Uveitis literature review 2018

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Disclosures

• RVG serves as
  – Associate Editor of *TVST*
  – Editorial Board Member of *Ophthalmology*
  – Editorial Board Member of *Ophthalmology: Retina*
  – Editorial Board Member of *Ocular Inflammation and Immunology*

• RVG laboratory received research funding in 2018 from:
  – National Eye Institute
  – Research to Prevent Blindness
  – Elasmogen

• Received no direct compensation
Purpose

To bring papers of potential significance and interest to the attention of the AUS membership and guests
Methods

• Literature search for ‘uveitis’ or ‘ocular inflammation’ on PubMed

• Limited to English language and added to database in the last year (10/1/17 to 9/30/18)

• Selected ~ 25 papers to discuss briefly based on impact in understanding or managing ocular inflammatory disease
Caveats

• This is a necessarily subjective process
• Less than 2% of the literature can be featured
• All omissions are exclusively my fault and should not be taken personally
• All studies are imperfect: my purpose is to draw attention to the literature, not critique.
Uveitis literature 2017-18

- 1775 papers in English
- 716 human
- 252 reviews
- 13 clinical trials
Most cited uveitis papers from 2016

1. Zika Virus Infection in Mice Causes Panuveitis with Shedding of Virus in Tears
   - Authors: Jonathan J. Minner, Abdoulaye Sene, Justin M. Richner, Amber M. Smith, Andrea Santeford, Nonimitsu Ban, James Wiegler, Francesca Manzella, Claudia Rückert, Jennifer Govero, Kevin K. Noguchi, Gregory D. Ebel, Michael S. Diamond, and Rajendra S. Apte
   - Citations: 92

2. Adalimumab in Patients with Active Noninfectious Uveitis
   - Authors: Glenn J. Jaffe, M.D., Andrew D. Dick, M.B., B.S., M.D., Antoine P. Brézin, M.D., Ph.D., Quan Dong Nguyen, M.D., Jennifer E. Thorne, M.D., Ph.D., Philippe Kestelyn, M.D., Ph.D., M.P.H., Talin Barisani-Asenbauer, M.D., Ph.D., Pablo Franco, M.D., Arnd Heiligenhaus, M.D., David Scales, M.D., David S. Chu, M.D., Anne Carnez, M.D., Nisha V. Kwatra, Ph.D., Alexandra P. Song, M.D., M.P.H., Martina Kron, Ph.D., Samir Tari, M.D., and Eric B. Suhler, M.D., M.P.H.
   - Citations: 67
...but first, a shameless self-plug for my colleagues at UW
Use of En Face Swept-Source Optical Coherence Tomography Angiography in Identifying Choroidal Flow Voids in 3 Patients With Birdshot Chorioretinopathy

Kathryn L. Pepple, MD, PhD, Macklin H. Nguyen, BS, Kayvon Pakzad-Vaezi, MD, Kathryn Williamson, MD, Naomi Orell, MD, MPH, Cicilia Lee, MD, MS, Thelma K. Levy, MD, MPH, Russell N. Van Gelder, MD, PhD

RESPONSE OF INFLAMMATORY CYSTOID MACULAR EDEMA TO TREATMENT USING ORAL ACETAZOLAMIDE

Kathryn L. Pepple, MD, PhD,* Macklin H. Nguyen, BS,* Kayvon Pakzad-Vaezi, MD,* Kathryn Williamson, MD, Naomi Orell, MD, MPH,* Cicilia Lee, MD, MS,* Thelma K. Levy, MD, MPH,* Russell N. Van Gelder, MD, PhD1

Swept-Source OCT Angiography of Serpiginous Choroiditis

Kayvon Pakzad-Vaezi, MD,1 Kayla Shahani, MD,1 Donna Rothermel, MD,1 Zhorng Chua, MSc,1 Russell N. Van Gelder, MD, PhD1,2,3

