Clinical Grand Rounds
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Background
- From Blowing Rock, NC
- Undergraduate
  - Appalachian State University
- Graduate
  - Indiana University
- Internship
  - Charlotte Eye, Ear, Nose & Throat
- Residency
  - WJB Dorn VAMC - Ocular Disease/Primary Care
Practice

- Purchased October 2016 (originally Visual Eyes Optometric)
- Solo private practice in Shelby, NC
- Located in a micro-urban town
Morning Commute

Research
Topical Flurometholone Protects the Ocular Surface of Dry Eye Patients from Desiccating Stress
A Randomized Controlled Clinical Trial

José Pires-Fraga, MSc,1,2 Alberto López-Miguel, PhD,1,2 María J. González-García, PhD,1,2
Isaí Fernández, PhD,1,2 Alberto López-de-la-Rosa, MSc,1 Arnaud Eustache-de-Salamanca, PhD,1,2
Michael E. Sams, PhD,3 Margarita Galán, MD, PhD,1,2

Purpose: To assess the efficacy of topical 0.1% flurometholone in dry eye disease (DED) patients for ameliorating the worsening of the ocular surface when exposed to adverse environments.
Design: Single-center, double-masked, randomized, vehicle-controlled clinical trial.
Participants: Forty-one patients showing moderate to severe DED.
Methods: Patients randomly received 1 drop 4 times daily of either topical 0.1% flurometholone (FML group) or topical polyvinyl alcohol (PVA group) for 22 days. Corneal and conjunctival staining, conjunctival hyperemia, tear film breakup time (TBUT), tear osmolarity, and the Symptom Assessment in Dry Eye (SANE) questionnaire scores were determined at baseline. Variables were reassessed on day 21 before and after undergoing a 2-hour controlled adverse environment exposure and again on day 22.

Main Outcome Measures: Percentage of patients showing an increase 1 point or more in corneal staining and a reduction of 2 points or more (0–10 scale) in SANE scores, after the controlled adverse environment exposure and 24 hours later.
Results: After 21 days of treatment, the FML group showed greater improvements in corneal and conjunctival staining, hyperemia, and TBUT than the PA group (P<0.03). After the adverse exposure, the percentage of patients having a 1-grade or more increase in corneal staining was significantly (P<0.03) higher in the PA group (83.1% vs. 23.6%, respectively). Additionally, the FML group showed no significant changes in corneal staining (mean, 0.86; 95% confidence interval [CI], 0.47–1.25 vs. mean, 1.05; 95% CI, 0.59–1.51, for visit 2 and 3, respectively), conjunctival staining (mean, 0.86; 95% CI, 0.54–1.37 vs. mean, 1.19; 95% CI, 0.75–1.63, and hyperemia (mean, 0.71; 90% CI, 0.41–1.02 vs. 1.14; 90% CI, 0.71–1.59) after the exposure, whereas the PA group, there was significant worsening (P<0.008) in these variables (corneal staining: mean, 1.85; 95% CI, 1.57–2.13; conjunctival staining: mean, 1.85; 95% CI, 1.29–2.40; TBUT: mean, 2.47; 95% CI, 2.07–2.86; hyperemia mean, 1.98; 95% CI, 1.63–2.36 vs. mean, 2.84; 95% CI, 2.62–3.07).

Conclusions: Three-week topical 0.1% flurometholone therapy is effective not only in reducing ocular surface signs in DED patients, but also especially in preventing exacerbation caused by exposure to a desiccating stress. Ophthalmology 2016;123:141–153 © 2016 by the American Academy of Ophthalmology

Inflammation in Dry Eye Disease
How Do We Break the Cycle?

Michelle K. Bhee, MD,2 Francis S. Mah, MD3

This article reviews the literature and summarizes the role of inflammation in dry eye disease. A PubMed search was performed using the keywords inflammatory cycle and dry eye. All searches were limited to articles published in or translated into the English language, dating from 1973 through March 2017. There were no restrictions on the study design. Advances in understanding the pathogenesis of dry eye disease has revealed that inflammation is a core driver: the so-called "vicious circle" of inflammation. Researchers continue to analyze the precise mechanisms by which inflammation occurs. This has led to therapeutic options to break the cycle. Continued animal and human studies reveal other potential sites for treatment in this complex host of disorders. Ophthalmology 2017;124:S14–S19 © 2017 by the American Academy of Ophthalmology

Establishment of Inflammation's Critical Role in Dry Eye Disease

Dry eye disease (DED) is a heterogeneous disorder of the ocular surface in which the common denominator is inflammation. The recognition of inflammation as a critical driver is reflected by its inclusion in the Dry Eye Workshop definition of DED: "Dry eye disease is a multifactorial disorder of the tears and ocular surface. associated with ocular surface homeostasis, and disruption of this leads to tear film instability. Tear production is regulated through a neural reflex loop; stimulation of nerves at the ocular surface or nasal mucosa sends impulses to the brain via the fifth cranial nerve, triggering a reflex response via nerves passing to the lacrimal glands. Pain, microbial or environmental insults, and emotion can stimulate this reflex loop. When any part of the lacrimal functional unit does not work properly, tear film instability and tear film hyperosmolarity occur. In earlier
Emergency Care

Factors Affecting Visits to the Emergency Department for Urgent and Nonurgent Ocular Conditions

Brian C. Stagg, MD, 1,2 Mustee M. Shah, MD, MS, 2 Naresh Talwar, MA, 2 Dolly A. Padovani-Claudio, MD, PhD, 3 Maria A. Woodward, MD, MS, 4,5 Joshua D. Stern, MD, MS 2

Purpose: To determine the frequency of emergency department (ED) visits for nonurgent and urgent ocular conditions and risk factors associated with ED use for nonurgent and urgent ocular problems.

Design: Retrospective, longitudinal cohort analysis.

Participants: All enrollees aged 21 years or older in a United States managed care network during 2001–2014.

Methods: We identified all enrollees visiting an ED for ocular conditions identified by International Classification of Diseases, billing codes. Diagnosis is well-described as urgent, nonurgent, or other. We assessed the frequency of ED visits for urgent and nonurgent ocular conditions and how they changed over time. Next, we performed multivariable Cox regression modeling to determine factors associated with visiting an ED for urgent or nonurgent ocular conditions.

