Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

Immediate Versus Delayed Spectacle Use in Toddlers With Moderate Hyperopia

June 2019

Although there is consensus that eyeglasses should be prescribed for children with moderate hyperopia and strabismus or amblyopia, optimal management of moderate hyperopia in the absence of the other conditions is unclear. **Kulp et al.** compared two strategies for young children with moderate hyperopia but no manifest strabismus: immediate use of eyeglasses versus observation only (unless circumstances warranted otherwise). Their findings were inconclusive but suggest that immediate spectacle use may confer a small or moderate benefit in some cases.

This randomized study included 130 toddlers (1- and 2-year-olds) with hyperopia ranging from +3.00 D to +6.00 D spherical equivalent (SE) in at least one eye, anisometropia ≤1.50 D SE, astigmatism ≤1.50 D based on cycloplegic refraction, and no evident strabismus. Patients were assigned randomly to receive eyeglasses (1.00 D less than the full cycloplegic hyperopia) or observation. Follow-up visits occurred every six months for three years.

During follow-up, children in the observation group were prescribed eyeglasses if they met prespecified deterioration criteria for distance visual acuity (VA) for age norm, if near stereoacuity fell below age norm, or if strabismus became evident. These criteria also were used to define failure in both study arms at the three-year mark.

All told, 106 children (82%) completed all three years of follow-up. There was no significant difference in failure rate between the two groups. Failure occurred in 21% of the spectacle group (11 of 53) and in 34% of the observation group (18 of 53; p = .14). In addition, 62% of the observation group and 34% of the spectacle group met the criteria for VA deterioration (e.g., requiring eyeglasses if not wearing them).

This study was limited by unsatisfactory enrollment, and the investigators acknowledged that larger studies are warranted to better estimate the effects of spectacle treatment in this age group and to determine the best approach for managing moderate hyperopia. However, it is clear from this study that whether or not spectacles are prescribed, VA deterioration is not uncommon, and young children with hyperopia should be monitored closely by eye care professionals.

The iStent inject for POAG: Safety and Efficacy Results

June 2019

Microinvasive glaucoma surgery (MIGS) may offer sustained reduction of intraocular pressure (IOP) while avoiding the drawbacks of ocular hypotensive drugs and filtering surgery. The first FDA-approved MIGS device, the iStent (Glaukos), has been used successfully in patients with open-angle glaucoma undergoing concomitant cataract surgery. A newer device, the iStent inject Trabecular Micro-Bypass System (also by Glaukos), creates two patent bypasses through the trabecular meshwork. **Samuelson et al.** looked at the safety and effectiveness of combining this approach with cataract surgery in patients with mild or moderate primary open-angle glaucoma (POAG). Relative to cataract surgery alone, the system achieved greater IOP reductions, and the two-year safety profile was good.

This multicenter study included 505 eyes with mild or moderate POAG that also required cataract surgery. Preoperative IOP was ≤24 mm Hg (with one to three medications), and unmedicated diurnal IOP ranged from 21 mm Hg to 36 mm Hg. After uncomplicated cataract surgery, eyes were randomized intraoperatively to receive either the iStent inject (treatment group, n = 387) or no stent (control group, n = 118). Follow-up lasted two years and included annual washout of ocular hypotensive medication. The effectiveness endpoints were ≥20% reduction from baseline to month 24 in unmedicated

diurnal IOP and change in unmedicated diurnal IOP from baseline to month 24. Safety measures included gonioscopy, pachymetry, and slit-lamp and fundus examinations; visual field and acuity tests; and documentation of adverse events.

The preoperative mean medicated IOP was 17.5 mm Hg in both groups; mean unmedicated diurnal IOP was 24.8 ± 3.3 mm Hg in the treatment group and 24.5 ± 3.1 mm Hg in controls. By 24 months, 75.8% of treated eyes and 61.9% of control eyes had a reduction from baseline in unmedicated diurnal IOP of at least 20% ($p = .005$). The mean reduction was greater in the treatment group (7.0 vs. 5.4 mm Hg; $p < .001$).

