

Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

Management Patterns and Sub-optimal Outcomes for AMD

September 2020

Studies of intravitreal anti-VEGF agents for treatment of neovascular age-related macular degeneration (AMD) indicate that vision protection is best achieved with regular intravitreal injections and frequent monitoring. However, the rigid routine can pose scheduling problems for patients and providers. Although personalized treatment plans without fixed monthly dosing can yield good visual results, analyses indicate that this method is not being employed carefully enough in clinical practice. Kiss et al. looked at treatment patterns and outcomes, as documented via electronic health records, for patients with wet AMD and found that injection frequencies were low, corresponding with only modest or suboptimal improvements.

For this retrospective cohort study, the authors searched the USRetina data repository to identify patients with neovascular AMD who received intravitreal injections of anti-VEGF drugs.

Collected information included the number of anti-VEGF injections during the 12 months following initial injection, changes in visual acuity (VA)

and anatomic structure, and changes in central retinal thickness (CRT) and ETDRS letter score.

Overall, 37,021 eyes met the inclusion criteria. In the first 12 months, the average number of anti-VEGF injections per eye was 6.0. Less than 20% of affected eyes received monthly injections. The mean improvement in VA was 0.6 ETDRS letters. CRT decreased 48 μm from the baseline value of 320

μm ; the degree of reduction increased linearly with the number of injections.

To achieve the benefits of monthly dosing, the authors said, treat-and-extend regimens should include regular optical coherence tomography exams and retreatment criteria,

especially when abnormal anatomic changes are present. They argued that VA alone may not be adequate to detect wet AMD early enough. To their knowledge, this study is the largest in the United States to include both morphologic and functional outcomes of anti-VEGF therapy for wet AMD. The findings of low injection frequency and suboptimal functional results suggest that the clinical management of the disease has room for improvement. (Also see related commentary by Carl D. Regillo, MD, in the same issue.)



Comparison of DMEK and Ultrathin DSAEK

September 2020

There have been many comparison studies of Descemet membrane endothelial keratoplasty (DMEK) and Descemet stripping automated endothelial keratoplasty (DSAEK) but only limited prospective research on DMEK versus ultrathin DSAEK (UT-DSAEK). Dunker et al. assessed DMEK and UT-DSAEK, looking primarily at high-contrast best spectacle-corrected visual acuity (BSCVA) in addition to endothelial cell density, refractive astigmatism, and perioperative complications. They found no difference in mean BSCVA at any post-op time point.

The study included 54 patients (54 eyes) from six centers in the Netherlands. All patients were pseudophakic adults with Fuchs endothelial corneal dystrophy. The authors defined ultrathin as central graft thickness of 100 μm . Participants were assigned to receive DMEK or UT-DSAEK by minimization randomization that included pre-op BSCVA and pre-op central corneal thickness.

All donor corneas except one were prepared at the same donor bank, and identical inclusion criteria were used for both procedures. Each of the six participating surgeons had performed hundreds of DSAEK and UT-DSAEK surgeries and at least 25 DMEK procedures. The surgeons were allowed to use their preferred DMEK and UT-DSAEK techniques during the operations. The primary outcome measure

was BSCVA 12 months after surgery.

Findings at 12 months showed no significant between-group differences in BSCVA ($p = .06$), endothelial cell density ($p = .12$), hyperopic shift ($p = .27$), or spherical equivalent ($p = .34$). The percentage of eyes that attained BSCVA of 20/25 was greater in the DMEK group (66% vs. 33%; $p = .02$), but the difference in the percentage that achieved 20/20 was not significant (24% vs. 4%; $p = .06$). The most common complication with both procedures was the need for rebubbling due to graft detachment (one UT-DSAEK case, seven DMEK cases).

The authors acknowledged that a larger sample size would be valuable, and they noted that differing procedural techniques may have affected the outcomes. They also pointed out that lacking a standard for reporting outcomes of these techniques makes it difficult to properly compare them across different studies. “It would be helpful to set standards on reporting the most important outcome measure, that is, visual acuity,” they wrote. (*Also see related commentary by Massimo Busin, MD, in the same issue.*)

COVID-19 Findings and Precautions for Eye Care Providers

September 2020

Qiao et al. aimed to estimate the incidence of symptomatic COVID-19 among eye professionals in Wuhan, China, with the goal of improving their safety and minimizing exposure risk. Results depicted the connection with direct patient care and suggested other risk factors, including older age and sleep deprivation. The transmission rate declined with widespread use of personal protective equipment (PPE), good hand hygiene, and the lower patient volume from Wuhan’s lockdown.

