Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

PAC Suspects: LPI Versus Initial Observation

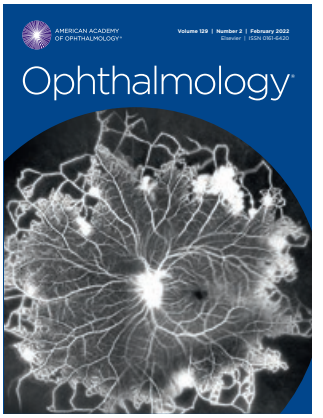
February 2022

In the Zhongshan Angle Closure Prevention (ZAP) trial, the incidence of primary-angle closure (PAC) was less than 7% within six years of identification as PAC suspects (PACS) by community screening. **Baskaran et al.** conducted a similar study in Singapore and found that the incidence of PAC and PAC glaucoma (PACG) was low throughout five years of follow-up. Eyes treated with laser peripheral iridotomy (LPI) fared better overall.

For this Singapore trial, the researchers prospectively evaluated 480 adults over 50 years of age who had received a diagnosis of PACS. PACS was defined as gonioscopy findings of two or more quadrants of appositional angle closure. All participants had bilateral asymptomatic disease; each underwent prophylactic LPI in one eye (selected randomly), and their fellow eyes served as the controls. The main endpoint was the development of PAC or PACG in either eye during five years of annual follow-up.

The study population was primarily Chinese (92.7%) and female (75.8%); the mean age was 62.8 years. Within five years, the eyes treated with LPI were less likely than control eyes to experience either PAC or PACG (5% in LPI patients vs. 9.4% in controls). The adjusted hazard ratio for progression to PAC among LPI-treated eyes, relative to controls, was .55. However, the overall progression rate was low, and there was no difference in the risk of developing PACG between groups. Older patients and eyes with high IOP at baseline were more likely to reach an endpoint.

The authors concluded by noting that their findings further support the recommendation that observation without LPI is a reasonable option for PACS. *(Also see related commentary by Ying Han, MD, PhD, in the same issue.)*



A Dual Modality Improves Dx of Glaucomatous Optic Neuropathy

February 2022

Xiong et al. developed a bimodal algorithm that combines visual field (VF) data and peripapillary circular OCT to detect glaucomatous optic neuropathy (GON). They compared the accuracy of their dual algorithm to that of each of its components and found that the dual modality outperformed either VF or OCT alone.

For this study, the authors gathered 2,463 pairs of VF and OCT images representing eyes of 1,083 Chinese patients. The majority of image pairs were used to train the FusionNet artificial intelligence algorithm to detect GON, which was defined as retinal nerve fiber layer thinning with corresponding VF defects. The other images were used for testing and validation. The dual algorithm incorporates pattern deviation probability plots from VF reports and from circular peripapillary OCT scans. VF data were collected with the Humphrey field analyzer, and OCT images were obtained from three devices.

The pairs of VF and OCT images were grouped into four datasets, with 1,567 pairs used for training, 441 for primary validation, 255 for internal testing, and 200 for external testing. In addition, four glaucoma specialists classified the cases independently. The main outcome measure was the diagnostic performance of FusionNet versus algorithms based only on visual field data (VFNet) or OCT data (OCTNet).

In the primary validation set, area under the receiver operating characteristic curve (AUC) was .950 for FusionNet, .868 for VFNet, and .809 for OCTNet. FusionNet also outperformed two glaucoma specialists (AUC, .882 and .883). In the internal and external test sets, the combination algorithm performed better than VFNet or OCTNet. Internal AUC data were .917, .854, and .811, respectively. The corresponding external AUCs were .873, .772, and .785. There was only one significant

difference between human assessment and FusionNet among the internal and external sets: the AUC for one specialist was .858. Generalizability was good across the three types of OCT.

These results support the hypothesis that multimodal machine-learning models are effective for GON detection. Multicenter studies are warranted to validate FusionNet in different ethnicities and with data from primary eye care providers, said the authors.

