

Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Stephen D. McLeod, MD

Unnecessary and Harmful Prescribing Practices: Antibiotics for Acute Conjunctivitis

August 2017

Differentiating between viral, bacterial, and other causes of acute conjunctivitis may be challenging because of similar clinical presentations. However, most patients with this condition do not require antibiotics. Shekhawat et al. looked at data in a large managed care network to determine the frequency of fills for topical antibiotics among patients who were diagnosed as having acute conjunctivitis. The researchers found that nearly 60% of the study population filled an antibiotic prescription for acute conjunctivitis and that 20% of the patients were prescribed an antibiotic-corticosteroid product, even though corticosteroids are not indicated for acute conjunctivitis.

This retrospective observational study included 340,372 patients with acute conjunctivitis who were diagnosed between 2001 and 2014. The percentage of patients who filled at least 1 prescription for a topical antibiotic within 14 days of initial diagnosis was calculated. Multivariable logistic regression analysis was used to determine demographic, medical, and other factors associated with filling these prescriptions.

Among the 340,372 participants, 198,462 (58.3%) filled at least 1 prescription for a topical antibiotic; 38,774

of these were for antibiotic-corticosteroid medications. Black and Latino patients were less likely to have an antibiotic prescription filled than were white patients, and more affluent and educated patients were more likely than their less-affluent and less-educated counterparts to have an antibiotic prescription filled.

The odds of a filled antibiotic prescription were lower if the diagnosis was made by an ophthalmologist as opposed to another provider. Fill rates did not differ between persons at risk for serious infection (such as those who wore contact lenses or had HIV/AIDS) and those without such risk.

The authors concluded that the high fill rates and frequent use of concomitant corticosteroids are potentially harmful practices that may prolong infection duration, promote antibiotic resistance, and increase costs.

Early CXL More Cost-Effective Than PKP for Keratoconus

August 2017

Although penetrating keratoplasty (PKP) is currently the most common corneal transplantation for advanced keratoconus, corneal collagen cross-linking (CXL) may prevent disease



progression in patients with early keratoconus, potentially obviating transplantation and preserving vision. Leung et al. performed a cost-effectiveness analysis in which simulated cohorts of patients with keratoconus were treated with CXL or conventional PKP. They found early treatment with CXL to be a cost-effective alternative to PKP, and they also noted that their results corroborated those of another study.

The authors created state-transition microsimulation models in which 100,000 individuals were diagnosed with keratoconus at age 25 and were managed by either modality. Health status and costs incurred were assessed monthly until death. Costs were evaluated from the perspective of a public third-party payer and included expenses for follow-up, diagnostic tests, and other procedures. Discounting of costs and health benefits (by 5%) was applied to account for expectations beyond the first year. Relative costs incurred versus quality-adjusted life years (QALYs) gained were expressed as incremental cost-effectiveness ratios (ICERs), with \$20,000 in Canadian currency (Can\$) to \$100,000/QALY considered cost-effective.

Even under conservative conditions, in which the potential costs and complications of CXL were maximized while those of PKP were minimized, early CXL proved cost-effective. The average lifetime cost of CXL was

