

**RESIDENT / FELLOW
RESEARCH DAY**

**Department of Ophthalmology
and Visual Sciences**

~

**Roy J. and Lucille A. Carver
College of Medicine**

University of Iowa Hospitals & Clinics

Iowa City, Iowa



Braley Auditorium, 01136 Lower Level, Pomerantz Family Pavilion

Friday, May 13, 2016



RESIDENT/FELLOW RESEARCH DAY – 2016

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Lindsay K. McConnell, M.D.
Matthew A. Miller, M.D.
Lorraine A. Myers, M.D.
Tyler B. Risma, M.D.

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GUEST FACULTY

EMILY Y. CHEW, M.D.

Emily Y. Chew, M.D. is the Deputy Director of the Division of Epidemiology and Clinical Applications (DECA), at the National Eye Institute, the National Institutes of Health in Bethesda, Maryland. She is also the Chief of the Clinical Trials Branch within the Division. She received her medical degree and her ophthalmology training at the U. of Toronto, School of Medicine, in Toronto, Canada. She completed her fellowship in Medical Retina at the Wilmer Eye Institute, the Johns Hopkins Medical Institutes and the U. of Nijmegen, the Netherlands.

Her research interest includes phase I/II clinical trials and epidemiologic studies in retinovascular diseases such as age-related macular degeneration, diabetic retinopathy, ocular diseases of von Hippel-Lindau Disease and others. She worked extensively in large multi-centered trials headed by the staff of NEI/NIH including the Early Treatment Diabetic Retinopathy Study, the Age-Related Eye Disease Study and the Age-Related Eye Disease Study 2, which she chairs. She also chairs the Actions to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study in participants with type 2 diabetes, working in collaboration with colleagues at the National Heart, Lung, and Blood Institute/NIH. Emily is also the director of the clinical program in the Macular Telangiectasia Project (Mac Tel Project) which is an international study conducted in 22 clinics in 7 countries along with 4 basic science laboratories.

Emily is also the director of the medical retina fellowship at the NEI. Along with the team in the Clinical Trials Branch, she provides the clinical training as well as education in conducting clinical trials. She is a member of the editorial board of Ophthalmology, IOVS and Retina.

OPHTHALMOLOGY RESIDENT/FELLOW RESEARCH DAY

SCHEDULE OF EVENTS

Friday, May 13, 2016, 7:30 AM - 3:05 PM

- 8:00 Coffee
- 8:30 Welcoming Statements
- 8:35 **Edwin M. Stone**, Wynn Institute For Vision Research – Hot research topics

9:00 – 10:00 Scientific Papers, Residents, Session I

Braley Auditorium

- 9:00 **Tyler B. Risma**, sponsors, Tony Klauer, Scott A. Larson, M.D., Erin M. Shriver..... 1
A Retrospective Review of Diplopia after Orbital Trauma
- 9:10 **Lorraine A. Myers**, sponsors, Aaron Fairbanks, Nasreen A. Syed 2
Investigating the clinical value of Urine β -2 microglobulin (U β 2M) levels in patients with tubulointerstitial nephritis and uveitis (TINU)syndrome
- 9:20 **Matthew A. Miller**, sponsors, Li Zhang, Kyungmoo Lee, Milan Sonka, Michael D. Abramoff..... 3
Automated Intraretinal Layer Segmentation of 3-D Macular OCT scans
- 9:30 **Lindsay, K. McConnell**, sponsor, Erin M. Shriver 4
Analysis of Conjunctival Map Biopsies in Sebaceous Carcinoma
- 9:40 **Thomas J. Clark**, sponsors, Wesley J. Klejch, Richard C. Allen, Jeffrey A. Nerad, Keith D. Carter, Erin M. Shriver..... 5
Hering's Law in Congenital Ptosis: Evaluation of the Contralateral Response to Unilateral Congenital Ptosis Repair
- 9:50 **Prashant K. Parekh**, sponsors, James C. Folk, Stephen R. Russell, Elliott H. Sohn, Michael D. Abramoff..... 6
Does Fluorescein Angiography Add Value in the Management of Suspected Choroidal Neovascularization?

10:00 – 10:30 Morning Break

10:30 – 11:10 Scientific Papers, Resident/Fellow, Session II

Braley Auditorium

- 10:30 **P. Christi Carter**, sponsors, Mark A. Greiner, Chase A. Liaboe..... 7
Assessing the Impact of Diabetes Mellitus on Donor Cornea Transplant Suitability

OPHTHALMOLOGY RESIDENT/FELLOW RESEARCH DAY

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10:50	Jiaxi Ding , sponsors, Daniel I. Bettis, Alan L. Robin, Suman Thapa, Chris A. Johnson,	9
	Utilizing Tele-Ophthalmology and Table Technology for Glaucoma Screening and Visual Field Assessment	
11:00	Matthew Weed , sponsors, Miriam Di Menna, Christina L. Donaghy, Dimitra Triantafilou, Scott A. Larson,	10
	Long-Term Surgical Outcomes for Large-Angle Esotropia in Children Utilizing Tele-Ophthalmology and Table Technology for Glaucoma Screening and Visual Field Assessment	

11:10 – 12:00

Keynote Speaker

Emily Y. Chew - Braley Auditorium

12:00-1:00

Buffet Luncheon

Melrose Conference Room 1 and 2

1:00	Randy H. Kardon , VA Center for Prevention and Treatment of Vision Loss – Hot Research Topics
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1:25 – 2:25

Fellow Scientific Papers, Fellows, Session III

Braley Auditorium

1:25	Chauni Van , sponsors, Geeta Lal, Nasreen A. Syed, Culver H. Boldt.....	11
	Extracellular matrix 1 (ECM1), a Potential Prognostic Marker for Uveal Melanoma is not Expressed in Primary Tumors at the Protein Level	
1:35	Jessica S. Watson , sponsor, Stephen R. Russell.....	12
	Long Term Followup of Ocular Histoplasmosis in the Anti-VEGF Era	
1:45	Andrew R. Carey , sponsor, Stephen A. Russell.....	13
	Cost-Benefit Comparison of Intravitreal anti-VEGF Injections for Neovascular Age-Related Macular Degeneration on a Treat-And-Extend Regimen	

**OPHTHALMOLOGY RESIDENT/FELLOW RESEARCH DAY
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2:15	Harinderpal S. Chahal , sponsor, Erin M. Shriver	16
	The Role of Scleral Contact Lenses in the Oculoplastic Patient	

2:25 – 2:35

Faculty Meeting/Judging For Research Day Awards

RESIDENT / FELLOW RESEARCH DAY – 2016

Morning Session: Paper 1

A Retrospective Review of Diplopia after Orbital Trauma

Tyler B. Risma, M.D.

