Dry Eye – How are we treating our patients?

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Spier 2019

DIRK BOOYSEN AND ASSOCIATES INC
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Systane Ultra or Optive Fusion?

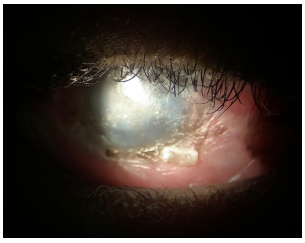


Photo curtesy of S F van den Berg
Hilliar & Grey Optometrists
KZN

Definition

" Dry eye is a multifactorial disease of the ocular surface characterized by 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"

TFOS DEWS 2, Craig et al. 2017

Prevalence

- Generally speaking around 25% of all your patients have dry eye
- Prevalence of DED with or without symptoms ranged from 5 – 50%
- DED based on signs only was higher and more variable – up to 75% in some populations
- DED increase with age and is more common in women and Asians

TFOS DEWS 2, Craig et al. 2017

Why is the prevalence so high?

- What changed in the last 30 years?
  - Computer/tablet/cellphone work
  - Environmental pollution
  - Diet
  - Medication
  - Sun exposure – spend more time indoors
  - Hormones in food
  - Small intestine bacterial overgrowth - SIBO

Ocular Rosacea: Treatment with Rifaximin, a Non-Systemic Antibiotic. Weinstock LB, Myers TL. Int J Clin Expl Dermatol, 2016

Epigenesis of ADDE and EDE

- We don't know what the initiating factors are, and it's probably not the same in all people – in other words the development of dry eye as a disease probably started out in different ways in different people
- It seem that everyone has some type of proclivity for developing it

Epigenesis of ADDE and EDE

- If a patient has a systemic disease that has an inflammatory component, the inflammatory state can include the lacrimal glands which are affected by inflammatory cells, which damage tissue and tear production and result in ADDE
- These are some of the patients who have the most severe form of the disease, which probably makes up less than 10% of the dry-eye population

Epigenesis of EDE

- If a patient has MGD, in which he or she is not producing enough of the right kind of oil, and water is evaporating from the tear film, the patient will get a concentrated tear film and EDE
- The extremely concentrated tears negatively affect the ocular surface
- Tear osmolarity increases and signals the lacrimal glands to start producing more tears reacting as a compensatory mechanism
- What initially starts off as a compensatory process then results in actually worsening the disease as it continues

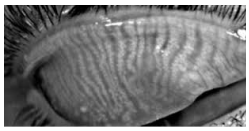
Epigenesis of DED - Osmolarity

- Tear osmolarity is one way of demonstrating this concentration and is considered the best identifier of dry eye - However, there was a lot of variability in tear osmolarity of dry-eye patients
- This raised concern that the test was not repeatable?
- However it was only not repeatable in dry-eye patients – which is a specific marker for dry eye disease
- After dry-eye patients are treated effectively with an anti-inflammatory or other drug, the tear osmolarity variability disappears

Curing DED

- Before we can cure DED we need to do a better job at diagnosing and classifying the condition based on the underlying problem
- This involves determining which glands are not functioning well and then maybe using targeted therapies, either medications, surgical therapies, or cell-based therapies, to try to treat that
- This treatment could involve the meibomian glands, the conjunctival goblet cells or the lacrimal glands

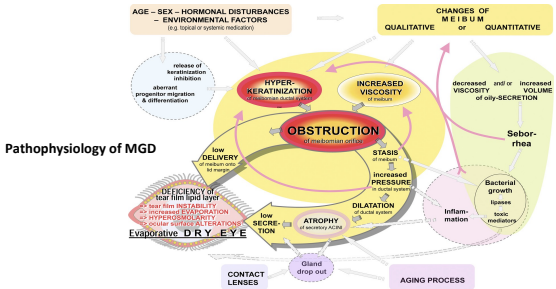
Definition and classification of MGD



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.

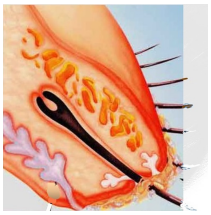
It may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease.

Nichols et al. IOVS, Special Issue 2011, Vol. 52, No. 4



Nichols et al. IOVS, Special Issue 2011, Vol. 52, No. 4

DEBS – Dry Eye and Blepharitis Syndrome



- Bacterial biofilm formation on the lid margin enables us to link dry eye and blepharitis with one common source of pathology
- Dry eye and blepharitis becomes one entity, presenting in different stages throughout life
- Normal lid flora s.epidermidis & S.aureus become over colonized and undergo pathogenicity during a patients lifetime
- Biofilm development is key to the development of lid margin disease - DED

Rynerson J M, Perry H D., DEBS – a unification theory for dry eye and blepharitis Clinical Ophthalmology 2016: 10 2455-2467