A Review of the Role of Intravitreal Corticosteroids as an Adjuvant to Antibiotics in Infectious Endophthalmitis

Dawn Ching Wen Ho, Medical Student1, Aniruddha Agarwal, MD2,3, Cecilia S. Lee, MD4, Jay Chhablani, MD, Vishali Gupta, MD, Monej Khati, MD, Jayabalan Nirmal, MD, Carlos Pavesio, MD, and Rupesh Agrawal, MD2,3,4

Viral posterior uveitis

Joanne H. Lee,1 Aniruddha Agarwal, MD,2 Padmamalini Mahendradas, MS, Cecilia S. Lee, MD, Vishali Gupta, MD, Carlos E. Pavesio, FRCPht, Rupesh Agrawal, MD2,3,4

Determinants of Outcomes of Adenoviral Keratoconjunctivitis

Cecilia S. Lee, MD, MS,1 Aaron Y. Lee, MD, MSCI,1 Lakshmi Akkeleshwaran, PhD,2 David Stroman, PhD,3 Kathryn Najaefar-Tajgil, MD,3 Steven Klebucuk, PhD,3 James Credo, MD, MPH,3 Amanda Magaret, PhD3,4, Anna Wald, MD, MPH1,2, Russell N. Van Gelder, MD, PhD1,2,5 on behalf of the BAYrostriation Study Group

Comparison of Aqueous and Vitreous Lymphocyte Populations From Two Rat Models of Experimental Uveitis

Kathryn L. Pepple,1 Leslie Wilson,1 and Russell N. Van Gelder1,3,5

LETTER

Automated three-dimensional cell counting method for grading uveitis of rodent eye in vivo with optical coherence tomography

Woo J. Choi1,2,3,4 and Kathryn L. Pepple1,5,6

Cytokines in uveitis

Jessica E. Weinstein and Kathryn L. Pepple

Tuberculous uveitis: association between anti-tuberculous therapy and clinical response in a non-endemic country

Kristina L. Sajema,1 Kayvon Pakzad-Vaezi,1 Thomas Nevin1 and Kathryn L. Pepple2,3,4,5
• Compared wide-field SS-OCTA to ICG angiography in 3 patients with BSCR
• Equivalent or higher sensitivity for detection of pathology with OCTA than ICG angiography
• May allow early, non-invasive diagnosis of disease
• Used SS-OCTA prototype to look at active and quiescent serpiginous
• Case series of six eyes of three patients
• Choriocapillaris perfusion slab size highly correlated with activity on FAF and FA
• Appeared to have higher sensitivity for active disease than FAF
Determinants of Outcomes of Adenoviral Keratoconjunctivitis

- Prospective study of 500 subjects with EKC
- 22% adenoviral-negative by PCR
- Remarkable diversity of adenoviral type with substantial type B and E
- Outcome strongly influenced by viral type
Comparison of intraocular lymphocytes in two animal models of uveitis: EAU and PMU

Both models produce comparable inflammation

Distinct but overlapping cell infiltrates with surprisingly robust CD4 response in PMU

May explain chronic uveitis following intraocular infection
Translation
• Studied EAU in wild-type and C9-/- mutant mice
• Found membrane attack complex and NLRP3 inflammasome activated in EAU, and IL1 and Th differentiation dependent on C9
• However, C9-/- mice still had retinal structure and function loss with EAU
• AAV delivery of sCD59 (C9 inhibitor) attenuated NLRP3 inflammasome and EAU pathology
• Soluble CD83 is extracellular domain of endogenous immunoregulatory factor
• During onset and recovery of EAU, levels rise in aqueous
• Systemic or topical administration of sCD83 protect strongly against EAU (after induction) with induction of tolerogenic dendritic cells
• However, increased mortality after systemic administration
• Anti-inflammatory peptide that blocks kinase activation of JAK2 and TYK2.
• Attached polyarginine (9) to create cell penetrant peptide
• Protected TNFα and IL-17 damage of ARPE-19 cells
• Topical administration blocked EAU both prophylactically and 7 days after immunization
76 patients with uveitis and 19 cataract samples
Tested for reactivity to 188 ocular antigens by multiplex immunoassay
22 antigens higher reactivity in uveitis than control
Most notable in post-infectious and MS-associated uveitis
Anti-tyrosinase weakly associated with CME
Discovery of tear biomarkers in children with chronic non-infectious anterior uveitis: a pilot study