Primary Supervisors: Tony Klauer, Scott A. Larson, M.D., Erin M. Shriver, M.D.

Background: Orbital trauma can have many debilitating consequences, and diplopia is commonly associated with orbital trauma. In many cases of orbital trauma the diplopia is self-limited, however some result in persistent strabismus and require surgical realignment which can be both clinically and surgically challenging for the strabismus surgeon. Orbital trauma can cause strabismus by multiple mechanisms including paretic strabismus from nerve or muscle trauma or ischemia; restrictive strabismus from fractures and scar tissue; and altered orbital anatomy. By identifying the predisposing factors that may lead to persistent diplopia and strabismus after orbital trauma in a large group of patients, we may be able to help the clinician make more informed decisions in the management of orbital fractures and subsequent strabismus.

Methods: IRB approval was obtained. Charts were reviewed from all patients seen at UIHC between 1995 and 2015 with the diagnosis of orbital trauma and diplopia (ICD 9 codes of 801.00, 801.01, 801.03, 801.04, 801.05, 801.06, 801.09, 802.4-9) (N=404). When available, the following information was gathered from the chart review: initial and postoperative visual acuity, age at presentation, smoking status, the presence of symptomatic diplopia in primary and/or downgaze, restriction on forced ductions, presence of enophthalmos (>2mm), fracture location, the presence or absence of radiologic evidence of extraocular muscle entrapment, surgical approach and implant type, time from injury to repair, pre and postoperative strabismus measurements, type of strabismus surgery performed with notes of any evidence of extraocular muscle flap tear.

Results: The patients were predominantly male (73.0%) and young (mean 35.0 years). At an interim analysis of 115 of these patients, 45.2% of patients underwent no surgery, 34.7% orbital surgery alone, 6% strabismus surgery alone, and 13.9% underwent both orbital and strabismus surgery. Patients with horizontal deviations at baseline were most likely to improve regardless of intervention. Patients with vertical deviations at baseline were significantly less likely to improve with observation when compared to the groups of patients who had orbital and/or strabismus surgery ($p = 0.007, 0.03, \text{ and } <0.0001$)

Conclusions: Here we present an interim analysis of a 20 year cohort of patients seen at UIHC with orbital trauma and diplopia. Early results suggest that vertical deviations are less likely to resolve without surgical intervention (orbital and/or strabismus surgery). Further investigation into fracture location, radiologic characterization of fracture size, and a complete analysis of the entire study group may reveal additional correlations which can help the orbital and strabismus surgeons evaluate appropriate patient identification and timing for surgical repair.

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Morning Session – Paper 2

Investigating the clinical value of urine β 2-microglobulin (U β 2M) levels in patients with tubulointerstitial nephritis and uveitis (TINU) syndrome

Lorraine A. Myers, M.D.

Primary Supervisors: Aaron Fairbanks, B.S., Nasreen A. Syed, M.D.

Background and Purpose: Studies indicate that laboratory testing of U β 2M and urinalysis increase the sensitivity of diagnosis for TINU syndrome. The literature also indicates that the course of the uveitis and the nephritis in this syndrome appear independent of one another. There is a paucity of data on whether specific tests may help predict the course of the uveitis in this condition, which is often the more chronic, relapsing component compared with the nephritis. We seek to determine whether U β 2M levels provide useful information on the course of uveitis i.e. severity, duration, or relapse. Early identification of patients at risk for a complex course may reduce long-term complications associated with chronic uveitis.

Methods: IRB-approved, retrospective review of patients with TINU syndrome treated at the University of Iowa from 2009 - 2015. A uveitis score was used to quantify the degree of inflammation.

Results: Nine patients were identified. Mean age was 35y (range 9-81y), 5 female, 8 Caucasian. Common presenting complaint(s): redness (89%), decreased vision (78%), photophobia (78%); 44% had bilateral, sequential onset. Of 18 eyes, initial visual acuity (VA) was $\geq 20/25$ in 50% and $\geq 20/50$ in 94%. Mean U β 2M was 7,351 $\mu\text{g/L}$, (range 1,069-17,494 $\mu\text{g/L}$). Mean U β 2M was 11,547 $\mu\text{g/L}$ for adults ($\geq 18\text{y}$) and 2,107 $\mu\text{g/L}$ for those $< 18\text{y}$. Serum creatinine was normal in 4 patients, and 7 had 0-trace protein on urinalysis. Uveitis scores ranged from 0-6. When grouped into $> 18\text{y}$ or $\leq 18\text{y}$, U β 2M levels trend with the uveitis score. Follow-up ranged from 0.48–5.1y, and 4 patients had uveitis scores > 0 at last follow up. Final VA was $\geq 20/25$ in 89% of eyes.

Conclusions: TINU is a disease that affects all ages. Uveitis symptoms are classic, involvement is often sequential, and renal involvement can be asymptomatic. A genitourinary review of systems (ROS) should be performed in all uveitis patients. Adults may present with more severe renal disease. Serum creatinine and urinalysis can be normal. U β 2M is a useful diagnostic tool and appears to trend with the degree of uveitis, which is often chronic. Visual prognosis is good.

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Morning Session – Paper 3

Automated Intraretinal Layer Segmentation of 3-D Macular OCT Scans

Matthew A. Miller, M.D.

Primary Supervisors: Li Zhang, M.D., Kyungmoo Lee, M.D., Milan Sonka, M.D., Ph.D., Michael D. Abràmoff, M.D., Ph.D.

Purpose: Intraretinal layer segmentation is of paramount importance to monitor the progress of retinal diseases including changes to the retinal nerve fiber layer, choroidal neovascularization, and diabetes. The purpose of this study is to develop and validate a fully automated method that can automatically segment 12 intraretinal surfaces, including a new virtual surface allowing detection of pigment epithelial detachment (PED), in 3-D macular optical coherence tomography (OCT) scans.

Methods: Eighty macular OCT scans were obtained from one eye of normal subjects using a Cirrus™ HD-OCT machine (Carl Zeiss Meditec, Inc., Dublin, CA). The 3-D graph search method hierarchically detected 12 retinal surfaces using simple 1D gradient magnitudes of the OCT volumes. The accuracy of segmented retinal surfaces in terms of unsigned border positioning error and absolute layer thickness will be evaluated by comparing to reference standards created by manual segmentation by two experts of all 10 slices in each of 80 OCT scans.

Results: We anticipate the differences between the full-automated segmentation algorithm and reference standards obtained from manual segmentation to be small.