Main Outcome Measures: Hazard ratios (HRs) with 95% confidence intervals (CIs) of visiting an ED for urgent or nonurgent ocular conditions.

Results: Of the 11,160,833 enrollees eligible for this study, 376,680 (3.4%) had 1 or more ED visit for an eye-related problem over a mean ± standard deviation of 5.4 ± 3.3 years' follow-up. Among these enrollees, 86,473 (23.0%) had 1 or more ED visits with a nonurgent ocular condition and 25,389 (8.7%) had at least 1 ED visit with an urgent ocular condition. Use of the ED for nonurgent ocular problems was associated with younger age (P < 0.0001 for all comparisons), black race or Latino ethnicity (P < 0.0001 for both), male sex (P < 0.0001), lower income (P < 0.0001 for all comparisons), and those who frequently sought treatment at an ED for nonophthalmologic medical problems in a given year (P < 0.0001). Enrollees with established eye care professionals had a 10% reduced hazard of visiting the ED for nonurgent ocular conditions (adjusted HR, 0.90; 95% CI, 0.88–0.92; P < 0.0001).

Conclusions: Nearly one-quarter of enrollees who visited the ED for an ocular problem received a diagnosis of a nonurgent condition. Better educating and incentivizing patients to seek care for nonurgent ocular diseases in an office-based setting could yield considerable cost savings without adversely affecting health outcomes and could allow EDs to better serve patients with more severe conditions. Ophthalmology 2017;11–16 © 2017 by the
We found that younger enrollees were more likely to seek treatment at the ED for nonurgent eye problems compared with older persons. This aligns with several studies in other areas of medicine looking at use of the ED for nonurgent medical conditions. Younger patients tend to have fewer chronic ocular diseases and thus are less likely to have an established eye care provider to go to for routine ocular problems. Younger patients may also not be as aware that costs of care tend to be higher in an ED setting and that EDs often are not staffed routinely by eye care professionals, and thus seeking care in an office setting is often preferable for nonurgent eye conditions. Younger patients are more likely to have work responsibilities during the hours when eye care providers’ offices are open. These persons may be unwilling to miss work to seek care in an office setting and find it more convenient to go to an ED after hours instead. In contrast, older patients may have regular eye care providers who are caring for them for cataracts and other common ocular diseases and would know to contact them when they experience nonurgent problems. Targeted educational initiatives to help younger persons understand the types of services offered and not offered in EDs and how costs are often much higher for care received in EDs may help steer them to care in outpatient clinics instead.

**Discussion**

From 2006 to 2011, more than 4 million ED visits occurred for conjunctivitis, subconjunctival hemorrhages, and styes. All 3 conditions pose no threat to vision and can be managed at eye clinics or urgent care, walk-in medical facilities across the country. Identifying strategies to shift these visits to eye clinics offers several important advantages. First, ED resources could be better focused on patients who truly need emergent care. Second, the patient would likely have a more expert evaluation by an eye care professional (most EDs do not have one). Third, those patients seen in an eye clinic likely would receive screening for potentially blinding conditions such as glaucoma, diabetic retinopathy, and macular degeneration. Fourth, national health care costs would be greatly reduced.

Nonurgent care costs 2 to 3 times more when provided in the ED compared with similar visits in other settings, and ophthalmic care is no exception to the rule. The cost of care for conjunctivitis, for example, is estimated to be $390 in the ED in our institution vs $101 in an urgent care center and $136 in an ophthalmologist’s office. Even in an after-hours setting, when ophthalmology offices are more likely to be closed, care provided at walk-in urgent care clinics is estimated to be far less costly than similar care provided in an ED setting. The cost burden of ED visits for eye conditions could be reduced if patients with the top 3 nonemergent conditions were seen at eye clinics during working hours or at urgent care centers after hours. However, the trend noted in our study has been otherwise: the proportion of emergent ED visits has decreased and that of nonemergent ED visits has increased from 2006 to 2011.
Why Emergency Care?

- The Eye and ED
  - Why do people go to the ED with eye issues?
    - Most Common ICD Diagnosis
      - Conjunctivitis 33%
      - Corneal injury 13%
      - Corneal FB 8%
      - Hordeolum 4%
    - Mean ED charge: $989.30 for eye visit
      - "Follow-up w your ophthalmologist optometrist"
    - Eye visits: 1.5% of all visits
    - 32,000 eye-related visits per year
**Why Emergency Care?**

- “...ED visits cost, on average, 4 times more than visits to an office setting for comparable medical problems, resulting in **$580 in higher costs per visit**.”
- “... nonurgent medical conditions may contribute to ED overcrowding, which can lead to delays in the care of other patients with more urgent medical problems.”
- “**We found a 30% increase in the number of enrollees visiting the ED for ocular problems from 2001 to 2014.**”
- “In conclusion, nearly one quarter of enrollees visiting the ED for ocular conditions do so for nonurgent conditions.”

- Oph. Nov 2017

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**24/7 Emergency Services**

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24/7 Emergency Services
Initial Resistance

- From Urgent Cares
- From MDs
- From healthcare providers

Solution
Role of Ophthalmology in Eye Care
Influences of Drug Cost on Patient Care
Influences of Drug Cost on Patient Care
Pred-Gati-Brom™ Suspension 3.5mL
(Prednisolone acetate 1%, gatifloxacin 0.5% and bromfenac 0.075%)

- Unit Size: 3.5 mL
- Package Size: 20 per Box
- Package Price: $760.00

Shipped in boxes of 20.
Guaranteed expiration date of 60 days.

SKU: 300000019267533
Manufacturer part number: LD005

$38/bottle
“Our compounded drugs are not FDA-approved as a whole, but each ingredient we use is FDA-approved. Since we are a compounding pharmacy, that is FDA-registered and inspected, we are able to compound these FDA-approved ingredients. Let me know if I need to explain a little clearer. If you have any other questions, please let me know. Thank you!”

- Imprimis
A Word About Steroids...