Intervention Program Lowers Myopia Risk for Preschoolers

February 2022

Although the age-specific prevalence and annual incidence of myopia are high among schoolchildren in Taiwan, little is known about myopia rates for preschoolers. In a study aimed at minimizing myopia risk, **Yang et al.** looked at the effects of a policy that promotes outdoor activity for this age group. Their research was conducted before and during the coronavirus pandemic. Once the intervention was introduced, the prevalence of myopia decreased continuously and did not escalate in 2020, despite the pandemic.

In August 2014, the Public Health Bureau Yilan County launched a large-scale population-based screening initiative known as the Yilan Myopia Prevention and Vision Improvement Program (YMVIP). Since then, countywide campus-based eye exams, including cycloplegic autorefraction, have been given to 5- and 6-year-olds throughout the county. Children who do not pass the eye exam are referred for further care. The intervention also includes annual caregiver surveys, public awareness strategies, and promotion of myopia-prevention measures such as limiting near work and encouraging outdoor activity for two hours a day.

For this analysis, the researchers included 21,761 kindergartners from seven school-year cohorts (2014-2020). The main outcome measure was the prevalence of myopia (spherical equivalent equal to or less than –.5 D in either eye) in each yearly cohort. The duration of exposure to myopia prevention strategies before eye screening was categorized as no exposure (2014 cohort), up to one year of exposure (2015 cohort), and up to two years of exposure (subsequent cohorts).

The investigators observed a continuous decrease in myopia prevalence in the two years following inception of the YMVIP. The prevalence rate was 15.5% in 2014, 13.5% in 2015, and 8.4% in 2016. Thereafter, it remained relatively stable (range, 8.5%-10.3%), even during the pandemic. Multivariate logistic regression analysis showed a relationship between prevention-strategy exposure and myopia prevalence (odds ratio of .86 for up to one year of YMVIP exposure and .56 for up to two years of exposure), after controlling for other myopigenic factors.

Even though myopia prevalence is high among preschoolers in Taiwan, prevention strategies such as the YMVIP program can be effective mitigators, as demonstrated in this study. An L-shaped trend toward decreased prevalence of myopia can be achieved through strategies that emphasize outdoor time and frequent school-based eye care. The authors suggest that the evidence from this study be used to support public policies to control and prevent myopia in young children.

—Summaries by Lynda Seminara

Ophthalmology Glaucoma

Selected by Henry D. Jampel, MD, MHS

Is Glaucoma Care a Bother? What Patients Really Think

January/February 2022

Stagg et al. set out to understand the treatment burden experienced by patients with primary open-angle glaucoma (POAG). They found that, by itself, the process of glaucoma treatment creates a significant burden for many patients. Moreover, they found that this burden can threaten patients' vision, as it interferes with medication and appointment adherence.

For this study, the authors conducted interviews with 22 patients with POAG who were recruited from a university clinic. The interviews lasted roughly 30 minutes each, and most were conducted face-to-face. Most of the patients had longstanding glaucoma (>10 years), and 11 of the 22 had severe disease.

The patients were asked about those activities that pose a burden (e.g., attending appointments, working with insurance companies, and monitoring symptoms and side effects). They also were asked to comment on how these activities impacted their quality of life and to discuss any additional factors that might interfere with medication and appointment adherence. The interviews were recorded, de-identified, and transcribed. The researchers then analyzed the transcripts using inductive thematic analysis and grounded theory to generate themes and to map these themes into a conceptual model of glaucoma treatment burden.

