister RR, Levinson RA. Aqueous humor pH changes after experimental alkali burns. *Am J Ophthalmol.* 1975; 79:414–9. [PubMed: 235843]
21. Chau JP, Lee DT, Lo SH. A systematic review of methods of eye irrigation for adults and children with ocular chemical burns. *Worldviews EvidBased Nurs.* 2012; 9:129–38.
22. Ikeda N, Hayasaka S, Hayasaka Y, Watanabe K. Alkali burns of the eye: effect of immediate copious irrigation with tap water on their severity. *Ophthalmologica.* 2006; 220:225–8. [PubMed: 16785752]
23. Maurice DM. The permeability to sodium ions of the living rabbit's cornea. *J Physiol.* 1951; 112:367–91. [PubMed: 14825218]
24. Shirzadeh E. Bilateral chemical burns of the cornea due to limewater: a specific case. *Iran Red Crescent Med J.* 2013; 15:11–2. [PubMed: 23487571]
25. Schrage NF, Schlossmacher B, Aschenbrenner W, Langefeld S. Phosphate buffer in alkali eye burns as an inducer of experimental corneal calcification. *Burns.* 2001; 27:459–64. [PubMed: 11451598]
26. Schrage NF, Kompa S, Haller W, Langefeld S. Use of an amphoteric lavage solution for emergency treatment of eye burns. First animal type experimental clinical considerations. *Burns.* 2002; 28:782–6. [PubMed: 12464478]
27. Rihawi S, Frentz M, Reim M, Schrage NF. Rinsing with isotonic saline solution for eye burns should be avoided. *Burns.* 2008; 34:1027–32. [PubMed: 18485603]
28. Al-Moujahed A, Chodosh J. Outcomes of an algorithmic approach to treating mild ocular alkali burns. *JAMA Ophthalmol.* 2015; 133:1214–6. [PubMed: 26226389]
29. Herr RD, White GL Jr, Bernhisel K, et al. Clinical comparison of ocular irrigation fluids following chemical injury. *Am J Emerg Med.* 1991; 9:228–31. [PubMed: 1850282]
30. Merle H, Donnio A, Ayeboua L, et al. Alkali ocular burns in Martinique (French West Indies) Evaluation of the use of an amphoteric solution as the rinsing product. *Burns.* 2005; 31:205–11. [PubMed: 15683694]
31. Hamill CE, Bozorg S, Peggy Chang HY, et al. Corneal alkali burns: a review of the literature and proposed protocol for evaluation and treatment. *Int Ophthalmol Clin.* 2013; 53:185–94. [PubMed: 24088945]
32. Saud EE, Moraes HV Jr, Marculino LG, et al. Clinical and histopathological outcomes of subconjunctival triamcinolone injection for the treatment of acute ocular alkali burn in rabbits. *Cornea.* 2012; 31(2):181–7. [PubMed: 22081154]
33. Brodovsky SC, McCarty CA, Snibson G, et al. Management of alkali burns : an 11-year retrospective review. *Ophthalmology.* 2000; 107:1829–35. [PubMed: 11013181]
34. Davis AR, Ali QK, Aclimandos WA, Hunter PA. Topical steroid use in the treatment of ocular alkali burns. *Br J Ophthalmol.* 1997; 81:732–4. [PubMed: 9422923]
35. Donshik PC, Berman MB, Dohlman CH, et al. Effect of topical corticosteroids on ulceration in alkali-burned corneas. *Arch Ophthalmol.* 1978; 96:2117–20. [PubMed: 214063]
36. Beams R, Linabery L, Grayson M. Effect of topical corticosteroids on corneal wound strength. *Am J Ophthalmol.* 1968; 66:1131–3. [PubMed: 5715619]

37. Reim M, Bahrke C, Kuckelkorn R, Kuwert T. Investigation of enzyme activities in severe burns of the anterior eye segment. *Graefes Arch Clin Exp Ophthalmol*. 1993; 231:308–12. [PubMed: 8319922]
38. Ralph RA. Tetracyclines and the treatment of corneal stromal ulceration: a review. *Cornea*. 2000; 19:274–7. [PubMed: 10832682]
39. Ling S, Li W, Liu L, et al. Allograft survival enhancement using doxycycline in alkali-burned mouse corneas. *Acta Ophthalmol*. 2013; 91:e369–78. [PubMed: 23387987]
40. Gabler WL, Creamer HR. Suppression of human neutrophil functions by tetracyclines. *J Periodontal Res*. 1991; 26:52–8. [PubMed: 1847418]
41. Seedor JA, Perry HD, McNamara TF, et al. Systemic tetracycline treatment of alkali-induced corneal ulceration in rabbits. *Arch Ophthalmol*. 1987; 105:268–71. [PubMed: 3813962]
42. Pfister RR, Nicolario ML, Paterson CA. Sodium citrate reduces the incidence of corneal ulcerations and perforations in extreme alkali-burned eyes--acetylcysteine and ascorbate have no favorable effect. *Invest Ophthalmol Vis Sci*. 1981; 21:486–90. [PubMed: 7275534]
43. Pfister RR, Haddox JL, Lank KM. Citrate or ascorbate/citrate treatment of established corneal ulcers in the alkali-injured rabbit eye. *Invest Ophthalmol Vis Sci*. 1988; 29:1110–5. [PubMed: 3417403]
44. Perry HD, Kenyon KR, Lamberts DW, et al. Systemic tetracycline hydrochloride as adjunctive therapy in the treatment of persistent epithelial defects. *Ophthalmology*. 1986; 93:1320–2. [PubMed: 3785891]
45. Pfister RR, Paterson CA. Ascorbic acid in the treatment of alkali burns of the eye. *Ophthalmology*. 1980; 87:1050–7. [PubMed: 7243199]
