Introduction

A Red eye is one of the most common presenting ophthalmologic conditions
- Inflammation of almost any part of the eye, including the conjunctiva, cornea, lacrimal glands, ocular adnexa, or faulty tear film can lead to a red eye

A true red eye is a cardinal sign of ocular inflammation, which can be caused by several conditions
- Most cases are benign and can be managed easily
- The key is recognizing those cases with a possible underlying disease that require more extensive management

Disclosures

- Allergan Pharmaceuticals Speaker’s Bureau
- Bio-Tissue
- BioDLogics, LLC
- Katena/IOP
- Seed Biotech
- Johnson and Johnson Vision Care, Inc.
- Shire Pharmaceuticals

Live Survey

Text NICHOLASCOLA090 to 22333 to join live poll

Then text A, B, C, D, E to answer
- Live
- Immediate
- Accurate

Order of Urgency

- Need to differentiate
  - Urgent
  - Emergent
  - Sight threatening

- Chemical Injuries
- Angle-closure glaucoma
- Ocular foreign body
- Uveitis
- Corneal abrasion
- Conjunctivitis
- Ocular surface disease
- Subconjunctival hemorrhage
Making the correct diagnosis can be overwhelming given the diversity of possible etiologies.

But when the red eye sitting in front of you doesn’t present in a textbook fashion, it can create a difficult challenge.

Recommend making a list of potential differential diagnoses.
- You can’t know what it is, until you know what it isn’t.
- However, red eye differentials are quite substantial.

### Differentials

- Acute Hemorrhagic Conjunctivitis
- Adult Blepharitis
- Allergic Conjunctivitis
- Bacterial Conjunctivitis
- Bacterial Endophthalmitis
- Chalazion
- Chemical Burns
- Contact Lens Complications
- Corneal Foreign Body
- Corneal Graft Rejection
- Corneal Ulcer
- Dacryocystitis
- Distichiasis
- Dry Eye Disease (Keratoconjunctivitis Sicca)
- Ectropion
- Emergency Care of Corneal Abrasion
- Ectropion

### Common Differentials

- Episcleritis
- Fungal Endophthalmitis
- Giant Papillary Conjunctivitis
- Acute Angle-Closure Glaucoma (AACG)
- Herpes Zoster
- Hordeolum
- Neonatal Conjunctivitis (Ophthalmia Neonatorum)
- Ophthalmologic Manifestations of Kaposi Sarcoma
- Orbital Cellulitis
- Postoperative Endophthalmitis
- Preseptal Cellulitis
- Pterygium
- Recurrent Corneal Erosion
- Red Eye Evaluation
- Stevens-Johnson Syndrome
- Viral Conjunctivitis (Pink Eye)

### Review of Systems

A systematic anatomic approach to the patient with a red eye will help reach a differential diagnosis that will include most of the causes of a red eye.

As with any diagnostic problem, the information obtained from a careful history and examination should direct the approach to management.

Examination of the skin, joints, and oral mucosa, can be valuable in formulation of the differential diagnosis.

By the end of the initial interview, you should have a reasonably complete differential diagnosis in mind before examining the patient.

### Anatomical Approach

A systematic examination of the eye and adnexa should be conducted starting anteriorly with the face and lids and moving posteriorly to globe.

The face, orbital area, and lids are inspected first, then the ocular movements, and finally the globe itself.

Pay particular attention to the type of injection.

### Conjunctival Injection

Appears as a diffuse area of dilated blood vessels and is more superficial and moveable.

### Ciliary Injection

Ring-like pattern of dilated blood vessels around the cornea, which indicates inflammation of the cornea, iris or ciliary body. Deeper and immobile.
**Papillae vs Follicle**

Papillae - Note the fibrovascular core in which the blood vessels arborize on reaching the surface.

Follicle - Note the large follicles with blood vessels sweeping up from the base over the convexity.

