Are You Practicing 21\textsuperscript{st} Century Therapeutics?
American Optometric Association
Seattle, Washington

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Disclosure Statement
- Alcon
- Allergan
- Bausch & Lomb
- Jobson Medical Publishing Group
- Shire Pharmaceuticals
- United States Pharmacopeia (USP)

Please silence all mobile devices.

My promise to you is that this lecture will be at least as unambiguous!
Self-Assessment Scoring System

- Keep track of your own score
- Be honest
- We’ll tally at the end of the lecture
- Only you will know your score

ANTIINFLAMMATORY THERAPY

Steroid Formulations Over The Years
Importance of Shaking Steroid Suspensions

Patient Compliance With Shaking

- 63% of patients did not shake their medications at all
- Patients were told to read the instructions carefully
- Clearly emphasized in red on the label to "shake well"


Dose Uniformity with Upright Storage and Shaking

Marlowe ZT, Davis SR. Dose uniformity of loteprednol etabonate ophthalmic gel (0.5%) compared with branded and generic prednisolone acetate ophthalmic suspension (1%). Clin Ophthalmol 2014;8:23-9.
Dose Uniformity with Upright Storage and No Shaking

Marlowe ZT, Davis SR. Dose uniformity of loteprednol etabonate ophthalmic gel (0.5%) compared with branded and generic prednisolone acetate ophthalmic suspension (1%). Clin Ophthalmol 2014;8:23-9.

Dose Uniformity With Inverted Storage and No Shaking

“No Shake” Steroid Options

- Prednisolone phosphate 1.0% (solution)
- Difluprednate (Durezol) (emulsion)
- Loteprednol (Lotemax) (gel)

When Starting Steroid Therapy, What Dosage Frequency Should Generally Be Used?

A. TID
B. QID
C. Q 1-2 H
D. I would prefer to use more than C, if only the patient would comply

I would prefer to use more than C, if only the patient would comply
HOW TO USE STEROIDS

In a word, “Boldly!”

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Total # Drops</th>
<th>↓ Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>q 4h</td>
<td>6</td>
<td>11%</td>
</tr>
<tr>
<td>q 2h</td>
<td>10</td>
<td>30%</td>
</tr>
<tr>
<td>q h</td>
<td>18</td>
<td>51%</td>
</tr>
<tr>
<td>q 30 min</td>
<td>34</td>
<td>61%</td>
</tr>
<tr>
<td>q 15 min</td>
<td>66</td>
<td>68%</td>
</tr>
<tr>
<td>f p q min x 5 min</td>
<td>90</td>
<td>72%</td>
</tr>
</tbody>
</table>

What If My Steroid Just Isn’t Working?

- Is the patient shaking the suspension?
- Did you pulse dose?
- Did the pharmacist dispense generic pred?
- Did the pharmacist dispense (illegally) generic FML?
- Does the patient have steroid-induced uveitis?
- Is the patient using Durasal instead of Durezol?

Self-Assessment Question 1

- Do you always tell patients to shake steroid suspensions, and you always pulse dose? If so, give yourself 1 point.
- If you don’t do both of these, give yourself 0 points.

Steroids in Microbial Keratitis
Steroids for Corneal Ulcers Trial (SCUT)

SCUT Conclusions

“We found no overall difference in 3-month BSCVA and no safety concerns with adjunctive corticosteroid therapy for bacterial corneal ulcers.”

“Adjunctive topical corticosteroid use does not improve 3-month vision in patients with bacterial corneal ulcers.”

*Exceptions: Patients with “finger counting” VA or worse at baseline, and patients with completely central ulcers.

2015 Update

- Adjunctive topical corticosteroid therapy may be associated with improved long-term clinical outcomes in bacterial corneal ulcers not caused by Nocardia species
- There may be a benefit with adjunctive topical corticosteroids if application occurs earlier (after 2-3 days) in the course of bacterial corneal ulcers
2015 Update

- After controlling for visual acuity at enrollment, BSCVA was not significantly different between the corticosteroid and placebo groups at 4 years.
- "There is inadequate evidence as to the effectiveness and safety of adjunctive topical corticosteroids compared with no topical corticosteroids in improving visual acuity, infiltrate/scar size, or adverse events among participants with bacterial keratitis."


