Amniotic Membrane Transplantation in the Management of Severe Ocular Surface Disease: Indications and Outcomes

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ABSTRACT **Since 1995, with the availability of cryopreserved amniotic membrane (AM), the use of AM as a patch or graft for ocular surface reconstruction has become recognized as an important alternative for treatment of persistent epithelial defects and sterile ulceration that are refractory to conventional therapy. A major problem with evaluating the efficacy of AM transplantation is the lack of controlled clinical studies. Moreover, for some diseases there is no accepted "standard" therapy, and the incidence of the disease is too low to allow proper randomization. In this review, we have attempted to assess the indications and outcomes of AM transplantation based on 661 cases reported in the peer-reviewed literature. Successful outcome was defined as the healing of an epithelial defect (corneal or conjunctival) over a specified time period and the lack of induced motility disturbance.**

KEY WORDS **amniotic membrane, aniridia, chemical injury, conjunctivochalasis, leaking filtering bleb, keratitis, neurotrophic keratitis, ocular surface disease, persistent epithelial defect, post-operative epithelial defect, pterygium, stem cell deficiency, symblepharon**

Accepted for publication May 2004

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Supported in part by the Richard A. Perritt Charitable Foundation.

The authors have no proprietary interest in any product or concept discussed in this article.

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Abbreviations are printed in **boldface** where they first appear with their definitions.

I. INTRODUCTION

Fetal membranes, including amnion and chorion, have been used for almost a century in the management of a variety of nonocular diseases. They were first used in 1910 by Davis et al for the management of skin transplantation.[1] Fetal membranes were thought to provide a barrier to infection, promote re-epithelialization and ameliorate pain.

In 1940, deRotth first described the use of fetal membranes for the management of ocular surface disorders.[2] He used fresh amnion and chorion to repair symblepharon in six patients. Since 1940, amniotic membrane (**AM**), both preserved and nonpreserved, has been used in the management of ocular surface diseases affecting the cornea and conjunctiva, mainly severe conditions, such as chemical burns. Brown used rabbit peritoneum to promote healing and inhibit necrosis following acute ocular chemical burn injury.[3] Later, in 1946, Lavery reported the use of an "amnioplastin graft," a chemically processed dry amniotic membrane, as a dressing in a patient with acute alkali injury; repeated applications were necessary.[4] Sorsby reported the use of amnioplastin alone to treat alkali injuries in a series of patients with reportedly good success.[5,6] In 1962, Forgacs et al reported the beneficial effects of placental extracts in promoting corneal epithelial healing in a rabbit model.[7] Batlle and Perdomo in 1993 reported in an abstract the use of alcohol-preserved AM (Russian method) as a graft for pterygium and other ocular surface diseases.[8] Finally, in 1995, Kim and Tseng reported the beneficial effect of AM in a rabbit alkali injury model.[9,10] Since that time there has been a resurgence of interest in AM for ocular surface reconstruction.

A. Characteristics of Amniotic Membrane

Amniotic membrane is the innermost layer of the fetal membranes. It consists of an epithelium, basement membrane, and an avascular stroma. Histologically, the collagen subchains (types IV, V and VII) of the basement membrane in AM are more similar to conjunctival than to corneal basement membrane.[11,12] Other basement membrane

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components include fibronectin, laminin, and a variety of integrins.[13,14] Amniotic membrane has been used fresh,[15] fresh/preserved,[16] frozen,[17] and dehydrated/decellularized.[18] There are no known stem cells in fresh AM, and frozen preserved AM is acellular.