Among responders, 84% of treated eyes and 67% of control eyes were not receiving ocular hypotensive agents at 23 months. By month 24, medication-free diurnal IOP ≤18 mm Hg was achieved in 63.2% of treated eyes and 50.0% of control eyes. The safety profiles were favorable and similar.

Is Subthreshold Nanosecond Laser Safe for AMD?

June 2019

In preclinical studies and a pilot study, the subthreshold nanosecond laser (SNL) suggested promise in patients with intermediate AMD (iAMD). Building on these findings, **Guymer et al.** performed a randomized trial of the efficacy and safety of SNL as treatment for iAMD. For patients without signs of late AMD on multimodal imaging (MMI), the authors observed similar progression rates for the SNL and sham groups.

This 36-month, multicenter, double-masked study included 292 patients with bilateral large drusen and no sign of atrophy as seen on optical coherence tomography. Participants were assigned randomly to receive either Retinal Rejuvenation Therapy SNL (2RT, Ellex; n = 147) or a sham procedure (n = 145) in the study eye. Each treatment was given at six-month intervals. The primary efficacy outcome was the time until occurrence of late AMD, defined by MMI.

As the speckled-beam profile of the 2RT laser causes selective RPE loss, it is biologically plausible that the laser's effect may vary according to the degree of RPE dysfunction. To investigate this, the authors conducted a post hoc comparison of data for patients with and without reticular pseudodrusen (RPD) or pigmentary abnormalities at baseline. Adverse events were documented to assess safety.

Overall, the SNL treatment showed no significant benefit for slowing AMD progression (adjusted hazard ratio [HR], 0.61; $p = .122$ vs. sham). However, the post hoc analysis found evidence of effect modification based on the coexistence of RPD (adjusted interaction; $p = .002$). SNL treatment resulted in slower progression in the 222 participants without RPD at baseline (adjusted HR, 0.23; $p = .002$) and faster but nonsignificant progression in the 70 patients with RPD (adjusted HR, 2.56; $p = .112$). There were no significant differences in serious adverse events between the study groups. Although no serious events were related to the device, deep retinal hemorrhage occurred in 10 patients (6.8%) at the site of laser delivery.

The efficacy results suggest that SNL treatment may help to slow AMD progression in the absence of RPD, but it could hasten the AMD process in patients with coexisting RPD. Therefore, the authors recommended caution when considering studies of SNL use in patients with RPD phenotypes. Based on evidence from this study, further trials of the 2RT laser in AMD are warranted, they said. *(Also see related commentary by Philip J. Rosenfeld, MD, in the same issue.)*

—Summaries by Lynda Seminara

Ophthalmology Glaucoma

Selected by Henry D. Jampel, MD, MPH

Can OCT Be Used to Evaluate Advanced Glaucoma?

May/June 2019

The common assumption is that optical coherence tomography (OCT) cannot be used to monitor eyes with advanced glaucoma. **Lee et al.** set out to examine the validity of this assumption by exploring the hypothesis that if eyes with advanced glaucoma have a 10-2 total deviation map with any points better than –8 dB, then the topographically corresponding regions on the circumpapillary retinal nerve fiber layer (cpRNFL) should show a preserved region. They found evidence to support this hypothesis and concluded that OCT scanning can be used to follow these preserved regions.

For this retrospective study, the researchers examined the cpRNFL scans of 39 eyes (33 patients). All eyes had a 24-2 visual field (VF) with a mean deviation (MD) of –15 dB or worse (mean, –18.94 ± 2.95 dB; range, –27.06 to –15.01 dB). 10-2 VFs and averaged OCT circle scans were available for all eyes. (The circle scans were acquired in a high-speed mode and set to average 100 times.)

When the circle scans were inspected, all 39 eyes showed a recognizable cpRNFL in the region associated with the macula. In 36 of the eyes, the cpRNFL region was clear and hyperdense. The other three eyes demonstrated visible cpRNFL, but it was of low contrast.