The Role of Steroids in My Clinic

- Steroids are by far the best drug ODs can prescribe across the board
- I prescribe oral and/or topical steroids on a daily basis, multiple times a day
- I have never had a single case get worse on steroids (hundreds of cases over 2 years)
- Think red eye, think steroids
- Aggressive dosing schedules
- I will not always taper a steroid
- Plenty of reasons to rx, ONE contraindication
  - Active epithelial herpetic infection
**Ester vs Ketone Corticosteroids**

### Ester

- Loteprednol

### Ketone

- Prednisolone
- Fluorometholone
- Dexamethasone
- Rimexolone
- Difluprednate

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**TOPICAL CORTICOSTEROID DRUGS**

<table>
<thead>
<tr>
<th>BRAND NAME</th>
<th>GENERIC NAME</th>
<th>MANUFACTURER</th>
<th>PREPARATION</th>
<th>BOTTLE/TUBE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durezol</td>
<td>difluprednate 0.05%</td>
<td>Alcon</td>
<td>emulsion</td>
<td>5ml</td>
</tr>
<tr>
<td>Lotemax gel</td>
<td>loteprednol etabonate 0.5%</td>
<td>Bausch + Lomb</td>
<td>gel drops</td>
<td>5g</td>
</tr>
<tr>
<td>Lotemax ointment</td>
<td>loteprednol etabonate 0.5%</td>
<td>Bausch + Lomb</td>
<td>ointment</td>
<td>3.5g</td>
</tr>
<tr>
<td>Pred Forte</td>
<td>prednisolone acetate 1%</td>
<td>Allergan and generic</td>
<td>suspension</td>
<td>5ml, 10ml, 15ml</td>
</tr>
<tr>
<td>generic prednisolone sodium phosphate</td>
<td>prednisolone sodium phosphate 1%</td>
<td>generic</td>
<td>solution</td>
<td>5ml, 10ml, 15ml</td>
</tr>
<tr>
<td>Maxidex</td>
<td>dexamethasone 0.1%</td>
<td>Novartis</td>
<td>suspension</td>
<td>5ml</td>
</tr>
<tr>
<td>Vexol</td>
<td>rimexolone 1%</td>
<td>Novartis</td>
<td>suspension</td>
<td>5ml, 10ml</td>
</tr>
</tbody>
</table>

**Moderate and Lesser Strength Steroids**

<table>
<thead>
<tr>
<th>BRAND NAME</th>
<th>GENERIC NAME</th>
<th>MANUFACTURER</th>
<th>PREPARATION</th>
<th>BOTTLE/TUBE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alrex</td>
<td>loteprednol etabonate 0.2%</td>
<td>Bausch + Lomb</td>
<td>suspension</td>
<td>5ml, 10ml</td>
</tr>
<tr>
<td>Flarex</td>
<td>fluorometholone acetate 0.1%</td>
<td>Novartis</td>
<td>suspension</td>
<td>5ml, 10ml</td>
</tr>
<tr>
<td>FML</td>
<td>fluorometholone alcohol 0.1%</td>
<td>Allergan and generic</td>
<td>suspension</td>
<td>5ml, 10ml, 15ml</td>
</tr>
<tr>
<td>FML ointment</td>
<td>fluorometholone alcohol 0.1%</td>
<td>Allergan</td>
<td>ointment</td>
<td>3.5g</td>
</tr>
<tr>
<td>Pred Mild</td>
<td>prednisolone acetate 0.12%</td>
<td>Allergan</td>
<td>suspension</td>
<td>5ml, 10ml</td>
</tr>
</tbody>
</table>
Lotemax in a Rat Model

Systemic Prednisone
- Most commonly prescribed systemic corticosteroid in medicine
- Common initial dosage 40-60mg
- Available generically in both tablets and DosePaks (5 or 10mg at 6 or 12 day course)
- Questions to ask prior to rx??
  - DM
  - Peptic Ulcer Disease
  - Tuberculosis
  - Pregnant
• Perspective on Oral Prednisolone
  • Using oral prednisolone at 1.250mg/day is equivalent to 1,000mg of IV methylprednisolone sodium succinate (Solu-Medrol) for 3 days in treating acute optic neuritis
  • “... no significant difference in adverse events between the groups.”
• And ODs concerned about using 40-60mg/day??

JAMA Neurology, June 2018
Maxitrol

Grand Rounds
Case 1

- Background
  - 34yo white female with slowly progressive eye pain OD x 3-4 days referred from PCP
  - H/o CL wear, sleeps in CLs
  - Light sensitive, difficulty opening eye, watery discharge
- VA
  - OD: 20/30, OS: 20/20
- IOP normal OU
- Gr trace AC rxn
- Pain 6/10
Case #1

Case #1
**PEDAL**

- Pain
- Epithelial defects
- Discharge
- Anterior chamber rxn
- Location

<table>
<thead>
<tr>
<th></th>
<th>Infective</th>
<th>Sterile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>Larger</td>
<td>Smaller</td>
</tr>
<tr>
<td>Progression</td>
<td>Rapid</td>
<td>Slow</td>
</tr>
<tr>
<td>Epithelial defect</td>
<td>Less common; large</td>
<td>Very common; small</td>
</tr>
<tr>
<td>Pain</td>
<td>Moderate/severe</td>
<td>Mild*</td>
</tr>
<tr>
<td>Discharge</td>
<td>Purulent</td>
<td>Watery</td>
</tr>
<tr>
<td>Single or multiple</td>
<td>Single</td>
<td>Multiple</td>
</tr>
<tr>
<td>Unilateral or bilateral</td>
<td>Usually unilateral</td>
<td>Either</td>
</tr>
<tr>
<td>Anterior chamber rxn</td>
<td>Severe</td>
<td>Mild</td>
</tr>
<tr>
<td>Location</td>
<td>Often central</td>
<td>Peripheral</td>
</tr>
<tr>
<td>Adjacent corneal rxn</td>
<td>Extensive</td>
<td>Limited</td>
</tr>
</tbody>
</table>
**Corneal Infiltrate**

- **Background**
- **How to treat?**
  - Suspend CL wear
  - Culture?
  - Tx?
  - **Antibiotic and steroid therapy**
    - Maxitrol/tobradex/zylet
- **Ulcer vs infiltrate**

### Sterile infiltrates vs. Infectious Infiltrates

<table>
<thead>
<tr>
<th>Sterile Infiltrates</th>
<th>Infectious Infiltrates (MK)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smaller lesion (&lt; 1 mm)</td>
<td>Larger lesion (&gt; 1 mm)</td>
</tr>
<tr>
<td>More peripheral</td>
<td>More central</td>
</tr>
<tr>
<td>Minimal epithelial damage</td>
<td>Significant epithelial defect</td>
</tr>
<tr>
<td>(Defect size compared to underlying infiltrate)</td>
<td>(Size of staining defect closely mirrors size of underlying stromal lesion)</td>
</tr>
<tr>
<td>No mucous discharge</td>
<td>Mucopurulent discharge</td>
</tr>
<tr>
<td>Loss pain and photophobia</td>
<td>Pain and photophobia</td>
</tr>
<tr>
<td>Little to no anterior chamber reaction</td>
<td>Anterior chamber reaction</td>
</tr>
<tr>
<td>No lid involvement</td>
<td>Lid edema</td>
</tr>
</tbody>
</table>


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**Six Layers of the Cornea?**

A recent paper identifies a sixth corneal layer—Dua's layer—between the posterior stroma and Descemet's membrane.