46. Pfister RR, Haddox JL, Dodson RW, Deshazo WF. Polymorphonuclear leukocytic inhibition by citrate, other metal chelators, and trifluoperazine. Evidence to support calcium binding protein involvement. *Invest Ophthalmol Vis Sci*. 1984; 25:955–70. [PubMed: 6430838]
47. Imanishi J, Kamiyama K, Iguchi I, et al. Growth factors: importance in wound healing and maintenance of transparency of the cornea. *Prog Retin Eye Res*. 2000; 19:113–29. [PubMed: 10614683]
48. Dillehay SM, Miller MB. Performance of Lotrafilcon B silicone hydrogel contact lenses in experienced low-Dk/t daily lens wearers. *Eye Contact Lens*. 2007; 33(6 Pt 1):272–7. [PubMed: 17993820]
49. Rosenthal P, Cotter J. The Boston Scleral Lens in the management of severe ocular surface disease. *Ophthalmol Clin North Am*. 2003; 16:89–93. [PubMed: 12683251]
50. Segal O, Barkana Y, Hourovitz D, et al. Scleral contact lenses may help where other modalities fail. *Cornea*. 2003; 22:308–10. [PubMed: 12792472]
51. Ruedemann AD Jr, Jardon F. Ten years experience with scleral lenses. *Trans Am Ophthalmol Soc*. 1970; 68:245–76. [PubMed: 5524207]
52. Kalwerisky K, Davies B, Mihora L, et al. Use of the Boston Ocular Surface Prosthesis in the management of severe periorbital thermal injuries: a case series of 10 patients. *Ophthalmology*. 2012; 119:516–21. [PubMed: 22133791]
53. Burns CL, Chylack LT Jr. Thermal burns: the management of thermal burns of the lids and globes. *Ann Ophthalmol*. 1979; 11:1358–68. [PubMed: 400375]
54. Shimmura S, Shimazaki J, Ohashi Y, Tsubota K. Antiinflammatory effects of amniotic membrane transplantation in ocular surface disorders. *Cornea*. 2001; 20:408–13. [PubMed: 11333331]
55. Dua HS, Gomes JA, King AJ, Maharajan VS. The amniotic membrane in ophthalmology. *Surv Ophthalmol*. 2004; 49:51–77. [PubMed: 14711440]
56. Bouchard CS, John T. Amniotic membrane transplantation in the management of severe ocular surface disease: indications and outcomes. *Ocul Surf*. 2004; 2:201–11. [PubMed: 17216092]
57. Lo K, Kohanim S, Trief D, Chodosh J. Role of amniotic membrane transplantation in acute chemical injury. *Int Ophthalmol Clin*. 2013; 53:33–41.
58. Tseng SC, Espana EM, Kawakita T, et al. How does amniotic membrane work? *Ocul Surf*. 2004; 2:177–87. [PubMed: 17216089]

59. Liu T, Zhai H, Xu Y, et al. Amniotic membrane traps and induces apoptosis of inflammatory cells in ocular surface chemical burn. *Mol Vis*. 2012; 18:2137–46. [PubMed: 22876141]
60. Kim JC, Tseng SC. Transplantation of preserved human amniotic membrane for surface reconstruction in severely damaged rabbit corneas. *Cornea*. 1995; 14:473–84. [PubMed: 8536460]
61. Meller D, Pires RT, Mack RJ, et al. Amniotic membrane transplantation for acute chemical or thermal burns. *Ophthalmology*. 2000; 107:980–9. discussion 90. [PubMed: 10811094]
62. Gomes JA, dos Santos MS, Cunha MC, et al. Amniotic membrane transplantation for partial and total limbal stem cell deficiency secondary to chemical burn. *Ophthalmology*. 2003; 110:466–73. [PubMed: 12623806]
63. Tandon R, Gupta N, Kalaivani M, et al. Amniotic membrane transplantation as an adjunct to medical therapy in acute ocular burns. *Br J Ophthalmol*. 2011; 95:199–204. [PubMed: 20675729]
64. Tamhane A, Vajpayee RB, Biswas NR, et al. Evaluation of amniotic membrane transplantation as an adjunct to medical therapy as compared with medical therapy alone in acute ocular burns. *Ophthalmology*. 2005; 112:1963–9. [PubMed: 16198422]
65. Clare G, Suleman H, Bunce C, Dua H. Amniotic membrane transplantation for acute ocular burns. *Cochrane Database Syst Rev*. 2012; 9:CD009379.
66. Baradaran-Rafii A, Javadi MA, Rezaei Kanavi M, et al. Limbal stem cell deficiency in chronic and delayed-onset mustard gas keratopathy. *Ophthalmology*. 2010; 117:246–52. [PubMed: 20018379]
67. Tseng SC. Amniotic membrane transplantation for ocular surface reconstruction. *Biosci Rep*. 2001; 21:481–9. [PubMed: 11900323]
68. Kheirkhah A, Johnson DA, Paranjpe DR, et al. Temporary sutureless amniotic membrane patch for acute alkaline burns. *Arch Ophthalmol*. 2008; 126:1059–66. [PubMed: 18695099]
69. Tseng SC, Di Pascuale MA, Liu DT, et al. Intraoperative mitomycin C and amniotic membrane transplantation for fornix reconstruction in severe cicatricial ocular surface diseases. *Ophthalmology*. 2005; 112:896–903. [PubMed: 15878073]
70. Tejwani S, Kolari RS, Sangwan VS, Rao GN. Role of amniotic membrane graft for ocular chemical and thermal injuries. *Cornea*. 2007; 26:21. [PubMed: 17198009]
71. Shekhar H, Titiyal J, Sinha R, Tinwala S. Amniotic membrane transplantation in ocular surface disorders: A review. *J Clin Ophthalmol Res*. 2013; 1:64–9.
