Evidence Based Medicine

Definition:
The integration of the best research evidence with clinical expertise and patient wishes to arrive at the appropriate management

Put another way:
Making clinical decisions based on valid evidence rather than intuition, hearsay, or peer practice while keeping the best interests of the patient.

What is evidence-based medicine?

“Evidence-based medicine is the integration of best research evidence with clinical expertise and patient values”

- Dave Sackett

Understanding of EBM

◆ EBM is a structure approach to literature, leading to decisions that are based on probability
◆ EBM "converts the abstract exercise of reading and appraising the literature into the pragmatic process of using the literature to benefit individual patients while simultaneously expanding the clinician's knowledge base."

Evidence Based Medicine (EBM)

◆ An important element of EBM is to assess the quality of evidence relevant to the risk and benefits of treatments (including lack of treatment).
◆ EBM seeks to clarify and apply scientific methods to ensure the best prediction of outcomes in treatment. Wikipedia
Realizations Leading to the Spread of EBM

- The disparity between our diagnostic skills and clinical judgment, which increase with experience …and our up-to-date knowledge and performance, which decrease with age
- Our inability to afford more than a few seconds per patient for finding and assimilating this evidence or to set aside more than a half hour per week for general reading and study

The Quest for Life-Long Learning

- The practice of EBM is a process of lifelong, self-directed, problem-based learning
- The caring for one's own patients creates the need for clinically important information about diagnosis, prognosis, therapy and other clinical and health care issues
- Instead of routinely reviewing the contents of dozens of journals for interesting articles, EBM suggests that you target your reading to issues related to specific patient problems

The Steps in the EBM Project

<table>
<thead>
<tr>
<th>The patient</th>
<th>1. Start with the patient – a clinical problem or question arises out of the care of the patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>The question</td>
<td>2. Construct a well built clinical question derived from the case</td>
</tr>
<tr>
<td>The resource</td>
<td>3. Select the appropriate resource(s) and conduct a search</td>
</tr>
<tr>
<td>The evaluation</td>
<td>4. Appraise that evidence for its validity (closeness to the truth) and applicability (usefulness in clinical practice)</td>
</tr>
<tr>
<td>The patient</td>
<td>5. Return to the patient – integrate that evidence with clinical expertise, patient preferences and apply it to practice</td>
</tr>
<tr>
<td>Self-evaluation</td>
<td>6. Evaluate your performance with this patient</td>
</tr>
</tbody>
</table>

Levels of Evidence and Grades of Recommendations

- There are various study designs; some carry greater value than others
- Types of studies include both experimental and observational: retrospective, cross sectional/prospective, case control, cohort and randomized clinical trials

Hierarchy of Evidence

My 1st Experience with EBM
Adenoviral Keratoconjunctivitis (EKC)

- Represents the most common external ocular infection
- Most frequent virus isolated from the conjunctiva
- Prevalence varies based on time of year and geographic location
- Adenovirus is associated with significant morbidity and high healthcare costs
- 20-65% of all conjunctivitis cases are viral
  - As many as 90% of these may be Adenovirus

Adenoviral Conjunctivitis

- Approximately 20 - 70% of infectious conjunctivitis is thought to be of viral etiology
- 65% - 90% is caused by adenovirus
- HSV may cause keratoconjunctivitis that is indistinguishable from adenovirus
- Clinical studies have shown that HSV may present as conjunctivitis without associated skin lesions in 1-5% of all cases of presumed viral conjunctivitis

Adenovirus vs. HSV

- 2,000 pts with acute conjunctivitis cultured
- 5% of clinically diagnosed cases of HSV were really adenovirus
- 4.8% of clinically diagnosed cases of adenovirus were really HSV

Adenovirus Transmission

- Can live on inanimate surfaces for 4-5 weeks
- Attack rates from 10-50%
- Stable to adverse chemical and physical conditions
- Can shed for 14-16 days after initial symptoms (contagious!)
  - Hand-to-eye
  - Airborne respiratory droplets

Spread of the Disease

- Antibiotics are ineffective against treating the viral form of the disease but are prescribed in up to 95% of conjunctivitis cases
- This leads many patients to return to school, work, or daycare while still contagious
  Proper diagnosis and patient education is important
  Can help stop the spread of infection!

