

# **Terapia Customizzata delle Disfunzioni Lacrimali**

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Genova

# Who is my patient with Tear Dysfunction ?

- ▶ the “aggressive environment prisoner”
  - (sick building, traveler, etc.)
- ▶ the computer user
- ▶ the patient with chronic allergy
- ▶ the peri-menopausal lady
- ▶ the patient with rheumatic disease
- ▶ the patient with systemic therapy
- ▶ the patient with blepharitis
- ▶ the contact lens wearer
- ▶ the refractive surgery patient
- ▶ the patient who had cataract or ocular surface surgery
- ▶ the patient in anti-glucoma topical therapy

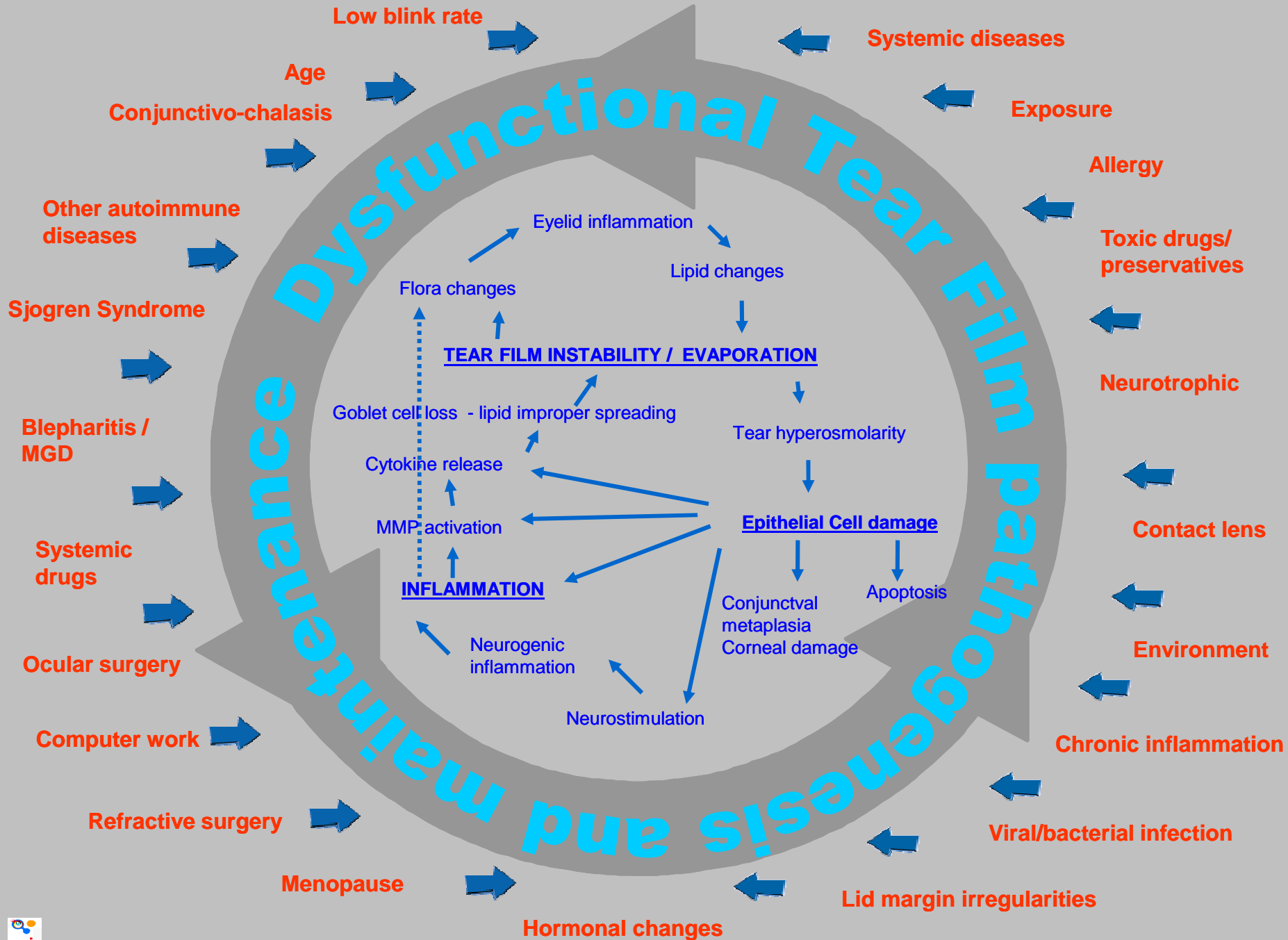