Amniotic membrane exhibits three major biological effects: promotion of epithelialization, inhibition of fibrosis, and reduction of inflammation. It supports epithelialization by promoting migration,[19,20] conjunctival epithelial cell differentiation,[21] and adhesion of epithelial cells.[22] It also restores the conjunctival[23] and corneal and limbal epithelial phenotypes.[24-26]

Amniotic membrane stromal matrix has been shown in vitro to reduce fibrosis by downregulation of TGF-β 1,2,3 signaling, and TGF-β receptor II expression. It also inhibits fibroblast proliferation and myofibroblast differentiation in normal corneal and limbal epithelium,[27] as well as in fibroblasts of normal conjunctiva and that excised from pterygia.[28]

Amniotic membrane reduces inflammation in part by inhibiting IL-1 expression by keratocytes, reducing PMNs in acute chemical injury, and preventing collagen degradation through inhibition of protease inhibitors.[29-31] AM also inhibits a wide variety of pro-inflammatory cytokines including: IL-1α, IL-1 β, IL-2, IL-8, IFN-γ, bFGF, PDGF.[32-34] Recently, Baum suggested that the efficacy of AM in the management of corneal epithelial defects may lie in the combined effects of maintenance of oxygenation, hydration of the epithelium, and mechanical protection from friction of the eyelids.[35]

Amniotic membrane also facilitates apoptosis of PMNs in HSV-1 keratitis.[36] AM can reduce corneal neovascularization.[37] It is nonimmunogenic[38-40] and also bacteriostatic.[41]

Amniotic membrane may provide the microenvironment necessary to restore the stem cell niche. This has been suggested by its ability to expand autologous[42] as well as allogeneic stem cells[43-45] over AM in vitro. In vivo, it may support stem cell viability when used concurrently with keratolimbal allografts.[46]

Actions and mechanisms of AM are discussed in detail in a review by Tseng et al, published in this issue of *The Ocular Surface*.[47]

B. Forms of Amniotic Membrane

Amniotic membrane is available in various forms and from various sources. For instance, in the USA, frozen-preserved AM (AmnioGraft™) is available from Biotissue, Inc. (Miami, FL), and dehydrated-preserved AM (AmbioDry™) is available from IOP, Inc. (Costa Mesa, CA). Discussion of requirements for procuring, processing, and determining suitability for transplantation, as well as detailed discussion of specific products, is beyond the scope of this review. In general, it should be noted that the US-Federal Drug Administration has established useful guidelines for Good Tissue Banking Practice, and precautions should be taken to prevent the transmission of infectious diseases and the loss of cytokines, etc., by some preservation methods.

The vast majority of studies of AMT have used the membrane frozen to –80°C in tissue culture media with antibiotics and antifungal agents for preservation. There are no comparative trials between differently preserved amniotic membranes, such as lyophilized (dehydrated) and frozen preserved.

C. Evaluating Efficacy of Amniotic Membrane Transplantation

One of the major problems with evaluating the efficacy of AM transplantation is the small number of properly controlled clinical studies. Moreover, for some diseases there is no accepted "standard" therapy, and the incidence of the disease is too low to allow proper randomization. Published reports on use of AM, however, have generally described use of this method after failure of conventional therapy, suggesting the efficacy of the tissue. We reviewed the published literature to assess the indications and outcomes of amniotic membrane transplantation.

II. METHODS OF REVIEW

We investigated the indications and outcomes of the use of amniotic membrane transplantation (**AMT**), incorporating data from peer reviewed articles from 1942 to

2003. We conducted a Medline search of all clinical papers using the search terms *amniotic membrane, amniotic, amnion, cornea, conjunctiva, transplantation*. We also reviewed all references from each published article to compile a comprehensive list of papers. We used English language papers only.

Data from published abstracts were not included. Also excluded were those cases where stem cell grafts were performed concurrently and those studying nonhuman subjects. 661 cases were identified, and grouped, where possible, into primary and secondary indications (Tables 1 and 2). Although the vast majority of cases used preserved AM, a few cases reported the use of fresh nonpreserved AM, and these are indicated in Table 4 by "NP."