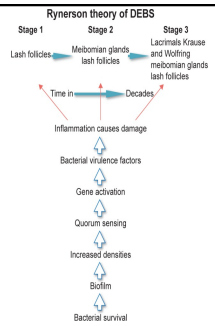
Biofilms

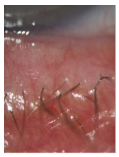
- Biofilm probably forms early in life but the film is not thick enough for quorum sensing to occur
- In the majority of patients the biofilm must be present for decades before quorum sensing occurs
- Both s.epidermidis and s.aureus are excellent biofilm formers, especially s.epidermidis
- Biofilms bind water and protects against host defences and provide more surface area for bacterial replication – a city of microbes
- Biofilms on the lids are not routinely removed and accumulates microscopically year after year

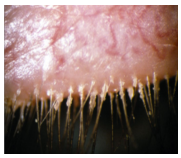
Lid damage

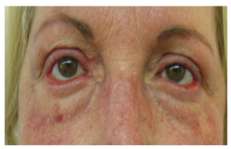
- The resulting chronic inflammation is nonselective in what it damages, nothing in the eyelid is immune and eventually all the lid structures are affected

Rynerson J M, Perry H D., DEBS – a unification theory for dry eye and blepharitis Clinical Ophthalmology 2016: 10 2455-2467







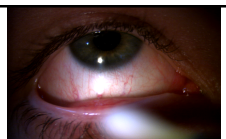


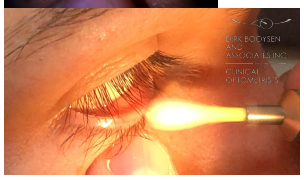
DEBS Explains

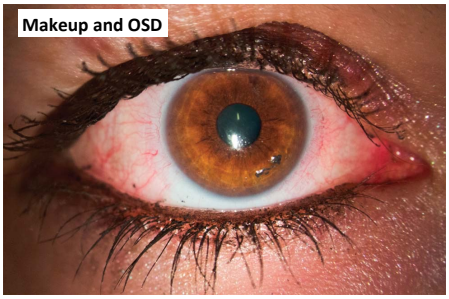
- Singular disease in stages over decades
- Overlap anterior & posterior blepharitis
- Cannot isolate aqueous def.
- Worsens with age
- Asymptomatic lids due to nerve damage
- Cilia loss in elderly
- Why we do not see biofilms in later stages

Rynerson J M, Perry H D., DEBS – a unification theory for dry eye and blepharitis Clinical Ophthalmology 2016: 10 2455-2467

Cotton Brush and Lipiflow

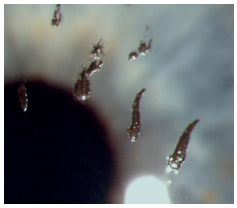






What beauty practices to look for in OSD patients

- Incomplete blink
- Abnormal eyelash length
- Eyelash growth serums
- Waterproof makeup
- Harsh makeup removers
- Retin-A
- Neurotoxins
- Tattoo eyeliner



Eyelash makeup and OSD

- Ten beauty products associated with OSD
  - Waterproof eye makeup
  - Eye makeup removers
  - Eyelid tattooing
  - Eyelash extensions
  - Eyelash tinting and eyelash perming
  - OTC eyelash growth serums
  - "Botox in a jar" – agireline, acetyl hexapeptide-3, acetyl hexapeptide-8
  - Botox injection for "crows feet"
  - Retin-A and most anti-aging creams
  - Eyeliner on the lid margin

Periman L.M., 2019, The everyday cost of eyelash makeup, Ophthalmology management
Ng A et al., 2015, Impact of eye cosmetics on the eye, adnexa, and ocular surface, Eye & Contact lens

Chemicals in eye makeup

- Many of the adhesion, emulsification, removal and preservative chemicals in eye makeup are known ocular surface toxins
- They include benzalkonium chloride (BAK), EDTA, parabens, cinnamates, and formaldehyde
- BAK interferes with the integrity of the superficial lipid layer (0.004%) of the tear film – reducing TBUT and tear film stability

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Chemicals in eye makeup

Impact of BAK on corneal health

- Decreased epithelial cell integrity (in which the barrier is compromised and healing is impaired, drug penetration increased);
- Increase in conjunctival inflammatory cells;
- Loss of goblet cells;
- Effects on the contractility of corneal fibroblasts, which can alter the shape of the cornea and measurement of intraocular pressure;
- Dose-dependent disruption of cytoplasmic membranes and cell detachment;
- Dose- dependent swelling and desquamation of superficial epithelial cells;
- Apoptosis

Chemicals in eye makeup

- Parabens (methylparaben, propylparaben, butylparaben) penetrate the skin and potentially disrupt hormone function interfering with the Meibomian gland
- Cinnamates are plant derived – "natural" – may be pro-inflammatory directly fueling DED.

