Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

Endophthalmitis Reduction With IC Moxifloxacin Prophylaxis for Cataract Surgery

June 2017

Building on favorable findings of a single-center study, **Haripriya et al.** instituted routine intracameral (IC) moxifloxacin prophylaxis for all cataract surgeries performed in a network of regional eye hospitals in Southern India. Their subsequent study demonstrated that this prophylaxis reduced the rate of postoperative endophthalmitis by 3.5-fold.

In the expanded study, electronic health data were examined for all cataract surgeries (N = 617,453) performed in the Aravind Eye Care System during a 29-month period. Endophthalmitis rates before and after institution of IC moxifloxacin prophylaxis were determined for all eyes and separately for eyes that underwent phacoemulsification, eyes treated by manual small-incision cataract surgery (M-SICS), and cases complicated by posterior capsular rupture.

IC moxifloxacin prophylaxis was used in 51% of eyes (314,638) and not used in 49% (302,815). The rate of endophthalmitis was significantly lower for prophylaxis-treated eyes (0.02% vs. 0.07%; $p < .001$). Among the 194,252 eyes that underwent phacoemulsification, the endophthalmitis rate was 0.01% with moxifloxacin prophylaxis and 0.07% without it ($p < .001$). The respective rates of endophthalmitis for the 414,657 eyes treated by M-SICS were 0.02% and 0.07% ($p < .001$). Among eyes with capsule rupture, the rate of endophthalmitis was significantly lower for those with prophylaxis (0.21% vs. 0.48%; $p = .034$). IC moxifloxacin was not associated with any adverse events.

M-SICS accounts for a large volume of cataract surgery in developing countries. The link between vancomycin and hemorrhagic occlusive retinal vasculitis, coupled with the unavailability of IC cefuroxime in many countries, emphasizes the need for safe and effective prophylactic antibiotics for cataract surgery.

The authors concluded that prophylaxis with IC moxifloxacin is safe and reduces the rate of endophthalmitis significantly. Moreover, IC moxifloxacin proved beneficial for eyes complicated by posterior capsule rupture, and therefore should be considered in such cases.

Nepafenac 0.3% After Cataract Surgery in Patients With Diabetic Retinopathy

June 2017

Singh et al. conducted 2 randomized phase 3 trials to determine the efficacy and safety of once-daily nepafenac 0.3% ophthalmic suspension in preventing postoperative macular edema after cataract surgery. They found that the treatment reduces the risk of postoperative macular edema and has a favorable safety profile, similar to that of nepafenac 0.1% dosed 3 times daily.

In these 2 multicenter, double-masked, vehicle-controlled studies, a total of 1,220 adults with diabetic retinopathy were randomized to receive topical nepafenac 0.3% or vehicle, once daily, starting the day before cataract surgery and continuing for 90 days thereafter. Key efficacy variables were the rate of macular edema based on OCT change within 90 days following surgery and the proportion of patients whose best-corrected visual acuity (BCVA) improved by at least 15 letters from preoperative baseline value through day 14 and was maintained through day 90. Secondary variables included safety through day 90 and BCVA improvement of ≥15 letters from baseline to days 60 and 90.

In both studies, the rate of macular edema within 90 days following surgery was significantly lower for patients who received nepafenac (study 1: 2.3% vs. 17.3% with vehicle; $p < .001$; study 2: 5.9% vs. 14.3% with vehicle; $p = .001$; pooled: 4.1% vs. 15.9% with vehicle; $p < .001$). In study 1, more patients who received nepafenac experienced BCVA improvement of at least 15

letters from baseline through day 14, and maintained it through day 90 (61.7% vs. 43.0% with vehicle; p < .001); in study 2, improvement rates were comparable for the 2 groups (48.8% vs. 50.5%, respectively; p = .671).

In both studies, secondary analyses showed greater efficacy for nepafenac versus vehicle at 60 and 90 days. No unanticipated adverse events were observed in either study. The incidence of treatment-emergent adverse events (TEAE) and of serious TEAEs was similar for the 2 study arms in both trials.

