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Severe Ocular Surface Diseases

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Ocular Graft-vs-Host Disease

- Complication after allogenic hematopoietic stem cell or bone marrow transplant (30-70%)
  - KCS most common ocular finding (22-80%)
- Activated donor immune cells attack the recipient's tissue
  - Predominantly T-cells (CD4+ and CD8+)
- Acute
  - Occurring within first 100 days
  - Most commonly involves skin, GI tract, and liver
  - Rarely ocular (7%), poor prognostic sign, higher GVHD mortality
- Chronic
  - Beyond 100 days
  - Skin, GI tract, lungs, liver, and more commonly ocular

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Grading Scale

- **NIH**
- Score 0-3
- Based on symptoms, use of ATs, and ADL impairment
- Schirmer testing and other slit lamp exam findings of KCS

- **ICC on chronic oGVHD**
  - more objective
- Schirmer test, corneal staining, conj injection, OSDI score
  - 0-3 points
- None, mild/moderate, severe
  - 0-11 points

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Acute oGVHD

Table 3: Clinical staging for acute conjunctival GVHD

Stage	Description
1	Conjunctival hyperemia
2	Conjunctival hyperemia with a chemotic response or serosanguinous exudates
3	Pseudomembranous conjunctivitis
4	Pseudomembranous conjunctivitis plus corneal epithelial sloughing

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Chronic oGVHD

- Lacrimal Glands
  - Preductal infiltration of T-cells
  - Myofibroblast proliferation leading to fibrosis
- Meibomian Glands
  - T-cell mediated damage to epithelial cells
  - Hyperkeratinization of duct epithelium and stromal fibrosis
- Conjunctiva
  - Subepithelial fibrosis, fine white lines under intact conj surface
  - Decreased goblet cell density, squamous cell metaplasia, surface keratinization

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Chronic oGVHD

- Cornea
  - Punctate keratitis, filaments, epithelial defects, stromal thinning and perforation
  - Neovascularization, rarely stem cell deficiency
  - Decreased sensation (loss of nerves in sub-basal plexus)
  - Endothelial cell loss
- Eyelids
  - MMP-9 degrades elastic fibers
  - Eyelid laxity, lagophthalmos, trichiasis

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Tear Biomarkers

- Elevated IL-6 and IL-8 compared with healthy controls
  - IL-6 regulates immune response (both pro and anti inflammatory)
  - IL-8 activates neutrophils
  - No reduction after treatment indicate response resistant
- Decreased IL-7 and epidermal growth factor (EGF)
  - IL-7 induces T-cell maturation and homeostasis
  - EGF increases cell growth
- Decreased lactoferrin, lysozyme, transferrin
  - Defense proteins in tear film
- Elevated MMP 9
  - Regulatory factor of neutrophil migration
  - Breakdown of extracellular matrix
- ICAM-1, IL-1B, IL-2, IL-10, TNF-α, BAFF, G-CSF, C2, C3a, C5/C5a

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Local Treatment

- Topical lubrication
  - Artificial tears, gels, ointments
- Topical cyclosporine and lifitegrast
  - Starting 1 month prior to transplant (Malta et al.)
- Topical corticosteroids and tarolimus
- Serum tears and PRP drops
- Eyelid hygiene and warm compresses
- Moisture goggles, humidifiers, fish oil supplements
- Punctal occlusion
- Amniotic membrane grafts
- Scleral lenses, PROSE lenses, and bandage lenses

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Systemic Treatments

- Corticosteroids
- Tacrolimus and Sirolimus
- Cyclosporine
  - Calcineurin inhibitor, involved in production of IL-2
- Intravenous immunoglobulins (IVIG)
  - Antibodies from healthy donor to help fight infection or regulate immune system
- Extracorporeal photopheresis (ECP)
  - Removes T-cells, expose to UV light, return to patient
  - Induces controlled apoptosis of activated T-cells
  - Shifts cytokine profile to anti-inflammatory

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Systemic Treatments

- Belumosudil (Rezurock)
  - ROCK2 inhibitor
  - 42% response rate in patients with refractory cGVHD
- Ruxolitinib (Jakafi)
  - Janus kinase 1 and 2 inhibitor
  - 26% response rate in ocular GVHD
  - Clinical trial with topical reduced corneal epitheliopathy
- Axatilimab-csfr (Niktimvo)
  - Monoclonal antibody that blocks the CSF1 receptor
- Ibrutinb (Imbruvica)
  - Tyrosine kinsase inhibitor
- Ixazomib (Ninlaro)
  - Used in treatment of Multiple Myeloma

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Ocular Cicatricial Pemphigoid

- Chronic vesciculobullous disease of conjunctival
  - can affect other mm such as mouth, oropharnyx, genitalia, anus, skin in 15% case (mucous membrane pemphigoid)
- Females older than 60 rare less than 30
- Rarely unilateral
  - one eye may be affected more than other
- Recurrent attacks of mild conj inflammation with mucopurulent discharge
- Clinical course is variable
  - remissions and exacerbations are common