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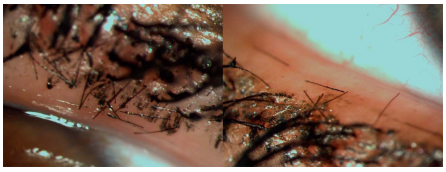
Tattooing

- Associated with MGD – patient self selection, chemical and mechanical damage or combinations of both
- Ink contain titanium oxide, lead, nickel, industrial grade paint pigments, and preservatives
- Microtrauma from the tattoo gun may lead to acute blepharitis and keratitis, subsequent Meibomian gland dropout and changes to lid margin architecture

Mascara



- Water based – waxes, pigments and resins to form an oil in water emulsion which dries after application. Additional wax is added to make mascara water resistant – easily contaminated by microorganisms – preservatives?
- Solvent based – water proof, petroleum distillates. Must be removed with oil based cosmetic removers. Lower preservative concentration. Can be more irritating to the eye
- Hybrid mascara?

Anti-aging treatments - Botox

- Botox for crows feet can disrupt the lacrimal "functional unit" and even prevent normal blink mechanics
- "Botox in a jar" – is a topical cream Argireline (acetyl hexapeptide-3) – this is a neuropeptide that signal facial muscles to relax
- These topical neurotoxins can potentially also affect the muscle of Riolan – important for meibum delivery

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Anti-aging treatments – Retinoids

- Effective in treating photodamaged skin, improve signs of fine wrinkles and pigmentation
- Actions are multifactorial;
  - Increasing dermal collagen synthesis
  - Inhibition of dermal collagen degradation
  - Reduction of melanin synthesis
  - Increased epidermal proliferation and differentiation
- Can develop Meibomian gland dysfunction and DED?

Ng A et al., 2015, Impact of eye cosmetics on the eye, adnexa, and ocular surface, Eye & Contact lens

Latisse (Allergan) – topical synthetic prostaglandin eyelash growth products

- Bimatoprost 0.03% FDA approved for hypotrichosis
- PGA's side effects include eyelash growth, orbital fat atrophy, discoloration of the skin and iris, vascular congestion of the eyelids
- PGA's also lead to MGD (MGD prevalence in POAG Px treated with PGA - 92% compared to 58% on other drugs)
- These OTC growth products also include high concentrations of preservatives such as BAK, formaldehyde and EDTA
- Formaldehyde in low concentrations cause corneal, conjunctival, and Meibomian cell death

Lash extensions

- Formaldehyde is used as preservatives for the adhesives which can lead to chemical conjunctivitis and allergic reactions
- These patients may also negate to clean their lid margins for fear of loosing the lashes which can contribute to MGD – DEBS
- Any interference with lashes can affect their protective and natural aerodynamic properties

Potential ocular complications of eye cosmetic use

- Increased risk of eye infection
- Risk of mechanical trauma
- Toxicity
- Allergy
- Changes in pigmentation of the conjunctiva and periocular skin
- Masses in the lacrimal system
- Changes in the tear film and lipid layer
- Changes in tear stability
- Changes in ocular comfort
- Changes in contact lens comfort

Management and therapy of DED

- Ultimate goal is to restore the homeostasis of the ocular surface and tear film through breaking the vicious cycle of the disease
- "Overall the treatment of DED remains somewhat of an art, not easily lending itself to a rigid evidence based algorithm that accommodates all patients with DED"

TFOS DEWS 2, Craig et al. 2017

Treatments for tear insufficiency: Tear replacement approaches

1. Artificial tear substitutes	2. Biological tear substitutes	3. Other agents

1.1 Aqueous supplementation
• Viscosity-enhancing agents
  • Carboxymethyl cellulose (CMC)
  • Hydroxypropyl methylcellulose
  • Hyaluronic acid (HA)
  • Combination of CMC and HA
  • Hydroxypropyl-guar (HP-guar)
  • Combination of HA and HP-guar
  • Hydroxypropyl cellulose
• Osmotic agents
• Osmo-protectants
• Antioxidants
• Preservatives
• Inactive agents
  • Buffers
  • Excipients
  • Electrolytes
1.2 Lipid supplementation
• Types and properties of lipids
	2.1 Autologous serum
	• Blood drop?
	2.2 Adult allogeneic serum
	2.3 Umbilical cord serum
		3.1 Mucolytics
		• TRPV1 receptor antagonist

Treatments for tear insufficiency: Tear conservation approaches

1. Punctal occlusion	2. Moisture chamber spectacles and humidifiers
• Punctal occlusion with plugs • Surgical punctal occlusion	

Treatments for tear insufficiency: Tear stimulation approaches

1. **Topical secretagogues**
   - Aqueous secretagogues - Diquafosol tetrasodium
   - Mucin secretagogues - Ribamipide
2. **Lipid stimulation**
3. **Oral secretagogues**
4. **Nasal neuro-stimulation**
5. **Various tear stimulation methods**