Table 1 Clinical Modes for Amniotic Membrane Transplantation

	Patch	Graft	Patch + Graft	Totals
Cornea/sclera	137	130	34	301
Conjunctiva		360		360
Totals	137	490	34	661

1. Patch (P): Temporary graft as anti-inflammatory "biological dressing"
2. Graft (G): Basement membrane "scaffold" for epithelialization and AM stroma for anti-inflammatory and anti-scarring actions.
3. Patch + Graft (P+G): Patch serves as a biological dressing to help the epithelium heal over the graft.

Outcomes were defined primarily as the healing of an epithelial defect (corneal or conjunctival) over a specified time period and lack of induced motility disturbance (Tables 3 [conjunctiva][16,48-63] and 4 [cornea]).[5,15,17,49,64-80] Azura-Blanco et al[49] and Meija et al[50] had both corneal and conjunctival/scleral cases, and their data are included in both tables. Unfortunately, in most cases, the vision preoperatively and postoperatively was not recorded consistently and, therefore, could not be used as an outcome measure. Follow-up was also recorded where available as a specific number of months, with or without a range. Recurrence rates were noted as documented. Multiple-surgeon studies were more common than single-surgeon studies and may introduce uncontrolled variability. There was only one controlled study, which was a noncomparative interventional case series of pterygium surgery.[59] All remaining studies were uncontrolled case series, generally following failure of conventional treatment.

For most cases, the indication for AMT included a failure of conventional therapy. There were a wide variety of concurrent and prior medical and surgical therapies in addition to the AMT procedure. Although this might potentially affect the influence of the AMT itself, most cases were severe and had failed prior therapy, and so the effect of the AMT was presumed to be independent.

Concurrent and prior medical therapy included in some, but not all cases, topical/systemic corticosteroids, topical autologous serum, topical cyclosporine, topical antibiotics, topical sodium chromoglycate, topical citrate (6%), ascorbic acid (10%), systemic doxycycline, bandage contact lenses, and patching. Surgical therapy included punctal occlusion, lateral tarsorrhaphy, lash electrolysis, entropion/ectropion repair, mucus membrane grafting, superficial keratectomy, epithelial debridement, penetrating keratoplasty, and stem cell transplantation (not included in this study).

Amniotic membrane was used in one of three ways (Table 1). First, it could be used as a "patch" (**P**), which was defined as the use of AM as an anti-inflammatory, "biological dressing" placed over the ocular surface in order to theoretically reduce inflammation and fibrosis and promote epithelium to migrate *beneath* the amniotic membrane. An AM "graft" (**G**) was defined as the use of amniotic membrane as a basement membrane substrate to promote epithelial healing/migration *over* the AM with or without the associated effect of reducing ocular inflammation. Occasionally, both a patch and a graft were used concurrently. This is noted in Table 4 as P+G. Finally, the "tectonic" indication was for replacement of tissue loss either from the cornea or sclera. These three methods were used in the treatment of ocular surface diseases that involved principally either conjunctival or corneal/scleral surface.

There were a variety of secondary indications for AMT (Table 2). For primarily conjunctival diseases (N=360), secondary indications as a graft included: 1) conjunctival tumors, scars or symblepharon (N=78); 2) primary ptery-

Table 2 Clinical Secondary Indications for Amniotic Membrane Transplantation

1. Conjunctival disease
   a. Conjunctival tumors, scars, symblepharon
   b. Primary pterygium
   c. Recurrent pterygium
   d. Conjunctivochalasis
   e. Leaking filtering bleb
2. Corneal disease
   a. Neurotrophic keratitis
   b. Persistent epithelial defect (PED) with inflammation
      i. Acute chemical injury
      ii. Post-infectious keratitis
      iii. Other (trauma, multiple surgeries, PKP, keratoconjunctivitis sicca, radiation, exposure)
   c. Persistent epithelial defect (PED) with stem cell deficiency (SCD)
      i. Aniridia
      ii. Chronic chemical injury
   d. Planned postoperative epithelial defect
3. Tectonic

gium (N=159); 3) recurrent pterygium (N=33); 4) conjunctivochalasis (N=61); 5) leaking filtering blebs (N=29).