All told, the participants described 10 categories of activities that they consider burdensome, eight themes comprising the consequences of this burden, and 25 additional themes that play a role in their quality of life. The findings suggest that the process of glaucoma care can be burdensome for many—but not all—patients. In addition, the researchers found, those patients who experienced high levels of treatment burden may have decreased quality of life even if they use eyedrops as prescribed. *—Summary by Jean Shaw*

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Analysis of Brolucizumab Safety

February 2022

Cases of retinal vasculitis and/or retinal vascular occlusion, typically occurring in the presence of intraocular inflammation (IOI), have been noted with the anti-VEGF agent brolucizumab. Because the HAWK and HARRIER trials comprise the most complete datasets for brolucizumab in neovascular age-related macular degeneration (AMD) at this time, **Singer et al.** evaluated IOI-related adverse events in these studies. They found that while most adverse events occurred within the first six months following brolucizumab injections, others occurred well after this time frame.

Of 1,088 eyes that received brolucizumab injections (3- and 6-mg cohorts combined), 49 demonstrated at least one IOI-related adverse event. Of these, 35 had one adverse event, while 14 had two or more, for a total of 70 adverse events. Twelve of the 49 eyes gained 15 or more letters of vision from baseline, nine lost 15 or more letters, and four lost 30 or more letters. Of note, seven eyes with poor visual outcomes also experienced retinal artery occlusion.

Thirty-eight of the 70 events were classified as mild, 28 were moderate, and four were severe. Sixty-one of the 70 IOI-related events were treated; treatment typically involved topical corticosteroids, with infrequent use of systemic and/or intraocular corticosteroids. Fifty-two of the 61 treated events were reported by the investigators as resolved. Another four events were reported as resolved with sequelae, and five had not resolved by the end of the study. Of the nine untreated adverse events, seven resolved completely, and two resolved with sequelae.

Most IOI-related adverse events occurred within six months of brolucizumab initiation and the first four injections. However, some were reported as late as 16 months after the first brolucizumab injection, after eight to 10 injections, and as late as 72 days after the last brolucizumab injection.

—Summary by Jean Shaw

Ophthalmology Science

Selected by Emily Y. Chew, MD

Quantifying Early Neonatal Oxygen Exposure in ROP

December 2021

Chen et al. evaluated oxygen's nuanced role in the development of retinopathy of prematurity (ROP), particularly treatment-requiring ROP (TR-ROP) and aggressive ROP (A-ROP). They found that data on early neonatal oxygen exposure can be extracted from the electronic health record (EHR) and quantified as a risk factor for TR-ROP and A-ROP.

For this proof-of-concept study, the researchers had three lines of inquiry: 1) Is it possible to develop quantitative variables for oxygen exposure from the EHR? 2) What is the relationship between these oxygen variables and incident TR-ROP and A-ROP? 3) Using machine learning, does the quantification of oxygen exposure add predictive value for incident TR-ROP?

The 244 premature infants in this retrospective analysis were screened for ROP at Oregon Health & Science University in Portland. All 244 were born at or before 30 weeks' gestational age. In addition, oxygen data for each infant was complete from birth to 30 weeks' postmenstrual age (PMA) in the EHR. The researchers manually extracted data on oxygen saturations and fraction of inspired oxygen (FiO2), and four oxygen variables were calculated on a weekly basis. Random forest models were trained with fivefold cross-validation using gestational age and cumulative FiO2 at 30 weeks' PMA to identify infants who developed TR-ROP.

For TR-ROP, the main outcome was cross-validation performance, assessed using area under the receiver operating curve (AUC) and precision-recall curve (AUPRC) scores. For A-ROP, there were not enough cases to build machine learning models; thus, the researchers calculated AUC and evaluated sensitivity and specificity at a high-sensitivity operating point.

Of the 244 infants, 33 developed TR-ROP, and 28 of the 33 were diagnosed with A-ROP. For TR-ROP, random forest models trained on gestational age plus cumulative minimum FiO2 were not significantly better than those trained on gestational age alone. However, models using oxygen alone had an AUC of .80 ± .09. In the secondary analysis for A-ROP, the AUC was .92.

