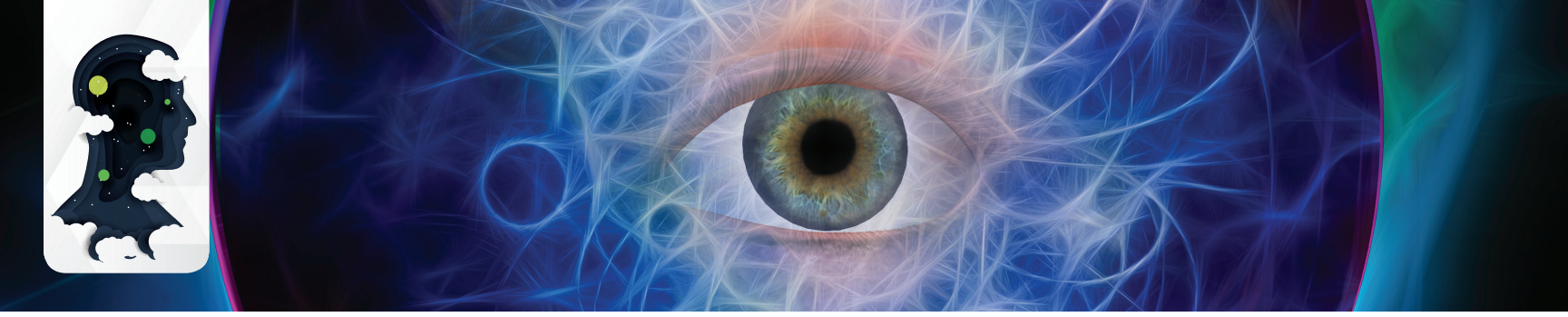


TALES OF CORNEAL CLARITY


Managing significant limbal stem cell deficiency.

BY BITA ASGHARI, OD, FAAO; AND SCOTT G. HAUSWIRTH, OD, FAAO

The limbus is a vital region of the ocular surface, the border between the cornea and conjunctiva. Histologically, it can be defined by two borders that are approximately 1 mm to 2 mm apart—the anterior border being the line between the ending of Bowman membrane and Descemet membrane and the posterior border being the line perpendicular to the surface of the globe that is centered on the scleral spur. Within this region is a wide variety of cells, including melanocytes, Langerhans cells, transient amplifying cells, and limbal stem cells (LSCs).

LSCs are adult stem cells that further differentiate into corneal epithelial cells for wound repair and preservation of normal homeostasis to maintain transparency of the cornea.[1-5] When LSCs are damaged, the barrier function of the limbus becomes compromised, leading to corneal neovascularization (CNV), loss of corneal clarity, and scarring. These are considered the hallmark signs of *limbal stem cell deficiency* (LSCD).[1-3] This article briefly explains how to recognize LSCD and outlines options for managing patients with LSCD.

WHAT IS LSCD?

LSCD is a pathologic condition in which there is damage to or dysfunction of the LSCs.[1-3] The loss of barrier function of the LSCs causes conjunctival epithelial cells to migrate to the cornea.[1,3] This process of *conjunctivalization* of the corneal surface results in the growth of abnormal vessels, or neovascularization, altering the normally avascular cornea.[1,3]

Clinically, the cornea in LSCD may appear neovascularized, opaque, keratinized, calcified, or scarred. This irregularity also causes an alteration of the normal epithelium and overlying glycocalyx and results in an unstable tear film.[1,3] Sodium fluorescein staining will show a whorl or vortex pattern in the epithelium that extends centripetally from areas of LSC dysfunction.[7]

Diagnosing LSCD is primarily clinical and can be supported with testing. The presence of goblet cells among the conjunctiva-derived cells on the corneal surface indicates conjunctivalization and is considered pathognomonic of LSCD.[2,8] Goblet cells on the corneal surface can be detected via impression cytology or with confocal microscopy.[8]

Pathologic mechanisms of LSCD can be primary or secondary. *Primary* LSCD is caused by genetic or genetically programmed loss of LSCs and is associated with conditions such as aniridia and ectodermal dysplasia.[1-6] *Secondary or acquired pathology* is caused by loss of the limbal microenvironment that is essential for LSC survival.[1-3] Acquired LSCD can be due to external factors such as chemical or thermal trauma, iatrogenic injury from surgery, and inflammation from ocular surface disease.