Slow-Release Dexamethasone in Proliferative Vitreoretinopathy

June 2017

Recurrent retinal redetachment may occur after procedures for detachments that are accompanied by proliferative vitreoretinopathy (PVR), and efforts to identify a single effective adjunct treatment have been unsuccessful. In the first randomized controlled trial of a slow-release corticosteroid implant for treatment of PVR, **Banerjee et al.** examined the effect of dexamethasone on outcomes of vitreoretinal surgery for detachments complicated by PVR. Although the treatment did not improve the anatomic outcome, it appeared to lower the rate of postoperative cystoid macular edema (CME).

In this 2-year, prospective, double-masked trial, 140 adults with PVR undergoing pars plana vitrectomy with silicone oil tamponade for recurrent retinal detachment received either standard care (control group [no adjunct], n = 70) or injection of 0.7 mg of slow-release dexamethasone (Ozurdex) at the time of vitrectomy and when the silicone oil was removed (adjunct group, n = 70). The primary outcome measure was stable retinal reattachment at the time of oil removal, without need for additional vitreoretinal surgery during the subsequent 6 months. Secondary outcomes included final visual acuity, CME occurrence, foveal thickness, macular volume, and other endpoints.

The proportion of patients who met the primary outcome was similar for the 2 study arms (adjunct, 49.3%; control, 46.3%; p = .733). However, the implant had a limited favorable effect on the CME rate at 6 months (adjunct, 42.7%; control, 67.2%; p = .004). Fewer patients in the adjunct group had central foveal thickness >300 µm (47.6% vs. 67.7%; p = .023).

Visual acuity at 6 months was comparable for the study groups. The fact that it was not better in the adjunct group suggests that a pathologic process other than macular edema is responsible for the poor visual outcome in patients with PVR.

The investigators concluded that slow-release dexamethasone does not improve the proportion of stable retinal reattachment but may be somewhat protective against CME. They recommended that studies be performed, aimed at improving anatomic and functional outcomes, testing other adjunct treatments, and establishing the cause of visual loss in eyes with PVR.

—Summaries by Lynda Seminara

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Vitreoretinal Interface Abnormalities in Healthy Adults

May/June 2017

In a study carried out at 17 ophthalmology services throughout Spain, **Zapata et al.** assessed the prevalence of vitreoretinal interface abnormalities in a general population of healthy adults who were older than age 45. The authors found that a significant proportion—2.7%—of those evaluated showed vitreoretinal interface abnormalities. As a result, they recommend that ophthalmologists screen patients, particularly those who are older, with optical coherence tomography (OCT) during any first routine consultation or preoperative assessment.

For this cross-sectional study, the researchers evaluated 2,257 people, using spectral-domain OCT (SD-OCT) or swept-source OCT (SS-OCT). The participants' mean age was 59.5 years (range, 45-90), and a total of 4,490 eyes were evaluated. Approximately two-thirds of the participants were women (n = 1,517). The researchers used the International Vitreomacular Traction Study Group's OCT-based anatomic classification system to evaluate their findings. All images were sent to a reading center to be evaluated; a total of 227 cases were handled in this manner.

All told, vitreoretinal interface abnormalities were found in 70 eyes (1.6%) of 61 patients (2.7%), and vitreomacular adhesion was detected in 1,317 eyes (29.3%). In addition, vitreomacular traction was observed in 14 participants (0.6%), epiretinal membrane (ERM) was noted in 44 (1.9%), and lamellar macular hole was observed in 3 (0.1%). The prevalence of vitreoretinal interface abnormalities increased with age, from 0.1% in those between the ages of 45 and 55 to 7.2% in those who were 75 and older.

Limitations of the study include the use of 4 different OCT devices and different scanning protocols. In addition, the OCT reading center was established specifically for this study, and the authors acknowledge that even though the readers were meticulously trained in the international classification system, such a reading center is not as neutral or professional as a formal or commercial reading center would be.

