Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

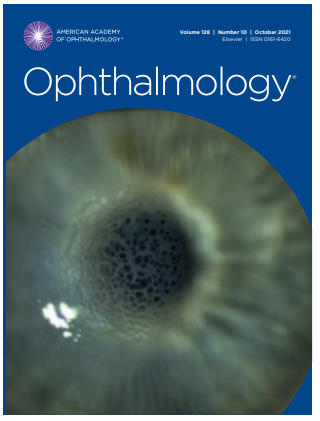
Ophthalmology

Selected by Stephen D. McLeod, MD

Update to the International ROP Classification System

October 2021

Chiang et al., representing the International Committee for the Classification of Retinopathy of Prematurity (ICROP), recently revised the international consensus statement for classifying ROP. The goal of the revised guidance is to elevate the quality and standardization of ROP care throughout the world.



The original consensus statement was published in 1984 and revised in 2005. Revisiting the guidance again was warranted to address multiple developments in the field, including new ophthalmic imaging and pharmacologic therapies, concerns surrounding the subjectivity of ROP classification, and recognition that ROP patterns in some parts of the world do not fit neatly into the existing classification system.

An international committee of ROP experts was assembled in 2019; the committee represents 17 countries and includes 20 retina and 14 pediatric ophthalmologists.

For the third edition of the classification system, ICROP3, the committee retained definitions such as zone (disease location), stage (disease appearance at avascular-vascular junction), and circumferential extent of disease. Major changes include refined classification metrics (including posterior zone II, notch, and subcategorization of stage 5) and recognition of the continuum of vascular abnormality that exists from normal to plus disease. Also included is a definition of aggressive ROP (to replace aggressive-posterior ROP) because of the growing awareness that aggressive disease can occur in large preterm infants and can extend beyond the posterior retina, particularly in parts of the world that have limited resources. ROP regression and reactivation are described in detail in ICROP3, and more information on long-term sequelae is provided.

ICROP3 marks a point in the journey to improve ROP care and outcomes, said the authors. They hope the updated material will improve the understanding of acute-phase ROP, including its regression and reactivation. They noted that more research is needed in areas such as quantification of vascular changes, characterization of clinical findings by other imaging modalities, and long-term risks of peripheral avascular retina. *(Also see related commentary by Michael X. Repka, MD, in the same issue.)*

Disparities at Initiation of Anti-VEGF Therapy for DME

October 2021

Although the risk factors for diabetic retinopathy (DR) and diabetic macular edema (DME) are fairly well understood, little is known about factors that are likely to stand in the way of prompt diagnosis and treatment of DME. Using data from the Academy's IRIS Registry, **Malhotra et al.** looked at presenting visual acuity (VA) and disease severity in relation to ethnicity, geographic location, and insurance status. They hypothesized that these factors may impede early treatment of DME, leading to poor VA and greater disease severity by the time treatment is begun. Their findings corroborated this hypothesis.

For this retrospective cross-sectional study, the authors gathered information for 203,707 patients who started anti-VEGF treatment of DME from 2012 through 2020. They performed multivariate regression analyses to explore relationships between baseline clinical features and ethnicity, insurance status, and location. The main outcome measures were VA and severity of DR.

The majority of patients were White (58.5%). With respect to insurance, 32.2% had private plans, 22.9% had Medicare, and 8.8% had Medicaid. Baseline VA was better for patients with Medicare or private insurance than for those with Medicaid (median, 2.31 and 4.17 more ETDRS letters, respectively; $p < .01$). White and non-Hispanic patients had better VA than Blacks and Hispanics (median, 0.68 and 2.53

more ETDRS letters, respectively; p < .01). DR severity was worse for Black and Hispanic patients than for their counterparts (odds ratio [OR], 1.23 and 1.71, respectively; p < .01). Patients on Medicaid had a 1.19 OR of having DR severity one level higher than that of privately insured patients (p < .01); the difference between Medicaid and Medicare members was not significant.