For this cross-sectional case-control study, the authors obtained a list of eye care professionals with symptomatic COVID-19, using the key informant method. The health care providers were diagnosed through February 2020 and included ophthalmologists, ophthalmic nurses, and technicians involved in patient care since the start of the

outbreak. The diagnosis had been established by reverse-transcriptase polymerase chain reaction and serum antibody testing. For each positive COVID case within a department, there were three or four control participants, chosen randomly from the same department, who tested negative for the virus and had no symptoms.

Twenty-eight eye care professionals from 10 hospitals contracted COVID and had pulmonary symptoms. Significant differences were found between affected professionals and controls. Those in the COVID-positive group tended to be older ($p = .01$), had practiced for longer ($p = .001$), were more likely to be sleep deprived ($p = .008$), spent more time with patients confirmed or suspected to have COVID ($p = .002$), and had less access to PPE ($p = .02$).

The incidence of symptomatic COVID among the 10 hospitals was 2.52%, and the rate of positive cases was similar for the three categories of professionals. Hospitals with the highest incidence were located closer to the Huanan Seafood Market, a purported epicenter of the outbreak. Of the 28 professionals who contracted COVID, eight had a severe case. Most cases ($n = 20$), including all that were severe, had been diagnosed before Feb. 7. There were three deaths; all were ophthalmologists who worked at the same hospital.

Given the risk of COVID-19 among eye care professionals, PPE use is highly recommended, said the authors. Once PPE use was emphasized, and patient visits were limited to urgent issues, only two cases occurred.

—Summaries by Lynda Seminara

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

IOP After Anti-VEGF Injections

September 2020

Gabrielle et al. set out to assess the impact of anti-VEGF injections on intraocular pressure (IOP) in patients seen outside of clinical trials. They found that, in most eyes, mean IOP did not change significantly from baseline following intravitreal injections. However, a small proportion of eyes—

particularly those with preexisting glaucoma—did experience clinically significant increases in IOP.

For this retrospective study, the researchers analyzed data from the Fight Retina Blindness! Project on treatment-naïve eyes that received injections of ranibizumab, aflibercept, or bevacizumab in routine clinical practice. Diseases treated included neovascular age-related macular degeneration, diabetic macular edema, and macular edema secondary to retinal vascular occlusion.

The researchers identified 3,429 treatment-naïve eyes of 3,032 patients. Participants had received at least three anti-VEGF injections and been followed up for at least 12 months; follow-up data extending to 24 months was available on 62% of the patients. The primary outcome measure was the mean change in IOP at 12 months. Secondary outcomes measured at 12 and 24 months included mean change in IOP from baseline and the proportion of patients who had a clinically significant IOP increase. The latter was defined as an increase of at least 6 mm Hg to an IOP of more than 21 mm Hg.

The overall mean change in IOP was -0.5 mm Hg at 12 months and -0.4 mm Hg at 24 months. Eyes that received aflibercept experienced a lower mean IOP change and fewer IOP elevations at the 12- and 24-month marks ($p \leq 0.01$ for each). A small subset of eyes experienced clinically significant rises in IOP; this affected 193 eyes (5.6%) at 12 months and 186 eyes (8.8%) at 24 months. Further evaluation indicated that glaucomatous eyes were more likely to experience IOP elevations following intravitreal injections. (*Also see related commentary by Matthew W. MacCumber, MD, PhD, in the same issue.*) —Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Corneal Defects Common in Wolfram Syndrome

September 2020

Knowledge of the corneal topography of patients with Wolfram syndrome

(WFS) is lacking. In a comprehensive study of the corneal features of WFS, Waszczykowska et al. found that corneal anomalies were common in both human and mouse corneas. The clinical and topographic features were similar to keratoconus. Results of immunohistochemistry confirmed wolframin expression in corneal tissue.

This study was a comparative longitudinal case series of 12 Polish patients with biallelic mutations in the *WFS1* gene and clinical symptoms of WFS. The control group consisted of 30 people with type 1 diabetes. All 42 participants underwent complete ophthalmic exams, computer videokeratography, and assessment of corneal thickness and endothelial features. Nine of the patients with WFS also had longitudinal videokeratography and Pentacam evaluation. Corneal features were documented and compared. In addition, human and murine corneas underwent immunohistochemistry and microscopic evaluation.

Clinical and topographic abnormalities, similar to those in keratoconus, were observed in 14 eyes of eight patients with WFS. The WFS and control groups differed substantially in flat keratometry, inferior-superior dioptric asymmetry, and skewed radial axis. They also differed with regard to indexes of keratoconus percentage, central keratoconus, surface variance, vertical asymmetry, height asymmetry, and height decentration. Immunohistochemistry showed wolframin expression in the human and mouse corneas. Moreover, differences in corneal thickness and epithelial features were found between *WFS1* gene knockout mice and wild-type mice.