—Summary by Jean Shaw

American Journal of Ophthalmology

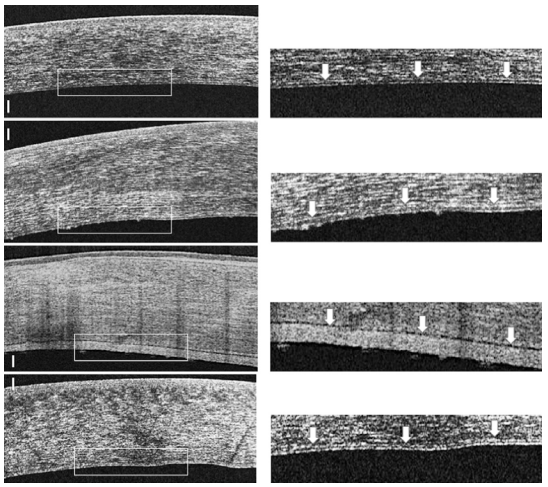
Selected by Richard K. Parrish II, MD

Early Detection of Corneal Graft Rejection

June 2017

Early detection of graft rejection is crucial to the success of corneal transplantation. **Abou Shousha et al.** assessed the utility of the endothelium/Descemet membrane (En/DM) complex in the diagnosis of corneal graft rejection and found it highly effective for this purpose.

Their diagnostic reliability study included 139 eyes imaged in vivo by high-definition optical coherence tomography (OCT). Ninety-six grafts had been used in penetrating keratoplasty or Descemet stripping automated endothelial keratoplasty (40 were clear, 23 actively rejecting, 24 rejected, and 9



GRAFT STATUS. *(Left column) These high-definition spectral-domain optical coherence tomography images show, from the top, a clear corneal graft, an actively rejecting graft, a rejected graft, and nonimmunologic failed grafts. (Right column) Presets show magnified images of the posterior part of the corresponding cornea on the left.*

were nonimmunologic failed grafts). The other 43 grafts served as healthy age-matched controls. The images obtained by OCT were used to describe the En/DM complex and to measure central corneal thickness (CCT) and central En/DM thickness (DMT). The En/DM rejection index (DRI) was computed to determine En/DM thickening relative to the entire cornea.

DMT and DRI were significantly greater in the actively rejecting grafts than in clear and control grafts ($p < .001$). Rejected grafts had the highest DMT (59 mm) and DRI (2.1) of all study groups ($p < .001$). DMT and DRI were highly accurate for differentiating actively rejecting grafts from clear grafts (100% and 96% sensitivity, respectively; 92.5% specificity for both) and for distinguishing actively rejecting from fully rejected grafts (88% and 83% sensitivity and 91% and 83% specificity, respectively). DMT and DRI differentiated nonimmunologic failed grafts from rejected grafts with sensitivity of 100% and with specificity of 88% (DMT) and 100% (DRI). DMT correlated significantly with rejection severity ($p < .001$). Both DMT and DRI were superior to CCT in terms of accuracy, sensitivity, and specificity.

Although current techniques to detect failure of corneal grafts may provide valuable clinical information, their ability to identify mild rejection and predict graft survival is limited. The authors concluded that DMT and DRI have excellent accuracy, sensitivity, and specificity for detecting the immunologic status of corneal grafts.

Concerns Reported by Patients With Glaucoma

June 2017

Mogil et al. examined the nature and degree of concerns expressed by patients with glaucoma and identified characteristics associated with those concerns. They noted various levels of trepidation about many factors affecting quality of life.

For this prospective cross-sectional study, the authors developed a comprehensive questionnaire and distributed it to patients with glaucoma, who had various stages of glaucomatous damage and a range of optic disc and visual field (VF) abnormalities. Concerns addressed by the questionnaire were grouped into 5 domains: general eyesight, socioeconomic issues, activities, visual symptoms, and other ocular symptoms (such as dryness and tearing). The severity of each concern was rated by the patient on a scale of 0 (no concern) to 5 (extreme concern).

The questionnaire was completed by 152 patients (mean age, 69 years). The VF mean deviation (MD) was –8.03 ± 7.86 dB in the better eye and –16.06 ± 10.22 dB in the worse eye. The greatest degree of concern pertained to general eyesight (2.92/5.00), followed by visual symptoms (2.78/5.00) and activities (2.20/5.00). Common specific concerns were difficulty reading small print (34%), blurry vision (32%), ocular dryness (32%), and medical costs (26%).