![Six Layers of the Cornea Diagram](image)
“Left untreated, infiltrates generally disappear within a week or two. Ocular steroids have been shown to be the best and only recognized drug therapy for sterile marginal infiltrates, and their application will shorten the course of inflammation, regardless of causative origin. For many patients, a quicker recovery from symptoms such as redness, tearing, and discomfort is important for improving their quality of life. Steroids are often prescribed in conjunction with an antibiotic in order to decrease the chance of developing a secondary infection or corneal ulcer and to protect against misdiagnosis.”

Case 2

Case #2

• Background
  • 27yo AAF referred from ER
  • Woke up yesterday, reports she cant see out of her OD at all
  • Unremarkable PMHx/FMHx
  • Minimal pain on eye movement
• 3+ APD OD
• VA
  • OD: HM
  • OS: 20/20-
Multiple Sclerosis

- Multiple Sclerosis
  - Optic Neuritis as an initial presentation of MS
    - Initial manifestation of MS in 20% of patients
- The 4 Types of MS:
  - Relapsing-remitting (RR) MS
  - Primary-progressive (PP) MS
  - Secondary-progressive (SP) MS
  - Progressive-relapsing (PR) MS
Multiple Sclerosis and the Body

Visual disturbances
(blurred vision, color distortions, loss of vision in one eye, eye pain)

Mental changes
(decreased concentration, attention deficit, memory loss)

Loss of sensation,
speech impediment,
tremors, or dizziness

Depression
Paranoid
Uncontrollable laughter
and weeping

Limb weakness,
loss of coordination
and balance

Muscle spasms,
fatigue, numbness,
prickling pain

Bladder and
bowel dysfunction
Symptoms of Optic Neuritis

- The patient will commonly have classic complaints in the setting of optic neuritis:
  - Loss of vision over a period of hours to days
    - Most patients are 20/40 or better
  - Pain on eye movement
  - **Typical age of patient 18 to 45**
    - Caucasian women
  - Typically unilateral, but may be bilateral especially in children after a viral infection
  - Decreased color vision
  - Decreased light perception
  - Weakness, numbness, tingling in extremities
  - Uthoff’s sign

Signs of Optic Neuritis

- Clinically, the doctor will often note one or several signs associated with multiple sclerosis:
  - RAPD
  - Visual Field Defect
    - Central, cecocentral, arcuate, altitudinal
  - Swollen disk - 1/3 of patients
    - Papillitis
    - Usually no associated flame shaped hemorrhages
  - Normal appearing disk - 2/3 of patients
    - Retrobulbar
**Differential Diagnosis**
- Ischemic Optic Neuropathy
- Acute papilledema
- Severe systemic hypertension
- Orbital tumor
- Intracranial mass affecting the afferent pathway
- Toxic optic neuropathy

**Etiologies of Optic Neuritis**
- Idiopathic
- **Multiple Sclerosis**
- Viral Infections
  - HZO - symptoms? Age appropriate?
- Granulomatous etiologies
  - Syphilis - “great mimicker”
  - Sarcoid
  - TB
Work-Up

- Careful history!
  - H/o pain with eye movement, previous episode?
- Pupil assessment, color vision, visual field, dilated exam
- **Blood pressure**; order other labs if granulomatous etiology is suspected
- **MRI of the brain and orbits with fat suppression**

- **Atypical presentation** (out of age range/no pain with eye movement)
  - Blood work: CBC with differential, VDRL, FTA-ABS, ANA, ESR, CRP, ACE, chest X-ray, PPD with anergy panel
Next Step?

Treatment
Treatment

- If the patient is seen acutely with **no prior history of multiple sclerosis** or optic neuritis:
  - **MRI reveals at least one area of demyelination:**
    - IV steroids (methylprednisolone 1g/day for 3 days)
    - Prednisone 1mg/kg/day p.o. for 11 days
    - Taper prednisone over 4 days
    - Should you use oral steroids as initial tx?
  - **MRI reveals two or more areas of demyelination:**
    - Treat with the protocol mentioned above, plus:
      - Interferon-B-1a or Gilenya within 28 days

- VA typically recovers in _________

Optic Neuritis Treatment Trial

- High dose IV methyl-prednisolone (**IVMP**) and low-dose oral prednisone (**OP**) compared
  - **457 patients with acute optic neuritis**
• **Findings: OP had no impact on visual recovery and doubled the recurrence rate of optic neuritis**

• Steroid treatment reduced progression to CDMS for 3 years

• Steroids increased the rapidity of visual return...
  • But **NOT** final visual outcome

• Patients with **one or more** demyelinated lesions on MRI had a **72%** chance of developing CDMS within 15 years

• With **no lesions** on MRI, the patient has a **25%** chance of developing CDMS within 15 years

• **Best predictor of optic neuritis developing into clinical MS?**

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**Case 3**
Case # 3

• Background
  • 23yo female referred from PCP for “the worst case of shingles I’ve ever seen in the eye for a young person”
  • H/o VARIVAX vaccine as a child
  • “OD swollen shut, swelling seems to be getting worse”
  • Started on Valtrex 500mg TID PO per PCP
• VA
  • OD: 20/150 OS: 20/20
• IOP
  • OD: 29 OS: 14
  • Gr 2 AC rxn OD
Periorbital Bullous Impetigo

- **Background**
  - Most commonly presents in newborns secondary to a bacterial infection
    - *Staphylococcus aureus*
  - Exotoxins cause the epidermis and dermis to separate
  - Vesicles enlarge to quickly form a blister rash