Misdiagnosis

- Misdiagnosis occurs in ~50% of conjunctivitis cases
- Significant overlap of signs and symptoms

References:

AdenoPlus

- Detects all known serotypes of Adenovirus
- Rapid – 10 minute results
- Easy to use – can be performed by a nurse or technician
- In-office (point-of-care) test
- Low cost – no additional equipment required
- One time use – disposable
- Accurate – high sensitivity and specificity
- Limit of detection – 6 ng/ml

AdenoPlus Clinical Trials

A prospective, multicenter, masked, sequential, clinical trial was performed at a combination of private ophthalmology practices and academic centers.

The study enrolled 128 patients presenting with a clinical diagnosis of acute viral conjunctivitis.

Thirty-one patients were confirmed positive for Adenovirus by viral cell culture.

<table>
<thead>
<tr>
<th>N = 128</th>
<th>Cell Culture</th>
</tr>
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<tbody>
<tr>
<td>AdenoPlus</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>-</td>
</tr>
</tbody>
</table>

- Sensitivity: 90% (28/31) 95% CI [74.2-98.0]
- Specificity: 96% (93/97) 95% CI [89.6-98.9]
- Negative Predictive Value: 97% (93/96) 95% CI [91.1-99.3]
- Positive Predictive Value: 88% (28/32) 95% CI [71.6-96.5]

Dry Eye

- Age-related dysfunction of the lacrimal gland
- Lead to aqueous tear deficiency or tear film instability
- Treatment aimed at lubricating and hydrating the ocular surface
- Provided palliative, transient symptomatic relief

Sensitivity and Specificity of the AdenoPlus Test for Diagnosing Adenoviral Conjunctivitis

Robert Sandbrink, MD; William Transcript, MD; Shaker Tadros, MD; Christopher Starr, MD; Murray Friedberg, MD; Thomas Roland, MD; Margarette McDonald, MD; Michael Gelfwood, MD; PMI; Bob Rabin, MD

Objectives: To compare the clinical sensitivity and specificity of the AdenoPlus test with those of both viral cell culture (CC) with confirmatory immunofluorescence (IF) and polymerase chain reaction (PCR) in detecting the presence of adenovirus in test fluid.

Methods: A prospective, sequential, masked, multicenter clinical trial enrolled 128 patients presenting with a clinical diagnosis of acute viral conjunctivitis with or without concurrent viral upper respiratory infection. Patients were tested with AdenoPlus, CC-IFA, and PCR to detect the presence of adenovirus.

Main Outcome Measures: The sensitivity and specificity of AdenoPlus were assessed for identifying adenovirus in test fluid.

Results: Of the 128 patients enrolled, 36 patients' results were found to be positive by either CC-IFA or PCR and 29 patients' results were found to be positive for AdenoPlus. AdenoPlus showed a sensitivity of 90% (28/31) and specificity of 96% (93/97). When compared only with PCR, AdenoPlus showed a sensitivity of 89% (20/22) and specificity of 90% (20/22). When compared with CC-IFA, AdenoPlus showed a sensitivity of 93% (27/29) and specificity of 94% (20/21). When compared with PCR, CC-IFA showed a sensitivity of 89% (20/22) and specificity of 90% (20/22).

Conclusions: AdenoPlus is sensitive and specific at detecting adenoviral conjunctivitis.

Trial Registration: clinicaltrials.gov Identifier: NCT00820195


Traditional Dry Eye

- Dry eye disease represents a “global disease process” that is not limited to the ocular surface
- Integrated process that incorporates:
  - Sensory innervation on corneal surface
  - Autonomic/CNS system
  - Lacrimal gland

Neuronal Feedback Loop

Lacrimal Functional Unit
The Healthy Eye

Normal tearing depends on a neuronal feedback loop.
Slow motor nerve impulses secretomotor nerves.
Tears support and maintain ocular surface.

Neural Feedback Loop

- Controls tear and mucin production.
- Incites inflammation when there is an imbalance in the feedback loop.
- This leads to a change in quantity and quality of the normal tears.

