Journal Highlights

NEW FINDINGS FROM THE PEER-REVIEWED LITERATURE

Ophthalmology

Selected by Russell N. Van Gelder, MD, PhD

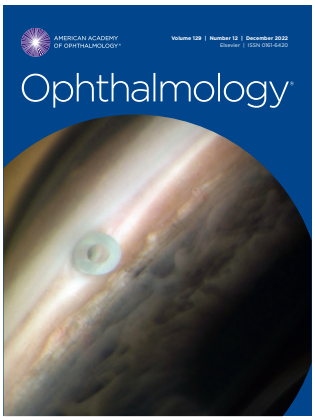
Emergency Department Usage Remains High Despite ACA

December 2022

Has the Affordable Care Act (ACA) boosted access to outpatient care and decreased reliance on emergency departments (EDs)? **Mir et al.** explored this topic and found that, for ophthalmic care, reliance on EDs for nonurgent eye conditions is still high.

For this cross-sectional study, the authors searched the U.S. Nationwide Emergency Department Sample to identify all patients who visited an ED to address an eye-related primary disorder. The database includes clinical, demographic, and socioeconomic characteristics, as well as ED and hospital costs. Each ED visit was classified as emergent, nonemergent, or indeterminate. The authors analyzed data for the pre-ACA period (2010-2013) and post-ACA period (2014-2017). The main objective was to compare national and regional incidences of ED visits per 100,000 people during the two time frames.

Altogether, there were 16,808,343 eye-related ED visits from 2010 to 2017. Of these, 8,088,203 occurred prior to the passage of the ACA, and 8,720,766 occurred after that point. Although the incidence of eye-related ED visits declined when the ACA was introduced, from 652.4 per 100,000 in 2013 to 593.0 in 2014, it climbed rapidly thereafter, to 658.5 in 2015 and to 746.6 in 2016. Patients in the lowest income quartile had the highest ED usage (964.0 per 100,000 in 2017). The percentage of uninsured patients decreased from 19% (2010-2013) to 14.3% (2014-2017). Overall, 38.3% of ED visits during the entire study period were for emergency conditions, and 44.8% were for nonemergent issues. The degree of urgency could not be determined for the remaining 16.9%.



Even though the ACA led to significantly more people being insured, the Act has not decreased reliance on EDs for ophthalmic care, as evidenced by this study. The authors acknowledged that "additional measures beyond expanding insurance coverage may be necessary to provide high-quality, efficient, and equitable outpatient ophthalmic care to all Americans."

Frailty Raises the Risk of Endogenous Endophthalmitis

December 2022

As the proportion of aging adults continues to grow, frailty is soon expected to affect all areas of medicine. In a population-based study of patients with septicemia, **Henry et al.** looked at the effect of frailty on the development of endogenous endophthalmitis (EE) and explored the clinical outcomes of patients hospitalized for septicemia. They found that among inpatients with bacteremia and EE, more than 22% had at least one characteristic of frailty.

For this retrospective cohort study, the authors included adult inpatients from the National Inpatient Sample (2002-2014) with a diagnosis of bacterial septicemia. The EE diagnosis was determined from ICD-9 codes, and the validated Johns Hopkins assessment tool was used to classify patients as frail or not frail. Multivariable logistic regression was applied to determine ORs for rates of EE development and in-hospital mortality according to frailty status. The authors also explored links between frailty and organism class (proven by blood culture), length of hospital stay, and charges billed to insurance providers.

EE occurred in 9,294 (.05%) of 18,470,658 inpatients with bacteremia. Of these, 2,102 (22.6%) had at least one frailty-defining feature. Malnutrition was the most common (68%), followed by decubitus ulcer (38%). The risk of EE development was 16.7% higher for frail patients (OR, 1.167) after controlling for age, sex, race, concomitant HIV/AIDS, pyogenic liver abscess, infectious endocarditis, cirrhosis, and chronically complicated diabetes. The likelihood of a frail patient with EE dying while hospitalized was 27.9%

higher than for healthier patients, independent of age, sex, race, or comorbidity score. Frail patients also had higher rates of methicillin resistant *Staphylococcus aureus* bacteremia (14.3% vs. 10.9%; p = .000016), gram-negative bacteremia (7.6% vs. 4.9%; p = .000003), and concurrent candidemia (10.4% vs. 7.0%; p = .0000004). Hospital stays were significantly longer for frail patients, and their insurance bills were significantly higher.