LCSD is commonly seen in conditions such as Stevens-Johnson syndrome,

AT A GLANCE

- Foundational therapy for limbal stem cell deficiency (LSCD) focuses on maintaining support of the ocular surface through lubrication and the reduction of inflammation.
- For moderate cases with a large area of LSCD, advanced pharmaceutical therapy, as well as autologous serum tears, amniotic membrane, and bandage soft contact lenses for acute epithelial breakdown, can be added to the steps of foundational therapy.
- Scleral lenses can improve comfort, support corneal healing, and optimize vision in patients with LSCD.

CLINICAL PEARLS FOR FITTING SCLERAL LENSES IN PATIENTS WITH LSCD

BEFORE YOU START

Determine whether the disease state is active (ie, uncontrolled conjunctival inflammation with progressive disease).

- Patients in the active disease phase are less likely to be successful with scleral lens wear.[13]

Photodocument baseline status.

- Take images in white light and blue light (with sodium fluorescein).
- These will allow you to monitor changes over time.

Use a Wratten filter.

- A Wratten No. 12 filter provides an enhanced view of corneal details.

Obtain baseline pachymetry map and/or anterior segment OCT.

- These will allow you to monitor for corneal changes with special consideration for epithelial edema.

FITTING PHILOSOPHY

Clear the limbus and beyond.

- Clearing the limbus in delicate corneas should be prioritized to avoid damage to the compromised limbus.[14]

Minimize suction and aim for a loose design.

- Consider a fluid-ventilated and/or air-ventilated lens design for optimal function (Figure 1).[15]
- Consider larger-diameter designs to provide more limbal clearance without compromising the landing zone diameter of the conjunctiva (Figure 2).

Minimize hypoxia.

- Maximize Dk/t through material and lens thickness selection.

Always remove the lens.

- Assess physiologic function by removing the lens for each fitting follow-up visit.
- Look for limbal edema, particularly microcystic edema, as this could indicate a tight or suctioned lens.

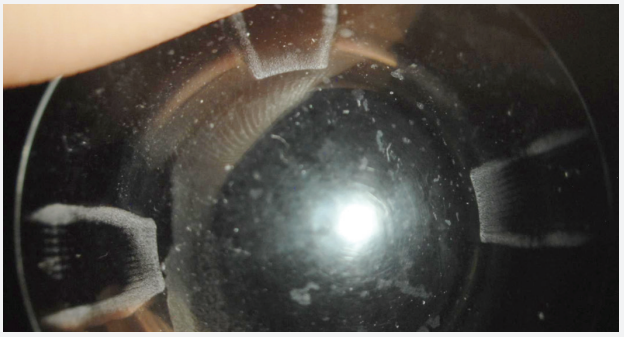


Figure 1. A PROSE device with three fluid-ventilating channels.

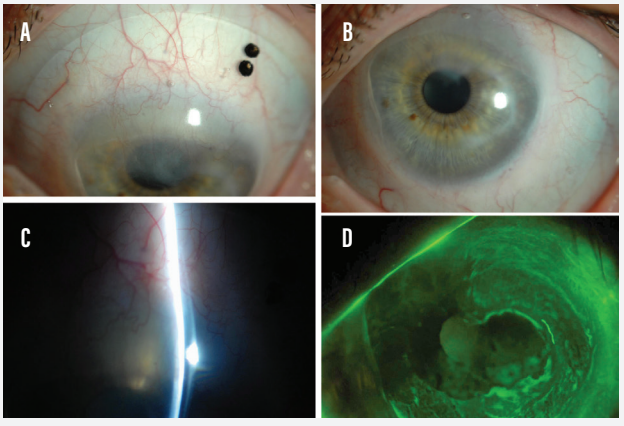


Figure 2. Patient with history of LSCD of unknown etiology wearing a large-diameter, fluid-ventilated lens design (A and B) with adequate limbal clearance (C). No corneal or limbal edema is noted on removal (D).