- **Diagnosis**
  - Appearance of skin
    - **Swab culture**

- **Treatment**
  - Antibiotics (oral/topical)
  - Cycloplegia
  - Steroid

Begin treatment w Augmentin s/p 24 hours
Day 4

Day 5
Day 6

Day 7
Day 10

Day 11
Present Day

Take Away

- Take a diagnosis at face value
- Do your own research!
- What may look intimidating can be very straightforward
Case 4

- Background
  - 25yo AA male c/o unilateral VA loss (OS) x several weeks
  - Painless, feels like there is a “drop of water in my vision”
- VA
  - OD: 20/20, OS: 20/70, PH: 20/50
- IOP
  - OD: 17 OS: 16
- Posterior seg...
Idiopathic Central Serous Chorioretinopathy

• Background
  • Refer?
  • Leakage of fluid from the choroid into the subretinal space
  • Typically in males aged 20-50yo
  • Typically unilateral, rare in AA
• Questions to ask?
  • Stress??
  • Steroid usage
  • Pregnancy
  • HTN
  • Cushing's
• Diagnostics
  • OCT
    • Subretinal fluid, thickened choroid
  • FA
    • "Smoke-stack" leakage

Idiopathic Central Serous Chorioretinopathy

• Treatment
  • Stop steroid use
  • Monitor, patient education
  • Laser photocoagulation?
  • PDT?
• What is the prognosis for visual recovery?
• Recurrence is seen in up to _____%
Serous Retinal Detachment

Pigment Epithelial Detachment

Acquired using enhanced depth mode.
Case 5

- Background
  - 12yo CM presents for trauma to OD x 3 hours
  - Hit in the eye with a wiffle ball in batting practice while the team was traveling out of town
  - Mother called our office and asked to prescribe maxitrol!
  - Pt reports 5/10 eye pain and blurry vision
  - Told her to go see a local MD OD in area
Blunt globe trauma

- Blunt trauma
  - Cornea
    - Abrasion, corneal edema, tears in Descemet
  - Hyphema
    - Common complication
    - Source of bleeding: iris root or ciliary body
  - Pupil
    - Radial tears in pupillary margin
    - Iris may become compresses with anterior surface of lens
    - Iridodialysis
  - IOP
  - Lens
    - Cataract, subluxation, dislocation
  - Globe rupture
  - Vit heme
  - Commotio retinae
  - Choroidal rupture
  - Retinal breaks
  - Traumatic optic neuropathy

Dear Dr. Vollmer,
I saw Walker Henderson on 10/12/16 for an emergency eye visit. He was struck in OD with a wiffle ball the evening before. Below are the findings from today’s exam:

Right eye: 20/20-2
Left eye: 20/20-1

Intraocular Pressure:
OD: 20 mm Hg

OD:
- Inferior hyphema - 1.5mm deep
- 2+ cell
- 2+ flare
dilated with 2gtts 1% tropic
poor views due to cells/flare but retina intact as viewed

The examination resulted in the following diagnoses and associated plans:

Secondary noninfectious iridocyclitis, right eye Hyphema, right eye

start pred QID, cyclo BID: Discussed with patient and mom that patient will be very light sensitive due to both gits and inflammation. Discused importance of limiting physical activity due to risk of rebleed. Phone consult with Dr. Crandall-recommends NO activity over the weekend due to risk of rebled-spoke with mom on the phone after phone consult to discuss. Pharmacy did not have cyclo-change to atropine QD. Patient
• Traumatic iritis

• Patient
  • Plays baseball all weekend anyway
  • Mother states “eye didn’t look that bad” to her; her kid seems fine
  • DOES take drops as directed
• At presentation 5 days after initial trauma:
  • Grade 4 cell, 3 flare, 2.5 mm hyphema, 3+ corneal microcystic edema, 2+ injection of bulbar conjunctiva
• VA
  • OD: 20/25, OS: 20/20
• IOP
  • OD: 17  OS: 14
• Now what?
Work-up

- Work-up
- R/o globe rupture
- Check IOP
- Measure hyphema height
- Grade AC rxn
- Perform DFE
Follow-up

First follow-up visit 4th day after trauma Pt reports some decreased pain
Taking durezol Q2H, atropine Q1H, timolol 0.25%

OAM
Cornea
Stable vision
OD: 18 OS: 16
Gr 2 microcystic edema
Hyphema
Regressed from 2mm to 1mm

Now what?

Traumatic iritis

New plan
• Stop pred forte
• Cont atropine OD
• Start durezol Q2H OD
• NO PHYSICAL ACTIVITY
• Shield over eye vs patch?

A note on steroids with children
Often will get rapid increases in IOP
Risk of cataracts with prolonged usage
Therefore...
Add timolol 0.25% QAM OD
IOP lowering agent to avoid?
Follow-up

- Second follow-up visit
  - 6th day after trauma
  - Pt reports some decreased pain
  - Taking durezol Q2H, atropine Q1H, timolol 0.25% QAM
- Stable vision
- IOP
  - OD: 17 OS: 15
- Cornea
  - Gr 1 microcystic edema
- Hyphema
  - <0.5mm
- AC rxn
  - Minimal improvement, still grade 3/3+ cell, gr 1+ flare
Follow up

- Third follow-up visit
  - 8th day after trauma
  - Pt reports some decreased pain
  - Taking durezol Q2H, atropine Q1H, timolol 0.25% QAM
  - Stable vision
  - IOP
    - OD: 14 OS: 15
  - Cornea
    - Gr trace microcystic edema
  - Hyphema
    - Resolved
  - AC rxn
    - Grade 3 cell; no flare
Follow up

- Fourth follow-up visit
  - 11th day after trauma
  - No pain
  - Taking durezol Q2H, atropine Q1H, timolol 0.25% QAM
  - Stable vision
  - IOP
    - OD: 15 OS: 16
  - Cornea
    - No microcystic edema
  - Hyphema
    - Resolved
  - AC rxn
    - Grade 2 cell; no flare

Follow up

- Fifth follow-up visit
  - 13th day after trauma
  - No pain
  - Taking durezol QID, atropine Q1H, timolol 0.25% QAM
  - Stable vision
  - IOP
    - OD: 13 OS: 14
  - Cornea
    - No microcystic edema
  - Hyphema
    - Resolved
  - AC rxn
    - Grade 1+ cell; no flare
Follow up

