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International Classification of Retinopathy of Prematurity, Third Edition

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Purpose: The International Classification of Retinopathy of Prematurity is a consensus statement that creates a standard nomenclature for classification of retinopathy of prematurity (ROP). It was initially published in 1984, expanded in 1987, and revisited in 2005. This article presents a third revision, the International Classification of Retinopathy of Prematurity, Third Edition (ICROP3), which is now required because of challenges such as: (1) concerns about subjectivity in critical elements of disease classification; (2) innovations in ophthalmic imaging; (3) novel pharmacologic therapies (e.g., anti−vascular endothelial growth factor agents) with unique regression and reactivation features after treatment compared with ablative therapies; and (4) recognition that patterns of ROP in some regions of the world do not fit neatly into the current classification system.

Design: Review of evidence-based literature, along with expert consensus opinion.

Participants: International ROP expert committee assembled in March 2019 representing 17 countries and comprising 14 pediatric ophthalmologists and 20 retinal specialists, as well as 12 women and 22 men.

Methods: The committee was initially divided into 3 subcommittees—acute phase, regression or reactivation, and imaging—each of which used iterative videoconferences and an online message board to identify key challenges and approaches. Subsequently, the entire committee used iterative videoconferences, 2 in-person multiday meetings, and an online message board to develop consensus on classification.

Main Outcome Measures: Consensus statement.

Results: The ICROP3 retains current definitions such as zone (location of disease), stage (appearance of disease at the avascular−vascular junction), and circumferential extent of disease. Major updates in the ICROP3 include refined classification metrics (e.g., *posterior zone II*, *notch,* subcategorization of stage 5, and recognition that a continuous spectrum of vascular abnormality exists from normal to plus disease). Updates also include the definition of aggressive ROP to replace aggressive-posterior ROP because of increasing recognition that aggressive disease may occur in larger preterm infants and beyond the posterior retina, particularly in regions of the world with limited resources. ROP regression and reactivation are described in detail, with additional description of long-term sequelae.

Conclusions: These principles may improve the quality and standardization of ROP care worldwide and may provide a foundation to improve research and clinical care. *Ophthalmology 2021;■:1−18 Published by Elsevier on behalf of the American Academy of Ophthalmology*

In 1953, Reese et al[1] published a classification of retrolental fibroplasia. By 1984, the International Classification of Retinopathy of Prematurity (ICROP) was developed by 23 ophthalmologists from 11 countries.[2] This classification of acute retinopathy of prematurity (ROP) facilitated the first multicenter clinical treatment study (the Cryotherapy for ROP Study), demonstrating that ROP could be treated successfully,[3] thereby establishing the need for screening worldwide to identify a major cause of preventable childhood blindness.

In 1987, the ICROP was expanded to include retinal detachment,[4] and in 2005, it was revisited to incorporate advances during the intervening years.[5] Now, a third revision, the International Classification of Retinopathy of Prematurity, Third Edition (ICROP3), is required for several reasons. First, certain components of the ICROP are subjective and open to interpretation. Second, innovations in ophthalmic imaging have occurred. Third, introduction of anti−vascular endothelial growth factor (VEGF) therapy has presented new challenges associated

with recognition of clinical features characteristic of posttreatment regression and reactivation.[6,7] Finally, the pattern of ROP in regions of the world with limited resources is not adequately described by the current classification system. Key features and changes in the ICROP3, which are intended to address these challenges, are summarized in Table 1. Each eye should be classified using the following examination parameters, defined in this article: zone, plus disease, stage, and extent. If aggressive ROP (A-ROP) is present, it should be noted.

Location of Vascularization: Zone

Retinal vascularization commences around the thirteenth week of gestation, proceeding centrifugally from the peripapillary region to the peripheral retina, which is fully vascularized by approximately term.[8] The location of retinal vascularization provides an indication of infant maturity and risk of ROP developing. The developing vasculature is lobular and closer to the optic disc nasally than temporally,[9] but as a practical matter, the state of vascularization (i.e., the zone) is recorded as circles with the optic disc at the center.

Three concentric retinal zones are centered on the disc and extend to the ora serrata (Fig 1). The location of the most posterior retinal vascularization or ROP lesion denotes the zone for the eye. The most posterior region, zone I, is defined by a circle with radius twice the estimated distance from the optic disc center to the foveal center. Zone II is a ring-shaped region extending nasally from the outer limit of zone I to the nasal ora serrata and with a similar distance temporally, superiorly, and inferiorly. The committee defined a region of 2 disc diameters peripheral to the zone I border as *posterior zone II* to indicate potentially more worrisome disease than ROP in the more peripheral zone II (Table 1).

The committee introduced the term *notch* to describe an incursion by the ROP lesion of 1 to 2 clock hours along the horizontal meridian into a more posterior zone than the remainder of the retinopathy. When present, this should be

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Table 1. Summary of Key Components of International Classification of Retinopathy of Prematurity, 3rd Edition Classification

1. Zone.
   a. Definition of 3 retinal zones centered on the optic disc. The location of the most posterior retinal vascularization or ROP lesion denotes the zone for the eye.
   b. Definition of a posterior zone II region that begins at the margin between zone I and zone II and extends into zone II for 2 disc diameters.*
   c. The term *notch* is used to describe an incursion by the ROP lesion of 1−2 clock hours into a more posterior zone. The ROP zone for such eyes should be noted by the most posterior zone of retinal vascularization with the qualifier "notch" (e.g., "zone I secondary to notch").*

2. Plus and Preplus Disease. Plus disease is defined by the appearance of dilation and tortuosity of retinal vessels, and preplus disease is defined by abnormal vascular dilation, tortuosity insufficient for plus disease, or both. Recognition that retinal vascular changes in ROP represent a continuous spectrum from normal to preplus to plus disease, with sample images demonstrating this range.* These changes should be assessed by vessels within zone I, rather than from only vessels within the field of narrow-angle photographs and rather than from the number of quadrants of abnormality.*

3. Stage of Acute Disease (Stages 1−3). Stage of acute disease is defined by the appearance of a structure at the vascular−avascular juncture as stage 1 (demarcation line), stage 2 (ridge), and stage 3 (extraretinal neovascular proliferation or flat neovascularization). If more than 1 ROP stage is present, the eye is classified by the most severe stage.

4. Aggressive ROP. The term aggressive-posterior ROP was used previously to describe a severe, rapidly progressive form of ROP located in posterior zones I or II. Because of increasing recognition that this may occur beyond the posterior retina and in larger preterm infants, particularly in regions of the world with limited resources, the Committee recommends the new term aggressive ROP.*

5. Retinal Detachment (Stages 4 and 5).
   a. Stages of retinal detachment are defined as stage 4 (partial: 4A with fovea attached, 4B with fovea detached) and stage 5 (total).
   b. Definition of stage 5 subcategories: stage 5A, in which the optic disc is visible by ophthalmoscopy (suggesting open-funnel detachment); stage 5B, in which the optic disc is not visible because of retrolental fibrovascular tissue or closed-funnel detachment; and stage 5C, in which stage 5B is accompanied by anterior segment changes (e.g., marked anterior chamber shallowing, iridocorneolenticular adhesions, corneal opacification), suggesting closed-funnel configuration.* Additional descriptors of funnel configuration (e.g., open-closed) may be applied if clinically useful.

6. Extent of Disease. Defined as 12 sectors in using clock-hour designations.

7. Regression. Definition of ROP regression and its sequelae, whether spontaneous or after laser or anti−vascular endothelial growth factor treatment. Regression can be complete or incomplete. Location and extent of peripheral avascular retina (PAR) should be documented.*

8. Reactivation. Definition and description of nomenclature representing ROP reactivation after treatment, which may include new ROP lesions and vascular changes. When reactivation of ROP stages occurs, the modifier reactivated (e.g., "reactivated stage 2") is recommended.*

9. Long-Term Sequelae. Emphasized beyond previous versions of the ICROP, including sequelae such as late retinal detachments, PAR, macular anomalies, retinal vascular changes, and glaucoma.

ICROP = International Classification of Retinopathy of Prematurity; PAR = persistent avascular retina; ROP = retinopathy of prematurity
Each eye should be classified based on zone, plus disease, stage, and extent. If aggressive ROP is present, it should be noted.
*Key changes compared with previous ICROP publications.
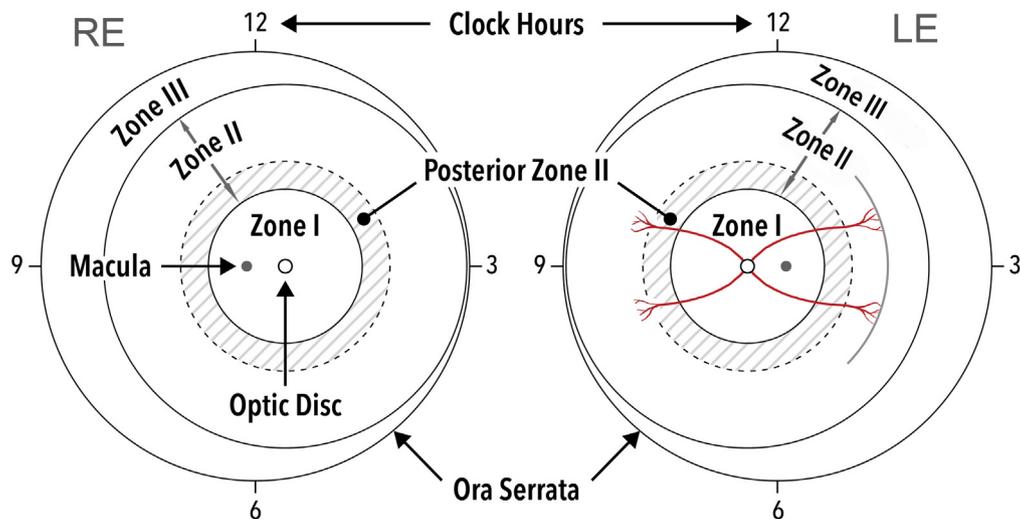
Figure 1. Schema of right eye (RE) and left eye (LE) showing zone borders and clock hour sectors used to describe the location of vascularization and extent of retinopathy. Solid circles represent borders of zones I through III, and dotted circles represent borders of posterior zone II (2 disc diameters beyond zone I). A hypothetical example of examination findings is shown in LE, representing approximately 3 clock hours of stage 1 disease in zone II (note single line on drawing to document presence of stage 1 disease).

recorded by the most posterior zone of retinal vascularization with the qualifier "secondary to notch" (Table 1). For example, ROP in zone II in most places, but with a temporal notch extending into zone I, should be noted as "zone I secondary to notch," thereby distinguishing it from an eye in which most disease is present in zone I.