72. Fernandes M, Sridhar MS, Sangwan VS, et al. Amniotic membrane transplantation for ocular surface reconstruction. *Cornea*. 2005; 24:643–53. [PubMed: 16015081]
73. Azuara-Blanco A, Pillai C, Dua HS. Amniotic membrane transplantation for ocular surface reconstruction. *Br J Ophthalmol*. 1999; 83:399–402. [PubMed: 10434859]
74. Vajpayee RB, Mukerji N, Tandon R, et al. Evaluation of umbilical cord serum therapy for persistent corneal epithelial defects. *Br J Ophthalmol*. 2003; 87:1312–6. [PubMed: 14609821]
75. Tsubota K, Goto E, Fujita H, et al. Treatment of dry eye by autologous serum application in Sjogren's syndrome. *Br J Ophthalmol*. 1999; 83:390–5. [PubMed: 10434857]
76. Tananuvat N, Daniell M, Sullivan LJ, et al. Controlled study of the use of autologous serum in dry eye patients. *Cornea*. 2001; 20:802–6. [PubMed: 11685055]
77. Poon AC, Geerling G, Dart JK, et al. Autologous serum eyedrops for dry eyes and epithelial defects: clinical and in vitro toxicity studies. *Br J Ophthalmol*. 2001; 85:1188–97. [PubMed: 11567963]
78. Panda A, Jain M, Vanathi M, et al. Topical autologous platelet-rich plasma eyedrops for acute corneal chemical injury. *Cornea*. 2012; 31:989–93. [PubMed: 22759830]
79. Goto E, Shimmura S, Shimazaki J, Tsubota K. Treatment of superior limbic keratoconjunctivitis by application of autologous serum. *Cornea*. 2001; 20:807–10. [PubMed: 11685056]
80. Jeng BH, Dupps WJ Jr. Autologous serum 50% eyedrops in the treatment of persistent corneal epithelial defects. *Cornea*. 2009; 28:1104–8. [PubMed: 19730088]
81. Sharma N, Goel M, Velpandian T, et al. Evaluation of umbilical cord serum therapy in acute ocular chemical burns. *Invest Ophthalmol Vis Sci*. 2011; 52:1087–92. [PubMed: 20538982]
82. Oh HJ, Jang JY, Li Z, et al. Effects of umbilical cord serum eye drops in a mouse model of ocular chemical burn. *Curr Eye Res*. 2012; 37:1084–90. [PubMed: 23025713]

83. Tanidir ST, Yuksel N, Altintas O, et al. The effect of subconjunctival platelet-rich plasma on corneal epithelial wound healing. *Cornea*. 2010; 29:664–9. [PubMed: 20458234]
84. Marquez De Aracena Del Cid R, Montero De Espinosa Escoriaza I. Subconjunctival application of regenerative factor-rich plasma for the treatment of ocular alkali burns. *Eur J Ophthalmol*. 2009; 19(6):909–15. [PubMed: 19882589]
85. Caramella CM, Sandri G, Rossi S, et al. New therapeutic platforms for the treatment of epithelial and cutaneous lesions. *Curr Drug Deliv*. 2013; 10:18–31. [PubMed: 22998040]
86. Alio JL, Arnalich-Montiel F, Rodriguez AE. The role of “eye platelet rich plasma” (E-PRP) for wound healing in ophthalmology. *Curr Pharm Biotechnol*. 2012; 13:1257–65. [PubMed: 21740369]
87. Kuckelkorn R, Schrage N, Reim M. Treatment of severe eye burns by tenonplasty. *Lancet*. 1995; 345(8950):657–8.
88. Casas VE, Kheirkhah A, Blanco G, Tseng SC. Surgical approach for scleral ischemia and melt. *Cornea*. 2008; 27:196–201. [PubMed: 18216576]
89. Kuckelkorn R, Redbrake C, Reim M. Tenonplasty: a new surgical approach for the treatment of severe eye burns. *Ophthalmic Surg Lasers*. 1997; 28:105–10. [PubMed: 9054480]
90. Wang S, Tian Y, Zhu H, et al. Tenonplasty combined with free oral buccal mucosa autografts for repair of sclerocorneal melt caused by chemical burns. *Cornea*. 2015; 34:1240–4. [PubMed: 26266433]
91. Lin MP, Eksioglu U, Mudumbai RC, et al. Glaucoma in patients with ocular chemical burns. *Am J Ophthalmol*. 2012; 154:481–5. e1. [PubMed: 22633350]
92. Highman VN. Early rise in intraocular pressure after ammonia burns. *Br Med J*. 1969; 1(5640): 359–60. [PubMed: 5762840]
93. Kuckelkorn R, Kottek A, Reim M. Intraocular complications after severe chemical burns--incidence and surgical treatment. *Klin Monatsbl Augenheilkd*. 1994; 205:86–92. German. [PubMed: 7967411]
94. Kheirkhah A, Raju VK, Tseng SC. Minimal conjunctival limbal autograft for total limbal stem cell deficiency. *Cornea*. 2008; 27:730–3. [PubMed: 18580269]
95. Kheirkhah A, Blanco G, Casas V, et al. Surgical strategies for fornix reconstruction based on symblepharon severity. *Am J Ophthalmol*. 2008; 146:266–75. [PubMed: 18514608]
96. Kheirkhah A, Ghaffari R, Kaghazkanani R, et al. A combined approach of amniotic membrane and oral mucosa transplantation for fornix reconstruction in severe symblepharon. *Cornea*. 2013; 32:155–60. [PubMed: 22735310]
97. Shi W, Wang T, Gao H, Xie L. Management of severe ocular burns with symblepharon. *Graefes Arch Clin Exp Ophthalmol*. 2009; 247:101–6. [PubMed: 18766363]
98. Takeda K, Nakamura T, Inatomi T, et al. Ocular surface reconstruction using the combination of autologous cultivated oral mucosal epithelial transplantation and eyelid surgery for severe ocular surface disease. *Am J Ophthalmol*. 2011; 152:195–201. e1. [PubMed: 21652025]
99. Shore JW, Foster CS, Westfall CT, Rubin PA. Results of buccal mucosal grafting for patients with medically controlled ocular cicatricial pemphigoid. *Ophthalmology*. 1992; 99:383–95. [PubMed: 1565450]
100. Eslani M, Baradaran-Rafii A, Ahmad S. Cultivated limbal and oral mucosal epithelial transplantation. *Semin Ophthalmol*. 2012; 27(3–4):80–93. [PubMed: 22784272]
101. Naumann G, Lang G, Rummelt V, Wigand M. Autologous nasal mucosa transplantation in severe bilateral conjunctival mucus deficiency syndrome. *Ophthalmology*. 1990; 97:1011. [PubMed: 2402410]
