The corneal epithelium, composed of nonkeratinized, stratified squamous epithelial cells, is essential to the normal functioning of the eye. In addition to providing a transparent conduit for visual stimuli to pass to the retina, the cornea—and specifically the corneal epithelium—provides one of the first lines of immunologic defense for the eye. The epithelial cells are connected by hemidesmosomes and gap junctions that prevent infectious agents from penetrating the eye under normal circumstances. The maintenance of a healthy functioning corneal epithelium is dependent on a healthy normal corneal nerve network. A breach in the integrity of the corneal epithelium results in a wound-healing response. Although most corneal epithelial defects heal quickly and without incident, under certain conditions the epithelial defect may be slow to heal, or it may not heal at all. When these defects do not heal within the normal time frame (usually defined in the literature as 2 weeks), they become known as persistent epithelial defects (PED).

Fortunately, PED of the cornea are uncommon, but in addition to their immediate adverse effects on vision and often on comfort, PED can have serious consequences for the health of the eye that include infection, scarring, melting, and perforation. Etiologies for PED include dry eye, exposure keratopathy, limbal stem cell deficiency, diabetic keratopathy, neurotrophic keratopathy following corneal transplant surgery (involving the anterior portion of the cornea), and herpetic infections.

Numerous standard therapies can be used in an attempt to heal PED. Additionally, a number of new therapies have recently been introduced, and there are promising alternatives in the pipeline. This article reviews these available and potential treatment options for treatment of PED.

LISTED BELOW IN ORDER IS A STEP-WISE APPROACH TO STANDARD THERAPIES FOR PED. STEPS MAY SOMETIMES BE SKIPPED BASED ON INDIVIDUAL CIRCUMSTANCES.

**Aggressive lubrication.** In general, traditional medical therapy of PED starts with aggressive lubrication using preservative-free artificial tears and ointments. In many instances, the ocular surface fails to heal simply because the surface is too dry. Discontinuation of medications. On occasion, epithelial defects fail to heal because the patient is using topical medications that contain preservatives toxic to the corneal epithelium, such as benzalkonium chloride. Sometimes the medications themselves are toxic and inhibit healing; these include fortified vancomycin drops. Simply stopping these medications, if appropriate based on the patient’s overall ocular situation, can be curative for PED.

**Punctal occlusion.** If the ocular surface can be freed from the toxic effect of unnecessary medications, then punctal plugging can augment the beneficial effects of aggressive lubrication by keeping the lubrication on the eye for a longer time. It is not recommended to plug the puncta when toxic medications are still being used because this will keep the toxicity in contact with the ocular surface for even longer.

**Bandage soft contact lens.** Bandage soft contact lenses are effective devices for treating PED. They can protect the fragile, healing epithelium from sloughing because of blinking. It is important, however, to keep the eye lubricated to protect the lens from drying out and sticking to the ocular surface. Therefore, it is recommended for all patients using bandage soft contact lenses to apply preservative-free artificial tears every 1 to 2 hours. Furthermore, there is a known risk of infectious keratitis with contact lens use, so it is recommended to prescribe a broad-spectrum topical antibiotic drop such as a fourth-generation fluoroquinolone or polymixin B-trimethoprim combination. Even with antibiotic prophylaxis, infectious keratitis can occur, so patients should be educated regarding the warning signs of infectious keratitis. However, because in many instances PEDs are neurotrophic, patients may not notice symptoms associated with infectious keratitis. Frequent follow-up in these patients is of utmost importance.

**Pressure patching.** Pressure patching is an alternative to bandage soft contact lenses. Although in routine corneal epithelial defects (not PED) pressure patching is a popular
TAKE-HOME MESSAGE

- A step-wise approach to standard PED therapies may include aggressive lubrication, discontinuation of medications, punctual occlusion, bandage contact lenses, pressure patching, debridement, and tarsorrhaphy.
- Alternative therapies include amniotic membrane grafting, topical autologous serum, and limbal stem cell transplantation.
- Thymosin beta 4, Nexagon, and scleral contact lenses are currently being investigated for treatment of nonhealing epithelial defects.

NEWER THERAPIES

In some cases, standard medical therapies for treating PED do not work. The following therapies have recently been popularized.

Amniotic membrane grafting. This approach has been suggested for use in accelerating the corneal epithelial wound healing process in PED. Additionally, it acts as a temporary bandage on the ocular surface, as it is believed that amniotic membrane contains growth factors and other substances that are crucial to the proliferation and migration of the corneal epithelial cells. Amniotic membrane, now available commercially in fresh-frozen (Amnion; Bio-Tissue, Inc., Miami) or freeze-dried (AmbioDry2; IOP Ophthalmics, Costa Mesa, California) forms, can be sewn into place over the PED. More recently, it has been suggested that the membrane can be glued in place using fibrin glue. Amniotic membrane is also available as a self-retaining device (ProKera; Bio-Tissue, Inc.) that can be inserted in the office.