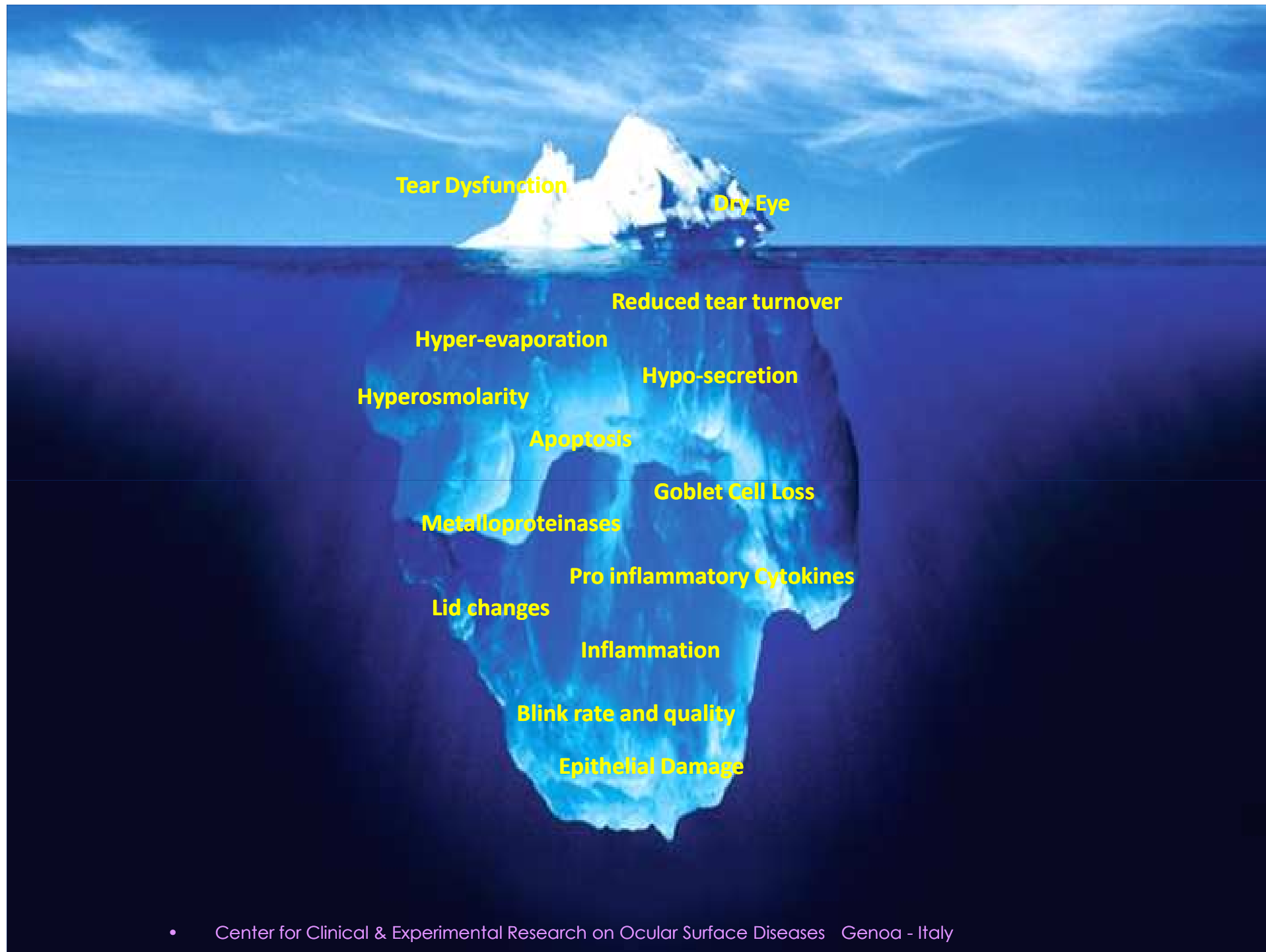
# The ocular surface system



- ▶ tear film
- ▶ corneal epithelium
- ▶ limbal epithelium
- ▶ conjunctival epithelium
- ▶ conjunctival goblet cells
- ▶ muco-epidermal junction
- ▶ lacrimal glands
- ▶ lacrimal sac and tear outflow system

( tear fluid, hormones, blood, nerves, cytokines...)





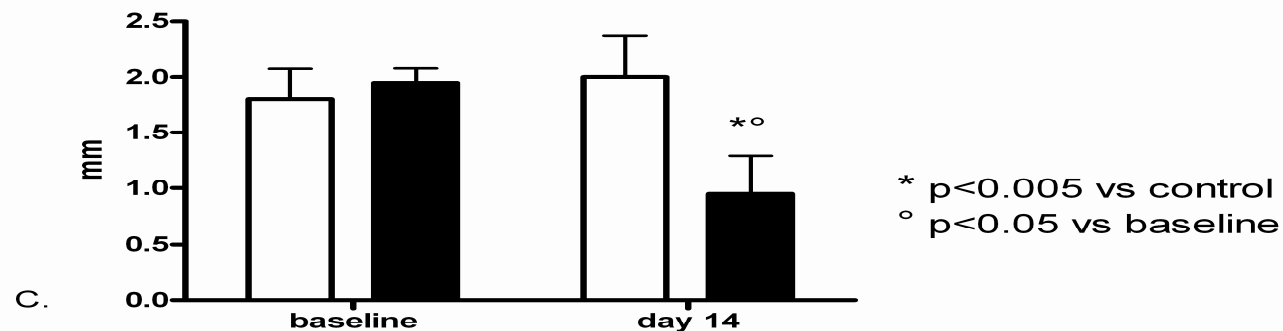
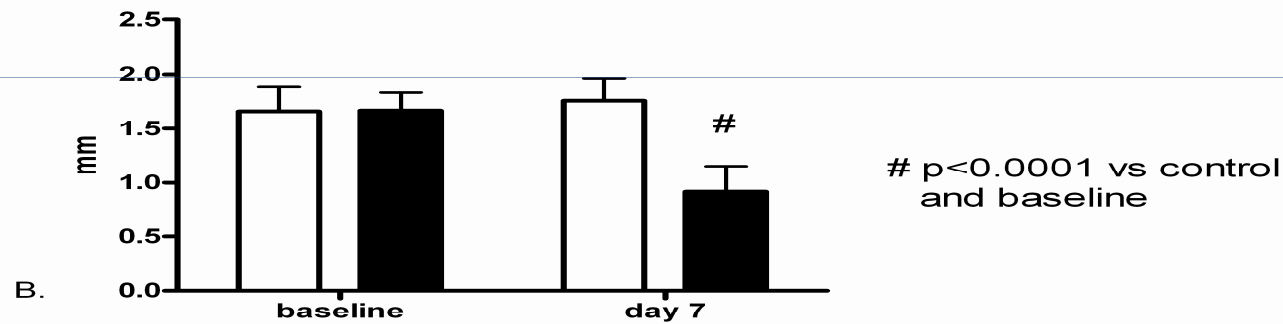
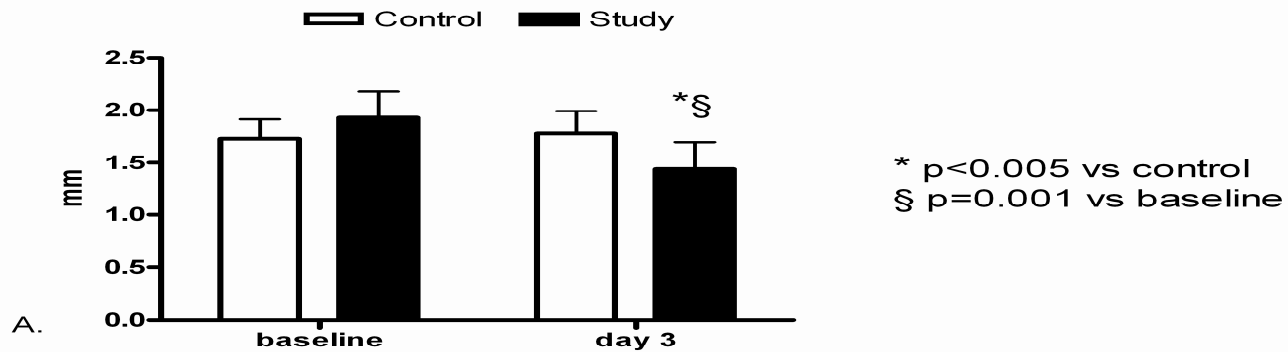
# Prolonged Environmental “Stress” Decreases Tear Secretion in Otherwise Normal Mice



Controlled Environment Chamber

- Temperature:  $22.3 \pm 0.7^{\circ}\text{C}$
- Relative Humidity:  $18.5\% \pm 4.5\%$
- Air flow: 15 l/min