The authors recommend incorporating frailty into the existing knowledge base of EE risk factors and into future studies of EE risk stratification.

Unsupervised AI System May Predict Rapid VF Loss

December 2022

Recent advances in models of artificial intelligence (AI), coupled with greater availability of data, represent promising objective tools to assess visual field (VF) data. Models of unsupervised learning do not require large clinically annotated datasets, nor do they need human expertise. Even so, it is crucial to assess these models with input from human experts to ensure their clinical relevance and utility. **Yousefi et al.** proposed an objective approach, based on machine-identified patterns of VF loss, to identify potential rapid glaucoma progression and subsequent vision loss. Their system was capable of identifying patterns of VF loss, which may pave the way for reproducible nomenclature to characterize early signs of visual defects and rapid glaucoma progression.

For this cross-sectional longitudinal study, the researchers included 2,231 abnormal VFs from 205 eyes (176 patients) in the Ocular Hypertension Treatment Study (OHTS), which included follow-up of approximately 16 years.

The VFs were assessed by an unsupervised deep archetypal analysis algorithm and by OHTS-certified VF readers. The 18 machine-identified patterns of glaucomatous damage were compared with the expert-identified patterns. To determine the extent and severity of glaucoma in eyes within each pattern cluster, the authors calculated the average mean deviation (MD) for each cluster. Based on longitudinal data, the patterns of VF loss with strong correlation to glaucoma progression were documented. The main outcome measure was machine-expert agreement on the patterns of VF loss that signify rapid progression.

According to the analysis, the average VF MD at conversion to glaucoma was –2.7 dB (SD, 2.4 dB), and the average MD of eyes at their last visit was –5.2 dB (SD, 5.5 dB). Fifty (24.4%) of 205 eyes had an MD rate of –1 dB/year or worse and were deemed rapid progressors. The mean rate of MD decline in nonprogressing eyes was .2 dB/year (SD, +2.1). Thirteen of the 18 machine-identified patterns were similarly identified by the experts. The most common expert-identified patterns were partial arcuate, paracentral, and nasal-step defects. The most prevalent machine-identified patterns were temporal wedge, partial arcuate, nasal-step, and paracentral defects. After adjustment for covariates, one machine-identified pattern was predictive of rapid VF decline. This pattern was present in 52% of fast-progressing eyes and 9% of nonprogressing eyes.

With further refinements and larger datasets reflecting a wide range of severity, the authors believe that the system may aid in glaucoma management. —*Summaries by Lynda Seminara*

Ophthalmology Glaucoma

Selected by Henry D. Jampel, MD, MHS

Acute Angle-Closure After Mydriasis in PACS

November/December 2022

Friedman et al. evaluated the risk of acute angle-closure (AAC) attacks following pharmacologic dilation in people who were classified as being primary angle-closure suspects (PACS). They found that the risk of incident AAC was extremely low in these individuals during six years of follow-up. They also found that prophylactic laser peripheral iridotomy (LPI) reduced this risk even further.

For this study, known as the Zhongshan Angle-Closure Prevention Trial, the researchers enrolled 889 PACS with bilateral disease. Participants' mean age was 59.3 ± 5 years (range, 50-70 years of age). Patients were treated with LPI in one randomly selected eye; the other eye served as an untreated control. During the 72 subsequent months, participants had their pupils dilated six times with 5% phenylephrine and .5% tropicamide. The main outcome measures were the incidence and risk of postmydriasis AAC in LPI- and untreated eyes.

In LPI-treated eyes, one bilateral AAC attack occurred after mydriasis at the two-week post-LPI visit. No other occurrences of AAC took place in these eyes. In the control (untreated) eyes, four eyes developed AAC. Two of these four attacks occurred spontaneously, for a risk of .44 AAC events per 1,000 eye-years—and two took place following dilation (one at 54 months and the other at 72 months of follow-up), for a postmydriasis risk of one AAC attack per 1,587 dilations in untreated eyes.