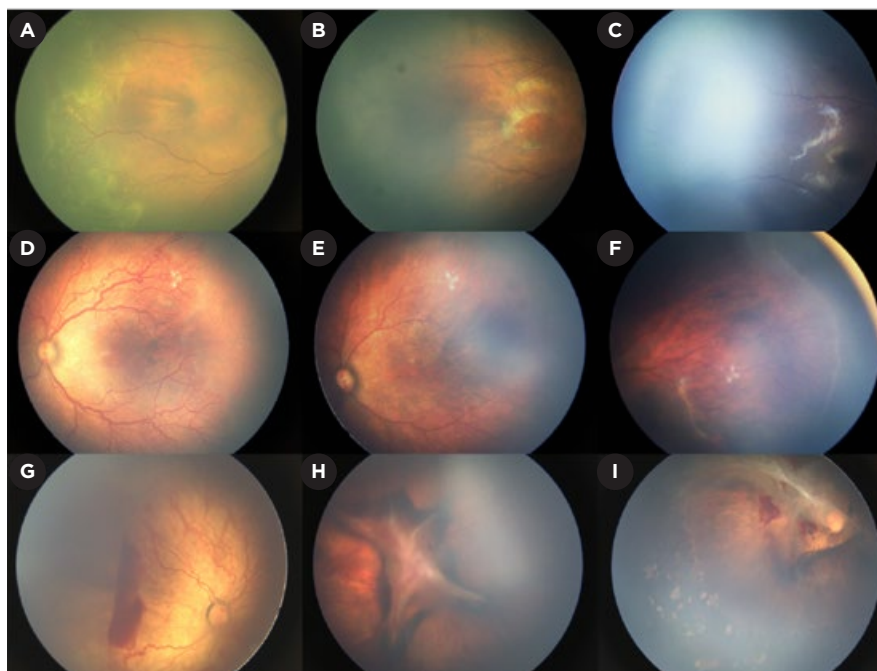
Can\$5,530, with 50.12 QALYs gained per patient (discounted: Can\$4,512, 16.42 QALYs). The cost for PKP was Can\$2,675, with 48.93 QALYs gained (discounted: Can\$1,508, 16.09 QALYs). The average discounted ICER for CXL versus PKP was Can\$9,090/QALY gained. Sensitivity analyses indicated that CXL's cost-effectiveness was superior for 40 of the 42 tested scenarios.

Treating ROP in China: Ranibizumab Proves Effective August 2017

To determine anatomic outcomes and influential factors of ranibizumab in the treatment of retinopathy of prematurity (ROP), **Huang et al.** reviewed data for infants with ROP in China who received intravitreal injections of the drug as primary therapy. They found that ranibizumab appeared to be effective in the treatment of these patients. In addition, the results indicated that patient age and ROP type may help predict the risk of disease reactivation.

For this retrospective study, the researchers included 145 patients (283 eyes) with type 1 ROP who received a single injection of ranibizumab in each eye (0.25 mg/0.025 mL, or half the adult dose) as primary treatment. Fundus photography was performed when the infants were initially screened for ROP and throughout follow-up, which continued for at least 6 months after the intravitreal injection.

A favorable response to ranibizumab was observed in 266 eyes (94%); in contrast, no response or worsening of disease was noted for 17 eyes (6%). Of those infants who responded favorably, 139 eyes had disease regression that was maintained throughout follow-up, and 127 eyes had regression with subsequent reactivation of disease. Vascular abnormalities or incomplete vascularization was noted in 8 eyes, despite absence of reactivation. At the last follow-up examination, the retina was attached in 278 eyes and detached in 5 eyes. Complications included cataract (2 eyes) and vitreous preretinal hemorrhage (1 eye). Overall, 152 eyes (54%) had laser or surgical treatment after intravitreal ranibizumab.



RESPONSE. In the regression without reactivation subgroup, this patient had zone II stage 2+ disease (A) that regressed after 1 week of treatment with intravitreal ranibizumab (B). After 40 weeks of treatment, the ROP had regressed with vascularization of zone III (C). A patient in the regression with reactivation subgroup was treated for aggressive posterior ROP (D) and experienced regression after 1 week of treatment (E). However, 9 weeks later, the disease had reactivated (F). A patient in the negative/no response subgroup was treated for aggressive posterior ROP (G). Following treatment, the posterior fibrosis worsened and the disease progressed to stage 4b (H). The patient was then treated with laser and vitrectomy; at the latest follow-up, the fibrous membrane traction was significantly released (I).

Results of classification tree modeling indicated that the likelihood of disease reactivation was 62% if ranibizumab was given at a gestational age (GA) of ≤ 29.5 weeks and only 30% if performed later. However, patients who received the drug at GA ≤ 29.5 weeks who also had zone II stage 2+ ROP had a relatively low incidence of reactivation (38% vs. 80% for other patients in this GA group).