In this study, ethnicity and type of insurance status were independently linked to worse VA and greater DR severity. Hispanic ethnicity and Medicaid insurance had the strongest correlations with poor ophthalmic health. Such information may boost clinician awareness of the disparities that exist when anti-VEGF treatment of DME is begun, said the authors.

Global Prevalence of Undetected Glaucoma

October 2021

The global extent of undetected glaucoma is still unclear despite insight from recent population-based studies on prevalence and risk factors. **Soh et al.** explored the extent of undetected glaucoma among communities worldwide to shed light on the effectiveness of current strategies used to find cases and to plan appropriate public health initiatives and resource allocation. They found that rates of undetected glaucoma remain high, exceeding 50% worldwide; prevalence was highest in Asia and Africa.

For this systematic review and meta-analysis, the authors searched multiple sources, including online databases and reports from nongovernmental organizations. The main outcome measure was the proportion of previously undetected glaucoma cases. "Manifest glaucoma" denoted any form of glaucoma reported in the studies, including primary open-angle glaucoma (POAG), primary angle-closure glaucoma, secondary glaucoma, or combinations thereof. "Undetected glaucoma" was defined as glaucoma that had not been identified before its diagnosis in the study. Cases of "possible" or "suspect" glaucoma were excluded. A random-effects meta-analysis was performed to estimate the pooled proportion of undetected glaucoma.

Altogether, the authors identified 61 articles (55 population-based studies), representing 189,359 participants and 6,949 cases of manifest glaucoma. Globally, more than half of all glaucoma cases had not been detected previously. Compared with Europe, undetected glaucoma was more common in Africa (odds ratio [OR], 12.70) and Asia (OR, 3.41). Countries with a low Human Development Index (HDI; <0.55) had higher percentages of undetected manifest glaucoma than did countries with medium, high, or very high HDI (≥0.55; p < .001 for each comparison). For 2020, it was projected that nearly 48 million cases of POAG were undetected; of these, 76.7% were in Africa and Asia.

These findings confirm that more strategies are needed to improve glaucoma detection. (Also see page 27.)

—Summaries by Lynda Seminara

Ophthalmology Glaucoma

Selected by Henry D. Jampel, MD, MHS

Building a Better Eyedrop Delivery Device

September/October 2021

Sanchez et al. set out to assess a novel eyedrop delivery device for glaucoma patients. They found that study participants preferred the device over traditional drops—and that its use led to greater success with drop delivery, decreased contact with the bottle tip, and fewer wasted eyedrops.

For this study, the researchers evaluated 50 glaucoma patients (100 eyes) who had reported having trouble with administering their eyedrops. The patients were taught how to correctly administer eyedrops with standard bottles and with the device, which consists of a silicone sleeve that rests on the bridge of the nose and holds an eyedrop bottle in a stable, secure position over the ocular surface.

The researchers filmed the patients administering drops with standard bottles and the device both before and after their education sessions. Two masked graders reviewed the film and assessed accuracy of eyedrop placement, amount of bottle tip contact, and number of eyedrops delivered. Primary success was defined as accurate placement and no contact; secondary success was defined as primary success with only a single drop dispensed. In addition, the patients completed a satisfaction survey and chose their preferred method of instilling drops.

Of the 50 patients, 47 preferred the novel device over traditional drop delivery. In addition, 49 of the 50 thought it was comfortable to use and stated that they would recommend it. Fewer eyes made contact with the bottle tip when using the novel device (10 eyes) than with standard bottles (33 eyes prior to and 25 eyes following training). The number of drops dispensed was lower with the device (1.7 ± 1.2) than with baseline traditional (2.2 ± 1.6; p = .017) and post-training traditional (2.4 ± 1.8; p = .006) bottles. Overall, use of the device led to greater primary and secondary success of drop delivery (86% and 54%, respectively) than did the baseline (66% and 28%, respectively) and post-training traditional (70% and 40%, respectively) approaches.

