Review Article

Amniotic membrane transplantation: an updated clinical review for the ophthalmologist

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Abstract: Although amniotic membrane transplantation (AMT) has long been used as an essential surgical technique for ocular surface reconstruction, its role continues to evolve and expand. In the management of numerous ocular surface disorders, ranging from inflammatory to infectious, traumatic to neoplastic, the ability to perform AMT is a valuable addition to the skillset of any ophthalmologist. The purpose of this paper is to provide ophthalmologists with an updated, evidence-based review of the clinical indications for AMT in corneal and conjunctival reconstruction, reviewing its common and even experimental applications known to date. The methods of amniotic membrane preservation, the available commercial amniotic membrane products to date, and future directions for amniotic membrane use, including amniotic membrane extract eye drops (AMEED), are also discussed. It is paramount for ophthalmologists to stay up-to-date on the applications of AMT so as to effectively incorporate this versatile treatment modality into their practice, both in the operating room and in the clinic. By familiarizing the general ophthalmologist with its diverse applications, we hope to motivate general ophthalmologists to incorporate the use of AMT into their clinical practice, or provide guidance on how to recognize when referral to a corneal specialist for amniotic membrane application is prudent.

Keywords: Amniotic membrane; epithelial defect; cornea; ocular surface reconstruction; ophthalmology

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Introduction

Background

In the field of bioengineering, the ideal biomaterial is one that can act as a supporting matrix while simultaneously delivering growth factors that promote healing in damaged tissues; amniotic membrane (AM) consistently meets these criteria. Unique advantages of AM over other human allografts include its ease of tissue processing and storage, non-immunogenicity, and lack of donor morbidity. This latter property and its avascularity relatively spares AM from the usual ethical and religious constraints that come with use of other human donor tissues.

Since its first use for ocular surface reconstruction in 1940 (1), amniotic membrane transplantation (AMT) has become a mainstay in the treatment of numerous ocular surface disorders due to its unique structural and chemical composition. The trophic components found within the epithelium and extracellular matrix (ECM) allow for wound healing and provide a scaffold for epithelialization,

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specifically promoting regeneration, migration, and adhesion of the epithelium. Five layers comprise the amnion: an epithelial layer, basement membrane, a stromal ECM layer, a spongy layer and chorion. The collagen composition of its basement membrane is similar to that of cornea and conjunctiva (2,3). The anti-inflammatory, anti-fibrotic, anti-microbial, and anti-angiogenic properties of AM make it a great alternative to the usual adjunctive measures to improve epithelial healing, such as tarsorrhaphy and bandage contact lens (BCL) (4).

Rationale and knowledge gap

AMT has revolutionized and expanded the way ocular surface disease can be managed, making it a valuable addition in the skillset of any ophthalmologist. With the exception of cost, in our institutional experience, there are no obstacles or controversial points in the use of AMT. The myriad of ways in which AMT can be applied, both in and out of the operating room, make it a versatile tool that not only promotes ocular surface healing, but also provides much needed pain relief. It is important for ophthalmologists to familiarize themselves with the diverse indications and techniques for AMT in order to provide their patients with best care possible.

Numerous papers have been published reviewing the applications of AMT. This review is unique in that we summarize not only the numerous indications for AMT in an easy to digest way for the general ophthalmologist, but we also provide a brief review of the available and experimental AM products that can be used in the outpatient and operative room settings. This review is therefore an essential "all-in-one" AMT resource for ophthalmologists looking to expand their repertoire in the treatment of ocular surface disease.

Objective

To keep ophthalmologists up-to-date on the various applications of AMT, we will discuss its evidence-based clinical indications, provide a brief overview of amniotic membrane extract eye drops (AMEED), and include practical suggestions based on our institutional experience.

Strengths and limitations

This review is geared towards the general ophthalmologist, and provides a comprehensive overview of the latest evidence regarding the indications of AMT. This review is meant to be used in the context of clinical practice, assisting the general ophthalmologist in deciding when AMT may be indicated. We also include expert pearls from our institutional experience. The purpose of this review is not to provide a review on the intricate biochemical mechanisms underlying AMT use, nor to provide a detailed discussion of the individual applications of all AM products available on the market.