In the future, the oxygen variables evaluated in this study could be made available at the time of first ROP screening along with standard demographic risk factors, the researchers noted. "Future work may build upon this study by examining oxygen concentrations at a more granular level to improve modeling for TR-ROP and other diseases related to oxygen exposure," they concluded.

—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Factors Affecting Survival of Patients With Eyelid Melanoma

February 2022

The incidence of cutaneous melanoma has soared globally in recent decades, and the morbidity and mortality rates remain high. **Go et al.** reviewed data for a large population of patients with this cancer and found several significant predictors of poor outcome: age at diagnosis, lymph node involvement, T4 disease stage, and the nodular histologic subtype.

All patients in the study had a diagnosis of primary melanoma of the eyelid, established between 1975 and 2016 and documented in the Surveillance, Epidemiology and End Results (SEER) database. Detailed data were extracted for each patient, including sex, race, age, tumor depth, cancer stage, histologic grade and subtype, and length of survival. Main outcomes were survival rates (Kaplan-Meier analysis) and mortality hazard ratios (HRs), assessed for overall survival and disease-specific survival.

Altogether, 2,257 patients qualified for the study. Of these, 1,380 had melanoma in situ, and 877 had invasive melanoma. Five years after diagnosis, the overall survival rate was 88.6% for patients with melanoma in situ and 77.1% for those with invasive melanoma. Disease-specific survival rates were 99.4% and 91.0%, respectively. Cox regression analysis of invasive melanoma showed lower survival rates for patients older than 74 years at diagnosis (HR, 2.17; $p = .04$), with stage T4 disease (HR, 8.45; $p < .001$), with lymph node involvement (HR, 3.61; $p = .03$), or with the nodular subtype (HR, 3.31; $p = .003$). The most common subtype of invasive melanoma was lentigo maligna (20.9%). Unlike findings of previous research, females did not fare better than males. Race and tumor ulceration did not affect the likelihood of survival.

To the authors' knowledge, this is the largest survival-related study of patients with cutaneous melanoma of the

eyelid. They stressed the importance of appropriate prognostic counseling for patients at risk of poor outcomes.

Optic Disc Hemorrhage Signals Glaucoma Progression

February 2022

In several randomized studies, optic disc hemorrhage was a strong risk factor for the development and progression of glaucoma. However, the etiology of disc hemorrhage remains unknown, and research has not determined whether it is a cause or consequence of glaucoma. **Margeta et al.** hypothesized that high-density minimum distance band (MDB) neuroretinal rim thinning may coincide with optic disc hemorrhage. They found that localized 3D evidence of neuroretinal rim progression preceded the occurrence of hemorrhage in many patients.

For this prospective longitudinal study, the researchers included 124 patients with open-angle glaucoma who underwent annual evaluation by disc photography, spectral-domain OCT, visual field (VF) measurements, and scans of optic nerve volume and the retinal nerve fiber layer (RNFL). All assessments took place on the same day and were repeated yearly during the five-year study period. The scans of optic nerve volume were used to calculate MDB thickness. Event-based analysis was applied to classify each patient's status with regard to glaucoma progression.

Findings of the study showed that 19 patients (15.3%) had at least one occurrence of disc hemorrhage noted by disc photography. The presence of hemorrhage correlated with localized 3D superior progression of neuroretinal rim thickness (odds ratio, 3.96; p = .04) but not with MDB progression (global or inferior), RNFL progression (global, inferior, or superior), VF progression, or progression noted on disc photography. In 82% of patients with MDB changes, the progression was observed before or during detection of the first disc hemorrhage. Women and patients with normal tension glaucoma were more likely to be affected, as noted in earlier studies.