102. Krachmer, JH.; Mannis, MJ.; Holland, EJ. *Cornea: Fundamentals, Diagnosis and Management*. Mosby; 2005.
103. Kim JY, Djalilian AR, Schwartz GS, Holland EJ. Ocular surface reconstruction: limbal stem cell transplantation. *Ophthalmol Clin North Am*. 2003; 16:67–77. [PubMed: 12683249]
104. Ang AY, Chan CC, Biber JM, Holland EJ. Ocular surface stem cell transplantation rejection: incidence, characteristics, and outcomes. *Cornea*. 2013; 32:229–36. [PubMed: 22668584]

105. Tsai JH, Derby E, Holland EJ, Khatana AK. Incidence and prevalence of glaucoma in severe ocular surface disease. *Cornea*. 2006; 25:530–2. [PubMed: 16783140]
106. Cade F, Grosskreutz CL, Tauber A, Dohlman CH. Glaucoma in eyes with severe chemical burn, before and after keratoprosthesis. *Cornea*. 2011; 30:1322–7. [PubMed: 22001817]
107. Kuckelkorn R, Keller GK, Redbrake C. Glaucoma after extremely severe chemical and thermal eye burns. Surgical possibilities. *Ophthalmologe*. 2001; 98(12):1149–56. German. [PubMed: 11799897]
108. Utheim TP. Limbal epithelial cell therapy: past, present, and future. *Methods Mol Biol*. 2013; 1014:3–43. [PubMed: 23690002]
109. Young AL, Cheng AC, Ng HK, et al. The use of autologous serum tears in persistent corneal epithelial defects. *Eye (Lond)*. 2004; 18:609–14. [PubMed: 15184926]
110. Geerling G, MacLennan S, Hartwig D. Autologous serum eye drops for ocular surface disorders. *Br J Ophthalmol*. 2004; 88:1467–74. [PubMed: 15489495]
111. Kim BY, Riaz KM, Bakhtiari P, et al. Medically reversible limbal stem cell disease: clinical features and management strategies. *Ophthalmology*. 2014; 121:2053–8. [PubMed: 24908203]
112. Anderson DF, Ellies P, Pires RT, Tseng SC. Amniotic membrane transplantation for partial limbal stem cell deficiency. *Br J Ophthalmol*. 2001; 85:567–75. [PubMed: 11316719]
113. Santos MS, Gomes JA, Hofling-Lima AL, et al. Survival analysis of conjunctival limbal grafts and amniotic membrane transplantation in eyes with total limbal stem cell deficiency. *Am J Ophthalmol*. 2005; 140:223–30. [PubMed: 16023069]
114. Tseng SC, Prabhasawat P, Barton K, et al. Amniotic membrane transplantation with or without limbal allografts for corneal surface reconstruction in patients with limbal stem cell deficiency. *Arch Ophthalmol*. 1998; 116:431–41. [PubMed: 9565039]
115. Bakhtiari P, Djalilian A. Update on limbal stem cell transplantation. *Middle East Afr J Ophthalmol*. 2010; 17:9–14. [PubMed: 20543931]
116. Djalilian AR, Mahesh SP, Koch CA, et al. Survival of donor epithelial cells after limbal stem cell transplantation. *Invest Ophthalmol Vis Sci*. 2005; 46:803–7. [PubMed: 15728534]
117. Fernandes M, Sangwan VS, Rao SK, et al. Limbal stem cell transplantation. *Indian J Ophthalmol*. 2004; 52:5–22. [PubMed: 15132374]
118. Liang L, Sheha H, Li J, Tseng SC. Limbal stem cell transplantation: new progresses and challenges. *Eye (Lond)*. 2009; 23:1946–53. [PubMed: 19098704]
119. Crawford AZ, McGhee CN. Management of limbal stem cell deficiency in severe ocular chemical burns. *Clin Exp Ophthalmol*. 2012; 40:227–9. [PubMed: 22490111]
120. Cauchi PA, Ang GS, Azuara-Blanco A, JMB. A systematic literature review of surgical interventions for limbal stem cell deficiency in humans. *Am J Ophthalmol*. 2008; 146:251–9. [PubMed: 18486098]
121. Baradaran-Rafii A, Eslani M, Jamali H, et al. Postoperative complications of conjunctival limbal autograft surgery. *Cornea*. 2012; 31:893–9. [PubMed: 22236787]
122. Welder JD, Pandya HK, Nassiri N, Djalilian AR. Conjunctival limbal autograft and allograft transplantation using fibrin glue. *Ophthalmic Surg Lasers Imaging*. 2012; 43:323–7. [PubMed: 22788584]
123. Nassiri N, Pandya HK, Djalilian AR. Limbal allograft transplantation using fibrin glue. *Arch Ophthalmol*. 2011; 129:218–22. [PubMed: 21320970]
124. Baradaran-Rafii A, Eslani M, Djalilian AR. Complications of keratolimbal allograft surgery. *Cornea*. 2013; 32:561–6. [PubMed: 23073489]
125. Espana EM, Di Pascuale M, Grueterich M, et al. Keratolimbal allograft in corneal reconstruction. *Eye (Lond)*. 2004; 18:406–17. [PubMed: 15069439]
126. Javadi MA, Baradaran-Rafii A. Living-related conjunctival-limbal allograft for chronic or delayed-onset mustard gas keratopathy. *Cornea*. 2009; 28:51–7. [PubMed: 19092406]
127. Solomon A, Ellies P, Anderson DF, et al. Long-term outcome of keratolimbal allograft with or without penetrating keratoplasty for total limbal stem cell deficiency. *Ophthalmology*. 2002; 109:1159–6. [PubMed: 12045060]

128. Dua HS, Azuara-Blanco A. Allo-limbal transplantation in patients with limbal stem cell deficiency. *Br J Ophthalmol.* 1999; 83:414–9. [PubMed: 10434862]
129. Daya SM, Ilari FA. Living related conjunctival limbal allograft for the treatment of stem cell deficiency. *Ophthalmology.* 2001; 108:126–33. [PubMed: 11150276]
130. Eslani, M.; Baradaran-Rafii, A.; Djalilian, A. Conjunctival-limbal autograft (CLAU). In: Thomsen, WL., editor. *Advances in Eye Research.* Vol. 1. Hauppauge, NY: Nova Biomedical Press; 2011.