The authors cautioned that this study has several limitations, including a small sample size and the study's retrospective nature. In addition, they said, the assessment of cpRNFL was qualitative. As a result, they called for a prospective study of eyes that have advanced glaucoma defined by a 24-2 VF MD worse than –15 dB, quantitative cpRNFL measurements, or both.

—Summary by Jean Shaw

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

International Practice Patterns in Postsurgical Endophthalmitis

June 2019

Solima et al. set out to study current practice patterns for the management of eyes with acute endophthalmitis following cataract surgery and intravitreal injections. They also assessed the likelihood that an affected eye would be

managed with pars plana vitrectomy (PPV) or intravitreal injections of antibiotics. They found that PPV was frequently performed in these eyes, regardless of the presenting vision—and that eyes with increased vitreous opacification were commonly managed with PPV.

For this retrospective nonrandomized study, the researchers evaluated data on 237 eyes with acute endophthalmitis. The information was provided by 57 retina specialists in 28 countries in Africa, Asia, Europe, and South America. Outcome measures included rates of PPV, repeat intravitreal injections, and adjunctive therapeutic regimens.

Of the 237 eyes diagnosed with acute endophthalmitis, 153 (64.6%) had undergone cataract surgery, 35 (14.8%) had received intravitreal injections, and 29 (12.2%) were diagnosed following a previous PPV. The remaining 20 eyes (8.4%) had undergone other intraocular surgeries, including glaucoma and cornea procedures.

With regard to treatment, all eyes received intravitreal antibiotics on the day of presentation. PPV was performed within the first week of presentation in 176 eyes (74.3%), while the remaining 61 eyes (25.7%) received antibiotics only. Data were available on the choice of antibiotic for 210 of the 237 eyes—of these, 191 received a combination of two drugs, most commonly vancomycin and ceftazidime (183 eyes). Early PPV was more likely in those eyes that developed endophthalmitis following cataract surgery and in those in which the disc and macula were not visualized. In addition, PPV was not limited to eyes with baseline light perception vision.

The authors emphasized that these results need to be interpreted with caution, given the study's uncontrolled retrospective design and absence of data from U.S. retina practices, among other factors. *(Also see related commentary by Bernard H. Doft, MD, in the same issue.)* —*Summary by Jean Shaw*

NOW IN PUBMED

Ophthalmology Retina is now being indexed in PubMed. The indexing process is underway with this year's issues; a request has been submitted for retroactive indexing to the inaugural issue (January/February 2017).

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Update on Rubella-Associated Uveitis

June 2019

Although vaccination programs have nearly eliminated congenital rubella virus from the Western world, associations of rubella with Fuchs uveitis syndrome (FUS) were noted in 2006. Since then, many have assumed that these conditions are linked. To explore this possibility, **Groen-Hakan et al.** evaluated clinical and lab findings of patients with rubella virus–positive uveitis, as well as aqueous humor samples from patients with FUS. The authors found that even though most cases of FUS included intraocular rubella infection, only some patients with rubella-associated uveitis displayed FUS.

This retrospective study, conducted between January 2010 and October 2016 at two sites in the Netherlands, involved consecutive patients with rubella virus–positive aqueous humor samples based on polymerase chain reaction (PCR) and/or Goldmann-Witmer coefficient (GWC) analysis. Anatomic classification and clinical characteristics were recorded, along with vaccination status. All patients with FUS received their diagnosis during the same period.

Among the 127 study participants (144 eyes), the virus was found in the aqueous fluid of 120 patients by GWC, 23 by PCR, and in 16 by both. Bilateral involvement was present in 17 patients (13%). Of the 39 patients with FUS phenotype, evaluated separately, 37 had positive rubella findings.

Blurred vision and floaters were common reasons for referral; ophthalmologic evidence included the combination of chronic anterior uveitis, keratic precipitates, vitritis, and absent posterior synechiae. Early development of cataracts and glaucoma was common, and cataract was the main cause of visual loss at presentation. Cystoid macular edema was unusual. None of the patients had been vaccinated against rubella virus at an early age.