# Tear Secretion



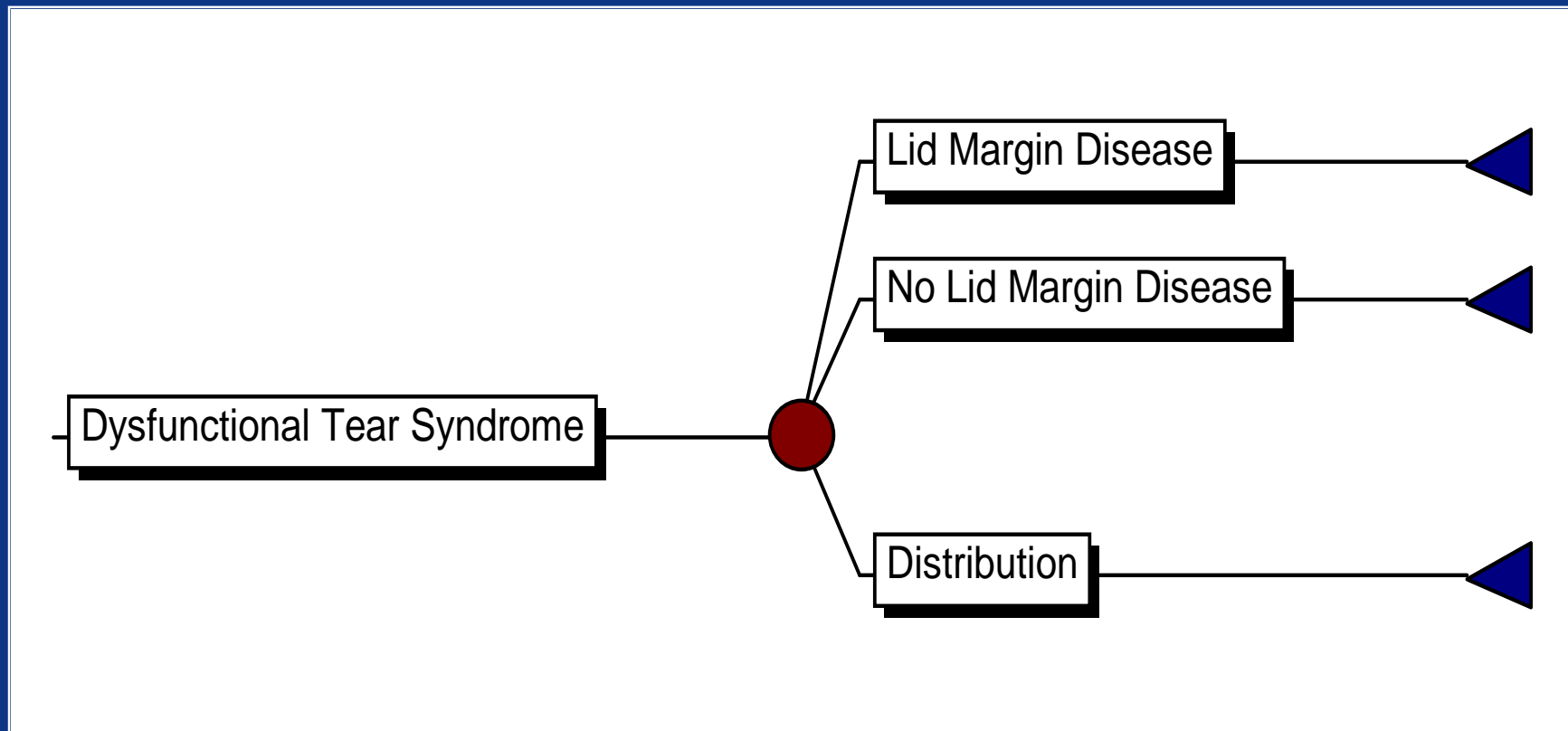
- Cotton threads embedded with phenol red
- Remove excessive tears (3")
- Test: 30"

# Risk Factors Associated With Dry Eye

Level of Evidence		
Mostly consistent	Suggestive	Unclear
<ul style="list-style-type: none"> <li>• Older age</li> <li>• Female gender</li> <li>• Postmenopausal estrogen therapy</li> <li>• Low dietary intake of omega -3 fatty acids</li> <li>• Medications</li> <li>• Antihistamines</li> <li>• Connective tissue disease</li> <li>• LASIK and refractive excimer laser surgery</li> <li>• Radiation therapy</li> <li>• Hematopoietic stem cell transplantation</li> <li>• Vitamin A deficiency</li> <li>• Hepatitis C infection</li> <li>• Androgen deficiency</li> </ul>	<ul style="list-style-type: none"> <li>• Asian ethnicity</li> <li>• Medications</li> <li>• Tricyclic antidepressants</li> <li>• Selective serotonin reuptake inhibitors</li> <li>• Diuretics</li> <li>• Beta -blockers</li> <li>• Diabetes mellitus</li> <li>• HIV/HTLV1 infection</li> <li>• Systemic chemotherapy</li> <li>• Large -incision ECCE and penetrating keratoplasty</li> <li>• Isotretinoin</li> <li>• Low -humidity environments</li> <li>• Sarcoidosis</li> <li>• Ovarian dysfunction</li> </ul>	<ul style="list-style-type: none"> <li>• Cigarette smoking</li> <li>• Hispanic ethnicity</li> <li>• Medications</li> <li>• Anticholinergics</li> <li>• Anxiolytics</li> <li>• Antipsychotics</li> <li>• Alcohol use</li> <li>• Menopause</li> <li>• Botulinum toxin injection</li> <li>• Acne</li> <li>• Gout</li> <li>• Oral contraceptives</li> <li>• Pregnancy</li> </ul>



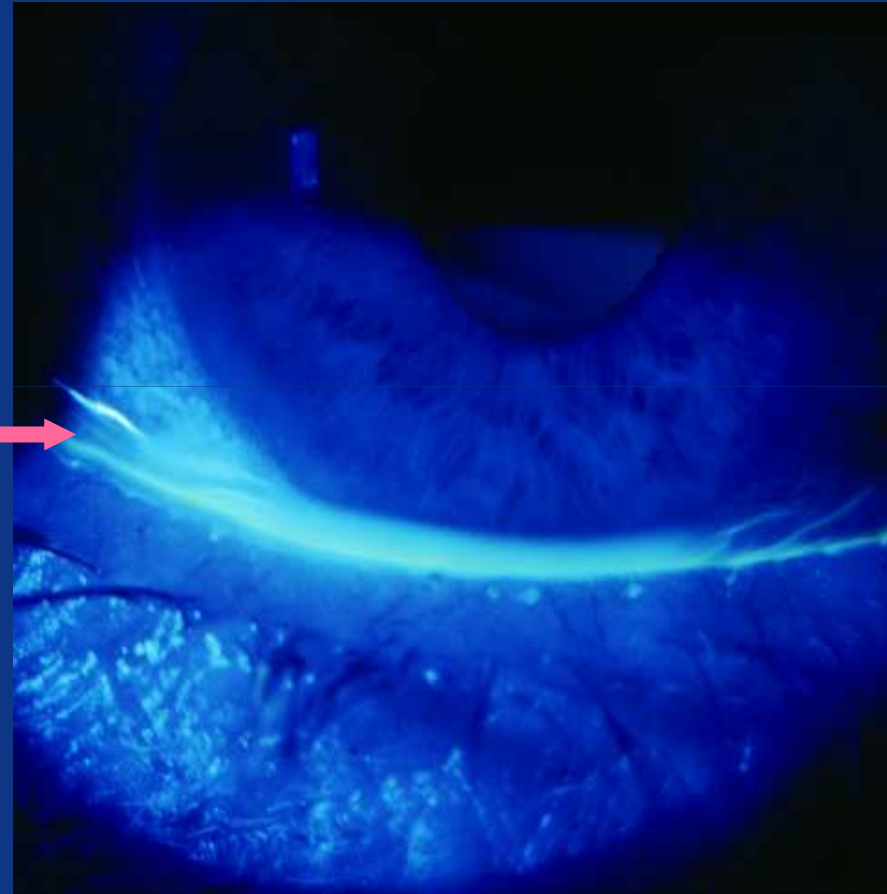
# Pragmatic, Treatment Oriented, Clinical Classification of Dry Eye