Overall, the results indicate that it is generally safe for patients to undergo dilation following iridotomy, the researchers said. They also suggested that it is reasonable to consider LPI for people who require frequent dilation—although they cautioned that a full discussion of risks and benefits of LPI needs to occur with potential candidates for the procedure.

Finally, as this study evaluated Chinese subjects, the results may not be fully generalizable to other racial and ethnic groups, the researchers noted.

—*Summary by Jean Shaw*

Ophthalmology Retina

Selected by Andrew P. Schachat, MD

Myopic Foveoschisis After Vitrectomy

December 2022

Beaumont et al. set out to assess time to resolution of myopic foveoschisis (MFS) following pars plana vitrectomy (PPV). They found that most of these cases completely resolve by the end of the first postsurgical year, and they suggested that a decrease in central foveal

thickness (CFT) and early resolution of inner retinoschisis (IRS) could be used as early biomarkers of surgical success.

For this retrospective observational case series, the researchers identified patients with a diagnosis of MFS in their database (N = 131). Those who underwent surgery and were followed for at least six months were included in the analysis (n = 36; 39 eyes). The researchers measured time to resolution of four morphological criteria: CFT, IRS when present, foveal outer retinoschisis (ORS), extrafoveal ORS, and foveal detachment (FD) when present.

Anatomical success occurred in 82% of cases at the end of follow-up (mean, 14.8 ± 12.9 months) and in more than 80% cases during the first year. At the 12-month mark, CFT had decreased by at least 50 µm in 97% of eyes.

IRS occurred in 18 eyes and had fully resolved in all 18 at a median time of one month (range, 1-6 months). Foveal ORS occurred in all eyes and resolved in 82% at a median of three months (range, 1-16 months). FD occurred in 23 eyes and resolved in 91% at a median of six months (range, 1-24 months). Extrafoveal ORS occurred in all eyes and resolved in 59% at a median of 12 months (range, 1-24 months).

In their discussion, the authors noted that IRS and CFT appear to be good indicators of final surgical success—and that the slower resolution of the ORS and FD suggests the involvement of both traction and cellular dysfunction.

—Summary by Jean Shaw

American Journal of Ophthalmology

Selected by Richard K. Parrish II, MD

ICD-10 Glaucoma Grade May Underestimate the Damage

December 2022

The ICD-10 system for classifying glaucoma severity is based on the location of visual field (VF) defects. The size and depth of perimetric defects are not included in the ICD-10 guidance for grading glaucoma. Given the poor sensitivity of the 24-2 test for detecting early-stage glaucoma and macular damage, **Leshno et al.** hypothesized that the current ICD codes may not represent the full extent of glaucomatous damage. In their retrospective analysis of the validity and reliability of the ICD-10 system in relation to OCT findings, a large number of eyes with macular structural damage were missed by 24-2 VF testing alone.

The authors began their study by collecting data for participants of the Macular Damage in Early Glaucoma and Progression Study. Independent glaucoma experts who were unaware of the purpose of the study reviewed data for all eyes that received OCT, disc photography, and 24-2 VF testing performed within a six-month period. The masked experts assigned an ICD-10 severity grade based on 24-2 VF and were asked to specify which regions contained defects (i.e., superior/inferior hemifield, superior/inferior central five degrees). Other masked examiners independently determined the presence of OCT-displayed structural damage in the same regions.

Overall, 80 eyes were evaluated. Based on 24-2 VF testing, the glaucomatous optic neuropathy (GON) was classified as advanced in 42 eyes, moderate in 23 eyes, and mild in 15 eyes. According to OCT findings, GON severity was higher overall: advanced in 67 cases, moderate in seven, and mild in six. OCT showed greater severity for 29 eyes (36%). In 33 eyes (41.3%), the macular damage detected by OCT was missed by the 24-2 test. In four eyes (5%), 24-2 VF testing overestimated the severity, which may be due to the variability of this test, said the authors.