This research not only negates the belief that rubella-associated uveitis always presents with the FUS phenotype but also exposes the diverse clinical nature of the condition, which often includes chronic unilateral anterior uveitis and vitritis. The authors stressed the importance of long-term IOP monitoring in patients with rubella-associated uveitis and emphasized diagnostic accuracy to ensure that immunosuppressant therapy is reserved for those who need it.

Cataract Surgery and Visual Field Progression in POAG

May 2019

Comorbid cataract and glaucoma present a clinical challenge, as glaucoma treatment can hasten cataract development, and the presence of cataract causes diffuse visual field (VF) loss. **Kim et al.** hypothesized that cataract surgery would slow rates of VF decay in patients with primary open-angle glaucoma (POAG), compared with rates during cataract progression. However, they found that despite improvement in intraocular pressure (IOP), VF decay accelerated significantly.

The authors reviewed medical records of patients with POAG who had four or more reliable VFs before and after cataract surgery, which involved placement of an IOL. The operations occurred during a 12-year period. The researchers also looked at a comparison group of pseudophakic eyes that had 10 reliable VFs after surgery. They then used the Glaucoma Rate Index (GRI), a new algorithm, to estimate the rate of change for the entire VF.

Among the 134 study eyes (99 patients; mean age, 66 years), the mean follow-up periods were 6.5 years before and 5.3 years after surgery. All IOP parameters improved after surgery. However, except for patients with previous trabeculectomy, VF indexes (mean ± standard deviation per year) showed

worsening rates of decay after cataract surgery versus beforehand.

Higher postoperative peak IOP and worse baseline mean deviation (MD) correlated significantly with faster postoperative peak VF decay. Subgroup analysis showed that VF decay measured by MD, VF index, and GRI was worse in the latter half of the postoperative period, which may relate to the nonlinear natural history of glaucoma.

In addition to concluding that reduced IOP after cataract surgery does not slow VF decay in POAG, the authors suggested that high postoperative peaks in IOP may signal further decline after surgery.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

High Calcium Intake May Slow Progression of AMD

May 2019

Studies of the effect of calcium intake on age-related macular degeneration (AMD) have produced conflicting results. In a secondary analysis of patients in the Age-Related Eye Disease Study (AREDS), **Tisdale et al.** evaluated the relationship between baseline calcium intake and the progression of AMD. They found that higher levels of dietary and supplementary calcium were linked to lower likelihood of progression to late AMD.

Baseline self-reported intake of dietary and supplementary calcium was documented during AREDS, then analyzed in relation to outcomes. The main outcome was the occurrence of late AMD, geographic atrophy (GA), or neovascular AMD. The 4,751 participants were predominately white (96%) and female (56%); their mean age was 69.4 years.

Compared with patients in the lowest quintile for dietary calcium intake, those in the highest quintile had a lower risk of late AMD (hazard ratio [HR], 0.73), central GA (HR, 0.64), and any GA (HR, 0.80). The risk of neovascular AMD was lower for patients in the highest tertile for calcium supplementation (HR, 0.70) than for those who did not take supplements. No adverse effects were noted.

Although the findings indicate that dietary and supplemental calcium may aid in protecting against late AMD, the authors acknowledged that chance, uncontrolled confounding, and recall bias might have contributed to the results, and they noted that increased calcium intake could simply reflect better overall health habits. They encouraged further investigation of the topic. *(Also see related commentary by Mårten E. Brelén, BMBCh, FRCOphth, PhD, Danny S. Ng, FRCS, MPH, and Carol Y. Cheung, PhD, in the same issue.)*

Effect of Impaired Visual Development on Self-Perception of Young Children

May 2019

Birch et al. looked at the relationship between amblyopia and self-perception in young children to assess whether altered self-perception correlates with impaired vision or fine motor skills. They found that children with amblyopia believed that they had lower peer acceptance and physical competence. Self-perception of physical competence among children with amblyopia correlated with aiming/catching skills and stereoacuity in their study.