Multiple Factors in Dry Eye

- May be stimulated by environmental conditions\(^1\) or other factors.
  - Medications
  - Drafts or desiccating environments
  - Prolonged visual concentration, causing decreased blink rate
  - Autoimmune disease
- Inflammation and ocular surface damage
- Altered tear film composition\(^2\)
- LASIK

Healthy Tears

- A complex mixture of proteins, mucin, and electrolytes.
- Antimicrobial proteins: Lysozyme, lactoferrin.
- Growth factors & suppressors of inflammation: EGF, IL-1RA.
- Soluble mucin 5AC secreted by goblet cells provides viscosity.
  - Membrane-bound mucins 1 & 4 help stabilize tear film.
- Electrolytes for proper osmolarity.

Tears in Chronic Dry Eye (CDE)

- Lesser concentrations of many proteins in CDE.
  - e.g. antimicrobial proteins.
- Growth factor concentrations decreased.
- Cytokine balance shifted, promotes inflammation.
- Soluble mucin 5AC greatly decreased.
  - Due to loss of goblet cells.
  - Impacts viscosity of tear film.
- Activated proteases.
  - Degradate extracellular matrix & tight junctions.
- Increased electrolytes.

Artificial Tears

- Artificial tears contain electrolytes –
  But they lack the complex mixture of proteins, mucins & other factors found in normal healthy tears.
- Provide temporary, palliative relief.
**Tear Film Osmolarity**

- A measure of the concentration of solutes in the tear film
- Elevated in both evaporative and aqueous deficient dry eye disease
- Tear film osmolarity has been proposed as a biomarker that could be used to diagnose and monitor dry eye disease

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**Intraocular Pressure**

- The pressure within the eye that helps maintain the shape of the cornea
- Increased pressure can lead to glaucoma
- Measured using a tonometer

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**Emerging Technologies:**

- **InflammaDry**
  - Detects elevated levels of MMP-9 in tear fluid
  - 10 minute in-office results
  - Easy to use – can be performed by technicians or nurses
  - Disposable – no additional equipment required

  **Limit of Detection:** the normal level of MMP-9 in human tears ranges from 3–41 ng/ml
  - Positive test result = MMP-9 ≥ 40 ng/ml
  - Negative test result = MMP-9 <40 ng/ml

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**How to Use InflammaDry: Four-step Process**

1. Gently dab the Sample Collector in 6-8 locations on the palpebral conjunctiva (lower eyelid) to collect a tear sample. Do not use a dragging motion.
2. Snap the sample collector into the test cassette and press firmly where indicated.
3. Dip the test cassette into the provided buffer vial for 20 seconds. Replace the cap.
4. Read the results: 2 lines (1 red, 1 blue) = positive, 1 line (blue) = negative
MMP-9 and Dry Eye Severity

<table>
<thead>
<tr>
<th>Patient’s Dysfunctional Tear Syndrome Level</th>
<th>Average MMP-9 Level</th>
<th>Statistical Significance vs Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (n=18)</td>
<td>8.39 ng/ml</td>
<td>NO</td>
</tr>
<tr>
<td>Severity Level 1 (n=15)</td>
<td>35.57 ng/ml</td>
<td>NO</td>
</tr>
<tr>
<td>Severity Level 2 (n=11)</td>
<td>66.17 ng/ml</td>
<td>YES</td>
</tr>
<tr>
<td>Severity Level 3 (n=9)</td>
<td>101.42 ng/ml</td>
<td>YES</td>
</tr>
<tr>
<td>Severity Level 4 (n=11)</td>
<td>381.24 ng/ml</td>
<td>YES</td>
</tr>
</tbody>
</table>

Positive Result = Chronic Dry Eye ≥ 40 ng/ml

InflammaDry Clinical Trial

<table>
<thead>
<tr>
<th>Clinical Criteria</th>
<th>N = 206</th>
</tr>
</thead>
<tbody>
<tr>
<td>InflammaDry</td>
<td>+ 121</td>
</tr>
<tr>
<td></td>
<td>– 22</td>
</tr>
</tbody>
</table>

Sensitivity 85% (121/143) Specificity 94% (59/63) Overall Agreement 87% (180/206)