—Summaries by Lynda Seminara

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

Laser Energy Settings and Visual Recovery After SMILE

August 2017

Although small-incision lenticule extraction (SMILE) has many benefits, recovery of visual acuity in the early postoperative period is slower than for

other refractive techniques, even with optimization of laser scanning patterns. **Ji et al.** experimented with different levels of femtosecond laser energy to assess their effect on clinical outcomes. They found that low levels (< 115 nJ) provided the best visual outcome and induced fewer corneal aberrations during the very early postoperative period.

This prospective randomized trial included 151 patients (151 eyes) who underwent SMILE for correction of moderate myopia. Fifty-eight eyes were treated with the femtosecond laser on low energy settings (100-110 nJ), and conventional energy settings (range, 115-150 nJ) were used on 93 eyes. The same surgeon performed all procedures. Complete ophthalmic exams were performed preoperatively and at the 1- and 3-month marks postoperatively.

Surgery was uneventful in all patients. Uncorrected distance visual acuity (UDVA) at day 1 and week 1 following surgery was significantly better

for the low-energy group; in contrast, substantially more corneal aberrations were induced by conventional energy at these time points. Within 1 to 3 months postoperatively, these between-group differences were not significant.

The investigators concluded that laser energy levels below 115 nJ lead to rapid visual recovery after SMILE and reduce the likelihood of corneal aberrations during the immediate postoperative period. They postulated that the lower levels may yield a better optical interface surface and emphasized that more research is needed to determine optimal laser settings for different systems and platforms.

Optimizing Glaucoma Screening in a High-Risk Population

August 2017

Zhao et al. reported first-year findings of the Screening to Prevent (SToP) Glaucoma study. Not surprisingly, the results confirm that many underserved individuals have undetected ophthalmic conditions requiring medical attention.

SToP Glaucoma is an ongoing project from the U.S. Centers for Disease Control and Prevention to implement an effective sustainable program for detecting glaucoma and other eye diseases in high-risk individuals. It focuses on African Americans who are 50 years old or older and live in inner-city neighborhoods of Baltimore. A goal of the project is to screen 9,000 individuals in a 5-year period.

The screening process is twofold. The first part occurs in a local community venue. A questionnaire is administered by trained personnel, who also assess visual acuity (VA), measure intraocular pressure, and perform digital fundus imaging and visual field testing. Individuals with positive findings are referred for subsequent (definitive) examination at the Wilmer Eye Institute. Both screenings are provided at no cost.

Of 901 people who were screened by October 2015, 95% were African American. All told, 107 (12%) required only corrective lenses, and 356 (40%) were referred for definitive diagnosis of other suspected eye conditions. Only 43% of referred individuals followed

through with the definitive exam.

The most common reasons for referral were ungradable fundus image (39% of those referred), best-corrected VA worse than 20/40 (15%), and ungradable autorefractometry (12%). The most common diagnoses established from definitive examination were glaucoma (51%) and cataract (40%). Based on the original study group of 901, the program's overall yield for significant eye disease (defined as glaucoma, cataract, diabetic retinopathy, or age-related macular degeneration) was approximately 15%.

—Summaries by Lynda Seminara

Rituximab Effective for Autoimmune Retinopathy

August 2017

Davoudi et al. set out to report outcomes for patients with autoimmune retinopathy (AIR) treated with rituximab as well as to evaluate whether adaptive optics scanning laser ophthalmoscopy (AO-SLO) is an effective monitoring tool for these patients. They found that visual acuity (VA) either improved or stabilized in the majority of the patients. They also found that AO-SLO findings remained stable during treatment; however, these results did not reach statistical significance.

For this retrospective case series, the investigators evaluated data on 16 AIR patients (30 eyes) who were examined at 1 center during 2010-2016. All were treated with a loading and maintenance dose of rituximab. In addition, all patients received ancillary testing, including electroretinograms (ERGs), visual fields, and spectral-domain optical coherence tomography (SD-OCT). A subset of patients (n = 4) had AO-SLO images that could be analyzed.