This cross-sectional study was conducted at a pediatric vision lab from January 2016 to May 2018. The researchers enrolled 110 healthy children between the ages of 3 and 7. Sixty of the children had amblyopia; 30 did not have amblyopia but had been treated for strabismus, anisometropia, or both; and 20 served as age-matched controls. Self-perception was assessed using the Pictorial Scale of Perceived Competence and Social Acceptance for Young Children, which includes the domains of cognitive competence, peer acceptance, physical competence, and maternal acceptance. Fine motor skills were evaluated with the Manual Dexterity and Aiming and Catching scales of the Movement Assessment Battery for Children (second edition). Visual acuity and stereoacuity were assessed as well.

Compared with controls, children with amblyopia (28 girls, 32 boys; mean age, 6.3 years) had lower mean scores for self-perception of peer acceptance (2.74 vs. 3.11; p = .04) and physical competence (2.86 vs. 3.43; p = .009). Among the children with amblyopia, self-perception of physical competence correlated strongly with aiming and catching skills ($r = 0.43$; p = .001) and stereoacuity ($r = -0.39$; p = .02). The mean physical competence scores for children without amblyopia who were treated for strabismus or anisometropia were lower than the scores for controls (2.89 vs. 3.43; p = .03).

The researchers noted that fine motor skills are essential to supporting the emergence of a child's independence and are crucial for developing positive self-esteem, proficiency, and academic skills. Further research is needed to determine whether rehabilitating visual acuity or stereoacuity would enhance self-perceptions in this age group.

Algorithm to Identify Ocular Conditions From EHR Data

May 2019

For "big data" research, investigators are tasked with identifying many patients with a disease or phenotype of interest. Often this is accomplished by relying on administrative billing codes alone. **Stein et al.** set out to devise a method to identify the presence or absence of specific ocular conditions using data from electronic health records (EHR). They developed, tested, and validated an algorithm to determine the presence/absence of exfoliation syndrome (XFS). Their approach proved superior to using billing codes alone.

This retrospective analysis involved EHR data for 122,339 patients in the Sight Outcomes Research Collaborative Ophthalmology Data Repository who received eye care at participating centers from August 2012 through August 2017. The researchers developed a comprehensive algorithm that searches structured and unstructured (free text) EHR data for conditions of interest. They then tested its ability to detect the presence or absence of XFS among a sample of patients with and without

XFS (n = 200) by reviewing ICD-9/ICD-10 billing codes, the patient's problem list, and text within the ocular exam section and the unstructured (free-text) section of the EHR.

The likelihood of XFS was estimated for each patient using logistic least absolute shrinkage and selection operator regression. The EHR data of all patients were run through the algorithm to generate an XFS probability score for each patient, and the algorithm was validated through EHR review by glaucoma specialists. The positive predictive value (PPV) and negative predictive value (NPV) of the algorithm were computed as the proportion of patients classified correctly as having or not having XFS.

The algorithm assigned XFS probability of less than 10% to 99% of patients (n = 121,085), probability of greater than 75% to 0.4% (n = 543), probability of greater than 90% to 0.3% (n = 353), and probability of greater than 99% to 0.07% (n = 83). According to the analysis by glaucoma specialists, the algorithm's PPV was 95% and NPV was 100%. When there was an ICD-9 or ICD-10 billing code for XFS, there also was XFS evidence elsewhere in the EHR in 86% or 96% of records, respectively. However, with clinical or free-text evidence of XFS, coexistence of ICD-9 codes was less common (~40%), and ICD-10 codes were even more scant (~20%). *(Also see related commentary by Kurt K. Benke, PhD, in the same issue.)* —*Summaries by Lynda Seminara*

OTHER JOURNALS

Selected by Deepak P. Edward, MD

PDL Treatment of Port-Wine Stains Without General Anesthesia in Infancy

JAMA Dermatology
Published online March 13, 2019

Recent concerns about repetitive use of general anesthesia in young children and infants have rekindled the debate on when to start laser treatment for port-wine stains. **Jeon et al.** reviewed outcomes for patients who began pulsed dye laser (PDL) therapy, without anesthesia, in the first year of life. They found the treatment to be effective as well as safe, with more than two-thirds of the treated children experiencing outcomes that were excellent or better.