Sheila T. Angeles-Han1,2*, Steven Yeh3, Purnima Pate4, Duc Duong4, Kirsten Jenkins5, Kelly A. Rouster-Stevens5,6, Mekibib Altaye8,9, Ndate Fall1,2, Sherry Thornton1,2, Sampath Prahalad6,7, and Gary N. Holland9

- Pilot study examining GC-Mass Spec of tears for cytokines involved in JIA
- Nine eyes of seven subjects with either JIA-uveitis or chronic idiopathic uveitis
- Found patterns indicative of JIA or chronic disease, including elevated S100A8/A9 and elevated TIMP in JIA
- Further work needed for validation
• Retrospective analysis of MYD88 PCR mutation analysis by droplet digital PCR in VRL and uveitis
• 96 samples from 63 patients, 23 with VRL
• L265P mutation detected in 17/23 with VRL and 0/40 with uveitis
• PPV = 100%; NPV 0.87
• Vitreous yields slight better than aqueous; generally concordant
• 8 patients with bilateral vitreoretinal lymphoma, 6 patients with uveitis control

• 8/8 vitreous biopsies positive for L265P mutation; 6/8 aqueous positive

• 0/6 controls positive
CAN YOU SEE ME?
Prospective RCT comparing periocular triamcinolone, intravenous triamcinolone, or intravitreal dexamethasone implant for the treatment of uveitic macular edema (POINT) Trial

- All groups showed improvement
- Periocular injection showed slowest and least improvement
- Risk of IOP elevation > 24 mm Hg greater in intravitreal groups than in periocular groups.

- 235 eyes of 192 patients
- All groups showed improvement
Randomized, controlled phase 2 study of suprachoroidal delivery of triamcinolone for uveitic edema

- Two doses (4 mg and 0.8 mg), primary outcome central subfield thickness
- 22 patients enrolled
- Significant reduction in central subfield thickness
- Minimal effect on IOP
• Retrospective study of 72 eyes of 58 patients with uveitic CME
• 43 eyes treated with difluprednate only had CST decrease by 17%
• Risk of IOP elevation > 24 ~20% by 90 days treatment
RESPONSE OF INFLAMMATORY CYSTOID MACULAR EDEMA TO TREATMENT USING ORAL ACETAZOLAMIDE

KATHRYN L. PEPPLE, MD, PhD,* MACKLIN H. NGUYEN, BS,* KAI VON PAKZAD-VAEZI, MD,* KATHLEEN WILLIAMSON, MD,* NAOMI ODELL, MD, MPH,* CECILIA LEE, MD, MS,* THELLEA K. LEVEQUE, MD, MPH,* RUSSELL N. VAN GELDER, MD, PhD††

• Retrospective study of 19 eyes of 16 subjects with recalcitrant CME
• Only medication modification addition of acetazolamide
• VA improved from 20/57 to 20/37
• Central subfield improved from 471 um to 358 um
Safety and Efficacy of Adalimumab in Patients with Noninfectious Uveitis in an Ongoing Open-Label Study: VISUAL III

