Diagnosis and Treatment of Ocular Surface Conditions: Focus on Allergy and Conjunctivitis

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Learning Objectives

After completing this lesson, optometrists will be able to:

- Understand the epidemiology and etiology of allergy and conjunctivitis
- Diagnose allergic ocular surface conditions and conjunctivitis
- Manage and recommend treatment for these conditions
- Counsel patients for better self-management

Ocular Surface Conditions

Allergy
- Epidemiology/Etiology
- Diagnosis
- Management/Treatment
- Cases

Allergic Eye Disease

- Seasonal allergic conjunctivitis (SAC)
- *Perennial allergic conjunctivitis (PAC)
- Giant papillary conjunctivitis (GPC)

With a potential of vision threat

- Atopic keratoconjunctivitis (AKC)
- Vernal keratoconjunctivitis (VKC)

* All type 1 hypersensitivity reactions

Ocular Allergy: Epidemiology

Acute Allergic Conjunctivitis

Seasonal Allergic Conjunctivitis
- Environmental allergens
  - Animal dander
  - Ragweed
  - Grass pollen
Perennial Allergic Conjunctivitis

- Milder than seasonal allergy
- Associated with asthma
- Year-round problem and indoors
- High pollen counts

70-80% allergic to dust mite droppings:
- Mites are 10-24µ
- 10-20 waste pellets/day
- 1 gram dust = 240,000 droppings
- After 5 years, 50% of pillow weight is dust mite droppings

Clinical Presentation

Symptoms:
- Ocular itching
- Burning
- Tearing
- Redness
- Sensitivity to light
- Grittiness/foreign-body sensation
- Blurred vision

Signs of Acute Allergic Conjunctivitis
- Hyperemia/chemosis of bulbar conjunctiva
- Micro or macro papillary changes
- Follicular response
- Possible eyelid swelling

Classic Allergic Conjunctivitis Presentation

With conjunctival chemosis, mild injection and tearing

SAC/PAC: Diagnosis

- Hallmark symptom: ITCHING!
- DDx vs. viral/bacterial conjunctivitis:
  - Personal/family Hx of atopic disorders
  - Pink/glossy conjunctiva
  - Quality of discharge
  - Stringy, ropy
Conjunctival Chemosis DDx

**Adenovirus/EKC**
- Pre-auricular lymphadenopathy present
- Pseudomembrane or SEIs could be present
- Symptoms include red eye with FB sensation but itching is not a typical symptom of adenovirus
- Duration: 7-21 days

**Treatment**

To understand the underlying allergic mechanisms

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**Allergic Sensitization**

- Antigen in tears
- Conjunctival epithelium
- B lymphocyte
- IgE antibodies
- Consequences:
  - Activated mast cell
  - Cytokines
  - Histamine
  - ECF-A

**The Early (Acute) Allergic Response**

- Antigen in tears
- Consequences:
  - Activated mast cell
  - Cytokines
  - Chemokines
  - Histamine
  - Eosinophil

**The Late Phase Allergic Response**

- Activated mast cell
- Consequences:
  - Leukotrienes
  - Cytokines
  - Prostaglandins
  - Lipids
  - Eosinophil
  - Basophil

**The Early (Acute) Allergic Response**

- Time frame is important to determine best treatment
- Early vs. late phase
- Early stage (first hours)
  - Treat with combination agent
- Later stage (>12-24h00)
  - Deal with inflammation
  - Treat with steroids
### Treatment Based on Symptoms

- Symptom severity
- "Affecting daily activities or lifestyle"
  - i.e., can’t work
- Once symptoms are under control can go to combination agents longer term

### SAC Treatment

- Mild will self-treat
- More than 50% of patients will try OTC antihistamines before visiting an eye doctor
  - OTC antihistamines/decongestants – vasoconstrictors
    - e.g. Visine®, Clear Eyes®, or Naphcon A®
  - Rebound hyperemia

### SAC/PAC: Treatment

- Palliative
  - Intensive lubrication (unpreserved if >q.i.d.)
  - Cold compresses
- Pharmaceutical
  - Mast cell stabilizers
  - Topical antihistamines (with or w/o decongestant)
  - Combination agents (mast cell stabilizers + antihistamines)
  - Topical steroids
  - Oral medications

### SAC/PAC: Management

- Counsel patients
  - Re: chronic nature of the condition
  - To practice avoidance
    - Stay indoors during peak pollen days
    - Minimize ocular exposure
      - Wash hair before sleeping
      - Lower ceiling fans
      - Wash linens, etc.
Preservative-Free Artificial Tears