Methods of preservation

Cryopreserved vs. dehydrated

While AM's biologic and molecular characteristics make it an ideal graft tissue, amniotic tissues—as with any allograft tissue—must be carefully processed to prevent the transmission of diseases. Thus, the tissue must undergo rigorous processing and storage procedures to preserve the tissue's structural and biologic properties. The tissue is acquired after being evaluated for donor eligibility and placental suitability. It is derived from donated human placental tissue following healthy cesarean section from full-term live births. The placental tissue is thoroughly cleansed with saline and other agents to remove blood, flora, and other potential contaminants. After processing, the tissue can undergo various methods of preservation—two of the most common methods are cryopreservation and dehydration (5).

The process of cryopreservation works by devitalizing living cells while maintaining their natural structural and biologic characteristics. This is accomplished by storing and transporting tissues at low temperatures (typically −75 to −80 ℃). Cryopreservation is performed using a cryomedium (1:1 mixture of glycerol cryoprotectant and Dulbecco's Modified Eagles Medium). Properly cryopreserved AMT products can be stored up to 12–24 months in temperatures ranging from −80 to 4 ℃ (5,6). Conversely, dehydration exposes tissue to heat to remove moisture within, while maintaining most biologic properties of the tissue. A sugar protectant, such as trehalose, is used to replace intracellular water and prevent major disruption of internal cellular structures during the evaporation process (7). Both methods of preservation aid in suppressing chemical reactions and microorganism growth, however, each method has its own advantages. Dehydrated AM is processed in a standardized manner and is delivered as a ready-to-use product. It is convenient and can be stored at room temperature for

Table 1 Available amniotic membrane products

Product name	Product type	Company/developer	Setting to use
AmnioGraft	Cryopreserved AM	Biotissue, Miami, FL, USA	Operative room
AmnioGuard	Cryopreserved UC	Biotissue, Miami, FL, USA	Operative room
Prokera	Cryopreserved AM	Biotissue, Miami, FL, USA	In-office
AmbioDisk	Dehydrated AM	Katena, Denville, NJ, USA	In-office
AmbioDry	Dehydrated AM	OKTOS Surgical Corporation, Costa Mesa, CA, USA	Operating room
AmioTek	Dehydrated AM	ISP Surgical LLC, Boston, MA, USA	Operating room
Aril	Dehydrated AM	Seed Biotech, Dallas, TX, USA	Operating room
BioDOptix	Dehydrated AM	Integra, Plainsboro Township, NJ, USA	Operating room
Biovance	Dehydrated AM	Versea Biologics, Tampa, FL, USA	In-office or operative room

AM, amniotic membrane; UC, umbilical cord.

two to five years. However, the handling, sterilization, and preservation process may hinder some of its biological properties.

On the other hand, a laboratory study by Cooke *et al.* demonstrated that cryopreservation is superior in maintaining the quality of high molecular weight hyaluronic acid and pentraxin-3 (8). Further, Thomasen and colleagues performed a study which demonstrated that cryopreserved AM was superior to air-dried AM in cultivating limbal epithelial cells, wound-healing modulation factors, and basement membrane components, which suggests that cryopreserved AM may outperform dehydrated (air-dried) AM in ophthalmic diseases (9). Allen *et al.* described a modified drying technique involving the use of trehalose or raffinose and performed a study showing that this method outperformed cryopreserved AM in factor retention, bioavailability, and corneal epithelial cell expansion (10).

Available amniotic membrane products

There are many commercial products and forms of AM available to date (*Table 1*). When it was launched in 1997, cryopreserved AM was the first commercially available amniotic tissue product for ocular reconstruction and wound healing (AmnioGraft; Biotissue, Miami, FL, USA). In 2004, the Food and Drug Administration (FDA) approved Prokera, a self-retained cryopreserved AM that did not need to be sutured (PROKERA; Biotissue, Miami, FL, USA). A cryopreserved umbilical cord product (AmnioGuard; Biotissue, Miami, FL, USA) was marketed as a barrier graft over glaucoma tube shunts in 2010.