**Ocular Adnexa**

**Hordeolum**

**Blepharitis**

**Ocular Rosacea**
How long ago did it begin?

Acute vs Chronic

Is there pain?
- Dull, stabbing, throbbing or gritty pain

Is there light sensitivity?

Is it just one eye or both?
- Did it start in one eye and go to the other

Is vision affected?
- Does it improve with blinking or AT

Type of discharge?
- nature, volume and persistence

Are they a contact lens wearer?

Has this happened before?

History of exposure?

Been around anyone else with a red eye?
Case History Questions

- Recent surgery?
- Recent trauma?
- Taking any topical medications?
- Taking any oral medications that have ocular SE’s?
- Any Associated symptoms?
  - Headache / Vomiting
  - Recent or concurrent upper respiratory tract infection
  - Skin and mucosal lesions
  - Muscular or skeletal pain
  - Joint stiffness
  - Genitourinary discharge
  - Dysuria

In office tests

- Visual acuity
- Pupils
- EOMS
- Confrontation Fields
- RPS Adnex Plus (Adenodetector)
- Lensometry / Refraction
- Slit Lamp
  - Distinguish between Conjunctival and Ciliary Injection
  - Distinguish between Papillae and Follicle
  - Shape, size and reaction of pupil
  - Anterior Chamber reaction
- Tonometry
- Palpate Nodes
- Corneal sensitivity
- Dilatation
  - Fundus evaluation
- Culture

Red Eye Algorithm

Features / Causes of red eye

Edinburgh Red Eye Diagnostic Algorithm

Treating the Red Eye
Case Study

- JM, 68 year old female
- Initial visit April 16, 2014
- Presented with complaint of:
  - Redness, discharge, swelling OD x 2 days
- Ocular/Medical Hx: Non-contributory

- Slit lamp exam OD
  - Chemosis, lid swelling, faint SEI inferior, subconj hemorrhage
- Slit lamp exam OS
  - Unremarkable

Initial Diagnosis

- Epidemic Keratoconjunctivitis
- Start Zirgan

Epidemic Keratoconjunctivitis

- Viral conjunctivitis caused by adenoviruses 8, 19
- Highly contagious
- Typically unilateral
- No sore throat / fever
- Redness
- Discomfort
- SEI
- Chemosis
- Photophobia

Make me better!!
Helpful to Tx EKC
- There are no FDA-approved medicines to kill adenoviruses
- But, an excellent off-label application of an FDA-approved drug is readily and inexpensive:
  - 5% Betadine Sterile Ophthalmic Prep Solution
- Decreases the viral load
  - Prevents entry into the anterior stroma stopping SEI
- Topical Antimicrobial
- OTC
- Used to apply and clean wound or prep for surgery
- MOA
  - Oxidizes cell constituents
  - Iodinates proteins and inactivates them
- Side Effects
  - Severe pain on application
  - Irritation
  - Pruritic
  - Erythema
  - Edematous erythema

Betadine (povidone iodine)
- Topical Antimicrobial
- OTC
- Used to apply and clean wound or prep for surgery
- MOA
  - Oxidizes cell constituents
  - Iodinates proteins and inactivates them
- Side Effects
  - Severe pain on application
  - Irritation
  - Pruritic
  - Erythema
  - Edematous erythema

Zirgan (0.15% ganciclovir ophthalmic gel)
- Approved 2009 for treatment of acute HSK or dendritic epitheliopathy
- Has been avail in Europe since 1995
- First FDA approval for this class in 3 decades to help treat one of the 60k (29k pts) new cases of HSK each yr
- 1 drop 5x/d (Q3H) until ulcer heals then TID for 7 d
- no toxicity, very quick resolution, very comfortable

Betadine
- Melton-Thomas EKC Betadine Protocol
  1. By history, rule out any allergy or sensitivity to iodine
  2. Instill a drop of 0.5% proparacaine
  3. Instill a drop or two of a topical NSAID.
  4. Instill four to five drops of 5% Betadine onto the eye.
  5. Ask the patient to gently close the eyes and roll them around to ensure thorough distribution of the Betadine across the ocular surfaces.
  6. After 1-2 minutes, lavage out the Betadine
  7. Instill another drop or two of the NEAID (or even proparacaine if the patient has any discomfort).