- RefreshTears®
- TEARS Naturale FREE®
- Bion Tears®
- THERA TEARS®
- iDrop®

SAC/PAC: Topical

Mast cell stabilizers

- Lodoxamide tromethamine ophthalmic solution 0.1% (Alomide®)
- Sodium cromoglycate (Opticrom®)
  - Delay for clinical action
  - Pre-seasonal application
  - Limited clinical effects

SAC/PAC: Topical

- Topical antihistamine (with or w/o decongestant)
  - Visine®, Murine® – not recommended
  - Inconvenient dosing (q.i.d.)
  - Rebound hyperemia w/ long-term use
  - Levocabastine eye drops
    - H₁ receptor antagonist (Livostin®)
    - Prescribed by GPs

SAC/PAC: Topical

- Combination agents
  - Provide rapid relief
    - 1st drop applied
  - No need to load dose in the system to become effective
  - Long-term management
  - Convenient dosing (die to b.i.d.)
    - Ketotifen 0.025% (Zaditor® [Rx], Alaway®, Refresh® Eye Itch Relief®)
    - Olopatadine hydrochloride 0.1% (Patanol®)

SAC/PAC: Steroids

- Topical ester steroids (Loteprednol etabonate 0.2% – Alrex®, loteprednol etabonate 0.5% w/v – Lotemax™)
  - Initial dosing
    - Moderate cases: q.i.d. x 2-3 wks
    - Severe cases: can be increased to q2 hrs for the first 2-3 days
    - Schedule follow-up at 3-4 weeks to check IOP and therapeutic response
    - No adverse effects reported with up to 4,000 doses over 36 months
  - IOP risk: 1-2%
  - Use
    - In non-compliant patients
    - In young male patients with asthma
    - In conjunction with olopatadine – Patanol®

Ester vs. Ketone Steroids

Loteprednol → Ester steroids

Prednisolone → Ketone steroids

Fluorometholone
Dexamethasone
Betamethasone

*S available in US only

Ester vs. Ketone Steroids

- **Ester Steroids** are inactivated by naturally occurring esterases
  - Fewer side effects, better safety profile*
  - No rebound effect
- **Ketone Steroids** are not inactivated and have propensity to remain in anterior chamber post-breakdown as active metabolites
  - Benefits/risk of use e.g., cost
  - Switching from other steroids to ester steroids


Allergy Could Be a Systemic Problem

**Allergic Sinusitis**

- P.O. Claritin®, Allegra®, Reactine®, Aerius®, Benadryl® q.d.
  - If sinus congestion is present:
    - P.O. Claritin®-D 24-hr or Allegra®-D 24-hr – q.d.
    - Contains pseudoephedrine
  - Avoid in patients with hypertension
  - Choose carefully in patients with dry eye

ORAL: Non-Sedating Does Not Mean Non-Drying!

- Not often prescribed with ocular signs/symptoms present only
- Maintain or increase preservative-free artificial tears
- Can exacerbate the ocular condition

SAC Oral

- Consider nasal inhalers
  - Antihistamine
    - Astelin® b.i.d., Dristan®, Otrivin®
  - Steroid
    - Beconase®, Flonase®, Vancenase®, Nasonex® b.i.d.
  - Cromolyn sodium OTC
    - Poor systemic absorption – few side effects

SAC Treatment

- Significant systemic involvement
  - Rhinitis, itchy throat, cough, sinus congestion
- Add oral medications to topical regimen
  - Diphenhydramine hydrochloride (e.g., Benadryl®)
  - Take before bed
- Consider consult with allergist depending on severity, duration and recurrence rates
SAC Treatment

- Although rare, risks still exist for steroid inhalers:
  - IOP rise
  - Conjunctivitis
  - Glaucoma
  - PSC formation

Giant Papillary Conjunctivitis (GPC): Diagnosis

- Almost always bilateral
  - Unless with foreign body or stitch
- Large papillae on upper tarsal conjunctiva
  - Can be easily missed if clinician does not evert and stain the lids
- Silicone hydrogels vs. pHEMA
- Good reason to recommend switch to daily disposable contact lenses