For the primary outcome, VA improved in 2 patients, stabilized in 11, and declined in 3. The variances may reflect the point in the disease course during which treatment was initiated, the authors said, as the 2 patients who experienced improvement started rituximab early on during their disease. ERG and SD-OCT parameters as well as AO-SLO cone densities were stable during treatment.

The authors noted that larger studies with longer follow-up are needed to prospectively assess the effectiveness of rituximab and the use of AO-SLO to monitor disease progression.

—Summary by Jean Shaw

JAMA Ophthalmology

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

Neurocognitive Decline Linked to Visual Field Variability

July 2017

Diniz-Filho et al. sought to determine whether cognitive dysfunction is associated with visual field (VF) variability in glaucoma. They found that global neurocognitive impairment is linked to increasing VF changes in patients with glaucoma as well as in glaucoma suspects.

For this prospective observational study, the researchers evaluated 115 patients (211 eyes) with a mean age of 67 years. The patients were followed for a mean of 2.5 years and were monitored with standard automated perimetry (SAP) during each visit. They also received longitudinal evaluation of cognitive ability with the Montreal Cognitive Assessment (MoCA), a multidomain tool designed to detect mild cognitive dysfunction.

Changes in cognitive scores were determined by calculating differences in MoCA scores from baseline to the latest follow-up visit. Hence, scores lower than baseline values indicated a decline in cognitive function. VF variability was estimated by standard deviation (SD) of the residuals of ordinary least-squares linear regressions of SAP mean deviation (MD) values over time. Linear regression models were applied to determine the potential association between cognitive decline and VF variability, with adjustment for possible confounding factors.

There was a strong association between change in MoCA scores and visual field variability over time. In a univariable model, a 5-point decline in MoCA score was associated with an increase of 0.18 dB in the SD of residuals of SAP MD values. In a multivariable

model with adjustment for baseline characteristics and test results, each 5-point decline in MoCA score coincided with an increase of 0.23 dB in the SD of residuals of SAP MD values.

The researchers concluded that the correlation between cognitive decline and increased variability of the VF suggests that monitoring cognitive function is important in the assessment of VF progression in patients with existing or suspected glaucoma. Studies with longer follow-up and more sensitive tests are warranted to gain greater understanding of this relationship and to comprehensively assess neuropsychological function. (*Also see related commentary by Joshua R. Erlich, MD, MPH, and Sayoko E. Moroi, MD, PhD, in the same issue.*)

Telemedicine Screening Increases Rates of Diabetic Retinopathy Detection

July 2017

Telemedicine is becoming vital in the assessment of diabetic retinopathy (DR), particularly in patients who live in rural areas. Research by Jani et al. suggests that telemedicine does improve the rates of DR evaluation among patients who do not have easy access to an ophthalmologist.

The authors conducted a pre- and postimplementation study at 5 primary care clinics that serve rural and underserved patients in North Carolina. The study included 1,787 adults with diabetes type 1 or 2 who received primary care at the clinics and underwent retinal telemedicine to determine the presence and severity of DR. Nonmydriatic fundus images were obtained, which were interpreted remotely by a single retina specialist (a coauthor of the study). Primary outcome measures included changes in the rates of screening and ophthalmology referrals, percentage of referrals completed, level of DR detected, and patient characteristics associated with the levels of DR.

Patients with complete data ($n = 1,661$; mean age, 55 years) were included in the statistical analysis. The mean rate of screening for DR before implementation of the telemedicine program

was 25.6%, which increased to 40.4% after implementation. Ninety-three referred patients (60%) completed an ophthalmology referral visit within the 22-month study period.

Older patients, African Americans, and other minorities were more likely to require ophthalmology referral than were their white and/or younger counterparts. The odds of referral also were greater for patients with higher hemoglobin A_{1c} levels, longer duration of diabetes, and systemic comorbidities, notably stroke or kidney disease.