Other Methods for Dry Eye Diagnosis

<table>
<thead>
<tr>
<th>Dry Eye Testing Method</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schirmer Tear Test</td>
<td>42%</td>
<td>76%</td>
</tr>
<tr>
<td>Tear Break Up Time</td>
<td>92%</td>
<td>17%</td>
</tr>
<tr>
<td>Corneal Staining</td>
<td>63%</td>
<td>89%</td>
</tr>
<tr>
<td>Questionnaire</td>
<td>89%</td>
<td>72%</td>
</tr>
<tr>
<td>TearLab Osmolarity</td>
<td>64-73%</td>
<td>71-92%</td>
</tr>
</tbody>
</table>

InflammaDry Sensitivity 85% Specificity 94%

**Tear Deficiency Is Not the Whole Story**

**Classic definition:**
"Dry eye disease is a disorder of the tear film due to tear deficiency or excessive evaporation which causes damage to the interpalpebral ocular surface and is associated with symptoms of discomfort."1

**Evolving understanding of condition:**
"...a syndrome in which an unstable tear film inadequately supports the health of the ocular surface epithelium, promotes ocular surface inflammation, and stimulates eye pain."2

**Other Methods for Dry Eye Diagnosis**

- Schirmer Tear Test
- Tear Break Up Time
- Corneal Staining
- Questionnaire
- TearLab Osmolarity

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DEWS Classification

Data From Clinical Trials for Cyclosporine Use for Treatment of Dry Eye Disease

- Cyclosporine is the only therapy clinically proven to increase tear production
- Decreased tear production presumed to be caused by inflammation
- Useful for patients with moderate and severe chronic dry eye
- In addition, cyclosporine has been studied for dry eye associated with contact lens use

A Modified Delphi Technique to Obtain Consensus on the Treatment of Dysfunctional Tear Syndrome

Dysfunctional Tear Syndrome (DTS): Pathophysiology

- Most DTS cases have inflammatory basis
  - Triggers or maintains condition
  - Sometimes difficult to clinically observe inflammation
- Presence of clinically apparent inflammation affects treatment choices
<table>
<thead>
<tr>
<th>Severity Level</th>
<th>Signs and Symptoms</th>
<th>Recommended Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Mild to moderate symptoms and no signs</td>
<td>Mild to moderate conjunctival signs</td>
<td>Patient counselling, preserved tears, environmental management, control allergy, use of hypoallergenic products, water intake. If no improvement, add level 2.</td>
</tr>
<tr>
<td>2 Moderate to severe symptoms</td>
<td>Tear film signs</td>
<td>Mild corneal punctate staining</td>
</tr>
<tr>
<td>3 Severe Symptoms</td>
<td>Marked corneal punctate staining</td>
<td>Central corneal staining</td>
</tr>
<tr>
<td>4 Severe symptoms</td>
<td>Severe corneal staining, erosions</td>
<td>Conjunctival scarring</td>
</tr>
</tbody>
</table>

- According to an international task force of cornea specialists convened at Wilmer Eye Institute, moderate and severe chronic dry eye (CDE) requires medical therapy to halt disease progression and allow patients to make their own tears.

- Anti-inflammatory Therapy for KCS
  - Anti-inflammatory therapy makes sense based on inflammatory etiology
  - Addresses the underlying mechanism of disease…it is the missing piece of the puzzle
  - Potential to heal rather than lubricate
  - Targeted therapy has a longer lasting effect than tears

- Why the Sudden Interest in Blepharitis?
  - Treatment has reared its ugly head

- Historical Prevalence of Blepharitis
  - Among 398 randomly selected, “apparently normal” patients presenting for routine vision examinations
    - 155 patients (39%) were judged to have MGD based on absent or cloudy MG secretions on expression
  - In a study of 1148 patients seeking an eye examination because of ocular discomfort or irritation, blepharitis was one of the most commonly diagnosed conditions (24% posterior; 12% anterior) followed by dry eye disease (21%).