GPC Management

- Degree of tarsal hyperemia and papillary response should dictate aggressiveness of response
- Patient education and lens wear changes to avoid recurrence
- Compliance and lens hygiene
- More frequent lens replacement
  - Daily disposable lenses reduce the risk of long-term symptoms and flare-ups
- Makeup can initiate flare-up of GPC
- Water-soluble makeup is preferred
- Refractive surgery may be an option
- Control of immune system reaction

GPC: Management Protocol

<table>
<thead>
<tr>
<th><strong>Initial Therapy</strong></th>
<th><strong>Long-Term Management</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Remove CLs for 2 weeks††Recommend daily disposable lenses to patients who are not willing to wear glasses</td>
<td></td>
</tr>
<tr>
<td>2) Topical steroids Loteprednol 0.5% (Lotemax™) q.i.d. x 2 wks, then b.i.d. with lens wear x 2-4 more wks</td>
<td></td>
</tr>
<tr>
<td>3) Consider to add combination allergy medications long term</td>
<td></td>
</tr>
</tbody>
</table>

Note: Loteprednol 0.5% is the only steroid that has been shown to be an effective and safe treatment for GPC*. 

**Vernal Keratoconjunctivitis (VKC)**
- Age of onset: 7 years
- Males
- Warm climate (Mediterranean, West Africa, Asia, etc.)
- Typical giant papillae (cobblestone in 20%)
- May be associated with keratitis, shield ulcers
- Trantas’ dots (17% of cases)
- Limbal papillae with white apical gelatinous swellings (eosinophils, fibroblasts, and necrotic epithelium)

**VKC**
- Hypersensitivity to histamine
- Rye grass = most common sensitizing agent
- Other causes include pollen, dust mites, animal dander, sun exposure, dust, wind
- Periods of exacerbation
  - 60% have recurrences year-round
  - 16% have perennial episodes

**Management of Chronic Allergic Conditions**

**VKC**
- Should be treated aggressively
- 1st line: topical antihistamine and mast cell stabilizers
- Systemic AH + aspirin (0.5-1.0 mg/day)
- Topical steroids in severe case for 1-2 wks
- Abundant lubrication
- Mucolytic agents (acetylcysteine)
- Topical prophylactic antibiotic if cornea is involved
- Frequent follow-up to monitor and adjust dosage
- Consult with an allergist

**Atopic Keratoconjunctivitis (AKC)**
- The most blinding of all ocular allergies
- Affects
  - Males
  - Begins late teens-early twenties
  - Peak at 30-50 y.o.
- Conjunctivitis associated with atopic dermatitis
  - 15-40% pts with atopic dermatitis will develop AKC
  - Hx of eczema (95%) with asthma (87%)

**AKC: Symptoms**
- Intense bilateral itching (eyelids + conj)
- Tearing
- Burning
- FBS
- Photophobia
- Stringy, ropy discharge
- Exacerbations possible
- Habitually year-round

**AKC: Signs**
- **Lids**
  - Due to the eczema in the periorbital area, the eyelids tend to be thick, indurated and red
  - Ptosis is frequent
  - Chronic blepharitis, MGD
  - Papillary hypertrophy of the upper and lower (+++) palpebral conjunctiva
- **Dry eye associated**
- **Hyperemia + chemosis more severe inferiorly**
- **Cornea/limbus**
  - Gelatinous nodules are present
  - Corneal neovascularization with edema
Management of Chronic Allergic Conditions

- AKC
  - Topical mast cell stabilizers
  - Topical steroids
  - Immunosuppressive medication (cyclosporine A)
  - Topical prophylactic antibiotic if cornea is involved
  - Therapy adjustment needed on a 2wk basis
  - Surgery for severe damages to the cornea
  - Consult with an allergist

Management of Contact Dermatitis

- Recommend steroid cream e.g., polymyxin B sulphate neomycin sulphate dexamethasone 0.05% (Maxitrol® ophthalmic ointment)

Management of Dry Eye and Allergy

- Comorbidities are common
- Consider drying effects of oral medications
- Patients who suffer from dry eye allow the allergens to stay on the ocular surface longer

SOME CLINICAL PEARLS...

