Clinical Policy Bulletin: Corneal Graft with Amniotic Membrane Transplantation or Limbal Stem Cell Transplantation

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Policy

Aetna considers preserved human amniotic membrane transplantation or limbal stem cell transplantation for ocular surface reconstruction medically necessary in members with limbal deficiency (hypofunction or total loss of stem cells) refractory to conventional treatment when the member has any of the following conditions:

**Total loss of stem cells:** (one eye involvement only)
- Chemical/thermal injuries of the ocular surface
- Contact lens-induced keratopathy or toxic effects from lens-cleaning solutions
- Multiple surgeries or cryotherapies to the limbal region
- Stevens-Johnson syndrome

**Hypofunction of stem cells:** (one or both eyes can be involved)
- Aniridia (hereditary)
- Bullous keratopathy
- Chronic limbitis
- Keratitis associated with multiple endocrine deficiency (hereditary)
- Neurotrophic keratopathy (neuronal or ischemic)
- Peripheral corneal ulcerative keratitis
- Pterygium (primary and recurrent) and pseudopterygium

Aetna considers amniotic membrane transplantation and limbal stem cell transplantation experimental and investigational for the following indications (not an all-inclusive list) because its effectiveness for indications other than the ones listed above has not been established.
Gelatinous drop-like corneal dystrophy (also known as subepithelial amyloidosis of the cornea)
Mooren's ulcer
Restrictive strabismus
Use in trabeculectomy for primary open-angle glaucoma

Aetna considers combined HLA-matched limbal stem cells allograft with amniotic membrane transplantation experimental and investigational as a prophylactic approach to prevent corneal graft rejection following penetrating keratoplasty because the effectiveness of this approach has not been established.

**Background**

The normal ocular surface is covered by corneal and conjunctival epithelium. The corneal epithelium is well-known for its rapid self-renewal process, with ultimate tissue regeneration relying on the existence of stem cells located in the limbal epithelium (the junction zone between the corneal and conjunctival epithelia). Total loss or hypofunction of the stem cells can occur as a result of certain conditions that cause damage or alteration of the corneal surface (termed limbal deficiency). Normal healing of corneal epithelial defects is prevented and a unique pathological state ensues manifested by poor epithelialization (persistent defects or recurrent erosions), chronic stromal inflammation (keratitis mixed with scarring), corneal vascularization, and conjunctival epithelial ingrowth. Since some of these features can be found in other corneal diseases, the sine qua non for making the diagnosis of limbal deficiency is the existence of conjunctival epithelial ingrowth onto the corneal surface. Clinically, this pathologic state can be confirmed by detecting conjunctival goblet cells on the corneal surface through the use of impression cytology.

Persistent corneal epithelial defects refractory to conventional treatment remain a therapeutic challenge that often requires surgical intervention. For those with hypofunction of limbal stem cells, treatment is directed at altering the microenvironment to maintain and activate the remaining stem cell population. For those conditions leading to a total loss of stem cells in 1 eye, limbal autograft transplantation is performed by taking a graft from the healthy fellow eye to replace the lost stem cell population. Obviously, this procedure is not applicable with patients having bilateral diffuse limbal involvement.

The transplantation of human amniotic membrane has been added to the therapeutic armamentarium. Amniotic membrane obtained from cesarean deliveries is prepared and cryo-preserved under sterile conditions and can be sutured onto the ocular surface. Amniotic membrane-covered surfaces have been shown to induce rapid re-epithelialization (in 2 to 4 weeks) to a smooth and wettable surface and reduce inflammation, vascularization, and scarring, thus allowing successful surface reconstruction.

For partial limbal deficiency with superficial involvement, amniotic membrane transplantation (AMT) alone has been shown to be sufficient and superior to autograft limbal transplantation (ALT) because there is no need to administer
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cyclosporine. For total limbal deficiency, additional ALT is needed, and AMT has been shown to enhance successful engraftment of ALT by preparing the perilimbal stroma and reducing inflammation and vascularization.