GPC


Giant Papillary Conjunctivitis

Significant improvement in primary clinical signs and symptoms

<table>
<thead>
<tr>
<th>Response</th>
<th>Number of Patients</th>
<th>Papillae</th>
<th>Itching</th>
<th>Lens intolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loteprednol etabonate 0.5%</td>
<td>221</td>
<td>76%</td>
<td>94%</td>
<td>91%</td>
</tr>
<tr>
<td>Placebo</td>
<td>222</td>
<td>51%</td>
<td>79%</td>
<td>78%</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>
Management of GPC

- Discontinue contact lens wear if possible
- If not, use daily disposables
- Lotemax Gel QID x 1-4 wks (no taper)
- No other classes of drugs are necessary
- Educate patient on CL hygiene, wearing schedule, etc.

Self-Assessment Question 2

- Is Lotemax your primary therapeutic intervention for GPC? If so, give yourself 1 point
- If not, give yourself 0 points
- If you use placebos, give yourself -1 point!

Dry Eye Disease: An Immune-Mediated Inflammatory Disorder

Lacrimal Glands:
- Neurogenic inflammation
- T-cell activation
- Cytokine secretion into tears

Interrupted Secretomotor Nerve Impulses

Cytokines

Inflammation disrupts normal neuronal control of tearing

Stern et al. Cornea. 1998;17(4):584
Keratitis Associated With Moderate to Severe Dry Eye

<table>
<thead>
<tr>
<th>Steroids for Treatment of Dry Eye Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>When used as monotherapy, Lotemax results in greater improvement in objective signs and symptoms of dry eye than artificial tears at both 2 and 4 weeks</td>
</tr>
<tr>
<td>Lotemax demonstrates no clinically significant IOP elevation, although IOP spikes are possible</td>
</tr>
<tr>
<td>Pretreatment with Lotemax prior to cyclosporine treatment shows:</td>
</tr>
<tr>
<td>• 75% lower stinging rate</td>
</tr>
<tr>
<td>• 68% lower dropout rate with cyclosporine</td>
</tr>
</tbody>
</table>

Why Do Patients Discontinue Restasis?

<table>
<thead>
<tr>
<th>Reason</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burning, stinging</td>
<td>21 (60.0%)</td>
</tr>
<tr>
<td>Physician instruction</td>
<td>8 (22.9%)</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>5 (14.3%)</td>
</tr>
<tr>
<td>Lack of understanding need for chronic treatment</td>
<td>3 (8.6%)</td>
</tr>
<tr>
<td>Cost</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>5 (14.3%)</td>
</tr>
</tbody>
</table>

Note: More than one reason may be given for discontinuation of initial trial.


Recommended Treatment Approach for Dry Eye Inflammation

Lotemax® QID (loteprednol etabonate ophthalmic suspension 0.5%)
Artificial Tears
Lotemax® BID (loteprednol etabonate ophthalmic suspension 0.5%)
Lotemax® up to QID for flare-ups (loteprednol etabonate ophthalmic suspension 0.5%)
Restasis® BID (cyclosporine ophthalmic emulsion 0.05%)
Thereafter

Sheppard JD, Donnenfeld ED, Holland EJ, et al. Effect of loteprednol etabonate 0.5% on initiation of dry eye treatment with topical cyclosporine 0.05%. Eye Contact Lens 2014;40:289-96.

Self-Assessment Question 3

- For your moderate to severe dry eye patients, do you use topical steroids as in the Sheppard, et al paradigm? If so, give yourself 1 point
- If not, give yourself 0 points
Topical Cyclosporine for Conditions Other Than Dry Eye

How Does Cyclosporine Work?
- Inhibits activation of T-cell-mediated immune response

Off-Label Uses of Topical Cyclosporine
- Atopic and vernal keratoconjunctivitis
- Thygeson’s SPK
- LASIK-induced dry eye
- Blepharitis/MGD
- Cyclosporine cannot currently be considered an effective sole agent in prophylaxis and treatment of allograft rejection (corneal transplantation)*

Self-Assessment Question 4

- Have you treated any of these “other” conditions with Restasis? If so, give yourself 1 point
- If not, give yourself 0 points