Co-existing Conditions


Blepharitis

13%

34%

65%

Allergy

Dry Eye

Prevalence

20%

Prevalence

13%

Prevalence

20%

Overlap between Dry Eye and Allergy

Blepharitis also tends to co-exist frequently with both of these conditions

Diagnostic and Therapeutic Challenges with Blepharitis

Chronic condition with exacerbations and remissions

No definite end point cure

Chronic condition

Several types and subtypes with overlapping signs and symptoms

Comorbidity with dry eye and other OSD

Overlap includes:

- Several types and subtypes
- Overlapping signs and symptoms
- Complex interaction of inflammation, infection, abnormal MG secretions and dysfunctional tear film

Although Anterior Blepharitis and Posterior Blepharitis (MGD) are distinct entities, they often coexist

Spectrum of Lid Margin Disease

Anterior Blepharitis

Mixed

Posterior Blepharitis (MGD)

Most Common

Lid Margin Disease → A Common Ocular Disorder

Anterior and Posterior Blepharitis

- Both share common signs & symptoms
  - Crusting of lids (am)
  - Loss of lashes
  - Collarettes
    - Scales that encircle lash
  - Lid margin redness
  - Conj hyperemia
  - Inflammation
  - Burning, itching, tearing
  - Foreign body sensation
  - Photosensitivity
  - Conjunctival hyperemia
  - Lid margin hyperemia

Anterior Blepharitis

- Crusting of lids (am)
- Loss of lashes
- Collarettes
- Scales that encircle lash
- Lid margin redness
- Conj hyperemia
- Inflammation

Blepharitis

Staphylococcal

Seborrheic

MGD

Chronic Red Eye

Dry Eye

Marginal Ulcer

Phlyctenules

Anterior

Posterior
Pathophysiology of Anterior Blepharitis

- Inflammation is caused by the impact of bacterial exotoxins and/or delayed hypersensitivity to antigens.
- Staphylococcal infection can be purulent or ulcerative and often causes angular blepharitis, a focal infection in the skin of the lateral canthus.

Posterior Blepharitis
Meibomian Gland Disease (MGD)

- Involves a change in composition of meibomian gland secretions.
- Leads to inflammation, irritation and an altered tear film.

Lipid Secretion: Meibomian Glands

- The lipid layer restricts evaporation to 5% to 10% of tear flow.
- Also helps lubricate.

Importance of Meibum Lipid

- Reduce evaporation and stabilize the tear film.
- Function as a lubricant during the blink.
- Form a hydrophobic barrier to prevent tear overflow onto the lids.
- The meibum acts as a surfactant as well as a barrier to the aqueous.

Meibum in MGD

- Changes in the viscosity and clarity of the lipid expressed.
- Results in increased tear film osmolarity.
- Increased evaporation.
- Unstable tear film.

Meibomian Gland Composition

- Synthesized Lipids
  - Wax esters: 44%
  - Sterol esters: 33%
  - Triglycerides: 5%
  - Demyglycerides: 2%
  - Monoglycerides: Tr
  - Fatty alcohols: Tr
  - Hydrocarbons: 2%
- Membrane Derived
  - Cerebrosides: 4%
  - Ceramides: Tr
  - Phospholipids
    - Zwitterionic: 6%
    - Polar: 2%
- Degradation Products
  - Free fatty acids: 2%
Meibomian Gland Function

- MG secretions may be modified by lipases produced by ocular bacteria
- Bacteria may degrade the lipids which lead to an unstable tear film and irritating free fatty acids
- Hormonal imbalances may alter lipid profiles to destabilize the tear film and produce evaporative dry eye

Because Not All MGD Is Obvious, Active Disease Identification Is Crucial

- MGD MAY BE PRESENT WITHOUT OBVIOUS SIGNS (NONOBVIOUS MGD [NOMGD])
- NOMGD MAY BE A PRECURSOR TO OBVIOUS MGD, HIGHLY PREVALENT AND UNDERDIAGNOSED

NOMGD with recalcitrant obstruction despite forceful expression
NOMGD yielding secretion with forceful expression

Meibomian Gland Function

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MDG Can Lead to a Downstream Cycle of Inflammation

Pathophysiology of Posterior Blepharitis and Its Role in Ocular Disease

- Bacterial lipase
- Hormone imbalance
- Alteration in tear film
- Inflammation
- Damage to lid margin
- Occlusive surface inflammation

IOVS March 2011
http://www.iovs.org/

IOVS Investigative Ophthalmology & Visual Science
Involved more than 50 leading clinical and basic research experts from around the world
- Completed 2010: based on more than 2 years of work
- Participants were assigned to subcommittees, reviewed published data and examined the levels of supporting evidence
- The report has also been translated, at least in part, into Chinese, Dutch, French, German, Greek, Italian, Japanese, Polish, Portuguese, Spanish, Russian and Turkish; these translations are available on the TFOS website.