Espana et al (2003) evaluated the long-term outcomes of epithelial debridement and AMT for pain and discomfort relief in patients with symptomatic bullous keratopathy and poor visual potential. This retrospective study included 18 eyes (18 patients) with bullous keratopathy presenting with intractable pain or discomfort and poor visual potential. After epithelial debridement, all eyes had AMT with the basement membrane side up. During a mean follow-up of 25.1 months +/- 9.6 (SD) (range of 12 to 45 months), pain relief, epithelial healing, and visual changes were analyzed. Pain relief was obtained in 88 % of patients; 66 % of eyes had complete resolution of ocular discomfort starting soon after the first post-operative day. One eye had evisceration for persistent pain 10 months post-operatively. Corneal epithelial healing was complete in all except 1 eye. Remaining complaints included foreign-body sensation (5 %), tearing (11 %), and photophobia (5 %). The authors concluded that AMT was a safe, effective, and long-lasting treatment modality for intractable pain associated with chronic bullous keratopathy in eyes with poor visual potential. It can be an alternative to conjunctival flaps for the long-term management of patients with bullous keratopathy in whom corneal transplantation is not indicated.

Chansanti and Horatanaruang (2005) assessed the outcomes of AMT for symptomatic relief in patients with bullous keratopathy. This retrospective study included 17 eyes (17 patients) with bullous keratopathy presenting with intractable pain or discomfort. Symptomatic relief epithelial healing, and visual changes were analyzed. During the follow-up period of 14.1 +/- 11.9 months (range of 1 to 36 months) after AMT, 14 eyes of 17 eyes (82.4 %) with intolerable pain pre-operatively had pain relief post-operatively. Corneal epithelial healing was complete in all except 2 eyes; 1 of which had evisceration because of severe corneal ulcer, and the other underwent penetrating keratoplasty soon after AMT. The authors concluded that AMT is a safe and effective treatment modality for pain relief associated with chronic bullous keratopathy. It can be an alternative to conjunctival flap, with better cosmetic appearance for the management of patients with bullous keratopathy.

Srinivas et al (2007) examined the effectiveness of AMT in relieving pain and discomfort in patients with painful bullous keratopathy and its role in improving vision in eyes with visual potential. A total of 7 eyes of 7 consecutive patients with painful corneal conditions were included in a retrospective interventional non-comparative case-series study. Pain relief, epithelial healing, and visual changes were evaluated. Pain relief and freedom from discomfort were considered for the success of the surgery. The mean follow-up was 26.57 weeks (range of 11 to 53 weeks). Pain relief was achieved in all 7 (100 %) eyes. Associated symptoms including foreign body sensation, photophobia, and tearing subsided significantly in all patients starting soon after the first post-operative day. Vision improved in 5 (71.42 %) patients. The authors concluded that AMT is an effective alternative for the management of patients with painful bullous keratopathy.

In a prospective, non-comparative interventional case-series study, Georgiadis et al (2008) reported the findings of cryo-preserved human AMT for the management
of symptomatic bullous keratopathy. Consecutive cases with symptomatic bullous keratopathy for more than 12 months not amenable to conservative treatment were managed with AMT. Patients were recruited over a 5-year period in 1 referral center. Only 1 eye of each patient (the worse affected eye in bilateral cases) was operated. A 360-degree conjunctival peritomy was followed by removal of the diseased corneal epithelium. Amniotic membrane was transplanted over the cornea as a patch and sutured to the free conjunctival edges. Primary outcome measures were ocular pain and epithelial defects; secondary measures were visual acuity (VA) and ocular surface inflammation. Four out of 85 recruited cases did not complete the minimum observation of 12 months and were excluded from the study. The mean follow-up period for the remaining 81 cases was 21 +/- 4.2 months (range of 14 to 34 months). Seventy-one (87.6 %) eyes became asymptomatic with healed epithelium, 7 required repeated AMT and 3 underwent penetrating keratoplasty. Visual acuity improved in 64 (79 %) patients and remained unchanged in 14. No complications were recorded. The authors concluded that AMT is a safe and effective treatment for symptomatic bullous keratopathy when penetrating keratoplasty is not available. It has been shown to alleviate pain, promote corneal epithelialization and reduce conjunctival inflammation whereas in some cases it may also improve VA.