Zone III is the residual crescent of peripheral retina that extends beyond zone II. To determine that ROP is in zone III, the ophthalmologist must ascertain that the nasal vessels are vascularized to the ora serrata and no ROP is present in the 2 nasal-most clock hours (Fig 1, nasally).

Practically, the temporal extent of zone I may be estimated using a 28-diopter (D) lens. For example, by placing the nasal edge of the optic disc at one edge of the view, the limit of zone I is approximately at the temporal edge of the view. With retinal photography, the fovea may not be clearly identifiable in premature infants before 39 weeks' postmenstrual age,[10–12] so the foveal location may be approximated as the center of the macula.

Plus and Preplus Disease

Severe ROP is associated with dilation and tortuosity of the posterior retinal vessels, termed *plus disease* in 1982.[13] A narrow-angle representative retinal photograph for plus disease was selected in the ICROP 1984.[2] A different photograph was selected for the Cryotherapy for ROP Study and subsequent clinical trials to represent the minimum severity of vascular dilation and tortuosity necessary for plus disease.[3,14] In the ICROP 2005, *preplus disease* was defined to represent retinal vascular dilation and tortuosity that is abnormal, but insufficient for plus disease.[5] Of note, the original ICROP description of plus disease in 1984 included features of vascular engorgement of the iris, poor pupillary dilation, and peripheral retinal

vascular engorgement with vitreous haze,[2] which are now recognized as signs of advanced disease but are not necessary for plus disease diagnosis.

The committee recommends that the plus disease spectrum be determined from vessels within zone I, rather than from only vessels within the field of narrow-angle photographs and rather than from the number of quadrants of abnormality (Table 1).[4,5,15,16] Representative examples of preplus disease (Fig 2A–C) and plus disease (Fig 2D–F) demonstrate this approximate field of view. The terms *preplus* and *plus* should continue to be used,[17] but the committee emphasizes that these terms represent a continuous spectrum of retinal vascular changes (Table 1). Figure 3 demonstrates gradings of this spectrum by members of the Committee. Although gradings along this spectrum of plus and preplus disease may vary among observers,[18–20] better agreement exists at the normal and severe ends.[21] Importantly, in clinical practice, assessment of disease severity may consider other factors, including clinical and demographic risk factors, examination method (e.g., digital retinal imaging vs. indirect ophthalmoscopy, lens power), zone of pathologic featured, and rate of progression.[22]

Stage of Acute Disease (Stages 1–3)

In the developing premature infant, the retina is vascularized incompletely (Fig 4). When no ROP lesion is present, the Committee suggests using the term *incomplete vascularization*, accompanied by the zone of vascularization (e.g., "incomplete vascularization into zone II"), rather than using terms such as *no ROP* or *immature retina*. When acute ROP vascular features develop at the junction of vascularized and avascular retina, the term *stage* is used to describe the appearance. If more than 1 ROP stage is present in the same eye, the eye is classified by the most severe stage.
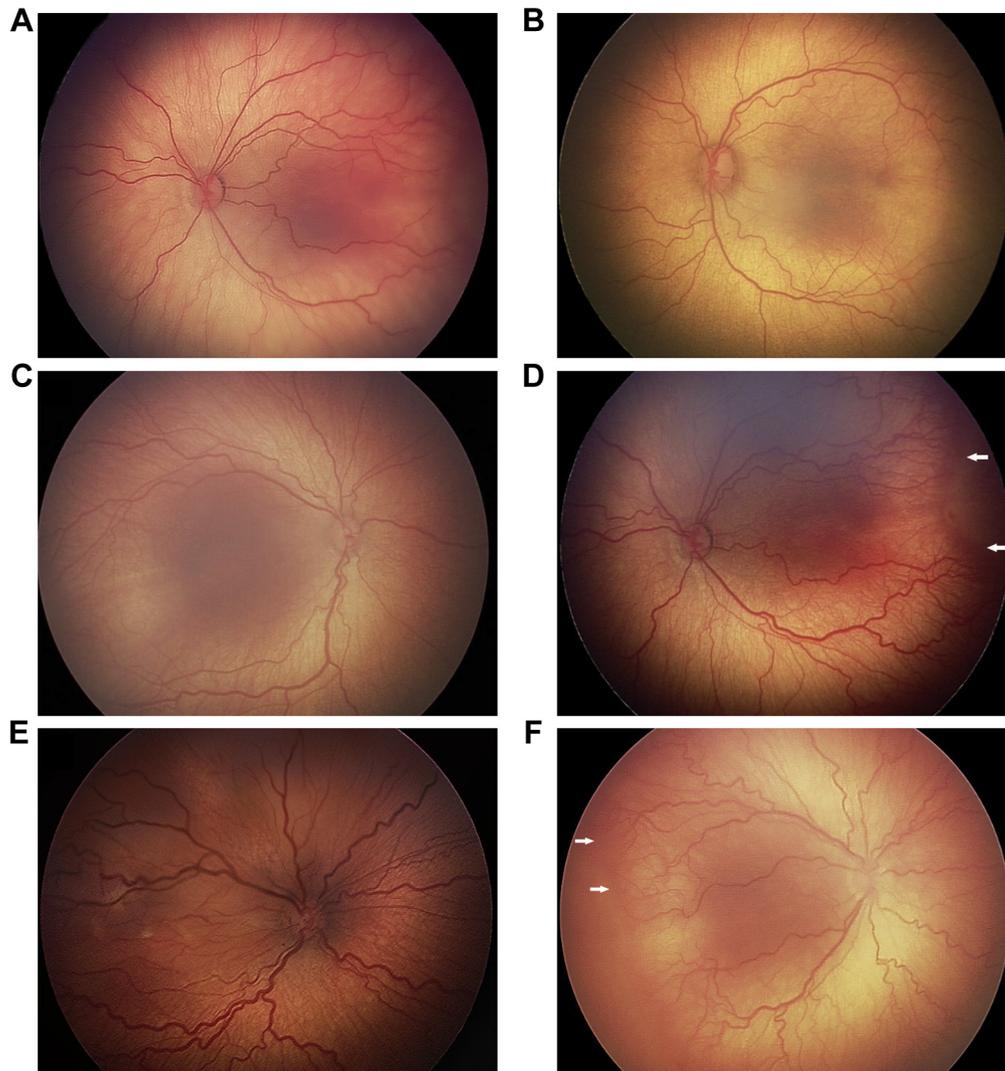
Figure 2. Wide-angle fundus photographs demonstrating examples of plus disease and preplus disease. Note varying levels of vascular abnormality, which are assessed in the central retina within the region of zone I. **A**, Mild preplus disease, with more arterial tortuosity and venous dilation than normal. **B**, Preplus disease, with notable arterial tortuosity but minimal venous dilation. **C**, Preplus disease, with moderate arterial tortuosity and venous dilation, but considered by most committee members to be insufficient for plus disease. **D**, Plus disease with notable venous dilation and arterial tortuosity. Note that plus disease is out of proportion to visible peripheral findings, suggestive of flat neovascularization (stage 3; white arrows). **E**, Severe plus disease, with dilation and tortuosity of both arteries and veins. **F**, Severe plus disease. Note presence of ill-defined posterior flat stage 3 (arrows), which, combined with severe plus disease, is typical of aggressive retinopathy of prematurity.

Stage 1: Demarcation Line

The demarcation line is a thin structure at the vascular–avascular juncture (Figs 5A, B and 6A), which is relatively flat and white, lies within the plane of the retina, and may be associated with abnormal branching of vessels posterior to the line. Dilatation and tortuosity of peripheral retinal vessels at the vascular–avascular juncture alone are insufficient for diagnosis of stage 1 disease.