Eric B. Suhler, MD, MPH,1 Alfredo Adán MD, PhD,2 Antoine P. Brézin, MD, PhD,3 Eric Fortin, MD,4 Hiroshi Goto, MD,5 Glenn J. Jaffe, MD,6 Toshikatsu Kubokai, MD,7 Michel Kramer, MD,8 Lyndell L. Lim, MBBS, FRANZCO,9 Cristina Muñoz, MD, MBA,10 Quan Dong Nguyen, MD, MSc,11 Joachim Van Calster, MD,12 Luca Cimino, MD,13 Martina Kron, PhD,14 Alexandra P. Song, MD, MPH,15 Jianzhong Liu, MD,16 Sophia Pathai, MBBS, PhD,17 Anne Czerny, MD,18 Ariel Schlaer, MD,19 Mairaj E.J. van Velthoven, MD, PhD,20 Albert T. Vitale, MD,20 Manfred Zeier, MD, PhD,20 Samir Tori, MD, MBA,20 Andrew D. Dick, MBBS, MD20

- Phase III open label extension study from Visual I/II
- Number with inactive uveitis increased from 35% at entry to 74% at week 78
- Steroid use reduced in active group from 13 mg/d to 3 mg/d
- Significant AE profile but no significant difference from initial trials
- Suggests durable effect for most patients treated with adalimumab
RCT for patients with JIA-uveitis and inadequate response to MTX

- 31 patients
- Used laser flare photometry as outcome marker
- At month 2, 9/16 responders to adalimumab vs 3/15 on placebo
• Study to evaluate interobserver agreement on uveitis diagnosis
• 5766 cases for 25 diseases evaluated by expert committees
• Overall kappa statistic 0.39, ranging from 0.23 (toxoplasma retinitis) to 0.79 (CMV anterior uveitis)
• Consensus could be achieved in 99% of cases after discussion
• Agreement among uveitis experts re: diagnosis is moderate at best
• Strongly suggest need for validated disease criteria
- Retrospective review of malpractice settlements
- Lawsuits related to uveitis searched from 1930-2014.
- 25 total cases
- Viral retinitis most common diagnosis
- 64% of findings favored defendant
- 7/25 suits resolved by settlement with mean indemnity of ~$725,000
The Scoop on Poop
Intestinal Metabolites Are Profoundly Altered in the Context of HLA–B27 Expression and Functionally Modulate Disease in a Rat Model of Spondyloarthritis

Mark Asquith,1 Sean Davin,1 Patrick Stauffer,1 Claire Michell,1 Cathleen Janowitz,1 Phoebe Lin,1 Joe Ensign-Lewis,2 Jason M. Kinchen,3 Dennis R. Koop,1 and James T. Rosenbaum1

Follow-up to previous work showing intestinal microbiome altered in B27 transgenic rats

- HPLC-MS characterization of 582 metabolites
- More than half significantly altered at 16 weeks
- Administration of propionate (short chain fatty acid); resulted in reduced inflammation
Fecal DNA analyzed from 38 AAU patients and 40 family members
- High throughput 16S analysis; metabolomics by GC-MS on 60 samples
- Eight genera reduced in AAU patients and one increased but none significant
- Strong correlation of metabolites with microbiome
- PCA analysis suggests patients could be identified by metabolomic analysis
Fecal transplants in spondyloarthritis and uveitis: ready for a clinical trial?

Rene Y. Choi\textsuperscript{a}, Mark Asquith\textsuperscript{b}, and James T. Rosenbaum\textsuperscript{a,b,c}

UVEITIS IN SPONDYLOARTHRITIS A MICROBIOME-DRIVEN DISEASE?

KEY POINTS

- Intestinal dysbiosis occurs in various subsets of SpA.
- SpA-related uveitis may be due to a gut microbiome regulated increase in intestinal permeability.
- Therapeutic modalities targeting the intestinal microbiome could be a future approach to treating SpA.
• Do we need to distinguish sarcoid uveitis from idiopathic disease?
• Studied 249 patients, 179 referred for idiopathic uveitis
• 53 underwent chest CT; 19 had presumptive sarcoid diagnosis made.
• Additional 14 patients previously diagnosed with sarcoid -> 33 total sarcoid patients