Dehydrated AM products have been available for wound covering since 2002 (AmbioDry; OKTOS Surgical Corporation, Costa Mesa, CA, USA). Overlay AM discs (AmbioDisk; Katena, Denville, JN, USA) can be placed under BCLs and have been used since 2011. Other dehydrated AM grafts include AmioTek (ISA Surgical LLC, Boston, MA, USA), Aril (Seed Biotech, Dallas, TX, USA), BioDOptix (Integra, Plainsoro Township, NJ, USA), OculoMatric (Sky Biologics, El Segundo, CA, USA), and VisiDisc (Skye Biologics, El Segundo, CA, USA). Biovance is a ringless, dehydrated AM with a 3-layered construction that can adhere to the ocular surface with or without sutures (Versea Biologics, Tampa, FL, USA).

While AMT has many applications for use in the operating room, sutureless AM options—such as Prokera and AmbioDisk—can be administered in-office. At our particular institution, these are the two sutureless AM options that are available. Prokera is a self-retained cryopreserved AM that is attached to a polycarbonate ring or an elastomeric band. AmbioDisk, on the other hand, is a dehydrated AM product that is applied to the ocular surface and secured by a BCL. Although comparative data is limited, Giannikas and colleagues published an abstract evaluating the indications and outcomes of ProKera and AmbioDisk and found that both were successful in promoting healing in eyes with microbial keratitis (MK), neurotrophic keratopathy (NK), and non-healing epithelial defects after keratoplasty. Both ProKera and AmbioDisk had similar success rates, however, Prokera was found to be difficult to tolerate for patients in about half the cases (11). To address this issue, Biotissue developed a product called

Prokera Slim, which is designed to be a lower profile device that contours the ocular surface to improve patient comfort.

Clinical indications—corneal reconstruction

In our years of academic experience at a large county hospital, we have learned to utilize layered AMT very early in corneal disease management to avoid worsening, which can necessitate other types of invasive interventions, such as corneal patch grafts or penetrating keratoplasty (PKP). We have also used AMT aggressively for chemical injury, MK, and any other causes of non-healing epithelial defects with success. Due to its temporizing nature, AMT avoids exacerbation of these disease states (i.e., perforation, infection of non-healing epithelial defects). Below, we summarize the evidence-based indications for AMT use in corneal disease.

Persistent epithelial defect (PED) and non-healing corneal ulceration (NHCU)

Both endogenous and exogenous etiologies can result in a PED or NHCU. Exogenous factors include infection, dryness, chemical burn, and trauma, and endogenous conditions include limbal stem cell deficiency (LSCD), inflammation, and NK. In NHCU and PED that do not respond to medical treatment, AMT can be considered.

In a retrospective analysis of treatment-refractory corneal ulcers, Schuerch *et al.* studied the success and time to epithelialization in 149 patients treated with AMT. The various etiologies of the ulcers included herpetic, rheumatic disease, bacterial, ulcers after prior PKP or other corneal surgery, LSCD from chemical burn or trauma, bullous keratopathy, and NK (12). Defects secondary to bullous keratopathy, MK, herpetic viruses, and NK were found to have the highest overall closure rates (79%, 80%, 85%, and 93% respectively) with AMT. Overall, AMT had a success rate of 70% in their study population, with epithelial closure being achieved within the first 3 months. The most difficult PED to epithelialize with AMT were those secondary to rheumatic disease (52%) and delayed wound healing after corneal surgery (57%). These patients required either a second AMT, PKP, discussions of conjunctival flap surgery, or even evisceration. Seitz *et al.* studied epithelial closure in post-PKP eyes, and found a closure rate of 70% within 4 weeks of AMT, with a success rate that was inversely proportional to the number of prior transplants (13).

In a retrospective, multicenter study by Lacorzana *et al.* involving 223 AMTs for PED, investigators found an overall re-epithelialization rate of 74.4%, and concluded that AMT is successful in re-epithelialization independent of ulcer etiology (14). The study also concluded that success rates of monolayer and multilayer AMT were similar across etiologies. Their study did not include ulcers secondary to rheumatic disease or previous corneal surgery.