Stage 2: Ridge

The hallmark of stage 2 ROP is a ridge with width and height that evolve from the demarcation line (Figs 5C–D, F and Fig 6B). The ridge may vary in height and its color

may appear to range from white to pink. Small isolated tufts of neovascular tissue lying on the surface of the retina, commonly called *popcorn*, can be seen posterior to the ridge (Fig 5D, F) but do not constitute stage 3 disease.[23,24]

Stage 3: Extraretinal Neovascular Proliferation

In stage 3 ROP, extraretinal neovascular proliferation extends from the ridge into the vitreous (Figs 5E, F and 6C) and is continuous with the posterior aspect of the ridge, causing a ragged appearance as proliferation becomes more extensive. Seemingly flat-appearing extraretinal neovascularization can occur in eyes with zone I or posterior zone II disease, in the absence of an obvious ridge or
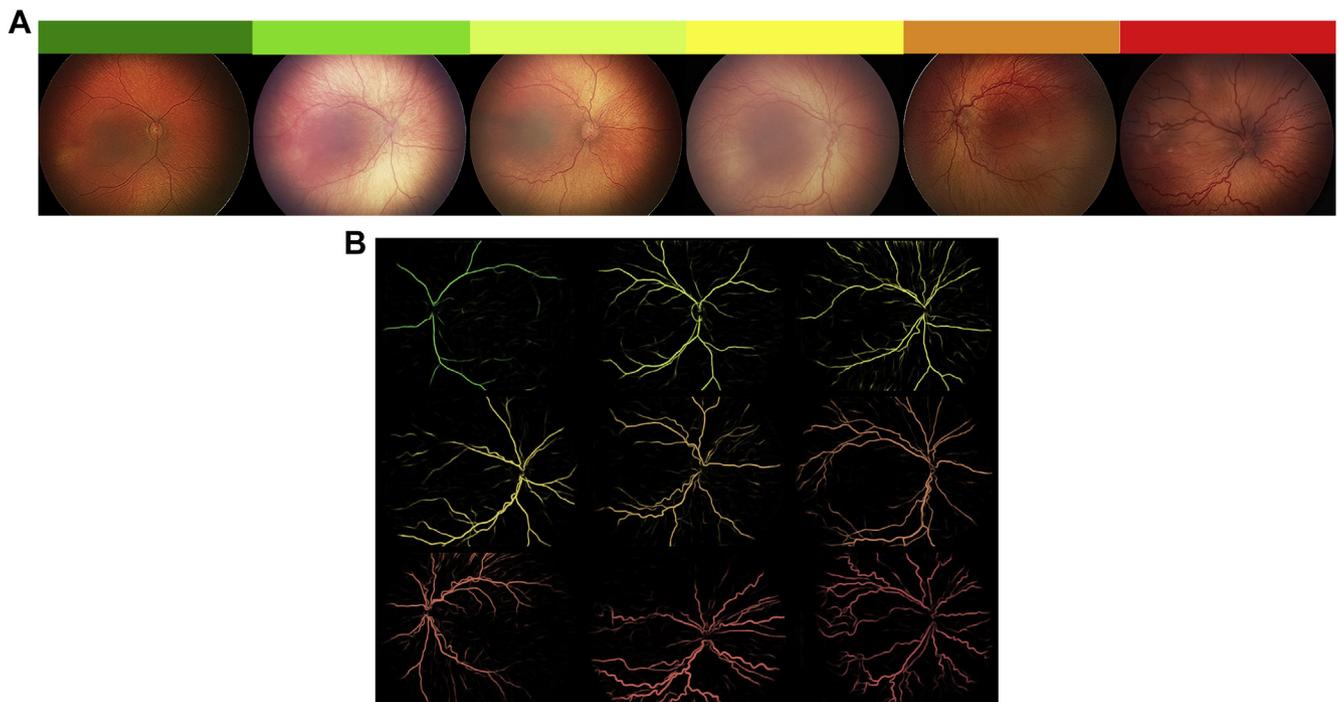
Figure 3. Continuous spectrum of vascular severity in retinopathy of prematurity from normal to plus disease. All 34 members of this committee graded 30 images as normal, preplus, or plus. Experts' opinions varied as to the level of disease severity that constitutes preplus and plus disease. **A,** Six representative images are displayed in which the color scale on top reflects the average grading of committee members (from green [normal] to red [plus disease]) and demonstrates that vascular severity presents on a continuum. **B,** Nine representative segmented images are displayed in which the color scale represents mean vascular severity grading by committee members for each image (from green [normal] to red [plus disease]) and demonstrates that vascular severity presents on a continuum.

demarcation line, and is also considered stage 3 disease. Varying degrees of extraretinal neovascular tissue may be associated with stage 3 disease (Figs 5E, F and 6C).

Figure 4. Wide-angle fundus photograph demonstrating incomplete vascularization into zone II in the right eye of a premature infant at risk for retinopathy of prematurity. Note progressive tapering and termination of retinal vascular arcades (white arrows). Permission to reproduce previously published images from *Arch Ophthalmol* 2005;123:991-999.

Aggressive Retinopathy of Prematurity

Aggressive-posterior ROP was added to the ICROP in 2005 to describe a severe, rapidly progressive form of ROP located in zone I or posterior zone II.[5] Previously known as *rush disease*, it may have been the florid acute ROP seen in the 1940s.[1] Aggressive-posterior ROP as originally described typically affected the smallest premature infants.[5,25] However, aggressive ROP is increasingly recognized also to occur in larger preterm infants and beyond the posterior retina, particularly in regions of the world with limited resources.[26] Therefore, because the key diagnostic features of this phenotype are the tempo of disease and appearance of vascular abnormalities, but not location of disease, the Committee recommends use of the new term *aggressive retinopathy of prematurity* (A-ROP) to replace aggressive-posterior ROP (Table 1).

The hallmark of A-ROP is rapid development of pathologic neovascularization and severe plus disease without progression being observed through the typical stages of ROP. In early A-ROP, the retina may exhibit capillary abnormalities posterior to the original border of vascularized retina, such as arteriovenous shunting resembling dilated vascular loops surrounding areas of vascular injury (Fig 7A). In some cases, this can be extreme with apparent loss of almost the entire
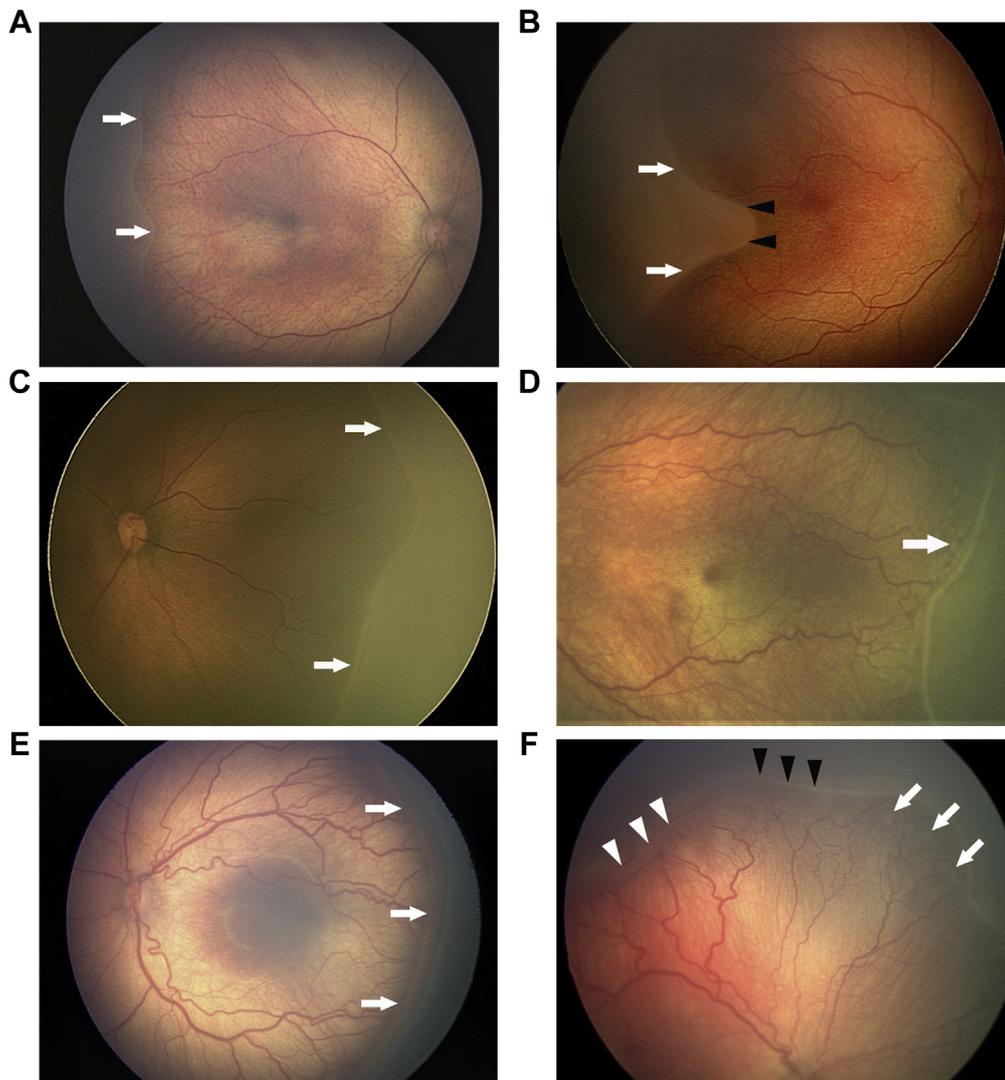
Figure 5. Wide-angle fundus photographs demonstrating examples of acute retinopathy of prematurity (ROP) stages 1 through 3. **A**, Stage 1 demarcation line at the border between vascular and avascular retina (white arrows). **B**, Stage 1 demarcation line (white arrows) and associated notch (black arrowheads) between vascular arcades that would be considered zone I secondary to notch. Note preplus disease with mild retinal vascular tortuosity and dilation. **C**, Stage 2 ridge, which is raised (white arrows) and thicker than stage 1. **D**, Stage 2 ridge. Note the so-called popcorn lesions posterior to the ridge (arrow) and preplus disease with mild vascular tortuosity and dilation. E, Stage 3 disease with extraretinal neovascularization (white arrows). Note plus disease with vascular tortuosity and dilation. **F**, Eye with both stage 2 (black arrowheads) and stage 3 (white arrowheads) disease and associated popcorn (white arrows). Note plus disease with vascular tortuosity and dilation. Figs 5E and 5F: Permission to reproduce previously published images from *Arch Ophthalmol* 2005;123:991-999.

vascularized retina (Fig 7). Eyes in which A-ROP develop with more posterior disease may have thin vessels within zone I early in the disease course. Eyes with A-ROP often demonstrate a form of stage 3 disease that may appear as deceptively featureless networks of so-called flat neo-vascularization (Fig 7B, C), which can be difficult to visualize using a 28-D lens on ophthalmoscopy, but the use of greater magnification (e.g., 20-D lens) or fluores-cein angiography may be helpful. Of note, extraretinal neovascularization as seen in classic stage 3 disease can also be seen in eyes with A-ROP (Fig 7C).[27]

Retinal Detachment (Stages 4 and 5)

Acute disease and its regression are not always demarcated clearly. This is particularly apparent in retinal detachment, where both may occur simultaneously.