For primarily corneal disease (N=301), the secondary indications for AMT included: 1) neurotrophic keratitis (herpes zoster keratitis, herpes simplex keratitis, V paresis, diabetes mellitus, N=18); 2) persistent epithelial defect with inflammation (vernal and atopic keratoconjunctivitis, N=9; acute chemical injury, N=59; post-infectious keratitis, N=35; and other causes [trauma, multiple surgeries, PKP, keratoconjunctivitis sicca, radiation, exposure, N=27]); 3) persistent epithelial defect associated with stem cell deficiency (ocular cicatricial pemphigoid and Stevens Johnson syndrome, N=16), chronic chemical injury (N=18), aniridia (N=6); and 4) postoperative epithelial defect (painful bullous keratopathy, band keratopathy, Salzman's degeneration, N=78). Some cases of persistent epithelial defect with inflammation had several secondary stated or implied etiologies (e,g., diabetes with postinfectious persistent epithelial defect) and were arbitrarily assigned to either the category of neurotrophic keratitis or persistent epithelial defect with inflammation.

Finally, AM has been used in multiple layers for tectonic indications (N=35).

Outcomes are summerized in Tables 5 and 6.

The most uniform surgical technique for AMT for conjunctival disease involved a thorough excision of diseased conjunctiva (scarring, symblepharon, and pterygium). Amniotic membrane was then cut freehand to fit the defect, either while the AM was still on the filter paper or after its removal from the filter paper (if preserved). The stromal side can be differentiated from the basement membrane side because the former is "sticky" to a Weck cell sponge. Because the membrane contracts somewhat, a generous section was used in most cases. Generally, when the AM was used as a graft, the membrane was placed on the ocular surface stroma to stroma, whereas if it was used as a patch, in general, the basement membrane was placed down facing the ocular surface. A few cases were reported in which the AM was placed with the basement membrane side "up." 9-0 vicryl or 10-0 nylon was used to sew the AM to the episclera and 10-0 nylon was used to sew it to the cornea. Sutures were generally removed in 2-3 weeks.

For the cornea, the surgical technique generally involved removal of the corneal epithelium outside the margin of the defect. In a few cases, a peripheral lamellar pocket was created for amniotic membrane to be inserted. 10-0 nylon sutures were used to secure the AM, using a running ("purse string"), interrupted, or combined technique. As a tectonic graft, several strips of AM were sewn or used together. A second graft of AM was used to provide a surface for epithelium to grow over the tectonic defect. Sutures were removed in 3-4 weeks.

III. DISCUSSION

A. General Discussion

Amniotic membrane is an alternative method for the treatment of persistent epithelial defects and sterile ulceration that are refractory to conventional therapy. AM may assist in promoting epithelial healing, limiting ulceration, and supporting repair.

In the past, conjunctival autografts have been used with good results. However, conjunctival autografts cannot be used in cases of bilateral disease (Stevens-Johnson syndrome, ocular cicatricial pemphigoid), nor can they be used successfully for corneal epithelial disease. Although conjunctiva provides a useful shield, it does not contain the limbal stem cells needed to restore corneal surface integrity. Often, the cornea becomes populated with conjunctival epithelial cells. Unfortunately, this epithelium is inferior to corneal epithelium. Conjunctival epithelium is vascularized and produces an irregular corneal surface, with the antecedent poor visual acuity, and recurrence of erosions.

Since AM provides a stable ocular surface, has unlimited supply and does not require systemic immunosuppression, it appears to be a useful alternative in the treatment of ocular surface disorders. Rapid epithelialization and reduced inflammation, vascularization, and scarring have been demonstrated when AM has been used for surface reconstruction. Further, impression cytologic examination shows that the basal cell density doubles on the amniotic membrane reconstructed surface.[81] In the cases we have reviewed, AM was successful in the majority of cases, although for some indications, the number of patients was small.