Concern about visual symptoms correlated with VF MD of the better eye ($r = –0.258$; $p = .001$) and worse eye ($r = –0.233$; $p = .004$). Activity-related concerns were associated with a history of glaucoma surgery ($r = 0.148$; $p = .023$) and VF MD of the better eye ($r = –0.284$; $p < .001$) and worse eye ($r = –0.295$; $p < .001$). Socioeconomic concerns correlated with age ($r = –0.260$; $p = .001$) and VF MD of the better eye ($r = –0.245$; $p = .003$). The degree of concern about general eyesight and ocular symptoms was not found to correlate with any demographic or clinical characteristic.

The researchers concluded that concerns vary widely among patients with glaucoma. Greater understanding of these concerns may help clinicians personalize the management of glaucoma, which could improve compliance.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

Ophthalmic Screening Patterns Among Youths With Diabetes

May 2017

Wang et al. assessed whether youths with diabetes are compliant with screening guidelines for diabetic retinopathy. They found that, despite having health insurance, many young patients do not receive an eye exam within 6 years of their diabetes diagnosis.

The authors' retrospective longitudinal study included 12,686 patients (≤21 years of age) with type 1 or 2 diabetes who were members of a U.S. managed care network. The time from diabetes diagnosis to first exam by an ophthalmologist or optometrist was estimated by Kaplan-Meier analysis. Multivariate Cox proportional hazards regression models were used to identify factors associated with receiving an ophthalmic exam within 6 years of the diabetes diagnosis.

Among the 5,453 patients with type 1 diabetes (median age at diagnosis, 11 years), 64.9% received an eye exam within 6 years of diagnosis. Of the 7,233 youths with type 2 diabetes (median age at diagnosis, 19 years), only 42.2% had an eye exam in this time frame.

Regression analysis showed that

black patients (n = 1,367 [10.8% of study sample]) and Latinos (n = 1,450 [11.4% of study sample]) were 11% and 18% less likely, respectively, than were white youths to have their eyes examined within 6 years of diagnosis (black youths: adjusted hazard ratio [HR], 0.89; Latino youths: adjusted HR, 0.82). Higher household net worth was associated with greater likelihood of having an eye exam within 6 years of diagnosis (net worth ≥$500,000 vs. <$25,000: HR, 1.50). Although lack of health insurance was not found to be a barrier to adherence, insurance copayment requirements may have contributed to the low rates of timely screening.

The authors concluded that more than one-third of children and adolescents with diabetes do not receive an eye exam within 6 years of diagnosis. Adherence to recommended guidelines appears especially challenging for minorities and those who are economically disadvantaged. Efforts should be made to improve the rate of timely ophthalmic screening among youths with diabetes. *(Also see related commentary by Seema Garg, MD, in the same issue.)*

Risk of Uveitis Among People With Psoriasis

May 2017

To better understand the relationship between uveitis and psoriatic arthritis, **Chi et al.** assessed the risk of incident uveitis among people with psoriasis. They found that patients with severe psoriasis and concurrent psoriatic arthritis had the greatest risk of uveitis.

This retrospective cohort study was conducted in Taiwan and included 147,954 people with mild or severe psoriasis (10,107 with concomitant psoriatic arthritis) and 147,954 nonpsoriatic controls. Patients were categorized by presence/absence of psoriatic arthritis as well as by disease severity. Patients with severe psoriasis were defined as those treated with systemic therapy and/or phototherapy; patients deemed to have mild psoriasis had not received either therapy.

The primary outcome measure was occurrence of incident uveitis. The incidence of uveitis per 100,000 person-years was calculated by dividing the number of people with incident uveitis by the number of person-years for each group. Kaplan-Meier analysis and the log-rank test were used to compare the risk of uveitis between groups. Cox proportional hazard models were used to estimate hazard ratios (HR). Because some ICD-9-CM codes may refer to subtypes of uveitis that are not considered associated with psoriasis or psoriatic arthritis, a sensitivity analysis was performed using more selective diagnosis codes.