Stage 4: Partial Retinal Detachment

Stage 4 describes partial retinal detachment, which either spares (stage 4A; Fig 8A, B) or involves (stage 4B; Fig 8C, E) the fovea. Clinical features suggesting retinal
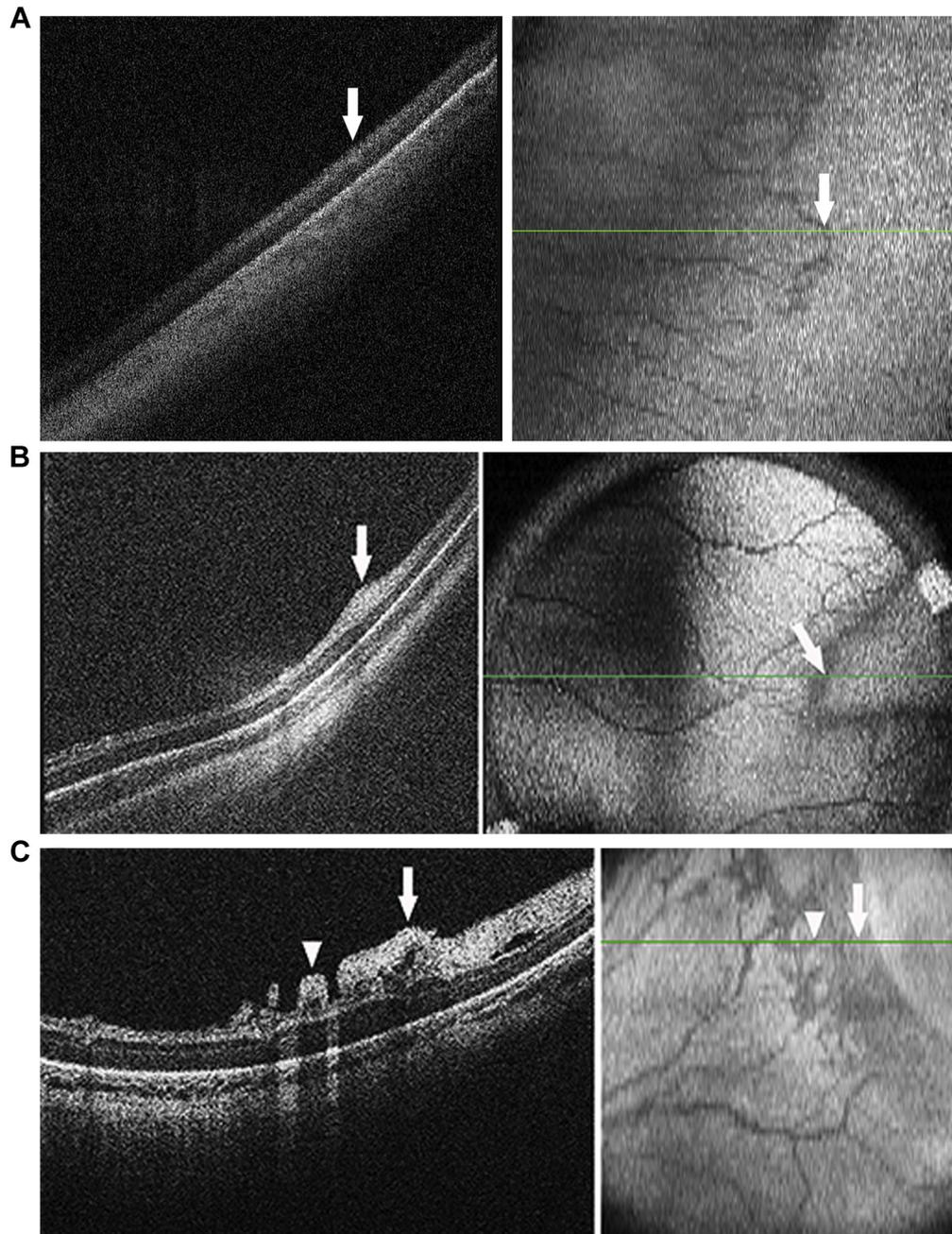
Figure 6. OCT images demonstrating examples of retinopathy of prematurity stages 1 through 3. OCT cross-sectional B-scans (left side) are extracted from the raster scans that make up the OCT volume, at the location of the green-line (right side). The en face OCT images (right side) are summed from the OCT volume, and blood in retinal vessels casts a shadow across the underlying retina and choroid. **A**, Stage 1 demarcation line (white arrows) on cross-sectional B-scan OCT image (left side) align with the retinal vascular−avascular junction (right side; note that the vascular retina is to the left in all images). **B**, Stage 2 ridge (white arrows) on cross-sectional B-scan OCT image (left side) at a site of focal thickening and bulge of inner retinal layers aligns with the en face (right side) wider dark border of the vascular−avascular junction. **C**, Stage 3 extraretinal neovascular proliferation at (white arrows) and posterior to (arrowheads) the vascular−avascular junction on cross-sectional B-scan OCT image (left side) and on en face view (right side). Note that blood in the extraretinal vessels also casts a shadow across the underlying retina and choroid.

detachment include loss of fine detail of choroidal vasculature or of granular pigment epithelium, a ground-glass appearance relative to adjacent attached retina, or both. Macular ectopia and straightening of arcade vessels are signs of peripheral traction. Subtle foveal involvement may be discerned most effectively using OCT imaging (Fig 9). Stage 4 ROP may be exudative or tractional, occur in treated or untreated eyes, and vary in appearance depending on the tractional vectors and presence of exudation.[28,29]
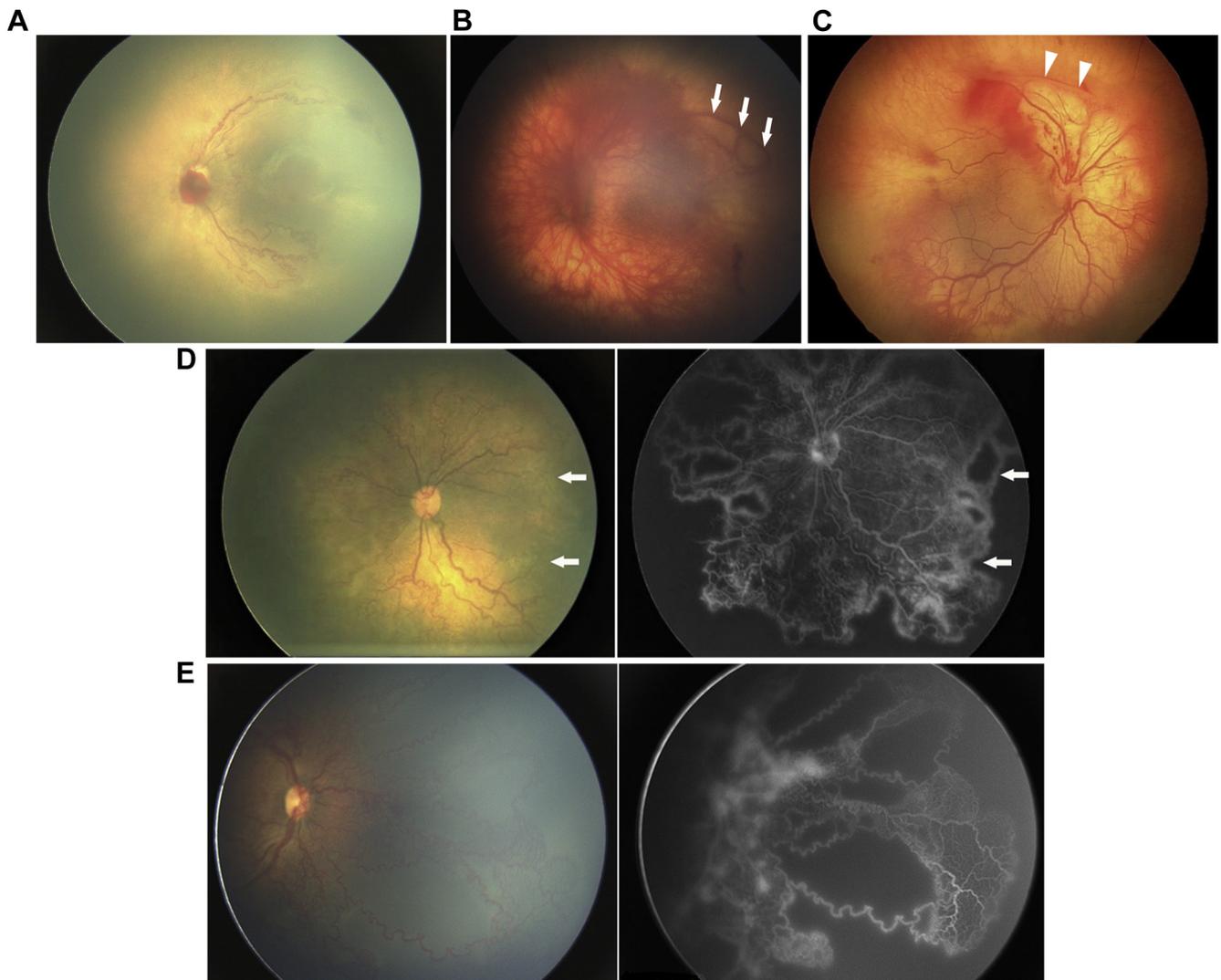
Figure 7. Images depicting aggressive retinopathy of prematurity (A-ROP). **A**, Fundus photograph showing aggressive ROP (A-ROP) with severe vaso-constriction, capillary nonperfusion, nonphysiologic dilated vascular loops, and arteriovenous shunts and plus disease in zone I. **B**, Fundus photograph showing A-ROP with border between vascular and avascular retina in zone I, dilated vascular loops (white arrows), diffuse flat extraretinal neo-vascularization most prominent superotemporally, and severe plus disease. Note the absence of a typical stage 3 lesion. **C**, Fundus photograph showing A-ROP in zone I with severe plus disease, flat extraretinal neovascularization with fibrosis, and early contraction superiorly (white arrowheads) and intraretinal and vitreous hemorrhage superotemporally. **D, E**, Wide-angle fundus photographs (left sides) demonstrating A-ROP with ill-defined junction between vascular and avascular retina in zone I (white arrows) and severe plus disease, and fluorescein angiography (right sides) demonstrating significant vaso-obliteration with capillary nonperfusion. Note that no typical ROP lesions appear and vasoattenuated areas appear posterior to the ridge.