For this study, the authors reviewed medical records of 197 children who received PDL therapy for port-wine stains at ≤1 year of age; treatment occurred between 2000 and 2017. The mean age at initial treatment was 3.38 months (range, 5-355 days), and the mean number of treatments per patient was 9.8 (range, 2-23). Most of the children (n = 149; 76%) had port-wine stains on their faces. Metal corneal shields were used to protect children who had lesions that involved the periocular region.

The primary outcome was improvement of the vascular birthmarks. Before-and-after images were graded by four physicians according to a five-point visual analog scale (VAS), with 1 = poor (0%-25% improvement) and 5 = complete (100% clearance). All told, 51 of the children (25.9%) had complete clearance, 81 (41.1%) had an excellent outcome, 44 (22.3%) had good results, 13 (6.6%) had fair outcomes, and eight (4.1%) had poor results. The mean VAS score was 3.65 (standard deviation, 1.26), denoting excellent clearance. The presence of a lesion at V1 (the first branch of the trigeminal nerve) correlated significantly with a higher clearance rate. No patient had scarring or a permanent change in pigment.

Based on the results, the authors support early in-office treatment of infants with port-wine stains, particularly if the patient's risk for complications is minimal. Early intervention with PDL therapy allows for treatment without general anesthesia, maximizing the likelihood of clearance before school age and, in turn, minimizing the negative consequences of these birthmarks.

DR and Diabetic Kidney Disease Are Risk Factors for Mortality

JAMA Network Open
2019;2(3):e191540

Sabanayagam et al. assessed the relationship between diabetic retinopathy (DR), diabetic kidney disease (DKD), and mortality in a large Asian population. They found that the presence of either condition is linked to higher risk of all-cause and cardiovascular-related mortality and that the risk is greater with DKD.

For this study, the researchers evaluated 2,964 adults with diabetes who participated in the Singapore Epidemiology of Eye Diseases study. Participants ranged from 40 to 80 years of age (mean, 61.8 years) and were Chinese (n = 592), Malay (n = 1,052), or Indian (n = 1,320). DR was identified from retinal photographs, and DKD was established from estimated glomerular filtration rates; these analyses revealed that 30% of the study population had DR, and 21% had DKD. Data for all-cause and cardiovascular disease (CVD) mortality were gathered from the National Registry of Births and Deaths.

During the median follow-up period of 8.8 years (range, 7.2-11.0 years), 610 deaths occurred (20.6% of the study population). Of these, 267 deaths were attributed to CVD. In separate models for all-cause and CVD mortality, multivariable hazard ratios were 1.54 and 1.74, respectively, for DR; and 2.04 and 2.29, respectively, for DKD. In models that included both DR and DKD, the subgroup with DKD alone contributed strongly to the excess risk of all-cause and CVD mortality (27.1% and 12.6%, respectively), followed by the subgroup with DR alone (6.5% and 5.2%). Compared with patients who had neither DR nor DKD, the hazard ratios for all-cause and CVD mortality were 1.89 and 2.26, respectively, for DKD alone and 1.38 and 1.64, respectively, for DR alone. For patients with DR as well as DKD, the respective hazard ratios were 2.76 and 3.41. The relative excess risk of the DR/DKD interaction was 0.49 (p = .20) for all-cause mortality and 0.51 (p = .50) for CVD mortality.

The authors concluded that the risk of all-cause and CVD mortality is high for patients with DKD and/or DR, and that DKD confers a greater risk than DR. Their findings highlight the importance of early identification, close monitoring, and proper management of these conditions to reduce the risk of death, particularly in Asian populations. —*Summaries by Lynda Seminara*