—Summary by Jean Shaw

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

When Subretinal Fluid Persists in AMD

October 2021

Core et al. assessed the presence of predominantly persistent subretinal fluid (SRF) in eyes receiving ranibizumab or bevacizumab on a pro re nata basis for their age-related macular degeneration (AMD). They then compared the visual acuity (VA) of these eyes to that observed in eyes with nonpersistent SRF. They found that both sets of eyes had similar VA outcomes through two years of follow-up. Moreover, they found that, at the foveal center, persistent SRF was typically absent or present only in small quantities.

For this secondary analysis of the CATT (Comparison of Age-Related Macular Degeneration Treatments

Trials) study, reading center graders evaluated OCT scans at baseline and monthly follow-up visits for SRF. Predominantly persistent SRF through week 12 was defined as SRF at baseline and at weeks 4, 8, and 12. Predominantly persistent SRF through years 1 or 2 was defined as SRF in 80% or more visits by those time points. The researchers used linear regression models to compare adjusted mean VA score and VA change from baseline in eyes with and without predominantly persistent SRF. The primary outcome measures were predominantly persistent SRF through year 1, adjusted VA score and VA change, and SRF thickness at the foveal center.

Of 406 eyes with baseline SRF, fluid persisted in 108 eyes (26.6%) through week 12, in 94 eyes (23.2%) through year 1, and in 77 eyes (19%) through year 2. The adjusted VA score was similar between eyes with and without persistent SRF at week 12, year 1, and year 2, as was adjusted change in VA. Among eyes with predominantly persistent SRF through year 1, fluid was absent in the foveal center in 46. In addition, thickness at the foveal center was 1 µm to 200 µm in 47 eyes and >200 µm in 1 eye at year 1.

The lack of effect of persistent SRF on VA observed in this study may help explain why attempts to resolve persistent fluid in previous studies by switching from one anti-VEGF agent to another did not always result in improvement in vision, the authors said.

—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Reproxalap Is Effective for Allergic Conjunctivitis

October 2021

Although histamine is a key contributor to allergic conjunctivitis, topical antihistamines often can't relieve ocular itching or inflammation. For the first time in decades, a new mechanism of action is being explored for this condition. In a phase 3 trial, **Clark et al.** assessed the postacute activity and clinical utility of topical reproxalap, a novel reactive aldehyde species inhibitor, in treating seasonal allergic conjunctivitis. They found that both 0.25% and 0.5% reproxalap were superior to the control vehicle for reducing ocular itching and achieving faster resolution of symptoms. Both concentrations of reproxalap were safe and well tolerated.

Participants of this parallel-group, double-masked, randomized trial were adults with a history of allergic conjunctivitis, a positive skin test result for seasonal allergies, and itching/redness scores of 2.5 or higher during conjunctival allergen challenge. Patients were assigned randomly (1:1:1) to receive reproxalap topical ophthalmic solution (0.25% or 0.5%) or vehicle 10 minutes before the challenge. The primary end point was area under the postacute ocular itching score curve (range of 0-4) from 10 to 60 minutes after the challenge. The main secondary end point was improvement of at least two points in the peak ocular itching score obtained at baseline.

Altogether, 318 patients were treated (62% women; mean age, 45.7 years). Area under the ocular itching score curve from 10 to 60 minutes was lower for both 0.25% and 0.5% reproxalap than for the vehicle control ($p < .0001$ and $p = .003$, respectively). Similarly, the proportion of patients with improvement of at least two points in their peak baseline itching score was greater for both concentrations of reproxalap ($p = .0005$ and $p = .02$ vs. vehicle, respectively). The time to achieve an ocular itching score of 0 was faster with 0.25% and 0.5% reproxalap than with vehicle ($p < .0001$ and $p = .001$, respectively), and the degree of ocular redness was lower in the active treatment arms. No major safety or tolerability issues occurred.

Reproxalap 0.25% not only resolved allergic conjunctivitis symptoms more quickly than vehicle but also increased the clinical response at least twofold. Although it outperformed the 0.5% solution in most analyses, the authors found no significant differences between the two concentrations. They urged further testing of reproxalap in other allergen-challenge models.