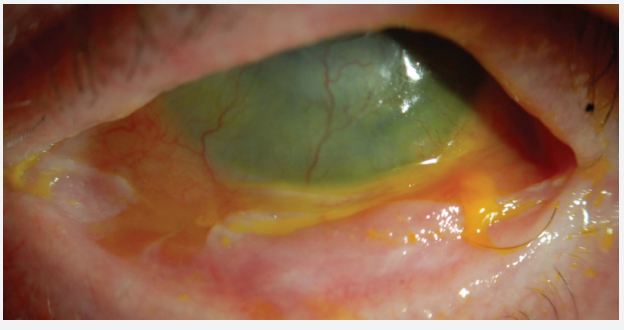


Figure 3. Patient with ocular graft-versus-host disease, LSCD, and scarring of the inferior tarsal conjunctiva. The patient was a daily scleral contact lens wearer who was no longer able to tolerate daily lens wear and was referred for mucous membrane graft consultation.

WHEN TO REFER

Refer to oculoplastic specialist:

- for consideration of mucous membrane graft in patients with poor tolerance for lens wear and concomitant tarsal conjunctival scarring (Figure 3).

Refer to cornea specialist:

- for consideration of surgical intervention in patients with progressive worsening of disease and/or limited visual function with lens wear.

graft-versus-host disease, and mucous membrane pemphigoid.[1,2,9] Other secondary causes of LSCD include drug-induced toxicity, neurotrophic keratopathy, ocular surface tumors, microbial infection, and abuse of soft contact lens wear, which often goes unrecognized and undiagnosed.[1-3,7] LSCD can also be associated with systemic conditions including Turner syndrome, lacrimo-auriculo-dento-digital syndrome and xeroderma pigmentosum.[2]

Patients with LSCD can experience a range of symptoms related to poor epithelial wound healing and subsequent potential recurrent erosions or persistent epithelial defects. In mild cases, signs and symptoms may consist of blurred vision, increased irritation, and conjunctival redness. In severe cases, patients may experience photophobia and pain, and the epithelium's inability to heal may result in corneal melting and perforation.[1-4]