# Delayed Tear Clearance

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**Depletion of  
OS Protective Factors  
Accumulation of Toxic /  
Inflammatory Factors**

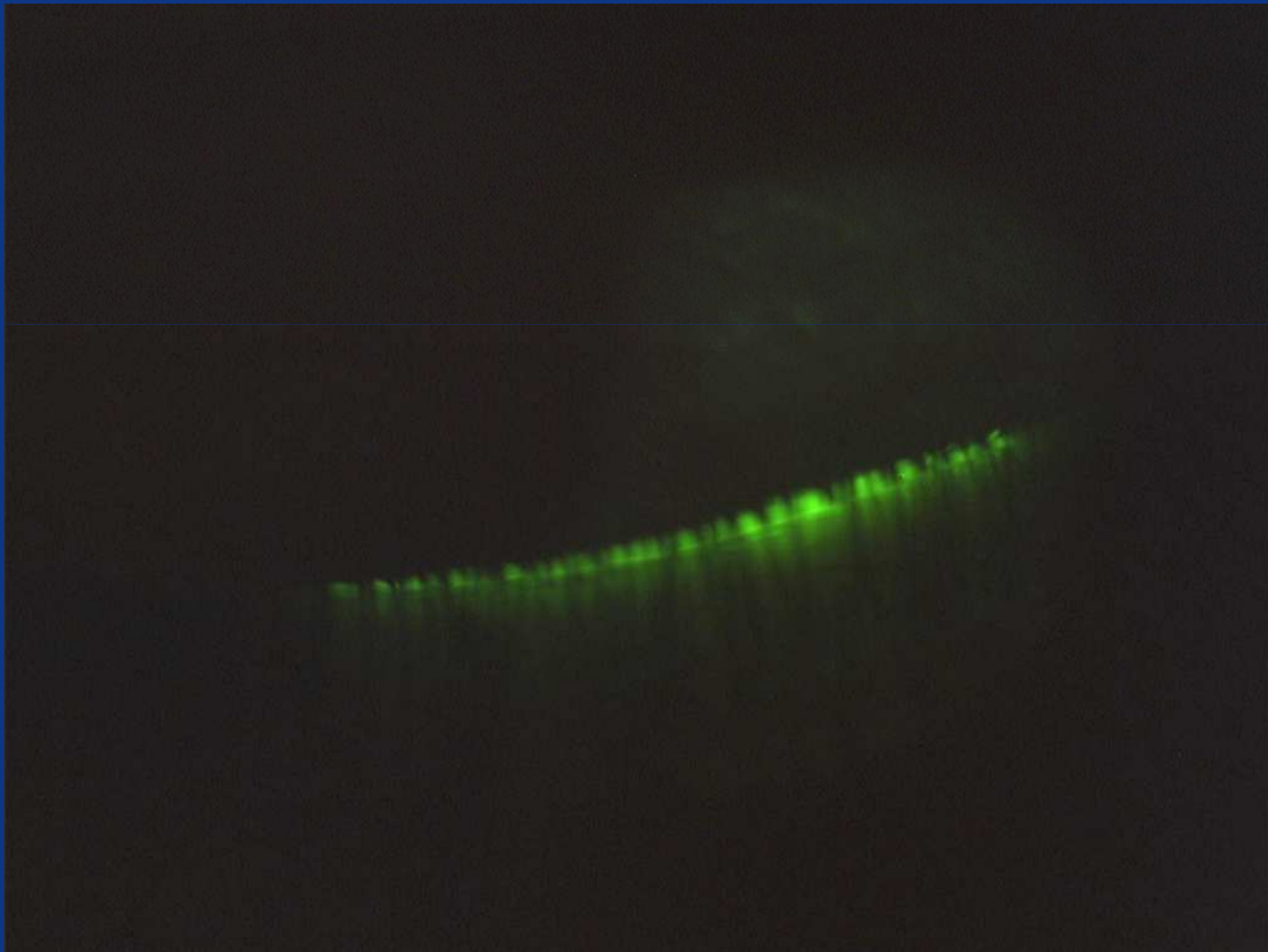


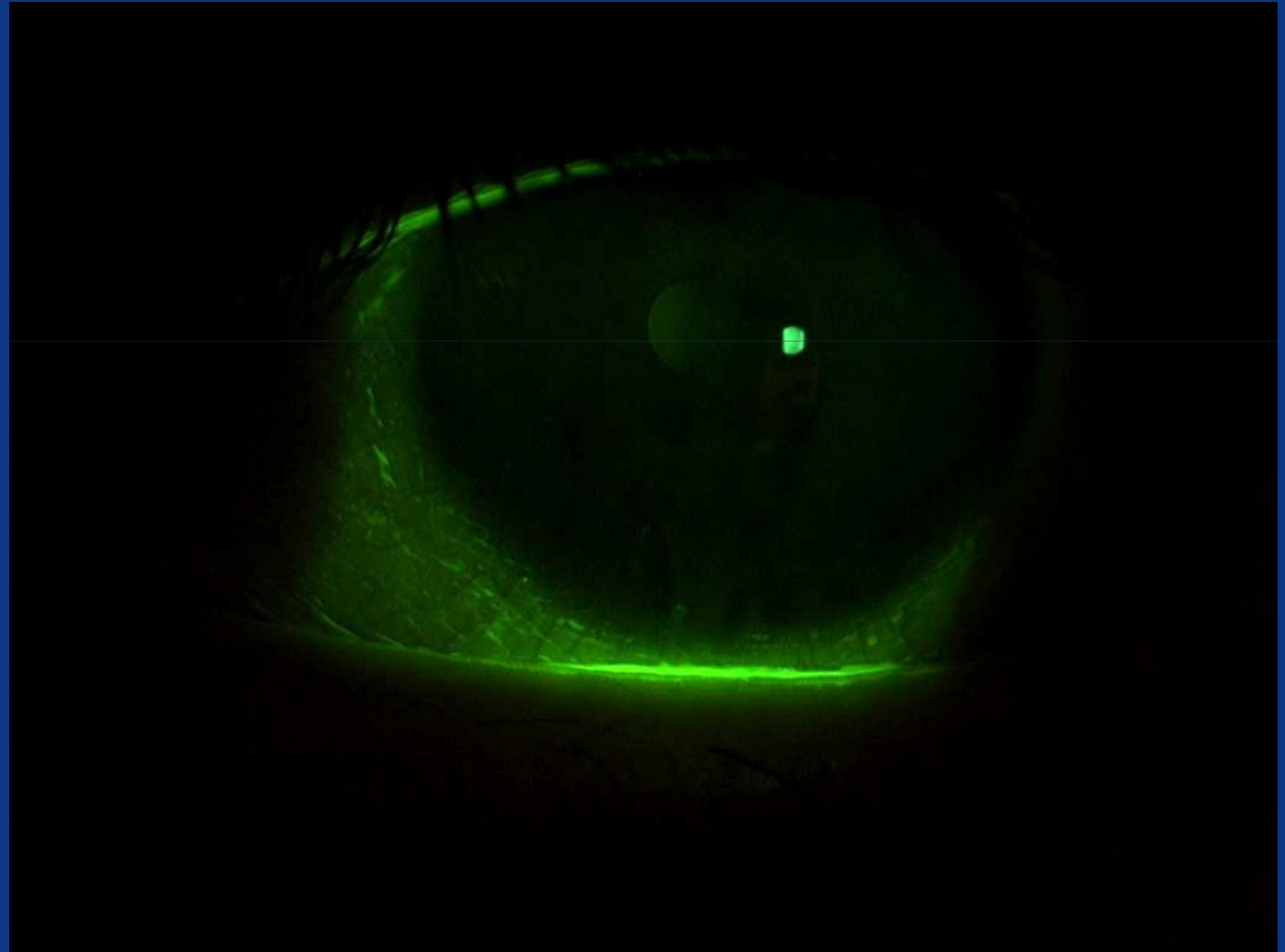
# THE TOXIC TEARS

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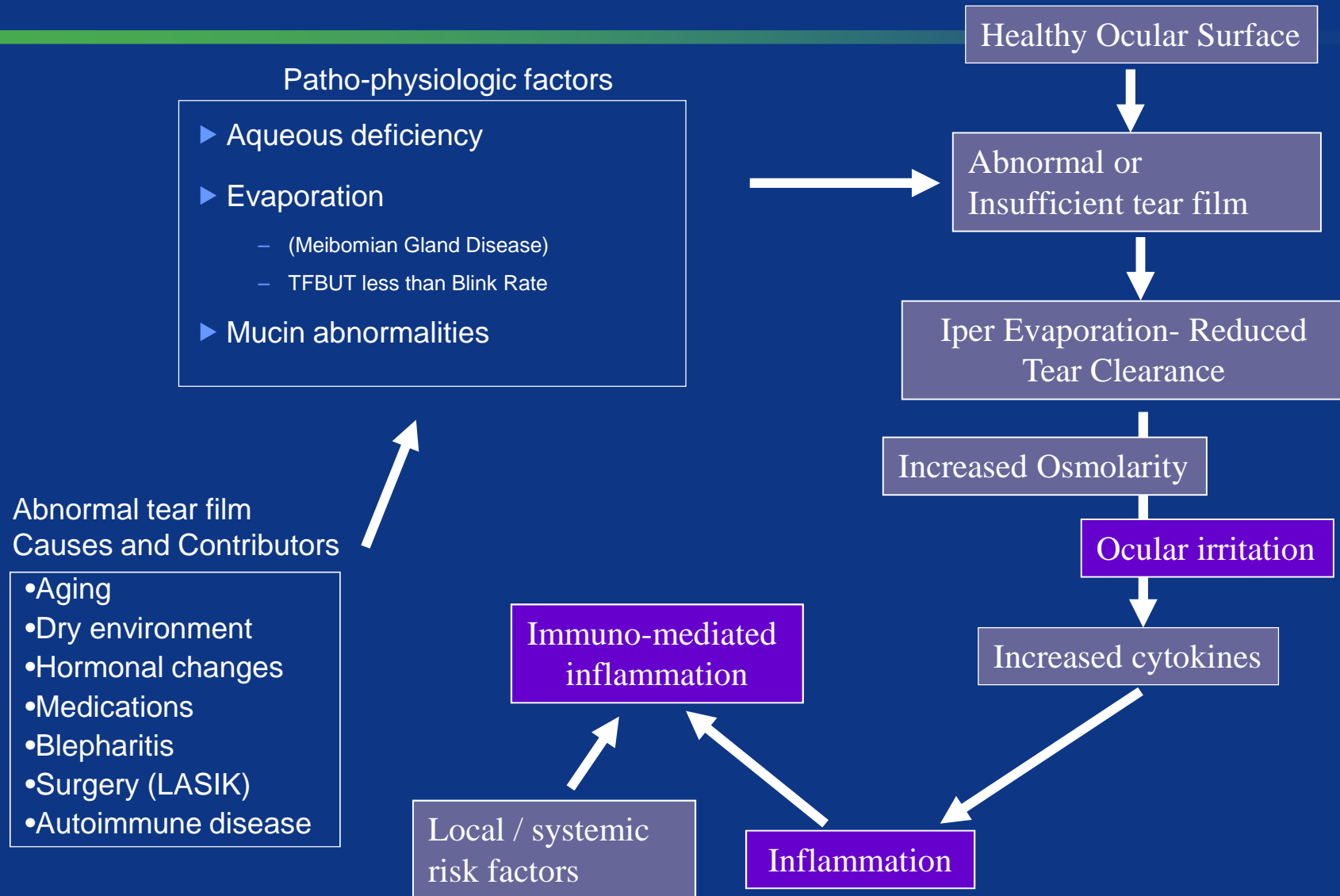
- ▶ *Pro inflammatory tears become toxic to the ocular surface epithelium*
- ▶ *The concept of “**toxic tears**” could help explain many of the symptoms reported by patients in the earliest phases of the disease—when almost no sign is present of ocular surface damage.*