131. Ozdemir O, Tekeli O, Ornek K, et al. Limbal autograft and allograft transplantations in patients with corneal burns. *Eye (Lond).* 2004; 18:241–8. [PubMed: 15004571]
132. Pauklin M, Fuchsluger TA, Westekemper H, et al. Midterm results of cultivated autologous and allogeneic limbal epithelial transplantation in limbal stem cell deficiency. *Dev Ophthalmol.* 2010; 45:57–70. [PubMed: 20502027]
133. Inatomi T, Nakamura T, Kojiyo M, et al. Ocular surface reconstruction with combination of cultivated autologous oral mucosal epithelial transplantation and penetrating keratoplasty. *Am J Ophthalmol.* 2006; 142:757–64. [PubMed: 16989763]
134. Inatomi T, Nakamura T, Koizumi N, et al. Midterm results on ocular surface reconstruction using cultivated autologous oral mucosal epithelial transplantation. *Am J Ophthalmol.* 2006; 141:267–75. [PubMed: 16458679]
135. Inatomi T, Nakamura T, Koizumi N, et al. Current concepts and challenges in ocular surface reconstruction using cultivated mucosal epithelial transplantation. *Cornea.* 2005; 24(8 Suppl):S32–S8. [PubMed: 16227821]
136. Higa K, Shimazaki J. Recent advances in cultivated epithelial transplantation. *Cornea.* 2008; 27(Suppl 1):S41–7. [PubMed: 18813074]
137. Basu S, Ali H, Sangwan VS. Clinical outcomes of repeat autologous cultivated limbal epithelial transplantation for ocular surface burns. *Am J Ophthalmol.* 2012; 153:643–50. 50 e1–2. [PubMed: 22265153]
138. Henderson HW, Collin JR. Mucous membrane grafting. *Dev Ophthalmol.* 2008; 41:230–42. [PubMed: 18453772]
139. Dogru M, Tsubota K. Current concepts in ocular surface reconstruction. *Semin Ophthalmol.* 2005; 20:75–93. [PubMed: 16020348]
140. Holland EJ. Management of limbal stem cell deficiency: A historical perspective, past, present, and future. *Cornea.* 2015; 34(Suppl 10):S9–S15. [PubMed: 26203759]
141. Biber JM, Skeens HM, Neff KD, Holland EJ. The Cincinnati procedure: technique and outcomes of combined living-related conjunctival limbal allografts and keratolimbal allografts in severe ocular surface failure. *Cornea.* 2011; 30:765–71. [PubMed: 21325942]
142. Pellegrini G, Traverso CE, Franzi AT, et al. Long-term restoration of damaged corneal surfaces with autologous cultivated corneal epithelium. *Lancet.* 1997; 349(9057):990–3. [PubMed: 9100626]
143. Nakamura T, Inatomi T, Sotozono C, et al. Transplantation of cultivated autologous oral mucosal epithelial cells in patients with severe ocular surface disorders. *Br J Ophthalmol.* 2004; 88:1280–4. [PubMed: 15377551]
144. Sangwan VS, Basu S, Vemuganti GK, et al. Clinical outcomes of xeno-free autologous cultivated limbal epithelial transplantation: a 10-year study. *Br J Ophthalmol.* 2011; 95:1525–9. [PubMed: 21890785]
145. Rama P, Matuska S, Paganoni G, et al. Limbal stem-cell therapy and long-term corneal regeneration. *N Engl J Med.* 2010; 363(2):147–55. [PubMed: 20573916]
146. Nishida K, Yamato M, Hayashida Y, et al. Corneal reconstruction with tissue-engineered cell sheets composed of autologous oral mucosal epithelium. *N Engl J Med.* 2004; 351(12):1187–96. [PubMed: 15371576]
147. Ricardo JR, Cristovam PC, Filho PA, et al. Transplantation of conjunctival epithelial cells cultivated ex vivo in patients with total limbal stem cell deficiency. *Cornea.* 2013; 32:221–8. [PubMed: 22580434]

148. Sangwan VS, Basu S, MacNeil S, Balasubramanian D. Simple limbal epithelial transplantation (SLET): a novel surgical technique for the treatment of unilateral limbal stem cell deficiency. *Br J Ophthalmol*. 2012; 96:931–4. [PubMed: 22328817]
149. Krakauer M, Welder JD, Pandya HK, et al. Adverse effects of systemic immunosuppression in keratolimbal allograft. *J Ophthalmol*. 2012; 2012:576712. [PubMed: 22523651]
150. Zhu J, Zhang K, Sun Y, et al. Reconstruction of functional ocular surface by acellular porcine cornea matrix scaffold and limbal stem cells derived from human embryonic stem cells. *Tissue Eng Part A*. 2013; 19(21–22):2412–25. [PubMed: 23675636]
151. Luo H, Lu Y, Wu T, et al. Construction of tissue-engineered cornea composed of amniotic epithelial cells and acellular porcine cornea for treating corneal alkali burn. *Biomaterials*. 2013; 34:6748–59. [PubMed: 23764112]
152. Griffith M, Poliseti N, Kuffova L, et al. Regenerative approaches as alternatives to donor allografting for restoration of corneal function. *Ocul Surf*. 2012; 10:170–83. [PubMed: 22814644]
153. Shafiq MA, Gemeinhart RA, Yue BY, Djalilian AR. Decellularized human cornea for reconstructing the corneal epithelium and anterior stroma. *Tissue Eng Part C Methods*. 2012; 18:340–8. [PubMed: 22082039]
154. Alio JL, Shah S, Barraquer C, et al. New techniques in lamellar keratoplasty. *Curr Opin Ophthalmol*. 2002; 13:224–9. [PubMed: 12165704]