Flanged Polypropylene Sutures in Scleral Fixation: Biomechanical Testing

October 2021

Yuan et al. performed biomechanical analyses of the polypropylene belt loop technique for scleral fixation of IOLs, using common materials and variations of them, and they compared their findings with those of studies that include long-term clinical data. They determined that the current use of flanged 5-0 and 6-0 polypropylene for scleral fixation is secure and that flanged 7-0, but not 8-0, polypropylene is a viable smaller-gauge alternative for this technique.

For this study, the flange disinsertion forces of polypropylene sutures using human cadaveric sclera and a tensile testing machine were compared with the breaking strengths of 9-0 and 10-0 polypropylene. The researchers also assessed modifications in suture gauge (5-0, 6-0, 7-0, or 8-0), amount of suture cauterized (0.5 or 1.0 mm), and sclerotomy size (27, 30, 32, or 33 gauge). In addition, four patients who underwent belt-loop intrascleral fixation with a 6-0 polypropylene/30-gauge needle or a 7-0 polypropylene/32-gauge needle were evaluated.

In general, the breaking force of each suture coincided with its cross-sectional area. Flange size decreased with smaller-gauge sutures, and smaller gauges had lower pull-through forces. The average forces to disinsert a flange created by melting 1.0 mm of 5-0, 6-0, 7-0, and 8-0 polypropylene sutures from human cadaveric sclera via 27-, 30-, 32-, and 33-gauge needle sclerotomies were 3.0 ± 0.5 in newtons (N), 2.1 ± 0.3 N, 0.9 ± 0.2 N, and 0.4 ± 0.1 N, respectively. When only 0.5 mm of suture material was melted, flange disinsertion forces were 72% to 79% lower ($p < .001$) and did not exceed the breaking force of 9-0 or 10-0 polypropylene for any suture size tested. In comparison, the breaking strengths of 9-0 and 10-0 polypropylene were $.91 \pm .04$ N and $.52 \pm .03$ N, respectively. In the patients with belt-loop fixation, best-corrected visual acuity was 20/32 before surgery and 20/21 afterward. Six

months postoperatively, there was no evidence of flange extrusion.

The authors postulated that the flanged belt-loop technique is a biomechanically sound method of scleral fixation when using 1.0-mm flanges of 5-0 to 7-0 polypropylene and 30- and 32-gauge sclerotomies. However, they said, 8-0 polypropylene and 0.5-mm flanges of any suture gauge likely would compromise long-term stability.

—Summaries by Lynda Seminara

JAMA Ophthalmology

Selected and reviewed by Neil M. Bressler, MD, and Deputy Editors

SARS-CoV-2 Viral Particles in the Human Retina

September 2021

Araujo-Silva et al. set out to determine whether particles of the SARS-CoV-2 virus and its characteristic proteins could be detected in the enucleated eyes of patients affected by COVID-19. They found presumed viral particles in several retinal layers, suggesting that the particles may be involved in some of the infection's ocular manifestations.

For this study, the researchers analyzed the retinas of three patients who died of COVID (age range, 69-78 years). All three had been in the intensive care unit before their deaths. Samples from their enucleated eyes underwent immunofluorescence and transmission electron microscopy processing.

Via immunofluorescence microscopy, the virus' S and N proteins could be seen in various regions of the retina, including the ganglion cell layer, inner and outer plexiform layers, and outer nuclear layer, as well as in the retinal pigment epithelium and the choroid. These findings are in close agreement with previous findings of the SARS-CoV-2 S1 protein in the neurosensory retina, the authors said.

Transmission electron microscopy scanning of thin sections showed the presence of presumed viral particles. These double-membrane vacuoles were located in the perinuclear region of retinal cells, including those of the inner and outer nuclear layers.