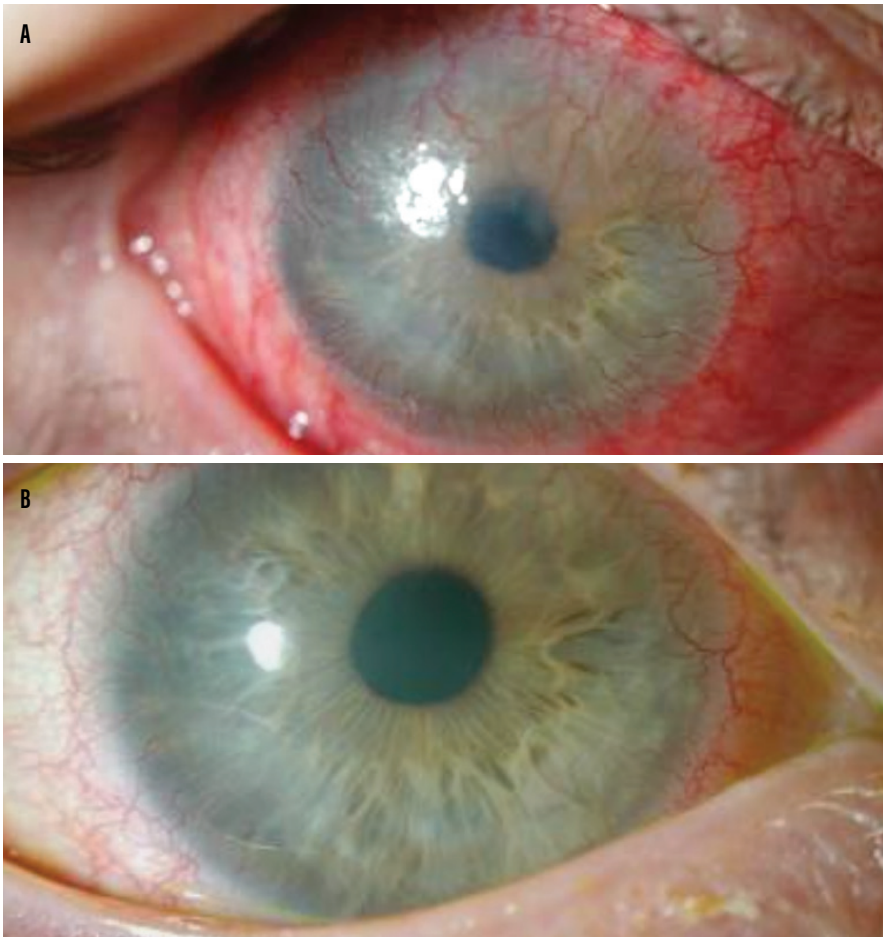
MANAGEMENT OF LSCD

Conventional Methods

Management of LSCD may be geared toward the degree of deficiency noted. In mild and moderate LSCD, principal goals include improving comfort, decreasing inflammation, and optimizing visual function. In severe disease, restoration of the LSC via transplantation can be considered.[1]

Foundational therapy focuses on maintaining support of the ocular surface through lubrication and the reduction of inflammation. Conventional foundational treatment includes lubricant eye drops, topical cyclosporine, and topical steroids. Elimination of chronic insult to the limbal region and to the existing LSCs is essential for rehabilitation. For example, when LSCD is noted in contact lens wearers, discontinuation of contact lens wear, along with foundational therapy, is recommended.

For moderate cases with a large area of LSCD, more advanced pharmaceutical therapy, as well as autologous serum tears, amniotic membrane, and bandage soft contact lenses, can be added to the steps of foundational therapy.[6]



Photos courtesy od Alan Kwok, OD, of BostonSight

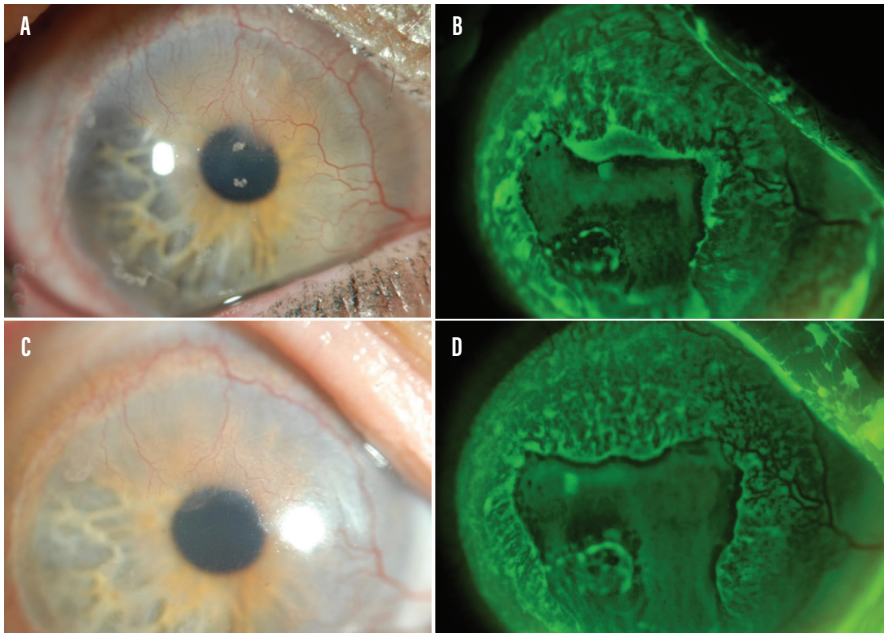
Figure 1. Patient with LSCD secondary to medicamentosa and chronic ocular surface disease at baseline (A) and after 2 years of daily scleral lens wear (B). Note the resolution of inflammation and the significant regression of CNV.