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Causes of cicatricial conjunctivitis	
Ocular surface neoplasia	Squamous cell carcinoma Sebaceous cell carcinoma
Inflammatory	Mucous membrane pemphigoid Stevens-Johnson syndrome Atopic conjunctivitis Graft-versus-host disease Sarcoidosis
Infective	Adenoviral conjunctivitis Herpetic disease
Trauma	Sharp trauma Chemical and thermal burns
Iatrogenic	Radiation treatment Topical antimetabolite therapy Topical glaucoma medication
Genetic	Ectodermal dysplasia

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Ocular Cicatricial Pemphigoid

- Stage I
  - Subepithelial fibrosis
  - Fine white linear opacities in conjunctiva
  - Chronic red eye
- Stage II
  - Shortening of fornices
  - Bullae on conjunctiva rupture and cause fibrosis esp medial
  - Loss of goblet cells
- Stage III
  - Symblepharon formation
- Stage IV
  - Restricted mobility secondary to adhesions between lid and globe

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Ocular Cicatricial Pemphigoid

- Conj biopsy sent for immunoflurorescent or immunoperoxidase staining
  - C3, IgG, IgM, and or IgA localized to BM
- Circulating anti-BM Ab in sera of some pts

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Treatment

Disease severity	Clinical signs	Systemic treatment
Mild	Conjunctival inflammation and/or mild fornix adhesions/shortening	Dapsone 100 mg once daily (G6PD testing) Sulphapyridine 500 mg bd Sulphasalazine 1g bd Methotrexate 10–15 mg per week
Moderate	Conjunctival inflammation and/or moderate or severe fornix adhesions/shortening	Mycophenolate 1–1.5g bd Azathioprine 50 mg bd-tds (TPMT testing)
Severe	Severe conjunctival inflammation with limbitis or persistent epithelial defects	Cyclophosphamide 1–2mg/kg/day orally (lifetime max 25g)
Recalcitrant	Conjunctival inflammation uncontrolled by conventional immune suppression	Rituximab 1g infusion ×2 14 days apart + maintenance treatment 4–6 monthly

- Topical and oral corticosteroids
  - acute exacerbations only
  - limited success alone
- IVIG therapy as adjuvant
- Multidisciplinary care
  - Derm, Dental, Rheum, ENT, GI, Gyn, Urology

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Treatment

- IV Rituxan
  - Two infusions 1g 2 weeks apart, possible retreat or maintenance every 4-6 months (RA protocol)
  - 375 mg/m2 weekly for 4 weeks (lymphoma protocol)
  - 375 mg/m2 weekly for 8 weeks then monthly until remission (Foster protocol)
- Repository corticotropin injection (Acthar gel)
  - Contains ACTH (adrenocorticotropic hormone)
  - Triggers release of cortisol and corticosteroids from adrenal gland
  - For use in various inflammatory and autoimmune conditions

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Surgical Treatment

- Surgery for eyelid deformities
- Eyelash ablation
- Fornix reconstruction
  - Hard palate or buccal mucosa
- Corneal transplant
  - Guarded prognosis
  - K-pros may do better

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Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

- Mucocutaneous disease
  - 2 to 7 million cases per year
- Antibiotics (sulfas) anticonvulsants, infections (mycoplasma)
- Sudden onset fever, arthralgia, malaise, upper or lower respiratory symptoms
- Classic target lesion in few days
  - Red center pale ring then red ring (face and trunk)
- Maculopapular or bullous lesions

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Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

- Erythema Multiforme Minor
  - skin only, no MM
  - typical target lesions or raised, edematous papules distributed on limbs
- Erythema Multiforme Major
  - typical target lesions or raised, edematous papules distributed on limbs
  - involvement of 1 or more MM
  - epidermal detachment involves less than 10% of total body surface area
- SJS/TEN
  - widespread blisters predominant on the trunk and face, presenting with flat erythematous or pruritic macules
  - 1 or more MM erosions
  - epidermal detachment is less than 10% TBSA for SJS and 30% or more for TEN
  - Often treated like burn patients, intubated in ICU

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Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

- Primary ocular finding is mucopurulent conjunctivitis and episcleritis
- Bullae and extensive necrosis can occur
- Late findings caused by cicatrization lead to conj shrinkage, trichiasis, and tear deficiency
- Higher risk for infection due to loss of epithelial barrier

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Treatment

- Supportive with tears and lubrication
- High dose IV corticosteroids
- Topical steroids controversial
  - may decrease inflammation and cornea vascularization but contribute to infection and thinning
- Symblephara lysis in acute phase
  - daily lysis may have poor results & may worsen inflammation and surface morbidity
- Amniotic membrane/symblepharon rings (Prokera)
- Entropion, trichiasis, and loss of fornices surgically corrected
- Corneal neovasularization often occurs and PKs often fail
  - K-pros better but long term stability may be problematic
- Ocular surface construction with amniotic membrane with limbal grafting

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Case

- 76 y/o female second opinion for 2 year history of progressive ocular surface scarring and progressive vision loss
- Had been treated by several previous ophthalmologists for possible OCP vs SJS
- Cataract surgery, glaucoma, tarsorrhaphy, Botox for blepharospasm, negative conj biopsy
- Currently on MTX and prednisone for RA, previously on MMF for possible OCP but stopped due to side effects
- Vision HM OU, IOP 30 mmHg OU