Dry Eye and Ocular Surface Disease

Management strategies for persistent epithelial defects of the cornea

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Abstract

Management of patients with persistent epithelial defects of the cornea can be challenging to even the seasoned ophthalmologist. It is essential that one understands not only the pathophysiology of the failure of the epithelium to migrate and close a wound appropriately, but also the mechanism of action of the available treatment modalities at one’s disposal. This article serves as a review of current standard therapies, recently introduced alternative therapies gaining in popularity, and a look into the newest developments that may change the way we manage corneal surface disease.

Keywords: Persistent epithelial defect, Non-healing epithelial defect, Autologous serum, Scleral contact lens, Amniotic membrane

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Introduction

The cornea accounts for two-thirds of the refractive power of the eye. It is a structure composed largely of collagen and water that is maintained and protected on its anterior and posterior surfaces by the epithelium and endothelium, respectively. Transparency and preservation of surface architecture are both of primary importance. Ocular disease that compromises the epithelium, in particular, can have devastating consequences to vision and overall ocular health. The epithelium, several layers thick, is a barrier composed of a tightly linked network of cells attached by hemidesmosomes and gap junctions, serving as the eye’s first line of immunological defense.1 After a corneal abrasion, for example, the eye typically epithelializes and resurfaces the wound quickly and uneventfully. In the presence of certain risk factors, including corneal hypesthesia, diabetic keratopathy, limbal stem cell deficiency, dry eye disease, exposure keratopathy, and neurotrophic keratopathy from herpetic infections or previous corneal transplantation, epithelial defects can persist beyond the usual treatment period despite standard therapies.2,3 In accordance with the literature, when a patient has been treated for approximately two weeks to no avail, they are said to have a persistent epithelial defect, or PED.4

Although uncommon, management of patients with PEDs can be quite challenging and may require an extended follow-up period. This article will serve as a review of current standard therapies, recently introduced alternative therapies gaining in popularity, and a look into the newest developments that may change the way we manage corneal surface disease.

Standard therapies

The first step in the management of any epithelial abnormality is to determine the etiology of the disease. The
definitive management of ocular surface disease (OSD) secondary to exposure keratopathy from thyroid eye disease, for example, may be vastly different from a patient with OSD who suffers from graft-versus-host disease (GVHD) or limbic stem cell deficiency (LSCD) from an alkali burn. In these cases, treatment of the underlying processes is necessary in order for local therapy for the OSD to be successful.

Aggressive lubrication

This is typically first-line therapy with either high frequency application of preservative-free artificial tears or sterile ophthalmic ointment. This may prove to be particularly difficult with the noncompliant patient.

Discontinuation of medications

An often overlooked reason for a PED may ultimately be iatrogenic. This is sometimes referred to as “medicamento-sa,” or toxic keratitis stemming from topical ophthalmic medications themselves. Common offenders tend to be antibiotics, antivirals, and anti-glaucoma medications; however preservatives such as benzalkonium chloride ubiquitous in ophthalmic preparations are usually the real culprit. Although discontinuation of the offending agent may not be medically indicated given the ocular circumstance, if indicated, however, shifting to a different agent or stopping altogether may prove to be curative.

Punctal occlusion

To increase epithelial contact time with lubricating tears and ointments, patients may benefit from temporary or permanent occlusion of the puncta. This is not recommended in circumstances requiring the continued use of toxic agents, as mentioned above.

Bandage soft contact lens

The use of soft lenses can be effective in the treatment of PEDs as they aid in the epithelialization process by protecting the advancing epithelial cells from being sloughed-off by the blinking eyelids, as well as by providing anesthetic relief. They cannot be used alone, however, as these patients are at risk for infectious keratitis as well as worsening of the epithelial defect from dry eye. Therapy should be supplemented with preservative-free artificial tears frequently to prevent the lens from sticking to the ocular surface, as well as a broad spectrum antibiotic drop. Even with antibiotic coverage, there is still a risk for infection and neurotrophic corneas may delay a patient’s presentation back to the clinic; therefore close follow-up is a necessity in this population.