While the above studies demonstrate that AMT can be a promising treatment for PED and NHCU, they did not evaluate epithelial stability or rate of epithelial breakdown after AMT therapy had been completed. The benefits of AMT in closing epithelial defects therefore should not be considered a permanent solution, but rather a temporary one. The use of AMT for PED and NHCU secondary to MK, NK, chemical and thermal injury, and LSCD is discussed below.

MK

MK is a challenging corneal condition to treat and can result in corneal scarring, corneal melt, perforation, glaucoma, and endophthalmitis (15). While fortified antibiotics are the mainstay of treatment, antibiotics can cause epithelial toxicity which can lead to PED (15). In the setting of poor corneal wound healing and impending corneal perforation, AMT is a valuable adjunctive therapy in management.

In-office application of AM has been shown to be a cost-effective option for the treatment of MK. In a comparative, retrospective case-control study, Yin *et al.* examined the effectiveness of the self-retained, cryopreserved AM, Prokera, in the treatment of MK (16). 24 patients with central and paracentral microbial corneal ulcers with vision worse than 20/200 were included, 11 of which underwent placement of Prokera (for at least five days) in addition to topical fortified antibiotics. They found that although patients who received Prokera had larger baseline corneal ulcers, they had significantly faster epithelization, were more likely to completely epithelialize, and had better BCVA and vision improvement compared to the control group.

Prokera, therefore, is a viable treatment option for PED that can act as a biological bandage for 3–5 days. When a PED may require longer coverage of 1–2 weeks, sutured fresh AMT may be preferred. Tabatabaei *et al.* performed a prospective randomized control trial (RCT) to compare the outcomes of patients who either underwent sutured AMT with fortified antibiotics versus those receiving fortified

antibiotics only in bacterial MK (15). Forty-nine patients were assigned to the AMT with antibiotics group, and 50 patients were assigned to the fortified antibiotics only group. They found that the AMT group had significantly better best corrected visual acuity (BCVA), uncorrected visual acuity (UCVA), and contact lens corrected VA at 6 months as compared to the control group. Scar size was also smaller, and neovascularization was significantly decreased. They concluded that early use of AMT was associated with better outcomes than antibiotic therapy alone. Additionally, early AMT at 48 hours combined with topical steroids has been shown to result in satisfactory pain control and epithelial healing (17).

In a recent meta-analysis of 28 clinical studies (including 4 RCTs), it was concluded that AMT is a useful adjunctive therapy in moderate-severe bacterial and fungal keratitis compared to standard antimicrobial treatment alone (18). Most studies regarding AMT and MK have focused on bacterial etiologies. Although the benefit of AMT in herpetic keratitis has not been studied in RCTs, Ting and colleagues' systematic review demonstrated that AMT led to a high rate of complete corneal healing (94%). Further studies are needed to assess the effect of AMT on *Acanthamoeba* keratitis.

Neurotrophic keratitis (NK)

NK is a challenging disease secondary to diminished corneal innervation, which causes decreased sensation and impaired delivery of trophic factors to the cornea. Patients subsequently develop PED, reduced blink rate, impaired tear film stability which can result in corneal ulcers and perforation. The management of NK begins with stopping all possible offending topical agents and initiating aggressive lubrication, treating underlying etiologies, BCL, and anti-inflammatories (19). Cenegermin drops are currently the only FDA-approved medical therapy for NK, and results have been promising. A recent multicenter observational study compared 38 patients with stage 2–3 NK being treated with either cenegermin or AMT; corneal healing, recurrence of disease, and patient satisfaction with treatment were evaluated (20). It was found that while both AMT and cenegermin had high rates of complete re-epithelialization (86% and 96% respectively), the cenegermin treatment group remained recurrence free for significantly longer, had better visual acuity, and a higher degree of patient satisfaction than with AMT. Despite these advantages, AMT is typically preferred in corneal perforation cases since cenegermin treatment typically takes 6 weeks and placement of the AMT can be done instantaneously.

In a RCT, Khokhar *et al.* compared the efficacy of AMT versus conventional management with tarsorrhaphy and BCL in 30 patients with neurotrophic ulcers refractory to medical management. Investigators demonstrated a success rate of 73.33% for AMT and 66.67% for the BCL and tarsorrhaphy group, a difference which was not considered statistically significant (21). However, eyes with post-herpetic NK were observed to have a higher success rate in the AMT group than the BCL and tarsorrhaphy group (86% *vs.* 57%), leading the authors to suggest AMT in this subset of NK. Current guidelines recommend AMT for stage 2–3 NK, however due to high recurrence rates of the epithelial defects once the AMT dissolves, it should be considered only as a temporizing measure in emergent cases, rather than a definitive treatment (22).