Zirgan
- Selectively inhibits synthesis of viral DNA
  - Competitive inhibition of viral DNA polymerase
  - direct incorporation into DNA primer strand
- SE’s
  - Blurred Vision (60%)
  - Irritation (20%)
  - SPK (3%)
  - Conj Hyperemia (5%)
- Off label Tx of EKC
  - Safety not established below age of 2
**Off Label Treatments - Zirgan**

- Research presented at ARVO 2001 by Tabarra et al
- 18 patients with EKC
- Compared topical ganciclovir to preservative free tears

<table>
<thead>
<tr>
<th></th>
<th>Recovery Time</th>
<th>Presence of subepithelial opacities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical ganciclovir 0.15%</td>
<td>7.7 days</td>
<td>22%</td>
</tr>
<tr>
<td>Preservative free artificial tears</td>
<td>18.5 days</td>
<td>77%</td>
</tr>
</tbody>
</table>

**Other future treatments**

- SHP640
  - Shire Pharmaceuticals
  - Phase III
  - PVP-Iodine 0.6% and Dexamethasone 0.1% Ophthalmic Suspension
  - Estimated study completion date: May 1, 2018

**Case Study**

- Clinical Exam (4/22/14)
  - Patient much more comfortable
  - Minimal injection
  - No photophobia

**Pre-Betadine**

![Pre-Betadine](image)

**Post-Betadine**

![Post-Betadine](image)
Mary M 54 yo WF presents C/O ocular pain OS.
- School psychologist
- Pressure feeling around eyes. Eyes are red OS>OD
  - Pain radiates up into temples
  - Went to PCP and had work up for sinuses and AB. NO help
  - Seem to water excessively
  - Symptoms began recently – days
  - Episodes are persistent
  - Discomfort is bothersome

Oc Hx
- Floppy Eyelid Synd
- PVD OS
- Myopia, Astig, presbyopia
- SCL wearer
- Med Hx
- Osteoarthritis
- HTN
- GERD
- Overactive bladder
- Fam Hx
  - RA mother

VA CC
- OD 20/25 OS 20/40 Prn 20/25
- Tonometry
  - OD 20mmHg, OS 20mmHg
- Pupils, EOM’s, Conf FULL
- SLE
- LL – cl
- Conj / Sclera
  - 3+ j OD
  - 2+ diffuse jg OS Suprinf
  - Does not blanch with PE
- Cornea – cl
- AC – Q/O
- T=cl
- L – cl
- Vit-cl
- ON – 2rd OU, flat
- Macula
  - OS Cl, OS ERM

Impression
- Diffuse Ant Scleritis OS

Plan
- ????
Scleritis almost always requires treatment with systemic medications.

First line is oral NSAID w or w/o topical steroid
- 100mg Naproxen TID PO
- 500mg Diflunisal BID PO
- 400-600mg Ibuprofen QID PO
- 75mg Indomethacin TID PO
- 750-1000mg Oxyphenbutazone QD
  
Response within 2-3 weeks
  - Sequential trials
  - Selective COX-2 inhibitor
  - 92% success in diffuse & nodular

Prednisone 1-1.5 mg/kg/day x 7-14 days
  - Taper 10mg/wk until 20mg then?
  - IV Methylprednisolone 1g/day x 3 days
  - Periorbital steroid
  - Sub conj
  - Total melting and perforation
  - Orbital floor
  - Amitriptyline for pain out of proportion of signs
  - Reduction in pain for all tx is good indicator of tx success

