MY FIRST CASE:

An 81-year-old white male was referred to our dry eye clinic for a consultation on severe keratitis sicca secondary to Sjögren's syndrome. His ocular history was remarkable for chronic "grittiness, scratchiness and burning" in both eyes that was recalcitrant to conventional therapy.

His current treatment regimen includes Lotemax (Loteprednol Etabonate 0.5%, Bausch + Lomb) B.I.D., Restasis (Cyclosporine A 0.05%, Allergan) B.I.D., Punctal occlusion of the lower lids, Systane Preservative-Free (Alcon) artificial tears every two to four hours while awake, and Genteal Gel (Novartis) at bedtime, all used bilaterally.

Additionally, the patient wears wraparound glasses when outdoors, and uses a cool-air mist humidifier in the living room and bedroom. The patient is pseudophakic OU.
MY 1ST CASE:

Pertinent exam findings include:

- **Best-Corrected Visual Acuity:** 20/25- O.D., 20/25- O.S.
- **Mild Conjunctival Injection O.U.**
- **Diffuse Superficial Punctate Keratopathy O.U.**
- **3+ Lissamine Green Staining O.U.**
- **Well-Positioned Freeman Style Silicone Punctal Plugs O.U.**
- **Intermittent Incomplete Closure on Blink O.U.**
- **Schirmer Tear Test without Anesthesia: <1mm in each eye**
- **Blink Rate: Frequent (approximately every three to four seconds)**

### Symptoms of Dry Eye

<table>
<thead>
<tr>
<th>Dry Eye Severity Level</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Symptoms</td>
<td>Mild Symptoms</td>
<td>Moderate Symptoms</td>
<td>Severe Symptoms</td>
<td>Severe Symptoms</td>
</tr>
<tr>
<td>Symptom</td>
<td>Never to Seldom</td>
<td>Sometimes</td>
<td>Frequent</td>
<td>Always</td>
</tr>
<tr>
<td>沙रिम टेयर स्टेस: मिड</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Vision: Blurring, Interrupted</td>
<td>No</td>
<td>No</td>
<td>Sometimes</td>
<td>Usually</td>
</tr>
<tr>
<td>Use of Artificial Tears</td>
<td>No</td>
<td>No</td>
<td>Several times per day</td>
<td>Several times per day</td>
</tr>
</tbody>
</table>


### Signs of Dry Eye

<table>
<thead>
<tr>
<th>Dry Eye Severity Level</th>
<th>1</th>
<th>2</th>
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<th>4</th>
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<tbody>
<tr>
<td>General Symptoms</td>
<td>Mild Symptoms</td>
<td>Moderate Symptoms</td>
<td>Severe Symptoms</td>
<td>Severe Symptoms</td>
</tr>
<tr>
<td>Conjunctival Staining</td>
<td>Mild</td>
<td>Moderate</td>
<td>Marked</td>
<td>Scarring</td>
</tr>
<tr>
<td>Corneal Staining</td>
<td>Mild punctate</td>
<td>Marked punctate central</td>
<td>Severe punctate erosions</td>
<td></td>
</tr>
<tr>
<td>Tear Film</td>
<td>Visual signs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Example Staining</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tear Film Breakup Time</td>
<td>&lt; 12</td>
<td>&gt; 2 - 17</td>
<td>&gt; 5</td>
<td>&gt; 3</td>
</tr>
<tr>
<td>Schirmer Score</td>
<td>&gt; 10</td>
<td>&gt; 3 - 10</td>
<td>&gt; 5</td>
<td>&gt; 2</td>
</tr>
</tbody>
</table>

**Continuum of Care**

**Severity Level**

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education</td>
<td>Environmental changes</td>
<td>Preserved tears</td>
<td>Add: Unpreserved tears</td>
</tr>
<tr>
<td>Gels</td>
<td>Oral</td>
<td>Cyclosporine A</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td>Ointments</td>
<td>Omega-3 fatty acids</td>
<td>Moisture goggles</td>
<td>Surgery</td>
</tr>
</tbody>
</table>

**Natural Tears**

- **A complex mixture of proteins, mucin, and electrolytes**
  - Antimicrobial proteins: CFP, lactoferrin
  - Growth factors & suppressors of inflammation: EGF, IL-1ra
  - Soluble mucin secreted by goblet cells for viscosity
  - Electrolytes for proper osmolality

Image adapted from: Dry Eye and Ocular Surface Disorders, 2004.
FUNCTIONS OF A HEALTHY TEAR FILM