Sixth follow-up visit
- 17th day after trauma
- No pain
- Taking durezol QID, atropine Q1H, timolol 0.25% QAM
- Stable vision
- IOP
  - OD: 13 OS: 14
- Cornea
  - No microcystic edema
- Hyphema
  - Resolved
- AC rxn
  - Grade 1 cell; no flare

Follow up

Seventh follow-up visit
- 21th day after trauma
- No pain
- Taking durezol BID, atropine Q1H, timolol 0.25% QAM
- Stable vision
- IOP
  - OD: 15 OS: 15
- Cornea
  - No microcystic edema
- Hyphema
  - Resolved
- AC rxn
  - Grade trace cell; no flare
Follow up

- Eighth follow-up visit
  - 28th day after trauma
  - No pain
  - Taking durezol QD OD
  - Stable vision
  - IOP
    - OD: 16 OS: 15
  - Cornea
    - No microcystic edema
  - Hyphema
    - Resolved
  - AC rxn
    - No cell
    - Resolution

Case 6
Case # 6

• Background
  • **Sudden** onset bilateral eye pain OS>>OD x 1 day
  • Very light sensitive, watery discharge presently OU
  • Went to the urgent care at the beach the day before
    • Diagnosed with viral conjunctivitis
    • Rx: ciprofloxacin QID OU
**Background**
- Sudden onset bilateral eye pain OS>>OD x 1 day
- Very light sensitive, watery discharge presently OU
- Went to the urgent care the day before
  - Diagnosed with viral conjunctivitis
  - Rx: ciprofloxacin QID OU
  - *No staining pattern noted OU*
- H/o CL wear
  - Sleeps in CLs and was wearing them in pool
- VA
  - OD: 20/70
  - OS: 20/400 EF
- IOP
  - OD: 18, OS: 14
- Gr 2 AC rxn OD; Gr 3 AC rxn OS
Bacterial Ulcers

• Background
  • Bacterial Ulcers
    • Small ulcers (< 2mm)
    • Large ulcers
      • Potential to quickly cause devastating loss of vision
      • Incidence 30,000 to 75,000 cases per year
• History
  • Ask about pain
    • Bacterial ulcer: “Feels like there is a rock in my eye/got poked”
    • FB sensation tells you that there is an epithelial defect
    • Nonbacterial or non-infectious keratitis: “A toothache in my eye, or when light hits my eye it really hurts”
• CL wear?
  • Swimming or sleeping in CLs? Cleaning?
  • Risk factors?
• Exam
  • VA, SL, IOP
  • SL findings?

Bacterial Ulcers

• Culture
  • Profile the ulcer
  • Infectious vs non-infectious
  • When to culture?
    • Peripheral ulcers?
    • Central ulcers greater than 2mm
• How to culture
  • Instill anesthetic
  • Kimura spatula
  • Remove mucous and necrotic tissue
  • Scrape the margins and base
  • Place and seal in tube to send to lab
    • Unless culture plates available
• Diagnosis?
Pseudomonas

- **Pseudomonas**
  - Gram (-)
  - **Aggressive**
  - Responsible for over 60% of CL related keratitis
- **Signs**
  - Epithelial defect with infiltrate involving a larger area
  - Severe injection
  - Corneal edema
  - AC rxn
  - Hypopyon
  - Chemosis and eyelid swelling
- **DDx?**
  - Why does this HAVE to be bacterial?

**Treatment**

- **Antibiotic monotherapy vs duotherapy**
- Topical fluoroquinolone
- Fortified antibiotics
- Cycloplegic
- Steroids?
  - **SCUT**
- When to rx systemic antibiotics?
  - Potential systemic involvement
  - Severe corneal thinning
  - Scleral involvement
Update on the Management of Infectious Keratitis

Ariana Austin, MD, Tom Lieman, MD, Jennifer Rose-Nussbaumer, MD

Infectious keratitis is a major global cause of visual impairment and blindness, often affecting marginalized populations. Proper diagnosis of the causative organism is critical, and although culture remains the prevailing diagnostic tool, newer techniques such as in vivo confocal microscopy are helpful for diagnosing fungus and Acanthamoeba. Next-generation sequencing holds the potential for early and accurate diagnosis even for organisms that are difficult to culture by conventional methods. Topical antibiotics remain the best treatment for bacterial keratitis, and a recent review found all commonly prescribed topical antibiotics to be equally effective. However, outcomes remain poor secondary to corneal melting, scarring, and perforation. Adjuvant therapies aimed at reducing the immune response associated with keratitis include topical corticosteroids. The large, randomized, controlled Steroids for Corneal Ulcers Trial found that although steroids provided no significant improvement overall, they did seem beneficial for ulcers that were central, deep or large, non-Nocardia or classicaly invasive Pseudomonas aeruginosa; for patients with low baseline vision; and when started early after the initiation of antibiotics. Fungal ulcers often have worse clinical outcomes than bacterial ulcers, with no new treatments since the 1960s when topical natamycin was introduced. The randomized controlled Mycotic Ulcer Treatment Trial (MUTT) showed a benefit of topical natamycin over topical voriconazole for fungal ulcers, particularly among those caused by Fusarium. MUTT showed that oral voriconazole did not improve outcomes overall, although there may have been some effect among Fusarium ulcers. Given an increase in nonsensory adverse events, the authors concluded that they could not recommend oral voriconazole. Viral keratitis differs from bacterial and fungal cases in that it is often recurrent and is common in developed countries. The Herpetic Eye Disease Study (HEDS) showed a significant benefit of topical corticosteroids and oral acyclovir for stromal keratitis. HEDS showed that oral acyclovir decreased the recurrence of any type of herpes simplex virus keratitis by approximately half. Future strategies to reduce the morbidity associated with infectious keratitis are multidimensional, with adjuvant therapies aimed at modifying the immune response to infection holding the greatest potential to improve clinical outcomes. Ophthalmology 2017;124:1676-1689 © 2017 by the American Academy of Ophthalmology