155. Chan CC, Biber JM, Holland EJ. The modified Cincinnati procedure: combined conjunctival limbal autografts and keratolimbal allografts for severe unilateral ocular surface failure. *Cornea*. 2012; 31:1264–72. [PubMed: 22406944]
156. Nassiri N, Djalilian AR. Keratoplasty: moving to the front. *J Ophthalmic Vis Res*. 2009; 4:5–7. [PubMed: 23056666]
157. Belin MW, Bouchard CS, Phillips TM. Background, immunology, and pharmacology. *Cornea*. 1990; 9:184–95. [PubMed: 2197063]
158. Dupont E, Wybran J, Toussaint C. Glucocorticosteroids and organ transplantation. *Transplantation*. 1984; 37:331–5. [PubMed: 6231748]
159. Hou JH, de la Cruz J, Djalilian AR. Outcomes of Boston keratoprosthesis implantation for failed keratoplasty after keratolimbal allograft. *Cornea*. 2012; 31:1432–5. [PubMed: 22236785]
160. Zerbe BL, Belin MW, Ciolino JB. Boston Type 1 Keratoprosthesis Study G. Results from the multicenter Boston Type 1 Keratoprosthesis Study. *Ophthalmology*. 2006; 113:1779, e1–7. [PubMed: 16872678]
161. Hicks CR, Crawford GJ, Dart JK, et al. AlphaCor: Clinical outcomes. *Cornea*. 2006; 25:1034–42. [PubMed: 17133049]
162. Harissi-Dagher M, Dohlman CH. The Boston Keratoprosthesis in severe ocular trauma. *Can J Ophthalmol*. 2008; 43:165–9. [PubMed: 18347618]
163. Bradley JC, Hernandez EG, Schwab IR, Mannis MJ. Boston type 1 keratoprosthesis: the University of California Davis experience. *Cornea*. 2009; 28:321–7. [PubMed: 19387235]
164. Dohlman CH, Schneider HA, Doane MG. Prostho-keratoplasty. *Am J Ophthalmol*. 1974; 77:694–70. [PubMed: 4596032]
165. Aldave AJ, Kamal KM, Vo RC, Yu F. The Boston type I keratoprosthesis: improving outcomes and expanding indications. *Ophthalmology*. 2009; 116:640–51. [PubMed: 19243830]
166. Chen JQ, Zhai JJ, Gu JJ, et al. Preliminary study of Boston keratoprosthesis in treatment of severe late stage ocular chemical burns. *Zhonghua Yan Ke Za Zhi*. 2012; 48:537–41. Chinese. [PubMed: 22943810]
167. Ciolino JB, Belin MW, Todani A, et al. Retention of the Boston keratoprosthesis type 1: multicenter study results. *Ophthalmology*. 2013; 120:1195–200. [PubMed: 23499061]
168. Kim MJ, Bakhtiari P, Aldave AJ. The international use of the Boston type I keratoprosthesis. *Int Ophthalmol Clin*. 2013; 53:79–89.
169. Khan BF, Harissi-Dagher M, Khan DM, Dohlman CH. Advances in Boston keratoprosthesis: enhancing retention and prevention of infection and inflammation. *Int Ophthalmol Clin*. 2007; 47:61–71. [PubMed: 17450007]

170. Aldave AJ, Sangwan VS, Basu S, et al. International results with the Boston type I keratoprosthesis. *Ophthalmology*. 2012; 119:1530–8. [PubMed: 22512986]
171. Phillips DL, Hager JL, Goins KM, et al. Boston type 1 keratoprosthesis for chemical and thermal injury. *Cornea*. 2014; 33:905–9. [PubMed: 25055151]
172. Goma A, Comyn O, Liu C. Keratoprotheses in clinical practice - a review. *Clin Exp Ophthalmol*. 2010; 38:211–24. [PubMed: 20398109]
173. De La Paz MF, De Toledo JA, Charoenrook V, et al. Impact of clinical factors on the long-term functional and anatomic outcomes of osteo-odonto-keratoprosthesis and tibial bone keratoprosthesis. *Am J Ophthalmol*. 2011; 151:829–39. e1. [PubMed: 21310387]
174. Hille K, Grabner G, Liu C, et al. Standards for modified osteodontokeratoprosthesis (OOKP) surgery according to Strampelli and Falcinelli: the Rome-Vienna Protocol. *Cornea*. 2005; 24:895–908. [PubMed: 16227830]
175. Lim P, Fuchsluger TA, Jurkunas UV. Limbal stem cell deficiency and corneal neovascularization. *Semin Ophthalmol*. 2009; 24:139–48. [PubMed: 19437349]
176. Yan H, Qi C, Ling S, et al. Lymphatic vessels correlate closely with inflammation index in alkali burned cornea. *Curr Eye Res*. 2010; 35:685–97. [PubMed: 20673045]
177. Ling S, Lin H, Liang L, et al. Development of new lymphatic vessels in alkali-burned corneas. *Acta Ophthalmol*. 2009; 87:315–22. [PubMed: 18811642]
178. Zhu J, Dugas-Ford J, Chang M, et al. Simultaneous in vivo imaging of blood and lymphatic vessel growth in Prox1-GFP/Flk1::myr-mCherry mice. *FEBS J*. 2015; 282:1458–67. [PubMed: 25688651]
179. Ellenberg D, Azar DT, Hallak JA, et al. Novel aspects of corneal angiogenic and lymphangiogenic privilege. *Prog Retin Eye Res*. 2010; 29:208–48. [PubMed: 20100589]
180. Cheng HC, Yeh SI, Tsao YP, Kuo PC. Subconjunctival injection of recombinant AAV-angiostatin ameliorates alkali burn induced corneal angiogenesis. *Mol Vis*. 2007; 13:2344–52. [PubMed: 18199977]
181. Sari ES, Yazici A, Aksit H, et al. Inhibitory Effect of sub-conjunctival tocilizumab on alkali burn induced corneal neovascularization in rats. *Curr Eye Res*. 2014; 1–8.
