Treating Ocular Surface Disease in the Clinical Setting

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Tear Film and Ocular Surface Society (TFOS)

• TFOS
  • DEWS I (2007)
  • DEWS II (July 2017 in Ocular Science)
• Purpose: To modernize the eye care community’s concepts and clinical practices surrounding dry eye disease
• 150 experts
• 23 countries
• Thousands of published dry eye disease articles

Evolution of Dry Eye Definition

• NEI/Industry Workshop (1995)
  “Dry eye is a disorder of the tear film due to tear deficiency or excessive tear evaporation which causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort.”

Evolution of Dry Eye Definition

• DEWS I (2007)
  “Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.”
Evolution of Dry Eye Definition

DEWS II (2017)
“Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.”

DEWS II: Classification of DED

- Asymptomatic with no signs
  - Normal
- Asymptomatic with signs of ocular surface disease
  - Reduced corneal sensitivity
  - Predisposition to dry eye
- Symptomatic with no signs
  - Neuropathic pain
  - Pre-clinical dry eye state
- Symptomatic with signs of ocular surface disease
  - Reduced corneal sensitivity
  - Predisposition to dry eye

Prevalence

- Beaver Dam Offspring Study
  - Prevalence: 14.5% (nearly 30 million people)
- 76% ECP’s reported increase in dry eye symptoms (18-34 year old)
- Digital device use
  - 88% adults > 2 hours/day
  - 1 in 10 spend 75% waking hours
- Increased prevalence in diabetic patients
  - 29 million Americans (9.3%) with diabetes mellitus
  - Half population has dry eye
- Less than 60% of DED patients are symptomatic
- Implications for cataract and refractive surgery
- Occurs more frequently in women than men
  - Attributed to effects of sex steroids
- Prevalence: 5-50% (DEWS II)
- Prevalence increases with age
- Asian populations higher risk than Caucasian populations
- Males higher prevalence for MGD
Risk factors

- Diabetes mellitus
- Systemic disease
- Contact lens wear
- Environmental exposures
- Computer screen use
- Refractive surgery

Symptoms

Ocular symptoms
- Dry
- Blurr
- Burning
- Irritation
- Stinging
- Sandy/gritty sensation

Psychological symptoms
- Depression
- Stress
- Anxiety

Complications of ocular surface disease

- Ocular surface damage
- Risk of infection
- Inflammation
- Corneal surface abrasion
- Corneal ulcers
- Contact lens intolerance
- Vision problems

Tear Film Model

Aqueous deficient dry eye (ADDE)

- “Where hyperosmolarity results from a reduced lacrimal secretion in the presence of a normal rate of tear evaporation.”
- Conditions affecting lacrimal gland

Evaporative dry eye (EDE)

- “Where tear hyperosmolarity is result of excessive evaporation from the tear film in the presence of normal lacrimal function.”
- Conditions affecting eyelid or ocular surface
  - MGD
  - Bleb abrasibilities
  - Mucin deficiency
  - Contact lens wear
- MGD important cause of EDE
Pathophysiology

- Acute inflammatory response
  - Immediate reaction
    - Release of acute-phase response cytokines
    - Intercellular adhesion molecule expression
    - Activates antigen-presenting cells
  - T cells migrate to ocular surface tissues
- Chronic autoimmune response
  - Decrease goblet cell density
  - Apoptosis
  - Overexpression of MMP3 and MMP9

Differential diagnoses

- Allergic conjunctivitis
- Giant papillary conjunctivitis (GPC)
- Atopic keratoconjunctivitis (AKC)
- Vernal keratoconjunctivitis (VKC)
- Viral conjunctivitis
- Bacterial conjunctivitis
- Blepharitis
- Demodex
- Parasitic infections

Meibomian gland dysfunction (MGD)

- More common in younger demographics
- Affects males/females equally
- Disruption of lipid layer
  - Keratinization of Meibomian gland duct
  - Debris accumulation

Make-up

- Average use of 12 products around and inadvertently in eyes
- Unregulated industry
  - Parabens
  - Isopropyl cloprostenate
- Ocular adnexa
  - Liquid foundation
  - Concealer
  - Eyeliner
  - Mascara