The results indicate that many patients with WFS have a host of corneal defects that seem compatible with subclinical or early keratoconus. To the authors' knowledge, this is the first published report of these anomalies in WFS. The mechanism by which wolframin deficiency causes corneal defects is not known. Possibilities include the autophagic lysosomal pathway and high endoplasmic reticulum stress. The authors recommend routine corneal surveillance in patients with WFS, and

they encourage long-term prospective studies to better understand the findings.

National Survey of Physician Assistants in Ophthalmology September 2020

Lee et al. surveyed ophthalmic physician assistants (PAs) to define the scope of their practice and training and to gauge interest in further training and involvement. They found that most respondents want more training in vision and ocular care, hope to continue their career in eye care, and would like to join a specialty organization for PAs in ophthalmology.

The survey was developed by the Wilmer Eye Institute and the American Academy of Physician Assistants (AAPA) and included 53 questions. It was administered to PAs listed in the AAPA database as working in ophthalmology. Participation was optional, and responses were anonymous.

Of the 94 listed PAs, 47 (50%) participated in the study. Their average time as a PA in ophthalmology was 9.8 years. About 60% had no previous experience in vision and ocular health before becoming a PA. Nearly 80% provide their primary clinical duties independently. The responsibilities of 65% of respondents also include assisting with ophthalmic surgery and procedures such as intravitreal injection and chalazion drainage. Less than 25% perform intravitreal injections on their own. Only two PAs had done Nd:YAG laser capsulotomy, and none had performed laser iridotomy, laser trabeculoplasty, or panretinal photocoagulation.

The majority of respondents reported high satisfaction with their career as a PA in ophthalmology (extremely satisfied, 77.5%; moderately satisfied, 12.5%). Most participants expressed interest in further training in vision and ocular care (69%), in continuing to serve in ophthalmology (87.5%), and in joining a specialty organization for PAs in eye care (88.1%).

According to the AAPA, more than 123,000 PAs practice throughout medicine in the United States. The relatively

low percentage of PAs in ophthalmology is likely multifactorial and may include regional restrictions on duties and insufficient exposure to the field during schooling, the authors said. They believe that formal PA postgraduate programs in ophthalmology may boost interest in the field and expand the pool of PAs who are qualified to work in eye care.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

Uveal Melanoma: Disparities in Treatment and Survival

August 2020

Rajeshuni et al. studied treatment and survival patterns of patients with uveal melanoma to determine if there are inequities by race, ethnicity, or socioeconomic status. They found that non-White and socioeconomically disadvantaged patients are more likely than others to receive primary enucleation, regardless of disease stage at presentation. They found no meaningful differences in disease-specific survival rates.

For this retrospective analysis, the authors turned to the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) 18 database. Data from these 18 SEER registries represented 28% of the U.S. population between 2004 and 2014.

Socioeconomic status was estimated by tertile according to the Yost Index composite score, which includes many related variables. Because uveal melanoma is uncommon in the non-White population, non-White and Hispanic patients were combined into one group for comparison with non-Hispanic Whites. Main outcome measures were treatment odds ratios (ORs), survival rates at years 1 and 5, mortality hazard ratios (HRs), and Kaplan-Meier survival curves.

Altogether, 4,475 individuals with uveal melanoma were identified (52% male). Non-Hispanic Whites represented 92% of the study population. Multivariate analyses showed that non-White patients (OR, 1.45) and socio-

economically disadvantaged patients (lowest status OR, 2.21; middle status OR, 1.86) were more likely than others to undergo enucleation.

Although the rates of primary enucleation decreased for all racial/ethnic and socioeconomic groups from 2004 to 2014, disparities persisted. Socioeconomically disadvantaged patients had lower five-year all-cause survival rates (lowest status, 69.2%; middle status, 68.1%; upper status, 73.8%). There were no significant differences in disease-specific survival rates according to race, ethnicity, or socioeconomic status. Mortality risk was linked to older age at diagnosis (1.70 HR for age 56-68 years; 3.32 HR for age \geq 69 years) and higher disease stage (1.40, 2.26, and 10.09 HRs for stages 2, 3, and 4, respectively), as well as treatment with primary enucleation (2.14 HR).