Conclusions: We hypothesize that the proposed method will be able to automatically segment 12 intraretinal layers from 3-D macular OCT scans comparably to two expert ophthalmologists on this dataset in terms of unsigned border positioning error and layer thickness. We anticipate validation of this model will allow for reliable study of intraretinal changes and may improve the diagnosis and management of patients with ocular diseases involving the retina.

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Morning Session: Paper 4

Analysis of Conjunctival Map Biopsies in Sebaceous Carcinoma

Lindsay K. McConnell, M.D.

Primary Supervisor: Erin M. Shriver, M.D.

Background/Purpose: To evaluate the need for standardized conjunctival map biopsies in periocular sebaceous carcinoma and to formulate recommendations regarding map biopsy number, location, size, and utility based on analysis of biopsy locations, results, and outcomes.

Methods: Retrospective consecutive series of patients with sebaceous carcinoma treated at a tertiary care hospital from 1988 to 2013. Main outcome measures included conjunctival biopsy locations, number, size, and pathology.

Results: A diffuse eyelid pattern was evident on presentation in 28/51 patients (54.9%) versus a solitary eyelid nodule in 23/51 (45.1%). Forty-five patients underwent a total of 429 conjunctival biopsies. The conjunctiva was negative in 277 specimens (64.6%), positive in 121 (28.2%), suspicious in 26 (6.1%), and nondiagnostic in 5 (1.2%). Intraepithelial conjunctival involvement was present in 36 patients (70.6%) of whom 23 (63.9%) presented with a diffuse eyelid appearance. There was no statistically significant correlation between primary tumor location and sites of positive biopsies or biopsy size. The pattern at presentation and location of primary tumor did not correlate with biopsy results. Clinical assessment regarding conjunctival involvement was incorrect in 10 of 23 patients (43.5%) with a solitary nodule. Despite primary tumor resection with clear margins confirmed on pathology, 5 of 45 (11%) patients had locally recurrent sebaceous carcinoma.

Conclusions: Conjunctival biopsy size does not correlate with the presence of tumor in the biopsy. Primary tumor location and pattern of tumor at presentation do not correlate with conjunctival biopsy results. Irrespective of the clinical tumor features, standardized conjunctival map biopsies are essential in staging periocular sebaceous carcinoma.

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Morning Session: Paper 5

Hering's Law in Congenital Ptosis: Evaluation of the Contralateral Response to Unilateral Congenital Ptosis Repair

Thomas JE Clark, M.D.¹

Primary Supervisors: Wesley J Klejch, B.S.²; Richard C. Allen, M.D., Ph.D., FACS³; Jeffrey A. Nerad, M.D., FACS⁴; Keith D. Carter, M.D., FACS¹; Erin M. Shriver, M.D., FACS¹

¹*Department of Ophthalmology and Visual Sciences, University of Iowa, Carver College of Medicine, Iowa City, IA;* ²*University of Iowa, Carver College of Medicine, Iowa City, IA;* ³*MD Anderson Cancer Center, Houston, TX;* ⁴*Cincinnati Eye Institute, Cincinnati, OH*

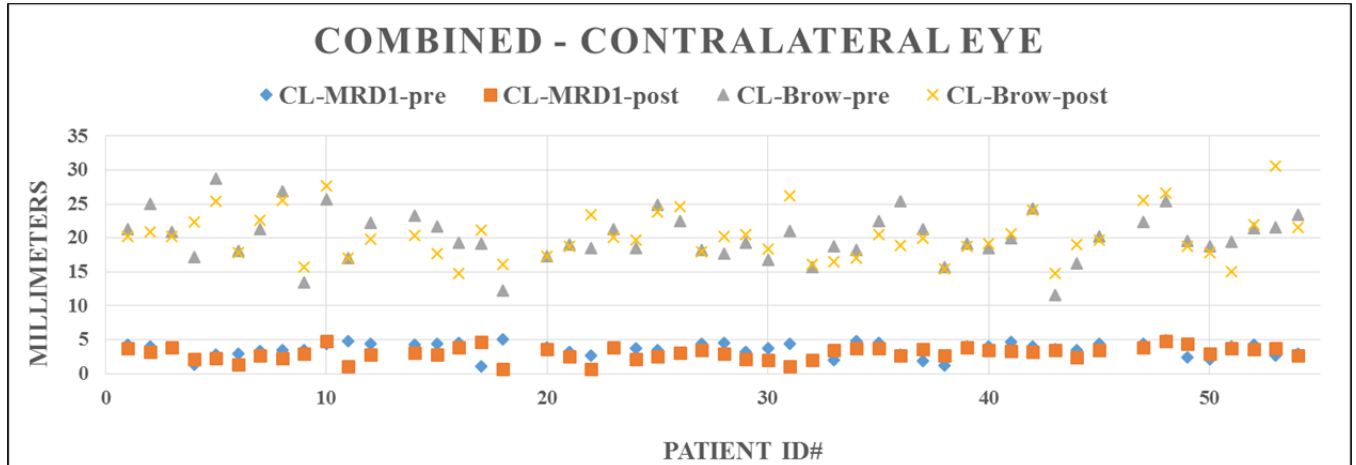
Purpose: To evaluate outcomes of unilateral congenital ptosis repair both on the operated and contralateral upper eyelid and brow. To understand the effect of Hering's Law in unilateral congenital ptosis in order to assess the need for bilateral surgery. To assess the role of brow elevation, a potential confounding variable, in final upper eyelid height.

Methods: Retrospective chart review and digital photo analysis of patients who underwent unilateral congenital ptosis repair by three surgeons (JAN, RCA, EMS) at the University of Iowa Hospitals and Clinics between January 1990 and February 25, 2015. Pre- and post-operative photographs were evaluated for eyelid height (MRD1) and brow position bilaterally using ImageJ analysis software. Measurements were extrapolated using a standardized limbus to limbus distance. Patients were eliminated from the study if they had less than 6 months of post-operative follow-up or if their photographs were not adequate for image analysis. IRB approval was obtained.