Demodex

- Common cause of dry eye symptoms
- Cylindrical dandruff and restoration
- Chronic inflammation of lids
- Madarosis
- Severe itch
  - Demodex folliculorum
  - Lash follicles of lids
  - Demodex brevis
  - Burrow into sebaceous and Meibomian glands
Diagnostic Testing

Case history
- Identify predisposing factors
- Can help confirm diagnosis
- Discuss symptoms occurring outside exam

Questionnaires
- Screening tool
  - Establish necessity for further DED evaluation
  - Monitor progression and response to treatment
  - Administer at first examination

Questionnaires
- Examples:
  - Ocular Surface Disease Index (OSDI)
    - Excellent reliability and validity
    - Scales: severity, and disability
    - Differentiates normal, mild, moderate, and severe
  - Dry Eye Questionnaire 5 (DEQ-5)
    - Objective value to subjective complaints
    - Impact of Dry Eye on Everyday Life (IDEEL)

Visual acuity
- Fluctuations in vision
- Frequent blinking
- Transient blur
  - Tear film instability
- Persistent blur
  - Gums staining
Slit lamp examination

- **Lids:**
  - Positioning
  - Laxity
  - Overall lid hygiene

- **Conjunctiva:**
  - Conjunctivochalasis
  - Exposed concretions
  - Pinguecula
  - Pterygium
  - Hyperemia

  - Papillary reaction

- **Cornea:**
  - Superficial punctate keratitis
  - Filaments
  - Corneal dystrophies

Tear breakup time

- **Tear breakup time (TBUT)**

- **Fluorescein breakup time (FBUT):**
  - Most commonly performed
  - Utilize sodium fluorescein (FBUT)
    - Reduces stability of tear film
    - May not be accurate
    - Varying volumes and concentrations

  - Narrow (1 mm) strips
  - Dry sterile applicators
  - Perform after osmolarity

  - Instructions:
    - Blink naturally 3 times, open until instructed
    - Fluorescein instilled outer canthus
    - Optimal viewing: 1-3 min. after instillation

  - Results:
    - Normal: > 10 seconds
    - Normal: > 5 seconds (utilizing smaller, more controlled fluorescein volume)

- **Non-invasive breakup time (NIBUT):**
  - Observation of specular reflection from tear film
  - Placido disk images corneal topography
  - More precise
  - White or infrared illumination
  - Longer measured values of breakup time

  - Instructions:
    - Blink naturally 3 times, hold
    - Average of 3 measurements
    - Cut off can be below 2.7 seconds
    - First indicator of dry eye disease
    - Identify subtle irregularities of ocular surface
    - Irregularly shaped placido discs

  - Examples:
    - Keratograph (Oculus)
    - EC300 Corneal Topographer (Medmont)
**Tear volume**

- Assessment of tear meniscus
  - Tear meniscus height (TMH)
  - Tear meniscus curvature (TMR)
  - Tear meniscus cross-sectional area (TMA)
- Influences:
  - Operator dependent
  - Time after blink
  - Location along lid margin measurement taken
  - Time of day
  - Temperature
  - Humidity
  - Air speed
  - Illumination

**Optical coherence tomography**

- Non-invasive
- Image capture rapid
- Measure upper/lower
  - Height (TMA)
  - Curvature (TMR)
  - Area (TMA)
  - Depth
  - Difficult analysis

**Dye testing**

- Staining guides
  - National Eye Institute/Industry Workshop guidelines
  - Collaborative Longitudinal Evaluation of Keratoconus (CLEK) schema

**Dye testing**

- Sodium fluorescein
  - Peak excitation wavelength = 495 nm
  - Cobalt blue filter peak = 450 nm
  - Peak excitation wavelength in pH range of tear film = 515 nm
  - Wratten filter required for optimal observation around 500 nm
  - Positive: > 5 corneal spots
  - Identify desiccated or injured cells
  - Disruption in superficial tight junctions
  - Defective glycocalyx