Chawla et al (2010) compared the safety and effectiveness of photo-therapeutic keratectomy (PTK) and AMT for symptomatic relief in painful bullous keratopathy. A total of 25 eyes (25 patients) with symptomatic bullous keratopathy and poor visual potential were randomized into 2 groups. In the PTK group (n = 13) after manual epithelial debridement, 100-microm excimer laser ablation was performed. In the AMT group (n = 12), the corneal epithelium was scraped and cryo-preserved amniotic membrane with basement membrane side up was secured with 10-0 monofilament nylon sutures. All patients were followed-up for at least 6 months. Outcome parameters included symptomatic relief, time taken for surface re-epithelialization, change in corneal thickness, and complications. At 6-month follow-up, a significant decrease was seen in the symptom scores from the baseline level in both the PTK and AMT groups (p = 0.011 and 0.017, respectively) with no difference between the groups (p = 0.593). Complete epithelialization was noted 2 weeks post-operatively in 13 of 13 eyes in the PTK group as compared with 8 of 12 eyes in the AMT group (p = 0.023). However, this difference was not significant at the end of 3 weeks (p = 0.288). One eye in the AMT group developed staphylococcus epidermidis keratitis. The authors concluded that both PTK and AMT are comparable in providing symptomatic relief in patients with bullous keratopathy and poor visual potential.

In a retrospective, interventional case series study, Strube et al (2011) reported the use of AMT in patients with restrictive strabismus. Chart review of 7 consecutive patients (8 eyes) who developed restrictive strabismus after peri-ocular surgery and were treated with surgical removal of restrictive adhesions and placement of an amniotic membrane transplant. Main outcome measures were intra-operative findings to explain the mechanism of restrictive strabismus, and clinical post-operative results, including ocular alignment, ductions and versions, symptom relief, and resolution of diplopia. Restrictive strabismus occurred after surgery for pterygium, retinal detachment, orbital floor fracture, dermoid cyst, and dermatochalasis. Restrictive strabismus was due to a combination of conjunctival contracture, fat adherence, or rectus muscle contracture. All patients developed
post-operative scarring, with failed additional standard surgery to remove the adhesions, including 1 patient treated with mitomycin C for recurrent scarring after pterygium. Re-operation using AMT was associated with improvement of ocular motility in 6 of the 7 patients; 1 patient had recurrence of scarring with persistent diplopia. The remaining 6 of 7 patients had no significant recurrence of scarring, and motility remained stable during the follow-up period of 5 to 13 months. The authors concluded that AMT may be an useful tool in the treatment of restrictive strabismus. Prevention of conjunctival scarring and fat adherence during primary surgery reamins the best option. Findings of this small study need to be validated by well-designed studies.

In a prospective, randomized study, Stavrakas et al (2012) examined the effectiveness of AMT on improving the outcomes of trabeculectomy in primary open-angle glaucoma (POAG). A total of 59 eyes affected by POAG were enrolled in this study; 32 eyes underwent amnion-shielded trabeculectomy (study group) and 27 eyes underwent trabeculectomy without any anti-metabolites (control group). Success was defined as intra-ocular pressure (IOP) less than 21 mm Hg without any medications at 24 months follow-up. The 2 groups were compared in terms of IOP, bleb morphology, bleb survival and risk of failure, glaucoma medications, and complications. There was no statistically significant difference in terms of post-operative IOP between the 2 groups and at 24 months median IOP was 15.5 mm Hg for the AMT group and 16.0 mmHg for the control group. Post-operative reduction of IOP was 8 mm Hg for the AMT group versus 6 mm Hg for the non-AMT group (p = 0.276). Two patients from the study group developed IOP greater than 21 mm Hg in contrast to 7 patients from the classic trabeculectomy group. The study group had 61.0 % less risk of developing IOP greater than 21 mm Hg (p = 0.203). No major complications in the AMT group were observed. Amniotic membrane transplantation blebs were diffuse with mild vascularization. The authors concluded that in patients with POAG, AMT showed favorable effects on bleb survival, however data failed to provide firm evidence that AMT could be used as a routine procedure in trabeculectomy.