Treatments for tear insufficiency: Treatments for lid abnormalities

1. Anterior blepharitis	2. Meibomian gland dysfunction	3. Blinking abnormalities and ocular exposure

1.1 Lid hygiene
• Bacterial overcolonization
  • Topical antibiotics
• Demodex infestation
  • Tea tree oil
  • Ivermectin
	2.1 Ocular lubricants
	2.2 Warm compresses
	• Blephasteam
	• MGDRx EyeBag
	• EyeGiene mask
	• Infrared warm compression device
	2.3 Physical treatments
	• Forceful expression
	• LipiFlow
	• Intense pulsed light
	• Intraductal probing
	• Debridement scaling
		3.1 Treatment for corneal exposure
		3.2 Entropion and ectropion
		3.2 Contact lenses
		• Therapeutic soft contact lenses (bandage lenses)
		• Rigid gas permeable scleral lenses

Treatments for tear insufficiency: Anti-inflammatory therapy

1. Topical glucocorticoids	2. Non-glucocorticoid immunomodulators	3. Lymphocyte function-associated antigen 1 antagonist	4. Inflammatory modulation with systemic and topical antibiotics	5. Macrolide therapy
	2.1 Cyclosporine A **2.2 Tacrolimus** **2.3 Non-steroidal anti-inflammatory drugs** **2.4 Biologics** • Recombinant human nerve growth factor • Tumor necrosis factor a-stimulated gene/protein-6 • Interleukin-1 receptor antagonist (IL-1Ra) • Anti-tumor necrosis factor-α therapy • Anti interleukin-17 (IL-17) therapy **2.5 Neuropeptides** • Substance P • Calcitonin gene-related peptide • neuropeptide Y • vasoactive intestinal peptide	**3.1 Lifitegrast - Xiidra**	**4.1 Tetracycline therapy**	

Treatments for tear insufficiency: Surgical, environmental, diet, and complementary medicine

Surgical approaches	Dietary modifications	Local environmental considerations	Complementary medicines
1. Tarsorrhaphy 2. Surgical treatment for conjunctivochalasis 3. Lid corrections 4. Dermatochalasis surgery 5. Blepharoptosis (ptosis) 6. Lower lid blepharoplasty 7. Conjunctival surgery and amniotic membrane grafts 8. Mechanical dacryo-reservoirs 9. Major salivary gland transplantation 10. Parotid duct transposition 11. Microvascular submandibular gland transplantation 12. Minor salivary gland auto-transplantation 13. Surgical punctal occlusion	1. General hydration state 2. Essential fatty acid (ω-3 and ω-6) 3. Lactoferrin 4. Other dietary considerations (beta-carotene, vitamins E, C, B, B6, D, zinc and copper)	1. Chronic topical medications 2. Systemic medications 3. Increase blink rate 4. Decrease desiccating conditions and environmental Pollutants 5. Contact lens wear	1. Herbal and natural products 2. Honey 3. Milk 4. Acupuncture

Diquafosol tetrasodium – Aqueous secretagogue

- Diquafosol is a P2Y2 receptor agonist that activates P2Y2 receptors
- Expression of the P2Y2 receptor occurs in the corneal epithelium, conjunctival epithelium, lacrimal gland ductal epithelium, meibomian gland sebaceous cells, and meibomian gland ductal cells
- Diquafosol rehydrates through increased fluid secretion from conjunctival epithelial cells (via accessory lacrimal fluid pump activation) and increased mucin secretion from conjunctival goblet cells
- Diquafosol also has some effect on the Meibomian glands
- It may directly affect the Meibomian gland ductal and sebaceous cells – not confirmed that topically applied diquafosol penetrates the Meibomian glands

Effect of topical 3% diquafosol sodium on eyes with dry eye disease and meibomian gland dysfunction. Amano S and Inoue K, Clin Ophthalmol. 2017; 11: 1677–1682.

Diquafosol sodium effects

- Improved Schirmer I test scores
- TBUT significantly increased over baseline values
- NaFl staining score significantly decreased from baseline after 3 months of topical diquafosol use
- The DEQS ocular symptoms score consistently decreased in each subject, but, when averaged, this change was only marginally significant
- The number of telangiectasia and plugged meibomian gland orifices as well as the meibum score and the meiboscore in each eye significantly decreased after 1 month of diquafosol use
- The MGD questionnaire score was also lower than baseline at 3 months, but this change was only marginally significant

Effect of topical 3% diquafosol sodium on eyes with dry eye disease and meibomian gland dysfunction. Amano S and Inoue K, Clin Ophthalmol. 2017; 11: 1677–1682.