These findings suggest the need to understand why treatment inequities have persisted, said the authors, particularly as globe-sparing therapies are now widely available. They noted that more research may “elucidate the potential role that clinicians and variation in practice patterns play in these disparities.” (*Also see related commentary by Jasmine H. Francis, MD, in the same issue.*)

Modifying Indoor Environments May Improve Dry Eye

August 2020

Most studies of dry eye syndrome involve the outdoor environment, but the ocular surface is sensitive to indoor conditions as well. Huang et al. assessed the relationship between dry eye and indoor atmosphere and found the biggest offenders to be high humidity and strong concentration of particulate air pollutants.

For this prospective cross-sectional study, the researchers included 97 veterans with a wide array of dry eye metrics. The participants were recruited from the Miami Veterans Affairs Healthcare eye clinic in 2017 and 2018. Dry eye metrics were assessed in the clinic first, then inside the home within the following week. A handheld particle counter was used for the latter. Dry

eye symptoms were documented from standard questionnaires, and physical signs were determined from ocular surface exams. Indoor environmental metrics included temperature, humidity, and the mass and count of particulate matter.

Eighty-one of the 97 participants were male; mean age was 58.2 years. Overall, their dry eye symptoms were moderate, with a mean Ocular Surface Disease Index (OSDI) score of 31.2. High humidity was correlated with worse symptoms and signs, including poorer OSDI ($r = 0.30$; $p = .01$) and Schirmer score ($r = -0.25$; $p = .03$), more inflammation ($r = 0.32$; $p = .01$), more meibomian gland dropout ($r = 0.27$; $p = .02$), and less eyelid vascularity ($r = 0.27$; $p = .02$).

In multivariate analyses, which were adjusted for demographics, comorbidities, and other factors, particulate matter of 2.5 μ m or less (PM2.5) was linked to dry eye. For example, each per-unit increase in instrumented PM2.5 level corresponded to a 1.59 increase in OSDI score ($p = .002$), a 0.39 decrease in Schirmer score ($p = .04$), a 0.07 increase in meibomian gland dropout ($p = .02$), and a 0.06 increase in inflammation ($p = .009$).

The finding of higher humidity causing dryer eyes is contradictory to studies in which low humidity was deemed the greater culprit. High humidity may increase microbial growth and the mass and size of particulate matter, said the authors. Their findings suggest that indoor environmental manipulations, such as regulating humidity and reducing airborne pollutants, may help some individuals with dry eye. (*Also see related commentary by Ian J. Saldanha, MBBS, MPH, PhD, in the same issue.*)

Using OCTA to Assess Amblyopia

August 2020

The diagnosis of amblyopia is established by exclusion, and little is known about the retinal microvasculature of this condition. Although high-resolution imaging has shed some light on microvascular issues, the clinical significance of the findings is unclear.

Wong et al. studied quantitative metrics of optical coherence tomography angiography (OCTA) in eyes with and without amblyopia to explore potential relationships with visual acuity (VA). They found that amblyopic eyes had abnormal macular microvasculature, including decreased foveal avascular zone (FAZ) circularity, lower fractal dimension, and greater vessel diameter index. The metrics associated with VA in their study were avascular zone circularity and vessel diameter index.

For this study, the authors recruited children between the ages of 6 and 8 from the population-based Hong Kong Children Eye Study. They defined amblyopia as best-corrected VA between 20/40 and 20/200 in one or both eyes, with no identifiable organic cause for the decreased vision.

Only eyes with strabismic or anisometropic amblyopia were included. For patients with bilateral amblyopia, the eye with poorer vision was used. Children with BCVA of 20/20 or better were included in the control group if a full ophthalmic exam showed no evidence of any ocular abnormality; only their right eyes were analyzed.

All participants underwent swept-source OCTA and detailed exams. Macular microvasculature of the superficial capillary plexus was quantified by a customized automated image-analysis program. Differences in OCTA metrics between amblyopic and control eyes were analyzed by multivariable linear regression, with adjustments for all known confounders. The metrics assessed were fractal dimension, FAZ area and circularity, vessel density, and vessel diameter index.

The analysis set included 30 children with amblyopia and 1,045 controls. Compared with control eyes, those with amblyopia showed decreased FAZ circularity (-0.058 ; $p = .002$), lower fractal dimension (-0.014 ; $p = .01$), and higher vessel diameter index (0.002; $p < .001$). There was no meaningful difference in FAZ area or vessel density. LogMAR visual acuity was associated with FAZ circularity ($s\beta$, -0.133 ; $p < .001$) and vessel diameter index ($s\beta$, 0.097; $p = .001$) but not with FAZ area or vessel density.