Based on these findings, OCT revealed a wider extent of damage across all grades and was able to identify macular structural damage missed by 24-2 VF testing. The ICD-10 system is an indicator of VF severity rather than glaucoma severity, said the authors, who called for clarification of the system's rationale. They believe that adding OCT data to the ICD-10 system would more accurately define the extent of glaucomatous damage. "If central involvement is to be considered a sign of severe glaucoma, it is possible to modify the current system to better assess it," they said.

Reliable AI System for DR Screening

December 2022

Mehra et al. looked at real-world outcomes after incorporating an artificial intelligence (AI)–based system into an existing primary care telemedicine diabetic retinopathy (DR) screening program. In their single-institution review, conducted at the Mayo Clinic, image gradeability was excellent, and there were no false-negative results.

For this study, the authors reviewed medical records of 1,052 adult patients who were screened for DR during an 18-month period. They gathered nonmydriatic fundus photographs and had them analyzed by the IDx-DR AI-based system, which was designed to detect greater-than-mild DR via analysis of two fundus photographs from each eye using a nonmydriatic fundus camera, in accordance with the Mayo Clinic DR screening program. For any nonmydriatic image that was not gradable, reflex dilation (1% tropicamide) and mydriatic photography were conducted before repeat AI-based analysis. Patient factors that interfered with image gradeability were analyzed, and all images underwent manual overread per the telemedicine screening protocol.

Altogether, 965 (91.7%) of the 1,052 patients had AI-gradable fundus photographs, and 580 (55.1%) had AI-gradable nonmydriatic images. Approximately 93% of patients with ungradable nonmydriatic photographs (440 of 472) had reflex dilation. Of the 965 with AI-gradable images, 138 (14.3%) were classified as positive (greater than mild disease) and 827 (85.7%) as negative. Compared with manual overread assessment of greater-than-mild nonproliferative DR, which required a comprehensive dilated eye exam, the sensitivity was 100%, specificity was 89.2%, positive predictive value was 27.5%, and negative predictive value was 100%. Few demographic variables affected the gradeability of images. The percentage of gradable images was higher for patients under 70 years of age (93.5% [61.9% nonmydriatic]) than for older patients (85.3% [31.0% nonmydriatic]) ($p < .001$).

The IDx-DR is the first AI-based system approved by the FDA for routine DR screening. Although the nonmydriatic images of older patients have a lower rate of gradeability, the authors believe that select patients of any age may benefit from having their images screened.

—Summaries by Lynda Seminara

JAMA Ophthalmology

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

Systemic Drugs and Acute Angle Closure

November 2022

Na and Park set out to identify drugs that are associated with acute angle closure (AAC) and to evaluate the risk of AAC associated with each drug. They compiled a list of 61 drugs linked to AAC development, with sumatriptan, topiramate, and duloxetine having the highest odds of this association.

For this study, the researchers turned to South Korea's Health Insurance Review and Assessment Service database, which contains medical information for the country's entire population. They used diagnostic and procedure codes to identify patients who were first diagnosed with AAC and treated between 2013 and 2019 (N = 13,531), and they collected information on all drugs that the study participants were prescribed as well as prescription dates up to 180 days before the onset of AAC. For each patient, the hazard period was defined as one to 30 days before AAC onset, and the time frame of 91 to 180 days before AAC onset served as the control period. The main outcome was those drugs associated with AAC and the odds of AAC development linked to each identified drug.

All told, 949 specific drugs were prescribed during the control period; of these, 61 were found to be associated with AAC. Of the 61, the antimigraine drug sumatriptan (OR, 12.60; 95% CI, 4.13-38.44) had the highest odds, followed by the antiepileptic topiramate (OR, 5.10; 95% CI, 2.22-11.70) and the antidepressant duloxetine (OR, 4.04; 95% CI, 2.95-5.54). In addition, several drugs not previously thought to be associated with AAC were identified, including two drugs used for gastrointestinal issues, lactulose (OR, 2.81; 95% CI, 1.72-4.61) and metoclopramide (OR, 2.52; 95% CI, 1.95-3.25).