Relative to the nonpsoriatic controls, patients with severe psoriasis plus psoriatic arthritis had the greatest risk of incident uveitis (adjusted HR, 2.40). The risk of uveitis also was higher for patients with severe psoriasis who did not have psoriatic arthritis and for patients with mild psoriasis plus psoriatic arthritis (adjusted HR, 1.42 for both groups). However, the risk was not higher among patients with mild psoriasis who did not have psoriatic arthritis (adjusted HR, 1.09). Results were confirmed by the sensitivity analysis.

The authors concluded that people with severe psoriasis and concurrent psoriatic arthritis have the greatest risk of uveitis. Findings of this study may serve as a guide for clinicians to stratify uveitis risk among patients with different inflammatory presentations of psoriatic disease. *(Also see related commentary by John A. Gonzales, MD, et al. in the same issue.)*

Ophthalmic Manifestations of Congenital Zika Syndrome

May 2017

Yepez et al. documented ophthalmic findings for infants with congenital Zika syndrome (CZS) in Colombia and Venezuela; they noted severe abnormalities, all of which were bilateral.

This prospective case series included 43 infants (mean age, 2.1 months) with microcephaly and a clinical diagnosis of CZS. The patients' mothers had no ophthalmic findings and did not report any ocular symptoms during pregnancy. All 43 infants underwent ophthalmic and systemic evaluations as well as serologic testing. Ocular examination included external assessment and dilated ophthalmoscopy. Choroidal anomalies were detected using wide-field digital imaging after pupillary dilation. Serologic testing was performed to rule out syphilis, rubella, toxoplasmosis, cytomegalovirus, and the human immunodeficiency virus.

Bilateral ocular manifestations were present in all infants. Five (12%) had optic nerve findings of hypoplasia with the double-ring sign, pallor, and elevated cup-disc ratio. Macular defects included mild to severe pigment mottling in 27 patients (63%) and lacunar maculopathy in 3 (7%). Chorioretinal scarring occurred in 3 patients (7%). Eleven infants (26%) had lesions of various types in the posterior pole. Congenital glaucoma was diagnosed in 5 patients (12%), based on the classic triad; this finding has not been previously documented for patients with CZS. The effect of these ocular abnormalities on vision is not known.

No other retinal defects were noted, and the retina was attached in all patients. No cases of uveitis were observed.

The authors concluded that CZS with microcephaly is associated with a high rate of severe macular and optic nerve defects (88%) and a substantial rate of anterior segment anomalies (12%). Bilateral ocular involvement was universal in their study. Therefore, they recommend that an ophthalmic examination be performed on all patients with CZS.

—Summaries by Lynda Seminara

OTHER JOURNALS

Selected by Deepak P. Edward, MD

Organic Retinal Prosthesis Restores Vision in Animal Study

Nature Materials

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Maya-Vetencourt et al. fabricated and validated a fully organic and biocompatible retinal prosthesis designed for long-term subretinal implantation. They tested it with mice and found that the device enabled the mice to recover light sensitivity and visual acuity, with

the benefits persisting up to 10 months following surgery.

For this study, the researchers used Royal College of Surgeons (RCS) rats, which are a preferred animal model of retinitis pigmentosa. The prosthesis comprised a flexible and highly conformable silk substrate covered with photoactive layers of conjugated polymers. As the prosthesis used no metal- or silicon-based electronics, and its sensitivity corresponded to irradiances that fell within daylight illumination levels, there was no need for a power supply or external cameras.

Restoration of visual function was evaluated at several stages of disease progression, and recovery was observed with regard to both visual cortical responses and visually driven behavior. Those improvements were accompanied by an increase in the basal metabolic activity of the primary visual cortex.

The researchers confirmed, via histochemical studies, that the improvements were not a secondary trophic effect of the implant. Instead, they concluded, the light-stimulated conjugated polymers directly activate residual neuronal circuitries in the retina. They acknowledged that a full understanding of the prosthesis' principle of operation remains uncertain, but they hypothesized that it depends on the photogeneration of long-lived excited states in the polymer layer and the subsequent interaction of these states with the retinal environment.