Scleritis – Associated Diseases

- Necrotizing w/inflamm 50%
  - Wegener
  - RA
  - Polyarteritis nodosa
  - Polyarteritis nodosa

- Necrotizing w/o inflam 100%
  - RA
  - Graft

- Posterior Scleritis 30%
  - RA
  - M.E.
  - Psoriatic arthritis
  - Wegener
  - PAN
  - Polyarteritis

- Infectious (lyme, rosea, etc)

- Underlying dx may not be Dx 22yr

Scleritis – Laboratory Testing

- The testing of scleritis even with the initial presentation requires a thorough diagnostic evaluation to include:
  - CBC – Non specific: infection, tumor, other
  - Urinalysis – kidney / liver dysfunction, metabolic disease
  - Serum chemistries
  - BUN, Creatine, CO2 – Non specific: vasculitis and renal dis
  - FTA-ABS and RPR – syphilis screening / determination
  - BF -RA
  - ESR – Non specific systemic inflammation
  - ANA – RA, SLE, Collagen Vascular Disease
  - ANCA – Wegener’s, polyarteritis nodosa
  - P-ANCA +, C-ANCA

- Chest radiograph – TB, Sarcoid, Wegener’s
**Scleritis – Laboratory Testing**

- Additional testing to consider in appropriate clinical context
  - HLA – typing (B27 etc) – HLA related inflam dis, A.S.
  - ELISA - Lyme serology, HIV
  - Sinus Radiography – Wegener’s granulomatosis
  - Sacroiliac Radiography – A.S.
  - PPD – TB
  - C-Reactive Protein – Non specific systemic inflamm
  - Uric Acid – gout
  - Circulating immune complexes – RA, SLE, Cogan’s
  - Cryoglobulins – RA, SLE
  - ACE - Sarcoid
  - B Scan ultrasound – post Scleritis suspected
  - Scleral biopsy – infectious dis, FB and rare causes

---

**Case Report**

- Impression
  - Diffuse Ant Scleritis OS

- Plan
  - 100mg Flurbiprofen TID PO
  - Pred Forte QID OS
  - Labs ordered (pt reports vials and vials of blood taken)
  - CBC, ANCA, FTA-ABS, RF, HLA, ANA, Lyme, Urinalysis, serum chem
  - NO SCL wear
  - RTO 2 weeks, immed if changes or if pain worsens

---

**Case Report**

- 2 week follow up exam
- Pt reports minimal improvement in pain and HA
- LL – cl
  - Conj / Sclera
  - CI OD, OSI; 1+ diffuse inj OS Sup > inf
  - Cornea – cl
  - AC = D/Q
  - I = nl
  - L = cl
- Ta OS= 34

---

**Case Report**

- Plan
  - D/C Flurbiprofen
  - Start Aleve (Naproxen 200mg) BID PO
  - Recommended Naprosyn 375-500 BID PO
  - D/C Pred Forte
  - Start combigan, Lotemax taper
  - Lab results
  - RTO 2 weeks

---

**Case Study**

- TD, 38 year old white male
- Referred to me by his PCP
- Patient complains of:
  - Redness, pain, photophobia OD x 6 days
  - Tobramycin QID not effective
- Reports unremarkable medical and ocular history
- Entering VA 20/20 OD, OS
- PERRL

---

**Case Report**

- 2 week follow up exam
  - 1 mo since presentation
- Pt reports improvement in pain and HA. Feeling back to normal
  - “Best I have felt in months”
- LL – cl
  - Conj / Sclera
  - OD = cl
  - OS
  - Cornea – cl
  - AC = D/Q
  - I = nl
- L = cl
- Ta OS= 16

---

**Case Report**

- Plan
  - Continue Aleve (Naproxen 200mg) QD PO
  - D/C Combigan
  - RTO 1 month
  - Recurrences

---

**Case Report**

- TD, 38 year old white male
- Referred to me by his PCP
- Patient complains of:
  - Redness, pain, photophobia OD x 6 days
  - Tobramycin QID not effective
- Reports unremarkable medical and ocular history
- Entering VA 20/20 OD, OS
- PERRL
Case Study, Day 1

- Slit lamp exam
  - 3+ cell OD, fine KP
  - Minimal injection
  - IOP 12 mm OD, OS

- Fundus exam
  - Unremarkable OU

- Diagnosis: ??