The mean period from prescription of one of the 61 drugs to AAC onset was 11.9 days (range, 10.9-12.8). Of note, polypharmacy emerged as a potential issue: of those who were taking at least one of the 61 identified medications, 47% were prescribed three or more of the drugs on the list—and 9% were prescribed six or more. *(Also see related commentary by Paul J. Foster, PhD, Robert Luben, PhD, and Anthony P. Khawaja, PhD, in the same issue.)*

Impact of Parental Leave on Residents' Performance

November 2022

Huh et al. examined the impact of parental leave on the performance of residents at 10 U.S. ophthalmology programs. They found no difference in performance metrics between those who took parental leave and those who didn't.

For this analysis, the researchers assessed deidentified information of all residents (N = 283) who graduated from the programs between 2015 and 2019. This included data on duration of parental leave, other types of leave, and whether a resident had an extension of learning. Primary outcomes were measures of resident performance on the Ophthalmic Knowledge Assessment Program (OKAP) scores, Accreditation Council for Graduate Medical Education (ACGME) milestones scores, board examination pass rates, research activity, and surgical volumes.

Of the 283 residents, 15.5% (n = 44) took a median parental leave of 4.5 weeks (range, 2-6). Those who pursued fellowship training were less likely to take parental leave (OR, .43; 95% CI, .27-.68; p <.001). In contrast, those who practiced in private settings following their residency were more likely to do so (OR, 3.56; 95% CI, 1.79-7.08; p <.001). Only two residents extended their training (and only one used parental leave). When stratified by sex, female residents tended to take longer leave (median, 6 weeks) than did their male counterparts (median, 2 weeks).

No differences in average OKAP percentiles, research activity, average ACGME milestones scores, or surgical volume emerged between those who took parental leave and those who didn't—and following residency, the two groups showed no differences in whether they passed their written or oral board examinations on their first attempt.

In their discussion, the authors noted that the data were obtained from programs that are mainly research institutions and led by program directors willing to participate in the study. They added that they believe that it is essential that "program and institution leaders continue active discussions on establishing consistent and transparent parental leave policies and strategizing ways to reduce burden on residents."

Doxycycline for Mild Thyroid Eye Disease

November 2022

Pan et al. evaluated the efficacy of doxycycline in treating mild thyroid-associated ophthalmopathy (TAO). They found that 50 mg of oral doxycycline, given daily, resulted in greater improvement of mild TAO-related symptoms at 12 weeks compared with placebo.

For this placebo-controlled double-masked trial, 100 patients at five centers in China were randomly assigned 1:1 to receive doxycycline or placebo once a day for 12 weeks. The primary outcome was the rate of improvement at the 12-week mark compared with baseline, assessed by a composite indicator of eyelid aperture (reduction ≥2 mm), proptosis (reduction ≥2 mm), ocular motility (increase of ≥8 degrees), and improvement on the Graves ophthalmopathy–specific quality-of-life scale (≥6 points). Adverse events were recorded, and medication compliance was checked during participant interviews and by counting excess tablets.

At week 12, 19 (38%) of those in the doxycycline group had improved, versus eight (16%) of those who received placebo. With regard to adverse events,

one person in the doxycycline group experienced mild acid reflux and was switched to omeprazole.

The researchers noted that the relatively short-term duration of follow-up and small sample size warrants longer-term studies with larger cohorts. *(Also see related commentary by Jiawei Zhao, MD, and Bita Esmaeli, MD, in the same issue.)* —*Summaries by Jean Shaw*

Other Journals

Selected by Prem S. Subramanian, MD, PhD

Chemically Modified Heparin Reduces CNV

Graefe's Archive for Clinical and Experimental Ophthalmology
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Developing drugs to target the angiogenic cascade of choroidal neovascularization (CNV) may improve the life of patients with age-related macular degeneration (AMD). Although heparin is known for its antiangiogenic and anti-inflammatory properties, it has potent anticoagulant activity that may limit clinical utility. Chemically modified forms of heparin, based on deleting N- and O-sulfated groups from the structure, can maintain the drug's antiangiogenic potential while limiting interference with hemostasis. Previously, **Kniggendorf et al.** observed that a heparinoid with low content of 2-O-sulfate groups, isolated from marine shrimp, had negligible anticoagulant and hemorrhagic activities but still reduced acute inflammation and angiogenetic processes. For this study, they explored the effects of a chemically modified heparin. They confirmed that it has potent antiangiogenic, -proliferative, and -migratory effects with virtually no anticoagulant action or retinal cytotoxicity.