- Lissamine green
  - Conjunctival damage
  - Line of Marx (lid margin)
  - Less toxic than rose Bengal
  - Red filter (657-634 nm) enhances contrast against sclera
  - Instill into far lower temporal lid in upgaze. Pull lower lid slightly temporally to avoid damage
  - Positive: > 9 conjunctival spots

**Dye testing**

- Rose Bengal
  - Stains epithelial cells unprotected by mucus or glycocalyx
  - Stains dead and degenerated cells
  - Stings upon instillation
Phenol red thread

- Thread cotton thread soaked with phenol red
- pH-sensitive dye
  - Dry = yellow
  - Wet (tears) = red
- Realistic measure of resting tear volume

Instructions:
- Insert folded end of thread on temporal 1/3 of eyelid
- Time: 15 seconds
- Without anesthesia

Results:
- Normal: > 20 mm
- Abnormal: < 20 mm

Schirmer's test

- Provides estimate of stimulated reflex tear flow
- Detection of aqueous deficient dry eye
- Gold standard

Instructions:
- Fold paper strip at notch
- Hook end over temporal 1/3 of lower lid margin
- With and without anesthesia
- Schirmer's I and Schirmer's II

Results:
- Measure length of wetting from notch
- Anesthesia
  - > 10 mm in 5 minutes
- No anesthesia
  - > 15 mm in 5 minutes

Osmolarity

- Salt concentration increases as aqueous volume decreases
- Accurately identified 81.3% of normal eyes and 90.7% of severe dry eye patients
- Normal tear osmolarity = 302 mOsm/L
- Inter-eye variability in DED
  - Loss of homeostasis = > 8 mOsm/mL
  - Mild-to-moderate = 11.7 ± 10.9
  - Severe = 26.5 ± 22.7
- Elevated and unstable tear film osmolarity in DED

Classification:
- Normal: 302.2 ± 8.3
- Cut-off: 306 mOsm/L
- Mild-to-moderate: 315.0 ± 11.4
- Cut-off: 316 mOsm/L
- Severe: 336.4 ± 22.3

Example:
- TearLab (TearLab Corporation)
Impression cytology

- Diagnose:
  - Dry eye disease
  - Limbal stem-cell deficiency
  - Ocular surface neoplasia
  - Specific viral infections

Blood analysis

- Identify autoimmune disease
  - Rheumatoid arthritis
  - Sjogren syndrome
    - SSA, SSB
  - Systemic lupus erythematosus
  - Mixed connective tissue disease
  - Chronic hepatitis
  - Stevens-Johnson syndrome
  - Chronic graft vs. host disease (GVHD)

Matrix metalloproteinases (MMP-9)

- One of many protease classes secreted in DED
- Destroy epithelial tight junctions
- Produced as inactive proenzymes
  - Cleaved to become active enzymes
- Measures MMP-9 tear assay levels in 10 minutes
- Results:
  - Positive result = > 40 ng/mL
  - Indicates inflammation, not necessarily related to DED
- Example:
  - InflammaDry® (Rapid Pathogen Screening)

Examination of lids

- Lid wiper = portion of upper/lower lids that wipes ocular surface
- Normally rich in goblet cells
- Lid wiper epitheliopathy (LWE)
  - Stains with sodium fluorescein and lissamine green
  - Increased friction during blinking
  - 88% of symptomatic patients had LWE

Blink/lid closure analysis

- Measure blink rate
  - Normal: 10-15 blinks/min.
  - Females > males
- Partial or incomplete closure
- Digital devices – more problematic
- Teens stare at computer: Average – 9 hours/day
  - Blink rate decrease 40%

Meibomian gland expression

- Assess quantity, quality, and expressibility
  - Normal: meibum clear, readily expressed
  - Abnormal (MGD): lose clarity to become cloudy and opaque
    - Increased viscosity, toothpaste-like
Meibography

- Observation of silhouette of Meibomian gland morphological structure
- Examine structural integrity of Meibomian gland
- Identify atrophy and truncated glands
- Difficult to visualize glands underneath the surface