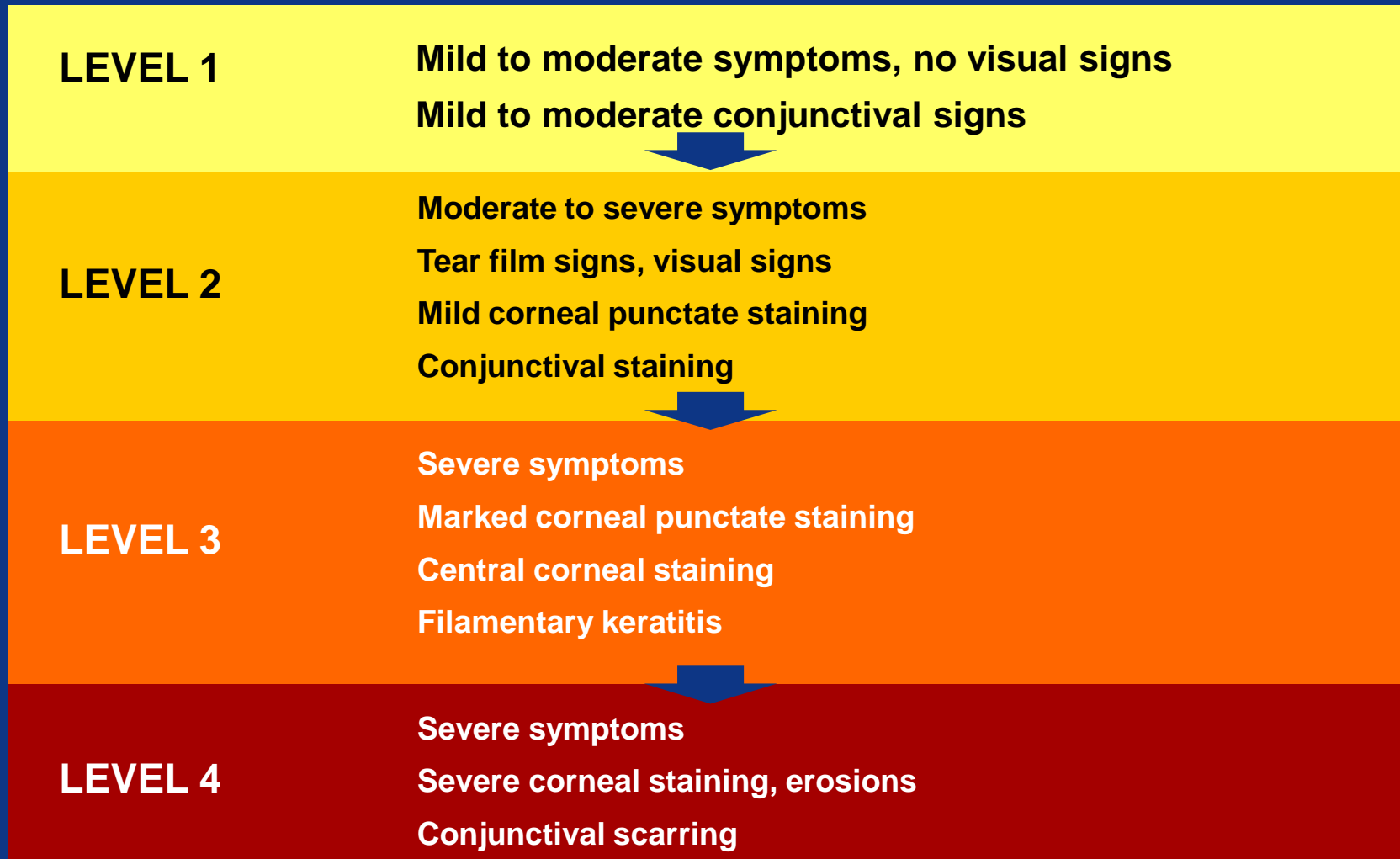
# Tear Dysfunction Cascade



A white cow with horns is lying in a green field. Above the cow is a thought bubble containing the text "and so, what ?...". The background shows a dark treeline under a blue sky.

and so,  
what ?...

# Progression of Dry Eye Severity Levels





# Aim of Dry Eye Therapy

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## ▶ Re-build the O.S. System homeostasis by addressing:

- Tear toxicity (remove / correct / prevent cytotoxic agents, pro-inflammatory agents, etc. )
- Tear volume (secretagogues, tear substitutes)
- Tear stability ( mild tensio active agents, lipid integration)
- Tear turnover ( secretagogues, tear substitutes)
- Tear distribution (correct lids, correct blinking habits)

## ▶ Improve symptoms (palliative)

- Improve quality of life ( tear substitutes, fatty acids)
- Improve quality of vision ( lipid containing / long lasting stabilizing tear substitutes)

# Chronic O.S. Diseases Therapy

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## ▶ Dynamic

- Set the target, obtain the result then change
  - Maximum effect low toxicity

## ▶ Multiple

- Tear volume
- Tear turnover
- Epithelial healing/protection
- Inflammation
- Lid conditions

## ▶ Simultaneous

- Addressing all the concurrent conditions at the same time, if possible

## ▶ Topical and systemic

# Treat All Conditions Together

## Break the Vicious Cycles

- ▶ increase tear volume
  - systemic pilocarpine
  - volumetric tear substitutes
  - punctum plugs
- ▶ Improve lubrication
  - Non Newtonian tear substitutes
- ▶ dilute tear film solutes
  - Increase tear turnover
- ▶ improve mucus conditions
  - gefarnate, Ecabet, N-Acetyl Cysteine, TSP, P2Y (?), 15-(S)-HETE., Rebopamide
- ▶ improve corneal epithelium
  - semi compressive eye patching
  - contact lenses
  - amniotic membrane
- ▶ reduce evaporation
  - lipid tears (?)
  - lateral tarsorrhaphy
  - life style adaptation
- ▶ treat the lids
  - Warm patches
  - Antibiotics
  - Steroids and combo
  - Omega 3-6 ointments
  - Blink exercises
  - loose & floppy eye lid correction
- ▶ control inflammation
  - steroids ,
  - NSAIDs
  - Cyclosporine A
  - Omega 3-6 Fatty Acids
  - Androgens
  - Tetracyclin & Derivatives
- ▶ supplement growth factors
  - autoserum eye drops
  - amniotic membrane
  - NGF

# Overcome Steroid Toxicity

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- ▶ Dry eye is a chronic disease that requires chronic therapy
- ▶ Toxicity of corticosteroids potentially limits their long-term use
  - Ocular hypertension and glaucoma
  - Posterior subcapsular cataracts
  - Infection
- Look for potentially safe topical steroids [ (very)Low doses, poor penetration formulations, target activated, rapidly inactivated, no active metabolite, etc...]
- Use pulsed or tapered therapy