—Summary by Jean Shaw

Novel PCR Test to Detect Ocular Infectious Disease Pathogens

Investigative Ophthalmology & Visual Science
2017;58(3):1553-1559

In an effort to improve on current methods to detect ocular infectious diseases, **Nakano et al.** developed and evaluated a multiplex solid-phase strip polymerase chain reaction (PCR) for concurrent detection of common pathogens. They found that their novel PCR assay is simple, fast, and reliable.

The multiplex strip PCR was designed to detect 24 common ocular infectious disease pathogens, including herpes simplex virus (HSV) type 1, HSV type 2, varicella-zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), adenovirus, *Candida* species, and various types of human herpes virus (HHV). The strip PCR was tested with a negative control (distilled water) and a standard positive control (DNA). Its utility was evaluated using infectious and noninfectious ocular samples from patients. Cutoffs of quantification cycle values were determined with noninfectious ocular samples to minimize false-positive results. DNA extraction and amplification were performed in different laboratories to avoid potential contamination.

In infectious samples, the strip test rapidly and effectively detected HSV types 1 and 2, VZV, EBV, CMV, adenovirus, HHV types 6 and 7, human T-cell lymphotropic virus type 1, *Propionibacterium acnes,* bacterial 16S, *Candida* species, *Aspergillus,* fungal 28S, *Toxoplasma gondii, Chlamydia trachomatis,* and *Acanthamoeba.* Strip PCR results with distilled water were negative for all items except glyceraldehyde 3-phosphate dehydrogenase (negative DNA control). Repeatability tests demonstrated the precision of the assay. Sensitivity was comparable to that of quantitative real-time PCR and better than that of capillary-type PCR.

The authors noted that the multiplex strip PCR test for simultaneous detection of 24 ocular infectious disease pathogens is quicker and simpler than capillary-type multiplex PCR assays. They believe that the new strip will be especially useful for patients who may acquire unexpected infectious diseases, such as patients who are immunocompromised because of drug treatment or infection with the human immunodeficiency virus. A large, prospective, multicenter study of the assay is planned.

Transplantation of Induced Stem Cell–Derived Retinal Cells in AMD

New England Journal of Medicine
2017;376(11):1038-1046

Mandai et al. conducted a feasibility study in which retinal pigment epithelial (RPE) cells, prepared from autologous induced pluripotent stem cells (iPSCs), were transplanted into the right eye of a patient with age-related macular degeneration (AMD). One year postoperatively, the authors determined that the patient had an intact graft, stable visual acuity, and persistent cystoid macular edema (CME).

The patient was a 77-year-old Japanese woman with bilateral neovascular AMD (subtype: polypoidal choroidal vasculopathy) and progressive loss of visual acuity. Preoperative findings included CME, a fibrotic neovascular membrane with polyps, and a large mass under the macula. (A second patient was enrolled in the study but declined to undergo transplantation.)

Skin fibroblasts from the patient were reprogrammed to iPSCs and then were differentiated into RPE cells. This cell type was validated with sequencing and methylation profiling of the whole genome and with gene expression analyses. Protein coding regions were found to be free of large de novo insertions, deletions, and copy-number variations. No known cancer driver mutations were detected. Absence of tumorigenic potential was confirmed by injecting the RPE cells into immunodeficient mice.

The patient underwent removal of the neovascular membrane and transplantation of a sheet of RPE cells (1.3 mm × 3.0 mm) under the fovea of the right eye. CME resolved immediately after surgery but recurred 4 weeks later and persisted during follow-up, despite treatment with glucocorticoid eyedrops. Although the graft margins initially appeared curled, they flattened gradually over 8 weeks.

One year postoperatively, there was no sign of graft rejection or recurrence of the neovascular membrane. According to optical coherence tomography, the outer nuclear layer was retained on the graft sheet, and the external limiting membrane and choroid space were intact. Microperimetry indicated that the graft was functional but fixation was unstable. Visual acuity neither improved nor declined during follow-up (without additional treatment). The investigators concluded that transplantation of RPE cells was safe and feasible for this patient.

—Summaries by Lynda Seminara