- Plan
  - Start Pred Forte Q1H OD
  - FML ointment QHS OD
  - Atropine 1% daily OD
  - RTO x 1 day

Patient slightly more comfortable
VA 20/20 OD, OS
Pupils: Dilated OD
2+ to 3 cell, fine KP
IOP 13 mm OU
Continue current treatment- RTO x 3-4 days
Blood work requested

There are no evidence-based guidelines for testing for uveitis
First episodes of acute anterior uveitis, especially if mild, unilateral, non-granulomatous, and responsive to topical corticosteroids probably do not require diagnostic evaluation unless there is evidence for an underlying etiology
- diagnostic testing for first episodes of uveitis should be obtained when there is a high index of suspicion regarding an underlying cause
- the inflammatory response appears granulomatous
- or the inflammation fails to respond to therapy within a reasonable time
Diagnostic evaluation is also recommended for all patients with recurrent or chronic inflammation
There is no "standard" uveitis workup
- The workup must be custom tailored for each patient depending on history, features of disease presentation, and risk factors

Laboratory Testing Guidelines

Blood work
- CRP: normal
- ESR: normal
- ANA: negative
- RF: normal
- Lyme serology: normal
- HLA B27: ??
- Resubmitted for blood draw
Case Study

- **Next steps**
  - Recommend establishing relationship with subspecialist
  - Educate patient on potential chronic, recurrent nature

- Long term options with recurrences?
  - Anecdotal evidence that Restasis may have some benefits in preventing or reducing frequency of recurrences
    - Topical cyclosporine A 0.05% for recurrent anterior uveitis
    - Prabhu SS, Shtein RM, Michelotti MM, Cooney TM
    - Poster Presentation ASCRS 2014

Human Leukocyte Antigen Testing

- Human leukocyte antigen disease
  - HLA-disease associations are simply associations between a major histocompatibility complex molecule, and a clinical condition
  - Testing for HLA can provide supportive evidence for a particular diagnosis but cannot make a definitive diagnosis
  - Statistically it is the increased frequency of an HLA haplotype in persons with that disease, as compared to the frequency in a disease free population
  - The ratio of these two frequencies is the "relative risk"

- Ocular disease associations with HLA Testing
  - HLA-B27
  - HLA-A29
  - HLA-B51
  - HLA-DPB1*0102

- Approximately ___% of acute anterior uveitis cases are associated with HLA-B27+
  - Makes up 20% (37%) of all cases of Chronic Uveitis
  - Makes up 70% of cases of Recurrent Uveitis
  - Lifetime risk of developing anterior uveitis in a patient with HLA-B27+ is approximately 25%
  - Prevalence of this allele in the general United States population is about 8%
    - False-positive rate of 8%
  - HLA-B27 is not a single allele but a family of at least 31 different alleles that encode for HLA-B27 subtypes
    - HLA-B27A1 to HLA-B27J
  - There is a varied distribution of these HLA-B27 subtypes in different populations
    - accounts for the varying strengths of HLA-B27-disease association observed in different ethnic groups
HLA-B27 positivity is associated with a number of presumed autoimmune diseases (seronegative spondyloarthropathy):
- Ankylosing spondylitis
- Reactive arthritis
- Psoriatic arthritis
- Inflammatory bowel disease

Acute, unilateral, sudden onset, non-granulomatous, anterior uveitis, particularly with hypopyon, is characteristic of HLA-B27–positive uveitis:
- Tendency towards recurrent attacks and more severe inflammation, including hypopyon formation
- Males are affected more frequently than females
- 2.5:1
- 20–40 years of age