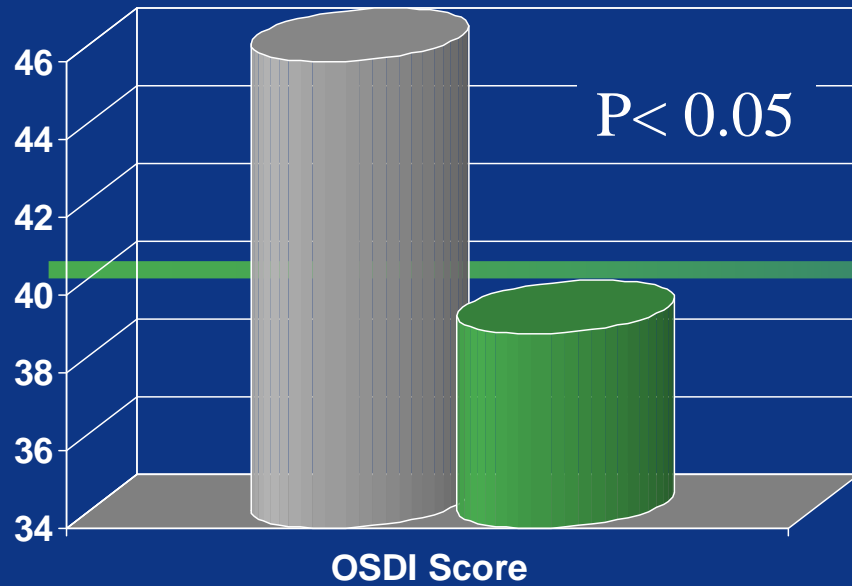
# Steroid Toxicity

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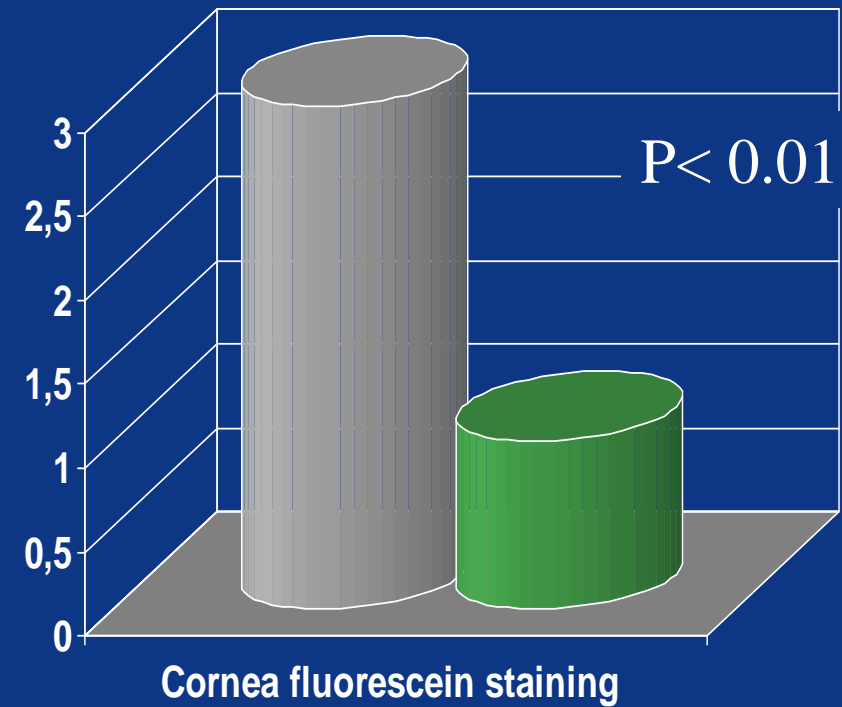
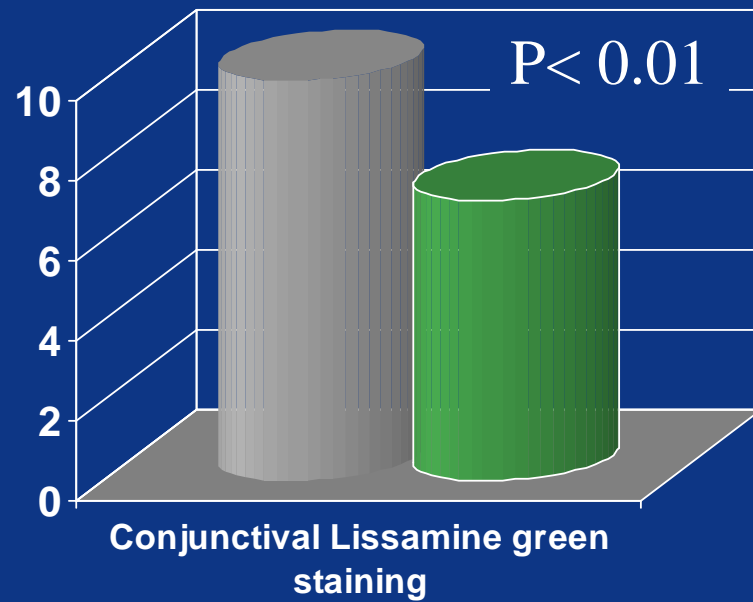
- ▶ Dry eye is a chronic disease that requires chronic therapy
- ▶ Toxicity of corticosteroids potentially limits their long-term use
  - Ocular hypertension and glaucoma
  - Posterior subcapsular cataracts
  - Infection
- ▶ Look for potentially safe steroids (loteprednol etabonate, rimexolon, etc...)
- ▶ Use pulsed or tapered therapy



## Differences at 12 months time

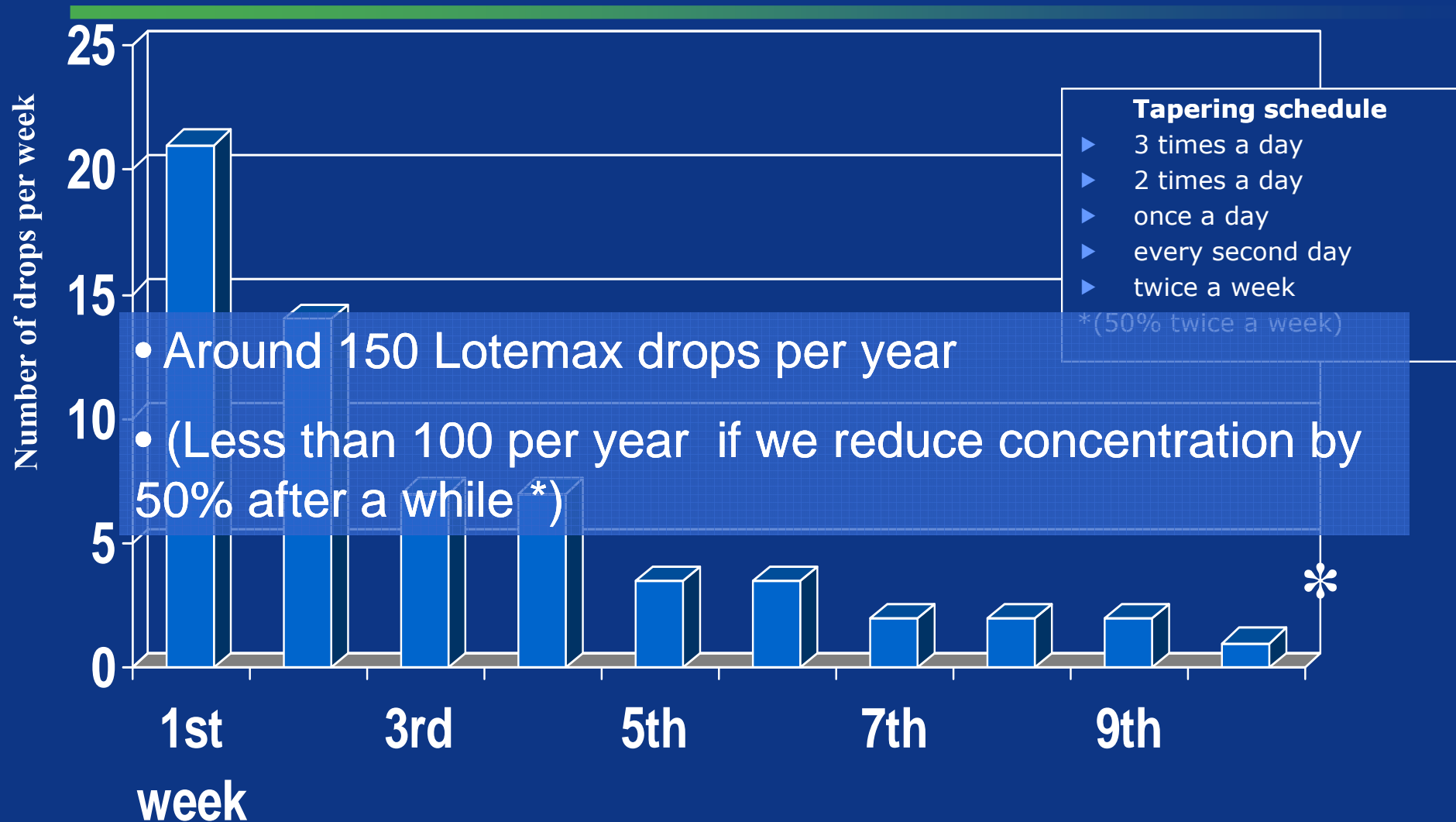


- Group 1 (Bolus)
- Group 2 (tapered minidose)



# Steroid Dosing for KCS Therapy

number of drops



# Dry Eye Treatment Chart

Severity Level	1	2	3	4
Symptoms	Mild to moderate	Moderate to severe	Severe	Severe
Conjunctival signs	Mild to moderate	Staining	Staining	Scarring
Corneal staining		Mild punctate staining	Marked punctate staining; central staining; filamentary keratitis	Severe staining; corneal erosions
Other signs		Tear film; vision (blurring)		