Further research is needed, the authors said, including investigations into whether these retinal changes are related to secondary microvascular and immunological changes, represent the direct presence of the virus, or signify a combination of these and other factors. *(Also see related commentary by Nasreen A. Syed, MD, and Charles Grose, MD, in the same issue.)*

Electronic Warning System for the Visually Impaired

September 2021

How effective are electronic mobility aids for visually impaired patients? **Pundlik et al.** assessed a collision warning device and found that it reduced the number of times patients bumped into various obstacles and hazards.

For this double-masked study, the researchers enrolled 31 independently mobile individuals who had severe visual impairments, including blindness (age range, 25-73 years). All habitually used either a long cane (n = 28) or a guide dog (n = 3) to navigate. The participants were fitted with a wearable device that included a chest-mounted video camera capable of detecting impending collisions and two wristbands that, when in active mode, vibrated when the collision risk was high.

The device was programmed to switch between active and silent modes on a randomized schedule. This schedule was not disclosed to the participants, who were told that the device was a prototype and might not provide warnings in some situations. After the participants underwent training, they took the device home. They were instructed to use it—along with their habitual mobility aid—at their discretion as they went about their day. They also were told that the camera would record whenever the device was on. After four weeks, they returned the device. The primary outcome measure was the rate of contacts per 100 true hazards (as seen on video) per hour.

A total of 368 hours of walking video data was available for analysis. The median (interquartile range) number of contacts was 9.3 (range, 6.6-14.9) in the active mode, versus 13.8 (range, 6.9-24.3) in the silent mode. Six participants reported a total of eight minor adverse events (minor contact/brushing against an object while walking); no serious adverse events occurred. These findings demonstrate a clear mobility benefit of using the device, the researchers said. *(Also see related commentary by Gerald McGwin Jr., MS, PhD, and Cynthia Owsley, PhD, MSPH, in the same issue.)*

Music to Tame Anxiety and Hypertension During Cataract Surgery

September 2021

Guerrier et al. evaluated whether having patients listen to music immediately prior to cataract surgery could lower the incidence of anxiety and hypertensive events during surgery. They found that it was effective on both fronts and that it also reduced the need for sedative medication during surgery.

For this single-masked study, the researchers evaluated 309 patients (mean age, 68.9 years) who were scheduled for their first cataract surgery. Of these, 36 patients were already being treated for hypertension. The patients were randomly assigned to either the experimental arm (headphones with music from a web-based app; n = 154) or the control arm (noise-canceling headphones without music; n = 155) for 20 minutes before surgery. The primary outcome was the occurrence of at least one hypertensive event during surgery (defined as systolic blood pressure [BP] of >160 mm Hg and/or diastolic BP >100 mm Hg plus a tachycardia level >85 beats per minute [bpm]). Secondary outcomes included the patients' anxiety levels at the end of the 20-minute pre-op sessions, as measured by a visual analog scale, and their need for antianxiety medication during surgery.

All told, 21 patients in the treatment arm and 82 in the control experienced hypertension with tachycardia during surgery. During these events, mean BP was 149/95 and mean heart rate was 94 bpm in those who listened to music before surgery. In contrast, the mean BP of controls was 179/118, and their mean heart rate was 119 bpm.

With regard to anxiety levels, the mean visual measure of anxiety was lower in the music arm than in the control arm (1.4 vs. 3.1, respectively). While the overall proportion of those who needed anxiolytic medication during surgery was similar between the two groups, the mean number of injections was lower in those who listened to music than in controls (.04 vs. .54, respectively).

Overall, these findings suggest that the simple nonpharmacologic approach of listening to music before cataract surgery can help reduce patient anxiety and the risk of intraoperative hypertensive events. However, the inability to mask the study participants could have biased the study in favor of the music arm. Patients were informed of the music or control intervention during the consent process and knew which arm they were being randomized to. If they knew music was being evaluated as an intervention to lower anxiety, it may have increased their anxiety if they realized that they were not getting the study intervention. This could have resulted in more episodes of hypertension or a greater requirement to need and receive anxiolytic drugs. *(Also see related commentary by Julie M. Schallhorn, MD, and Jennifer Rose-Nussbaumer, MD, in the same issue.)* *—Summaries by Jean Shaw*