Rebamipide – Mucin secretagogue

- Rebamipide is a novel ophthalmic suspension which was initially used in treating gastric ulcers due to its mucin secretagogue activity
- It is an amino acid analog of 2 (1H)-quinolinone
- Rebamipide increases corneal and conjunctival mucin-like substances by upregulating the gene expression of MUC1, MUC4, and MUC16 which are expressed on the apical surface of the conjunctival and corneal epithelia
- Rebamipide also has anti-inflammatory properties and has been shown to increase goblet cell count in normal rabbits as observed by impression cytology

Efficacy of rebamipide 2% ophthalmic solution in the treatment of dry eyes. Saurabh Shrivastava, Priyanka Patkar, Reshma Ramakrishnan, Minal Kanhere, and Zahna Riaz. Oman J Ophthalmol. 2018 Sep-Dec; 11(3): 207–212.

Rebamipide conclusion

- Rebamipide modifies epithelial cell function, is a mucin secretagogue, improves tear stability and conjunctival healing, suppresses inflammation, and improves goblet cell counts in the absence of any known major side effects
- Rebamipide can also be used in treating other ocular surface disorders such as lagophthalmos, lid wiper epitheliopathy, and persistent corneal erosion
- The only side effect observed was bitter taste or dysgeusia in 10% patients

Efficacy of rebamipide 2% ophthalmic solution in the treatment of dry eyes. Saurabh Shrivastava, Priyanka Patkar, Reshma Ramakrishnan, Minal Kanhere, and Zahna Riaz. Oman J Ophthalmol. 2018 Sep-Dec; 11(3): 207–212.

Anti-Inflammatory Therapies and Immuno-modulators - Steroids

- Corticosteroids are one among several anti-inflammatory drugs to treat DES
- Reduces cellular infiltration, restores vascular permeability and inhibits chemotaxis,
- Steroids also decrease fibroblast proliferation, reduce capillary dilation and suppress collagen deposition
- However, efficacy is limited to short-term usage (4 weeks or less) as long term use leads to IOP elevation and the formation of cataracts

Anti-Inflammatory Therapies and Immunomodulators – Cyclosporine A (CsA)

- CsA is a broad spectrum, topical immuno-modulator, first approved by the FDA in 2002 (Restasis®) for treating dry eye by increasing tear production and by the European Union in 2015 (Ikervis®)
- CsA is a fungal-derived peptide that has an anti-inflammatory and immuno-modulatory mode of action.
- Topically, CsA acts as an immuno-modulator, and systemically, it acts as an immunosuppressant
- It inhibits T-cell activation and consequently inhibits the inflammatory cytokine production (selective inhibition of IL-I)
- CsA also inhibits apoptosis by blocking the opening of the mitochondrial permeability transition pore and by increasing the density of mucous producing conjunctival goblet cells

Anti-Inflammatory Therapies and Immunomodulators – CsA

- Studies found a statistically significant improvement in 15% to 5% with CsA compared to placebo – **15% ?**
- Multiple studies have reported minimal side effects other than stinging and irritation associated with topical application of CsA
- In summary,

This drug elicits anti-inflammatory properties by inhibiting cell-mediated reactions and preventing the release of pro-inflammatory cytokines, while upregulating the production of anti-inflammatory cytokines and increasing the density of conjunctival goblet cells

Lifitegrast 5% ophthalmic solution - Xiidra

- (Xiidra – Shire) is a lymphocyte function-associated antigen-1 (LFA-1) antagonist, for treatment of the signs and symptoms of dry eye disease
- LFA-1 is a protein expressed on leukocyte surfaces that binds to intracellular adhesion molecule-1 (ICAM-1), which may be overexpressed in the corneal and conjunctival tissue of patients with dry eye disease.
- The resulting interaction is believed to stimulate T-cell activation and migration, leading to propagation of pro-inflammatory factors and inflammation of the ocular surface

Lifitegrast 5% ophthalmic solution - Xiidra

- Lifitegrast is thought to reduce ocular surface inflammation by binding to LFA-1, preventing its interaction with ICAM
- The most common adverse effects associated with use of lifitegrast (reported in 5 - 25%of patients) were eye irritation, dysgeusia, and reduced visual acuity; most reactions were mild to moderate in severity
- Twice-daily lifitegrast ophthalmic solution (Xiidra) appears to be safe and at least modestly effective in treating the signs and symptoms of dry eye disease.