Patients with severe LSCD who have loss of limbal architecture and conjunctivalization of the cornea may be candidates for surgical repair. It is important to note that corneal transplantation in the absence of restoration of a functional LSC unit predisposes the new cornea to failure. To address this, the surgeon may consider also performing LSC transplantation via techniques such as keratolimbal allografts, simple limbal epithelial transplant, and other approaches. In addition, keratoprosthesis surgery, is another option for those who have near total LSCD and are in need of corneal surgery.

Management With Scleral Lenses

Scleral lenses may also be used to improve comfort, support corneal healing, and optimize vision in patients with LSCD. Management of LSCD with scleral lenses can allow patients to delay or avoid more aggressive surgical intervention.[4-6]

Patients with secondary LSCD in the setting of conjunctival disease (ie, Stevens-Johnson syndrome or mucous membrane pemphigoid) often experience exacerbated symptoms due to the interaction between the diseased conjunctival tissue and the highly innervated cornea, leading to pronounced corneal dryness, tear-layer dysfunction, and pain.[10] Scleral lenses can improve comfort, reduce photophobia, prevent epithelial breakdown, and improve vision by supporting the ocular surface, by holding fluid against the cornea, by acting as a barrier between the cornea and diseased conjunctiva,



Photos courtesy of Alan Kwok, OD, of BostonSight

Figure 2. Patient with LSCD at baseline (A and B) and at 4-year follow-up (C and D) after daily scleral lens wear. Note the stabilization of the corneal epithelium (B and D).

and by providing a smooth refractive surface.[4-5,10-15] As such, scleral lenses should be considered for patients with LSCD when they have not responded to other conventional therapies (see *Clinical Pearls for Fitting Scleral Lenses in Patients With LSCD*).

Rosenthal and Croteau evaluated the benefits of scleral lens wear in 232 eyes diagnosed with corneal stem cell disorders, 210 of which were due to Stevens-Johnson syndrome.[12] In that study, 13 of 22 eyes referred for treatment of persistent epithelial defect had associated LSCD. All patients experienced relief of pain and photophobia, expressly those with conjunctival keratinization and cicatricial changes.[12] It was noted that, although the presence of bulbar conjunctival scarring, shortened fornices, and symblepharon complicated the fitting process, they did not prevent scleral lens fitting.[12]

Long-term benefits of scleral lens wear in patients with LSCD have also been reported. In one published case, reversal of corneal opacification due to CNV was observed in an eye with LSCD and neurotrophic keratopathy over a 3-year period of daily wear of Prosthetic Replacement of the Ocular Surface Ecosystem (PROSE; Boston Foundation for Sight) lenses.[11]

Regression in corneal opacity and neovascularization occurs when the ocular surface integrity is maintained with reduced inflammation, which leads to stromal remodeling.[16] Scleral lenses provide a corneal environment that supports healing and protect the surface by serving as a barrier, potentiating stromal remodeling and regression in CNV (Figure 1).[11]

Although regression in corneal opacity and neovascularization has been documented and observed clinically, this does not occur in all LSCD eyes with scleral lens wear.[5,6,12] The primary goal of scleral lens wear in LSCD is to stabilize the epithelium and prevent epithelial breakdown (Figure 2).[4,5,10-12]

WHEN THE GOING GETS TOUGH, GO SCLERAL

Clinically, we have recognized significant benefits of prescribing scleral lens wear as a treatment for patients with LSCD, including halting progression of the disease, promoting corneal epithelialization, and reversing CNV and scarring. Prescription of scleral lenses should be considered to reduce ocular pain, improve visual function, and prolong the need for surgical intervention in patients with LSCD.