The outer surface of the eye is covered by 2 distinct cell layers: (i) the corneal epithelial layer that overlies the cornea, and (ii) the conjunctival epithelial layer that overlies the sclera. These cell types are separated by a transitional zone known as the limbus. The corneal epithelial cells are renewed every 3 to 10 days by a population of stem cells located in the limbus. Limbal stem cell transplantation (LSCT) has been employed for corneal generation (Health Quality Ontario, 2008).

Ram et al (2010) examined the long-term clinical results of cell therapy in patients with burn-related corneal destruction associated with limbal stem-cell deficiency. These investigators used autologous limbal stem cells cultivated on fibrin to treat 112 patients with corneal damage, most of whom had burn-dependent limbal stem-cell deficiency. Clinical results were assessed by means of Kaplan-Meier, Kruskal-Wallis, and uni-variate and multi-variate logistic-regression analyses. They also assessed the clinical outcome according to the percentage of holoclone-forming stem cells, detected as cells that stain intensely (p63-bright cells) in the cultures. Permanent restoration of a transparent, renewing corneal epithelium was attained in 76.6 % of eyes. The failures occurred within the first year. Restored eyes remained stable over time, with up to 10 years of follow-up (mean of 2.91 +/- 1.99; median of 1.93). In post-hoc analyses, success -- that is, the generation of
normal epithelium on donor stroma -- was associated with the percentage of p63-bright holoclone-forming stem cells in culture. Cultures in which p63-bright cells constituted more than 3% of the total number of clonogenic cells were associated with successful transplantation in 78% of patients. In contrast, cultures in which such cells made up 3% or less of the total number of cells were associated with successful transplantation in only 11% of patients. Graft failure was also associated with the type of initial ocular damage and post-operative complications. The authors concluded that cultures of limbal stem cells represent a source of cells for transplantation in the treatment of destruction of the human cornea due to burns.

In a retrospective, consecutive cohort study, Miri et al (2010) evaluated the long-term results of LSCT in patients with ocular surface (OS) disease. Case records of 27 eyes of 26 patients (19 males and 7 females) who presented with unilateral or bilateral total limbal stem cell deficiency and treated at the Department of Ophthalmology were examined. All eyes that were treated with LSCT and that had at least 1-year follow-up were included. There were 12 auto-limbal and 15 allo-limbal transplants. Of the latter, 9 were from living related donors (LRDs) and 6 were from cadaver donors (CDs). A total of 9 eyes underwent LSCT and penetrating keratoplasty (PKP), and 11 eyes underwent LSCT and AMT. Cataract extraction with implant was carried out in 4 eyes. Some eyes had more than 1 associated procedure; 9 eyes had LSCT only. Patients with allo-limbal transplants also received systemic immunosuppression. Surgical success was measured by the duration for which a healthy corneal epithelium was maintained after LSCT. Visual success was measured by improvement VA in the operated eye during the follow-up period. The follow-up period of all eyes was up to 119 months (mean of 38 +/- 35.9 months, median of 24 months). Survival of LSCT, as determined by the maintenance of healthy corneal epithelium until last follow-up, was seen in 22 eyes (82%). The surface failed within 3 months in 4 eyes (1 with LRD and 3 with CD) and after 43 months in the 5th patient (with CD). Subsequently, 6 eyes required PKP to achieve their maximum visual potential. The VA (measured in decimal fraction) improved over a period of 1 year from a mean of 0.121 (SD of 0.184) pre-operatively to a mean of 0.313 (SD 0.348) post-operatively. The authors concluded that limbal stem cell transplantation, in isolation or in combination with other procedures, is effective in improving corneal clarity and vision. Autografts have the best long-term outcome followed by LRD allografts. Cadaver donor allografts have a comparatively poor outcome. This may partly reflect the difference in case mix between unilateral and bilateral OS conditions.