OTHER JOURNALS

Selected by Prem S. Subramanian, MD, PhD

Myopia Progression in Chinese Children During the Pandemic

Graefe's Archive for Clinical and Experimental Ophthalmology
Published online July 21, 2021

The Ministry of Education of the People's Republic of China estimated that more than 220 million Chinese children and adolescents have been educated online during the pandemic. **Ma et al.** aimed to determine whether this method of learning affects the time students spend on near work and outdoors, which could influence the incidence and progression of myopia. They found that the pandemic is hastening myopia progression in East Asia, where myopia prevalence is historically very high.

The study included 8- to 10-year-old children from Handan in the Hebei province of China. A control group of children treated before the pandemic was established for comparison purposes. Control participants had been admitted to Beijing Tongren Hospital before August 2018 and received follow-up care. All participants had logMAR best-corrected visual acuity of at least 0.0 or better. Reasons for exclusion were previous eye disease or injury, atropine use, orthokeratology, and any condition that could influence myopia.

Baseline data were collected in July 2019. Participants attended follow-up appointments in January 2020 and August 2020, which included comprehensive and standardized ocular exams. A detailed questionnaire was completed during the second follow-up visit. Uncorrected visual acuity (UCVA), mydriatic spherical equivalent (SE), and axial length were compared for the two groups. Large correlation coefficients were observed for cycloplegic SE between the two eyes ($r = 0.73$, $p < .001$); therefore, only right eyes underwent analysis.

Altogether, there were 208 children in the pandemic cohort and 83 in the pre-pandemic control group. Myopia progression was significantly greater during the pandemic (–0.93 vs. –0.33 D; $p < .001$). However, there were no clinically meaningful differences in UCVA change or axial elongation between the study groups. According to logistic regression analysis, changes in SE were associated with baseline axial length ($p = .028$), online learning ($p = .02$), and digital screen time ($p < .005$). During the pandemic, children spent less time outdoors (1.04 vs. 1.75 hours per day beforehand).

Risk Factors for Undetected POAG

British Journal of Ophthalmology
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Chan et al. looked at data from the European Prospective Investigation of Cancer (EPIC)-Norfolk Eye Study to explore possible links between undiagnosed primary open-angle glaucoma (POAG) and ocular, socioeconomic, and other factors. They found that overreliance on pretreatment intraocular pressure (IOP) hinders the detection of POAG.

In the EPIC-Norfolk Eye Study, ophthalmic data were collected for 8,623 patients between 2004 and 2011. For this cross-sectional study, Chan et al. augmented that data with details such as family history of glaucoma, self-reported problems with eyesight and use of corrective lenses, and general health status. They also conducted systematic screenings, including assessments of the optic nerve head and peripapillary nerve fiber layer. Patients with findings suggestive of glaucoma were referred to a glaucoma specialist for further evaluation. Logistic regression was used to analyze risk factors for previously undiagnosed POAG. Factors that were significant in the univariable model were entered into multivariable analyses.

Among the 8,623 participants, 363 were diagnosed as having glaucoma, including 314 with POAG. Of the POAG cases, 207 had been diagnosed previously, and 107 were newly identified during the study. In the final multivariate model, factors significant for previously undetected glaucoma were lower IOP before treatment and lack of reported eyesight problems. Insignificant factors were age, current employment, visual field mean deviation, pseudophakia, absolute refractive error, cup/disc ratio, glaucoma type, and family history of glaucoma.

In the United Kingdom, POAG is diagnosed by opportunistic case finding, which relies on patients presenting to an eye care professional, with subsequent referral to the Hospital Eye Service under the National Health Service if glaucoma is suspected. Those at high risk of glaucoma (age >60 years; age >40 years with first-degree family history) can get an optician's eye test free of charge.

The most important implication of this research is to "avoid being falsely reassured by a lower level of IOP in glaucoma case finding," the authors said. (Also see page 24.)

—Summaries by Lynda Seminara