- Avoid eye rubbing
  - Mechanical mast cell degranulation
- Refrigerate drops
  - Soothing and effective
- Environmental management
  - Pillows
  - Ceiling fans etc.
  - Wash sheets more often in allergy season
  - Shower before sleeping
**Allergic Pearls**

- Contact lens use?
- Depends on:
  - Severity and contributing factors
  - Evert lid:
    - Papillae
    - Hyperemia
- Recommend daily disposable lenses or hiatus
- Use preservative-free contact lens solution e.g., $\text{H}_2\text{O}_2$
- Re-wet lenses during the day

**Allergic Pearls**

- When treating w/topical steroids e.g., loteprednol, schedule a F/U exam within 4 weeks
- Educate patient to call office if red painful eye
- Confirm compliance, efficacy, symptom relief
- Evaluate IOP and educate about long-term management
- Steroids in CL wearers:
  - Use *b.i.d.* (before and after lens wear)

**Practice Management**

**Generic Guidelines**

**What can I hope for?**

**How often should I bring the patient back in?**
- For allergy re-checks: 1-4 wks depending on severity
- For dry eye: 3-4 weeks
- Provincial jurisdiction/regulation

**Cost of treatment**
- Consider substitution if cost is prohibitive
- Determine drug plan coverage

**Conjunctivitis**

**One of the most common reasons for acute eye-related primary care visits**
- 15% of all pediatric referrals to Wills Eye Institute
- 1-in-8 pediatric visits are for pink eye

*A non-specific term for inflammation of the conjunctiva*

**Conjunctivitis**

**Diverse range of etiologies:**
- Allergic
- Viral
- Bacterial
- Chlamydial
- Nonspecific / Toxic / CLARE
- Associated with lid and dermatologic problems
Elements of an Effective Physical Exam

- Examine the periorbital skin closely and note any lesions on face or scalp
- Palpate for preauricular and submandibular lymph nodes (viral)
- Ask about upper respiratory infection (URI)

Symptoms of Viral Conjunctivitis

- Redness
- Clear watery discharge
- FB sensation or pain
- Photophobia
- Decreased vision possible

Viral Conjunctivitis

- Most commonly caused by adenovirus (>60%)
  - Pharyngoconjunctival fever (PCF)
  - Associated with URI
  - Epidemic keratoconjunctivitis (EKC)
  - Hemorrhagic conjunctivitis

  Other implicated viruses
  - Herpes simplex (HSV)
  - Epstein-Barr

Conjunctival Chemosis Related to Adenovirus

Viral Conjunctivitis: Epidemic Keratoconjunctivitis (EKC)

- Children or adults
- Acute red eye and watery discharge
- Begins in one eye and spreads to fellow eye within a few days
- Preauricular submandibular lymph node swelling on the ipsilateral side
- After one week without treatment will see SEIs
- Highly contagious
- Hx of recurrent contact lens intolerance
  - Young female
  - On and off C.L. for several weeks
  - Moderate redness

Key Diagnostic Indicators of EKC

- Slight decrease in vision – most other forms of conjunctivitis do not affect vision
- Periorbital edema
- Small conjunctival vesicular hemorrhages
- May be present without infiltrates
Rapid Pathogen Screening (RPS) Adeno Detector
- Rapid Pathogen Screening (RPS) Adeno Detector facilitates diagnosis (available in US)
- $12-$13 per test
- Will ship to Canada

Management of Viral EKC
- Consider severity of presentation
- Early/mild: Supportive therapy alone
- Recommend daily disposable lenses
- More symptomatic: suppress inflammation with steroids and temporarily cease contact lens wear

EKC Treatment
- If sub-epithelial infiltrates and reduced V/A
- Steroids q.i.d. x 1 month (or longer), then taper slowly
  - May have rebound – less likely with loteprednol
- Tapering
  - With ester steroids may not be necessary
  - With non-ester steroids – duration depends on severity but is required
- Povidone-iodine
- Broad-spectrum microbicide
- Indicated for "irrigation of the ocular surface"

Povidone Iodine
- “Off label” use: Tx adenoviral keratoconjunctivitis
- Anesthetize with proparacaine
- Instill 1 or 2 drops of NSAID
- Instill several drops Betadine® 5% in eye(s), close eye(s)
- Swab or rub excess over eyelid margin
- After 1 minute, irrigate with sterile saline
- Instill 1 or 2 drops of NSAID
- Rx Lotemax™ q.i.d. x 4 days
- No reports in clinical trials of adverse reactions
- Avoid use if patient is allergic to iodine

Off-label Applications and Standard of Care
- Standard of care
- A diagnostic and treatment process that a clinician should follow for a certain type of patient, illness, or clinical circumstance based on:
  - What an average prudent doctor would do in that given situation
  - Evidence-based medicine and research
  - Previous precedents