Pressure patching

This is a common treatment modality for large corneal abrasions, and it is an alternative therapy for PEDs offering similar benefits conferred by the contact lens use. Drawbacks include the need to see patients every 24–48 h as prolonged patching may impair wound healing, while also being a risk factor for infectious keratitis. Given the typical length of time involved in resolution of these defects, requiring such frequent examination may be inefficient for the practitioner and taxing on the patient.

Debridement

At times, the leading edges of the healing epithelium may thicken and become stagnant, impeding subsequent growth across the defect. In this case, the leading edges may be removed thereby permitting the more peripheral, younger, and healthier epithelium to continue its migration across the cornea.

Tarsorrhaphy

Less frequently implemented, but highly effective is the use of temporary or permanent tarsorrhaphy in the management of the PED. This therapy limits corneal exposure and permits repair even in the harshest environments. Simple lid taping, especially in the evening, is effective for 24–48 h at a time, while lid opposition with cyanoacrylate glue may last up to 5 days. Temporary suture tarsorrhaphy with bolsters may last up to 6 weeks which can be less intimidating for the patient concerned about cosmetic appearance from a permanent procedure. Some specialists advocate for the injection of botulinum toxin A into the levator muscle to keep the surface covered for months at a time still permitting frequent ocular examination, if needed, but without the need to surgically close the eyelids. Each of these options can be conveniently performed in a minor procedure room.

Newer therapis

Amniotic membrane grafting

Amniotic membrane patching and grafting have been shown to decrease inflammation, vascularization, and scarring of the cornea while promoting the re-epithelialization of the cornea. It is thought to achieve this through the release of certain growth factors and proteins. It is now readily available commercially in fresh frozen (Amnion; Bio-Tissue, Inc., Miami, FL) and freeze-dried forms (Ambiodry2; IOP Ophthalmics, Costa Mesa, CA). The tissue may be sutured or glued in place with fibrin glue. There is also a self-retaining amniotic membrane device that can be placed in the office (ProKera; Bio-Tissue, Inc., Miami, FL).

Autologous serum (AS)

Standard therapies for PEDs mentioned above such as artificial tears, punctal occlusion, and tarsorrhaphy fail to introduce the cornea the essential growth factors found in natural tears. Topical tears formulated from a patient’s own centrifuged serum is gaining popularity, and studies continue to report favorably on its efficacy in the management of many types of OSD, including PED. 47–83% of PEDs recalcitrant to standard therapies have been shown to be closed within four weeks of initiating autologous serum tear therapy. Its beneficial effects are thought to be due to high concentration of key components involved in the proliferation and migration of the epithelium; components that are found in varying concentrations in natural tears, but are generally scarce or lacking in artificial tears. These factors include vitamin A, vitamin E,
epidermal growth factor (EGF), transforming growth factor-B (TGF-B), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), fibronectin, substance P, insulin-like growth factor (IGF), and nerve growth factor. Unfortunately, obtaining autologous serum tears is not without its difficulties. There is no validated, standardized protocol for developing the tears from whole blood, although Liu and colleagues have offered what they believe to be their optimized protocol. As a result, regulatory restrictions on the manufacturing of autologous serum tears continue to keep this beneficial therapy from more mainstream use both on national and international levels. In addition, it is not known what is the optimal concentration of autologous serum eye drops. Although 20% autologous serum is a popular concentration (thought to be optimal because this percentage dilutes the concentration of TGF-B to that which is the normal level in the tears), other concentrations such as 50% and 100% are used by some authors. It is possible that different OSD entities may respond differently to different concentrations, but there have been no clinical trials that have offered us this information at this time.