Exudative stage 4 detachments occur most commonly within days after laser treatment. They are typically convex, sometimes localized, and self-limited. Tractional detachments are associated with progressive fibrovascular organization and vitreous haze and may be associated with lipid or subretinal hemorrhage or both (Fig 8D). Distinction by clinical examination between retinoschisis and detachment can be difficult. Eyes with A-ROP can demonstrate a unique posterior so-called volcano trac-tional detachment[28] generally involving the fovea, in which the peripheral retina remains attached (Fig 8E). Although the clinical appearance is reminiscent of a stage 5 funnel-shaped detachment, these are more correctly considered stage 4B disease because the treated

peripheral retina remains attached and the detachment therefore is not total.

Stage 5: Total Retinal Detachment

Total retinal detachment is designated as stage 5 (Fig 10) and currently classified by configuration of the funnel: open-open (open anterior and posteriorly), open-closed (open anteriorly and closed posteriorly), closed-open (closed anteriorly and open posteriorly), or closed-closed (closed anteriorly and posteriorly). When fibrosis pre-cludes visualization of the posterior pole, the extent of detachment must be examined by B-scan ultrasonography. To permit classification of stage 5 by bedside examination,
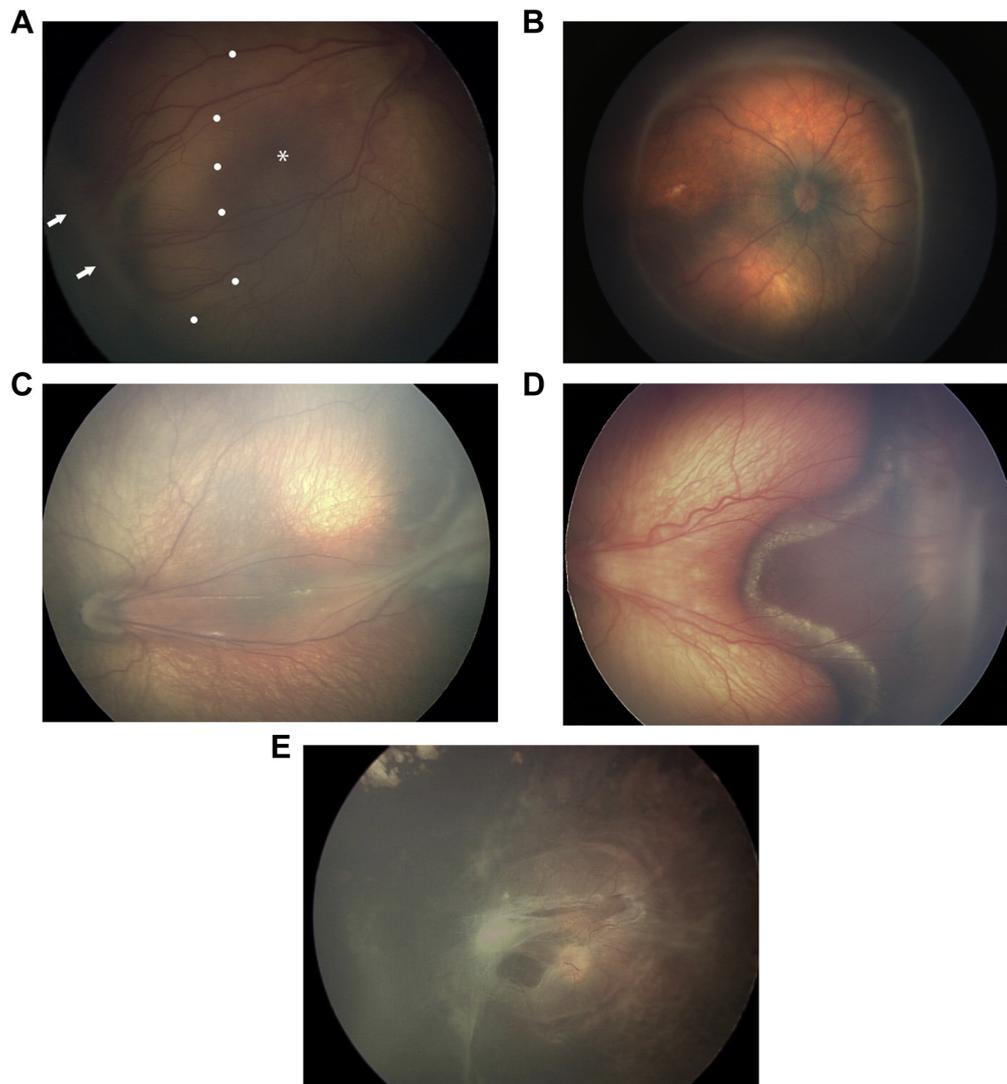
Figure 8. Wide-angle fundus photographs demonstrating examples of retinopathy of prematurity (ROP) stage 4. **A,** Stage 4A ROP in the temporal retina. Traction on extraretinal neovascularization leads to retinal elevation (white dots), which may be recognized during ophthalmoscopy by subtle change in brightness and loss of visible retinal pigment epithelium granularity and choriocapillaris detail. Note that the approximate foveal center (asterisk) is not elevated and the extraretinal neovascularization (white arrows) may be significantly more peripheral than the posterior extent of the detachment. **B,** Stage 4A ROP with 360° tractional retinal detachment in the area of the peripheral ridge. **C,** Stage 4B detachment involving the macula. Note straightening of the arcuate vessels and dragged of the optic disc appearance. **D,** Stage 4B detachment with associated subretinal hemorrhage and lipid exudation into the macula. **E,** Volcano-shaped stage 4B ROP. In eyes with posterior ROP, contraction of pathologic neovascularization can result in detachment of vascularized retina into a volcano-shaped configuration. Fig 8C: Permission to reproduce previously published images from *Areh Ophthalmol* 2005;123:991-999.

the Committee now recommends that total detachment be subcategorized into 3 configurations:[30−32] stage 5A, in which the optic disc is visible by ophthalmoscopy (Fig 10A, suggesting open-funnel detachment); stage 5B, in which the optic disc is not visible secondary to retrolental fibrovascular tissue or closed-funnel detachment (Fig 10B, C); and stage 5C, in which findings of stage 5B are accompanied by anterior segment abnormalities (e.g., anterior lens displacement, marked anterior chamber shallowing, iridocapsular adhesions, capsule-endothelial adhesion with central corneal opacification, or a combination thereof; Fig 10D, suggesting a closed-funnel configuration).[4,33] Additional descriptors of funnel configuration (e.g., open-closed) may be applied if clinically useful.

Extent

Extent of disease is classified using 30° sectors with boundaries along clock-hour positions (Fig 1).