The Work Loss Data Institute's 2010 clinical practice guideline on "Eye" listed amniotic membrane transplantation as well as kerato-limbal allograft/LSCT as procedures that were considered and recommended for the management of individuals with occupational eye injuries.

In a retrospective study, Sangwan et al (2011) evaluated the effectiveness of xeno-free autologous cell-based treatment of limbal stem cell deficiency. This study included 200 patients, above 8 years of age, with clinically diagnosed unilateral total limbal stem cell deficiency due to OS burns treated between 2001 and 2010. A small limbal biopsy was obtained from the unaffected eye. The limbal epithelial cells were expanded ex-vivo on human amniotic membrane for 10 to 14 days using a xeno-free explant culture system. The resulting cultured epithelial
monolayer and amniotic membrane substrate were transplanted on to the patient's affected eye. Post-operative corneal surface stability, visual improvement and complications were objectively analyzed. A completely epithelialized, avascular and clinically stable corneal surface was seen in 142 of 200 (71 %) eyes at a mean follow-up of 3 +/- 1.6 (range of 1 to 7.6) years. A 2-line improvement in VA, without further surgical intervention, was seen in 60.5 % of eyes. All donor eyes remained healthy. The authors concluded that autologous cultivated limbal epithelial transplantation using a xeno-free explant culture technique was effective in long-term restoration of corneal epithelial stability and improvement of vision in eyes with OS burns.

In a retrospective, non-comparative, case-series study, Huang et al (2011) evaluated outcomes of allo-limbal transplantation from living-related donors to treat partial limbal deficiency secondary to ocular chemical burns. This study included 17 patients (17 eyes) with partial limbal deficiency (less than or equal to 50 %) secondary to ocular alkali burns (11 eyes) or acid burns (6 eyes). Recipient eyes were treated by removing the conjunctivalized pannus. Superior limbal grafts (mean length of 3 to 5 clock hours) from HLA antigen-matched living-related donors were transplanted into deficient areas of recipient eyes. No recipients received systemic cyclosporine A therapy. Main outcome measures included corneal re-epithelialization, reduction in vascularity, improved corneal clarity, and best-corrected visual acuity (BCVA). All eyes achieved epithelialization a mean (SD) of 10.1 (1.9) days after surgery. Corneal re-epithelialization, reduction in vascularity, and improved corneal opacity were seen in all eyes. No eyes demonstrated recurrent epithelial defects or fibro-vascular tissue, but gradual recurrence of peripheral corneal vascularization was observed in 7 eyes during the follow-up period. Allograft rejection developed in 3 eyes (17.6 %), all of which were successfully treated; BCVA improved in all eyes, and 10 eyes (58.8 %) had achieved BCVA of 0.5 or better (greater than or equal to 20/10 Snellen) at the last follow-up visit. The authors concluded that transplantation of limbal tissue from live-related donors successfully reconstructed the ocular surface. Long-term graft survival in patients with partial limbal deficiency secondary to ocular chemical burns can be accomplished without the use of systemic immunosuppression.

In a prospective, non-comparative, interventional case-series study, Marchini et al (2012) investigated the long-term effectiveness of auto-limbal transplantation in patients with limbal stem cell deficiency. A total of 16 eyes from 16 patients with severe, unilateral limbal stem cell deficiency caused by chemical burns were included in this study. Autologous ex-vivo cultured limbal stem cells were grafted onto the recipient eye after superficial keratectomy. Main outcome measures included clinical parameters of limbal stem cell deficiency (stability/transparency of the corneal epithelium, superficial corneal vascularization and pain/photophobia), VA, cytokeratin expression on impression cytology specimens and histology on excised corneal buttons. At 12 months post-surgery, evaluation of the 16 patients showed that 10 (62.6 %) experienced complete restoration of a stable and clear epithelium and 3 (18.7 %) had partially successful outcomes (re-appearance of conjunctiva in some sectors of the cornea and instable corneal surface). Graft failure (no change in corneal surface conditions) was seen in 3 (18.7 %) patients. Penetrating keratoplasty was performed in 7 patients, with VA improving up to 0.8 (best result). For 2 patients, regeneration of the corneal epithelium was confirmed by molecular marker (p63, cytokeratin 3, 12 and 19, mucin 1) analysis. Follow-up
times ranged from 12 to 50 months. The authors concluded that grafts of autologous limbal stem cells cultured onto fibrin glue discs can successfully regenerate the corneal epithelium in patients with limbal stem cell deficiency, allowing surgeons to perform successful cornea transplantation and restore vision.