The compound they tested was N-desulfated Re–N-acetylated heparin. In vitro assays included cell tube formation, viability, proliferation, and migration. Endothelial cells (EC) were counted after 24 hours of treatment with the modified heparin (10, 100, or 1,000 ng/mL) or balanced saline solution (BSS; controls). In vivo assessment was performed after laser induction of CNV in rats, followed by a 5-µL intravitreal injection of modified heparin (100, 1,000, or 10,000 ng/mL) or BSS. After 14 days, the CNV underwent immunofluorescence analysis.

Relative to BSS controls, the modified heparin significantly reduced cell proliferation, tube formation, and migration, but it did not alter cell viability. Within 24 hours of in vitro treatment, all quantities of the heparin solution significantly inhibited EC proliferation ($p = .0011$); the higher dose was significantly more effective than either of the lower doses ($p < .05$). In vivo intervention yielded mean CNV measurements that were significantly smaller ($p = .0065$) with modified heparin: 54.84×10^6 pixels/mm with 100 ng/mL, 58.77×10^6 pixels/mm with 1,000 ng/mL, and 59.42×10^6 pixels/mm with 10,000 ng/mL. The mean CNV area in the control group was 72.23×10^6 pixels/mm. Mean perimeter values also were significantly better with the heparin solution ($p = .0235$).

Based on the findings, the authors believe that this form of heparin may be a candidate for treatment of neovascular AMD and other angioproliferative diseases.

Apraclonidine Is an Eye Opener

Frontiers in Ophthalmology
Published online Aug. 9, 2022

Apraclonidine reverses anisocoria and is often preferred to cocaine for confirming Horner syndrome. It also raises the upper eyelid and thus may help if the pupillary response to pharmacologic testing is equivocal. **Fierz et al.** conducted a quantitative study of eyelid aperture effects in Horner syndrome and found changes in eyelid opening to be a promising diagnostic adjunct.

Their investigation included adults referred to the neuro-ophthalmology unit of a university hospital for evaluation of anisocoria during a three-year period. Qualifying participants received binocular pupillometry before and after testing with 1% apraclonidine eyedrops (one drop in each eye). Pupillometry was performed on each eye simultaneously and in synchrony.

The diagnosis of Horner syndrome was based solely on apraclonidine response, irrespective of any causative lesion, ptosis, or heterochromia. Pupillary size was measured before and after instillation of apraclonidine and was expressed as the median size from three to four seconds after lights off, derived from the pupillometry reading. The apraclonidine test was deemed positive (indicating Horner syndrome) if the smaller pupil dilated and the larger pupil constricted.

Infrared video recordings obtained during pupillometry were analyzed by customized software. Eyelid aperture was measured manually and reflected the distance between the two eyelids, using a pre-set vertical line at the pupillary center. These measurements were attained in a fixed interval, within the first five seconds of lights off while blinking was avoided. Several readings from individual pupillometry cycles were averaged, and inter-eye differences in vertical aperture were calculated. Receiver operating characteristic curves were used to determine the optimal cutoff value for eyelid aperture change before and after apraclonidine.

Two of 38 qualifying participants were excluded because dermatochalasis obscured their eyelid margin, preventing accurate measurements. Half of the remaining 36 patients had a positive result with apraclonidine, indicating Horner syndrome. The others were considered to have physiologic anisocoria. A decrease in inter-eye aperture difference of at least .42 mm characterized Horner syndrome and distinguished it from physiological anisocoria, with sensitivity of 80% and specificity of 75%. The mean increase in eyelid aperture was 2.01 mm in eyes with Horner syndrome and 1.08 mm in unaffected eyes. The eyelid-raising effect of apraclonidine was more pronounced in eyes with a sympathetic denervation deficit.

"Measuring eyelid aperture on pupillometry recordings may improve the diagnostic accuracy of apraclonidine testing in Horner syndrome," said the authors. They believe that combining pupil and aperture measurements could further optimize accuracy.

—*Summaries by Lynda Seminara*