Autologus & Allogeneic serum

- Autologous serum (patients own blood) was first successfully used in patients with dry eye in 1984, and it gained widespread acceptance as an adjuvant therapy in different ocular-surface disorders in 1999
- It lubricates the eye, is anti-inflammatory, antimicrobial and epitheliotrophic - through biomolecules that are similar in composition to natural tears
- Patients can use autologous serum as often as hourly
- Allogeneic serum from healthy blood donors can be used if a patient's own serum is unavailable
- Additionally, platelet-rich plasma products and 20% concentration umbilical cord blood serum have successfully treated cases of severe dry eye that didn't respond to conventional therapy

Reflections on Dry Eye Syndrome Treatment: Therapeutic Role of Blood. Drew V J et al., Front. Med., 23. February 2018

Autologus & Allogeneic serum

- In one study, umbilical cord serum eye drops decreased symptoms and increased goblet-cell density in severe dry-eye syndrome more effectively than autologous serum drops
- The therapeutic benefits of blood-derived serum eye drops (SED) are probably multifactorial and may be explained by a composition that, in part, shares similarities with that of tears

Reflections on Dry Eye Syndrome Treatment: Therapeutic Role of Blood. Drew V J et al., Front. Med., 23 February 2018

	Tears	Serum	Physiological function possibly relevant in ocular defect treatment
Physico-chemical parameters (55, 57)			
Osmolality, mosm/l	302	300	Maintains physiological osmolality and pH
pH	7.2–7.4	7.2–7.4	
Proteins (53, 55, 56, 74)			
Total proteins, mg/mL	7.37	60–70	Support tear surface tension, physiological hydration of the ocular surface, and ocular homeostasis
Albumin, mg/mL	0.05	35–40	Anti-apoptotic activity, detoxification
Fibronectin, µg/mL	21	200–300	Adhesion protein supporting wound healing
IgG, mg/mL	0.002	8–12	Anti-microbial
IgA, mg/mL	0.41	–	Anti-microbial
IgM, mg/mL	–	0.5	Endotoxin binding
IgD, µg/mL	–	3–300	
IgE, µg/mL	–	0.28–0.7	
Alpha 2-macroglobulin		2.6	Anti-collagenase
Complement system			Anti-microbial; bacteriostatic
Lactoferrin, mg/mL	1.81	–	Anti-microbial and anti-inflammatory
Transferrin, mg/mL	–	2–3	Iron carrier; anti-microbial
Lysozyme, mg/mL	1.4	6	Iron carrier; anti-microbial
Growth factors (53, 55–57, 61)			
TGF-β1, ng/mL	2–10	6–50	Epithelial and stromal repair processes
PDGF, ng/mL	0.09–1.7	30–100	Enhances mitosis and scarring
EGF, ng/mL	0.2–3	0.5–1	Accelerates the migration of epithelial cells; anti-apoptotic
HGF, ng/mL	0.2–0.5	0.1–1	Supports corneal epithelial cells
VEGF, ng/mL	0.019	1–5	Supports conjunctival endothelial permeability
Vitamins (53)			
A, ng/mL	18–20	800–1000	Prevents squamous metaplasia and helps maintain the normal histology in the conjunctiva
C, µg/mL	117	7–20	Antioxidant
Antioxidants (53)			
Tyrosine, µM	45	77	
Glutathione, µM	107	ND	
Electrolytes (53)			
$Na+$, mEq/L	145	136–146	
$K+$, mEq/L	24.1	3.5–5.0	
Ca^{2+}, mM	1.5	1.1	
Cl^-, mM	128	96–108	
HCO_3^-, mM	26	21–29	
NO_3^-, mM	0.14	0.10	
PO_4^{2-}, mM	0.22	1.42	
SO_4^{2-}, mM	0.39	0.53	

Reflections on Dry Eye Syndrome Treatment: Therapeutic Role of Blood. Drew V J et al., Front. Med., 23 February 2018

OptiSerum drops

OptiSerumTM eye drops are prepared from the umbilical cord blood collected from donors during the birthing process. All donors are sourced and counselled through the Netcare Transplant Unit.

- Contains growth factors and crucial tear components required for epithelial renewal
- Possesses a bacteriostatic effect due to anti-bacterial agents such as IgG, lysozymes and complement found in the serum
- Confers no immunogenicity and particularly useful in patients with auto-immune diseases and those with poor general health
- More effective than autologous serum eye drops in healing epithelial defects due to 2-3 times higher growth factor content
- Does not contain any preservatives thus preservative toxicity can be avoided

SED - Risks

- Autologous SED do not essentially present risks of extraneous virus contamination when produced under GMP restricting the risks of cross-contamination or mislabeling with SED from another patient
- Preservative solutions are not added in SED; preparation procedures should therefore be carefully controlled and monitored to prevent bacterial contaminations
- Allogeneic blood donors donating blood for the production of SED should be screened for virus markers using the same standards that are applied to donations devoted to the manufacturer of transfused blood products

Reflections on Dry Eye Syndrome Treatment: Therapeutic Role of Blood. Drew V J et al., Front. Med., 23 February 2018

SED - Risks

- The main transfusion transmitted infections associated with allogeneic serum are viruses, most notably human immunodeficiency virus, and hepatitis B and C viruses
- Emerging viruses, like West Nile virus, Dengue virus, Chikungunya virus, Ebola virus, and Zika virus, may also be a potential threat
- However, efficient safety measures in place in blood establishments, namely donors' screening and donation testing, dramatically restrict the risks of viral transmissions in a regulated blood collection jurisdiction

Reflections on Dry Eye Syndrome Treatment: Therapeutic Role of Blood. Drew V J et al., Front. Med., 23 February 2018

Finger prick Autologous Blood (FAB) in Severe Dry Eye Disease (DED) (FAB)

The treatment that we are investigating involves placing a drop of your own blood from your finger into your eye four times per day. ONLY USE YOUR OWN BLOOD

Preparation

You will be supplied with lancets, finger wipes and a sharps box. Please cut your nails short on the finger(s) that you wish to use.