Pharyngoconjunctival Fever (PCF)
- Usually in children
  - Almost always unilateral
- Accompanied by
  - Mild sore throat or URI
  - Low fever, some malaise
- Adenopathy in severe cases
Management of PCF

- Self-limiting
  - Usually resolves within 2 weeks without treatment
- Support and educate family
- Supportive therapy
  - Cool compresses
  - Artificial tears
- In more severe cases
  - Low-dose ester steroid to reduce inflammation
  - First, rule out lid involvement/signs of HSV
  - Antibiotic/steroid combination if corneal involvement

Herpetic Conjunctivitis

- Herpes simplex (HSV) conjunctivitis
  - Usually presents with lid involvement first
  - First exposure early in life
- Clearest signs of HSV conjunctivitis
  - Unilateral, rarely bilateral, involvement with watery discharge AND
  - Ulceration of the lid margin and/or
  - Vesicles on the face or around the eyes

Zoster

- Be suspicious of herpes zoster in patients >50 yrs. with nonspecific pain in 1 eye
  - Have patient seen quickly, won’t usually get dendrites (although may have pseudodendrites in rare circumstances)
  - Iritis is more common in HZO than corneal involvement
  - Tell the patient to report any lesions on the eyelids, skin or scalp
  - < 5% of all patients

Management of Herpetic Conjunctivitis

- Herpes simplex – primarily infectious
  - With lid/dermatologic involvement: oral antiviral therapy (acyclovir, valacyclovir, famciclovir)
    - In children over 6 years dosing per adults; ask pediatrician in children under 6 years of age and in low-weight children
  - Caution: topical steroids will worsen HSV

Zoster Treatment

- Herpes zoster – secondary inflammatory keratoconjunctivitis and iritis
  - Treat aggressively with topical steroids (prednisolone 1% or loteprednol 0.5%)
  - Oral antivirals at twice the dose of HSV

Bacterial Conjunctivitis

- Acute bacterial conjunctivitis
- Hyperacute bacterial conjunctivitis
- Adult inclusion (Chlamydial) conjunctivitis
- Blepharitis
  - Anterior
  - Posterior
- Phlyctenular conjunctivitis (PKC)
Acute Bacterial Conjunctivitis
- Occurs in 1 of 8 children every year\(^1\)
- Most cases of conjunctivitis are acute bacterial conjunctivitis\(^2\)
- \(\sim 1\%\) of all consultations in primary care\(^2\)
- Most common causative pathogens\(^3\)
  - *Haemophilus influenzae*\(^*\)
  - *Streptococcus pneumoniae*\(^*\)
  - *Staphylococcus aureus*\(^**\)
  - *Staphylococcus epidermidis*\(^*\)

\(^*\) More common in children \(^**\) More common in adults

How to Effectively Manage Childhood Conjunctivitis
- Rule out trauma
  - Less likely to respond
  - More difficult to diagnose
- It can alter the management plan
  - i.e., involve a pediatrician
- Increased risk for gram-positive infection, such as MRSA or Streptococcal cellulitis

Bacterial Conjunctivitis Presentation
- Meaty red eye
- Discharge or debris in tear film

Conjunctivitis Tool Box
Algorithm:
1. Diagnose
2. Treat
3. Resolution
4. No Resolution
   - Culture (check antibiotic against culture pathogen)
   - Re-treat

Ideal Profile for Treatment of Bacterial Conjunctivitis
- Broad spectrum
- Potent activity against prevalent pathogens
  - Bactericidal
- Low propensity for resistance development
- Low incidence of adverse events (AEs)
- Convenient dosing
- Long dwell time at site of infection (ocular surface)
- Local treatment for a local disease

Treatment with a Broad Spectrum Antibiotic
- Many choices
- Best to use the strongest product – dead bugs don’t mutate
**Fluoroquinolones**

- Use right tool at right time
- More economical
- Time away from work/school decreased
- Decrease chance of resistance
- Evidence-based standard of care

**Besifloxacin is a New Chemical Entity Fluoroquinolone (FQ)**

- Unique combination of substituents at C7 and C8 positions of FQ core structure

![Chemical structure of Besifloxacin](image)

- Besifloxacin mode of action is consistent with newer FQs (inhibition of DNA gyrase and topoisomerase IV)

**DuraSite® Technology**

- Proprietary mucoadhesive delivery system
- Polymer composed of polycarbophil, edetate disodium dihydrate, sodium chloride
- May prevent tearing out medication in children