Definition
- Meibomian gland dysfunction (MGD) is a chronic, diffuse abnormality of the meibomian glands
- Commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion
- It may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease

MGD/Posterior Blepharitis Semantics
- As MGD progresses, symptoms develop and lid margin signs, such as changes in meibum expressibility and quality and lid margin redness, may become more visible
- At this point, an MGD-related posterior blepharitis is said to be present
- The term MGD is regarded as appropriate for describing the functional abnormalities of the meibomian glands. Meibomian gland disease is used to describe a broader range of meibomian disorders

Tests to Diagnosis MGD
MG Expression – most important!
- The application of moderate digital pressure to the central lower lid
- Asymptomatic adults
  - It is appropriate to include gland expression
  - A diagnosis of MGD may require that the patient be further assessed for ocular surface damage and dry eye, using appropriate diagnostic techniques
Tests for Diagnosing MGD

- Administration of a symptom questionnaire
- Measurement of the blink rate and calculation the blink interval
- Measurement of lower tear meniscus height
- Measurement of tear osmolarity (if available)
- TBUT and Ocular Protection Index (OPI)
- Grading of cornea/conj stain
- Schirmer’s or alternate (phenol red thread test)

MGD Complications

- Chronic blepharoconjunctivitis
- Keratitis
  - Neovascularization
  - Ulceration
  - Scarring and thinning
- Chronic pain
- Loss of vision

Ocular Rosacea Findings

- Meibomian gland Dz
  - Foamy tears
- Recurrent chalazia
- Chronic blepharitis
  - Staph blepharoconjunctivitis
  - Lid margin telangiectasia
- Papillae, follicles
- Hyperemia

Ocular Rosacea Findings

- Corneal vascularization
- Sterile corneal infiltrates
- Corneal ulceration
- Corneal perforation
- Episcleritis
- Scleritis
- Iritis

Treatment Recommendations

A Stepwise Approach

- Step 1 – Lid Hygiene: LS, HC, AT
- Step 2 – Topical Medications
  - Steroids (FML, Lotemax, PF)
  - Antibiotic ointment (Erythromycin)
  - AzaSite
- Step 3 – Systemic antibiotics
  - Tetracycline/Erythromycin
  - Doxycycline
  - Azithromycin

Traditional Treatments

- Lid Hygiene
  - Baby shampoo
  - Hot compresses
- Poor compliance
Lid Margin Disease Treatment
- Good penetration into lid tissue → high levels of drug at site of disease
- Anti-infective activity → reduce bacterial colonization/load
- Anti-lipase activity → inhibit degradation of meibomian gland lipids
- Anti-inflammatory effect → reduce the inflammation to aid in patient symptom improvement and ocular/lid redness
- Convenient dosing → promote good compliance

Blepharitis Treatment: Beyond Lid Hygiene
- Oral Doxycycline
  - 100 mg/day for 1 wk, 50 mg/day X 6-8 wks
  - Low dose doxycycline
    - Perostat (Doxy 20 mg) bid
- AzaSite: topical azithromycin

Mechanism of Action of Tetracyclines
- Reduction of the bacterial load on the eyelid
- Anti-inflammatory action
  - Inhibits the production of free fatty acids
    - Degradation product of MG lipids
    - Free fatty acids can destabilize the tear film leading to inflammation
  - Inhibition of lipases
  - Inhibition of matrix metalloproteinases

Anti-Inflammatory Effects of Macrolides
- Macrolides prevent the formation of:
  - Pro-inflammatory mediators
  - Cytokines
  - Prostaglandins
  - TNF-α
  - Inhibit matrix metalloproteinase (MMP) activity a
  - Interleukin-1 (IL-1) synthesis