Is AzaSite an appropriate strategy for treating blepharitis and MGD?
FDA Warning Letter to Inspire Pharmaceuticals (April 14, 2011)

AzaSite as an Anti-inflammatory

Unsubstantiated Claims

The Journal Ad includes the claim, “AzaSite® Can Restore a Healthy Ocular Surface By Delivering Significant Anti-Inflammatory and Antinociceptor Effect Directly to the Site of the Problem.” (bolded emphasis in original; underlined emphasis added) This claim is misleading because it implies that AzaSite® delivers anti-inflammatory effects, whereas this has not been demonstrated by substantial evidence or substantial clinical experience.

Practical Approach to MGD

- Hot compresses and digital massage
- Lipid-replacing artificial tears
- Oral doxycycline 50 mg bid x 2-4 wks

Oral azithromycin versus doxycycline in meibomian gland dysfunction: a randomised double-masked open-label clinical trial
Mohsen Bahrami Kashefi,1 Ali Jalili Fazel,1 Victoria Kavash,1 Masdin Najomi,2 Lella Ghaziani2

ABSTRACT
Background: To assess the efficacy and safety of oral azithromycin compared with oral doxycycline in patients with meibomian gland dysfunction (MGD) who had failed to respond to prior conventional management.
Methods: 110 patients (122 eyes) with MGD were randomized to receive azithromycin (500 mg on day 1 and then 250 mg daily for 4 weeks) or doxycycline (100 mg on day 1 and then 50 mg daily for 1 month) or doxycycline (100 mg on day 1 and then 50 mg daily for 1 month). Clinical response, signs, and quality of life were assessed.
Results: No statistically significant differences were found between the groups in terms of clinical response, signs, and quality of life.

- 5-day oral azithromycin is recommended for its better effect on improving the signs, better overall clinical response, and shorter duration of treatment.


Arita Meibomian Expressor

- Can be used on upper or lower lid
- Nasal or temporal approach
- Topical anesthetic

Mastrota Paddle

- Can also be used for traumatic compression of meibomian glands
Self-Assessment Question 5

- Do you specifically target lipid-replacing artificial tears for your MGD patients and use oral azithromycin or low-dose doxy for your moderate-to-severe patients? If so, give yourself 1 point
- If not, give yourself 0 points
CURRENT MANAGEMENT OF OCULAR ROSACEA

Antilipase Activity and Matrix Metalloproteinase (MMP-9) Inhibition
Typical Response to Treatment

Is Your Rosacea Patient Pregnant or Allergic To Doxycycline?

What If My Rosacea Patient Can’t Take Tetracycline?

- Azithromycin 500 mg 3 times/wk is at least as effective as doxycycline in the treatment of rosacea
- Oral azithromycin 500 mg/day for 2 weeks is effective for treatment of intractable rosacea

Topical Dermatologic Therapies

- Metronidazole (MetroGel, MetroCream)
- Azelaic acid gel (Finacea)
- Brimonidine gel (Mirvaso)
- Ivermectin cream (Soolantra)

Brimonidine Gel (Mirvaso)

- 0.33% topical dermatologic gel for persistent facial erythema of rosacea
- FDA approved on August 23, 2013
- Applied once daily
- Effective for up to 12 hr
- Sustained effect for at least 12 months
Self-Assessment Question 6

- Do you advise patients on the availability of Finacea, Mirvaso, or Soolantra for the dermatologic manifestations of rosacea? If so, give yourself 1 point
- If not, give yourself 0 points

OCULAR ALLERGY

Therapeutic Options

- Mast cell stabilizers
- Antihistamines
- Antiarrhythmics
- NACs (N-acetylcysteine)
- Antivirals
- Thrombolytics
- Corticosteroids
Product Comparisons

- OTC ketotifen is comparable to olopatadine 0.1% (Patanol) in reducing itching associated with SAC, although possibly somewhat less comfortable
- Lastacaft may have longer lasting improvement of itching and chemosis than does olopatadine 0.2% (Pataday)


Ackerman S, D’Ambrosio F, Jr, Greiner JC, Villanueva L, Calhoun JB, Hollander DA. A multicenter evaluation of the efficacy and duration of action of alcaftadine 0.25% and olopatadine 0.2% in the conjunctival allergen challenge model. J Asthma Allergy 2013;6:43-52.