**Besivance™ Indication Similar to Other FQs**

BESIVANCE™ (besifloxacin ophthalmic suspension) 0.6% w/v is indicated for the treatment of patients one year of age and older with bacterial conjunctivitis caused by susceptible strains of the following organisms:

**Aerobic, Gram-Positive**

- CDC coryneform group G
- Staphylococcus aureus
- Staphylococcus epidermidis
- Streptococcus mitis
- Streptococcus oralis
- Streptococcus pneumoniae

**Aerobic, Gram-Negative**

- Haemophilus influenzae

**Besivance™ Dosage**

- BESIVANCE™ is a 7-day course of therapy for bacterial conjunctivitis.
- Dosing is 1 drop in the affected eye(s) 3 times a day for 7 days.

**Besifloxacin Mechanism of Action**

Besifloxacin binds to and inhibits two enzymes that are essential for maintaining bacterial DNA in the proper conformation:

- DNA gyrase
- Topoisomerase IV
Besifloxacin Inhibition of DNA Gyrase and Topoisomerase IV Catalytic Activity

<table>
<thead>
<tr>
<th>Inhibitory concentration (IC_{50}, µM)</th>
<th>S. pneumoniae</th>
<th>FO</th>
<th>Gyrase</th>
<th>Topo IV</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>40</td>
<td>5</td>
<td>8</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>10</td>
<td>2.5</td>
<td>4</td>
<td>1</td>
<td>2.5</td>
</tr>
<tr>
<td>Besifloxacin</td>
<td>2.5</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Ratios approaching 1 represent more balanced dual targeting activity
- Dual targeting besifloxacin activity also demonstrated in cleavable complex assays
- Lowest concentrations are the best

Prevalence of MRSA in Bacterial Conjunctivitis

<table>
<thead>
<tr>
<th>Collection period</th>
<th>MRSA, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994-95</td>
<td>10</td>
</tr>
<tr>
<td>1996-97</td>
<td>15</td>
</tr>
<tr>
<td>1998-99</td>
<td>20</td>
</tr>
<tr>
<td>2000-01</td>
<td>25</td>
</tr>
<tr>
<td>2002-03</td>
<td>30</td>
</tr>
</tbody>
</table>

- Prevalence of methicillin-resistant S. aureus (MRSA) among S. aureus conjunctivitis isolates collected at Bascom Palmer Eye Institute increased steadily from 1994 to 2003

ARMOR Ocular Surveillance

**ARMOR**

Antibiotic Resistance Monitoring in Ocular Microorganisms

**Purpose**

Monitor antibiotic susceptibility trends in ocular isolates after the introduction of besifloxacin

**2009 ARMOR Surveillance: All S. aureus (n=200)**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC Range</th>
<th>MIC_{50}</th>
<th>MIC_{90}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>0.25 – 2</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Besifloxacin</td>
<td>≤0.008 – 4</td>
<td>0.03</td>
<td>8</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>≤0.008 – 64</td>
<td>0.06</td>
<td>8</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>≤0.06 – 256</td>
<td>0.5</td>
<td>256</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>≤0.06 – &gt;256</td>
<td>0.5</td>
<td>256</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>≤0.25 – &gt;512</td>
<td>128</td>
<td>&gt;512</td>
</tr>
</tbody>
</table>

- 39% of ocular S. aureus isolates were MRSA
- 38% of ocular S. aureus isolates were FQ-resistant

**2009 ARMOR Surveillance: All Coagulase-Negative Staphylococci (n=144)**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC Range</th>
<th>MIC_{50}</th>
<th>MIC_{90}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>0.12 – 2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Besifloxacin</td>
<td>≤0.015 – 8</td>
<td>0.06</td>
<td>8</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>≤0.015 – 64</td>
<td>0.12</td>
<td>16</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>≤0.06 – &gt;512</td>
<td>0.5</td>
<td>64</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>≤0.06 – &gt;256</td>
<td>0.12</td>
<td>32</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>≤0.25 – &gt;512</td>
<td>64</td>
<td>&gt;512</td>
</tr>
</tbody>
</table>

- 53% of ocular CoNS isolates were MRSA
- 43% of ocular CoNS isolates were FQ-resistant
Pharmacokinetics In Humans Following Multiple Topical Ocular Doses

Maximum plasma concentration (C\text{\text{max}}) in each patient after first and last dose: <1.3 ng/mL