- Optical clarity, refractive power
- Ocular surface comfort, lubrication
- Protection from environmental and infectious insults
- Antibacterial, protease, antivirus, complement
- Reflex tears flush away particles
- Trophic environment for corneal epithelium
- Necessary electrolytes maintain pH
- Protein factors for growth and wound healing
- Antioxidants

AU·TOL·O·GOUS

DEFINITION:
DERIVED OR TRANSFERRED FROM THE SAME INDIVIDUALS BODY!
**AUTOLOGOUS SERUM EYE DROPS**

- Serum = fluid component of full blood which remains after clotting
- Use first described in 1984 by Fox et al (for keratoconjunctivitis sicca)
- Unpreserved, non-antigenic
- Biomechanical and biochemical properties similar to natural tears

**UNSTIMULATED TEARS VERSUS SERUM**

- pH = 7.4
- Osmolarity = 296
- EGF (ng/ml) = 0.5
- TGF-β (ng/ml) = 6 – 33
- Vitamin A (mg/ml) = 46
- Lysozyme (mg/ml) = 6
- SIGA (ug/ml) = 2
- Fibronectin (ug/ml) = 205
- Hepatocyte GF, NGF, IGF-1, Substance P, Complement, Fibrinogen, Ig, other Ig, etc.

**AS – IN VITRO ACTIONS**

- Contains epithelio-trophic / modulating factors
- Promotes growth and migration of ocular surface epithelial cells in vitro
- Dose-dependent effect on SV40 transfected human corneal epithelial cell line (Tsubota)
- Expression of MUC-1 from immortalized conjunctival epithelial cells (Tsubota)
AS – IN VITRO ACTIONS

- Maintains corneal epithelial cell morphology and function better than pharmaceutical tear substitutes (Gerrling et al)
- Increases transcription of RNA for nerve growth factor and transforming growth factor-beta in cultured human keratocytes (Enner et al)

AUTOLOGOUS SERUM EYE DROPS

- Keratoconjunctivitis sicca due to
  - Sjoegren syndrome
  - Graft-versus-host disease
  - Neurotrophic keratitis
  - Superior limbic keratoconjunctivitis
  - Rheumatoid arthritis

PREPARATION OF ASE

- Protocols in published reports are incomplete and vary significantly
- Concentration → 20 – 100 % (diluent BSS or NaCl)
- Frequency of application → TID to hourly
- Antibiotic as preservative (e.g. chloramphenicol)
- Clotting time prior to centrifugation → 0 – 2 days
- Storage conditions → -20 to +4 degrees Celsius
PREPARATION OF ASE

- Duration and Force of Centrifugation: 1500 – 5000 RPM (300 – 4000 G) / 5 – 20 minutes
- Filter Sterilization (0.2 um)
- Laminar Air Flow Hood and Positive Pressure Clean Room
- Culture of Product Prior to Usage
- No FDA-Approved Standardized Protocol in United States

CLINICAL RESULTS

- 7 Major Reports
- N = 135 Eyes
- 20 – 100% ASE at 4 X/DAY to Hourly Frequency
- Overall Success
  - RB Staining: 33 – 68%
  - F Staining: 39 – 61%
  - Subjective Improvement: 30 – 100%
  - Impression cytology: 44%
- Symptoms recur with ASE discontinuation and crossover to conventional therapy

SEVERE DRY EYE

- 7 Major Reports
- N = 135 Eyes
- 20 – 100% ASE at 4 X/DAY to Hourly Frequency
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  - RB Staining: 33 – 68%
  - F Staining: 39 – 61%
  - Subjective Improvement: 30 – 100%
  - Impression cytology: 44%
- Symptoms recur with ASE discontinuation and crossover to conventional therapy
PROSPECTIVE COHORT STUDY WITH 11 PATIENTS (GOTO ET AL)
- Used 20% ASE as additional therapy 10 times daily
- Within 4 weeks discomfort improved in 9 of 11 and epitheliopathy improved in all patients
- Significantly increased TBT and decreased conjunctival squamous metaplasia
- Discomfort recurred with discontinuation of ASE

PROSPECTIVE COHORT STUDY OF 11 PATIENTS WITH UNILATERAL POST-TRAUMATIC RES (DEL CASTILLO ET AL)
- Used NPAT and ASE 20% TID for 3 months in tapered fashion
- Mean recurrence rate was reduced from 2.2 to 0.028/month of F/U (mean F/U 9.4 months)
- Given self-healing nature of post-traumatic RES, the fact the duration since trauma was not specified, and the failure to state if other previously used modalities were suspended during ASE use, these data have to be reviewed with care