Prognosis with Oral Therapy
- Good with ongoing Tx
- Most improve within 4 weeks
  - Often relapse within 3 month if Tx stopped
- Should be maintained on antibiotic therapy for up to 3 mo or longer
- Most improvement occurs after 4 wks
- TCN may work faster but = by 4 wks
AzaSite

- 1% topical azithromycin
- Macrolide
- Broad spectrum of action particularly against gram-positive organisms
- It works by inhibiting protein synthesis

Topical Azithromycin

- Azithromycin accumulate in the sebum and decreases bacterial lipase production
- Lowers the concentration of free fatty acids
- Decreases production of microbial inflammatory mediators through inhibition of protein synthesis

DuraSite®: The AzaSite™ Vehicle

- DuraSite® contains
  - Polycarbophil USP
  - Sodium chloride, edetate disodium (EDTA), benzalkonium chloride (BAK 0.003%), purified water and sodium hydroxide to adjust pH¹
- DuraSite® is an advanced synthetic polymeric mucoadhesive matrix that stabilizes small molecules like azithromycin
- DuraSite® allows for a stable formulation of azithromycin¹ and increase the bioavailability of azithromycin in tissue²

The Claim:

- Azithromycin accumulate in the sebum and decreases bacterial lipase production
- Lowers the concentration of free fatty acids
- Decreases production of microbial inflammatory mediators through inhibition of protein synthesis

Unsubstantiated Claims

The Journal Ad includes the claim, "AzaSite® Can Restore a Healthy Ocular Surface By Delivering Significant Anti-Inflammatory and Antimicrobial Effects 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, when this has not been demonstrated by substantial evidence or substantial clinical experience.

Conclusion and Requested Actions

For the reasons discussed above, the Journal Ad misbrands AzaSite in violation of the Act, 21 U.S.C. 352 (a), 321(n), and FDA implementing regulations. 21 CFR 201.1(a)(5); (e)(10); (j)(3); & (v)(l).

DOMAG requests that you immediately cease the dissemination of violative promotional materials for AzaSite that contain violations such as those described above. Please submit a written response to this letter on or before April 28, 2011, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date for AzaSite that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications. 5901-B Ammendale Road, Beltsville, MD 20705-1248, facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMS # 16525 in addition to the NDA number. We remind you that only written communications are considered official.
LipiFlow® Output

**Assess the Tear Film With LipiView®**

LipiView uses advanced interferometric technology and captures detailed digital images of the eye’s tear film to capture, archive, manipulate, and store the oily lipid layer of tear.

- **Light source:** the illuminator
- **Chin rest:**
- **Camera, eye, and drivers are housed by the device**
- **Device dimensions:** 28” x 17” x 17”
- **Measurement time:** 20 seconds per eye

**Pressure and Pulsation for MGD**


**Meibomian Gland Probing**

A. **LipiFlow® Thermal Pulsation System**
   - **Lid Warmer:** Applies directional heat to inner eyelid
   - **Eye Cap:** Applies intermittent pressure to the outer eyelid
   - **Insulated Component:** Shields eye from heat and stands above the cornea to prevent corneal contact

B. **Warm Compress Therapy**
   - **Inflatable air bladder:** Adjusts to contour to the lid surface

Meibomian Gland Dysfunction Treatment
What is the Basis for Treating with FQ?

**0.3% Ofloxacin (Ocuflox) vs Fortified Antibiotics**

- Bacterial Keratitis Study Research Group
- 248 pts enrolled:
  - 148 pts culture (+) randomized 0.3% ofloxacin solution (73 pts) or combination of the fortified antibiotics (67 pts)
  - 1.5% tobramycin and 10.0% cefazolin solutions
- 28 centers participated
  - Arch of Ophth. October 1995. 113: 1257-1265

- 0.3% Ofloxacin (Ocuflox) vs Fortified Antibiotics
  - Bacterial Keratitis Study Research Group
  - 7 days: 37% Oflox vs 38% FA healed
  - 28 days: 89% Oflox vs 86% FA healed
  - Oflox pts less burning, stinging, easier to use
  - More ocular side effects with FA’s
  - Oflox was equivalent to fortified antibiotics
  - Arch of Ophth. October 1995. 113: 1257-1265

- 0.3% Ciprofloxacin vs. Fortified Tobramycin-Cefazolin
  - Ciprofloxacin Bacterial Keratitis Study Group
  - Double masked randomized clinical trial
  - 324 pts: 160 to ciprofloxacin and 164 to fortified tobramycin-cefazolin
  - Ciprofloxacin monotherapy was equivalent clinically and statistically to the fortified antibiotics regimen
    - No difference in clinical efficace: ciprofloxacin (91.5%) vs. standard therapy (86.2%) (P = 0.34).