In our institutional experience managing NK, other invasive interventions such as corneal patch graft and PKP have a higher risk of re-perforation, rejection, and failure. We have found AMT to be a stabilizing measure that allows time for treatment of the NK with long-term treatments (i.e., scleral lens, serum tears, tarsorrhaphy, cenegermin).

Acute chemical or thermal injury

In the acute phase of chemical or thermal injury to the ocular surface, AMT is an excellent option although the majority of studies supporting its use have been nonrandomized or noncompetitive case series (23). Sharma *et al.* found that AMT combined with medical therapy led to faster re-epithelialization compared to medical therapy alone. However, after 3 months, there was no difference in visual outcome, symblepharon formation, tear film status, and lid abnormalities (24). AMT was also compared to umbilical cord serum; while both the AMT and umbilical cord serum groups showed a reduction in pain at day 7 of treatment, serum out-performed AMT in reducing pain scores. A recent 2019 RCT by Eslani *et al.* compared outcomes of conventional medical treatment with combined medical treatment and AMT in patients with Roper-Hall grade IV ocular chemical injury (23). Combined treatment with AMT was not found to accelerate corneal epithelialization or improve final visual acuity in patients with severe chemical injury. A systematic review was performed in 2012, however the lack of suitable RCTs precluded a meta-analysis (25). The authors concluded

that overall, in mild burn injuries, AMT is not indicated due to excellent prognosis, while for severe burns, AMT is typically insufficient to prevent severe sequelae. Data on use in moderate burns is lacking. Although AMT has not been shown to improve epithelialization or final visual acuity, pain and inflammation may be improved with AMT, with most studies recommending the use of AMT within 7 days of initial injury. Authors of this article utilize its use early on in chemical or thermal injury patients.

LSCD

Healthy corneal epithelium is maintained by a unique subset of stem cells at the limbus. When these are damaged, numerous sequelae can develop, including superficial neovascularization, chronic inflammation, scarring, and poor epithelial integrity, which can lead to PED. In cases of partial LSCD, AMT has been successfully used in promoting re-epithelization through expansion of remaining limbal epithelial stem cells (26-28).

For more severe cases of LSCD, limbal stem cell transplantation (LSCT) procedures are needed. These procedures are also dependent on the use of AM, both as a temporary, adjunctive measure to stabilize the ocular surface, and as a supportive substrate for both *ex vivo* and *in vivo* limbal stem cell expansion. A main challenge with LSCT is the contamination of corneal limbal stem cells with conjunctival epithelial cells. In techniques such as simple limbal epithelial transplantation (SLET) and Amnion-Assisted Conjunctival Epithelial Redirection (ACER) however, the risk of contamination is mitigated by using AM as a key substrate. In SLET, after a 360-degree peritomy and removal of fibrovascular pannus, AM is placed over the irregular stromal surface, secured, and small pieces of donor tissue explants are placed on top (29). SLET has been shown to be a safe and effective surgical technique (20,30,31). In ACER, explants of limbal tissue are covered by cryopreserved or vacuum dried amnion (Omnigen) (32,33). The edge of AM is tucked under and sutured to peritomized and recessed conjunctiva, redirecting conjunctival epithelial cell migration onto AM rather than onto the healing corneal surface.

AM can also be used in cultured limbal epithelial transplantation (CLET) to maximize donor limbal tissue while reducing the risk of inducing LSCD in a donor eye (34). In CLET, AM used as a substrate to expand donor limbal stem cells *ex vivo*, with <1 mm^2 of donor tissue required for adequate expansion (35). Numerous studies have demonstrated CLET as a successful surgical technique with low rejection rates one year postoperatively, however, long-term studies are still needed to elucidate the longevity of this technique (34,36).