Results: A total of 82 patients underwent unilateral congenital ptosis repair by one of the three surgeons during the designated time frame and 51 of these patients met the study inclusion criteria in terms of length of post-operative follow-up as well as image clarity and orientation. The 51 patients evaluated ranged in age from 5 months to 24 years and had an average post-operative follow-up period of 9 months. The overall mean elevation in the surgical eyelid post-operatively (as measured by image derived margin-reflex distance-1 (iMRD1)) was 1.1 mm (SD = 1.5 mm). The mean descent of the non-operative eyelid was 0.55 mm (SD = 1.3 mm) with 29% (n = 15) demonstrating a greater than 1 mm descent. Within each surgical subset, the mean changes in operative and non-operative upper eyelid heights were +0.83 mm (SD = 1.7 mm) and -0.82 mm (SD = 1.2 mm) for the frontalis sling (n = 12), +1.2 mm (SD = 1.3 mm) and -0.65 mm (SD = 1.5 mm) for the levator resection or advancement (n = 31), and +1.1 mm (SD = 2.0 mm) and +0.24 mm (SD = 0.91 mm) for the Mueller's muscle conjunctival resection (n = 8). Post-operatively, the mean difference in upper eyelid height between the operated and non-operated upper eyelids was 1.2 mm (SD = 1.2 mm) compared to 2.7 mm (SD = 1.5 mm) pre-operatively. No patients underwent subsequent ptosis repair on the contralateral eyelid. The ipsilateral and contralateral brow positions remained stable with overall mean elevations of 0.04 mm (SD = 3.0 mm) and 0.14 mm (SD = 2.8 mm) respectively. Mean changes in ipsilateral and contralateral brow position for the frontalis sling, levator resection or advancement, and Mueller's muscle conjunctival resection procedures were -0.44 mm (SD = 3.0 mm) and -0.19 mm (SD = 2.59 mm), +0.10 mm (SD = 3.0 mm) and +0.11 mm (SD = 2.6 mm), and +0.51 mm (SD = 3.6 mm) and +0.76 mm (SD = 4.0 mm) respectively.

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Conclusions: Following unilateral surgical repair of unilateral congenital ptosis, the contralateral upper eyelid height, on average, demonstrates a small amount of descent that is likely a result of Hering's law. Although the degree of descent is statistically significant, the clinical relevance is likely small as no patients underwent subsequent contralateral ptosis repair. This may be due to the fact that adequate symmetry between the operated and non-operated upper eyelids was routinely achieved. Evaluation of brow position confirmed that compensatory brow elevation did not play a significant role in the post-operative eyelid height. Unilateral surgical intervention is an appropriate treatment strategy for the correction of unilateral congenital ptosis.



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Morning Session: Paper 6

Does Fluorescein Angiography Add Value in the Management of Suspected Choroidal Neovascularization?

Prashant K. Parekh, M.D., M.B.A.

Primary Supervisors: James C. Folk, M.D., Stephen R. Russell, M.D., Elliott H. Sohn, M.D., Michael D. Abramoff, M.D., Ph.D.

Background/Purpose: Fluorescein angiography (FA) has long been the standard modality to diagnose and manage choroidal neovascularization (CNV), and is a requirement for Medicare reimbursement for managing this condition. However, FA is costly, has a mortality of 1 per 220,000 and considerable morbidity from allergic reactions. Since the advent of anti-VEGF therapy for CNV, optical coherence tomography (OCT), a non-invasive imaging method free of these disadvantages, is used extensively to manage CNV, while FA is primarily used to make the initial diagnosis. A recent study found the sensitivity and specificity of OCT compared to FFA in diagnosis of CNV to be 100 and 80.8%, respectively¹. We hypothesize that FA changes the management of patients that are initially suspected of having CNV in less than 10% of cases. If this hypothesis is confirmed, it would cast doubt on the clinical utility as well as cost-effectiveness of FA for diagnosing CNV.

Methods: We retrospectively reviewed the clinical histories, fundus photos, FA, and OCT of 99 initial visits from 99 patients (99 eyes) who had an initial presentation of later confirmed CNV. After de-identification, retinal specialists—masked to each other—reviewed, in randomized order, the standardized brief clinical history, the posterior pole color fundus image, and complete OCT scan of the initial visit. They then chose whether to manage each case by observation or anti-VEGF injection (FA-arm). After re-randomization, corresponding early, mid, and late phase FA images were added to each patient's case data, and the experts again chose from these 2 management options (FA+ arm). We determined for each expert, the case concordance (i.e., the percentage of cases where the management decision agreed between FA- and FA+) and inter-observer concordance (i.e., percentage of cases where both experts agreed). Statistical analysis was then performed to determine the reliability of decision-making.

Results: For our experts, the intra-observer reliability was 0.92 (95% CI 0.88-0.94) and 0.89 (95% CI, 0.84-0.92). The kappa coefficient was 0.77 (95% CI 0.68-0.86). The case concordance for the FA- arm was 0.85 (95% CI 0.78-0.89) and 0.88 (95% CI 0.83-0.92) for the FA+ arm.

Conclusion: Our data indicates that there was no statistically significant difference in the management of suspected CNV, whether or not FA was utilized as a diagnostic modality. There was a strong level of inter-rater reliability between the retinal experts. Although there is a certain degree of intra-observer variability in clinical decision-making, this was minimal (less than 5%). These preliminary data support the common trend among retinal specialists to defer utilization of FA for the management of CNV, except in treatment failures or non-standard cases.

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References:

1. Wilde C, Patel M, Lakshmanan A, et al. The diagnostic accuracy of spectral-domain optical coherence tomography for neovascular age-related macular degeneration: a comparison with fundus fluorescein angiography. *Eye (Lond)*. 2015;29(5):602-9.
2. Chhablani J, Deepa MJ, Tyagi M, Narayanan R, Kozak I. Fluorescein angiography and optical coherence tomography in myopic choroidal neovascularization. *Eye (Lond)*. 2015;29(4):519-24.
3. Chhablani J, Mithal K, Rao H, Narayanan R. Diagnosis of subretinal neovascularization associated with idiopathic juxtafoveal retinal telangiectasia - fluorescein angiography versus spectral-domain optical coherence tomography. *Graefes Arch Clin Exp Ophthalmol*. 2014;252(4):549-53.

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Morning Session: Paper 7

Assessing the Impact of Diabetes Mellitus on Donor Cornea Transplant Suitability

P. Christi Carter, M.D.

Primary Supervisor: Mark A. Greiner, M.D.

Medical Student: Chase A Liaboe, BA

Background: As the rate of diabetes mellitus increases, and with evidence that diabetes impairs corneal endothelial cell health, it is necessary to assess this disease's impact on tissue suitability for keratoplasty.

Purpose: To report the prevalence of diabetes mellitus (DM) among cornea donors at Iowa Lions Eye Bank (ILEB); to determine the impact of DM on donor endothelial cell health.

Methods: A retrospective review was performed of donor records for all corneas recovered in 2014-15. Donor tissues were grouped by donor diabetes status (DM+ or DM-). For all corneas cleared for surgery, we analyzed suitability for endothelial keratoplasty and/or penetrating keratoplasty (TS=suitable, NTS=non-suitable) and endothelial cell density before graft preparation (ECD, cells/mm²) between groups.