Because of the lack of viable cellular elements in AM, we speculate that the duration of the anti-inflammatory effects associated with soluble factors is probably short. In the preserved tissue (–80°C), Sato demonstrated a 50% decrease in TGF-β 1 and 2, bFGF, and HGF after 1 month.[13] Although its role as a substitute basement membrane for conjunctival disease may be apparent, the underlying mechanism of this acellular tissue in the management of more complex reconstructive procedures remains unclear.

The lack of adequate prospective trials with good controls limits adequate assessment of the true efficacy of amniotic membrane transplantation. The reported cases may also be a biased sample, as failures may not be published. Nonetheless, from the results in the published literature, there is evidence that AM provides an effective tool for the management of corneal and conjunctival diseases that are refractory to conventional therapy.

B. Results of Use of Amniotic Membrane in Specific Disorders

1. Symblepharon, Scarring (Table 3)

A success rate of 77% appears good, depending on how success is defined, for cases of symblepharon, with the goal of creating a deep fornix and lack of motility disturbance. Many of the cases had short follow-up periods that were inadequate for appropriate assessment of efficacy. The definition of success was also variable. Eyes with autoimmune disease or ongoing inflammation demonstrated

Table 3. Conjunctival Indications and Outcomes Following Amniotic Membrane Transplantation (Graft)

Indication	Total Eyes (Number)	Success (Number)	Success (%)	Follow-up Mean (mo)	Follow-up Range (mo)	First Author/Year
Scars, symblepharon, etc.						
	14	11	78	11.8	3-28	Tseng, 1997[48]
	10	5	50	10	2-28	Azuara-Blanco, 1999[49]
	1	1	100	3	3	Mejia, 2000[50]
	2	2	100	10	10	Moore, 2001[51]
	4	3	75	17.6	3-28	Paridaens, 2001[52]
	1	1	100	8	8	Shields, 2001[53]
	25	22	88	17.8	12-24	Ti, 2001[54]
	4	4	100	35	34-36	John,2002[55]
	17	14	82	37	9-84	Solomon, 2003[56]
Subtotals	**78**	**63**	**80.7**	**16.7**	**2-36**	
Primary pterygium	46	41	89	10.4	2.5-28	Prabhasawat, 1997[57]
	80	77	96	13.8	6-43	Ma, 2000[58]
	33	32	97	12.8	6.1-23.6	Solomon, 2001[59]
Subtotals	**159**	**150**	**94**	**12.3**	**2.5-43**	
Recurrent pterygium						
	8	5	63	13.3	2.5-23	Prabhasawat, 1997[57]
	4	3	75	14	4-24	Shimazaki, 1998[16]
	21	19	90	14.3	16.3-23.8	Solomon, 2001[59]
Subtotals	**33**	**27**	**82**	**13.9**	**2.5-25**	
Conjunctivochalasis						
	2	2	100	6	NA	Tseng, 1997[48]
	47	46	98	6.9	3-11	Meller, 2000[60]
	12	12	100	8	6-11	Georgiadis, 2001[61]
Subtotals	**61**	**60**	**98**	**7**	**3-11**	
Leaking blebs						
	14	13	93	29.6	26-36	Fujisjima, 1998[62]
	15	8	53	19	NA	Budenz, 2000[63]
Subtotals	**29**	**21**	**72**	**24.3**	**26-36**	
TOTALS	**360**	**321**	**89.1**	**15**	**2-43**	

worsening recurrence. Because the conjunctival phenotype is preserved with AM, this may be superior to buccal or nasal mucosa. Concurrent corticosteroids were also used in most cases.

2. Pterygium (Primary [Table 3])

At about one year follow-up, the recurrence rate for primary pterygium following AMT averaged 6% (N=10/159). All authors had some cases that were followed for less than 6 months, which is not an adequate time period to determine recurrence. The literature on recurrence rates for primary pterygium varies widely. Recurrence rates with free conjunctival grafts also have been reported as 0-39%. The definition of recurrence is also important but less well standardized; i.e., there may be mild, moderate or severe recurrences, but most classify success as either with or without recurrence. Authors may also have different definitions of recurrence. For advanced or diffuse conjunctival involvement, AM may offer an important alternative to conjunctival autografts.