Table 1. Relevant Randomized Clinical Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Question</th>
<th>Finding</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacurad Keratitis</td>
<td>Ocular keratitis vs. placebo</td>
<td>All treatments resulted in similar outcomes and rates of adverse events</td>
<td>Single-blind, high vs. low dose</td>
</tr>
<tr>
<td>Conigliaro et al., 2007</td>
<td>Ocular keratitis vs. placebo</td>
<td>89 cases</td>
<td>Low back pain, no significant difference</td>
</tr>
<tr>
<td>Delphax et al., 2007</td>
<td>Ocular keratitis vs. placebo</td>
<td>89 cases</td>
<td>Low back pain, no significant difference</td>
</tr>
<tr>
<td>Erdin et al., 2007</td>
<td>Ocular keratitis vs. placebo</td>
<td>89 cases</td>
<td>Low back pain, no significant difference</td>
</tr>
<tr>
<td>Kaustov et al., 2008</td>
<td>Ocular keratitis vs. placebo</td>
<td>89 cases</td>
<td>Low back pain, no significant difference</td>
</tr>
<tr>
<td>O'Brien et al., 2009</td>
<td>Ocular keratitis vs. placebo</td>
<td>89 cases</td>
<td>Low back pain, no significant difference</td>
</tr>
<tr>
<td>Paredes et al., 2009</td>
<td>Ocular keratitis vs. placebo</td>
<td>89 cases</td>
<td>Low back pain, no significant difference</td>
</tr>
<tr>
<td>Pumar et al., 2009</td>
<td>Ocular keratitis vs. placebo</td>
<td>89 cases</td>
<td>Low back pain, no significant difference</td>
</tr>
<tr>
<td>Olmos et al., 2009</td>
<td>Ocular keratitis vs. placebo</td>
<td>89 cases</td>
<td>Low back pain, no significant difference</td>
</tr>
<tr>
<td>Peppe et al., 2009</td>
<td>Ocular keratitis vs. placebo</td>
<td>89 cases</td>
<td>Low back pain, no significant difference</td>
</tr>
<tr>
<td>Salk et al., 2009</td>
<td>Ocular keratitis vs. placebo</td>
<td>89 cases</td>
<td>Low back pain, no significant difference</td>
</tr>
<tr>
<td>Sharma et al., 2009</td>
<td>Ocular keratitis vs. placebo</td>
<td>89 cases</td>
<td>Low back pain, no significant difference</td>
</tr>
</tbody>
</table>

*Results may not be generalizable.
Making a fortified antibiotic

- You will need:
  - IV gentamicin (2cc vials with 40mg/cc)
  - Ophthalmic gentamicin (5cc bottle with 3mg/ml)
  - 18 gauge needle
- Sterilely inject IV gentamicin into the gentamicin bottle
- Yields: 7cc of fortified gentamicin (13.6 mg/cc)
- Very broad gram (-) and gram (+) coverage

Bacterial Keratitis

In the United States, bacterial keratitis is most associated with contact lens use. Severe cases can progress rapidly and cause permanent vision loss requiring corneal transplantation.

Antibiotics

Topical antibiotics remain the first-line treatment for bacterial keratitis. Clinicians weigh many factors when choosing an antibiotic regimen, including broad-spectrum coverage, toxicity, availability and cost, and region-specific epidemiology of pathogens and resistance patterns. Indeed, a recent international survey of cornea specialists found that concerns over several of these factors were predictive of antibiotic choice.
Treatment

• Treatment
  • Continue ciprofloxacin OU alternating with fortified gentamicin Q30min OU
  • Cycloplegic QID OU
  • Polysporin ointment at night
  • Steroid?

OD: Day 4
OS: Day 4

OS: Day 7
OS: Day 10

OS: Day 14
Reminder

• Assume all ulcers are bacterial until proven otherwise
• DON’T wait for results for culture before starting therapy
• Refer to ophthalmology?

Case 7
Case #7

- Background
  - 6yo CF with mucous discharge OU x 4 days and slowly getting worse
  - Referred from a friend
  - Mild fever, eyes are sore and hurt, FB sensation

Presentation
Bacterial Conjunctivitis

- **Work-up**
  - Preauricular node involvement?
  - K-involvement?
- **Etiology**
  - Commonly *Staphylococcus aureus*, *Staphylococcus epidermis*, or *Haemophilis influenza*
  - Hyperacute?
    - *Gonococcus*
    - Examine entire corneal for peripheral ulcers due to risk of penetration
  - Must report to DSS
- **Treatment**
  - Topical antibiotic therapy, warm soaks, Keflex
- **Follow-up**
  - 2 days

---

Bacterial Conjunctivitis

- Unilateral or bilateral red eye(s) with purulent or mucopurulent discharge of varying degree
- SPK?
- Chemosis may be present in more severe cases
- **Therapy:**  
  - **Adults:** Tobramycin, Polytrim, or Fluoroquinolone
  - **Children:** Polytrim or Azasite solution or Polysporin
- Treat for five to seven days as a rule
### Bacterial Conjunctivitis: Keflex dosing

<table>
<thead>
<tr>
<th>WEIGHT (LB)</th>
<th>WEIGHT (Kg)</th>
<th>125 mg/5 ml</th>
<th>250 mg/5 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>5</td>
<td>1/2 tsp</td>
<td>1/4 tsp</td>
</tr>
<tr>
<td>22</td>
<td>10</td>
<td>1 tsp</td>
<td>1/2 tsp</td>
</tr>
<tr>
<td>33</td>
<td>15</td>
<td>1 1/2 tsp</td>
<td>3/4 tsp</td>
</tr>
<tr>
<td>44</td>
<td>20</td>
<td>2 tsp</td>
<td>1 tsp (250 mg cap)</td>
</tr>
<tr>
<td>66</td>
<td>30</td>
<td>–</td>
<td>1 1/2 tsp</td>
</tr>
<tr>
<td>88+</td>
<td>40+</td>
<td>–</td>
<td>2 tsp (500 mg cap)</td>
</tr>
</tbody>
</table>

*Photograph following morning*
Case 8

- Background
  - 2yo CM referred from urgent care for swollen OS, suspect orbital cellulitis
  - Sudden onset, woke-up like this
  - NO pain, NO fever
Eyelid edema

Presentation

- Work-up
  - Fever?
  - Pain on eye movement?
  - Discharge?
  - Onset?
  - Tender to touch?
  - VA, IOPs, SL
- Treatment
  - Children’s Benadryl: maximum dose as directed
  - Lotemax drops q2h
  - Ice compresses as much as possible
Mosquito bite follow-up

Mosquito bite follow-up
Mosquito bite follow-up

Mosquito bite follow-up
Mosquito bite follow-up
Case 9

- Background
  - 34yo HF presents for eye infection (OS) that has been getting worse over 5 days
  - Lower lid is tender and very sore to touch
  - No h/o CL wear
  - Trace mucous discharge from lesion on lower lid
  - No decreases in VA
• Hordeolum
  • Symptoms: acute swelling and tenderness
  • Signs: well-defined subcutaneous nodule in the eyelid, clogged MG orifice, localized tenderness, associated blepharitis/roacea
  • DDx: preseptal cellulitis, pyogenic granuloma, sebaceous carcinoma
  • Treatment
    • Warm compress, lid massage
    • Topical antibiotic/steroid combination
    • Oral antibiotic: penicillin, cephalosporins, tetracyclines, macrolides, fluoroquinolones
    • Non-resolving: incision and curettage, injection of steroid?