Results: Of 1884 donors, 598 (31.7%) were DM+. Among corneas included for analysis (N=3094), NTS status was more prevalent in the DM+ group (15.6% vs 11.7%; $P<0.05$). Among only TS tissues (N=2688), mean ECD was lower in the DM+ group (2675 vs 2739; $P<0.05$).

Conclusion: Comparing diabetic and non-diabetic tissue, we determined that the prevalence of diabetes within donors is over 30%; non-suitability for EK and/or PK was greater for diabetic corneas; and mean ECD is lower in diabetic versus non-diabetic corneas suitable for transplant. Diabetes is prevalent among cornea donors, and impacts pre-preparation ECD and suitability for transplants requiring healthy endothelial cells.

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Morning Session: Paper 8

Definition of a positive apraclonidine pupil test in the diagnosis of an oculosympathetic palsy: evaluation of normal, physiologic anisocoria, and Horner syndrome populations

Christopher A. Kirkpatrick, M.D.

Primary Supervisor: Randy H. Kardon, M.D., Ph.D.

Background: The clinical diagnosis of Horner Syndrome (HS) is based on miosis, ptosis and anhidrosis and can be equivocal, requiring confirmation with pharmacological eye drop testing. In recent years, apraclonidine, an alpha-2 agonist with weak alpha-1 properties, has gained acceptance over cocaine testing for the diagnosis of HS. However, criteria for a positive apraclonidine test for diagnosing HS have been lacking. A positive test, currently defined as reversal of anisocoria, is influenced by the development of alpha-1 adrenergic supersensitivity and its magnitude, which depends on the duration of the oculosympathetic deficit and the amount of deficit causing it.

Purpose: Objective criteria for a positive apraclonidine test for diagnosing HS were developed based on ocular responses of normal subjects to topical apraclonidine which were compared to patients.

Methods: Pupillary measurements in 100 normal healthy control subjects were obtained from digital infrared video frames before and 30 minutes after one drop of 0.5% apraclonidine OU in dim light. Pupillary responses were analyzed as a ratio of pupil/limbus diameter (P/I ratio) and the normal range of pupil response to apraclonidine was objectively defined. A retrospective chart review of patients receiving apraclonidine testing – carrying either the diagnosis of physiologic anisocoria or HS (based on cocaine testing, imaging or clinical objective criteria other than a positive apraclonidine test) – were evaluated against these results to critically assess the sensitivity and specificity of the apraclonidine test and to propose objective criteria for its use to diagnose HS.

Results: In the normal population (N=100), after apraclonidine, the mean change in pupil diameter was -0.044 ± 0.033 (range -0.142 to 0.088) using the P/I ratio. The mean change in anisocoria was 0.019 ± 0.016 (range 0.00004 to 0.076) using the P/I ratio. In the HS group (N=32), the mean change in anisocoria was 0.133 ± 0.051 (range 0.053 to 0.233). When compared to the control population, 29 of 32 patients (90.63%) fell outside of the 5th-95th predictive limits of a normal apraclonidine response. In the physiologic anisocoria group (N=38), the mean change in anisocoria was 0.029 ± 0.025 (range -0.090 to 0.076). When compared to the control population, 1 of 38 patients (2.63%) fell outside of the 5th-95th predictive limits of a normal apraclonidine response. Comparing the HS group and the physiologic anisocoria group (N=70) to the 5th-95th predictive limits of a normal apraclonidine response results in a sensitivity of 90.62% (95% CI: 74.95% - 97.91%) and a specificity of 97.37% (95% CI: 86.14% - 99.56%).

Conclusions: Pupil responses to apraclonidine in normal subjects and in patients can be utilized to develop objective criteria for the diagnosis of HS. Some patients with Horner syndrome show a decrease in anisocoria with apraclonidine, indicating a positive test, even though the change is not great enough to result in a reversal of anisocoria.

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Morning Session: Paper 9

Utilizing tele-ophthalmology and tablet technology for glaucoma screening and visual field assessment

Jiaxi Ding, M.D.¹

Primary Supervisors: Daniel I. Bettis, M.D.¹, Alan L. Robin, M.D.², and Suman Thapa, M.D., Ph.D.³, Chris Johnson, Ph.D., DSc¹

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Purpose: In developing countries, glaucoma often remains undetected due to limited resources and geographic inaccessibility.¹ Incorporation of modern portable technology with tele-communication capabilities could be a vital step towards enhancing detection and prevention of blindness globally.² Our team aimed to investigate the glaucoma burden among a Nepalese cohort as well as the usefulness of tele-ophthalmology and tablet technology to accurately screen these patients.

Methods: Non-mydratic fundus photos of 450 Nepalese eyes were independently assessed by two ophthalmologists and categorized as non-glaucomatous, glaucoma suspect, or glaucomatous based on defined criteria. These classifications will also be compared to visual field data collected using a novel tablet app (Photo 1) for which the mean deviation has 0.79 correlation with Humphrey automated perimetry.³

Results: Of the 420 eyes surviving exclusion criteria, 221 (52.6%) were deemed non-glaucomatous, 119 (28.3%) glaucoma suspects, and 80 (19%) glaucomatous. Concordance rate of the two graders independently assigning the same category was 74% overall.

Discussions: Tele-ophthalmology has intrinsic limitations related to photo quality and loss of the live exam dynamics. However, it bypasses geographical constraints in areas without local ophthalmologists and allows for simultaneous review by multiple consultants. In our study, we identified likely glaucomatous optic nerve damage in approximately one-fifth of Nepalese eyes screened by tele-ophthalmology (Photo 2). Almost an additional third had features suspicious for a path towards glaucomatous optic neuropathy.