Currently, there is limited literature to support full understanding of LCS function as it relates to scleral lens wear. Furthermore, long-term monitoring and investigation of how eyes with LSCD of varying etiologies respond to scleral lenses, and why some patients continue to progress despite intervention, is needed. ■

1. Le Q, Xu J, Deng SX. The diagnosis of limbal stem cell deficiency. *Ocul Surf*. 2018;16(1):58-69.
2. Lim P, Fuchsluger TA, Jurkunas UV. Limbal stem cell deficiency and corneal neovascularization. *Semin Ophthalmol*. 2009;24(3):139-148.
3. Jawaheer L, Anijeet D, Ramaesh K. Diagnostic criteria for limbal stem cell deficiency—a systematic literature review. *Surv Ophthalmol*. 2017;62(4):522-532.
4. Schornack MM. Scleral lenses: a literature review. *Eye Contact Lens*. 2015;41(1):3-11.
5. Schornack MM. Limbal stem cell disease: management with scleral lenses. *Clin Exp Optom*. 2011;94(6):592-594.
6. Kojima T, Hasegawa A, Nakamura T, Isogai N, Kataoka T, Ichikawa K. Five-year PROSE treatment for aniridic keratopathy. *Optom Vis Sci*. 2016;93(10):1328-1332.
7. Rossen J, Amram A, Milani B, et al. Contact lens-induced limbal stem cell deficiency. *Ocul Surf*. 2016;14(14);419-434.
8. Singh R, Joseph A, Umapathy T, et al. Impression cytology of the ocular surface. *Br J Ophthalmol*. 2005;89(12);1655-1659.
9. Sejpal K, Yu F, Aldave AJ. The Boston keratoprosthesis in the management of corneal limbal stem cell deficiency. *Cornea*. 2011;30(11):1187-1194.
10. Rosenthal P, Cotter J. The Boston Scleral Lens in the management of severe ocular surface disease. *Ophthalmol Clin North Am*. 2003;16(1):89-93.
11. Cressey A, Jacobs DS, Remington C, Carrasquillo KG. Improvement of chronic corneal opacity in ocular surface disease with prosthetic replacement of the ocular surface ecosystem (PROSE) treatment. *Am J Ophthalmol Case Rep*. 2018;10:108-113.
12. Rosenthal P, Croteau A. Fluid-ventilated, gas-permeable scleral contact lens is an effective option for managing severe ocular surface disease and many corneal disorders that would otherwise require penetrating keratoplasty. *Eye Contact Lens*. 2005;31(3):130-134.
13. Lim P, Ridges R, Jacobs DS, Rosenthal P. Treatment of persistent corneal epithelial defect with overnight wear of a prosthetic device for the ocular surface. *Am J Ophthalmol*. 2013;156(6):1095-1101.
14. Schornack M, Nau C, Nau A, Harthan J, Fogt J, Shorter E. Visual and physiological outcomes of scleral lens wear. *Cont Lens Anterior Eye*. 2019;32(1):3-8.
15. Rosenthal P, Cotter JM, Baum J. Treatment of persistent corneal epithelial defect with extended wear of a fluid-ventilated gas-permeable scleral contact lens. *Am J Ophthalmol*. 2000;130(1):33-41.
16. Hassell JR, Birk DE. The molecular basis of corneal transparency. *Exp Eye Res*. 2010. 91(3):326-335.

BITA ASGHARI, OD, FAAO
- BostonSight PROSE Provider, BostonSight, Needham, Massachusetts
- Adjunct Clinical Faculty, Massachusetts College of Pharmacy and Health Sciences University School of Optometry, Worcester, Massachusetts
- basghari@bostonsight.org
- Financial disclosure: None

SCOTT G. HAUSWIRTH, OD, FAAO
- Assistant Professor, the University of Colorado Anschutz Medical Campus, Aurora, Colorado
- scott.hauswirth@cuanschutz.edu
- Financial disclosure: Consultant (Allergan, BioTissue, Dompé, Eyevance Pharmaceuticals, Kala Pharmaceuticals, Novartis, Ocular Therapeutix, Shire, Sun Ophthalmics); Investigator (Dompé, Ocular Therapeutix)