• Cephalexin - 1st generation cephalosporin
  • More gram +
  • Effective against most gram positive pathogens
    • Some earlier generation cephalosporins share about a 1% cross-allergenicity to PCN
  • Dosed typically at 500 mg bid x 1 week
  • Useful in soft tissue staph infections, such as internal hordeola, preseptal cellulitis, etc.
Amoxicillin/Clavulanic Acid (Augmentin)

- Clavulanic acid enables amoxicillin to be bactericidal against common gram positive pathogens
- Also useful in treating soft tissue infections
- Cannot use if patient is allergic to penicillin
- Dosage: 250, 500 & 875 (generic) or 1000 mg (branded only) tablet q 12 hrs x 7-10 days
- Can be taken with meals

Allergies to Penicillins

- Macrolides
- Tetracyclines
- Fluoroquinolones
"For example, in one retrospective study that included more than 65,000 patients with a history of penicillin allergy who received more than 127,000 courses of cephalosporins (which are beta-lactam antibiotics like penicillins), only 3 cases of anaphylaxis were associated with the drugs. That was not statistically different from anaphylaxis rates in non–penicillin-allergic patients who received cephalosporins."
Case 10

• Background
  • 22yo CM referred from ER for eye laceration
  • Playing basketball, incurred a fingernail scratch
  • VA
    • OD: 20/25, OS: 20/20
    • IOPs normal OU
  • Patched from ER and sent for evaluation
  • Eye pain 6/10 + light sensitivity
  • Gr 2 AC rxn
Presentation

Conjunctival Laceration

• Treatment
  - Inspect area under conjunctiva
  - Antibiotic ointment
  - Pressure patch
  - Cycloplegia?
  - Suture?
1 week f/u

Case 14
Case #14

- Background
  - 4yo CM at daycare hit in OD with metal hanger sent from ER
  - Severe pain, photophobia, and decreased VA
  - Conjunctival injection, eyelid chemosis, epithelial defect
  - Unable to obtain VA

Presentation
Deep Corneal Abrasion

- Work-up
  - Nature of injury
  - VA, IOP, SL, AC rxn?
  - Evert eyelids
  - Stain
  - Seidel sign?
- Treatment
  - Antibiotic
  - Cyclo
  - Patching?
  - NSAID
- Follow-up?
  - Called the patient the next day and...
    - # disconnected!
    - Pt walked in 3 days later

Follow-up
Case 14

• Background
  • 65yo CF manager at local BBQ restaurant was reaching to get a metal pan located above her head
  • Pan fell out of her hand and edge hit her OS
  • Severe pain, unable to open, cannot see out of it
  • VA
    • OD: 20/25-, OS: 20/400
  • IOP
    • OD: 13, OS: 8
  • 3+ bulbar inject, 2+ AC rxn, large epithelial staining defect and…
Corneal Laceration

• Work-up
  • Nature of injury
  • VA, IOP, SL, AC rxn?
  • Evert eyelids
  • Stain
  • Seidel sign?
    • Concentrated fluorescein is dark orange but turns bright green under blue light after dilution
    • This indicates AC leakage which is diluting the green dye
  • Check for staining beyond the limbus
  • Evaluate depth of AC!
    • Our patient did have a shallower AC compared to OS
Corneal Laceration w Seidel Sign

- Treatment
  - Cycloplegic
  - Antibiotic drops/ung
  - Aqueous suppressant?
  - Bandage CLs?
  - Steroids?
    - Avoid

Corneal laceration follow-up
Case 13

• Background
  • 26yo CM referred from urgent care for “bad case of pink eye”
  • Started in OD and moved to OS
  • Started on polysporin TID OU per UC
  • Swollen eyelids OU
  • 4+ injection of bulbar conjunctiva OU
  • Perfuse, watery discharge, no mucous discharge
  • No corneal staining in either eye
Antibiotics for “pink eye”
Treatment of Acute Conjunctivitis

- “Conjunctivitis is the most common cause of red or pink eye in patients seeking primary care treatment.”
- “Estimates regarding the percentage of conjunctivitis of various causes vary by age and season, but most (up to 80%) are viral.”
- “As expected, the vast majority of patients (83%) were initially diagnosed with acute conjunctivitis by primary care providers, rather than by ophthalmologists or optometrists.”
- “A survey in The Netherlands found that 80% of patients with acute conjunctivitis were prescribed topical antibiotics.”
- “Most cases of acute conjunctivitis are nonbacterial in origin, and even among those with a bacterial cause, antibiotics have only a modest benefit in reducing symptom duration. The complications of acute conjunctivitis are so rare that there is no evidence from systematic reviews that antibiotics reduce rates of complications.”
  - Oph, Aug 2017

Epidemic Keratoconjunctivitis

- Symptoms: itching, burning, watering, light sensitive, FB sensation
- Signs: watery discharge, swollen eyelids, inferior palpebral follicles, swollen lymph nodes, SEIs?
  - Pseudomembranes: coagulated exudate that is loosely adherent to the inflamed conjunctival epithelium
- Most commonly caused by types 8 and 19
- Usually bilateral but may be asymmetrical
- Mistaken for periorbital cellulitis
- Rapid Pathogen Screening (RPS) Adeno Detector
- Betadine wash...
Epidemic Keratoconjunctivitis

- How to perform a betadine wash

Epidemic Keratoconjunctivitis

- Treatment
  - Betadine wash
    - Contraindication?
  - Patient education
  - PF ATs Q2H
  - Cold compresses
  - Lotemax QID
    - Reduces quantity and density of SEIs
What is this??
Thank you!

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