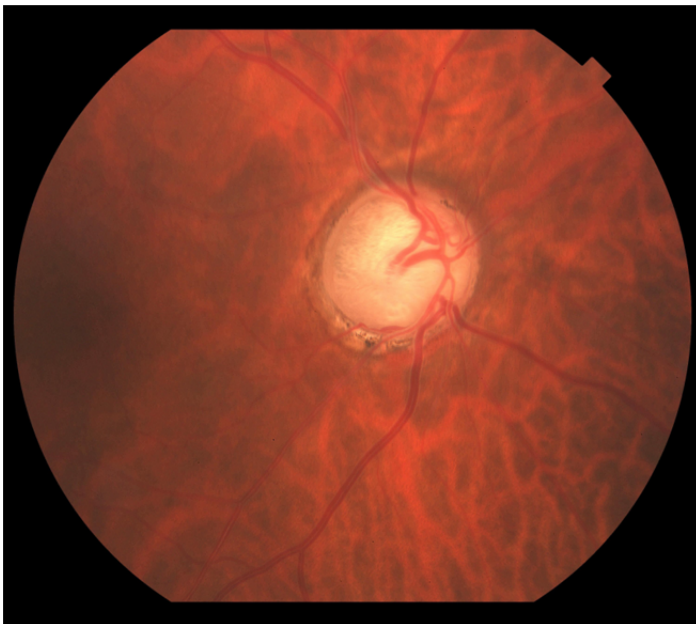
Conclusions: There is a high need amongst the Nepalese population for detection and care of glaucoma, a silently blinding eye disease. Tele-ophthalmology with non-mydratic fundus photo interpretation is imperfect for diagnosis, but a valuable screening tool. We will further correlate the photographic structural analysis to visual field functional assessment.

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Photo 1: Nepalese patient performing the tablet visual field screening test.



Photo 2: Sample of non-mydratic fundus photo with optic nerve that is highly suspicious for glaucomatous optic nerve damage



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Current State/Outcome: Technological advancements in the form of tele-ophthalmology and a novel tablet app for visual field testing are valuable glaucoma screening tools especially where limitations exist in resource availability and accessibility.

Best Practice: In developing countries, glaucoma management is often hindered at the initial step of detection due to limitations in resource availability and accessibility. Our team is evaluating technological developments that bypass geographical constraints in areas without local ophthalmologists.

Learning Objective: In our study, by tele-ophthalmology, we identified 19.0% of 420 Nepalese eyes screened to likely have glaucomatous optic nerve damage. Another 28.3% of eyes had features suspicious for a path towards glaucomatous optic neuropathy. These patients should undergo additional glaucoma work-up to prevent silent vision loss and blindness.

Summary: There is a high need amongst the Nepalese population for detection and care of glaucoma, a silently blinding eye disease. Tele-ophthalmology with non-mydratic fundus photo interpretation is imperfect for diagnosis, but a valuable screening tool. We will further correlate the photographic structural analysis to visual field functional assessment.

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Morning Session: Paper 10

Long-Term Surgical Outcomes for Large-Angle Esotropia in Children

Matthew C. Weed, M.D.

Primary Supervisors: Miriam Di Menna, C.O., Christina L. Donaghy, B.S., Dimitra Triantafilou, C.O., Scott A. Larson, M.D.

Introduction: Debate exists regarding whether two-muscle ("uniform approach") or three/four-muscle surgery ("selective approach") is the better initial surgical management of large-angle esotropia (1-3).

Methods: Chart review of patients from a 45-year period at a single center who presented with large-angle esotropia (≥ 45 prism diopters at either distance or near), had strabismus surgery before age 7, and had at least two years of follow-up data available. Children with a known systemic syndrome or ocular comorbidity were excluded.

Results: A total of 272 patients met inclusion criteria -- 50 patients treated with the selective approach and a randomly-selected sample of 222 patients treated via the uniform approach. The mean age at first surgery was 2.00 years. Surgical success was defined as < 10 prism diopters of horizontal strabismus in primary position. As expected, patients treated with the uniform approach had smaller average preoperative deviations than those treated with the selective approach. The single-surgery success rate was statistically equivalent between these groups (34% vs 30%). Undercorrection was more common with the uniform approach ($p=0.0074$) while overcorrection was more common with the selective approach ($p=0.0002$). The reoperation rate, average number of muscles per reoperation, and rate of amblyopia treatment after surgery was statistically equivalent between the two groups. The number of muscles initially operated did not have a measurable effect on the final alignment outcome after any and all required reoperations.

Discussion: While our study did not achieve sufficient power to determine whether the uniform or selective approach was superior, it suggests that success rates are similar.

Conclusions: Rates of long-term satisfactory alignment after surgery for large-angle esotropia are moderate regardless of surgical approach. Rates of undercorrection via the uniform approach are similar to rates of overcorrection with the selective approach.

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2. Minkoff OV, Donahue SP. Three-muscle surgery for infantile esotropia in children younger than age 2 years. *J Pediatr Ophthalmol Strabismus* 2005; 42:144-148.

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Afternoon Session: Paper 11

Extracellular matrix 1 (ECM1), a potential prognostic marker for uveal melanoma is not expressed in primary tumors at the protein level

Chaunhi Van, M.D.

Primary Supervisors: Geeta Lal, M.D., Nasreen A. Syed, M.D, Culver Boldt, M.D.

Background/Purpose: Uveal melanomas account for 5-10% of all melanomas and are the most common primary intraocular malignancy of adults [1]. Once uveal melanomas metastasize, they are highly resistant to therapy and there is no standard treatment that has been proven effective for overall survival [2, 3] Gene expression profile studies demonstrate that metastasis of uveal melanomas can be predicted using a PCR-based 15-gene assay composed of 12 discriminatory genes and 3 endogenous genes. One of these genes is Extracellular Matrix 1 (ECM1). While it has been demonstrated that high ECM1 RNA expression correlates with poor prognosis, there are no studies examining ECM1 protein expression in uveal melanomas and whether this correlates with clinical outcome for survival.

Methods: ECM1 expression was examined by immunohistochemistry in 80 eyes with uveal melanomas that were enucleated between 2008 and 2013. Data on survival was to be obtained from the Iowa Cancer Registry in order to correlate finding with patient survival.

Results: There were no uveal melanomas that stained positive for ECM1 protein using either diaminobenzidine (DAB) staining technique or 3-amino-9-ethylcarbazole (AEC) technique. Outcome data could not be analyzed due to the results of immunohistochemistry in these tumors. Appropriate positive and negative control tissues were used.

Discussion: Although RNA expression studies suggested ECM1 overexpression in high-risk uveal melanomas, this was not discernable at the protein level. This may be related to mRNA decay, translation inhibition by microRNA, and/or protein degradation. The findings are in keeping with other studies which show that mRNA levels cannot be used as surrogate markers for protein levels. Identifying significant prognostic factors for uveal melanomas is key to identify patients at high risk for developing metastasis and would potentially benefit them through intensified surveillance, earlier detection, entry into clinical trials for adjuvant therapy and development of targeted therapies.

References:

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2. Blum, E.S., et al., *Clinical Management of Uveal and Conjunctival Melanoma*. Oncology (Williston Park), 2016. **30**(1): p. 29-32, 34-43, 48.
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Afternoon Session: Paper 12

Long Term Follow-up of Ocular Histoplasmosis in the Anti-VEGF Era

Jessica S. Watson, M.D.