In a retrospective case-series study, Basu et al (2012) reported the clinical outcomes of repeat auto-limbal epithelial transplantation in patients with recurrence of limbal stem cell deficiency after a failed primary procedure. The study included 50 patients, above 8 years of age, with clinically diagnosed unilateral limbal stem cell deficiency following ocular surface burns. Following failure of primary surgery all patients underwent a repeat limbal biopsy from the unaffected eye. The limbal cells were expanded ex-vivo on a human amniotic membrane substrate for 10 to 14 days using a completely xeno-free explant culture technique. The resulting cultured epithelial monolayer and amniotic membrane were transplanted onto the patient's affected eye. All patients underwent a comprehensive ophthalmic examination of both eyes at every follow-up visit. Post-operative corneal surface stability, change in VA, and complications were objectively analyzed. At a mean follow-up of 2.3 +/- 1.4 (median of 1.96, range of 1 to 7.5) years, 33 of the 50 recipient eyes (66 %) maintained a completely epithelialized, avascular, and clinically stable corneal surface. A 2-line improvement in VA was seen in 38 of the 50 recipient eyes (76 %). None of the donor eyes developed any clinical features of OS disease, conjunctival overgrowth of the donor site, or decrease in vision throughout the follow-up period. The authors conclude that repeat autologous cultivated limbal epithelial transplantation successfully restores corneal epithelial stability and improves vision in eyes with recurrence of limbal stem cell deficiency, following failed primary surgery for ocular burns, without adversely affecting donor eyes.

Gelatinous drop-like corneal dystrophy (GDLD), also known as subepithelial amyloidosis of the cornea, is a rare autosomal recessive disorder. Gelatinous drop-like corneal dystrophy is rare in many countries, but relatively prevalent in Japan. The typical finding of GDLD is grayish, mulberry-like, protruding subepithelial depositions with a prominent hyper-fluorescence of the cornea. Histologically, GDLD corneas are characterized by subepithelial amyloid depositions that were identified as lactoferrin by amino acid sequencing analysis. In 1998, the TACSTD2 gene was identified as a causative gene for this disease through a linkage analysis and a candidate gene approach. To-date, 14 reports have demonstrated 21 mutations comprised of 9 missense, 6 nonsense, and 6 frame-shift mutations from 9 ethnic back grounds. Currently, it is hypothesized that the loss of TACSTD2 gene function causes decreased epithelial barrier function, thereby facilitating tear fluid permeation into corneal tissue, the permeated lactoferrin then transforming into amyloid depositions via an unknown mechanism. For the visual rehabilitation of patients with GDLD, ophthalmologists currently employ various types of keratoplasties; however, almost all patients will experience a recurrence of the disease within a few years after such interventions. Wearing of a soft contact lens is sometimes considered as an alternative treatment for GDLD (Kawasaki and Kinoshita, 2011).

In a non-comparative interventional case-series study, Movahedan et al (2013) reported the outcomes of allograft LSCT for recurrent GDLD. A total of 4 eyes of 3 consecutive patients with recurrent GDLD underwent allograft LSCT; 2 eyes
underwent concomitant penetrating keratoplasty while the other 2 underwent simultaneous superficial keratectomy. Main outcome measures were best spectacle corrected visual acuity, IOP and corneal clarity. Patient age ranged from 28 to 63 years. Mean follow-up after surgery was 23 ± 10 (median of 22; range of 12 to 36) months. Mean VA improved from 2.70 ± 0.61 logMAR pre-operatively to 1.05 ± 0.06 logMAR at final post-operative visit (p = 0.066). Intraocular pressure was normal in all eyes at baseline and remained within normal limits at all post-operative visits. All corneas remained smooth and clear during the follow-up period with no episode of rejection or recurrence. All patients maintained ambulatory vision until final follow-up. The authors concluded that the findings of the present study provided further evidence that LSCT may be an effective therapeutic alternative in patients with GDLD. These findings need to be validated by well-designed studies.