Autologous serum. Topical autologous serum has been reported to be efficacious in treating persistent epithelial defects. First described for this purpose in 1999 by Tsubota and colleagues, this modality has become quite popular. With use of autologous serum, 47% to 83% of PED recalcitrant to standard therapies healed within 4 weeks of initiation of autologous serum therapy. A recent study found that, for PED recalcitrant to standard therapies, the length of time a defect is left open prior to treatment is directly related to the length of time required for healing. Thus, theoretically, the earlier in the course of the disease treatment is initiated, the faster the PED will heal.

Unfortunately, the use of topical autologous serum is often troublesome because there is no standardized protocol for processing whole blood to be made into autologous serum eyedrops. Therefore, few clinical laboratories and clinics are equipped to prepare this product. Liu and colleagues have recommended an optimized protocol for the processing of whole blood for autologous serum, but this protocol has not yet been validated. Additionally, at this time, regulatory restrictions are still limiting the ability to produce autologous serum for therapeutic use in some areas. Umbilical cord serum has been investigated as an alternative to autologous serum, given the potentially higher levels of nutrients in this product, but there are regulatory issues with using this blood product as well.

Limbal stem cell transplantation. In the event that an identifiable etiology can be established, specific treatments can sometimes be instituted. For example, in PED secondary to limbal stem cell deficiency, limbal stem cell transplantation can be employed.

IN THE PIPELINE

Several novel treatments are now being tested for use in healing the nonhealing corneal epithelium.

Thymosin beta 4. Thymosin beta 4 (Tb4) is a synthetically produced copy of a naturally occurring 43-amino acid peptide that is found in high concentrations in most tissue types, with the highest concentrations in blood platelets and white blood cells, and extracellularly in blood plasma and wound fluid. It is one of a family of at least 16 highly conserved peptides, collectively called beta-thymosins, which are present in high concentrations in almost every cell type. Tb4 has wound-healing and antiinflammatory properties, and it is thought to exert its therapeutic effect through promotion of keratinocyte and endothelial cell migration, increased collagen deposition, and stimulation of angiogenesis. Preclinical and animal models have suggested that this compound has applications not only for dermal epithelial...
healing, but also for the corneal epithelium. A series of compassionate use studies, such as one conducted by Dunn and colleagues, have demonstrated promising results for the use of this compound for treating PED.22

**Nexagon.** Nexagon (connexin43 antisense gel; CoDa Therapeutics, Inc., New Zealand) is a novel selective inhibitor of connexin43 expression being developed for the treatment of ocular and skin wounds. Connexin43 is one of 20 human connexins, the constituent proteins of gap junctions. Gap junctions serve as conductive channels that connect adjacent cells to allow the transmission of molecules and ions, mostly small intracellular signaling molecules such as triphosphoinositol and calcium. Previous research has revealed that direct cell-to-cell communication through connexin43 gap junction channels plays a major role in wound healing; dying cells induce apoptosis in neighboring cells in direct proportion to the number and density of gap junctions within the dying cells.23 This process, known as bystander death, leads to an increase in wound size referred to as lesion spread. Topical administration of Nexagon to wounds has been shown to bring about a transient downregulation of connexin43 protein levels, resulting in reduced lesion spread and a dramatic increase in the rate of wound closure.24 Nexagon has recently shown encouraging results in compassionate use applications on the corneas of eyes with PED, all of which were caused by chemical burns (personal communication). A prospective clinical trial of using this compound in the setting of nonhealing defects from oculr burns is ongoing, and other trials are investigating the use of this compound in healing PED from other causes.

**Scleral contact lenses.** The use of large fluid-ventilated scleral contact lenses has recently gained popularity in treating severe ocular surface disease, including dry eye secondary to graft-versus-host disease and chemical burns. These lenses have also been used successfully to treat ectasia when standard contact lens therapies have been unsuccessful. Formerly called the Boston Scleral Lens, this device is now called the Prosthetic Replacement of the Ocular Surface Ecosystem (PROSE; Boston Foundation for Sight, Needham, Massachusetts). The distinguishing characteristic of this lens is that it vaults over the entire cornea and limbus and bathes the cornea in fluid. This device has been used to heal PED, but, as with bandage soft contact lenses, infection is still possible.25 Placing an antibiotic drop in the reservoir before insertion may mitigate the risk of corneal infection.

**CONCLUSION**

PED, while rare, can have devastating consequences. This condition can be recalcitrant to standard treatment modalities, and many new modalities have been investigated. Given that PED treated earlier in the course of the disease may heal faster, we should consider prophylactically treating eyes at risk for developing PED. Alternative approaches to treating PED are currently being investigated, and it is hoped that these will add to our armamentarium of treatment modalities against PED. ■

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