Regression, Reactivation, and Long-Term Sequelae

To date, ROP classification has focused on acute disease, with less attention to regression.[4,5,33] The introduction of anti-VEGF agents has presented new challenges. The clinical features and time course of regression after anti-VEGF treatment of ROP differ compared with those of laser-treated
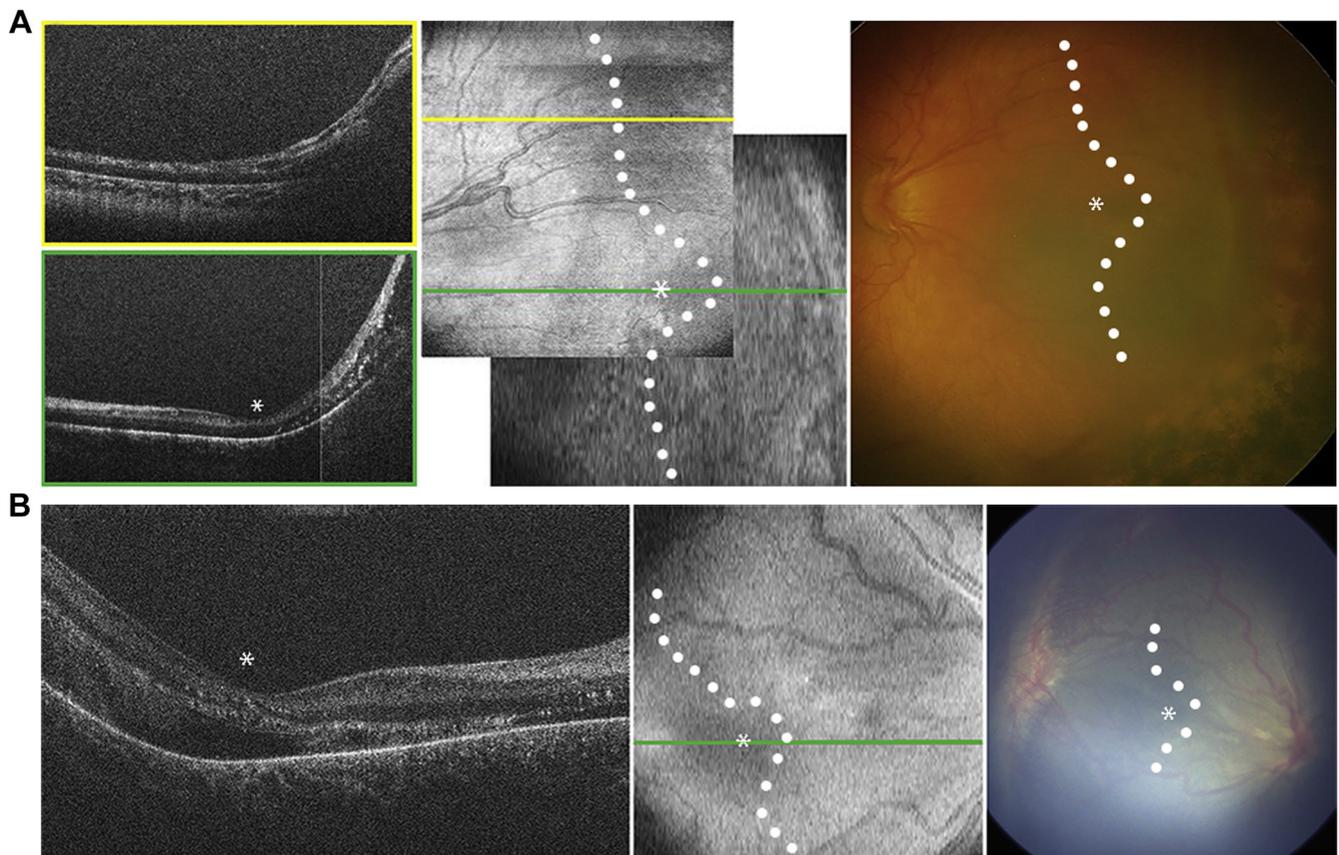
Figure 9. OCT images demonstrating examples of stage 4 disease. OCT cross-sectional B-scans (left side) are extracted from the raster of scans that make up the OCT volumes, viewed as summed en face images (middle) with corresponding color photographs (right side). Note that in the color photographs, it is difficult to discern the extent of retinal detachment, especially foveal involvement. In the en face OCT images and color photographs, the location of the fovea (asterisk) and margin of detachment (white dots) are determined from OCT B-scans. Blood in retinal vessels casts a shadow across the underlying retina and choroid in the en face views. **A,** Stage 4A retinal detachment. On the en face OCT image (middle), the yellow line demonstrates the location of the B-scan superior to the foveal center (upper left side, yellow box) and the green line demonstrates the location of the B-scan through the foveal center (bottom left side, green box). Note the attached retina on B-scan at the foveal center (asterisk), along with intraretinal exudates (hyperreflective dots), peripheral retinal detachment, and retinoschisis. **B,** Stage 4B retinal detachment. Note detachment of the retina at the foveal center (asterisks), which was very difficult to appreciate on ophthalmoscopic examination.

eyes. When describing later phases of ROP, the Committee recommends use of 2 terms (Table 1): (1) *regression*, which refers to disease involution and resolution; and (2) *reactivation*, which refers to recurrence of acute phase features. Regression may be complete or incomplete, including persistence of retinal abnormalities. Regression and reactivation should not be regarded as either the reverse or the repetition of acute ROP.

Regression

Patterns of acute-phase regression in ROP differ between spontaneous regression and those occurring after treatment. The Committee highlights features of regression related to vasculature as well as peripheral ROP findings in Figure 11.

The first visible signs of regression are typically vascular and tend to occur more rapidly after anti-VEGF therapy (as early as 1−3 days)[34] than after laser photocoagulation

(approximately 7−14 days) or during spontaneous regression.[33,35,36] These signs include decreased plus disease, where components of vascular dilation and tortuosity may become uncoupled (e.g., after anti-VEGF injection, reduced vessel dilatation can occur before reduced tortuosity, which may or may not occur), and vascularization into peripheral avascular retina, which can occur spontaneously or after anti-VEGF treatment. Other clinical signs of regression include involution of tunica vasculosa lentis, better pupillary dilation, greater media clarity, and resolution of intraretinal hemorrhages.

Regression of the ROP lesion is characterized by thinning and whitening of neovascular tissue. After spontaneous or treatment-induced regression, vascularization into the peripheral avascular retina can be complete or incomplete, the latter being termed *persistent avascular retina* (PAR; Fig 12). Persistent avascular retina may occur in either the peripheral or posterior retina. Compared with peripheral PAR after spontaneous regression, PAR after treatment
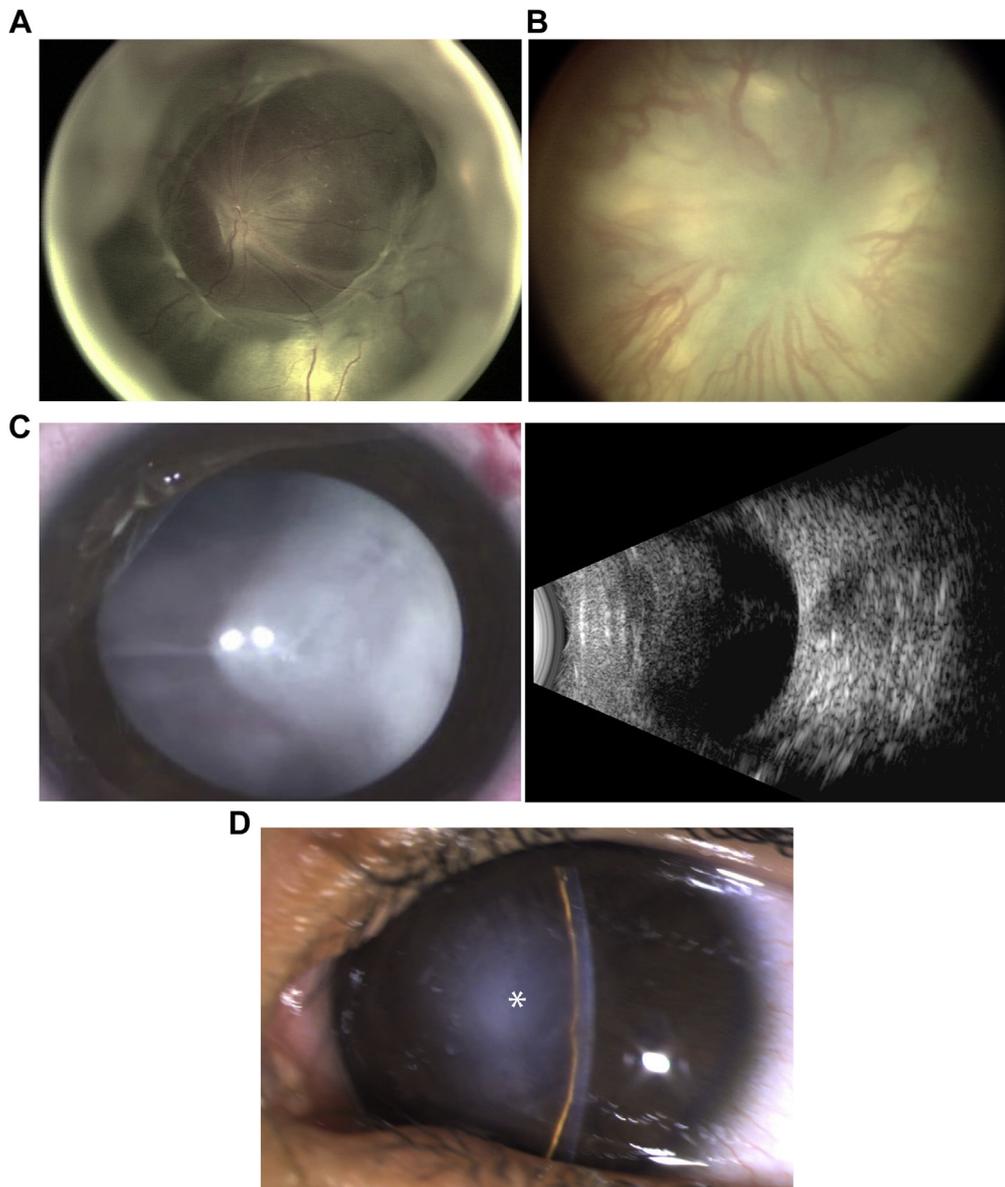
Figure 10. Images demonstrating examples of stage 5 retinopathy of prematurity (ROP). **A,** Wide-angle fundus photograph showing stage 5A ROP, characterized by a total retinal detachment with visible optic disc. Note the open-funnel configuration. **B,** Wide-angle fundus photograph showing stage 5B ROP, with no view of the optic disc because of fibrovascular tissue. **C,** External photograph of the normal anterior segment in stage 5B ROP (left side), with no view of the optic disc or retina secondary to retrolental fibrovascular tissue. B-scan ultrasonography (right side) reveals total retinal detachment with a posteriorly closed funnel configuration. **D,** External photograph showing anterior segment characteristic of stage 5C ROP with anterior lens displacement, marked anterior chamber shallowing, central iridocapsular endothelial adhesion, and central corneal opacification (asterisk) that prevent view of a closed-funnel retinal detachment. Fig 10B: Permission to reproduce previously published images from *Arch Ophthalmol* 2005;123:991-999.

with anti-VEGF agents seems to occur with greater frequency and involve a larger retinal area.[37] Persistent avascular retina should be described by its location (e.g., posterior zone II) and extent (e.g., nasal).