Patients should be questioned carefully for history of:
- Axial arthritis
- Lower back stiffness and pain (worse on wakening)
- Sacroiliac films can be diagnostic of ankylosing spondylitis
- Relatively low sensitivity
- A positive review of systems should prompt referral to a rheumatologist for workup

40% patients with idiopathic AAU have undiagnosed SpA

A simple to apply algorithm is described with excellent sensitivity and specificity:
- 95% Sensitivity
- 98% Specificity

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>Diagnostic Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic bilateral anterior uveitis, pediatric population</td>
<td>ANA, RF, careful questioning and examination for arthritis (RA, GCA), HLA-B27</td>
</tr>
<tr>
<td>Symptomatic bilateral anterior uveitis, pediatric or young adult population</td>
<td>Urinary beta 2 microglobulin (TINU syndrome)</td>
</tr>
<tr>
<td>Bilateral intermediate uveitis, anterior</td>
<td>Question for neurologic symptoms from demyelinating disease, consider MRI (multiple sclerosis)</td>
</tr>
<tr>
<td>Unilateral severe anterior uveitis (especially with hypopyon)</td>
<td>HLA-B27 (sero-negative spondyloarthropathies: ankylosing spondylitis, reactive arthritis, psoriatic arthritis, inflammatory bowel disease)</td>
</tr>
<tr>
<td>Anterior uveitis</td>
<td>MRI (intraocular lymphoma), 18F-FDG PET/CT</td>
</tr>
<tr>
<td>Bilateral interstitial choroiditis with vitritis due to inflammatory bowel disease</td>
<td>HLA-A29 (birdshot retinochoroidopathy)</td>
</tr>
<tr>
<td>Unilateral retinochoroiditis</td>
<td>Toxoplasma serology (Toxoplasma retinochoroiditis)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>Diagnostic Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic bilateral anterior uveitis, pediatric population</td>
<td>ANA, RF, careful questioning and examination for arthritis (RA, GCA), HLA-B27</td>
</tr>
<tr>
<td>Symptomatic bilateral anterior uveitis, pediatric or young adult population</td>
<td>Urinary beta 2 microglobulin (TINU syndrome)</td>
</tr>
<tr>
<td>Bilateral intermediate uveitis, anterior</td>
<td>Question for neurologic symptoms from demyelinating disease, consider MRI (multiple sclerosis)</td>
</tr>
<tr>
<td>Unilateral severe anterior uveitis (especially with hypopyon)</td>
<td>HLA-B27 (sero-negative spondyloarthropathies: ankylosing spondylitis, reactive arthritis, psoriatic arthritis, inflammatory bowel disease)</td>
</tr>
<tr>
<td>Anterior uveitis</td>
<td>MRI (intraocular lymphoma), 18F-FDG PET/CT</td>
</tr>
<tr>
<td>Bilateral interstitial choroiditis with vitritis due to inflammatory bowel disease</td>
<td>HLA-A29 (birdshot retinochoroidopathy)</td>
</tr>
<tr>
<td>Unilateral retinochoroiditis</td>
<td>Toxoplasma serology (Toxoplasma retinochoroiditis)</td>
</tr>
</tbody>
</table>
Conclusion

- Red eyes can present a diagnostic dilemma and are frequently encountered.
- Stick to a methodical anatomical approach, and pair it with your case history to help make your differentials more easily attainable.
- Pay attention to onset of duration, localization, type of injection, as well as pain and photophobia to help guide your differential.

Thank you

Please feel free to contact us:
Nicholas Colatrella, OD, FAAO, Dipl AAO, ABO, ABCMO
NColatrella@pineconevisioncenter.com

Jeffrey Varanelli, OD, FAAO, Dipl ABO, ABCMO
SECJRVOD@gmail.com