4 MAJOR REPORTS
- N = 112 EYES
- 20–100% ASE at 6x/day to hourly frequency
- Overall success ~73%
- Most healed within 2–4 weeks of ASE initiation
- 18% recurred upon ASE discontinuation
**ADJUNCTIVE TREATMENT IN OCULAR SURFACE RECONSTRUCTION**

- 14 EYES OF 10 PATIENTS RECEIVING LIMBAL STEM CELL TRANSPLANT, AMNIOTIC MEMBRANE, AND/OR PK WERE TREATED WITH 20 % ASE (TSUBOTA ET AL)
- OCP/SJS WITH SCHIRMER = 0
- 12 OF 14 HAD STABLE EPITHELIUM AT 20 WEEKS
- 2 PATIENTS UNDERGOING PK FOR PED (POON ET AL)
- ACHIEVED STABLE EPITHELIUM WITH ASE
- EPITHELIOPATHY RECURRENT UPON ASE DISCONTINUATION

**CRITICISMS**

- VARIATIONS IN THE STUDY POPULATIONS SUCH AS DEGREE OF AQUEOUS DEFICIENCY
- VARIATIONS IN PRODUCTION AND TREATMENT PROTOCOL FOR ASE
- ADDITIVE RATHER THAN SUBSTITUTIVE THERAPY
- THERAPEUTIC CTI OR PUNCTAL OCCLUSION
- INCREASING FLUID SUPPLY RATHER THAN THE EPITHELIO-TROPHIC NATURE OF ASE MAY HAVE YIELDED THE BENEFICIAL EFFECT
- COMPARISON OF PUBLISHED DATA IS FURTHER LIMITED BY VARIATIONS IN REPORTING "SUCCESS OF TREATMENT" AS
  - NUMBER OF PATIENTS IMPROVING
  - MEAN CHANGE IN PARAMETER

**COMPLICATIONS**

- NUMBER OF COMPLICATIONS IN THE 255 PATIENTS REPORTED TO HAVE BEEN TREATED WITH ASE IS SMALL
- SCLERAL VASCULITIS AND MELTING IN 20 PATIENTS
- IMMUNE COMPLEX DEPOSITION WITH 100 % SERUM
- PERIPHERAL CORNEAL INFLAMMATORY AND ULCER (N=1)
- INCREASED DISCOMFORT OR EPITHELIOPATHY (N=5)
- MICROBIAL ARRESTS IN PATIENTS WITH EPITHELIC (N=3)
- TEMPORARY BACTERIAL CONJUNCTIVITIS (N=5)
- EYELID ECZEMA (N=2)
- SOME COMPLICATIONS POSSIBLY DUE TO UNDERLYING DISEASE OR OTHER THERAPY (RETIAINED SUTURE MATERIAL, BANDAGE CTI)
“EFFECT OF AUTOLOGOUS SERUM EYEDROPS IN THE TREATMENT OF SEVERE DRY EYE”

- Prospective randomized case-control trial
- 37 eyes of 20 severe dry patients without punctal occlusion
- After 2 week wash-out, randomly assigned to two groups
  - A – only preservative-free artificial tears
  - S – only autologous 20% serum eyedrops 6 times a day
- Improved mean T/BUT, F/RB staining scores, and subjective symptom scores improved

FURTHER STUDY NEEDED:

- Development of FDA-approved manufacturing protocol
  - Stability
  - Sterility
  - Storage
- Clinical trials
  - Tight inclusion and exclusion criteria to achieve homogeneous patient populations
  - Dose-response investigation
  - Cross-over studies
- Expansion of indications
- Eventual –
  - Fractionation of serum components to determine active portion
  - True chemical substitution

CASE EXAMPLE

DIAGNOSIS AND TREATMENT

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Severity Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Sjögren’s Syndrome</td>
<td>4</td>
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</table>

This patient

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Eye Care Professional</th>
<th>Rheumatology</th>
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<tbody>
<tr>
<td>Initial</td>
<td>Education</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>Cyclosporine</td>
<td>Ciclosporine</td>
</tr>
<tr>
<td></td>
<td>topical corticosteroids</td>
<td>Hydrocortisone</td>
</tr>
<tr>
<td></td>
<td>Nonpreserved artificial tears</td>
<td>Minocycline</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Nighttime lubricant gel</td>
<td>Prednisone (oral)</td>
</tr>
<tr>
<td></td>
<td>Punctal plugs</td>
<td>Methotrexate</td>
</tr>
<tr>
<td></td>
<td>Rituximab clinical trial</td>
<td></td>
</tr>
</tbody>
</table>
THANK YOU!