Other whole blood-derived products

Not all patients are ideal candidates for autologous serum: this includes those patients who are systemically ill, are in poor general health, or suffer from active infection; or those patients with disease whereby excess pro-inflammatory cytokines may be present in the serum, such as in a patient with GVHD or the Sjogren Syndrome. Alternative therapies gaining more recent attention include umbilical cord blood serum (CBS) tears and platelet-rich fibrin (PRF) tears. Some studies have shown CBS to be more efficacious than autologous serum in the resolution of epithelial defects, thought to be due, in part, to elevated growth factor levels and more anti-inflammatory cytokines as compared to autologous serum. Vajpayee and colleagues conducted a prospective, randomized, controlled clinical trial of 60 eyes of 59 patients assigned to either the umbilical cord serum treatment group or the autologous serum control group in the management of persistent corneal epithelial defects. They found that the cord serum group had significantly faster healing times and a greater number of defects with complete re-epithelialization as compared to the autologous serum group. Yoon et al. compared the difference in therapeutic effect between autologous serum and umbilical cord serum in the treatment of dry eye syndrome and found that the cord serum was more effective at decreasing symptoms and keratoepitheliopathy in severe dry eye syndrome as well as increasing goblet cell density in the Sjogren Syndrome. Its efficacy is also well substantiated for numerous conditions including but not limited to dry eye, PEDs, recurrent corneal erosions, chemical burns, and neurotrophic keratopathy. One primary advantage of making tears from CBS is the fact that blood taken from the umbilical vein can supply tears to many patients all at once; and be available for pickup immediately upon prescribing, rather than the alternative time-consuming process involved in having a patient undergo phlebotomy followed by waiting for ophthalmic preparation. The chief disadvantage, however, is the risk of transmission of blood-borne infectious disease from pregnant donors. For this reason the blood must be tested rigorously before becoming available to a patient. This may ultimately prove to be less desirable to some patients. A newer alternative to AS is platelet rich plasma tears (PRP). Platelets are better recognized for their role in hemostasis and vascular injury, but they also play a significant part in wound repair throughout the body, influencing angiogenesis and inflammation. The alpha-granules released from activated platelets contain growth factors and cytokines including PDGF, EGF, TGF-B, FGF, and IGF-1. It is thought that because PRP contains a higher concentration of these vital epitheliotrophic factors than serum, this therapy may prove to be more valuable than AS. In the first comparison of AS to PRP, Kim and colleagues found that the rate of epithelial healing was significantly greater in the PRP group. PRP is similar to AS in that it, too, has no standardized and validated protocol making its availability to treating physicians problematic.

Limbal stem cell transplantation

If the etiology of the PED is due to the deficiency of the stem cells that are responsible for repopulating the epithelium, then surgical replacement with stem cell allografts is indicated. This is frequently seen in conditions such as ocular cicatricial pemphigoid, Stevens Johnson Syndrome, and severe alkali burns. However, care must be taken to assess whether a stem cell transplant will have a reasonable likelihood of surviving given the ocular surface condition. A major disadvantage of this procedure is that allografts of limbal stem cells require that the patient is systemically immunosuppressed and long-term follow-up of these patients has demonstrated disappointing survival rates. Recently, Boston keratoprosthesis implantation has emerged as an effective modality for visual rehabilitation in such patients.

Scleral contact lenses

Becoming more frequently utilized in dry eye disease secondary to GVHD or chemical burns, the Boston Scleral Lens, now referred to as the PROSE (Prosthetic Replacement of the Ocular Surface Ecosystem; Boston Foundation for Sight, Needham, Massachusetts) has demonstrated efficacy in the treatment of PEDs. It is known that a continuous supply of oxygen is needed to support the repair and growth of a healthy epithelium. During sleeping hours, however, closed eyelids decrease the partial pressure of oxygen on a contact lens surface which is even further attenuated as this fluid diffuses through the lens matrix to the ocular surface. In the PROSE, the fluid-tear interchange under the haptic provides an additional route for oxygen delivery during sleep that bandage contact lenses and pressure patching cannot provide. Its unique design integrates a series of radial venting channels between the haptic and the sclera that function as a safety valve through which tears get aspirated alone, without air bubbles, and without the development of suction. Of course similar to other ocular surface lenses, eyelid-corneal friction is also eliminated. Consideration of concurrent prophylactic antibiotic therapy is warranted if used for PED.