Only 31% of patients with superior MDB progression also exhibited hemorrhage in the same (superior) quadrant. Although inferior hemorrhage was the most common type (63% of patients), only 50% of them had inferior MDB progression. The authors explained that the discordance between the location of disc hemorrhage and the area of progression has been noted in other studies: It may relate to the transient nature of disc hemorrhage or the fact that progression is infrequently accompanied by hemorrhage and generally does not lead to glaucomatous damage. Results of this study support the theory that disc hemorrhage is an indicator of ongoing glaucoma progression rather than a cause of it.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

Nutritional Supplements May Promote Neurorecovery in Glaucoma

January 2022

De Moraes et al. investigated whether the combination of nicotinamide (a form of vitamin B3) and pyruvate could improve retinal ganglion cell function in glaucoma patients with moderate functional loss. They found that it yielded short-term improvement in visual field (VF) sensitivity.

For this phase 2 study, 42 participants with mild or moderate glaucoma and moderate VF loss in at least one eye were randomized to receive either placebo or oral nicotinamide plus pyruvate. All patients were taking IOP-lowering medications. To minimize learning effects of VF testing, the patients were required to have undergone at least three VF exams in the three years before enrollment.

Thirty-two of the participants completed the study and were included in the final analysis. The primary outcome measure was the number of VF test locations improving beyond normal variability in the study eye. Secondary endpoints included pattern standard deviation and VF index.

Participants in the treatment group (n = 21) took ascending doses of a combined supplement of nicotinamide (1,000 to 3,000 mg/day) and pyruvate (1,500 to 3,000 mg/day) during the first three weeks. VF tests were performed at baseline and at the end of weeks 2 and 3. The supplement was then discontinued, and a final VF test was taken at the end-of-study visit. Median time of follow-up was 2.2 months (range, 2-2.4 months).

The results showed that the number of improving test locations was higher in the treatment group than in the placebo group (median, 15 [6-25] vs. 7 [6-11]; p = .005). Logistic mixed-effects regression also revealed that eyes treated with the supplement were more likely to experience improving test locations (odds ratio [OR], 3.20; 95% confidence interval [CI], 1.25-8.16; p = .01).

The rates of VF pattern standard deviation were higher in the treatment group (median, –.06 [–.03 to .06] dB per week, vs .02 [–.07 to 07] dB per week; 95% CI, .02 to .24; mixed-effects model p = .02). However, there was no difference between groups regarding rates of change of the VF mean deviation or the VF index. While no serious adverse events were reported during the study, 33% of those in the treatment group experienced mild gastrointestinal distress that improved with continued dosing. *(For more on this study, see page 13. Also see related commentary by Pradeep Y. Ramulu, MD, MHS, PhD, in the same issue.)*

Diabetic Retinopathy Outcomes in Young Patients

January 2022

Bai et al. set out to assess the risk of developing diabetes-associated ocular complications among young people with type 1 and type 2 diabetes. They found that those with type 2 diabetes were more likely to develop diabetic retinopathy (DR) after a shorter duration of disease—and to do so at a higher rate than those with type 1 diabetes.

For this retrospective population-based study, the researchers reviewed the medical records of children and

teenagers who were diagnosed with diabetes from Jan. 1, 1970, through Dec. 31, 2019. All were younger than 22 years of age and lived in Olmstead County, Minnesota, at time of diagnosis. The main outcome measure was the risk of developing ocular sequelae over time.

A diagnosis of diabetes was confirmed via ophthalmic examination in 525 children and teenagers during this 50-year period, with 461 diagnosed with type 1 disease and 64 with type 2. The mean age at diagnosis was 12.1 (range, 73 days to 21.8 years). The majority (83.3%) of those with type 1 diabetes were White. In contrast, the ethnicity of those with type 2 disease was more varied, as 54.7% were White, 18.7% were Black, and 14.1% were Asian.

Diabetes-associated complications occurred in 147 (31.8%) of those with type 1 diabetes during a mean follow-up of 14 years (range, 1 day to 37 years) and in 17 (26.6%) of those with type 2 disease during a mean follow-up of nine years (range, 18 days to 24 years). All told, the prevalence of DR, including both proliferative and nonproliferative disease, was 30.6% for type 1 and 52.7% for type 2 disease. Other outcomes for type 1 and type 2 were as follows: diabetic macular edema, 5% versus 4%; a visually significant cataract, 1% versus 9%; and the need for pars plana vitrectomy by 15 years after diabetes diagnosis, 2% versus 8%.