Primary Supervisor: Stephen R. Russell, M.D.

Purpose: Since the advent and widespread off-label use of anti-vascular endothelial growth factor (anti-VEGF) for non-age-related macular degeneration associated choroidal neovascularization (CNV), few and limited studies have evaluated anti-VEGF effects on CNV associated with presumed ocular histoplasmosis (CNV-POHS). We performed a retrospective study to report the epidemiology, intravitreal treatment response, and long-term visual outcomes of patients with CNV-POHS treated with intravitreal anti-VEGF.

Methods: We reviewed the medical records of all subjects coded with a diagnosis of POHS who received intravitreal anti-VEGF at the University of Iowa from January 2004 to December 2014, and who had at least 1-year of follow-up. Data were compiled from 193 subjects meeting entry criteria. Data included subject age, pre- and post- treatment visual acuity and optical coherence tomographic (OCT) and fluorescein angiographic characteristics, if available.

Results: 50 of 81 eyes (62%) were treated with anti-VEGF alone. Of the remaining eyes, all received another treatment either preceding or following anti-VEGF: thermal laser [17 eyes (55%)], photodynamic therapy (PDT) [5 eyes (16%)], thermal laser and intravitreal steroid [3 eyes (10%)], intravitreal steroid [2 eyes (6%)], submacular surgery [1 eye (3%)], oral prednisone [1 eye (3%)], thermal laser and intravitreal steroid [1 eye (3%)], PDT and intravitreal steroid [1 eye (3%)], and observation [1 eye (3%)]. There was no statistically significant difference between the visual acuity of patients treated only with anti-VEGF and those pre-treated with either thermal laser or PDT ($p > 0.05$ for all reactivations). Of patients who received only anti-VEGF as treatment for their CNV, there were 94 “activations” of the CNV. 28 eyes of 50 (56%) reactivated at least once [18 reactivated once (36%), 6 reactivated twice (12%), 2 reactivated three times (4%), and 2 reactivated four times (4%)]. The average number of reactivations was 1.57 (SD 0.92; median 1). The average time between CNV activity was 13.4 months (SD 10.6; median 10). The average number of injections given per activation was 6.5 (SD 6.3; median 3).

Conclusions: With the use of intravitreal anti-VEGF treatments, patients with POHS complicated by CNV can expect to maintain excellent visual acuity, even with CNV reactivation.

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Afternoon Session: Paper 13

Cost-Benefit Comparison of Intravitreal anti-VEGF Injections for Neovascular Age-Related Macular Degeneration on a Treat-and-Extend Regimen

Andrew R. Carey, M.D.

Primary Supervisor: Stephen Russell, M.D.

Background: Neovascular Age-Related Macular Degeneration (nAMD) is the leading cause of severe vision loss in people over age 65 in the United States (US). The World Health Organization estimates there are 20-25 million people worldwide with Age-Related Macular Degeneration (AMD) and will increase to 75 million by 2050. In 2014 there were 2.2 million people in the US with AMD and this number is expected to increase to 4.4 million by the year 2050. In 2004 there were 1.2 million cases of nAMD with an expected 150,000 new cases each year. Between 2008 and 2009, Medicare was billed for 936,382 Bevacizumab injections and 696,927 Ranibizumab injections for nAMD resulting in \$40 million spent on Bevacizumab and \$1.1 billion on Ranibizumab. There are now three medications commonly injected into the vitreous cavity for the treatment of nAMD : Bevacizumab (IVB), Ranibizumab (IVR), and Aflibercept (IVA). There have been multiple studies demonstrating efficacy of different administration regimens including monthly (q4w) treatment (MARINA, ANCHOR, VIEW1/2), as needed or PRN treatment (CATT, IVAN), and treat-and-extend (TAE). There has been some debate as to the most effective medication and dosing regimen. The cost differs for each medication: Medicare reimburses IVB \$6.82, IVR \$1542, and IVA \$1537. The results of the CATT & IVAN studies demonstrated the cost benefit of IVB over IVR on a PRN over q4w basis, but there has not been a similar analysis for a TAE regimen.

Purpose: The purpose of this study is to examine the cost-benefit of IVB compared to IVR and IVA in a TAE regimen.

Methods: A mathematical model was created comparing the cost of a patient encounter for nAMD being treated on a TAE regimen with IVB, IVR, or IVA for three different payors: Self pay patient (SPP), Medicare (M), and Medicare Patient Co-Pay (MPC) in both the hospital based clinic (HBC) and ambulatory clinic (AC) setting. In a TAE regimen, the patient is treated at each visit, and thus the cost of each visit is the same. The cost of treatment was then calculated for each medication administered on a q4w and on a TAE model where 3 loading doses were administered 4 weeks apart and then the follow-up interval was extended by 2 weeks at each visit to a maximum of 12 weeks resulting in 7 visits in the first year and 4 visits in subsequent years. The cost of IVB was compared to IVR and IVA in these two models as well as the cost of IVB in the q4w regimen to IVR & IVA in the TAE regimen. A retrospective chart review was then performed evaluating all patients treated with a TAE regimen for nAMD between 2006 and 2016. The baseline logMAR visual acuity (logMAR VA), number of injections, and logMAR VA at each year after initial treatment were recorded and then applied to the cost model to analyze cost-benefit of IVB compared to IVR & IVA on a cost per line gained basis.

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Afternoon Session: Paper 14

Outcomes Following Intra-vitreous Injection Associated Endophthalmitis

Elaine M. Binkley, M.D.

Primary Supervisor: Elliott H. Sohn, M.D.

Background/Purpose: Though the use of intravitreal agents has revolutionized the treatment of exudative age related macular degeneration (AMD) and diabetic macular edema (DME), they can lead to complications, including infectious endophthalmitis. To better understand the effect of endophthalmitis on exudative AMD and to determine its influence on the need for future injections we performed a single center, retrospective study of subjects who developed endophthalmitis after intravitreal injection.

Methods: We searched the electronic medical record for all subjects from 2008 to 8/15/15 whose record included CPT and ICD-9 codes for both intravitreal injection and endophthalmitis. In addition, we examined the time to recurrence of intraretinal or subretinal fluid and/or hemorrhage after resolution of endophthalmitis in a subset of subjects with exudative AMD. We recorded the median number of injections required one and two years before and after the date of their infection.