* Adult patients with suspected bacterial conjunctivitis treated bilaterally t.i.d. (16 total doses)
* Mean C\text{\text{max}} = 0.37 ng/mL on Day 1, 0.43 ng/mL on Day 6
* Average elimination half-life in plasma after multiple dosing: 7 hours

Essentially no systemic absorption

MICs vs. Cipro-R Staphylococci (2005-2008) S. aureus (100% Ocular), S. epidermidis (67% Ocular)

Eurofins Retrospective Surveillance Study

Why Low IC\text{50}s + Balanced Inhibition is Important

* Low IC\text{50}s + balanced inhibition =
  * Fewer survivors in a treated population
  * Less capacity for mutant survival
  * Besifloxacin demonstrates low rates of spontaneous resistance development
  * Improved activity against resistant Gram+ pathogens

MIC Values for Ciprofloxacin-resistant S. aureus (n=39)

<table>
<thead>
<tr>
<th>Organism</th>
<th>Antimicrobial</th>
<th>Total N</th>
<th>Range</th>
<th>MIC C\text{\text{max}} (\mu g/mL)</th>
<th>MIC C\text{\text{50}} vs Besi %R</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus (100% Ocular)</td>
<td>Besifloxacin</td>
<td>102</td>
<td>0.25 - 8</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin</td>
<td>102</td>
<td>1 - 64</td>
<td>8</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>Gatifloxacin</td>
<td>102</td>
<td>2 - 200</td>
<td>6</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>Ceftolozane</td>
<td>102</td>
<td>5 - 200</td>
<td>32</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>Ceftazidime</td>
<td>102</td>
<td>5 - 200</td>
<td>128</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>Ceftazidime</td>
<td>102</td>
<td>2 - 512</td>
<td>32</td>
<td>256</td>
</tr>
<tr>
<td>S. epidermidis (67% Ocular)</td>
<td>Besifloxacin</td>
<td>33</td>
<td>0.25 - 8</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
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<td>33</td>
<td>2 - 64</td>
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<td>64</td>
</tr>
<tr>
<td></td>
<td>Gatifloxacin</td>
<td>33</td>
<td>2 - 128</td>
<td>32</td>
<td>128</td>
</tr>
<tr>
<td></td>
<td>Ceftolozane</td>
<td>33</td>
<td>3 - 150</td>
<td>64</td>
<td>64</td>
</tr>
</tbody>
</table>
* Dashed line indicates that CLSI interpretive breakpoints are not available.

MIC Values for Ciprofloxacin-resistant S. epidermidis (n=33)

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* Breakpoint: the point above which the agent is no longer systemically effective.

What’s Your Diagnosis?


* Breakpoint: the point above which the agent is no longer systemically effective.
**Ocular Infection Pearls**

- Systemic involvement in children presenting with conjunctivitis is necessary to rule out and refer to a pediatrician
  - Preseptal cellulitis
  - Cellulitis
  - Otitis media
  - URI

**Non-Allergic Conjunctivitis**

- Environmental triggers e.g.:
  - Ozone
  - Cold
  - Dry air
  - Perfumes

**Phlyctenular Conjunctivitis**

- Usually secondary to staphylococcal blepharitis
  - In adults, associated w/rosacea, dry eye
- In zones of poverty: associated with tuberculosis
- Presentation
  - Scratchy, FB sensation
  - Sectoral injection, raised bump on conj
  - No discharge

**Preseptal Cellulitis**

- One of the most common complications associated with acute bacterial conjunctivitis

- Examine skin and adnexa around the orbit for a discrete reddish sheen

- Patients often have ethmoidal or maxillary sinus involvement, which results in orbital tenderness

**When to Refer to a Pediatrician / Pediatric Ophthalmologist**

- Fever or general malaise
  - Purchase a tympanic or forehead thermometer
- Acute earache or ear infection
  - Approximately one-third of all childhood cases are otitis-conjunctivitis syndrome
- A notable red sheen around the eyelids
  - Preseptal cellulitis or cellulitis
- Significant purulent rhinorrhea or an upper respiratory infection associated with any fussiness or sleeplessness

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Management of Phlyctenular Conjunctivitis

- Staphylococcal
- Combination antibiotic/steroid q 2-4 hrs for 1-2 days, then q.i.d. for 7-10 days
- Lid therapy
  - Warm compresses and eyelid scrubs
  - Doxycycline 50 mg b.i.d. for 1 month then q d 1 month
  - Long-term prevention in recurrent cases
- Tubercular – if no signs of Staph, consider tuberculosis
- Co-manage with patient’s doctor