These findings suggest that the natural history of DR among young people diagnosed with type 2 diabetes may differ from that observed in those with type 1 disease, the authors said. As a result, they noted, children with type 2 diabetes may require ophthalmic examinations as frequently—or perhaps more frequently—than those with type 1 disease. *(Also see related commentary by Jennifer K. Sun, MD, MPH, in the same issue.)*

Infectious Conjunctivitis During COVID-19

January 2022

Ferres et al. evaluated whether public health interventions adopted during the COVID-19 pandemic could be correlated with internet searches and emergency department (ED) visits for infectious conjunctivitis. They found that searches for information on and ED visits for this highly communicable condition fell after public health measures like social distancing and travel restrictions were put into place.

For this study, the researchers gathered ED data from the University of Washington in Seattle for diagnoses of conjunctivitis made between February 2015 and February 2021. They also collected Google search and mobility data for the United States from Feb. 21, 2016, to Feb. 6, 2021. The ED and Google data were analyzed using a counterfactual control method, with the goal of building a model to show what would have happened if there had been no COVID-related lockdowns or changes in behavior.

Results showed that, shortly after pandemic-related infection control measures were instituted in March 2020, online searches about conjunctivitis dropped by approximately 34%. This trend was corroborated by a 37% decrease in the number of patients who presented to the University of Washington's ED for conjunctivitis treatment. In contrast, search data and ED visits related to noncommunicable ophthalmic conditions—including corneal abrasions—did not change during the pandemic. *(Also see related commentary by Alfred Sommer, MD, MHS, in the same issue.)* *—Summaries by Jean Shaw*

OTHER JOURNALS

Selected by Prem S. Subramanian, MD, PhD

Horner Syndrome: Using Apraclonidine Drops in Children

Journal of AAPOS

Published online Nov. 2, 2021

Apraclonidine eyedrops are commonly used to diagnose Horner syndrome, but whether they are safe for infants and children is a topic of debate, as the drug may cross the blood-brain barrier in this population. **Eldib et al.** looked at the safety and systemic side effects of topical apraclonidine drops in 46 children suspected of having Horner syndrome, many of whom were infants. The researchers observed no local or systemic adverse events.

For this investigation, the authors reviewed records of patients with clinically suspected Horner syndrome who had undergone testing with apraclonidine .5% eyedrops at the same children's hospital between February 2016 and October 2020. Data collected included allergic reactions and the presence of somnolence, shallow respiration, pallor, and extreme fussiness, as observed by the examiner or the patients' parents. Also documented was the amount of time spent under observation.

During the study period, 46 patients presented with unequal pupil size and were tested for Horner syndrome by administration of apraclonidine .5%. The mean age was 3.2 years; the youngest was 7 weeks of age. Twenty-four patients were ≤1 year old, and 16 were ≤6 months old. All but three patients received the test as outpatients. The test result was positive for 15 patients (32.6%), in whom the anisocoria was reversed. No topical or systemic side effect was noted by the examiner or parents of any patient during either the exam or the observation period. However, it is possible that minor side effects such as transient irritation may not have been detected or documented for some patients. The time spent under observation was noted for 25 patients (range, 40-140 minutes).

To the authors' knowledge, this study represents the largest safety evaluation of apraclonidine eyedrop testing in children with suspected Horner syndrome. Results indicate that severe systemic adverse reactions to a single administration of apraclonidine eyedrops are rare in children, even in infants. It is possible that repeated exposure to apraclonidine may be problematic, as noted in other studies. A prospective study of apraclonidine testing that includes objective monitoring may help validate the findings, said the authors. *—Summary by Lynda Seminara*

MORE ONLINE. For a study on macular hole measurement, see this article online at aao.org/eyenet.