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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

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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 limbal 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.[2] 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 ''medicamentosa,'' 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.[5,6] 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.[1]

### *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,[7–9] 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[10,11] 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.[12] Each of these options can be conveniently performed in a minor procedure room.

## Newer therapies

### *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.[13–15] 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.[16] 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 to 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.[3,17–21] 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,