

## Evolving resistance to fluoroquinolones: Unfinished business and key challenges

by Terrence P. O'Brien, MD



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**D**uring the past decade, ophthalmologists have seen the harmonious convergence of cataract and refractive technologies, and we are now fully immersed in the modern refractive cataract surgery era.

With all of the technological advances, it seems counterintuitive that endophthalmitis rates after cataract surgery would be on the rise; however, a number of studies seem to suggest that the rates of endophthalmitis are actually increasing rather than decreasing with the advances in technology.<sup>1</sup>

The most frequent source of endophthalmitis is the periocular flora, the omnipresent organisms that are located at the scene of cataract surgery. In a recent multicenter study conducted in the United States, cultures were positive in 80.5% of the eyelid samples and in 57.4% of the conjunctival samples.<sup>2</sup> *Staphylococcus epidermidis* and *Staphylococcus aureus* were the most frequently isolated organisms from both the lids and the conjunctiva.

Some eloquent molecular microbiologic studies have confirmed that the patient's own external flora is most likely the culprit in cases of endophthalmitis, with recovery of these organisms from the vitreous and aqueous humor in cases of endophthalmitis that match the patient's own external bacterial flora.

The Endophthalmitis Vitrectomy Study highlighted the importance of gram-positive organisms, with 94% of the

endophthalmitis cases being due to gram-positive pathogens, notably coagulase-negative *Staphylococci*. This correlates well with our data from Bascom Palmer Eye Institute where coagulase-negative *Staphylococci*, *Staphylococcus aureus*, *Streptococcal* species, and *Enterococcal* species were much more common than gram-negative organisms.

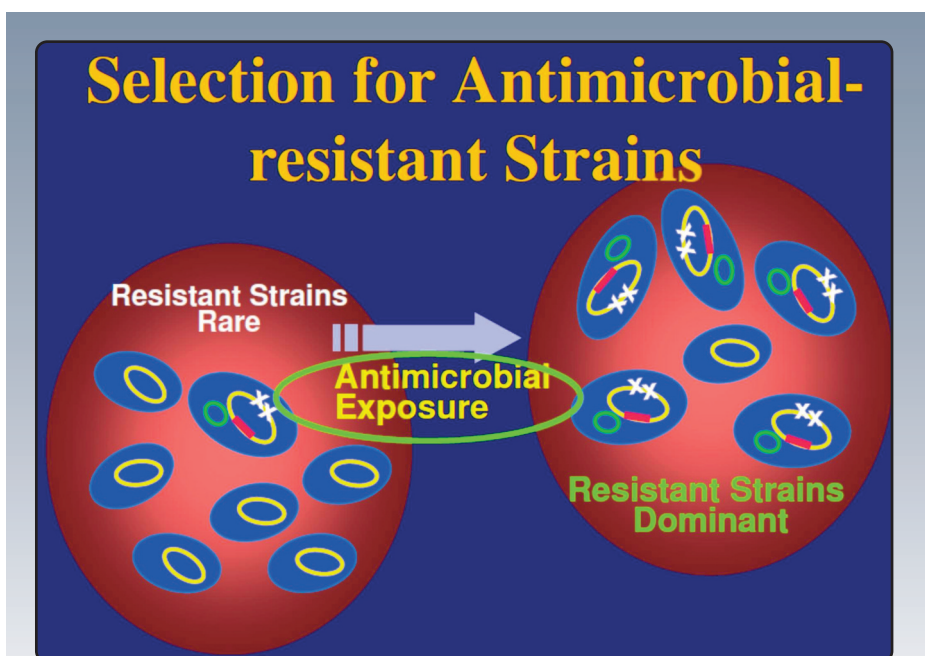
There are increasing global concerns that bacteria are becoming so clever they're defying our efforts to eliminate them. It is clear that bacteria communicate and mutations happen. While resistant strains may be rare, with inappropriate use of antibiotics and antimicrobial exposure, these strains can become predominant.

There are three principal mechanisms of resistance to fluoroquinolones: an active efflux pump that can eject the fluoroquinolone from the cell, decreased cellular permeability where the molecule itself cannot cross the bacterial membrane, and a genetic mutation to one or the other of the most important bacterial enzymes involved in DNA replication, mainly DNA gyrase or topoisomerase IV.

### Reducing the risk of infection

The time-honored techniques for preventing endophthalmitis have been to limit the number of organisms entering the eye by decreasing the organisms on the surface, prevent intraoperative contamination, and prevent postop bacterial contamination with watertight wound closures. The traditional methods to try to reduce surface contamination have been preparing the skin with a 5% to 10% povidone iodine scrub and preparing the conjunctiva with 5% povidone iodine solution directly to the ocular surface. Simply using povidone iodine alone has been shown to statistically reduce the clinical occurrence of endophthalmitis by 75% to 80%. Combining the antiseptic with an antibiotic for preparing the conjunctiva, especially using advanced generation fluoroquinolone antibiotics, has shown to be even more effective at reducing the colonization. We must also prepare the patient in a sterile manner using adhesive drapes to sequester the cilia and the meibomian glands from the operative field.

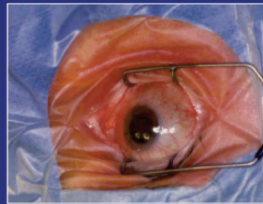
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**While resistant strains may be rare, with inappropriate use of antibiotics and antimicrobial exposure, these strains can become predominant.**

## Proposed Methods of Prophylaxis

1. Preoperative povidone-iodine antiseptics
2. Preoperative topical antibiotics
3. Properly sized and constructed incision
4. Antibiotics in irrigating solution
5. Antibiotics injected into AC
6. Postoperative subconjunctival antibiotics
7. Postoperative topical antibiotics



However, the most controversial subject is how to eradicate organisms that may enter the eye during uncomplicated surgeries and whether the application of topical antibiotics plays a significant role in reducing contamination and endophthalmitis. We don't know whether a topical antibiotic alone is sufficient prophylaxis. One thing is certain: There's no universally omnipotent, effective protection from infection using a single antimicrobial agent.

Fluoroquinolones possess many of the ideal properties of an antibiotic: being broad-spectrum, bactericidal, biocompatible, and bioavailable with favorable pharmacodynamics. Over the years, these molecules have evolved to have an expanded spectrum of activity to include gram-positive organisms, such as *Staphylococcus*, *Streptococcus*, *Enterococcus*, and even anaerobes. Yet we've seen that the coagulase-negative *Staphylococci* causing endophthalmitis have become less susceptible over time to even the 8-methoxy fluoroquinolones gatifloxacin and moxifloxacin.

The Ocular TRUST is a surveillance study in the United States to track resistance across the country, and the conclusion is if methicillin-resistant *Staphylococcus* is a suspected pathogen, alternatives to fluoroquinolones should be considered like older agents, such as tobramycin, or even agents such as bacitracin, trimethoprim, and polymyxin B.<sup>3</sup>

Besifloxacin is an exciting new chlorofluoroquinolone that has balanced, dual targeting activity, which greatly enhances the potency of this molecule compared to the 8-methoxy fluoroquinolones. It has a unique combination of substituents at the

C7 and C8 positions of the fluoroquinolone core structure, and its mode of action is consistent with the other fluoroquinolones, which is inhibition of the DNA gyrase and topoisomerase IV. It has potent antibacterial activity against prevalent ocular pathogens, including current drug-resistant strains, and it retains bactericidal activity against strains that are resistant to other fluoroquinolones. Additionally, it has lower rates of spontaneous resistance development in clinical and nonclinical studies.

This has been documented in the Antibiotic Resistance Monitoring in Ocular microorganisms (ARMOR) program that we have participated in at Bascom Palmer Eye Institute. The ARMOR study was conducted to monitor the antibiotic susceptibility trends in ocular isolates after the introduction of besifloxacin.<sup>4</sup>

The 2009 ARMOR surveillance included 200 cases of *Staphylococcus aureus*. In these cases, besifloxacin had an MIC<sub>90</sub> comparable to vancomycin and much lower than moxifloxacin, ciprofloxacin, tobramycin, and azithromycin. The same was true for coagulase-negative *Staphylococcus* isolates, with besifloxacin having a roughly equivalent MIC<sub>90</sub> to that of vancomycin and much lower than ciprofloxacin, moxifloxacin, tobramycin, and azithromycin. Many of these organisms were drug resistant, both to methicillin and to ciprofloxacin.

The latest ARMOR results from 2012 and 2013 have been reassuring.<sup>5</sup> There has not been any increase in the resistance to besifloxacin during the past

3 years of continuous surveillance and monitoring. However, multiply drug-resistant strains continue to be prevalent, which correlates well with our data from Bascom Palmer Eye Institute.<sup>6</sup> In our study of 243 nonconsecutive ocular isolates identified between 2003 and 2008, besifloxacin MIC values were 4 to 8 times lower than moxifloxacin and 16-fold to 32-fold lower than ciprofloxacin for *Staphylococcus aureus*, for methicillin-resistant *Staphylococcus* and for ciprofloxacin-resistant *Staphylococcus aureus*, and for coagulase-negative *Staphylococcus* that is both resistant to methicillin and ciprofloxacin.

To prevent endophthalmitis, the preferred proposed methods of prophylaxis include the following:

- Preoperative povidone iodine antiseptics
- Preoperative topical antibiotics
- Properly sized and constructed incision
- Antibiotics injected into the anterior chamber for higher risk cases
- Postoperative subconjunctival antibiotics
- Postoperative topical antibiotics

Only povidone iodine and intracameral antibiotics have been clinically proven to be effective with level I evidence.

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### Summary

The preferred practices for prevention of endophthalmitis include careful aseptic technique, preparation of the ocular surface, antiseptics and antibiotics, careful wound construction, avoidance of hypotony and ingress of fluid, and consideration of the use of intracameral antibiotics.

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# Defining glistening-free vision: enVista and enVista Toric

by Manfred R. Tetz, MD



Manfred R. Tetz, MD

**T**he optimal modern IOL would be based on an ideal platform IOL of low water content, a sharp functional 360-degree edge, and glistening-free material, and it would be injectable through a small incision and resistant to optic surface or haptic damage.

The enVista and enVista Toric IOLs (Bausch + Lomb) deliver all of these features. Both are 1-piece aspheric lenses.

The water content is low, around 4%. The lens comes in a minimal amount of water and is a true hydrophobic IOL. It has a sharp functional edge, and importantly, it is glistening-free and virtually unable to be scratched on the surface. I believe these are the two most important factors for providing the best optical performance.

## Glistening-free lens material

I have been exposed to this lens material for almost 10 years. Originally, the material was produced by AVS in the United States. I have had more than 8 years of experience implanting lenses made of this material, and most of my initial 150 eyes have more than 6 years of follow-up. The eyes with more than 6 years of follow-up were implanted with 3-piece acrylic posterior chamber IOLs with modified C-loop PVDF haptics (the original AVS IOL). At all postop visits, the material showed no glistenings.

In 2010, Bausch + Lomb acquired the rights to this material, and my colleagues and I performed a very small study that same year on the enVista 1-piece lens.

The enVista lens has a 6-mm optic, and it has some fenestration holes in the haptics to increase flexibility. It is available in a broad dioptric range.

In the initial study, 14 eyes were implanted with the enVista IOL. Clinical examinations were performed preoperatively and at 1 day and 2 to 4 months postoperatively. We achieved very good corrected and best corrected visual acuity in these patients on the first day and during the first 3 months postoperatively. Eighty-five percent of patients achieved best corrected visual acuity of better than 0.1 logMAR.

Additionally, no glistenings were documented on slit lamp exam in any IOL at any visit, and the lenses were resistant to abrasion and surgical surface damage during injection. There were no marks or surface scratches and no broken haptics.

In 2011, we performed more enVista implantations. In 102 eyes, the best corrected distance visual acuity at 1 to 3 months postop was 0.1 logMAR ( $0.77 \pm 0.25$ ). There were no discernable glistenings and no surface scratches from injection and/or implantation. There was one YAG capsulotomy in the series at 1 year and a low early posterior capsule opacification (PCO) rate.

The lens' sharp edge is intended to reduce the incidence of PCO. The enVista has a 360-degree sharp edge with a step height of 80  $\mu\text{m}$  to 100  $\mu\text{m}$ . If the step is not high enough, the lens epithelial cells will more easily "crawl" around the edge onto the posterior, as they are only approximately 20  $\mu\text{m}$  in size.

For years, we have been studying this in our research institute. Initially, we started with lenses with different rounded edges. We put those in cell cultures and looked at whether cells were going to stop when they approached the edge of a lens. We found that cells typically stop when they find a sharp edge, while they immediately grow across a round edge.

In part two of the microedge study, which was published in 2008, we measured the edge of different hydrophobic lenses from different companies. Many companies label the edge as sharp, but there had been no scientific definition of sharpness. In an attempt to develop a definition, the lenses were examined by scanning electron microscopy, mounted

perpendicularly, 1000x magnification, and a 40- $\mu\text{m}$  circle was taken. This is twice the size of a lens epithelial cell, and in this radius, we then measured the deviation from true squareness. An ideal square lens would have 0  $\mu\text{m}$  squared deviation; an inferior lens has a growing number.

Interestingly, silicone lenses still have some of the sharpest edges, but the acrylics have a big variation in edge sharpness. In fact, in a study by **Liliana Werner, MD**, 7 of 30 silicone IOLs reviews had sharpness values similar or even better than a reference high quality PMMA IOL. Acrylic IOLs were found to have statistically significantly less overall sharpness and a wider variation in that sharpness level compared to silicone IOLs. Currently the enVista has some of the sharpest square edges of hydrophobic IOLs measured in our lab.

## Rotational stability

Another key element for success with the enVista platform is the rotational stability of the toric lens. In the U.S. study of rotational stability of the enVista, 91% of patients had less than 5 degrees of deviation from the time of surgery to 6 months postop. The mean rotation was 3 degrees. Data published on competitive IOLs are not quite as good.

In the European enVista Toric Registry that originally included complete data on 22 eyes, 86% of patients with a spherical equivalent were  $\pm 0.50$  D, and the refractive cylinder was 0.5 D or less in 91% of eyes.

In my own first 20 implants, my average deviation from intended position was 3.3 degrees. This was in our test setting among the best features we measured with several toric IOL models.

## Summary

When choosing an IOL, top considerations should be an ideal platform, low water content, glistening-free material, and resistance to optic surface or haptic damage.

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# Early Asian experience with the enVista Toric

by Robert Ang, MD



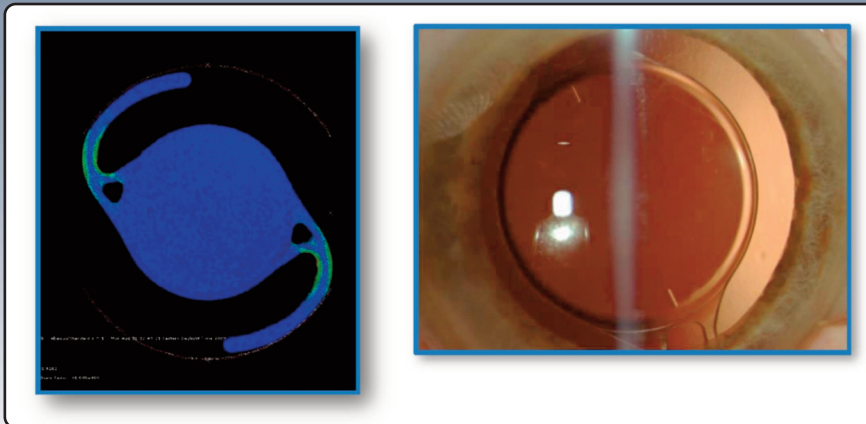
Robert Ang, MD

**T**he enVista Toric (Bausch + Lomb) is a monofocal hydrophobic acrylic toric lens made from a glistening-free material. It is a clear lens without a yellow tint, and it has zero asphericity. The IOL has a high surface hardness, which may result in fewer scratches during surgical manipulation, and it has a square edge design, which results in a lower rate of posterior capsule opacification.

The enVista Toric has advanced optics, or a zero aspheric optic, meaning that it does not try to correct the corneal positive spherical aberration. The goal is to leave behind a small amount of optical positive spherical aberration for more depth of focus; retaining a small amount of positive asphericity in the eye results in a small amount of a semi-accommodative or semi-presbyopia-correcting effect.

When placing an IOL inside the eye, the goal is to center it in the bag. With a negative aspheric lens, any decentration will cause more blur than with a zero aspheric lens. So with an aberration-free lens, even if it is decentered, the image is the same whether you're looking through the center or through one of the sides. In contrast, looking through the edge of a negative aspheric lens results in an irregular astigmatism, or a coma effect, which causes some decrease in sharpness of vision.

When retroilluminated, the enVista Toric is perfectly crystal clear. The only imperfections that can be seen are wrinkles or imperfections on the posterior capsule.



The enVista Toric retroilluminated

## Preoperative markings, calculations

The enVista Toric calculator is similar to the Alcon calculator. However, the major difference is that the steep axis must be plugged in before the flat axis on the enVista calculator, which is the reverse of the Alcon calculator, in which the flat axis must be plugged in first before the steep axis.

The preoperative marking determines the lens' alignment and position and is critical for success. My practice uses the Asico electronic calculator, and we align it at the 3 o'clock and 9 o'clock positions. Then, we orient it vertically, so we also mark it at the 12 o'clock and 6 o'clock positions.

We use a slit beam to make sure that the alignment is perfect with the patient's head straight. It is important to double check that the patient's head is perfectly straight while marking the lens.

## Intraoperative and postop considerations

When using the Victus platform (Bausch + Lomb TECHNOLAS) for femtosecond laser cataract surgery, we create the incision with the Victus first, and then we examine the patient at the slit lamp. For this reason, it is helpful to have a slit lamp in the operating room. Next, the patient is marked and brought to the operating room. We don't mark before creating the incision with the Victus because the ink marks might affect where the laser will fire during the corneal incision. Remember to do the femto first before marking.

On the day after the procedure, the patient is examined at the slit lamp. I orient the slit beam along the axis of the toric marks so that I see from the slit lamp marks which axis I put the lens in. If it is deviated on the first day postop, then it was placed in the wrong axis.

The main advantage of a toric IOL is reduction of astigmatism. According to the enVista U.S. FDA trial, if the lens is 10 degrees off-axis, astigmatic correction is reduced by 33%. If the lens is 30 degrees off-axis, there is no correction of astigmatism, and if the lens is 90 degrees off-axis, astigmatism is doubled. It is important to be on-axis as much as possible, and the trial found that 92% of eyes implanted with the enVista lens had 5 degrees or less of rotation at 4 to 6 months.

Additionally, in a small study I conducted with nine patients, all had uncorrected distance vision of 20/40 or better. These are very early results: Two patients are at the 1-month follow-up and the others are at the 1-week follow-up.

In terms of mean refractive spherical equivalent, all patients are below 0.25 D except one patient who is  $-1.00$  D at the 1-week follow-up. The difference between the targeted and residual sphere is  $+0.51$  D; however, I need to adjust my nomogram because the results are still a bit too positive in terms of my targeting. Adjust your nomograms accordingly as you gain experience with the lens.

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## Experience with the Victus Femtosecond Laser

by Mike P. Holzer, MD, FEBO



Mike P. Holzer, MD, FEBO

**F**emtosecond lasers have been on the market for more than a decade. One of the main advantages of laser cataract surgery compared with conventional cataract surgery is the better centration and shape precision of the capsulotomy provided by the femtosecond laser.

Using a femtosecond laser for both refractive and cataract surgery is currently only possible with the Victus Femtosecond Laser (Bausch + Lomb TECHNOLAS). Surgeons can perform refractive surgery, corneal therapeutic procedures, and of course, cataract surgery.

### Initial studies

One of the first clinical evaluations of the Victus laser came from Dr. Reddy's clinic in Hyderabad, where many of the first procedures were performed. This study evaluated 62 eyes treated with a 5.5-mm capsulotomy: 31 eyes underwent the procedure with the Victus platform and 31 eyes underwent a manual rhexis. The diameter, centration, and circularity were evaluated.

The intended diameter was 5.5 mm, and the measured diameter was  $5.50 \pm 0.12$  mm, which is amazing. This very small standard deviation is difficult to achieve with a manual capsulotomy, even by well-experienced surgeons.

The Victus capsulotomy has a nice round structure. A grade of 1.0 would be the ideal grade for circularity, and the femtosecond laser achieved close to that—0.97 compared with 0.93 for a very experienced surgeon doing a manual capsulotomy.

Centration was also better with the femtosecond laser. In this study, there was a slight decentration of  $95 \mu\text{m}$  with the femtosecond laser compared to  $160 \mu\text{m}$  with a manual capsulotomy.

A more precise capsule opening may enable surgeons to have more predictable effective lens position, and thus less postoperative residual refractive error.

Before the laser was CE approved, surgeons were only allowed to perform these procedures in very specific cases, and we obtained IRB approval for a case with a very mature cataract and pseudoexfoliation syndrome. The procedure and the capsulotomy were no problem, and the initial acuity outcome for the patient was excellent. Because of the very severe cataract, the preoperative visual acuity was only at 1.3 logMAR. Three weeks postoperatively, it was corrected at 0 logMAR, and there were no complications during the surgery or postoperatively.

### Phase 4 study results

This led to further evaluation of this procedure, where we compared laser refractive cataract surgery to manual surgery in the fellow eye. A phase 4 study conducted in Heidelberg was designed to include 30 to 35 patients older than 18 years who had bilateral cataract. One eye was treated with a femtosecond laser, and the fellow eye was treated with a manual rhexis.

Preoperatively, several diagnostic devices were used, and endothelial cell count was performed. Then the lens position and anterior chamber depth were measured with the LENSTAR or Allegro BioGraph. Zywave, Orbscan, and flare meter measurements were performed to

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## Visual Acuity

Preop UDVA	UDVA on last follow-up	BCDVA on last follow-up
20/100	20/30	20/30
20/50	20/20	20/20
20/60	20/40	20/25
20/80	20/20	20/20
20/70	20/40	20/40
20/40	20/25	20/20
20/80	20/40	20/30
20/60	20/30	20/25
20/50	20/25	20/20

### Early visual acuity results

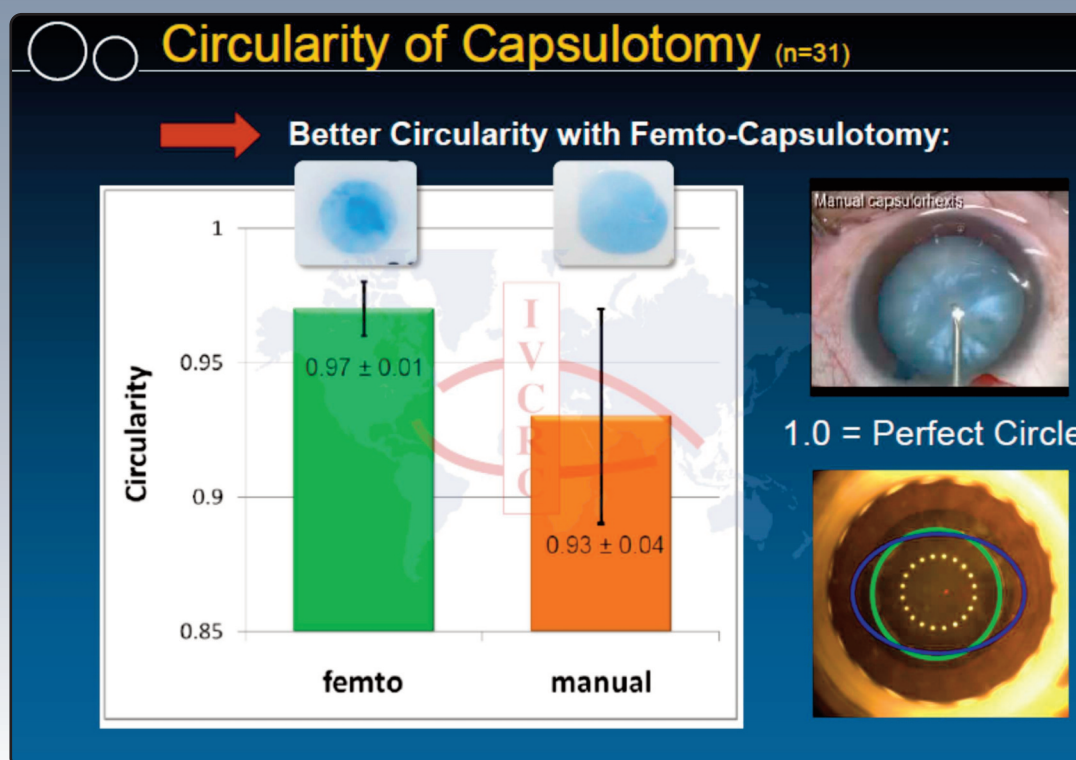
Additionally, cylinder was reduced by at least half. Some of the patients still have some residual cylinder, so the calculator may need some refinement. In this study, the rotation from day 1 to the last follow-up is very low, less than 2 degrees.

Again, the two most important things for success with toric IOLs are lens choice and alignment. I have learned that off-axis preoperative marking will definitely lead to an off-axis implantation.

### Summary

When using a toric IOL, keys to success include a glistening-free material, a solid online calculator, easy handling, predictable and stable astigmatic reduction, high quality of vision, and a low PCO rate with the IOL platform.

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**A grade of 1.0 would be the ideal grade for circularity, and the femtosecond laser achieves close to that.**

see if there was any kind of inflammatory reaction after the laser procedure.

All of these patients received the monofocal version of the enVista IOL (Bausch + Lomb). All of the preoperative exams were repeated, and patients were followed up to 6 months.

Preoperatively, all patients were between -10 and +2 D, and all were in the cataract age range (median: 70 years). The study included 28 eyes (14 underwent the Victus procedure and 14 underwent the manual procedure).

For both the manual and the laser procedure, there were excellent visual outcomes. When comparing the intended versus the achieved postoperative refraction, and that would correlate most probably with the IOL position, there was slightly less difference between the intended and achieved refraction for the Victus compared to the manual procedure. While we don't see a statistical difference with this number of eyes, the tendency was there.

Regarding intraocular pressure, there was no difference between the groups on day 1. At 1 week, there was a slightly higher IOP in the Victus group (12 mmHg compared with 11 mmHg), which is statistically significant but not clinically significant.

In the Victus group, laser energy was obviously put into the eye, with more energy being used for higher grades of cataract; however, on the first day postoperatively, there was no difference in flare between the two groups, and this was also seen 1 week after the procedure.

There was a significant difference between the groups with regard to effective phaco time, with the Victus' effective phaco time about half of the effective phaco time for the manual procedure.

When evaluating the 1-month numbers of endothelial cell loss, there was a statistically significant difference between the groups, with the Victus eyes having had significantly less endothelial cell loss

than the eyes that underwent the manual procedure (median of 88 compared with 296).

In conclusion, the Victus system is safe and predictable, and there were statistically significant differences with regard to effective phaco time and postoperative endothelial cell count between the eyes that underwent the Victus procedure and the eyes that underwent the manual procedure.

### Summary

Keys to success with laser cataract surgery include a well-centered, precise capsulotomy, and a platform that can deliver reduced EPT, improved endothelial cell count, and can handle both complicated and conventional cases.

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