182. Onder HI, Erdurmus M, Bucak YY, et al. Inhibitory effects of regorafenib, a multiple tyrosine kinase inhibitor, on corneal neovascularization. *Int J Ophthalmol*. 2014; 7:220–5. [PubMed: 24790861]
183. Lee CM, Jung WK, Na G, et al. Inhibitory effects of the platelet-activating factor receptor antagonists, CV-3988 and Ginkgolide B, on alkali burn-induced corneal neovascularization. *Cutan Ocul Toxicol*. 2014; 34:53–60. [PubMed: 24754407]
184. Wang Z, Zhao H, Ma JX, Xu X. Inhibition of pathological corneal neovascularization by a small peptide derived from human apolipoprotein (a) Kringle V. *Cornea*. 2014; 33:405–13. [PubMed: 24452210]
185. Zhou AY, Bai YJ, Zhao M, et al. KH902, a recombinant human VEGF receptor fusion protein, reduced the level of placental growth factor in alkali burn induced-corneal neovascularization. *Ophthalmic Res*. 2013; 50:180–6. [PubMed: 24008241]
186. Han Y, Shao Y, Lin Z, et al. Netrin-1 simultaneously suppresses corneal inflammation and neovascularization. *Invest Ophthalmol Vis Sci*. 2012; 53:1285–95. [PubMed: 22323486]
187. Li X, Zhou Q, Hanus J, et al. Inhibition of multiple pathogenic pathways by histone deacetylase inhibitor SAHA in a corneal alkali-burn injury model. *Mol Pharm*. 2013; 10:307–18. [PubMed: 23186311]
188. Kitano A, Okada Y, Yamanka O, et al. Therapeutic potential of trichostatin A to control inflammatory and fibrogenic disorders of the ocular surface. *Mol Vis*. 2010; 16:2964–73. [PubMed: 21203344]
189. Liu X, Lin Z, Zhou T, et al. Anti-angiogenic and anti-inflammatory effects of SERPINA3K on corneal injury. *PLoS One*. 2011; 6:e16712. [PubMed: 21304961]
190. Bignami F, Giacomini C, Lorusso A, et al. NK1 receptor antagonists as a new treatment for corneal neovascularization. *Invest Ophthalmol Vis Sci*. 2014; 55:6783–94. [PubMed: 25228541]
191. Lin HC, Chang JH, Jain S, et al. Matrilysin cleavage of corneal collagen type XVIII NC1 domain and generation of a 28-kDa fragment. *Invest Ophthalmol Vis Sci*. 2001; 42:2517–24.

192. Duenas Z, Torner L, Corbacho AM, et al. Inhibition of rat corneal angiogenesis by 16-kDa prolactin and by endogenous prolactin-like molecules. *Invest Ophthalmol Vis Sci.* 1999; 40:2498–505. [PubMed: 10509642]
193. Wu PC, Liu CC, Chen CH, et al. Inhibition of experimental angiogenesis of cornea by somatostatin. *Graefes Arch Clin Exp Ophthalmol.* 2003; 241:63–9. [PubMed: 12545294]
194. Ambati BK, Joussea AM, Ambati J, et al. Angiostatin inhibits and regresses corneal neovascularization. *Arch Ophthalmol.* 2002; 120:1063–8. [PubMed: 12149060]
195. Joussea AM, Beecken WD, Moromizato Y, et al. Inhibition of inflammatory corneal angiogenesis by TNP-470. *Invest Ophthalmol Vis Sci.* 2001; 42:2510–6. [PubMed: 11581191]
196. Phillips K, Arffa R, Cintron C, et al. Effects of prednisolone and medroxyprogesterone on corneal wound healing, ulceration, and neovascularization. *Arch Ophthalmol.* 1983; 101:640–3. [PubMed: 6188447]
197. Haynes WL, Proia AD, Klintworth GK. Effect of inhibitors of arachidonic acid metabolism on corneal neovascularization in the rat. *Invest Ophthalmol Vis Sci.* 1989; 30:1588–93. [PubMed: 2473047]
198. Benelli U, Ross JR, Nardi M, Klintworth GK. Corneal neovascularization induced by xenografts or chemical cautery. Inhibition by cyclosporin A. *Invest Ophthalmol Vis Sci.* 1997; 38:274–82. [PubMed: 9040459]
199. Joussea AM, Kruse FE, Volcker HE, Kirchhof B. Topical application of methotrexate for inhibition of corneal angiogenesis. *Graefes Arch Clin Exp Ophthalmol.* 1999; 237:920–7. [PubMed: 10541903]
200. Kruse FE, Joussea AM, Rohrschneider K, et al. Thalidomide inhibits corneal angiogenesis induced by vascular endothelial growth factor. *Graefes Arch Clin Exp Ophthalmol.* 1998; 236:461–6. [PubMed: 9646092]
201. Kobayashi N, Kabuyama Y, Sasaki S, et al. Suppression of corneal neovascularization by culture supernatant of human amniotic cells. *Cornea.* 2002; 21:62–7. [PubMed: 11805510]
202. Stevenson W, Cheng SF, Dastjerdi MH, et al. Corneal neovascularization and the utility of topical VEGF inhibition: ranibizumab (Lucentis) vs bevacizumab (Avastin). *Ocul Surf.* 2012; 10:67–83. [PubMed: 22482468]
203. Dursun A, Arici MK, Dursun F, et al. Comparison of the effects of bevacizumab and ranibizumab injection on corneal angiogenesis in an alkali burn induced model. *Int J Ophthalmol.* 2012; 5:448–51. [PubMed: 22937503]
204. Dastjerdi MH, Al-Arfaj KM, Nallasamy N, et al. Topical bevacizumab in the treatment of corneal neovascularization: results of a prospective, open-label, noncomparative study. *Arch Ophthalmol.* 2009; 127:381–9. [PubMed: 19365012]
205. Sener E, Yuksel N, Yildiz DK, et al. The impact of subconjunctivally injected EGF and VEGF inhibitors on experimental corneal neovascularization in rat model. *Curr Eye Res.* 2011; 36:1005–13. [PubMed: 21999227]
206. Papathanassiou M, Theodossiadis PG, Liarakos VS, et al. Inhibition of corneal neovascularization by subconjunctival bevacizumab in an animal model. *Am J Ophthalmol.* 2008; 145:424–31. [PubMed: 18207123]
207. Yoeruek E, Ziemssen F, Henke-Fahle S, et al. Safety, penetration and efficacy of topically applied bevacizumab: evaluation of eyedrops in corneal neovascularization after chemical burn. *Acta Ophthalmol.* 2008; 86:322–8. [PubMed: 17995975]
208. Azar DT. Corneal angiogenic privilege: angiogenic and antiangiogenic factors in corneal avascularity, vasculogenesis, and wound healing (an American Ophthalmological Society thesis). *Trans Am Ophthalmol Soc.* 2006; 104:264–302. [PubMed: 17471348]
209. Yao L, Bai H. Review: mesenchymal stem cells and corneal reconstruction. *Mol Vis.* 2013; 19:2237–43. [PubMed: 24227919]
210. Espandar L, Afshari N. Adult corneal stem cells and alternative sources for regenerative therapy for the cornea. *CML – Ophthalmology.* 2013; 23(1):1–6.