Interferometry

- Measures time between blink and first discontinuity in lipid layer
- Does not measure TBUT
- Example:
  - LipiView (TearScience)
    - Measures thickness of lipid layer of tear film
    - Results:
      - Normal: > 75 nm
      - Abnormal (MGD): < 75 nm

Thermography

- Tear film evaporation results in cooling of ocular surface
- Measures absolute temperature and change in temperature during blink
- Ocular surface cools faster in patients with DED
- Infrared thermography
  - Non-invasive measurement

Management and Treatment

- Artificial tears
- Lacrem
- Osmotic agents
- Preservatives
- Analogueous serum
- Mucolytics
- Punctal occlusion
- Necrotizing
- Noninflammation
- Moisturizing chamber spectacles
- Antimicrobial
- Warm compresses
- LipiFlow
- Lid hygiene
- Contact lenses
- Anti-inflammatories
- Antimicrobial membrane
- Fatty acid supplements

MGD Treatment

- Lid hygiene
  - Baby shampoo
  - All-natural
  - Jojoba oil
  - Coconut oil
  - Olive oil
  - Lid scrub wipes
  - Lid foam cleansers
- Warm compresses
  - Temperature: 100°F/40°C
- Breaker mask
- Thermolux (OcuScience)
- TheraPearls (B+L)
- TranquilEyes (Eye Eco)
MGD Treatment

- **Lipiflow (TearScience)**
  - Heats Meibomian glands from inside out
  - Evacuates meibum with air bladder
  - 12 minute procedure
  - LF vs. warm compresses
  - LF improved symptoms, Meibomian gland secretion, and TBUT at 1 month
  - LF vs. warm compresses: improvement in symptoms
- **MiBlow (Mibo Medical Group)**
  - Heats Meibomian glands from outside in
  - Manual Meibomian gland expression

MGD Treatment

- **Eyelid debridement (10-15 sec./lid)**
  - Opens up keratinized epithelium
  - Golf club spud
  - Cotton swab
  - Butt end of jeweler's forceps
  - BlephEx (Rysurg)
  - Mastrota Meibomian Paddle (OCuSoft)

Demodex Treatment

- **Tea tree oil**
  - Anti-inflammatory
  - Antibacterial
  - Antifungal
  - Toxic to
  - Natural oil from *Melaleuca alternifolia* leaves
  - 4% solution
  - Causes ocular stinging and irritation

Demodex Treatment

- **Examples:**
  - Cliradex (Bio-Tissue)
  - SteriLid (TheraTears)
  - Blephadex (Lunovus)
  - OCuSoft scrubs (OCuSoft)

Demodex Treatment

- **Hypochlorous acid**
  - Avenova with Neutrox 0.015 HOCl (NovaBay)
  - Hypochlor gel 0.02% HOCl (OCuSoft)

Artificial tears

- **Aqueous supplements**
  - Viscosity-enhancing agents
  - Immune cell film thinners, promotes desiccation
  - Preservatives
  - Maintain normal flow rates
  - Improve goblet cell density
  - High viscosity – increase retention time
  - Transient visual disturbances
  - Unsuitable for eye glues
  - Very high viscosity – overnight use
Artificial tears

- Emulsions with liquid lipids
  - Charged microemulsions
    - Retaine MGD
    - Systane Balance
  - Uncharged microemulsions
    - Refresh Optive Advanced
- Do not target underlying pathophysiology
- Target one or more layers of tear film

Artificial tears

- Instill 4-6x daily
  - Lipid-based
    - Systane Balance (Alcon) - mineral oil
    - Soothe XP (Bausch + Lomb) – light mineral oil, mineral oil
    - Refresh Optive Advanced (Allergan) – castor oil
    - Retaine MGD (OCuSoft) – glycerol
  - Aqueous-based
    - Systane Ultra
    - Refresh Optive
    - Blink Tears
  - Gel-based
    - Systane Gel
    - Refresh Gel
    - OcuPure

Lacrisert

- Hydroxypropyl cellulose ophthalmic insert (Bausch + Lomb)
- Dissolvable hydroxypropyl cellulose insert
- Placed inferior cul-de-sac
- 12 hour dissolvable
- Inserted once a day