Lastacaft vs Pataday 16 h After Dosing


Olopatadine 0.2% (Pataday) vs 0.7% (Pazeo)

- Pazeo (0.7% olopatadine) has better efficacy at 24 hr compared to Pataday
- No difference in safety
- Pazeo was launched in US on March 10, 2015
Distinguishing Features of AH/MCSs

- **Patanol**
  - FDA approved for “redness”
  - All others, including Pataday and Pazeo, approved for itching, not redness

- **Bepreve**
  - May offer improvement of nasal congestion and rhinorrhea
  - Available in 10 ml bottle/one copay

- **Lastacaft**
  - The safest (cat. B) for use during pregnancy

- **Ketotifen**
  - OTC


Most eye allergy drugs are approved for “itching”... what can we do about the redness?
Two Recent Paradigm Shifts
- **Toward** more targeted anti-inflammatory therapy and rapid symptom relief
- **Away from** systemic antihistamines for seasonal allergies
  - Cause dry eye and ↑ ocular symptoms
- **Topical therapy** for ocular symptoms
- **Inhaled or intranasal steroids** for nasal/sinus symptoms
Steroids in SAC Management

- No longer considered a last resort
- Use when there are significant signs or more severe symptoms
- Limit therapy to ester-based steroids (loteprednol)
- In severe cases, pulse dosing is mandatory
- Schedule follow-up in 2-4 weeks to check IOP and therapeutic response

Lu E, Fujimoto LT, Vejabul PA, Jew RL. Steroid-induced ocular hypertension with loteprednol etabonate 0.2%—a case report. Ophthalmology 2011;118(7):1399-402.

Should The Optometrist Recommend Intranasal Steroids?

- Allergic rhinoconjunctivitis (ARC) presents as nasal symptoms, eye watering and itching
- Intranasal corticosteroids (INSs) are the most effective treatment for the nasal symptoms of seasonal allergic rhinitis (SAR) and are considered first-line therapy for nasal congestion

Should The Optometrist Recommend Intranasal Steroids?

- INSs provide some relief from ocular symptoms of SAR and seasonal ARC in adults, and are better than oral antihistamines
- INSs are safe for use over several months


Absolutely!


Self-Assessment Question 7

- Do you use Lotemax or Alrex as first-line therapy of patients with severe symptoms or hyperemia associated with SAC? If so, give yourself 1 point
  - If not, give yourself 0 points
- Will you recommend INS therapy for some of your patients with ARC?
  - If so, give yourself a bonus point!
Recent Prices for Prescription Ocular Allergy Drugs

- Patanol
  - $131/5ml
- Pataday
  - $127/2.5ml
- Lastacaft
  - $112/3ml
- Beprevé
  - $118/5ml, $210/10ml

OTC Ketotifen 0.025% Products

- Zaditor (Novartis)
- Alaway (Bausch & Lomb)
- Refresh Eye Itch Relief (Allergan)
- Ketotifen (Alcon, Apotex, Akorn)
- Claritin Eye Allergy Relief
  - $12-15/10ml
  (Alaway)


OTC Ketotifen in Children

- Excellent treatment option for children
- Inhibits their ocular itching as well as reduces redness, chemosis, and lid swelling
- Adverse ocular effects are insignificant

ANTIMICROBIAL THERAPY

How Would You Handle The Following Patient?
MRSA UPDATE

Methicillin-Resistant Staphylococcus Aureus

The acronym MRSA signifies that the isolates are resistant to all beta-lactam antibiotics, not just methicillin

Evolving Prevalence of MRSA

- In the US, approx 14% of S. aureus isolates (bacterial conjunctivitis) are methicillin-resistant
- Blepharoconjunctivitis accounts for about 80% of ocular MRSA infections
Best Therapeutic Options