Reactivation

Reactivation is seen more frequently after anti-VEGF treatment than after spontaneous regression and rarely if ever occurs after complete laser photocoagulation. Reactivation may occur after incomplete or complete regression

of the original ROP lesion. Although the maximum interval until reactivation after anti-VEGF injection is unknown, current evidence suggests it most commonly occurs between 37 and 60 weeks' postmenstrual age. However, this may be affected by choice and dosage of anti-VEGF agent and may occur significantly later, especially if reinjections are performed.[38,39]

Signs of reactivation range from development of a new self-limiting demarcation line to reactivated stage 3 with plus disease. The Committee highlights features of disease reactivation related to vasculature and ROP lesions in
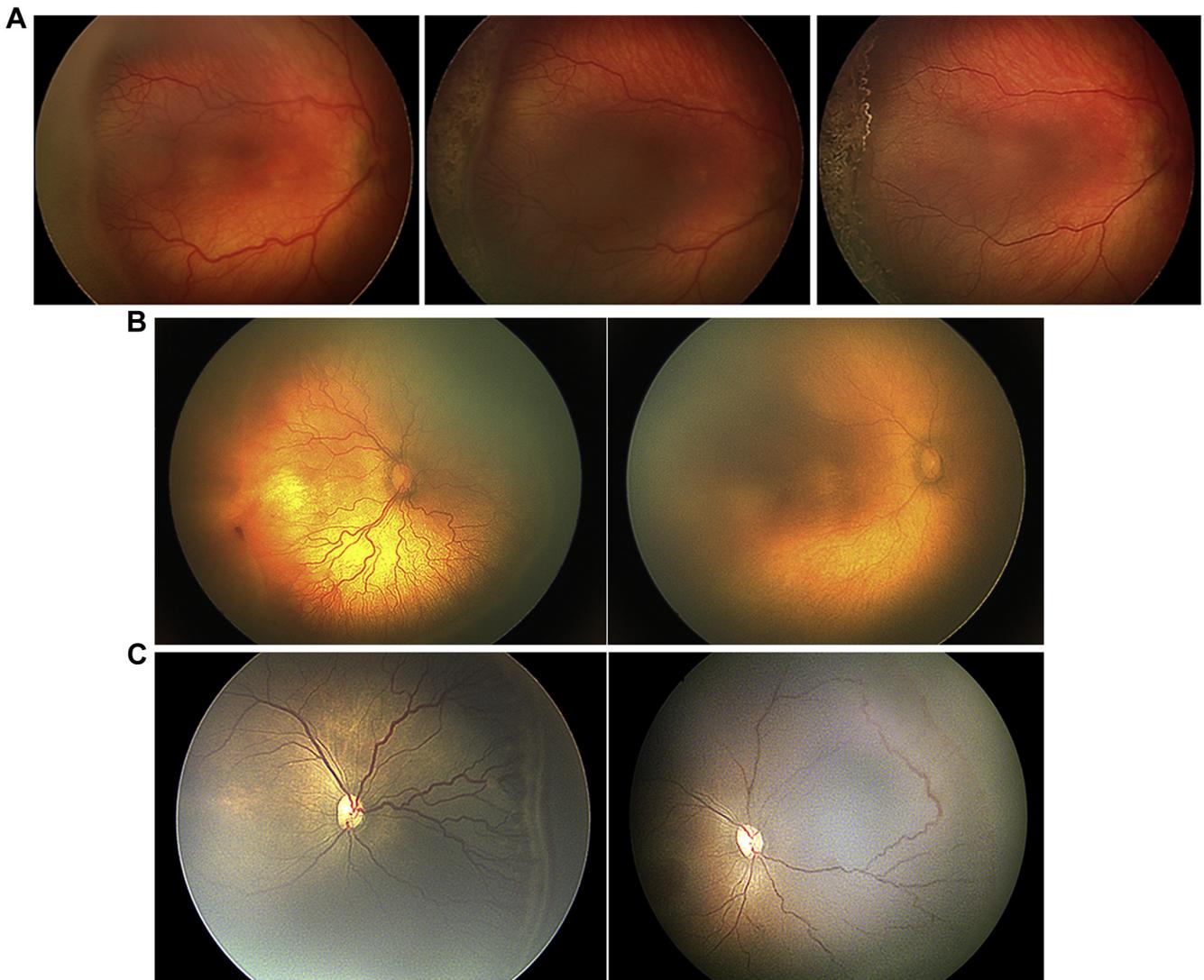
Figure 11. Wide-angle fundus photographs demonstrating examples of retinopathy of prematurity (ROP) regression. **A,** Regression after laser treatment. Left image obtained before treatment showing stage 3 ROP with plus disease. Middle image obtained 1 week after treatment showing that stage 3 ROP is thinner and whiter. Right image obtained 1 month after treatment showing disease regression. **B,** Regression of plus disease after anti−vascular endothelial growth factor (VEGF) injection for aggressive ROP. Left image obtained before treatment showing plus disease and flat neovascularization (stage 3 ROP). Right image obtained 2 weeks after treatment showing improvement in plus disease with no visible ROP lesion. **C,** Regression after anti-VEGF injection. Left image obtained before treatment. Right image obtained 4 weeks after treatment showing absence of stage 3 ROP and improvement in plus disease, with vascularization into peripheral avascular retina. Note the circumferential anastomosis in the area of original stage 3, along with reactivated stage 1 more anteriorly.

Figure 13 and notes that reactivation may not progress through the normal sequence of stages of acute-phase disease.

Vascular changes in ROP reactivation include recurrent vascular dilation, tortuosity, or both, similar to acute-phase preplus or plus disease. Extraretinal new vessels can occur and may be relatively delicate compared with those of acute ROP, making them difficult to visualize. Hemorrhages can occur around fronds of extraretinal vessels. Alternatively, extraretinal vessels may appear as a fibrovascular ridge, which may progress to fibrosis, contraction, and tractional detachment.[28,29,40]

Documentation of reactivation should specify presence and location(s) of new ROP features, noted by zone and stage using the modifier *reactivated*. For example, presence of a demarcation line during reactivation would be noted as "reactivated stage 1." Reactivation typically occurs at the site of the original ridge, at the new leading edge of intraretinal vascular growth, or both but also may occur elsewhere within the vascularized retina. If multiple ridges are present, the modifier *reactivated* is applied to the more anterior ridge, which is typically more active. Signs of reactivation may be relatively subtle (Fig 13G). Reactivation with progression to stages 4 and 5 ROP is associated with
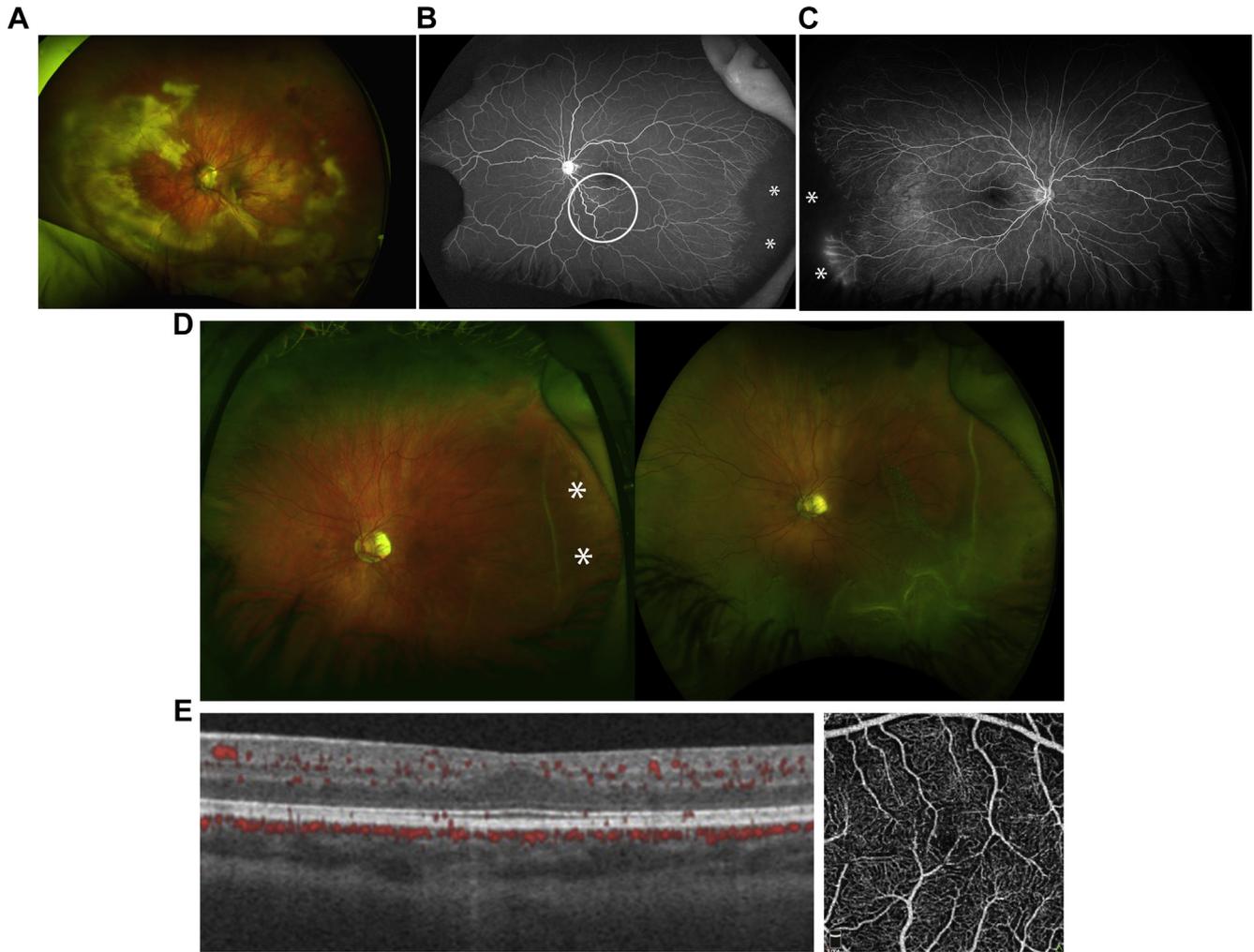
Figure 12. Examples of persistent avascular retina (PAR) and long-term sequelae of retinopathy of prematurity (ROP). **A,** Combined tractional and exudative detachment in an 18-year-old with a history of untreated ROP whose fellow eye was phthisical as a result of ROP. **B,** Ultra-widefield fluorescein angiogram (FA) demonstrating PAR (asterisks) in a 7-year-old with a history of spontaneously regressed ROP. Note the abnormal vascular configuration, particularly inferotemporally (circle). **C,** Ultra-widefield FA from a 7-year-old with spontaneously regressed ROP but with PAR and leakage in incompletely regressed stage 3 disease inferotemporally (asterisks). **D,** Ultra-widefield fundus image (left side) displaying an incompletely regressed ridge (white arrowheads) with PAR (asterisks) in a 15-year-old with a history of extreme prematurity and no prior ROP treatment. Ultra-widefield fundus image obtained 2 years later (right side) when the patient demonstrated a macula-involving rhegmatogenous retinal detachment. The fellow eye had a similar appearance and disease course. **E,** OCT angiography image of an incompletely developed foveal contour (left) and poorly defined foveal avascular zone (right) in a 7-year-old with history of type 1 ROP treated with laser therapy.