Producing a fingertip drop of blood

Wash your hands with soap and warm water and wipe dry with a clean towel. Then use an alcohol finger wipe to wipe a finger on your non-dominant hand. Creating a drop of blood on a finger of the non dominant hand is usually easier.

Take a *new* lancet and use it to prick the finger as per instructions on the lancet box. Then throw the lancet away in the sharps box. When your sharps box is full, please return it closed to the eye clinic on your next visit, where you will be provided with a *new* sharps box.

A small drop of blood will slowly form on your finger. You may need to squeeze your finger slightly to encourage the drop of blood to form. Pricking your finger in some places can cause much less pain than in others. It takes time to find the best place. You can use a different finger each time if you prefer.

Applying the blood drop to the eye

Looking in the mirror, pull down the lower lid of the eye to be treated with the hand that has not been pricked and touch the inside of the lower lid with the drop of blood.

Your vision may become slightly blurred or tinted red for a minute, but then returns to normal. It should not hurt or sting. If it does, report this to your doctor.

Wipe your finger again with an alcohol swab.

Helpful tips

- If treating both eyes with finger prick drops of blood, please ensure you use a different finger for each eye to avoid spreading infection from one eye to the other.
- If you develop *any* infection or persistent pain at your fingertips, please stop using that finger and contact your GP and the research team (contact details can be found on your patient information sheet).

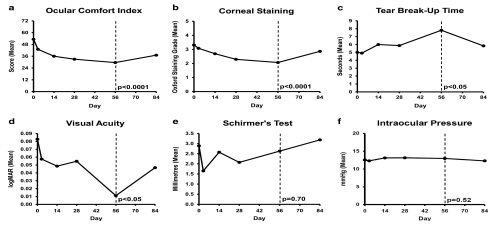
Fingerprick autologous blood: a novel treatment for dry eye syndrome. Than J et al., Eye (Lond). 2017 Dec;31(12):1655-1663

Results

- **Is the composition of finger prick blood plasma comparable to venous plasma?**
- The clinical improvement seen on FAB in this study suggests that the concentration of growth factors and other factors crucial to corneal epithelial maintenance might be greater than that found in venous plasma
- It is conceivable that platelet activation and hence growth factor release occurs during FAB application
- Traumatic injury to capillaries and tissue via lancet, blood stasis during expression on the fingertip, and prolonged contact of blood with the ocular surface all present opportunities for platelet activation to occur
- It is not presently clear how the erythrocytes and leucocytes of FAB affect the ocular surface.
- There is evidence that erythrocytes, usually considered to be passive cells, are able to release growth factors and regulate neighbouring T cells, fibroblasts, and dendritic cells, and this is likely to have an impact on the corneal surface in FAB therapy.

Fingerprick autologous blood: a novel treatment for dry eye syndrome. Than J et al., Eye (Lond). 2017 Dec;31(12):1655-1663

Results



FAB - Risks

- Although this study did not highlight any complications of FAB therapy, theoretical complications exist

- The risk of ocular infection through transfer of skin pathogens via repeated close contact between finger and eye exists, though this is minimised by diligent cleaning of the finger with an alcohol steret.

- The risk of transmission of blood-borne pathogens to the anterior eye is biologically plausible, hence the exclusion criterion of existence of systemic infection.

- Repeated finger pricks might lead to tissue damage at the fingertips, and traumatic neuroma formation at the site of finger prick has been previously reported

Fingerprick autologous blood: a novel treatment for dry eye syndrome. Than J et al., Eye (Lond). 2017 Dec;31(12):1655-1663

Mesenchymal stem cells

- Mesenchymal stem cells have been proposed as cell therapy for many diseases with an inflammatory and immuno-mediated component
- Mesenchymal stem-cell therapy in experimental dry-eye syndrome models was found to improve tear volume and tear-film stability, increasing epithelial recovery and the number of goblet cells and decreasing the number of meibomian gland injuries in the conjunctiva – regenerating the glands

Other medical treatments

- Lubricin is another potential treatment that's in the early stage of research
- Lubricin is a protein in the tear film (and joints) that facilitates the lubrication between the lid and the surface of the eye as you blink
- "Lubricin is thought to be decreased in dry eye, and there is now a manufactured protein (ECF843 by Novartis) that is identical to it, which is being used in orthopedics and is in early stages of development for dry-eye disease"