Bacterial Keratitis

Case S.P. History

- 26 y.o. Caucasian male
- “Painful eye,” “light sensitivity” and “eye is red”
- Long-standing contact lens wearer
- Began this morning – acute onset

Examination

- 2+/3- conjunctival injection
- Slight lid edema
- Pupils normal
- Cornea –small peripheral infiltrate, SPK over infiltrate
- AC grade 2 cell and flare

<table>
<thead>
<tr>
<th>SYMPTOMS</th>
<th>Infectious (If one item is +, lesion is suspected infectious)</th>
<th>Non infectious (sterile) (If all items apply, lesion is suspected sterile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain++---+</td>
<td>Hyperemia /redness ++ to +++ x 360 deg</td>
<td>Normal except if many infiltrates in the visual axis</td>
</tr>
<tr>
<td>Discomfort</td>
<td>Photophobia ++ to +++</td>
<td>Normal</td>
</tr>
<tr>
<td>Visual acuity</td>
<td>Reduced</td>
<td>Normal</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SIGNS</th>
<th>Infectious (If one item is +, lesion is suspected infectious)</th>
<th>Non infectious (sterile) (If all items apply, lesion is suspected sterile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>Single</td>
<td>More than one</td>
</tr>
<tr>
<td>Position</td>
<td>Pupillary area, mid-periphery</td>
<td>Mid-periphery to periphery</td>
</tr>
<tr>
<td>Size</td>
<td>&gt; 1.5 mm</td>
<td>&lt; 1.5 mm</td>
</tr>
<tr>
<td>Edges</td>
<td>Not well defined</td>
<td>Well defined</td>
</tr>
<tr>
<td>WBCs surrounding the lesion</td>
<td>limited to the lesion area</td>
<td>Normal</td>
</tr>
<tr>
<td>Colour</td>
<td>White to yellow</td>
<td>White to greyish</td>
</tr>
<tr>
<td>Shape</td>
<td>Concave with large epithelial defect</td>
<td>Convex with small epithelial defect</td>
</tr>
<tr>
<td>Corneal staining</td>
<td>= or &gt; infiltrate</td>
<td>&lt; infiltrate, negative staining</td>
</tr>
<tr>
<td>Corneal edema</td>
<td>Striae and folds</td>
<td>None</td>
</tr>
<tr>
<td>Endothelium</td>
<td>Precipitates</td>
<td>None</td>
</tr>
<tr>
<td>Lids</td>
<td>Superior lid ptosis</td>
<td>Normal</td>
</tr>
<tr>
<td>Anterior chamber</td>
<td>+ reaction (cells and flare)</td>
<td>Non active</td>
</tr>
</tbody>
</table>
Symptoms

- Acute onset
- Pain
- Photophobia
- Discharge – mucopurulent
- Decreased vision
- Redness
- Excessive tearing, lid edema, blepharospasm

Signs

- Conjunctival hyperemia and ciliary flush
- Lid edema
- Tear film debris – thick & cells present
- Epithelial defect
- Grayish-white stromal infiltrate
- AC reaction
  - From few cells to hypopyon

Bacterial Keratitis Treatment

- Loading dose first –
  - q 15 minutes x 1-2 hours
- Never taper antibiotics beyond therapeutic dosing
- Cycloplegic drops for pain
- Fortified medication?

Treatment

- At night:
  - Tobramycin ointment in suspected gram negative
  - Polymyxin B sulfate – gramicidin – e.g., Polysporin® ointment in all others

Practice Management: Bacterial Keratitis

When to culture:

- 1,2,3 Rule:
  - 1 mm from visual axis
  - 2 infiltrates (or more)
  - 3 mm or greater in size
- Nosocomial infections
- Immuno-compromised patient
- Post-surgical
Ocular Infection Pearls

- Check for lymph adenopathy
- Pre-auricular or submandibular pea-shaped node may indicate viral or AIC

- Look at tear film closely under high magnification
- A murky tear film can indicate a bacterial conjunctivitis discharge

Summary

- Ocular allergies and conjunctivitis
  - Two most common reasons for visits to a pediatrician
  - Accounting for over 20% of all visits

- DDx of allergies and appropriate tx = critical

- DDx infectious conjunctivitis vs. keratitis is key
  - To optimize results and to prevent spread or comorbidity

- Make a confident diagnosis and be aggressive in treatment