The authors concluded that implementing retinal telemedicine in primary care clinics increases the rate of evaluation for DR among rural and underserved patients. They inferred that this strategy also may increase access to care among patients with DR requiring treatment. (*Also see related commentary by Daniel Shu Wei Ting, MD, PhD, and Gavin Siew Wei Tan, MD, in the same issue.*)

Atrophic Lesions and Progression in Patients With Stargardt Disease

July 2017

Strauss et al. set out to determine the incidence of atrophic lesions of the retinal pigment epithelium among patients with Stargardt disease. They found that approximately 50% of eyes without areas of definitely decreased autofluorescence at the initial visit developed an atrophic lesion within 5 years.

For this retrospective multicenter study—known as the Natural History of the Progression of Atrophy Secondary to Stargardt Disease (ProgStar) Study—the researchers assessed 217 patients (390 eyes). All of the patients had disease-causing variants in the adenosine triphosphate (ATP)—binding cassette subfamily A member 4 (*ABCA4*) gene. To be enrolled in the study, they had to meet the following 2 criteria: 1) They had to have at least 1 well-demarcated area of atrophy ≥ 300 μm in diameter, with the total area of atrophic lesions ≤ 12 mm^2 in at least 1 eye at the most recent visit, and 2) they had to have fundus autofluorescence images for at least 2 visits, with a mini-

mum of 6 months between at least 2 of these visits.

All patients were ≥ 6 years old at baseline (mean, 22 years), and the mean follow-up time was 3.9 years (range, 0.7–12.1 years). The primary outcome measure was the incidence of atrophic lesions determined by fundus autofluorescence imaging; areas of definitely decreased autofluorescence (DDAF) and questionably decreased autofluorescence (QDAF) were outlined and quantified.

At the 3-year mark, 24% of eyes that did not show DDAF on initial evaluation had developed a DDAF lesion. However, by 5 years of follow-up, approximately 50% displayed the lesion. For eyes without DDAF initially, the median time to develop a DDAF lesion was 4.9 years. Among eyes without QDAF on initial evaluation, the median time to QDAF occurrence was 6.3 years. Eyes with DDAF at the first visit were less likely than were those without DDAF to develop a QDAF lesion. The latter finding may imply that DDAF lesions grow over time but do not increase in number. In a forthcoming ProgStar study, incidence rates will be evaluated further, and structural and functional consequences will be identified.

In conclusion, the authors said, the results augment knowledge about the natural course of Stargardt disease, and they added that the fact that many eyes developed DDAF in less than 5 years suggests that the incidence of DDAF may be an appropriate outcome measure for treatment trials. (*Also see related commentary by Catherine Cukras, MD, PhD, and Brett G. Jeffrey, PhD, in the same issue.*)

—Summaries by Lynda Seminara

OTHER JOURNALS

Selected by Deepak P. Edward, MD

Teprotumumab Effective for Thyroid-Associated Ophthalmopathy

The New England Journal of Medicine 2017;376(18):1748-1761

The pathogenesis of thyroid-associated ophthalmopathy, which is commonly associated with Graves disease, is poorly

understood, and current treatments are inconsistently effective and potentially unsafe. **Smith et al.** investigated whether teprotumumab was effective at treating active ophthalmopathy. They found that the drug, a human monoclonal antibody that inhibits insulin-like growth factor I receptor (IGF-IR), was more effective than placebo in reducing proptosis and Clinical Activity Score (CAS).

This double-masked, 3-phase multicenter trial involved 87 patients (age range, 18-75 years) with ophthalmopathy who were diagnosed within 9 months after symptom onset and had a CAS tally of ≥ 4 points (out of 7) in the study eye. During the 24-week intervention phase, patients were assigned randomly to receive either 8 intravenous infusions of teprotumumab ($n = 42$) or placebo ($n = 45$), with 1 infusion delivered at baseline (10 mg/kg) and the others (20 mg/kg) delivered at 3-week intervals. The primary outcome was response in the study eye, defined as a decrease of ≥ 2 points in CAS and ≥ 2 mm in proptosis by week 24. Secondary outcomes included proptosis and CAS results (i.e., continuous variables). Adverse events (AEs) were evaluated as safety endpoints.