Recurrent corneal erosion (RCE) and photorefractive keratectomy (PRK) post-operative care

Use of Prokera for the treatment of RCE has been described with success. Huang *et al.* applied Prokera on 11 eyes and found only one eye to have recurrence requiring retreatment (37). Prokera, however, is more expensive than traditional treatment with BCL or phototherapeutic keratectomy, which may limit its use in the treatment of RCE (38). Further studies are needed to elucidate the benefit of AMT compared to traditional therapies in RCE.

In eyes undergoing PRK, studies have shown that in-office Prokera post-operatively does not improve overall corneal clarity, time to complete re-epithelialization, or optical quality of the cornea compared to traditional BCL (39,40). The beneficial effect of AM on preventing corneal haze in PRK therefore remains unproven.

Dry eye disease (DED)

Especially given the advent of in-office application methods, AMT is now an option in the stepwise treatment of severe DED, and can be considered after failure of serum tears and therapeutic contact lenses (41). Numerous studies support the use of Prokera in the treatment of DED (42-44). The Dry Eye Amniotic Membrane Study (DREAM) showed that after treatment with Prokera for an average of 5.4±2.8 days, 88% of patients had improved ocular surface at 3 months, with only 10% requiring repeat treatment for complete healing (44).

Cost-effectiveness analysis comparing Prokera versus cyclosporine in moderate to severe DED showed that Prokera was overall the less expensive option due to improved outcomes and better patient productivity, with patients missing less days of work and/or being more productive at work (45). AMT has also been shown to induce beneficial, lasting changes by promoting corneal nerve regeneration (43). In a RCT, John *et al.* compared the use of Prokera versus conventional therapy (i.e., artificial tears, serum tears, steroids, cyclosporine) in patients with DED. They found improved signs and symptoms in the Prokera group, with no change in the control group. To measure corneal nerve density, *in vivo* confocal microscopy was also performed in patients

at baseline, 1 month, and 3 months. A significant increase in corneal nerve density was found in the Prokera group along with an increase in corneal sensitivity, with no change in the control group. In our institutional experience, we have found AMT to be a helpful adjunctive therapy as patients are starting long term therapy.

Corneal perforation

Full thickness corneal injuries can result from infectious, inflammatory, and traumatic conditions. Management of perforations is dependent on the size, location, and underlying cause of the perforation (46). The initial goals of management are to stabilize the eye by ensuring a watertight globe, thus mitigating risk of hypotony, infection and epithelial ingrowth (47,48). This allows for the preferred staged approach of performing eventual keratoplasty once inflammation has decreased (48).

For wounds that are too large to be managed with BCL and tissue glues, too irregular or gaped, or if there is ongoing tissue loss (i.e., corneal melt) to be managed with direct suturing, AMT can be used to reestablish globe integrity (49). Several techniques to repair corneal perforation using AM have been described. AM can be sutured to the ocular surface and covered with a BCL, or can be secured with fibrin glue, plugging the perforation site (50). AMT in conjunction with fibrin glue has been shown to effectively close perforations up to 3 mm in size (51). Multilayered AMT of 3–4 layers has been described with success in perforations <1.5 mm in size (52). Piled, multilayered AMT using 5 or 7 ply AM has been shown to even treat defects >3 mm (53). Various stuffing techniques, in which AM is folded in various configurations to maximally fill a defect, have also been described with success (46,49).

Meduri *et al.* recently described their success with sutureless AMT secured with a BCL and steri-strip tarsorrhaphy for corneal perforations secondary to inflammatory etiologies (54). A case of a 2-mm traumatic perforation successfully closed with dried amniotic membrane (Omnigen) and Histoacryl glue in the outpatient setting has also been described (55). In active inflammatory conditions such as rheumatologic melts or PUK, performing urgent keratoplasty can result in repeat melts; thus AMT is an optimal temporary solution until the inflammatory disease is controlled systemically. If corneal patch graft or keratoplasty are necessary given the size of the perforation in active disease, AMT can still be used as an adjuvant to decrease inflammation (56).