vitreous condensation, haze, fibrotic contraction, retinal breaks, or a combination thereof.[4,5,28,29,33,40]

Long-Term Sequelae

Patients with a history of premature birth, even without a history of ROP, exhibit a spectrum of ocular abnormalities that may lead to permanent sequelae (Fig 12), as outlined below.[4,33,41]

- Late tractional, rhegmatogenous, or, rarely, exudative retinal detachments (Fig 12D).[42] Retinal detachment occurring in the absence of signs of ROP activity should not be designated as being the result of reactivation but rather as a sequela.[43]

- Retinoschisis from chronic traction of involuted stage 3 may progress without retinal detachment into the macula and may threaten visual field and visual acuity.
- Persistent avascular retina (Fig 12A−C). Avascular retina is prone to retinal thinning, holes, and lattice-like changes and may be associated with retinal detachments later in life.[42−45]
- Macular anomalies including smaller foveal avascular zone[46−48] and blunting or absence of the foveal depression (Fig 12E). These may be related to the degree of acute-phase ROP and may be more apparent with fluorescein angiography or OCT imaging.[24,37]
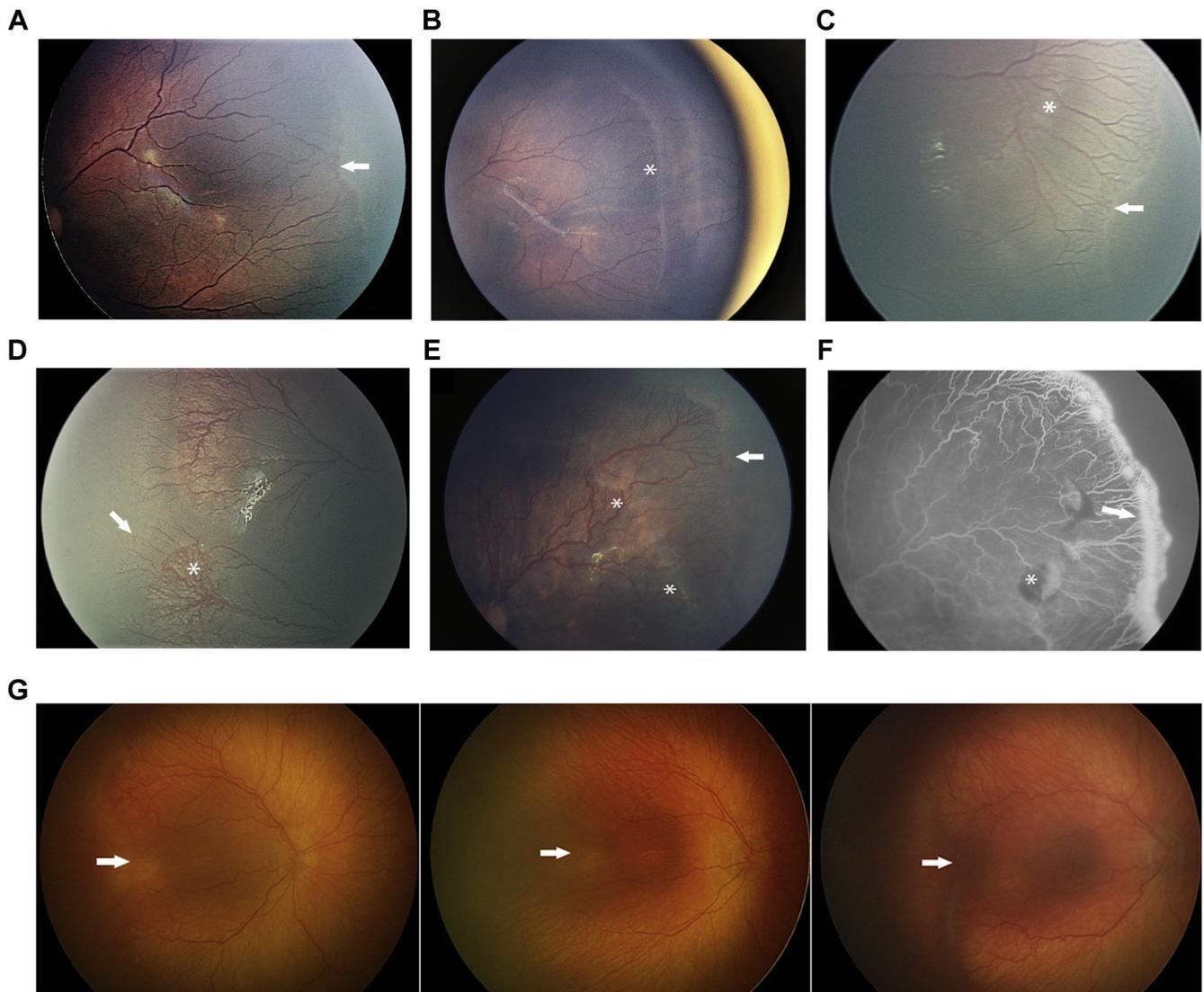
Figure 13. Examples of retinopathy of prematurity (ROP) reactivation. **A**, Image obtained at 38 weeks' postmenstrual age (PMA) after intravitreal anti—vascular endothelial growth factor (VEGF) injection at 32 weeks' PMA with vascularization into the peripheral avascular retina. Demarcation line (arrow) at the leading edge is reactivated stage 1 ROP. **B**, Image showing a left eye at 100 weeks' PMA after treatment with intravitreal anti-VEGF injection at 38 weeks' PMA. Vascularization into the peripheral avascular retina is present. Often notable vascular abnormalities are present at the site of the original ridge and, in some cases, residual fibrosis (asterisk), which is not indicative of reactivation unless accompanied by increasing vascular activity. **C**, Image showing vascularization into the peripheral avascular retina with reactivated stage 1 disease (arrow) at 68 weeks' PMA, after treatment with intravitreal anti-VEGF injection at 37 weeks' PMA. Note multiple circumferential vascular loops at the site of the original ridge (asterisk). **D**, Image showing reactivation in a right eye at 67 weeks' PMA that had undergone intravitreal anti-VEGF injection at 33 weeks' and again at 52 weeks' PMA. Reactivated stage 3 disease (asterisk) is present posterior to the leading edge of vascularization (arrow). **E**, Image showing a left eye with reactivated stage 3 ROP at the leading edge (arrow) at 50 weeks' PMA, after intravitreal anti-VEGF injection at 36 weeks' PMA. Vascularization into the peripheral avascular retina has occurred between the original ridge (asterisks) and anterior reactivation. **F**, Fluorescein angiogram obtained at 45 weeks' PMA of a left eye that had received an intravitreal anti-VEGF injection at 34 weeks' PMA. Leakage is present both at sites of leading edge reactivation (arrow) and at the original border (asterisk). **G**, Image showing right eye with zone I disease treated with intravitreal anti-VEGF injection at 34 weeks' PMA (left side, arrow) and that appeared regressed on clinical examination at 38 weeks' PMA (middle image, arrow). At 51 weeks' PMA, the eye demonstrated reactivated stage 3 ROP at the same site (right side, arrow) without evidence of vascularization into peripheral avascular retina.

- Retinal vascular changes. These may include persistent tortuosity, straightening of the vascular arcades with macular dragging, and falciform retinal fold. Abnormal nondichotomous retinal vessel branching, circumferential interconnecting vascular arcades, and

- telangiectatic vessels occur frequently. Vitreous hemorrhage may occur.
- Glaucoma. Eyes with history of ROP can demonstrate secondary angle-closure glaucoma later in life.[49,50]

Conclusions

Understanding of disease pathophysiologic features and clinical management of ROP have evolved with advances in science, technology, and the art of medicine. Since the ICROP publication in 2005, some specific advances have involved neonatal care, anti-VEGF therapy, ophthalmic imaging, machine learning, and pediatric vitreoretinal surgery. This article updates ROP classification in response to those advances by integrating review of evidence-based literature with expert consensus opinion. Table 1 summarizes how the ICROP3 maintains many existing classification metrics, while refining and adding others such as revised classification metrics (e.g., posterior zone II, notch, subcategorization of stage 5, and recognition of a continuous spectrum of vascular abnormality while maintaining the terms *preplus disease* and *plus disease*), the definition of A-ROP to replace aggressive-posterior ROP, and the definition of nomenclature representing ROP regression and reactivation. These principles will provide a foundation for improving research and clinical care in the future.

Nevertheless, the ICROP3 simply marks a point in the journey toward improving ROP care and outcomes. We hope this will lead to increased understanding of acute-phase ROP, its regression, and its reactivation. Areas in need of additional research include methods for quantifying vascular changes, including rate of disease progression; characterizing clinical findings using other imaging methods (e.g., fluorescein angiography, OCT); understanding long-term risks of PAR; and elucidating signs and timing of ROP reactivation. Further collaboration with other caregivers and investigators will improve the quality and standardization of ROP care worldwide.

Footnotes and Disclosures

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