By week 24, 29 of 42 teprotumumab recipients (69%) demonstrated a response, versus 9 of 45 patients (20%) in the placebo group. Onset of response occurred earlier in the teprotumumab group, with 18 of 42 patients (43%) responding by week 6, versus 2 of 45 patients (4%) in the placebo group. Between-group differences increased with time. Most AEs were mild and resolved without treatment. Hyperglycemia, the only drug-related AE, was controlled with medication adjustments.

Although 1-year follow-up is ongoing, the authors concluded that 24-week teprotumumab therapy is clinically beneficial for active moderate-to-severe thyroid-associated ophthalmopathy. The comprehensive effects suggest that the therapeutic mechanism is upstream from the orbital inflammation. The U.S. Food and Drug Administration has since designated teprotumumab a breakthrough therapy.

Year 7: MUST Results Support Systemic Therapy for Uveitis

Journal of the American Medical Association
2017;317(19):1993-2005

Kempen et al., representing the Writing Committee for the Multicenter Uveitis Steroid Treatment (MUST) Trial and Follow-up Study Research Group, evaluated visual acuity (VA) among patients with uveitis who had received a fluocinolone acetonide implant or been treated with corticosteroids and supplementary immunosuppression. They observed that, during 7 years of monitoring, systemic therapy produced greater improvement in VA.

At earlier time points in the MUST randomized trial (at the 2- and 4.5-year marks), VA and systemic outcomes were similar for the 2 treatment groups. Nonprespecified extended monitoring of the study population was conducted to determine whether the treatment groups diverged in VA by 7 years.

In the initial trial, patients were randomly assigned to undergo systemic therapy or implant placement in at least 1 eye. For the extended follow-up study, patients were advised to continue their assigned treatment unless contraindicated. The primary outcome was change in best-corrected VA; the minimal clinically important difference for change in letters read was 7 letters. Secondary outcomes included ocular and systemic effects.

Of the 497 uveitic eyes originally enrolled in the MUST trial, 7-year follow-up data were available for 328 (approximately 70% of each treatment group). Change in VA from baseline favored systemic therapy by 7.1 letters; this difference was confirmed by sensitivity analyses. By 7 years, the proportion of patients with legal blindness decreased by 1% in the corticosteroid group but increased by 8% in the implant group. Patients with implants were more likely to experience visual impairment related to the chorioretinal lesion as well as glaucoma, cataract, and elevated intraocular pressure. Systemic therapy was associated with greater likelihood of infection requiring treatment.

The authors concluded that by 7 years of follow-up, systemic therapy is moderately superior to implantation in terms of VA. However, they said, the results should be interpreted with caution, as many patients from the original trial were lost to follow-up or received crossover treatment.

—Summaries by Lynda Seminara

Eyedrops Investigated for Choroidal Neovascularization

Investigative Ophthalmology & Visual Sciences
2017;58(5):2578-2590

In a preclinical study, **Cogan et al.** compared 2 methods of delivering anti-vascular endothelial growth factor (VEGF) drugs for the treatment of choroidal neovascularization: intravitreal injections and topical administration. They found that their topical eyedrops, which contained cell-penetrating peptides (CPPs) as well as an anti-VEGF drug, were as effective as intravitreal injections in delivering medication to the posterior segment of animal eyes.

In the first phase of this study, the researchers investigated CPP toxicity in 3 cell cultures: rat retinal, adult human retinal pigment epithelial, and adult human corneal fibroblast. They found no evidence of toxicity after 3 days in culture.

In the study's second phase, the researchers applied eyedrops that contained CPPs and either bevacizumab or ranibizumab to rat, mouse, and pig eyes. The results indicate that the CPP-drug complex can access retinal tissues and effectively attenuate neovascularization, matching the effectiveness of a single intravitreal injection. However, the effect of topical delivery may be short lived: In the rat model, the anti-VEGF drug was cleared from the retina by 24 hours. This suggests that daily dosing would be necessary to sustain therapeutic concentrations of the drug in the eye.

The researchers concluded that their eyedrops could have a significant impact on the treatment of neovascular age-related macular degeneration by revolutionizing drug delivery options.

—Summary by Jean Shaw