3. Pterygium (Recurrent [Table 3])

To evaluate "recurrence," the definition of recurrence is important. Solomon et el presented standard photos that were used to grade recurrences,[59] but the other authors did not present standard definitions of recurrence. Solomon et al also suggested that the degree of subepithelial fibrous excision and the use of depot triamcinolone acetonide (4-8 mg) played an important role in reducing the recurrence rate, and this could have been a confounding influence on the recurrence rates in their series. AMT may be useful in cases where adequate conjunctival tissue is not available, such as in bilateral or advanced cases, or in those with glaucoma, where preservation of the conjunctiva is important for possible filtration surgery. More recently, Shimazaki et al presented a combination of AMT and conjunctival graft vs limbal grafts and found no benefit from limbal grafts when associated with AMT.[83] Data from that study is not included in this review because of the combination therapy.

Table 4. Corneal Indications and Outcomes Following Amniotic Membrane Transplantation

Indication	Total Eyes	Patch/ Graft	Healed Defect	Improved Vision	Success (%)	Follow-up (Months)	First Author/Year
NEUROTROPHIC KERATITIS							
	2	G	2	NA	100	8.9	Lee, 1997[64]
	1	P	1	NA	100	NA	Azuara-Blanco[49]
	1	P	1	1	100	8	Chen, 2000[65]
	9	P+G	9	6	100	16.7	Chen, 2000[65]
	5	P+G	4	NA	80	NA	Gris, 2002[66]
Subtotals	**18**		**17**		**94**		
PED WITH INFLAMMATION							
Vernal and atopic	1	p	1	0	100	7	Letko, 2001[67]
	1	G	1	0	100	32	Letko, 2001[67]
	7	P	7	NA	100	NA	Sridhar, 2001[68]
Subtotals	**9**		**9**		**100**		
Acute chemical injury							
	30	P	27	27	90	NA	Sorsby, 1946[5]
	28	P	25	25	89	NA	Sorsby, 1947[6]
	10	P	9	9	90	10.1	Meller, 2000[69]
	1	P	1	1	100	4	Sridhar, 2000[70]
Subtotals	**59**		**62**		**90**		
Post-infectious keratitis							
	3	G	3	NA	100	12.7	Lee, 1997[64]
	3	G	1	NA	33	NA	Azuara-Blanco, 1999[49]
	12	P	11	12	92	18	Kim, 2001[71]
	6	P+G	4	2	67	18	Kim, 2001[71]
	3	G	3	2	100	18	Kim, 2001[71]
	5	P	4	NA	80	5.8	Letko, 2001[67]
	3	G	3	NA	100	8.7	Letko, 2001[67]
Subtotals	**35**		**29**		**83**		
Miscellaneous							
	1	G	1	NA	100	12.5	Lee, 1997[64]
	3	G	3	2	100	8.6	Tseng, 1998[17]
	1	P	NA	0	0	NA	Azuaro-Blanco, 1999[49]
	3	P	2	2	67	7.7	Meller, 2000[69]
	1	P+G	1	1	100	15	Pires, 2000[72]
	8	P	4	2	50	5.75	Letko, 2001[67]
	1	G	1	1	100	3	Letko, 2001[67]
	8	P	2	NA	25	NA	Gris, 2002[66]
Subtotals	**27**		**15**		**56**		

***Table 4** continues on following page*

4. Conjunctivochalasis (Table 3)

Although the authors state that these cases were symptomatic and failed conventional therapy, because of the lack of control subjects, the exact benefit of AM itself over conjunctival excision alone could not be determined. Liu reported the beneficial effect of simple conjunctival excision.[82] Patients in this series were also symptomatic and had failed conventional nonsurgical therapy. There were a small number of cases of scarring and symblepharon following the repair, which may be an acceptable risk in symptomatic patients.