• EKG obtained in 14/33
• 9/14 had abnormal EKG
• 4/9 with paroxysmal ventricular tachycardia requiring defibrillator
• Suggest that patients older 40 with history of idiopathic uveitis be evaluated by chest CT and/or EKG
• Retrospective review of 143 patients with uveitis and sarcoidosis
• Determined rate of development of symptomatic systemic sarcoid from uveitis onset
• Uveitis presenting complaint in 79%.
• 20% developed symptomatic systemic sarcoid with median time 12 months
• No ocular predictors of systemic disease
• Suggests clinically significant systemic sarcoidosis can develop late in patients presenting with ocular disease
• Case control study of 61 patients with uveitis (21 with sarcoid)
• CD4/CD8 ratio in aqueous and blood determined by flow cytometry.
• Mean ratio in AH 6.3 in sarcoid compared with 1.6 in non-sarcoid
• Ratio > 3.5 had odds ratio of 38 of being associated with sarcoidosis
• Bayesian utility less as PPV 0.26 and NPV 0.73
• Validation study of 884 uveitis patients, 30% with likely sarcoid
• 180/264 met IWOS criteria
• Signs with highest predictive values were bilaterality, snowballs, mutton fat KP, iris nodules
• ACE/lysozyne elevated in 62%
• Current criteria need revision; certain signs (elevated LFT) not useful
Describes two cases of possible syphilitic choroiditis with vitreous FTA-Abs and RPR.

- One case positive for both but with negative serum RPR responded well to PCN therapy.
- Second case (figure) negative for FTA-Abs and RPR did not respond to PCN; diagnosed with serpiginous and responded to IMT.
Global Variations and Challenges With Tubercular Uveitis in the Collaborative Ocular Tuberculosis Study

Rupesh Agrawal,1–3 Dinesh Viswa Gunasekeran,1,2,4 Dhananjay Raje,5 Aniruddha Agarwal,6 Quan Dong Nguyen,7 Onn Min Kon,8 Carlos Pavesio,9 and Vishali Gupta10; for the Collaborative Ocular Tuberculosis Study Group

1National Healthcare Group Eye Institute, Tan Tock Seng Hospital, Singapore
2 Moorfields Eye Hospital, National Health Service Foundation Trust, London, United Kingdom
3 Singapore Eye Research Institute, Singapore
4 School of Medicine, National University of Singapore, Singapore
5 MDS BioAnalytics, Nager, India
6 Advanced Eye Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India
7 Byers Eye Institute, Stanford University, Palo Alto, California, United States
8 Chest and Allergy Clinic, St. Mary’s Hospital, Imperial College Healthcare National Health Service Trust, London, United Kingdom

- International collaboration on ocular tuberculosis
- Retrospective study of 945 patients with presumed TB uveitis
- Primary outcome = treatment failure/recurrent disease/inability to taper steroid
- Majority of patients without signs, symptoms, or radiographic evidence of TB
- African, Hispanic, and immigrant status associated with worse outcomes
- No significant effect of treatment with steroid or ATT on primary outcome
Retrospective cohort analysis of 199 eyes of 129 patients with uveitis and latent TB

- 69% received antitubercular therapy
- Overall 35% with recurrence of uveitis
- Odds ratio of recurrence with ATT = 0.47
- Treated eyes recurred at median 122 months vs 51 months with no treatment
Identification of an Amino Acid Motif in HLA-DRβ1 That Distinguishes Uveitis in Patients With Juvenile Idiopathic Arthritis


• Analysis of 576 patients with JIA (from 2 cohorts), 214 with uveitis by GWAS
• High linkage with presence of serine at position 11 of HLA-DRβ1 (OR 2.6) which was specific to girls.
• Amino acid in peptide binding domain
• Likely affects antigen binding and presentation
• Group of pediatric rheumatologists, ophthalmologists, and lay members

• Developed two consensus treatment plans with >95% consensus for treatment of JIA-associated uveitis