The findings suggest that children with amblyopia have morphologic anomalies in macular microvasculature; such changes are linked to poorer VA. The authors believe that OCTA and specific OCTA metrics have the potential to be reliable, objective, automated tools for recognizing amblyopia. (*Also see related commentary by Tock H. Lim, MBBS, MMed, and Colin S. Tan, MBBS, MMed, in the same issue.*)

—Summaries by Lynda Seminara

OTHER JOURNALS

Selected by Prem S. Subramanian, MD, PhD

Outdoor Time and Myopia Risk for Children Born Prematurely

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Several studies have found outdoor time to be associated with reduced myopia prevalence in children. It remains unclear if this effect is mediated directly by being outside or if hormonal changes, such as increased vitamin D from sun exposure, might be responsible. Given the high prevalence of myopia in children with a history of premature birth, Chou et al. set out to evaluate the potential role of both time outdoors and serum vitamin D levels in altering myopia risk among school-aged children born prematurely, some of whom had retinopathy of prematurity (ROP). They found that myopia prevalence was inversely associated with time spent outdoors. However, they did not find a relationship with vitamin D levels; in fact, the majority of participants were deficient in vitamin D irrespective of time spent outdoors.

For this prospective study, the researchers enrolled 99 children (99 eyes) born before 37 weeks' gestation. The mean age at assessment was 6.8 years. The children were assigned to the myopic or nonmyopic group, based on cycloplegic refraction results. The eye with the lower spherical equivalent was evaluated.

The authors looked for potential relationships between myopia status and prespecified factors, including time spent outdoors, time spent on near-

work activities, and serum concentration of 25-hydroxyvitamin D. Exposure times to different activities were estimated from information given by parents in a questionnaire.

The results showed that the mean time spent outdoors was significantly greater for children without myopia (n = 76) than for those with myopia (n = 23): 0.9 versus 0.7 hours per day, respectively. After adjusting for age and gender and incorporating demographic and other variables (e.g., ROP severity, vitamin D level, near-work time, parents' myopia status) into a multivariable logistic regression model, more time spent outside (hours/day) correlated with lower risk of myopia (odds ratio [OR], 0.13). However, mean serum vitamin D concentrations were similar for the two groups. More than half the study population (57%) was found to have vitamin D insufficiency, defined as 30-50 nmol/L.

In other findings, no significant between-group difference was seen in time spent on near-work activities or watching television. Type I ROP was associated with a higher risk of myopia (OR, 3.82), and mean axial length was significantly greater in myopic children.

The authors cautioned that their study was limited by semiquantitative data on exposure times. For children born preterm, they recommend extending outdoor time as a noninvasive intervention to possibly minimize myopia.

Physician Distress Goes Beyond Burnout: A Call to Action

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Physician wellness has become a trending topic. Reports from Canada, the United States, and elsewhere have shown soaring rates of burnout, depression, and suicidal ideation among physicians. However, "burnout" is an inadequate umbrella term that fails to capture the complex and nuanced circumstances that physicians deal with daily. In a call-to-action report, Wong describes the personal struggles, systemic dynamics, and moral suffering that physicians endure while striving to provide high-quality care with empathy

and thoughtful stewardship. Greater emphasis on training in empathy, communication, and self-care is needed to improve physician well-being, as is the development of healthier work environments.

Physician distress is influenced by personal, interpersonal, and systemic factors. For instance, the heavy focus on fact-based evidence and clinical diagnostics for decision-making has taken precedence over "soft" skills such as communication, collaboration, and advocacy.

Long work hours, the need to perform mundane or irrelevant tasks, and reduced interaction with patients also contribute to physician dissatisfaction. Moreover, lack of consistent support and recognition for efforts can lead to distress, perceived loss of autonomy, and greater cognitive dissonance.

Pressures from the current health care system to do more, ever faster and with fewer resources, can lead to frustration and obsession. The system's intense focus on cost reduction has interfered with physicians' traditional approach to making treatment decisions for patients. Economic rationality "deprives physicians of the moral experience of doctoring—to restore health and alleviate human suffering," said Wong, which is what "sustains, energizes, and engages them."

To combat the myriad factors causing burnout and distress for physicians, Wong emphasized the need for specific skills to be learned and put into practice. "By looking deeply into physician distress, we can commence the process of transforming medicine into a healthy system that acknowledges not only the condition, personhood, and struggle of the sick, but also those of physicians," said Wong. "By healing the healers and the health care system, we can return medicine back to its original fundamental core—a deeply interpersonal, relational practice that resonates with both physicians and patients about the joys and pains of living and dying, our common humanity, the purpose and meaning of life, and, ultimately, the true nature of our existence."

—Summaries by Lynda Seminara