Clinical indications—conjunctival reconstruction

Pterygia

In the treatment of pterygium, the current treatment standard is to use a conjunctival autograft for coverage of the residual conjunctival defect (7). This is supported by a large Cochrane meta-analysis review of twenty RCTs, in which conjunctival autograft was compared with AMT (57). The review concluded that conjunctival autograft was more effective than AMT in preventing recurrence 6 months post-operatively, with autograft treated eyes having a 47% lower risk of recurrence compared to the AMT group. AMT is still preferred over conjunctival autograft, however, in cases of large residual conjunctival defects after pterygium removal (i.e., primary double headed pterygia, large recurrent pterygia), previously scarred conjunctiva (i.e., prior strabismus surgery), or in cases where the conjunctiva must be reserved for future surgeries (i.e., glaucoma-filtering surgeries) (58). A retrospective review by Rosen found that use of AMT with short exposure of MMC led to low rates of pterygium recurrence (59). Despite the benefit of conjunctival sparing in this technique, no definitive conclusions can be drawn regarding the adjunctive effect of MMC with AMT due to an insufficient number of studies.

Cicatrizing conjunctivitis

AMT has been successfully used in the management of cicatrizing conjunctivitis of various etiologies, such as acute chemical/thermal injury, Stevens Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN), Graft versus Host Disease, and mucous membrane pemphigoid (MMP) (60,61). Early application for grade 2 or 3 SJS/TEN is recommended in the acute phase (62,63). In the only RCT comparing AMT with medical management in SJS-TEN, Sharma *et al.* found that patients treated with adjunctive AMT had significantly better BCVA, longer tear break up times, and decreased conjunctival hyperemia (an indicator of active ocular inflammation). As opposed to the medically managed group, no cases of symblepharon, LSCD, or corneal haze occurred in the AMT group. They concluded that AMT is useful in maintaining BCVA and stable ocular surface in acute ocular SJS-TEN (64). Sheets of AM can be sutured, or even be applied in-office or at bedside using cyanoacrylate glue with good success (65). In cases where a patient cannot tolerate a bedside procedure without sedation, Prokera can be applied. However, as Prokera only covers the cornea and perilimbal conjunctiva, it may

not prevent eyelid margin and forniceal sequelae to the same degree as AMT (66). Ma *et al.* developed their own technique for amnion application using large single sheet of AM with a custom-made forniceal ring that provides eyelid margin and forniceal coverage (67). They advocate that their technique combines the ease of Prokera with the complete ocular surface coverage of the multiple AM sheet technique, allowing for faster bedside application without anesthesia.

Neoplasia

AM has been successfully used in conjunctival reconstruction following the excision of conjunctival tumors. In a retrospective review by Agraval, 53 patients underwent conjunctival lesion excision using a no-touch technique (2 mm margins) and intraoperative cryotherapy, and the residual defect was covered with fresh frozen AM. They found low rates of scarring, symblepharon formation, and granuloma. Authors recommended the use of AM for improving healing and allowing for wider surgical margins, thereby achieving lower margin positivity rates (68). Palamar and colleagues found similar results in their long-term evaluation of ocular surface squamous neoplasia (OSSN) cases undergoing AMT after excision. They concluded that in cases of OSSN requiring greater than 10 mm diameter of lesion excision, AMT is a safe and cosmetically favorable procedure for closing residual defects. The use of AMT precludes the need for large conjunctival autografts, thus avoiding the numerous comorbidities that come with conjunctival autografts, such as scarring, symblepharon, and LSCD (69). Studies evaluating the use of AMT in conjunction with either mitomycin C (MMC) and topical interferon alfa-2b have also shown favorable results in the surgical management of OSSN, restoring a healthy ocular surface with low rates of recurrence (70,71).

Refractory conjunctivochalasis (CCh)

In refractory cases of CCh, AMT has been found to alleviate symptoms, and has also been successfully used to reconstruct the conjunctival surface after removal of the redundant conjunctiva (72-74). In prior studies, favorable results were seen in patients undergoing sutured cryopreserved AM for CCh. In a study by Kheirkhah and colleagues, AMT was secured using fibrin glue rather than sutures to cover bare sclera (74). All eyes in the study achieved a smooth conjunctival surface with significant improvement of symptoms. This may be a useful technique that bypasses the need for sutures, which have the known disadvantages of increased operating time, postoperative discomfort, and suture-related complications (i.e., abscess, granuloma) (74).