## Treatment Options

<ul style="list-style-type: none"> <li>• Patient education</li> <li>• Environmental modification</li> <li>• Preserved tears (?)</li> </ul> <p><i>If no improvement, add level 2 treatments</i></p>	<ul style="list-style-type: none"> <li>• Unpreserved tears</li> <li>• Gels, ointments</li> <li>• <b>Topical steroids, cyclosporine A</b></li> <li>• Secretagogues</li> <li>• Nutritional support</li> </ul> <p><i>If no improvement, add level 3 treatments</i></p>	<ul style="list-style-type: none"> <li>• Oral tetracyclines</li> <li>• Punctal plugs (once inflammation is controlled)</li> <li>• Autologous serum</li> </ul> <p><i>If no improvement, add level 4 treatments</i></p>	<ul style="list-style-type: none"> <li>• Systemic anti-inflammatory therapy</li> <li>• Oral cyclosporine A</li> <li>• Acetylcysteine</li> <li>• Moisture goggles</li> <li>• Surgery (punctal cautery)</li> </ul>
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Meibomian gland disease—treatment options  
Lid hygiene; thermomassage; oral tetracyclines



# Level 1 Treatment Options

Level 1 is characterized by mild to moderate symptoms and conjunctival staining

- ▶ Patient education
  - Improve habits during computer use, reading
- ▶ Environmental modification
  - Avoid desiccating environments
    - Use humidifier
- ▶ Preserved tears\*
- ▶ Control allergy or lid changes

\* If used more than QID better unpreserved

# Level 2 Treatment Options

Level 2 is characterized by moderate to severe symptoms and mild corneal punctate staining

- ▶ Unpreserved tears
- ▶ Gels, ointments
- ▶ Topical anti-inflammatory therapies
  - Topical steroids
    - Useful but potential side effects, look for safe molecules
  - Cyclosporine 0.05% ophthalmic emulsion
  - Topic Omega 3
- ▶ Secretagogues
- ▶ Nutritional support
  - Fatty acid supplements (omega 3)

# Level 3 Treatment Options

Level 3 is characterized by severe symptoms and marked corneal punctate staining

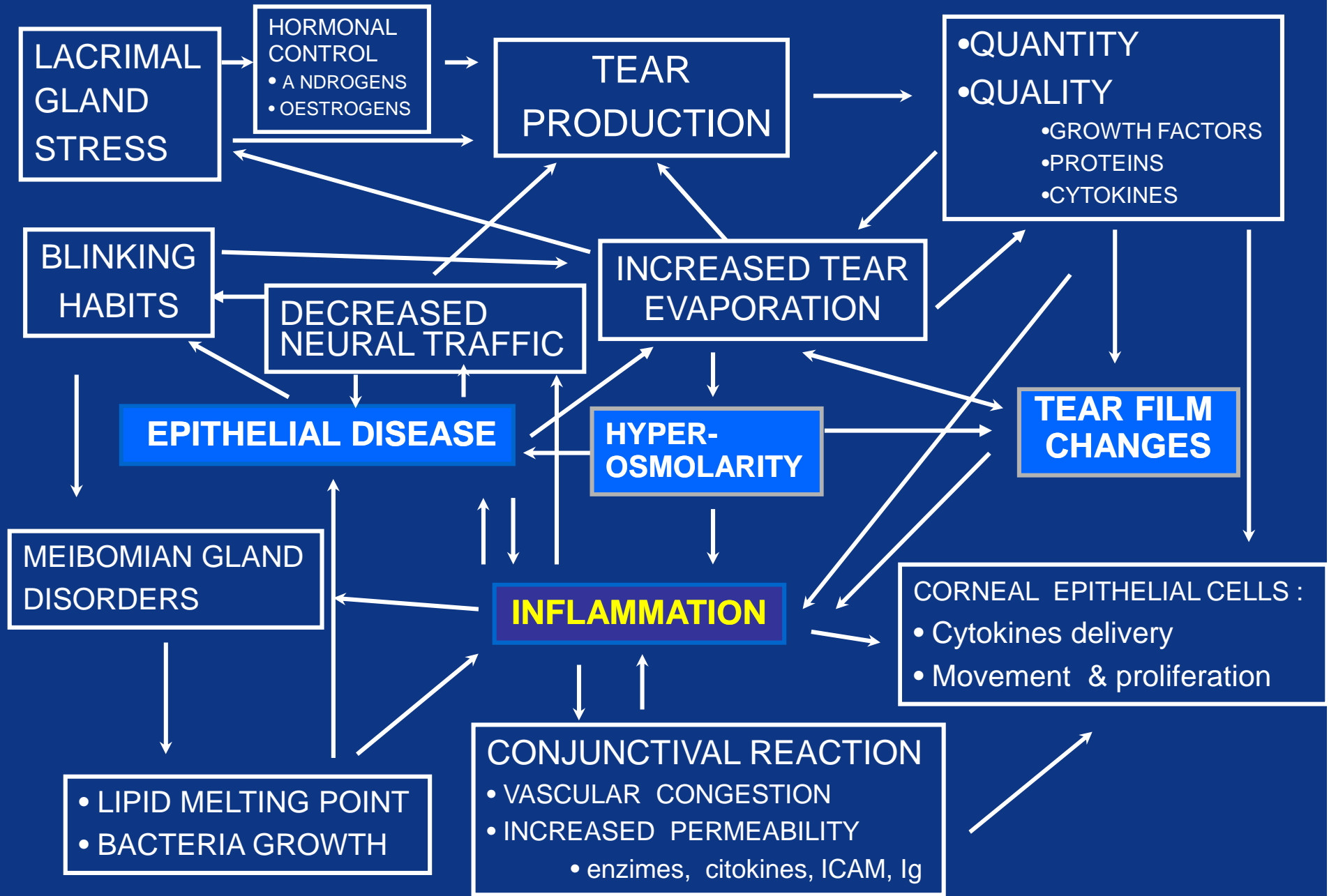
- ▶ Oral tetracyclines
- ▶ Punctal plugs
  - May increase comfort and reduce the use of supplemental lubrication<sup>1</sup>
  - Plugs may increase damage to the ocular surface if inflammation is not controlled first<sup>2</sup>
- ▶ Autologous serum

1. Balaram et al. *Am J Ophthalmol*. 2001;131:30-36;  
• Behrens et al. *Cornea*. 2006;25:900-907.

# Level 4 Treatment Options

Level 4 consists of severe symptoms, conjunctival scarring, and severe corneal staining

- ▶ Systemic anti-inflammatory therapy
- ▶ Oral cyclosporine A (?)
- ▶ (Acetylcysteine)
- ▶ Moisture goggles
- ▶ Surgery (punctal cautery, etc.)





# Think Tear Dysfunction in the Ocular Surface System !

- ▶ assess your (prevalent) diagnosis
  - local and systemic
- ▶ Always consider the “functional unit” theory
  - lids
  - epithelial cells
  - mucins
  - cornea sensation
  - tear turnover and volume
- ▶ treat all conditions together
  - break the vicious cycles
- ▶ be dynamic
  - Adapt your therapy to the conditions as they change
- ▶ avoid toxicity
  - too much is too much
- ▶ explain the disease and the treatment
- ▶ teach prevention
- ▶ support the patient