Therapies in development

Novel therapies recently being investigated are beginning to show promise in the treatment of the nonhealing corneal epithelium.
Thymosin beta 4 (Tb4)

Thymosin beta 4 is a synthetically produced copy of a 43-amino acid peptide found in most tissue types, with the highest concentration being in blood platelets and white blood cells, and extracellular in blood plasma and wound fluid. It has been demonstrated to promote corneal wound re-epithelialization, diminish inflammation, and inhibit apoptosis. Its most unique property is its anti-inflammatory effects, although the precise mechanism is still under investigation. In vivo studies suggest that it interrupts the transcription of the pro-inflammatory mediator involved in many ocular diseases, decreasing levels of other transcription factors including NF-kB and its downstream cytokines are shown to be destructive to the cornea. TNF-alpha is a well-known, potent pro-inflammatory mediator involved in many ocular diseases (infectious, auto-immune, and sterile inflammatory). Therapy directed at modulating this particular pathway may have beneficial effects on the eye that spread far beyond ocular surface disease. Sosne and colleagues, for example, are currently working on a TB4 drug delivery system through specially formulated hydrogel bandage contact lenses. There is limited data with human trials, as studies are limited to FDA-approved compassionate use only, although results thus far seem promising.

Nexagon

Nexagon (connexin43 antisense gel; CoDa Therapeutics, Inc., New Zealand) is among the latest of novel drugs aimed at healing PEDs, in particular in those due to severe ocular burn or chemical injury. Connexin43 is one of the 20 human connexin proteins that comprise cellular gap junctions. Gap junctions provide a direct communication between cells, permitting transfer of molecules and ions which can subsequently influence a multitude of signaling pathways. Preclinical models have shown that the decreased translation of connexin43 has led to a decrease in edema, inflammation, apoptosis, and overall improved healing. This has been observed in skin incisions, skin burns, the cornea, cardiac ischemia, and the central nervous system. Connexin43 gap junctions also seem to play a role in bystander death, a term used to describe the process of apoptotic spread among cells. Dying cells have been shown to induce apoptosis in nearby cells in direct proportion to the number and density of gap junctions within the dying cell. This process of cell death leads to stagnation of wound closure or enlargement of wound defects, referred to as lesion spread. Results from compassionate use non-controlled human trials with Nexagon in chemical and thermal ocular injury leading to PEDs have been encouraging.

Mesenchymal stem cells

Autologous adipose-derived mesenchymal stem cells (MSCs) have recently been introduced as a potential breakthrough therapy for PED and stromal ulceration. These cells are multipotent and therefore have the capacity to differentiate into any human cell type. Although used experimentally in animal research, the first known application in a human cornea was published in 2011 of a patient with keratoconus and a persistent epithelial defect following trauma. He was scheduled for a penetrating keratoplasty due to his high risk for perforation, and he was offered this experimental therapy in the interim before surgery. The defect successfully closed within a month without further sequelae. The mechanism of action remains unclear, although several theories exist. Whether it will be secretion of trophic factors and cytokines influencing neighboring cells, its immunomodulatory effects, or its direct differentiation into corneal stromal cells, autologous MSC transplantation calls for further investigation into its mechanism and application in corneal regenerative therapy.

Conclusion

Managing the persistent epithelial defect can be both an arduous task for the ophthalmologist and a burden to the patient; the conventional therapies tend to be ineffective thereby prolonging patient discomfort and their diminished visual acuity, as well as requiring frequent clinic follow-up at a cost to society and worker productivity. Interestingly, one study has shown that the length of time a defect is left open and unhealed is directly proportional to the time it will take for the defect to be fully repaired. This would argue for prophylactically managing patients at high risk for developing PEDs: it may be prudent to be more aggressive at the onset of epithelial compromise in certain patient populations. There is an encouraging future for the management of persistent epithelial defects, as alternative treatment modalities are proving beneficial and efficacious, while promising newer therapies are under investigation.

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Conflict of interest

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References