**Fluoroquinolones**

- The 1st safe, broad-spectrum ophthalmic antibiotics
- 1st released for ophthalmic use in early 1990’s
- Represented an important break-through for clinicians
- For the 1st time strong commercially available antibiotics available to treat bacterial conjunctivitis and ulcerative keratitis
- Broad spectrum including pseudomonas

**Fluoroquinolones**

- Ophthalmology July 1999; 106 (7): 1313-8
- The BIG problem with the fluoroquinolones has been bacterial resistance!
  - 1993 – 5.8% resistance
  - 2 yrs after release of fluoroquinolones
  - 1997 – 35% bacterial resistance
  - 2001 – 100% resistance to staph aureus isolates cultured in endophthalmitis
  - Resistance to cipro, oflox, levoflox
4th Generation Fluoroquinolones

When Would You Recommend Steroids?
1. Right from the beginning
2. Never
3. I would wait 48-72 hrs
4. I would wait until the lesion was re-epithelialized

Guidelines: The Use of Topical Steroids in Bacterial Keratitis

Risks vs. Benefit:
- **For:** Minimize scarring
- **For:** Steroids do not interfere with the ability of a bactericidal antibiotic, in sufficient concentration, to kill susceptible organisms

- **Against:** May slow healing
- **Against:** For some organisms – steroids can be like candy: fungal
- **Against:** Difficult to quantify scarring, therefore it’s never been proven that steroids minimize scarring.

Guidelines: The Use of Topical Steroids in Bacterial Keratitis

- Avoid if fungal infection or atypical mycobacterium is suspected
- Avoid if there is severe thinning, enlarging epithelial defect, poor wound healing (diabetes), or immuno-suppression.

Corticosteroids for Bacterial Keratitis

Objective: To determine whether there is a benefit in combined treatment with the use of topical corticosteroids as an adjunctive therapy in the treatment of bacterial corneal ulcers.

Methods: Randomized, placebo-controlled, double-masked, multicenter trial comparing prednisolone acetate 1%, 0.5%, and placebo at baseline for the treatment of bacterial corneal ulcers. Subjects were randomized in a 1:1:1 fashion to either prednisolone acetate 1%, 0.5% or placebo for 10 days. The primary outcome measure was complete healing at the end of 10 days.

Results: Between September 1, 2009, and February 22, 2010, 690 patients were recruited for the study and 600 patients were included. No significant difference was observed in the proportion of patients achieving complete healing with the use of topical corticosteroids (P = 0.45) or with no corticosteroids (P = 0.90).

Conclusions: Topical corticosteroids are not efficacious in the treatment of bacterial corneal ulcers.

October 2011

ONLINE FIRST
Corticosteroids for Bacterial Keratitis

The Steroids for Corneal Ulcers Trial (SCUT)

- 9/1/2006 – 2/22/2010, 1769 patients were screened for the trial and 500 patients were enrolled
- No significant difference was observed in the 3-month BSCVA, time to reepithelialization, or corneal perforation
- A significant effect of corticosteroids was observed in subgroups of baseline BSCVA, and ulcer location
  - At 3 months, patients with vision of counting fingers or worse at baseline had 0.17 logMAR better visual acuity with corticosteroids (95% CI, −0.31 to −0.02; P = .03) compared with placebo,
  - Patients with ulcers that were completely central at baseline had 0.20 logMAR better visual acuity with corticosteroids

SCUT Study

- At 3 months, patients with vision of FC or worse at baseline had 0.17 logMAR better visual acuity with corticosteroids (95% CI, −0.31 to −0.02; P = .03) compared with placebo
- Patients with ulcers that were completely central at baseline had 0.20 logMAR better visual acuity with corticosteroids