211. Prockop DJ, Oh JY. Medical therapies with adult stem/progenitor cells (MSCs): a backward journey from dramatic results in vivo to the cellular and molecular explanations. *J Cell Biochem.* 2012; 113:1460–9. [PubMed: 22213121]

212. Prockop DJ, Oh JY. Mesenchymal stem/stromal cells (MSCs): role as guardians of inflammation. *Mol Ther.* 2012; 20:14–20. [PubMed: 22008910]
213. Weng J, He C, Lai P, et al. Mesenchymal stromal cells treatment attenuates dry eye in patients with chronic graft-versus-host disease. *Mol Ther.* 2012; 20:2347–54. [PubMed: 23070118]
214. Le Blanc K, Frasson F, Ball L, et al. Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study. *Lancet.* 2008; 371(9624):1579–86. [PubMed: 18468541]
215. Hare JM, Fishman JE, Gerstenblith G, et al. Comparison of allogeneic vs autologous bone marrow-derived mesenchymal stem cells delivered by transendocardial injection in patients with ischemic cardiomyopathy: the POSEIDON randomized trial. *JAMA.* 2012; 308(22):2369–79. [PubMed: 23117550]
216. Griffin M, Iqbal SA, Bayat A. Exploring the application of mesenchymal stem cells in bone repair and regeneration. *J Bone Joint Surg Br.* 2011; 93:427–34. [PubMed: 21464477]
217. Agorogiannis GI, Alexaki VI, Castana O, Kymionis GD. Topical application of autologous adipose-derived mesenchymal stem cells (MSCs) for persistent sterile corneal epithelial defect. *Graefes Arch Clin Exp Ophthalmol.* 2012; 250:455–7. [PubMed: 22012407]
218. Yao L, Li ZR, Su WR, et al. Role of mesenchymal stem cells on cornea wound healing induced by acute alkali burn. *PLoS One.* 2012; 7(2):e30842. [PubMed: 22363499]
219. Lee JY, Jeong HJ, Kim MK, Wee WR. Bone marrow-derived mesenchymal stem cells affect immunologic profiling of interleukin-17-secreting cells in a chemical burn mouse model. *Korean J Ophthalmol.* 2014; 28:246–56. [PubMed: 24882959]
220. Javorkova E, Trosan P, Zajicova A, et al. Modulation of the early inflammatory microenvironment in the alkali-burned eye by systemically administered interferon-gamma-treated mesenchymal stromal cells. *Stem Cells Dev.* 2014; 23:2490–500. [PubMed: 24849741]
221. Lin HF, Lai YC, Tai CF, et al. Effects of cultured human adipose-derived stem cells transplantation on rabbit cornea regeneration after alkaline chemical burn. *Kaohsiung J Med Sci.* 2013; 29:14–8. [PubMed: 23257251]
222. Jiang TS, Cai L, Ji WY, et al. Reconstruction of the corneal epithelium with induced marrow mesenchymal stem cells in rats. *Mol Vis.* 2010; 16:1304–16. [PubMed: 20664793]
223. Yoshida S, Shimmura S, Shimazaki J, et al. Serum-free spheroid culture of mouse corneal keratocytes. *Invest Ophthalmol Vis Sci.* 2005; 46:1653–8. [PubMed: 15851565]
224. Li GG, Zhu YT, Xie HT, et al. Mesenchymal stem cells derived from human limbal niche cells. *Invest Ophthalmol Vis Sci.* 2012; 53:5686–97. [PubMed: 22836771]
225. Cejkova J, Trosan P, Cejka C, et al. Suppression of alkali-induced oxidative injury in the cornea by mesenchymal stem cells growing on nanofiber scaffolds and transferred onto the damaged corneal surface. *Exp Eye Res.* 2013; 116:312–23. [PubMed: 24145108]
226. Bray LJ, Heazlewood CF, Munster DJ, et al. Immunosuppressive properties of mesenchymal stromal cell cultures derived from the limbus of human and rabbit corneas. *Cytherapy.* 2014; 16:64–73. [PubMed: 24094499]
227. Amano S, Yamagami S, Mimura T, et al. Corneal stromal and endothelial cell precursors. *Cornea.* 2006; 25(10 Suppl 1):S73–7. [PubMed: 17001199]
228. Oh JY, Roddy GW, Choi H, et al. Anti-inflammatory protein TSG-6 reduces inflammatory damage to the cornea following chemical and mechanical injury. *Proc Natl Acad Sci U S A.* 2010; 107(39):16875–80. [PubMed: 20837529]

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).

Management of the Acute Phase

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 pseudopteria 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	$\frac{0.1 \text{ to } 3}{1 \text{ to } 29.9}$
III	Good	>3 to 6	>30 to 50	$\frac{3.1 \text{ to } 6}{31 \text{ to } 50}$
IV	Good to guarded	>6 to 9	>50 to 75	$\frac{6.1 \text{ to } 9}{51 \text{ to } 75}$
V	Guarded to poor	>9 to <12	>75 to <100	$\frac{9.1 \text{ to } 11.9}{75.1 \text{ to } 99.9}$
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 ₂ O)	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 LSCT 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 LSCT.
	KLAL, lr-CLAL	C	Multiple interventional case series suggest benefit in patients with bilateral total LSCT. 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 LSCT.
	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; LSCT = 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.