Mooren's ulcer is a chronic ulcerative inflammation of the cornea. The exact pathogenesis remains unclear; but it can or will lead to loss of vision if untreated. Severe pain is common in patients with Mooren's ulcer and the eye(s) may be intensely reddened, inflamed and photophobic, with tearing. There are a number of therapies employed for the treatment of this condition (e.g., anti-inflammatory drugs (steroidal and non-steroidal), cytotoxic drugs (topical and systemic), conjunctivectomy as well as cornea debridement (superficial keratectomy)). However, there is no evidence to show which is the most effective amongst these treatment modalities.

Lavaju et al (2013) reported a case of Mooren's ulcer treated with AMT supplemented with autologous serum eye drops. A 22-year old male presented with history of pain, redness, watering and diminution of vision of the right eye for 1 year. Examination of his eyes revealed the BCVA of 6/60 and 6/6 in his right and left eyes, respectively. Slit lamp examination of the right eye showed a peripheral ulcer extending from 2'0 to 11'0 clock positions with peripheral thinning and the features suggestive of Mooren's ulcer. The condition did not improve with topical steroids and cyclosporine A eye drops. Therefore, 360-degree conjunctival peritomy with cauterization of the base was performed. Since there was no obvious improvement, AMT was done with supplementation of autologous serum eye drops 20 % 4 times a day. The patient showed symptomatic improvement in 1 week. There was cessation of the progression of the ulcer and decreased vascularization. One month later, a small corneal perforation was noted and was managed well with cyanoacrylate glue and bandage contact lens application. At 9 months of follow-up, the patient was symptomatically better, the ulcer had healed, the vascularization had decreased and the anterior chamber was well formed. The authors concluded that AMT appeared to be a promising treatment of Mooren's ulcer refractory to immunosuppressive therapy. Addition of autologous serum eye drops seems to be an effective supplementary therapy.

Schallenberg et al (2013) reported on a retrospective case-series of patients treated with systemic immunosuppressive therapy and additional AMT. Medical records from 7 patients (11 eyes), 4 males and 3 females, with severe progressive Mooren's ulcer were analyzed retrospectively. The mean follow-up was 88.4 ± 80.8 months (range of 12 to 232 month). A HLA-typing was performed in all patients. A systemic immunosuppressive therapy was administered in all patients. The amniotic membrane was transplanted after the base of the ulcer
was resected. Multiple AMTs were necessary in 6 patients. The visual outcome of all patients was poor. No patient achieved a VA better than 20/630 Snellen chart; 5 patients were positive for HLA-DQ2 and 4 patients were positive for HLA-DR17(3). The authors concluded that the aggressive and highly inflammatory form of Mooren’s ulcer is difficult to treat and the progression of the disease is hard to influence positively even under systemic immunosuppressive therapy. Therefore, the main intention of therapy is to achieve a stable epithelialized corneal surface without the risk of perforation. They stated that AMT is not able to cure severe forms of Mooren's ulcer. However it supports the immunosuppressive therapy in acute situations as in critical corneal thinning.