Ocular TRUST 2: *S. aureus* Susceptibility

**MSSA (N=71)**

- 99%
- 93%
- 62%
- 17%

**MRSA (N=84)**

- 100%
- 99%
- 18%
- 95%


Antibiotic | MIC Range | MIC<sub>50</sub> | MIC<sub>90</sub> |
--- | --- | --- | --- |
Vancomycin | ≤0.25 – 2 | 0.5 | 1 |
Besifloxacin | ≤0.008 – 4 | 0.03 | 1 |
Moxifloxacin | ≤0.008 – 64 | 0.06 | 8 |
Gatifloxacin | ≤0.03 – 256 | 0.12 | 8 |
Ciprofloxacin | ≤0.015 – 512 | 0.5 | 256 |
Tobramycin | ≤0.06 – >256 | 0.5 | >256 |
Azithromycin | ≤0.25 – >512 | 128 | >512 |

Besifloxacin MIC<sub>90</sub> for All *Staphylococcus aureus* Isolates

- 50.0% of ocular *S. aureus* isolates were MRSA
- 39.9% of ocular *S. aureus* isolates were FQ resistant

Besifloxacin Tear Concentrations Relative to MIC$_{90}$ for Ciprofloxacin-Resistant MRSA and MRSE

- At 12 hours postinstillation, concentration of besifloxacin remains higher than the MIC$_{90}$ for MRSA-CR and MRSE-CR


Treatment Options for Initial Empirical Therapy of MRSA

- Topical
  - Vancomycin
  - Besifloxacin
  - Trimethoprim/polymyxin B

Self-Assessment Question 8

- When thinking about MRSA, are besifloxacin and trimethoprim/polymyxin B your favorite topical ocular antibiotics? If so, give yourself 1 point
- If not, give yourself 0 points

GLAUCOMA THERAPY

True or False??

Topical CAIs Can Be Used (Safely) In Patients Allergic To Sulfa Antibiotics.
True!!

Cross-Reactivity References
Self-Assessment Question 9

- Unless otherwise contraindicated, do you routinely use topical CAIs for treatment of glaucoma in patients with a history of “sulfa” allergy? If so, give yourself 1 point
- If you purposefully avoid CAIs in these patients, give yourself 0 points
- If you don’t treat glaucoma, give yourself 0 points

DRUG USE DURING PREGNANCY

Current FDA Drug Pregnancy Categories

<table>
<thead>
<tr>
<th>FDA Category</th>
<th>Clinical Implication</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>No risk to fetus</td>
<td>Levothyroxine, vitamin B₆</td>
</tr>
<tr>
<td>B</td>
<td>No evidence of risk</td>
<td>Azithromycin, erythromycin, brimonidine, cephalin</td>
</tr>
<tr>
<td>C</td>
<td>Risk cannot be ruled out</td>
<td>Clarithromycin, ciprofloxacin, steroids, phenylephrine, latanoprost</td>
</tr>
<tr>
<td>D</td>
<td>Risk to fetus</td>
<td>Tetracycline, doxycycline</td>
</tr>
<tr>
<td>X</td>
<td>Definite risk!</td>
<td>Misoprostol, isotretinoin</td>
</tr>
</tbody>
</table>
Caveats

- Some drugs have different categories according to pregnancy trimester
  - ACE inhibitors (C, D, D)
- Some drugs have precautions despite “B” labeling
  - Ibuprofen (risk premature closure of fetal ductus arteriosus third trimester)
  - Brimonidine (CNS depression)
- FDA Pregnancy Labeling Task Force

Final Rule Effective June 30, 2015

- Replaces current letter categories: A, B, C, D, X
- Three new detailed subsections provide explanations about potential benefits and risks for mother, fetus, and breastfeeding child
  - Pregnancy
  - Lactation
  - Females and males of reproductive potential
- New requirements phased in gradually for existing products

Self-Assessment Question 10

- Are you now aware of the new FDA drug-use-in-pregnancy rule that becomes effective next week? If so, give yourself 1 point
- If you were sleeping during the last 5 min, give yourself 0 points
It’s Time To Tally Your Score!

- 0-2
  - You’re practicing 1980s optometry
- 3-5
  - You’re practicing 1990s optometry
- 6-8
  - You’re practicing “early 21st century” optometry
- 9-11
  - Congratulations! I need a new optometrist as my personal doctor. Are you taking any new patients?!!