Glaucoma surgery

AMT may be a helpful tool in glaucoma filtering surgery, however there is no consensus on its beneficial effects. In a systematic review, Shen *et al.* reviewed five RCTs which compared use of intraoperative AMT in trabeculectomy against a trabeculectomy-only control group. They concluded that the AMT group had significantly lower mean intraocular pressure (IOP) postoperatively at 3 and 12 months, had higher success rates, and had decreased complications of flat anterior chambers and hyphema, leading the authors to recommend adding AMT to trabeculectomy during glaucoma filtering surgery (75). Yazdani and colleagues studied the application of AMT intraoperatively during Ahmed tube shunt placement in a three-armed RCT, comparing AMT against MMC and conventional implantation (76). They found that although AMT was a safe adjunct to the conventional Ahmed tube shunt technique, it did not improve success rates or IOP outcomes.

AMT has also been studied in the management of bleb leaks. Budenz and colleagues performed an RCT to assess whether AMT would be a suitable alternative to conjunctival advancement in the surgical management of late-onset bleb leaks (77). In their technique, AMT was performed after bleb excision. They found no difference in mean IOP between the two groups, however conjunctival advancement had superior survival rate, leading to the conclusion that AMT is not a more effective alternative to conjunctival advancement. In a later retrospective review by Sethi *et al.*, however, a different surgical technique for bleb leak repair with AMT was used, specifically by eliminating the step of bleb excision, and advancing the conjunctiva over the AM (78). They found this subconjunctival AM draping technique to have favorable results. All 17 patients had complete resolution of bleb leak, with significant IOP and visual acuity improvement. Further studies with larger sample sizes are still needed to fully clarify the role of AMT in glaucoma surgery.

AMEED

AMEED are a new avenue of amniotic membrane use, currently being studied in the biologic tear substitute arena. AMEED has already been used to treat dry eye, PED, chemical burns, partial LSCD, cicatricial ocular surface disease, bullous keratopathy, and corneal ulcers with success in small studies (79-84). AMEED has been found to have many of the same properties of cryopreserved AM, with high concentrations of trophic factors. In *in vitro* models, AMEED was found to have immunosuppressive effects on activated lymphocytes, suppressing the activation of natural killer and $CD8^+$ T-cells (85). Growth factors found in AMEED were found to penetrate the cornea successfully in *ex vivo* models (85). AMEED also had lower concentrations of vascular endothelial growth factor than natural tears, making it potentially suitable for conditions in which development of neovascularization is a comorbidity (i.e., chemical burns) (85).

Unlike serum tears, AMEED have the advantage of not needing to be kept frozen. Instead, they can stay at room temperature until reconstituted, after which they can be used for 2 weeks. Furthermore, given that AM used in AMT is devoid of epithelial cells due to cryopreservation, AMEED prepared from fresh tissue may have epithelial cells that can serve as stem cells for epithelial regeneration (86). Unlike AMT, AMEED does not require a surgical procedure, and the treatment can be continued as long as needed for adequate healing (79,86). When used as an adjunctive therapy along with AMT, AMEED may also prolong the efficacy of AMT by intermittently providing necessary growth factors (84,86).

Further studies are required to assess the long-term effects of AMEED, and controlled clinical trials are still needed to determine AMEEDs role in ocular surface disease. To date, there are no studies comparing AMEED against serum tears. Manufacturing processes for AMEED have still not been standardized, and the best method of producing AMEED has yet to be studied.

Conclusions

As shown above, AMT is a valuable adjunctive treatment in the management of numerous ocular surface diseases, with further clinical indications and methods of application being continuously elucidated and developed. It is imperative for ophthalmologists to stay up-to-date on the uses of AMT so as to effectively incorporate this versatile treatment modality into their practice. The main challenge of effectively incorporating AMT in both academic and private practice settings is its inherent cost. Knowledge on how to manage pre-authorizations and appropriate billing is essential since use of AMT can be costly. We recommend having dehydrated AMT available in clinic for emergent needs (i.e., non-healing epithelial defects). In the operating room, having the non-dehydrated form is preferable for the more complex anterior segment surgeries which require multiple layers of AMT.

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