Punctal plug occlusion (PO) for Dry eye syndrome

- Preservation of natural tears
- Insufficient amount of tears
- Occlude puncta superior +/ inferior
- Improve quality & quantity of tear film
- TFOS DEWS II :2nd level treatment

(1st level: education, environmental modification, diet, systemic medications, eyelid hygiene, tear supplements)

Attend workshop for practical session on punctal occlusion

Ervin A-M et al., 2018 Br J Ophthalmology

IPL – Intense pulsed laser treatment

- IPL is widely used in the cosmetic industry as well as therapeutically for the removal of hypertrichoses, benign cavernous haemangiomas, benign venous malformations, telangiectasia, port-wine stains, and pigmented lesions
- The device emits polychromatic light from 515 nm to 1200 nm which is absorbed by the skin tissue as well as the targeted structure
- This results in the production of heat (>80°C) which destroys the targeted skin lesions

Raulin et al., 2003, Craig et al., 2015 , Toyos et al., 2015

IPL – Intense pulsed laser treatment

- The wavelength can be changed by filters to target different structures and control the penetration depth of the treatment
- The blood cells in the abnormal telangiectasia's absorb light, heat up and coagulate, finally closing the blood vessels
- It is thought that as in the case of rosacea the secretion of inflammatory mediators is reduced by closing the telangiectasia's

Raulin et al., 2003, Craig et al., 2015 , Toyos et al., 2015

IPL – Intense pulsed laser treatment

- It is also proposed that 500 nm light also eradicate commensal bacteria improving MGD and DED
- IPL seems to liquefy the abnormal viscous meibum secretion and dilate the glands facilitating gland expression by patients
- Studies have shown that IPL therapy led to improved tear break up times and lipid layer grades, as well as self-reported patient satisfaction

Raulin et al., 2003, Craig et al., 2015 , Toyos et al., 2015

IPL – Intense pulsed laser treatment

- Although increased meibum secretions are often seen after a single treatment, multiple treatments are usually recommended over several months (7 to 8 treatments per year) to improve MGD and DED
- Although IPL therapy results in improved meibum secretions and patient symptoms, expression of the Meibomian gland in conjunction with the therapy is recommended to maximize results.
- In future IPL therapy may evolve into a Botox-like procedure that requires consistent reapplication to maintain effect

Raulin et al., 2003, Craig et al., 2015 , Toyos et al., 2015

IPL – Intense pulsed laser treatment

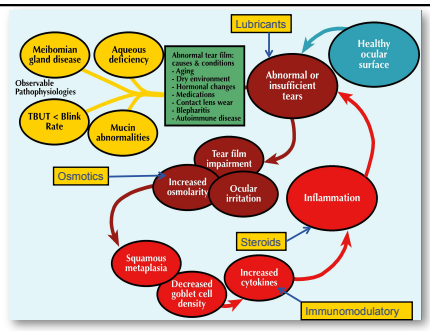
- Treatment can cause mild discomfort and redness that can persist for several days before resolution
- Adverse effects: include blistering (red spot lasting <1 week),
  - cheek swelling,
  - conjunctival cysts,
  - floaters,
  - hair loss at the brow and forehead,
  - light sensitivity,
  - and redness of the face.
- In most cases the adverse effects self-resolved within 1 week

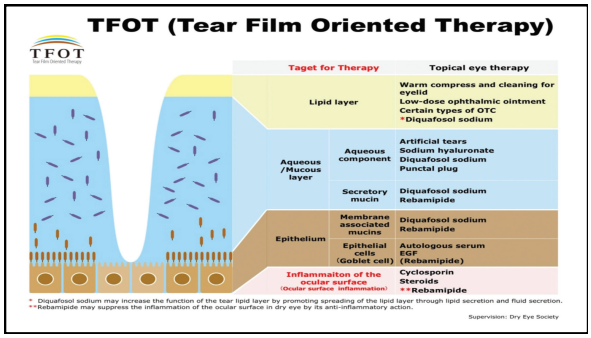
Raulin et al., 2003, Craig et al., 2015 , Toyos et al., 2015

Outcomes of intense pulsed light therapy for treatment of evaporative dry eye disease*

- 100 patients with diagnosis of MGD and EDE underwent on average 4 IPL sessions
- There was significant **decrease** in scoring of: ($p < 0.001$)
  - lid margin oedema
  - facial telangiectasia
  - lid margin vascularity
  - meibum viscosity
  - and OSDI score
- There was a significant **increase** in:($p < 0.001$)
  - oil flow score
  - and TBUT
- No significant changes in intraocular pressure or acuity were noted
- There were no cases of adverse ocular effects.

**Gupta et al., 2016*





"Before I came here I was confused about this subject. Having listened to your lecture I am still confused. But on a higher level."

Enrico Fermi

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