5. Leaking Filtering Blebs (Table 3)

Amniotic membrane transplantation does not seem to be effective in the management of leaking filtration blebs when placed over the bleb leak. Although the success rates appeared higher when the AM was placed within the trabeculectomy flap to inhibit fibrosis, there was a high percentage of complications, including flat chambers, as well as the need for repeated procedures.

6. Neurotrophic Keratitis (Table 4)

Although the outcomes appeared excellent for this indication, it was difficult to evaluate the mechanism of action of AM because 14/18 cases used AM as both a patch and a graft. The follow-up periods were adequate. The presence and degree of stromal lysis was not indicated and may influence the outcomes of the procedure. Again, the results are good considering that these cases failed con-

Table 4. Corneal Indications and Outcomes Following Amniotic Membrane Transplantation *continued*

Indication	Total Eyes	Patch/ Graft	Healed Defect	Improved Vision	Success (%)	Follow-up (Months)	First Author/Year
PED WITH SCD OCP/SJS							
OCP, SJS, SCD	10	G(NP)	10	6	100	13.5	Honavar, 2000[15]
	1	P(NP)	1	1	100	9	Mejia, 2000[50]
	2	P	1	1	100	9.5	Letko, 2001[67]
	2	P	1	1	50	5.5	Letko, 2001[67]
	1	P	1	1	100	23	Letko, 2001[67]
Subtotals	**16**		**14**	**10**	**88**	**12.1**	
Anirida							
	3	P	3	3	100	17	Tseng, 1998[17]
	1	G	NA	NA	0	12	Letko, 2001[67]
	2	P	1	NA	50	NA	Gris, 2002[66]
Subtotals	**6**		**4**		**67**		
Chronic chemical injury							
	4	P	4	4	100	11.5	Tseng, 1998[17]
	6	P	1	NA	17	NA	Azuaro-Blanco, 1999[49]
	2	G	1	2	50	36	Anderson, 2001[73]
	3	P	1	1	33	5	Letko, 2001[67]
	1	G	1	NA	100	2	Letko, 2001[67]
	2	P	1	NA	50	1	Gris, 2002[66]
Subtotals	**18**		**9**		**50**		
POST-OPERATIVE PERSISTENT DEFECT							
	1	G	1	NA	100	14	Lee, 1997[64]
	50	G	45	9	90	33.8	Pires, 1999[74]
	14	G	13	3	93	14.6	Anderson, 2002[73]
	3	P	3	NA	100	NA	Gris, 2002[66]
	1	P	1	1	100	22	Letko, 2001[67]
	9	G	9	NA	100	9.2	Mejia, 2002[75]
Subtotals	**78**		**72**		**92**		
TECTONIC							
	4	G	3	NA	75	4.1	Lee, 1997[64]
	11	G	9	6	82	12	Kruse, 1999[76]
	1	G	1	1	100	12	Rodrigues-Ares, 1999[77]
	4	G	2	3	50	28	Chen, 2000[65]
	2	P+G	2	1	100	13.75	Chen, 2000[65]
	1	G	1	1	100	5	Gabler, 2000[78]
	11	P+G	8	3	70	10.2	Hanada, 2001[79]
	1	G	1	1	100	6	Su, 2000[80]
Subtotals	**35**		**27**	**16**	**77**	**11.4**	
GRAND TOTALS	**301**		**258**		**85.7**		

NP= non-preserved AM. NA=not applicable
OCP=ocular cicatricial pemphigoid. PED=persistent epithelial defect. SCD=stem cell deficiency. SJS=Stevens-Johnson syndrome.

ventional management. The success rates were also variable, with recurrence of epithelial defects a concern.

7. Vernal and Atopic Keratoconjunctivitis (Table 4)

The small number of cases in this category limits the significance of the excellent reported outcome.