In a Cochrane review, Alhassan et al (2014) evaluated the effectiveness of the various interventions (medical and surgical) for the treatment of Mooren's ulcer. These investigators searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (The Cochrane Library 2013, Issue 5), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to June 2013), EMBASE (January 1980 to June 2013), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to June 2013), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). They did not use any date or language restrictions in the electronic searches for trials. They last searched the electronic databases on June 4, 2013. These researchers planned to include randomized controlled trials (RCTs) or discuss any prospective non-RCTs in the absence of any RCTs. The trials included would be of people of any age or gender diagnosed with Mooren's ulcer and all interventions (medical and surgical) would be considered. Two authors screened the search results independently; they found no studies that met their inclusion criteria. As these investigators found no studies that met their inclusion criteria, they highlighted important considerations for conducting RCTs in the future in this area. The authors concluded that they found no evidence in the form of RCTs to assess the treatment effect for the various interventions for Mooren's ulcer. They stated that high quality RCTs that compare medical or surgical interventions across different demographics are needed. Such studies should make use of various outcome measures, (i.e., healed versus not healed, percentage of area healed, speed of healing, etc.) as well as ensuring high quality randomization and data analysis.

Capozzi and colleagues (2014) examined if the use of combined HLA-matched limbal stem cells allograft (LAT) with AMT is a safe and effective prophylactic surgical procedure to prevent corneal graft after PKP. These investigators reported the case of a 17-year old patient with a history of congenital glaucoma, trabeculectomy and multiple corneal graft rejections, presenting total limbal cell deficiency. To reduce the possibility of graft rejection in the left eye after a new PKP, a 2-step procedure was performed. At first the patient underwent a combined HLA-matched LAT and AMT and then, 10 months later, a new PKP. During 12 months of follow-up, the corneal graft remained stable and smooth, with no sign of graft rejection. The authors concluded that in this patient, the prophylactic use of LAT from HLA-matched donors and AMT before PKP, may result in a better prognosis of corneal graft survival. These preliminary findings need to be validated by well-designed studies.
CPT Codes / HCPCS Codes / ICD-9 Codes

**CPT codes covered if selection criteria are met:**

- **65778**  Placement of amniotic membrane on the ocular surface; without sutures
- **65779**  Single layer, sutured
- **65780**  Ocular surface reconstruction; amniotic membrane transplantation, multiple layers
- **65781**  Limbal stem cell allograft (e.g., cadaveric or living donor)
- **65782**  Limbal conjunctival autograft (includes obtaining graft)

**Other CPT codes related to this CPB:**

- **65450**  Destruction of lesion of cornea by cryotherapy, photocoagulation or thermocauterization

**HCPCS codes covered if selection criteria are met:**

- **V2790**  Amniotic membrane for surgical reconstruction, per procedure

**ICD-9 codes covered if selection criteria are met:**

- **370.00 - 370.07**  Corneal ulcer
- **370.35**  Neurotrophic keratoconjunctivitis
- **371.23**  Bullous keratopathy
- **371.40 - 371.49**  Corneal degenerations
- **371.50 - 371.58**  Hereditary corneal dystrophies
- **371.82**  Corneal disorder due to contact lens
- **372.40 - 372.45**  Pterygium
- **372.50**  Pseudopterygium
- **695.1**  Erythema multiforme [Stevens-Johnson syndrome]
- **743.45**  Aniridia
- **940.0 - 940.9**  Burn confined to eye and adnexa
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941.02  Burn of face, head, and neck, unspecified degree, eye (with other parts of face, head, and neck)
941.12  Burn of face, head, and neck, erythema [first degree], eye (with other parts face head and neck)
941.22  Burn of face, head, and neck, blisters, epidermal loss [second degree], eye (with other parts of face head and neck)
941.32  Burn of face, head, and neck, full-thickness skin loss [third degree nos], eye (with other parts of face head and neck)
941.42  Burn of face, head, and neck, deep necrosis of underlying tissues [deep third degree], without mention of loss of a body part, eye (with other parts of face head and neck)
941.52  Burn of face, head, and neck, deep necrosis of underlying tissues [deep third degree], with loss of a body part, eye (with other parts of face head and neck)

ICD-9 codes not covered for indications listed in the CPB:

365.11  Primary open angle glaucoma
370.07  Mooren's ulcer
371.52  Other anterior corneal dystrophies [gelatinous drop-like corneal dystrophy]
378.00 - 378.9  Strabismus and other disorders of binocular eye movements [restrictive]

The above policy is based on the following references:


