Review

THE CUTTING EDGE OF RETINOPATHY OF PREMATURITY CARE

Expanding the Boundaries of Diagnosis and Treatment

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Purpose: To discuss the latest advances and controversies in the diagnosis and care of infants with retinopathy of prematurity (ROP).

Methods: Literature review.

Results: Retinopathy of prematurity remains a major global issue. Industrialized nations now treat profoundly premature infants with posterior and aggressive disease, and middle-income nations are experiencing ROP epidemics. Remote digital imaging may address the decreasing ratio of ROP providers to premature infants, in addition to improving patient care. Widefield angiography, optical coherence tomography, and the *Wnt* signaling pathway have provided new insights into ROP pathogenesis. Anti–vascular endothelial growth factor treatment is increasing in popularity, but the dearth of information to guide dosing, unpredictable reactivation, persistent vascular abnormalities, the "crunch" phenomenon, and the presently unknown effects of systemic vascular endothelial growth factor suppression remain issues to continue investigating. Neurodevelopmental delay has been raised as a potential consequence, but the evidence currently is weak. Vitrectomy is the treatment of choice for Stages 4 and 5. Illumination techniques, ab interno incisions, plasmin-assisted vitrectomy, staged surgery in the interest of corneal clearing for advanced Stage 5, and immediate sequential bilateral vitreoretinal surgery, are useful techniques.

Conclusion: We are making progress in ROP management. Our goal as clinicians is to continue expanding the boundaries of our abilities to keep this blinding disease in check globally.

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The history of retinopathy of prematurity (ROP) since its first descriptions in the 1940s[1] is relatively short. Seminal translational studies and clinical trials in subsequent decades have uncovered the pathophysiology of ROP and rendered it an often preventable disease under ideal circumstances. Retinopathy of prematurity is arguably the best-understood vasoproliferative retinopathy in terms of pathogenesis, timing, and severity of disease progression, and treatment response. Yet, there is still much to do, as ROP continues to be a leading cause of blindness among prematurely born infants worldwide. This review will discuss the latest advances and controversies in the clinical care of infants with ROP.

Global Focus

Retinopathy of prematurity was born as a consequence of medical progress. Advances in neonatology in the 20th century allowed more premature infants to survive. Positive pressure mechanical ventilation was one of these developments, but oxygen delivery was unregulated. The

combination of prematurity and high oxygen exposure resulted in ROP as a new disease entity.[1] Since then, outcomes have improved in industrialized countries with the development of sophisticated oxygen delivery/monitoring technologies, diligent programs for screening at-risk infants, and treatments based on large prospective, multi-center clinical trials.[2,3] Although advanced ROP (Stages 4 and 5 ROP) is uncommon in such high-income countries, micropremature infants—the smallest, youngest, and sickest infants who tend to develop more aggressive disease—remain a challenge even under ideal circumstances.[4,5] Conversely, premature infants born in low-income countries still have poor chances of survival because of inadequate resources. The incidence of ROP is therefore relatively low in these nations.[6]

The regions currently experiencing epidemics of ROP are the middle-income countries.[7] Neonatal medicine has improved in middle-income countries, but in many circumstances, neonatal intensive care units (NICUs) still lack sophisticated technology for the monitoring of oxygen delivery. Oxygen blenders and pulse oximeters, for example, which are in widespread use in the United States are not readily available in many NICUs throughout the world. This unfortunately recreates the situation that industrialized nations experienced at the onset of the ROP epidemic when oxygen was unregulated. As a consequence, infants are at risk of developing ROP despite greater gestational ages and birth weights.[6–9] Retinopathy of prematurity providers in middle-income countries are currently inundated with ROP patients, often with limited manpower and access to digital imaging technologies for screenings and treatment. The current bedside screening model may not be sustainable, and new paradigms for education, screening, and treatment may be required to thwart this epidemic.

Remote Digital Fundus Imaging

Bedside examination with binocular indirect ophthalmoscopy has been the gold standard for ROP screening. However, there is an increasing discordance between the number of premature infants requiring screening and the number of ophthalmologists performing it. Communities with limited access to ROP providers may be burdensome to isolated providers covering multiple hospitals over wide geographic areas. Lower volume and lower acuity NICUs may also not provide physicians tasked with disease surveillance with adequate experience in managing atypical or advanced stages. Photographic screening using digital fundus imaging addresses these logistic issues. Neonatal intensive care unit staff can be trained to obtain fundus images that can be forwarded to the ROP provider for interpretation. Infants with ROP findings severe enough to require bedside examination or treatment can be promptly and efficiently identified. Images of challenging cases could be easily sent for expert consultants in a timely manner. Inherently related to this topic is the complex medicolegal climate surrounding ROP. Photodocumentation is a method of demonstrating sound clinical practice and judgment, should legal action occur.

In addition to its logistic and legal advantages, the data quality of photographic screening is more objective than binocular indirect ophthalmoscopy examinations. Data logged in the chart after binocular indirect ophthalmoscopy examinations are subjective schematic renditions of the actual fundus findings. Sequential digital images for side-by-side comparison provide more accurate documentation of clinical features fundamental to detection of disease progression.[10–16] With more than 15 years of studies validating the accuracy and sensitivity of "store-and-forward" telemedicine in ROP screening, clinical trials and live telemedicine programs have demonstrated that photographic screening using contact widefield digital fundus images can effectively detect treatment and/or referral-warranted ROP.[10–14] These results are consistent among different camera operators, including trained ophthalmologists,[14,17,18] trained neonatal personnel,[19,20] and ophthalmic photographers.[20–22] Analytical software can also enhance remote digital fundus imaging (RDFI) analysis. Weight gain–based risk prediction models[23,24] and automated quantification of vascular tortuosity[25,26] are two such examples.

In our current RDFI programs at our institutions, trained NICU nurses obtain weekly digital fundus photographs of all infants who meet the screening criteria. The weekly imaging paradigm eliminates the risk of skipped examinations resulting from misinterpreted disease severity, as it may occur when the timing of subsequent examinations is predicated on the examiner's sense of the stage of ROP and plus disease status. The images are securely uploaded to a server

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and ROP providers receive message alerts that there are images to be interpreted. The physicians then securely interpret the images remotely, and the images and recommendations are provided to the NICU and included in the chart. Bedside examinations are performed for potentially treatment warranted infants or if there are any questions of image quality.

Remote digital fundus imaging will hopefully improve access to care for at-risk infants. The current live programs have been successful to date, not only because of the benefits of RDFI screening, but also because the inherent limitations are taken into consideration. For example, image artifacts, poor dilation, and media opacities may not permit accurate grading of images. Bedside examinations should be performed in those instances, particularly if there are concerning risk factors. Another limitation is the relative difficulty of imaging the far periphery. Most infants in the NICU with Type 1 ROP have disease that is posterior enough to adequately image with wide-angle cameras. However, milder disease in anterior Zone II and Zone III may be more difficult to capture.[27] Telescreening programs should therefore always have a clear backup algorithm for timely bedside examinations. Finally, another consideration is that ROP screening schedules were developed for bedside examinations. We circumvent the follow-up schedule of 1 weeks versus 2 weeks by photographing weekly, but it is still unclear when to stop screening. Fortunately, infants are usually discharged from the NICU and are being screened in clinic by this point. If not, a bedside examination is generally recommended to make such decisions. At the current time, RDFI should be used to enhance ROP screening programs as an adjunct, without completely replacing bedside indirect ophthalmoscopy.[27]

Innovative Imaging in Retinopathy of Prematurity

Imaging technologies have transformed the management of ROP. The RetCam system is currently the most widely used for fundus imaging, with which widefield (up to 130°) digital color images and fluorescein angiography can be obtained bedside or under anesthesia. Noncontact Optos imaging (Optos, Marlborough, MA) by holding infants in clinic have been shown ("flying-baby"), but the safety of this technique must be properly evaluated, because these infants are often the youngest, smallest, and sickest neonates.[28,29] Widefield fluorescein angiography (WFA) and spectral domain optical coherence tomography have been the two major advances in ROP imaging for the past several years.

Widefield Fluorescein Angiography

Although the diagnosis of ROP is based on ophthalmoscopy or color photography findings, WFA is a useful ancillary test in several situations—particularly in eyes with atypical findings (Figure 1). The characteristic Stage 3 ridge tissue seen when ROP is located primarily in Zone 2 is often absent in eyes with aggressive posterior ROP, with Stage 3 characterized by flat neovascularization that can be difficult to identify, especially if the view is limited from poor dilation, vitreous haze of prematurity, or a dense tunica vasculosa lentis. Widefield fluorescein angiography helps in identifying the flat neovascularization and more accurately delineates the borders between vascular and avascular retina. However, for milder disease, WFA allows early identification of vascular changes that are not yet detectable by ophthalmoscopy or color photography.[30,31] Overall, WFA seems to improve the sensitivity of diagnosis compared with photography alone.[32–34] Studies have also shown that WFA is useful in monitoring disease progression and regression.[35–37] Finally, when the tempo of disease is not fully consistent with ROP, or if the severity is disproportionately worse for the gestational age/birth weight, other syndromic and familial vitreoretinopathies should be considered in the differential diagnosis,[38–40] and WFA is useful to distinguish these clinical entities (discussed below in ROP or familial exudative vitreoretinopathy [FEVR]? or Both?).

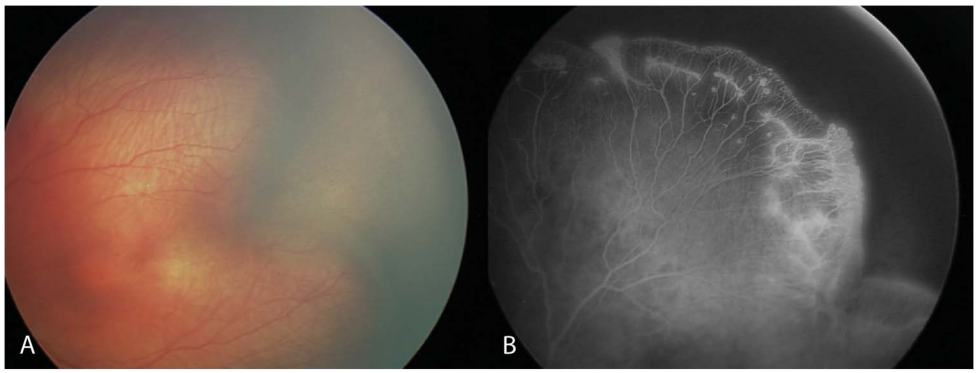

Fig. 1. Widefield fluorescein angiography of Stage 3 ROP. Digital color fundus imaging shows a temporal notch with neovascular ridge tissue (**A**). Fluorescein angiography more clearly delineates the vascular–avascular junction and extent of Stage 3 (**B**). Superiorly, there are also neovascular tufts posterior to the leading edge.

Spectral Domain Optical Coherence Tomography

The micrometer-level axial resolution in vivo imaging of spectral domain optical coherence tomography has provided new insights into the microstructural features of ROP. The development of custom OCT platforms[41,42] and hand-held (Envisu; Leica, Buffalo Grove, IL)[43–45] or mountable (iVue/iStand; Optovue, Fremont, CA)[46,47] devices have allowed imaging of infants and young children.

Spectral domain optical coherence tomography evaluation of the posterior pole of premature infants has revealed heretofore unrecognized acute features of the disease, including foveal hypoplasia with persistent inner retinal layers,[42,46–48] cystoid macular changes,[43,47,49–51] retinoschisis,[42,45,52] posterior hyaloidal organization, and vitreoretinal traction.[45] Of interest, many of these features remain or become more pronounced in adolescent and adult patients with histories of ROP (Figure 2).[53] Regarding the foveal hypoplasia, it has been demonstrated that the structural changes seen on spectral domain optical coherence tomography do not consistently correlate with visual acuity,[54] similar to findings in FEVR.[55] However, the choroid has been shown to be thinner in eyes with advanced ROP compared with spontaneously regressed ROP, and choroidal thinning appears to be independently associated with worse vision in these patients.[56]

Our understanding of ROP has been enhanced through the use of spectral domain optical coherence tomography technologies. We hope that intraoperative OCT will also have meaningful impact on the surgical approach and clinical decision making of these patients in the near future.

Wnt Signaling Pathways, a New Angle

Premature birth disrupts the well-orchestrated sequence of normal retinal vascular development. *Wnt* signaling is an evolutionarily conserved signal transduction pathway that modulates cellular and tissue differentiation.[57] Regarding ocular development, the norrin-FZD4 segment has been identified as playing a pivotal role in retinal angiogenesis and vascular maintenance.[58–60] Mutations affecting genes of this pathway can result in several pediatric vitreoretinopathies, such as Norrie disease, FEVR, and pseudoglioma (term ascribed to describe the appearance of the detached retina in affected patients) and osteoporosis syndrome. Of interest, studies have identified *FZD4*, *LRP5*, and *TSPAN 12* mutations in patients with advanced ROP.[61–63] Two avenues for further investigation are introduced below.

Placental Homeostasis

Wnt signaling plays an important role in placental homeostasis.[64,65] Markers for angiogenesis and vascular formation are reduced in the corpora lutea of *FZD4*-null mice, and these mice are infertile.[66] Likewise, norrin has been localized to the uterine blood vessels and decidual cells of rats,[67] and *NDP* knockout mice have defects in vascular development and decidualization in pregnancy that leads to embryonic loss.[68] In humans, the expression of *NDP* has been established in the placenta, and *FZD4* expression has been localized to placental villous mesenchymal cells. Our laboratory recently showed that a double missense mutation in *FZD4* (p.[P33S(;)P168S]) was associated with lower than normal birth weights for gestational age in infants with ROP compared with other premature infants. This finding suggests that *wnt* signaling defects may contribute to ROP pathogenesis, indirectly through intrauterine growth retardation, and directly through retinal vascular developmental alternations.[64,69]

Retinopathy of Prematurity or Familial Exudative Vitreoretinopathy? or Both?

One occasionally encounters infants who have a discrepancy between their birth history and fundus

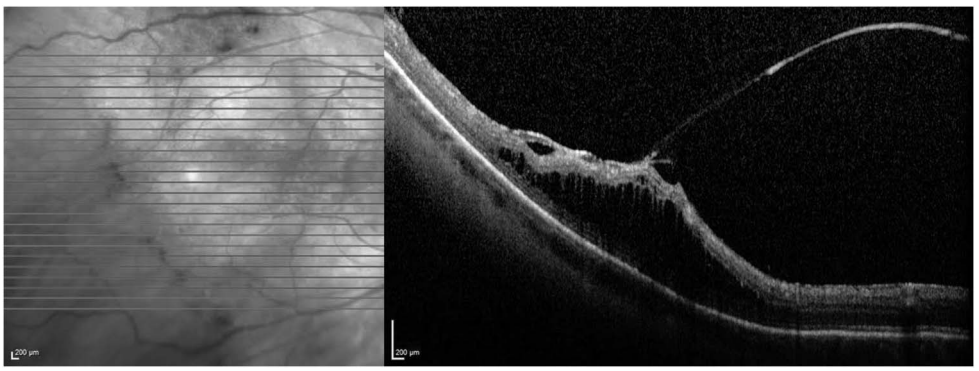

Fig. 2. Spectral domain optical coherence tomography of adult ROP. Spectral domain optical coherence tomography of the superior macula in an adult patient with a history of untreated ROP demonstrates an anomalous dense posterior hyaloid with vitreoretinal traction and underlying cystoid macular changes.

appearance. These infants are premature but not significantly so, yet present with very severe retinopathy. The possibility for a *wnt* signaling mutation should be entertained in these atypical cases, as these mutations may be disease modifying with potential for prognostic implications. Widefield fluorescein angiography can provide valuable information by identifying angiographic characteristics of ROP versus FEVR-like changes. For example, ROP will have ridge tissue, arteriovenous shunting, and tuft formations. On the contrary, FEVR will have more arborization that may not lead to a ridge, venous–venous shunting, peripheral vessel pruning that may not leak as much as expected for ROP, and relatively more exudation. Circumferential hyaloidal contraction is also much more characteristic of ROP. When patients with angiographic findings suggestive of FEVR are born prematurely, or if premature infants show angiographic signs of FEVR, the distinction between the two can be difficult, and the angiograms may contain features of both. We have identified that these patients may harbor *wnt* signaling pathway mutations, and term these infants fROP.[38] They have also been termed ROPER.[39,40] In general, the tempo of disease progression is slower, but unlike classic ROP, recurrences of vasoactivity may occur in fROP/ROPER despite timely and appropriate therapy. Severe detachments can also be seen, characterized by extensive avascularity and a rapidly contractile posterior hyaloid. We recommend angiography and genetic testing when in doubt, because the correct diagnosis will alter treatment, follow-up, and family counseling. Further study of this phenomenon is required.

Laser Photocoagulation

The International Classification of Retinopathy of Prematurity standardized the nomenclature of ROP and laid the groundwork for the landmark treatment trials, Cryotherapy for Retinopathy of Prematurity (CRYO-ROP), and Early Treatment for Retinopathy of Prematurity (ETROP).[2,3,70,71] CRYO-ROP established the safety and efficacy of peripheral retinal ablation in threshold ROP.[72] There was a 50% reduction in unfavorable structural outcomes compared with untreated eyes.[72,73] In planning for ETROP, post hoc analysis of the CRYO-ROP natural history cohort stratified eyes into high-risk (Type 1) or low-risk (Type 2) prethreshold disease.[74] Laser was preferred over cryotherapy due to lower risks of postoperative inflammation, hyaloidal contraction, myopia, and ease of posterior treatment.[75,76] ETROP randomized infants to treatment at Type 1 ROP or Type 2 (threshold) ROP, and demonstrated a further reduction of unfavorable structural outcomes with earlier intervention.[3]

Laser Techniques

Laser peripheral retinal ablation for ROP presents a variety of challenges, both in terms of treatment technique as well as coordinating multidisciplinary efforts involving anesthesiology, neonatology, and the NICU staff. A near-confluent pattern of the laser (half a spot diameter apart) is superior to less confluent treatment.[77,78] The endpoint should be a grayish burn, not chalky white. The laser power should be titrated appropriately because the posterior pole will require higher power, whereas the thinner anterior retina requires less power. Anterior segment ischemia is a rare, but potentially blinding, complication that may occur if the laser is too confluent and hot.[79] The laser spans the avascular retina anterior to the ridge to the ora serrata. The most common locations for missed laser are anteriorly (technically challenging) or in the temporal notch (poor uptake). Neovascular fronds and the ridge should not be directly lasered, as it may cause bleeding. Flat neovascularization that characterizes aggressive posterior ROP may pose a challenge because the fronds can overlie the underlying avascular retina. Staged laser has been shown to be effective in such cases: the flat neovascular fronds will regress with the first laser treatment, and the underlying avascular retina will then be exposed, and can be treated during a subsequent session.[80] Finally, we also caution against severely anemic/thrombocytopenic infants who are at higher risk for bleeding.

Retinopathy of prematurity laser treatment results in well-described and predictable regression patterns. In the rare instances that laser fails, it fails in a predictable manner. Almost all eyes treated with laser will succeed or fail within the first 9 weeks posttreatment.[81] In ETROP, 9% of eyes progressed to retinal detachment,[82] but laser spots were allowed to be up to one spot diameter apart in the study.[83] As discussed above, near-confluent laser results in better outcomes,[77,78] and the failure rates at specialized centers are much lower.[84] When lasered eyes do progress to retinal detachment, they do so in a fashion similar to untreated ROP. However, the peripheral retina treated with laser almost never detaches, which helps maintain surgical planes during vitrectomy.

Role of Anti–Vascular Endothelial Growth Factor Treatment

Vascular endothelial growth factor is one of the key cytokines that modulates the pathogenesis of ROP.

The VEGF-driven vasoproliferative phase of advanced ROP develops in response to the avascular peripheral retina, and therefore it is logical that anti-VEGF treatment would be considered for ROP. The benefits compared with laser include the technical ease of administration, general accessibility and lower cost of bevacizumab (Avastin; Genentech, South San Francisco, CA), ergonomic benefits for the treater, the ability to perform the procedure without sedation/intubation, less induced myopia, relative preservation of visual fields, and faster regression of neovascularization. Off-label use of anti-VEGF treatment is therefore increasing in popularity, and many studies have demonstrated the efficacy in providing rapid ROP regression.[85–90]

However, most of the aforementioned benefits of anti-VEGF treatment are logistic in nature, physician-centered issues, or ophthalmic issues that would be insignificant unless the retina is attached. Potential drawbacks include, but are not limited to, the following: "crunching" of the fibrovascular proliferation with progressive retinal detachment, unpredictable early and late reactivation, and systemic exposure of anti-VEGF medication. The incidence and predisposing factors for these potential issues are currently unknown at the time of writing.

The BEAT-ROP Controversy

Many neonatologists and ophthalmologists cite the BEAT-ROP study as justification for anti-VEGF monotherapy for ROP. The study randomized infants with Stage 3 ROP to bevacizumab or laser therapy and concluded that bevacizumab was superior to laser for Zone I ROP, but not for Zone II. The trial without doubt provided new information in a landscape that was only composed of case series, but the data should be interpreted with caution because of several imperfections in study design and execution:

1. The laser failure rate for Zone I in BEAT-ROP was 42%. This is a high laser failure rate that is more than double the rates reported previously.[5,91–93] Had the laser treatment success rates been comparable with previous reports, there would not have been a statistically significant difference between bevacizumab and laser treatment in Zone I.[94]
2. The definition of laser failure is different than other reports. Most would consider progression to retinal detachment a laser failure. However, BEAT-ROP's definition was recurrence of neovascularization. This does not take into account that infants with aggressive posterior ROP may require more than one laser session.[80] If progressive retinal detachment was used as the definition of laser failure, there were 2 Zone I eyes treated with laser that progressed, compared with 0 for bevacizumab. This would not be a significant difference. Also note that for Zone II eyes, there were 2 treated with bevacizumab that progressed to retinal detachment, compared with 0 for laser.
3. The primary endpoint of the study was altered during the course of the study, and it is unclear why.
4. A reading center was not established until 20 months into the study.
5. The study recommends injecting 2.5 mm posterior to the limbus, which poses a high risk for retinal perforation in the infant eye. We recommend injecting through the pars plana, 0.5 mm to 1.0 mm posterior from the limbus.

Beyond these limitations in design and execution, there are several noteworthy incorrect statements in the Discussion section

1. that anti-VEGF injections are a one-time treatment and that there will not be recurrences (see Early and Late Reactivation discussion below)
2. that anti-VEGF injections do not leave the eye into the systemic circulation (see Systemic Exposure discussion below)
3. that anti-VEGF treatment will allow full retinal vascularization (see Persistent Vascular Abnormalities discussion below).

Although the BEAT-ROP study was influential, we caution practitioners to interpret the data critically.[95]

Incorporating Anti–Vascular Endothelial Growth Factor Treatment Into Practice

In general, laser monotherapy is our preferred treatment paradigm for Type 1 ROP, and vitrectomy for Stages 4 and 5. Nevertheless, there are three clinical scenarios for which we consider anti-VEGF treatment for Type 1 ROP:

1. When the fovea has not fully vascularized and laser would affect a large portion of the macula. Interestingly though, the macula does vascularize after laser treatment to a surprising degree, so the laser can be very close to the fovea, or even partially involving it, and the macula can broaden anatomically with further ocular development over time.[96] However, we do not know yet if normal foveal development takes place.
2. When poor fundus visualization precludes laser treatment. This can occur as a consequence of a prominent tunica vasculosa lentis, cornel stromal haze, vitreous haze of prematurity, or vitreous hemorrhage. If the latter, the view should be good

enough to confirm that there is no retinal detachment or fibrotic components may crunch. Otherwise a vitrectomy would be indicated.
3. When the anesthesia risk is too high for laser treatment.

At the time of writing, there are no hard indications or contraindications for anti-VEGF treatment, and many groups use combinations of laser and anti-VEGF treatments successfully. We provide our personal preferences based on the currently available literature, our patient population, and ROP management experiences in the paragraph above. Robust data to allow standardization of treatment and follow-up of eyes managed with ant-VEGF agents are currently lacking.[97]

RAINBOW Study

To that end, the RAINBOW study (RAnibizumab Compared With Laser Therapy for the Treatment of INfants BOrn Prematurely With Retinopathy of Prematurity; NCT02375971) was designed to provide a better assessment of anti-VEGF treatment for ROP. RAINBOW is an ongoing, Phase 3, randomized, multicenter, prospective clinical trial that investigates the efficacy and safety of ranibizumab (Lucentis; Genentech) in infants with Type 1 ROP compared with laser therapy. The primary outcome is visual function at the patients' fifth birthdays. Secondary outcome measures were anatomical outcomes, ocular and systemic adverse events, absence of active ROP beyond 52 weeks after treatment and recurrence of ROP. In addition, systemic measures such as head circumference, leg length, weight, hearing, and respiratory function will be assessed. It is hoped that this study will provide better information on the dosing regimen (0.2 and 0.1 mg ranibizumab) as well. Of note, the RAINBOW trial is not investigating bevacizumab, but the Pediatric Eye Disease Investigator Group is currently recruiting for a smaller prospective study to examine lower dosing of bevacizumab (NCT02390531).

Anti–Vascular Endothelial Growth Factor Injection Technique

When we use anti-VEGF agents in our practices, we prefer to use 0.17 mg (a third of 0.5 mg) to 0.25 mg (half dose) of ranibizumab when possible. The concentration of systemic exposure and the degree and length of systemic VEGF suppression are favorable compared with bevacizumab and aflibercept,[98] although it is unknown if these pharmacokinetic differences are clinically significant.[99] The two problems are that ranibizumab is not reimbursed for ROP, and most hospitals do not have it on formulary. Samples or extensive research protocols are thus usually required. The majority of practices therefore use a quarter to half dose of bevacizumab, and there is absolutely no fault in doing so until there are advancements in regulatory processes.

After topical and/or subconjunctival anesthesia, the intravitreal injection is performed 0.5 mm to 1.0 mm posterior to the limbus after povidone iodine prep of the conjunctiva and a pediatric speculum has been placed. Because the injected volume is small, care should be taken that the medication is actually delivered. The smallest possible syringes are therefore recommended. The intraocular pressure can rise dramatically. After injection, optic nerve perfusion should therefore be confirmed.

In our practices, most patients also receive subsequent laser treatment if possible to prevent early and late reactivation. The timing of this subsequent laser varies and is tailored to the individual infant's eye, health, and logistic issues: earlier if there are signs of reactivation,[100] and later if there are systemic issues that should be well controlled first to minimize the anesthesia risk,[3] and as needed if the patient may be discharged home to where ROP care may be limited.

Considerations in Anti–Vascular Endothelial Growth Factor Treatment

Early and Late Reactivation

Pharmacologic suppression of VEGF is currently provided as a bolus dose through intravitreal injections. When the medication is cleared from the eye, there is a resurgence of VEGF unless the underlying cause of the retinopathy has been addressed. Although the VEGF surge is intense yet short-lived in ROP compared with most adult retinopathies such as diabetic retinopathy, some infants will require more than one treatment session. Anti-VEGF treatment of ROP is far from a "one and done" paradigm. The rates of recurrence or incomplete response requiring multiple injections or laser supplementation are not clearly known. Rates after bevacizumab have varied from 0%,[101] 2%,[102] 7%,[103] 14%,[104] to 46%,[105] and after ranibizumab, as low as 0%[102] and as high as 83%.[106] The variability is likely due to relatively small sample sizes, different patient populations, variable follow-up, and because the timing of anti-VEGF treatment is not standardized. Nevertheless, the recurrence rate is not negligible and necessitates a meticulous follow-up schedule, as recurrent disease activation and progressive detachment can occur as late as 2.5

years after treatment.[107] In general though, reactivations tend to occur within 1 month to 3 months after initial treatment.[100,103,108] Anti-VEGF treatment should be avoided if the infant's family may not be able to keep strict follow-up appointments.

Persistent Vascular Abnormalities

After laser treatment, follow-up examinations occur every 1 week to 2 weeks based on examination findings, with clear endpoints for cessation of acute examinations.[109] However, there are no long-term prospectively acquired data to guide follow-up of infants treated with anti-VEGF monotherapy. Many infants treated with anti-VEGF agents have vascular abnormalities and/or persistently avascular peripheral retina even after years of follow-up (Figure 3).[36,110,111] These peripheral retinal abnormalities are theoretically risk factors for early or late recurrences, or other pathologies. Peripheral avascular retina is prone to lattice-like changes, retinal breaks, and retinal detachment in teenage years.[112,113] Consequently, we prefer treating persistent avascular retina with laser to help control the acute disease,[104,108] to avoid the uncertainty of reactivations, and to minimize late ROP-associated rhegmatogenous retinal detachment.[114,115] In our practices, patients after anti-VEGF treatment are clinically followed, but fluorescein is very helpful if there is any suspicion for reactivation, and/or if the decision is made for laser.

Crunch Phenomenon

The dynamic cytokine milieu of the developing retina is complex and not fully understood yet. Vascular endothelial growth factor and many other cytokines are involved in ROP pathogenesis.[116] Anti-VEGF injections alter multiple cytokines, including elevation of TGF-β, a potent profibrotic agent.[117–119] In addition to this iatrogenic rise in TGF-β, premature infants experience an endogenous rise of TGF-β as they approach term.[120,121] This unopposed TGF-β can cause rapid contraction of the fibrovascular membranes to cause progressive retinal detachment. Such "crunching" has been most commonly discussed in proliferative diabetic retinopathy[117] but has been reported in ROP as well.[100,122–126] This phenomenon is likely not common, and incidence data are not available to date. When detachment occurs on the heels of anti-VEGF pharmacotherapy, they are more likely to be atypically configured.

In an effort to better characterize eyes with ROP that "crunch" after anti-VEGF treatment, we organized an international multicenter study to examine such cases.[126] We found that progression to retinal detachment was noted a mean of 70 days after the anti-VEGF injection; 11% within 1 week, and 49% within 4 weeks. The time to detachment negatively correlated with the postmenstrual age at injection, i.e., younger infants had a longer latency period before detachment, and older infants detached more quickly. Three "crunch" configurations were noted: conventional progression, very posterior with prepapillary contraction, and relatively peripheral but with very tight circumferential tractional vectors (Figure 4). We hypothesize that anti-VEGF agents may induce fibrosis and contraction of the immature prepapillary vascular precursor cells for the prepapillary configuration, and of the flat neovascularization for the circumferential configuration. All eyes with conventional detachments were repaired successfully, but the anatomical success rate for the prepapillary and circumferential configurations were approximately two-thirds each. Because these detachments are difficult to repair, we recommend trying to avoid anti-VEGF agents in eyes with evidence of fibrotic change along the ridge, as well as in eyes with existing tractional retinal detachment.

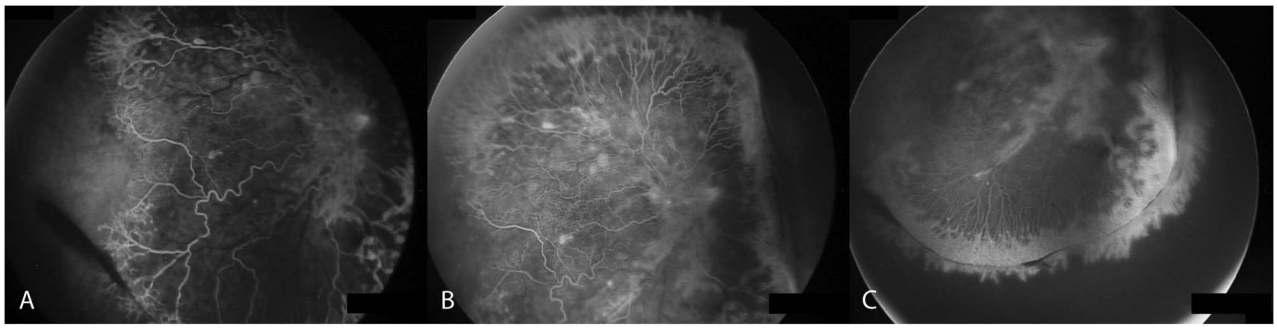

Fig. 3. Persistent vascular abnormalities after anti-VEGF for aggressive posterior retinopathy or prematurity (AP-ROP). One month after anti-VEGF injection for AP-ROP, there are large areas of avascular peripheral retina and persistent neovascularization (**A**). Nasally, there is hyaloidal contraction with an evolving traction retinal detachment (**B**). There is diffuse vascular leakage throughout the posterior pole, not just from the neovascular tissues (**A**–**C**). There are vessels that have grown anteriorly at the previous vascular–avascular junction, but only a meager amount, and these are incompetent vessels that leak fluorescein (**C**).

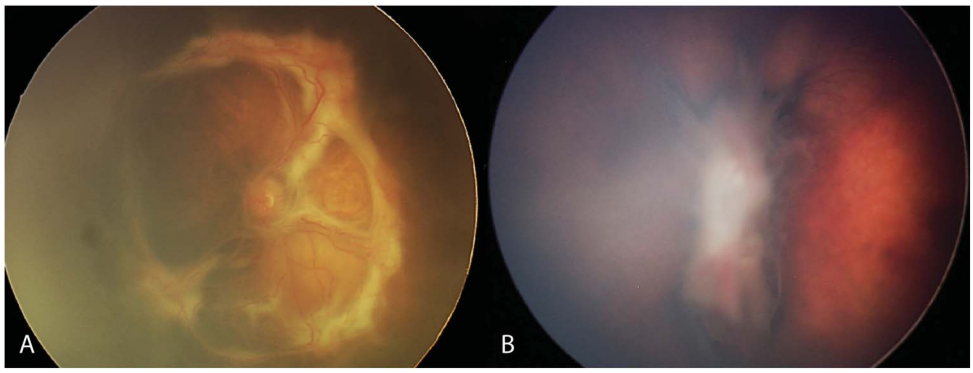

Fig. 4. Crunch phenomenon after anti-VEGF treatment. **A.** Circumferential type of anti–VEGF-associated progressive retinal detachment, which was noted 1 week after bevacizumab for an infant with aggressive posterior ROP. **B.** Prepapillary type of anti–VEGF-associated progressive posterior retinal detachment that was noted several weeks after bevacizumab for Zone I disease.

Systemic Exposure

Vascular endothelial growth factor overexpression is implicated in many pathologic states of the retina, but we must remember that the growth factor plays a critical role in organogenesis and maintenance of microvascular environments throughout the body. During development of the embryo/fetus, its importance has been demonstrated in lung maturation, cardiac development, neuronal survival, ocular development, renal development, pancreatic development, and bone growth.[127] Although anti-VEGF agents are delivered locally in the vitreous, the agents do enter the circulation and systemic VEGF is suppressed in ROP infants.[128] Studies have demonstrated that bevacizumab is detectable in the circulation for 8 weeks after intravitreal injection for ROP, with corresponding systemic VEGF suppression.[129–131] One case report that measured VEGF levels after ranibizumab showed VEGF suppression for 3 weeks.[132] There are many adult studies also showing that the systemic VEGF suppression is much more pronounced and longer with bevacizumab and aflibercept (Eylea; Regeneron, Tarrytown, NY), compared with ranibizumab[98,133–136] and pegaptanib (Macugen; Bausch + Lomb, Bridgewater, NJ).[137] We currently do not know whether the temporary systemic VEGF suppression will have lasting effects, but the potential should be carefully discussed during the parental informed consent process.

Neurodevelopmental Controversy

It is well established that VEGF plays vital roles in neurogenesis.[138] Previous small studies did not show particularly concerning results.[139,140] However, two recent studies have drawn attention to potential neurodevelopmental consequences of anti-VEGF therapy in infants with ROP.[141]

Lien et al[142] from Taiwan recently reported in a retrospective study that infants treated with a combination of bevacizumab and laser (n = 16) had poorer neurodevelopment compared with infants treated with laser alone (n = 33), or bevacizumab alone (n = 12). The laser + bevacizumab group, however, had the highest percentage of eyes with zone I disease, and overall smaller and younger infants. This means that this group likely underwent more anesthesia sessions (neurotoxicity of general anesthesia is also a debated issue[143,144]), were sicker at baseline, and had less mature organ systems.

A recent study by the Canadian Neonatal Network published 2 months after the Taiwanese study reviewed infants treated with bevacizumab (n = 27) or laser (n = 125), who underwent neurodevelopmental testing at 18 months. The authors noted that infants treated with bevacizumab were more likely to have poorer motor scores and severe neurodevelopmental disabilities. The study has many limitations and needs to be interpreted with caution. Most importantly, this was a small retrospective chart review, which is prone to incomplete data, lack of randomization, selection bias, and in this case recall bias also because some data were obtained from parental interviews.

Many issues placed the bevacizumab group at a disadvantage. More infants had Zone I disease, and this difference was not accounted for in the regression analysis. Important factors such as birth weight, race, and use of mechanical ventilation were also not factored into the model. Risk factors such as male sex and longer hospitalization trended toward placing the bevacizumab arm at a disadvantage, but they were not considered because of lack of statistical significance. Multiple "trends" that each does not attain a desirable *P* value can compound and cause a cumulative real effect.

Subject grouping was also another issue. For example, three infants had bevacizumab + laser, and were included in the bevacizumab group. These infants likely required combination treatment because of aggressive disease, which is more likely to be seen in smaller and sicker infants. In addition, the laser group contained 11 infants who were treated for Type 2 ROP, which potentially means that those infants

were systemically healthier also, further placing the bevacizumab group at a disadvantage.

The neurodevelopmental assessment was also imperfect. For example, scores were not calculated if the children were too developmentally delayed. There were nine such cases in the laser group, and only 1 in the bevacizumab group. This removed nine very developmentally delayed infants from the laser arm. Also, 20/70 vision or worse was one definition for "severe neurodevelopmental disability." An otherwise healthy child with 20/70 vision is different from a child with severe cognitive impairments from cerebral palsy. Furthermore, visual acuities were partially collected from parental interviews, and not actual examinations.

The study was one step toward learning more about potential systemic issues with using anti-VEGF agents for ROP. However, the observations noted above suggest that the study design was biased against the bevacizumab group. Better designed studies are required before making any conclusions regarding neurodevelopmental issues.

Advanced Surgical Techniques for Stages 4 and 5

The history of surgical management for ROP is a chronicle of expanding limits.[145–147] Once considered to be a largely inoperable disease, advanced retinal detachments from ROP have been rendered operable—however challenging—through a combination of improved pathophysiologic understanding, revised surgical expectations, and novel techniques (Figure 5).

Learning to view retinal detachments in the setting of ROP as a progressive tractional disease with predictable vectors (Figure 6),[148] all serving to distort a highly elastic retina, allows treating physicians to perform more targeted surgeries while leaving the crystalline lens intact.[149] Shorter surgeries reduce anesthetic risk for vulnerable patients, and less-extensive dissections reduce the risk of retinal breaks and the subsequent devastating effects of proliferative vitreoretinopathy.

The goal of intervention for ROP-related retinal detachments varies with the severity of the detachment. In contrast to the repair of retinal detachments in adults, in which relieving all points of traction (and, if relevant, reattaching the macula) is the sine qua non of successful treatment. Conversely, repair of retinal detachments in ROP is a balancing act: removing critical points of traction when one can safely do so without making a retinal break. The goal for extramacular retinal detachment (Stage 4A ROP) is an undistorted/minimally distorted posterior pole, total retinal reattachment and preservation of the lens, and central fixation vision. This goal is achieved in 90% of eyes with Stage 4A ROP.[139] Surgery for traction retinal detachments involving the macula (Stage 4B ROP) is performed to minimize retinal distortion and prevent total detachment (Stage 5). Successful surgical therapy in more advanced detachments is often performed in a stepwise fashion, with intervals between surgeries to allow for the progressive reapproximation of the retina toward the underlying pigment epithelium, which highlights further surgical planes to address during subsequent operations—in more succinct terms, success by successive approximation.

Various manifestations of ROP have been brought into the surgical fold through novel techniques that have expanded surgical indications. For example, the posterior detachments that we more commonly see now in micropreemies or eyes treated with anti-VEGF agents have very tight dissection planes, and may benefit from hybrid-gauge vitrectomy, with 27-gauge cutters introduced through 23- or 25-gauge cannulas.[150] Shorter cannulas and instruments have recently been developed for vitreoretinal surgery in infants.

Although surgical approaches and goals are different between ROP and adult surgeries, advances in adult vitreoretinal surgery can be appropriately applied to ROP surgery. Examples include small gauge

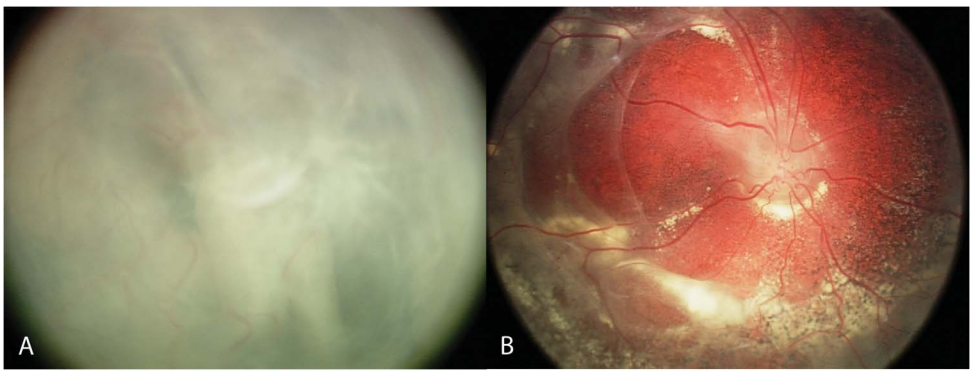

Fig. 5. Surgery for Stage 5 ROP. Preoperatively, the infant presented with a total retinal detachment with a dense anterior hyaloidal plaque, which was dissected after a lensectomy and capsulectomy (**A**). Several months later, the posterior pole is attached and the infant has brisk light perception.

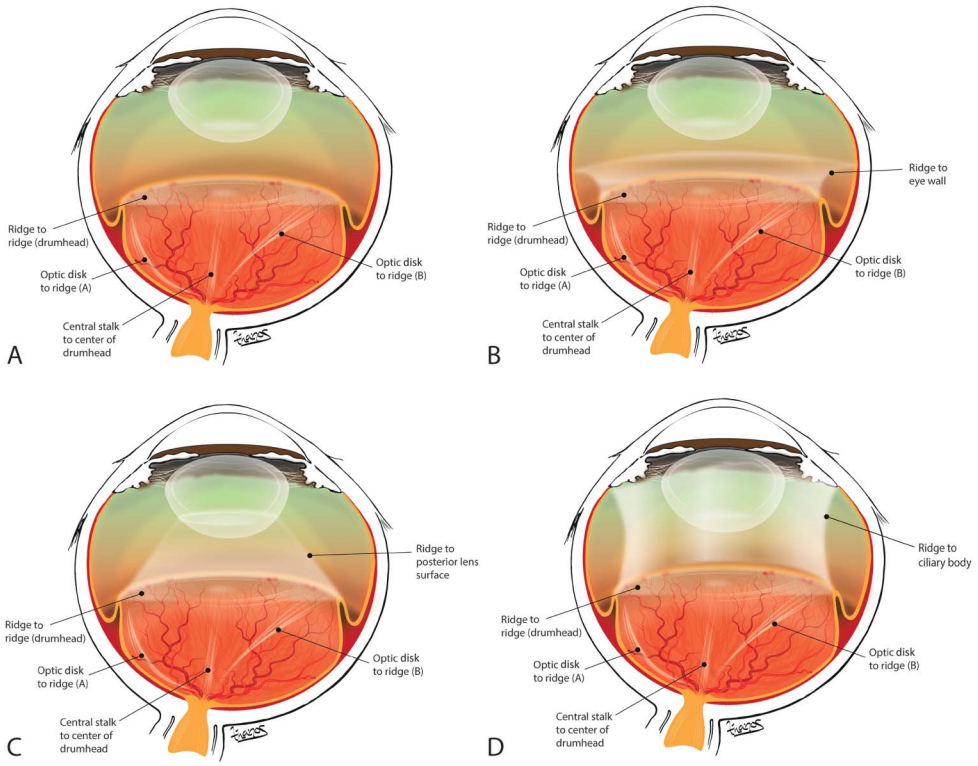

Fig. 6. Tractional vectors in advanced ROP. The primary tractional vectors in ROP are (**A**) ridge to ridge (we call this the drum head), ridge to optic disk, (**B**) ridge to eye wall, (**C**) ridge to ciliary body, and (**D**) ridge to lens. These vectors need to be transected by vitrectomy to allow retinal reattachment.

instrumentation[151–153] and endoscope-assisted vitrectomy.[154,155] Several more broad concepts to facilitate repair of complex ROP-related retinal detachments are discussed below:

Novel Illumination Techniques

Successful surgery in ROP is rooted in visualization, but the nuances of the pathologic anatomy can sometimes be obscured by the standard diffuse en face lighting of the operating microscope. To overcome this obstacle, simple positional maneuvers with the standard lightpipe can be used. In brief, the maneuvers involve using oblique illumination emitted from a standard endoilluminator, positioned transcorneally or intracamerally to highlight subtle tissue planes and distinguish dysplastic vitreous from underlying retinal tissue. The endoillumination probe is positioned obliquely about the surgeon's viewing axis through the operating microscope, directed at the surgical plane of interest. The probe is positioned either intracamerally through one of the three ports or transcorneally (held by an assistant) when bimanual dissection is required. The surgical field is viewed using an unlit operating microscope. Each of the illumination techniques—direct, retroillumination, and transcleral—helps to render safer opportunities for surgical approaches by making dissection planes more apparent.[156]

Ab Interno Incisions

With appropriate visualization, one can then begin to address the difficult task of transecting the vectors of traction to relax the retina while preserving the lens and avoiding retinal breaks.[149] True to the original description of "retrolental fibroplasia," the retina is often pulled forward to just behind the lens by sheets of fibrous proliferation extending from the ridge toward the lens and ciliary body, narrowing the available space for surgical approach. Radial or circumferential retinal folds and/or tractional retinal detachments that are in close approximation to the posterior lens capsule can extend for many clock hours. This can be difficult to manage without removal of the lens because the surgical entry space is too narrow for a vitreous cutter. However, lens removal in the pediatric population is fraught with sequelae including inhibition of visual development and development of aphakic glaucoma.

These complications can be avoided by using the previously described technique of ab interno incisions using a microvitreoretinal blade.[157] With the ab interno technique, once the sclera is entered, the microvitreoretinal blade is first directed carefully posterior and then inserted into the space or tissue between the retina and posterior lens capsule. The transvitreal proliferative sheet extending anteriorly from the ridge is interrupted using the blade for sharp dissection. This

relieves anterior retinal traction, and posterior relaxation of the retina is immediately apparent with creation of adequate space for the ensuing vitrectomy and dissection of proliferation along the retinal surface which spares the crystalline lens.[157] This ab interno incision can be extended for many clock hours by sweeping in the surgical space parallel to the lens capsule using the sclerotomy as a pivot point or by sliding the blade like a saw to release any tractional vectors, as described (Figure 7). Care must be taken to avoid violating the lens equator or causing an unintentional retinal break. Favorable long-term outcomes of this technique have been reported.[158]

Plasmin-Assisted Vitrectomy

Safe, successful surgery in ROP requires removal of tractional vectors, mainly in the form of dysplastic vitreoretinal adhesions. In pediatric patients, the hyaloidal attachment to the retina is particularly strong. This strong attachment can lead to more difficult vitreous separation during vitrectomy and higher risks associated with the procedure. Retinopathy of prematurity eyes have incomplete regression of the primary hyaloid (including the tunica vasculosa lentis), incomplete development of anterior segment structures (such as trabecular meshwork, ciliary processes), and areas of atrophic retina, making this step even more difficult. In fact, the hyaloid is left in place in many scenarios without forcing vitreous separation. One of the next horizons for surgery in this population is augmenting the surgeon's ability to create separation of the posterior vitreous, most prominently through pharmacologic means.

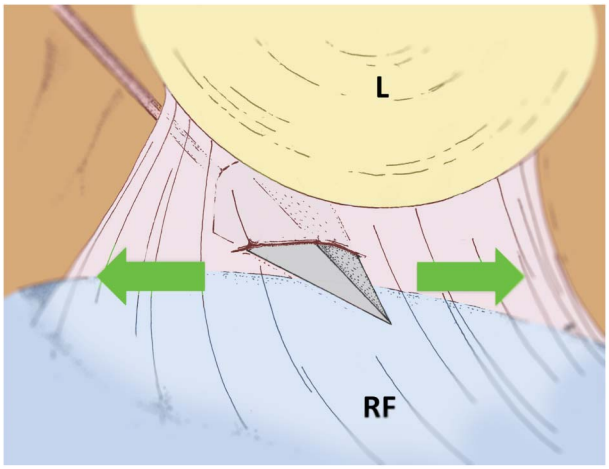

Fig. 7. Ab interno transection of retrolental membrane. A microvitreoretinal blade is inserted through the pars plicata into the surgical space between the lens (L) and the retinal fold (RF). The membrane is first punctured and then swept laterally. This allows a safer entry site for the vitreous cutter.

Both human-derived plasmin enzyme (both autologous and heterologous) and ocriplasmin (Jetrea; Thrombogenics, Leuven, Belgium) have been used as pharmacologic vitreolysis agents to facilitate the induction of posterior vitreous detachment during vitrectomy. Ocriplasmin is a serine protease and truncated form of plasmin that is active against substrates, such as fibronectin and laminin, and cleaves the vitreoretinal interface to treat vitreomacular traction in adults. The use of plasmin enzyme to assist surgery has been reported in the ROP population.[159–161]

The data regarding plasmin were retrospective in nature and lacked control arms, but it did demonstrate an acceptable safety profile and appeared to augment vitreous separation. Further studies are warranted here. Ocriplasmin demonstrated slightly less encouraging results in a prospective study of pediatric vitreoretinopathies.[162] Although the data presented in that study do not show a clear-cut benefit to the use of ocriplasmin as an adjunct in pediatric retinal surgery, the complexity of these surgeries and the small sample size limited the analysis and left open the door for future studies and pharmacologic agents. The investigators did note that vitrectomy appeared to be easier in the treatment arms after the unmasking. In general, the overall ability to dissociate the hyaloid from the retina with less mechanical force and the improved visualization of surgical planes are advantageous. Ongoing studies will hopefully be better able to delineate the role for these agents in complex ROP surgery.

Corneal Clearing

A final point of expanding surgical limits pertains to ROP eyes with advanced pathology that demonstrate shallowing of the anterior chamber with subsequent lens–cornea touch and central corneal opacification. These cases often present late (and are predominately seen in areas with poor ROP screening and treatment infrastructures), and although often considered inoperable due to the corneal status, are indeed amenable to surgical intervention.[146]

The surgical approach involves entering through the iris root or limbus at the nasal horizontal meridian with a bent 23-gauge butterfly needle that allows tissue entry with simultaneous infusion (the needle is attached to an infusion line of lactated Ringer's solution). A temporal wound is made at the horizontal meridian with an microvitreoretinal blade, then a standard vitreous cutter is inserted into the crystalline lens and lens material is endoaspirated to deepen the anterior chamber. The iris can then be mechanically swept from the posterior corneal surface with a cyclodialysis

spatula in a side-to-side motion or viscodissected, after which the cutter is again used to remove the fibrotic pupillary margin (enlarging the pupil beyond the margins of the central corneal opacity) and performing surgical iridectomy if required, followed by removal of the remaining lens material and capsule. Afterward, the eye is placed on topical cycloplegics, steroids, topical ocular hypotensive, and hypertonic sodium chloride drops. In most cases, the cornea will clear sufficiently to allow posterior segment surgery within 2 weeks to 4 weeks, thereby allowing therapeutic benefit in eyes with an otherwise abysmal prognosis.

Immediate Sequential Bilateral Vitreoretinal Surgery

Infants with ROP often have multiple life-threatening comorbidities and are the retina surgeon's highest anesthesia risk population.[163,164] Repeated sessions may not be desirable or even feasible. However, ROP is a rapidly progressive bilateral vitreoretinopathy, where both eyes commonly require surgical intervention. This had traditionally required repeated visits to the operating room for each eye, which compounds the anesthesia risk each surgery. Furthermore, the Stage 4A eye could progress to a 4B while awaiting surgery, and the visual potential has now been drastically reduced. Many of these infants have active comorbidities that may prevent them from returning to surgery for the second eye in a timely fashion.

One way to circumvent these issues of anesthesia risk (mortality) and progressive retinal detachment (blindness) is to operate on both eyes consecutively during the same anesthesia session.[165] We termed this technique immediate sequential bilateral pediatric vitreoretinal surgery (ISBVS).[165] Each eye is treated as a completely separate procedure with re-preping, re-draping, re-scrubbing, and new sets of instruments, medications, and intraocular fluids. Based on the reported incidence of postvitrectomy endophthalmitis of 0.03% to 0.08%, the risk of bilateral endophthalmitis would be 1 in 500,000 to 10,000,000 simultaneous vitrectomy procedures.[166,167] In comparison, the risk of anesthesia-related death in children is as high as 1 in 10,000, all-cause perioperative mortality is 1 in 100 to 1,000, even higher in neonates, and even higher in premature infants.[168,169] In 2 small studies of infants undergoing ROP surgery, serious anesthesia complications occurred in 1 in 29, and 1 in 13.[170,171] The risk of bilateral endophthalmitis is miniscule compared with these risks of morbidity and mortality, and therefore justifies the employment of ISBVS in appropriate cases. We conducted a study of 344 surgeries from 172 ISBVS procedures from 24 centers worldwide, speaking to its feasibility and safety.[165] Of note, we do not advocate ISBVS for all infants. The majority of infants can be treated with staged bilateral surgery, but ISBVS can be a powerful option for appropriately selected cases.

Future Horizons

Retinopathy of prematurity may seem to be something we have a firm hold of: We know the risk factors, and how to screen and treat effectively in the majority of at-risk and affected infants. Yet, ROP persists as a major cause of childhood blindness worldwide. Retinopathy of prematurity is deeply interwoven with socioeconomic dynamics and medical progress, and its most prominent clinical manifestations have evolved over the past several decades since Terry's first description in 1942.[1] Current challenges include aggressive posterior disease seen most commonly in profoundly premature infants, as well as clarifying and defining the role of anti-VEGF therapy. The epidemics of the middle-income nations need to be addressed through training programs[172–174] and paradigm-shifts toward remote digital image screening. We hope that translational studies will result in the eradication of ROP one day.[175,176] Until then, the goal should be to widen and strengthen our net to identify all infants at risk for the development of ROP—as those who enter the treatment pathway have a theoretical success rate of 99% (90% anatomical success with laser, and 90% anatomical success with Stage 4A ROP). Our goal as clinicians is to expand the boundaries of our abilities to keep this blinding disease in check globally.

Key words: anti-VEGF, fluorescein angiography, laser, optical coherence tomography, pediatric retina, retinal detachment, retinopathy of prematurity, telemedicine, vitrectomy, wnt signaling.

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