• Identified areas for further research within consortium
Methotrexate in juvenile idiopathic arthritis: advice and recommendations from the MARAJIA expert consensus meeting

• The Rheumatology Italian Study Group consensus recommendations
• PICO based evidence-based literature assessment

• MTX is first line treatment
• CBC/LFT monitoring every 4-8 weeks initially, then q12-16 weeks
• Dose of 10-15 mg/m²/week
• SQ treatment preferred
• MTX may be discontinued after 6 months of stable remission
• Folic acid 1 mg/day
• MTX + anti-TNF for recalcitrant cases
European consortium generating recommendations for management of JIA

- Used evidence-based consensus methodology
- 22 recommendations with >80% agreement

Methotrexate is first choice for systemic IMT
- Non-Etanercept anti-TNF is second line
- Recommend 2 years of inactive disease off topicals before IMT holiday
- Consider tocilizumab, rituximab, and abatacept as 3rd line treatment
• Retrospective case control analysis of claims data from 558 noninfectious uveitis cases and 2790 controls
• All had vitamin D levels drawn within 1 year
• Patients with normal vitamin D levels had odds ratio 0.79 for uveitis compared with controls
• Effect more pronounced in black patients (OR 0.49)
• Retrospective case-control study of 333 uveitis cases, 103 scleritis cases, and 329 controls
• Odds ratio 1.92 for uveitis for low vitamin D levels (p < 0.0003)
• Primarily factor for anterior uveitis and scleritis
• 5% lower risk for every 1 U increased vitamin D level
unique
different
concept
leadership
uniqueness
individuality
idea
business
creativity
forward
healthy
independent
inspiration
strategy
distinct
special
competition
outstanding
manager
distinguished
unusual
original
many
colorful
object
nature
influence
boss
success
content
crowd
leader
individual
direction
strategy
courage
standout
strategy
education
Ocular Inflammation Associated With Fibers From Eyelash Extensions

Mohammad Samir Dowlat, MBCHB, FRCOphth; Yousry Ahmed, MBCHB; Angela Knox, FRCOphth

Figure. The white arrowheads indicate linear subconjunctival fibers and the associated localized hyperemia.

A woman in her 40s with a history of using eyelash extensions/fibers (Moodstruck 3D Fiber Lashes +; Younique) presented with redness, irritation, and pain in her right eye. An examination revealed several fibers (approximately 1 mm long) overlying the conjunctiva, with at least 6 in the subconjunctival space.

The patient’s eyes were too tender for removal of the subconjunctival foreign bodies at slitlamp. These fibers are described as being made from nylon and enriched with several chemicals (propylene glycol, squallane, tocopheryl). She was prescribed a course of topical chloramphenicol, 0.5%, and dexamethasone, 0.1%, 4 times daily. Three days later she was still symptomatic, and the fibers were subsequently removed in the operating room under a local anesthetic (Figure). Nylon is inert; however, the chemicals presumably caused the localized reaction. The patient’s symptoms resolved following the removal of the fibers while continuing the course of topical chloramphenicol and dexamethasone for 2 weeks.
Copy-editor of the year award
Effectiveness and safety of *Glycyrrhizae Decoction* for Purging Stomach-Fire in Behcet disease patients

Study protocol for a randomized controlled and double-blinding trail

Yong Chen, MD, PhD, Dan Luo, MS, MD, Jian-Fei Cai, MS, MD, Chen-Hong Lin, MD, PhD,
Yan Shen, MD, PhD, Jun Zou, MS, MD, Jian-Long Guan, MD, PhD

**Background:** Behcet disease (BD) is a worldwide-occurred autoimmune disorder and currently lack of optional successful treatment. An ancient traditional Chinese medical formula called *Glycyrrhizae Decoction* for Purging Stomach-Fire (GDPSF) was recorded and nowadays has been observed to be effective for BD patients. However, the strict randomized controlled and double-blinding trail is needed to further assess this alternative medicine.
Thank you!