Preservative toxicity

- Benzalkonium chloride (BAK)
  - Cytotoxic to ocular surface epithelium
  - Frequently used preservative in drops
  - Complications:
    - Epithelial cell apoptosis
    - Damage corneal nerves
    - Delayed corneal wound healing
    - Goblet cell loss

Preservative toxicity

- New variant
  - Sodium chlorite
  - Poloxamer
  - OcuPure
  - Sodium polyborate
  - GenSqua
  - Polyquaternium-1 (Polysporad)
  - SozZa

NSAIDs

- Inhibit cyclooxygenase enzyme
  - Prostaglandin decrease
  - Bromfenac 0.075%
  - DuraSite vehicle
Corticosteroids

- Corticosteroid
  - Lotemax gel or original suspension (Bausch + Lomb)
  - Off-label use for dry eye disease inflammation
- Fluorometholone 0.1% ophthalmic suspension
- Directions:
  - QID x 2 weeks
  - BID x 2 weeks
  - Pulse dose QID x 1 week (1-2x/year)

Restasis (cyclosporin 0.05%, Allergan)

- Active ingredient: Cyclosporine
- Reduced inflammation by T-cell inhibition
- Downregulates inflammatory cytokines
- Enhances tear production
- Multi-dose bottle available

Xiidra (lifitegrast 5%, Shire)

- Lymphocyte function-associated antigen-1 (LFA-1) antagonists
- Inhibits T-cell recruitment and activation
- Single-use vial
- BID
- Side effects:
  - Irritation upon instillation
  - Dryness (metallic aftertaste)
  - Blurred vision immediately following use

Punctal plugs

- Increase tear meniscus height
- Prolong inflammatory cytokines
- Tear inflammation prior
- Absorbable
  - Temporary inserts
  - Collagen-based plugs
  - Non-absorbable
  - Silicone based
  - Partial occlusion

Secretagogues

- Aqueous
  - Stimulate water and mucin secretion
- Mucin
  - Mucin-like glycoproteins
- Lipid
  - Increased lipid secretion

Neuromodulation

- Intranasal lacrimal neurostimulator
  - Induce normal tear production
  - Stimulation of nasolacrimal reflex
  - Electrical current to anterior ethmoidal nerve
- Example:
  - TrueTear Intranasal Tear Neurostimulator (Allergan)
  - FDA approved for temporary increases in tear production
**Oral medications**

- Minocycline
- Doxycycline
  - 50 mg daily (3-4 months)
  - Take with breakfast or lunch (reduce gastroesophageal reflux)
  - Higher risk of yeast infection
  - Photosensitivity
- Azithromycin

**Fish oil**

- Omega-3 fish oil supplement (2,000 mg/day)
  - 4-6 months for effect
- Liquid supplements
  - Coromega Orange Squeeze
  - Nordic Naturals
  - 1g omega-3/day = 30% reduction risk of DED

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**Autologous serum**

- Most natural treatment option
- Blood plasma
  - Anti-inflammatory factors
- Blood serum
  - Promote enhanced epithelial wound healing
  - Inhibit release of inflammatory cytokines
  - Increase number of goblet cells and mucin expression
- Improved dry eye symptoms
  - After 10 days (60%)  
  - After 2 months (79%)

**Autologous serum**

- Contains
  - EGF
  - NGF
  - Albumin and Fibronectin
  - Supports proliferation and migration of epithelial cells

**Contact lenses for DED**

- Soft contact lenses
  - Daily disposables (sphere, toric, multifocal)
- Gas permeable lenses
  - Scleral lenses
    - Liquid reservoir

**Amniotic membranes**

- Promote healing
- Reduce inflammation
- Treatment of persistent corneal epithelial defects
Lifestyle changes

- Frequent breaks from digital devices
- Computer programs that encourage blinking
- Computer: prefer slight down gaze
  - Reduces palpebral aperture size
  - Tear film more stable
  - Reduces muscle strain

Conclusion

- Dry eye disease is more common than we think
- Improvement in diagnostic testing
- Numerous treatment and management options available
- Improved quality of life for patients

THANK YOU!

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