8. Acute Chemical Injury (<10 days [Table 4])

Although the results of Meller et al[69] provide evidence that acute chemical injury (<10 days) is an appropriate indication for AMT, we decided to also include data from the early series of Sorsby and Symons[5] in this category, even though Sorsby and Symons did not use the same preparation of AM as the frozen tissue used by Meller et al. The severity of the injury plays a significant role in determining the efficacy of AM in this group of patients. For severe burns in the study of Meller et al, AM was not effective in reducing the development of limbal stem cell deficiency. These cases were all treated within less than 10 days of injury, about the same time period in which the

epithelium begins to heal with more conventional methods. The series was small without a control group.

9. Post-Infectious Keratitis (Table 4)

Amniotic membrane was used following the eradication of the infectious organism. The role of metalloproteinases (MMP-1 and MMP-2) in the process of stromal melting is well known. There may be a theoretical benefit from AM in reducing collagenolysis.[31] Clinically, there was noted reduction in inflammation with the AM. AM may also mechanically block the migration of PMNs to the site. AM may also promote healing and prevent progressive melting.

Table 6. Indications and Outcomes Summary: Corneal Disease

Primary Diagnosis	Secondary Diagnosis	Success Rate
Neurotrophic keratitis PED with inflammation		94%
	Vernal and atopic	100%
	Acute chemical/thermal	90%
	Post-infectious	83%
	Miscellaneous	56%
PED with SJS, SCD, OCP		
	OCP, SJS, SCD	88%
	Chronic chemical injury	50%
	Aniridia	67%
Primary surgical defect		92%
Tectonic		77%

10. Ocular Cicatricial Pemphigoid and Stevens-Johnson Syndrome (Table 4)

Although many studies have examined the use of AM with stem cell transplantation, the results herein are for AM alone. Complete reepithelialization as a measure of success occurred in 88% of cases. The follow-up periods were adequate. The corneal pannus recurred in most patients, consistent with the diagnosis of stem cell deficiency.

11. Aniridia

About 67% of defects healed. The only graft of AM did not heal.[67] The numbers were small in this group, so conclusions are uncertain.

12. Chronic Chemical Injury

In eyes with persistent epithelial defects from chemical injury, AM was not effective as a patch. There was wide variability in the results, which may be secondary to severity of the stem cell deficiency and degree of inflammation.

13. PED Postoperative (Primary Procedure)

In patients with poor visual prognosis secondary to retinal disease, the use of AM may be beneficial. The Gunderson flap is another option, with its associated side effects of upper lid ptosis, worse postoperative appearance, and a more prolonged postoperative course. AM seems to be more resistant to bullae, easy to perform, and aesthetically more acceptable. In locations where preserved AM is not available or its cost is prohibitive, nonpreserved AM is sometimes used. If used, it should be used with caution and with awareness of potential problems associated with it, e.g., transmission of infectious agents.

Table 5. Indications and Outcomes Summary: Conjunctival Disease

Diagnosis	Success Rate
Conjunctivochalasis	98%
Leaking filtering blebs	72%
Pterygium 1'	94%
Pterygium 2'	82%
Scarring	81%

14. Tectonic (Multiple Layers)

The 76% success rate of AMT in this category may be misleading. The results were quite variable, with a variety of adjunctive procedures performed, including bandage contact lenses, tissue glue, patch and graft. Most cases had deep ulceration, and a few had frank perforations. In most cases, the degree of inflammation was reduced after AMT, although in none of the cases reported in the studies reviewed herein did the membrane reduce the degree of neovascularization. When the defects did heal, they seemed to last for up to one year. Failures were associated with autoimmune disease.

IV. SUMMARY

Amniotic membrane appears to provide an important resource to ophthalmic surgeons in the management of patients with severe ocular surface disease who have failed conventional medical and surgical therapy. Although the published literature suggests that AM may be superior to conventional therapy, prospective, controlled clinical trials are certainly needed to properly assess the clinical efficacy of this tissue. Although there are several suppliers of the tissue, the high cost of the membrane and low but real potential for transferring disease remain a concern.

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