MD Roundtable, Part 2: Corneal Cross-Linking for Pediatric Keratoconus

Corneal collagen cross-linking (CXL) techniques can be distinguished by the amount of corneal epithelium that is removed. The standard Dresden protocol\(^1\) entails an “epi-off” treatment, whereas transepithelial, or “epi-on,” procedures minimize removal of the epithelium. In the final segment of this two-part series, James Reidy, MD, FACS, at the University of Chicago, continues a roundtable discussion with Kathryn Hatch, MD, of Massachusetts Eye and Ear Waltham and Harvard Medical School, and Erin Stahl, MD, of Children’s Mercy Hospital at the University of Missouri, Kansas City. Focusing on CXL in the pediatric age group, the experts share their thoughts on epi-on and epi-off techniques, indicators of surgical success and failure, and the future of treatment for children with keratoconus.

Stromal Demarcation Line

**Dr. Reidy:** How much importance do you give to the stromal demarcation line—that is, the boundary between the cross-linked stroma of the anterior cornea and the untreated posterior cornea?

**Dr. Stahl:** I perform epi-off CXL by the Dresden protocol in a pediatric practice. My patients require general anesthesia for this surgery and sometimes are uncooperative with our testing. I do look at the cornea in every case, but I don’t always get to study it for long. When I can visualize the demarcation line in my patients, I notice that it slowly fades over time.

**Dr. Hatch:** I don’t routinely see a stromal demarcation line in every patient. I sometimes see either this demarcation line or a reticular haze pattern that subsequently fades. I don’t, however, put a lot of emphasis on the presence or absence of these findings, as a deep line does not necessarily predict better outcomes.\(^2\)

Epi-off Versus Epi-on

**Dr. Reidy:** When a patient undergoes epi-off CXL, he or she typically will have blurry vision and a hazy cornea for approximately a month after surgery. Do epi-on techniques avoid these effects?

**Dr. Hatch:** The epi-off procedure results in hypertrophy of the epithelium in the first postoperative month. During this time, the keratometry becomes steeper, visual acuity often decreases, and corneal haze is present. Patients also avoid using contact lenses while the cornea heals. Epi-on procedures avoid many of these drawbacks to a greater extent.

The hybrid or transepithelial procedure that I perform is off-label, but it allows patients to return to contact lens use and to see well in the early postoperative period. Some patients even experience better vision early on.

Progression and Failure

**Dr. Reidy:** In a prospective study, Godefrooij and colleagues\(^3\) evaluated 36 pediatric patients with keratoconus (54 eyes) who received up to five years of follow-up. They found disease progression in 22% of patients after epi-off CXL. In an earlier retrospective study, Chatzis and Hafezi\(^4\) found an even higher rate of post-CXL progression: 88% in 42 patients (59 eyes) with a mean follow-up of approximately two years.

How frequently do you observe postoperative disease progression in your patients, and what constitutes failure of the procedure?

**Dr. Hatch:** There are multiple ways to assess progression, such as change in \(K_{\text{max}}\), worsening topography and thinning, as well as a change in corrective prescription and loss of best-corrected visual acuity. I think it’s crucial that we agree on how we define progression.

I assess progression, in part, by monitoring maximum keratometry...
readsings (K_max), but I do not use this measurement in isolation. I have seen post-op changes in K_max that are concerning (such as an increase of more than 1.0 D^2), but if the patient has stable vision or unchanged refractive properties, I wouldn’t necessarily consider the disease to be progressing. Occasionally, I obtain slightly different results from repeat topography testing that same day. In such cases, I ask the patient to return (for instance, in six to eight weeks) for serial topographic analysis. Sometimes the culprit is dry eye or how the patient wears contacts and there is resultant warpage on the scans rather than true disease progression. A patient’s K_max results certainly can indicate progression. When this result is substantiated by other visual and topographic results, I would regard this as progression and re-treat accordingly.

I’ve been using the Photrexa system (Avedro) since 2016, and my retreatment rate has been, in general, less than 5% after two years. I also was part of the CXLUSA Study Group from 2011 to 2016, and most of our data corresponded to epi-on patients with a 0% rate of progression in the first two years. Among my patients, the eyes necessitating retreatments were eyes with advanced keratoconus at presentation.

Dr. Stahl: I’ve performed the Dresden CXL procedure on 36 eyes since January 2017. A few of my patients have shown fluctuation on follow-up tests, but only one patient has had definitive progression. He experienced hydrops on post-op day 3, and I also remove the bandage contact lens that day.

Dr. Reidy: I believe that sterile infiltrates are the biggest problem because they often result in corneal scarring and subsequent thinning. In epi-on CXL, sterile infiltrates do not occur, correct?

Dr. Hatch: That’s correct.

Future of CXL in Children

Dr. Reidy: How do you think our techniques of CXL will change in the next few years?

Dr. Hatch: I would like to see pediatric keratoconus treatment evolve toward earlier screening and earlier detection. It would be very helpful if we had a way to inexpensively screen children—in schools, for instance, as part of a vision screening. The goal would be to perform transepithelial cross-linking very early—even before the disease becomes clinical—to prevent progressive ectasia.

Additionally, practitioners outside of the United States are performing modified CXL protocols, including accelerated cross-linking with more intense ultraviolet A (UVA) light for a shorter amount of time. I hope those techniques will eventually be incorporated into the array of keratoconus treatments in the United States.

Dr. Stahl: I agree. Sterile infiltrates have developed in three of the 36 eyes I have treated. In these cases, I have adjusted the patient’s steroid regimen accordingly. I think this rate of infiltrates is consistent with other findings.

Dr. Reidy: I agree. Your rate of 8.3% (3/36 eyes) is similar to the infiltrate rate of 7.6% found by Koller and colleagues in their study of 99 patients with primary keratectasia who underwent CXL.

Dr. Stahl: Children seem to have a more vigorous healing response than adults after CXL. One patient even had a significant central healing response in which the cornea flattened, thinned, and left a scar. Fortunately, this patient’s results have been improving, but I wouldn’t be surprised if sterile infiltrates occur a bit more frequently in children than in adults.

Dr. Reidy: In my experience, when a child develops an infiltrate, it occurs within the first week, typically by three or four days post-op. Sometimes these patients don’t present with an infiltrate until the epithelium has already healed.

Dr. Stahl: Yes, the sterile infiltrates I’ve seen usually develop in healed epithelium on post-op day 2. All but one of the children I’ve treated have had complete healing of the epithelium on post-op day 3, and I also remove the bandage contact lens that day.
continuous, UVA light, which decreases the amount of oxygen that’s consumed. It is possible that the concentration and formulation of riboflavin applied during CXL could be optimized to achieve increased penetration through intact corneal epithelium.

Pediatric patients are probably the most difficult to treat, but they’re also the ones who may benefit the most from CXL. Early screening is crucial, and it doesn’t necessarily have to be high tech. I find that examining the cornea with retroillumination, using a retinoscope or a direct ophthalmoscope, enables visualization of the cone—often before the patient is symptomatic.


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