Results: We identified 46,874 intravitreal injections performed at our institution during the study period. Eighteen eyes of 17 subjects presented with endophthalmitis causally related to injection. Six of these were referred following injections performed outside of our institution. Thirteen eyes had been treated for exudative AMD, 2 for DME, and 3 for edema secondary to vein occlusion. In 7 eyes treated for exudative AMD whose vision was hand motions or better after infection and for whom data were available, there was recurrence of retinal edema after the endophthalmitis event. The median number of days to recurrence after resolution of infection was 49 (range 20-104). Six eyes had injection data one year before and after infection and 4 eyes had two year data. A median of 10 (range 8-13) injections were required one year before and 21.5 (range 19-25) two years before infection. To control recurrent fluid, a median of 8 (range 4-12) injections were needed one year after and 16.5 (range 14-20) two years after infection. Though the sample size was small, there was a trend towards needing fewer injections two years after infection compared to before.

Conclusions: For some subjects, who developed endophthalmitis after intravitreal injection, exudative AMD remained active or recurred, requiring reinstitution of intravitreal injection therapy. In these patients there may be a trend towards needing fewer injections in the long term after the infection has cleared.

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Afternoon Session: Paper 15

Incidence and Outcomes of Positive Donor Corneoscleral Rim Fungal Cultures After Keratoplasty

Jesse M. Vislissel, M.D.

Primary Supervisors: Michael D. Wagoner, M.D., Ph.D., Kenneth M. Goins, M.D., M. Bridget Zimmerman, Ph.D., Mark A. Greiner, M.D.

Purpose: To determine the incidence of positive corneoscleral donor rim fungal cultures following keratoplasty and to investigate the clinical outcomes of grafts with culture-positive donor rims.

Methods: A retrospective chart review was performed of consecutive keratoplasty cases at a single tertiary referral center over 20 years. The primary outcome measure was positive donor corneoscleral rim fungal culture and the secondary outcome measure was the development of fungal keratitis or endophthalmitis after keratoplasty using the corresponding corneal tissue.

Results: A total of 3,414 keratoplasty cases were included in the statistical analysis. Seventy-five (2.2%) cases were associated with a fungal culture-positive donor rim. *Candida* species were cultured in 40 culture-positive cases (52.6%). The positive culture rate did not differ by season ($P=0.109$), but there was a higher incidence of positive rim culture over the last 5 years of the analytic period compared to the first 15 years ($P=0.046$). Fungal keratitis developed in 4 cases (5.3% of culture-positive donor rims) and all patients required further surgical intervention to achieve cure. There were no cases of fungal endophthalmitis. Empiric antimycotic prophylaxis initiated at the time of culture result reduced the incidence of keratitis from 13.0% in untreated cases to 1.9% in treated cases ($P=0.083$).

Conclusion: We found a 2.2% incidence of positive donor corneoscleral rim fungal cultures following keratoplasty and a 5.3% risk of developing fungal keratitis in individuals with positive cultures. The incidence of positive donor rim fungal cultures increased over the time period of this study but antimycotic prophylaxis reduced the incidence of keratitis nearly 7-fold in those with a culture-positive donor rim.

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Afternoon Session: Paper 16

The Role of Scleral Contact Lenses in the Oculoplastics Patient

Harinderpal S. Chahal, M.D.

Primary Supervisor: Erin M. Shriver, M.D.

Purpose: Evaluate the use and efficacy of scleral contact lenses (SCLs) in patients presenting to oculoplastic surgeons.

Methods: Retrospective review of SCL patients examined by oculoplastics from 1990-2014. The indication for SCL use and outcomes of oculoplastic treatments and SCL therapy were noted.

Results: 40/659 SCL patients were seen by oculoplastics and 13/40 patients required the SCL for corneal decompensation despite prior oculoplastic surgical intervention. Surgeries included: tarsorrhaphies; weights; and ectropion or retraction repair with spacers, skin grafts, or cheek lifts. These 13 patients presented with CN VII palsy (5), CN V and VII palsy (4), neurotrophic keratitis (3), and cicatricial ectropion (1). 13/13 patients had improved vision and comfort with the SCL.

Conclusions: Patients with corneal decompensation despite oculoplastic surgical intervention should be considered for SCLs. SCLs may be considered primarily in cranial nerve V and VII palsy patients.

Residents and Fellows who have Completed Research Projects (Submitted and/or Published)

Stephen Christiansen (PGY2)

Christiansen SM, Oetting TA, Herz NL, Law JC, O'Brien CP, Patel PS, Patel R, Pettey JH, Shiba DR, Sun G, Fountain T. Twitter at the 2014 and 2015 Annual Meetings of the American Academy of Ophthalmology. *Ophthalmology*. 2016 Apr 7. doi: 10.1016/j.ophtha.2016.03.012.] PubMed PMID: 27067923.

David Phillips (PGY3)

Phillips DL, Hager JL, Goins KM, Kitzmann AS, Greiner MA, Cohen AW, Welder JD, Wagoner MD. Boston type 1 keratoprosthesis for chemical and thermal injury. *Cornea*. 2014 Sep;33(9):905-9. PubMed PMID: 25055151.

Philip Niles (PGY3)

The Cost Discrepancy of Differing Practice Patterns for the Treatment of Pediatric Hyperopia. *Ophthalmology*, submitted

Jaclyn Haugsdal (PGY3)

Haugsdal JM, Goins KM, Greiner MA, Kwon YH, Alward WL, Wagoner MD. Boston type 1 keratoprosthesis for primary congenital glaucoma. *Br J Ophthalmol*. 2016;100(3):328-31. PubMed PMID: 26206789.

Jesse Vislislis (Cornea)

Incidence and Outcomes of Positive Donor Corneoscleral Rim Fungal Cultures after Keratoplasty. *Cornea*, submitted 2016

Nathanial Roybal (Retina)

Skeie JM, Roybal CN, Mahajan VB. Proteomic insight into the molecular function of the vitreous. *PLoS One*. 2015 May 28;10(5):e0127567. PubMed PMID: 26020955; PubMed Central PMCID: PMC4447289.

Lucas Lenci (PGY2)

Dermoid Cysts: Clinical Predictors of Complex Lesions and Surgical Complications. *Ophthalmic Plastic and Reconstructive Surgery*, submitted 2016

Johanna Beebe (PGY4)

Diagnostic Imaging in Patients with Isolated Horner Syndrome. *Neurologic Clinics*, submitted 2016

Yasser Elshatory (Retina)

Management of Pediatric Aphakic Glaucoma with Vitrectomy and Tube Shunts. *Journal of Pediatric Ophthalmology and Strabismus*, in press 2016

William Flanary II (PGY4)

Cystoid Macular Edema after DMEK and Recent Versus Remote Cataract Surgery. *Cornea*, in press 2016

Rachael Mercer (Neuro-Ophthalmology)

Will present in June