Learning Objectives

• Recognize a healthy eye based on funduscopic exam
• Understand refraction and the cause of refractive errors
• Appreciate the etiologies and pathologies of major acquired ophthalmic conditions, incl. conjunctivitis, glaucoma, diabetic eye disease and diabetic retinopathy, age-related macular degeneration, retinal detachments, retinal vein occlusion and retinal artery occlusion.
• Understand retinitis pigmentosa and appreciate the clinical and ethical challenges with gene therapy
• Recognize the impact of health disparities and access to health care in diagnosis and clinical management of ophthalmic disease
• Appreciate the impact of visual disability on performing daily tasks and quality of life

Outline

• Anatomy Recap
• Funduscopic exam and OCT: healthy eye
• Refractive errors
• Conjunctivitis
• Uveitis
• Cataract
• Glaucoma
  • Open-angle glaucoma
  • Angle-closure glaucoma
• Age Related Macular Degeneration – dry and wet
• Diabetic Retinopathy
• Central retinal artery occlusion
• Central retinal vein occlusion
• Retinal detachment
• Central serous chorioretinopathy
• Retinitis pigmentosa
Anatomy Recap

**Three concentric tissue layers**

- **External Layer (dura)**
  - Sclera & cornea
  - Avascular
  - Dense connective tissue
  - Densely innervated

- **Middle Layer (pia mater)**
  - Uvea
  - Choroid capillaries (PR), pigmented (melanin)
  - Ciliary body
  - Retina
  - Anterior chamber
  - Posterior chamber
  - Vitreous body

- **Inner Layer (CNS)**
  - Retinal pigment epithelium (tapetum nigrum)
  - Neural retina
  - Retinal detachment, separation of the optical

The normal eye

The normal eye
Refractive errors

The normal eye

Refractive errors

Optical power of the eye (~ +60 D)
- curvature of the cornea (+41.1 D)
- curvature of the lens (+20 D to +30 D)
- increased by the opposing elasticity of the lens and the ciliary zonule fibers on the lens capsule

Refractive errors

- Hyperopia: Common cause of impaired vision, correctable with glasses.
- Myopia: Also known as “shortsightedness,” eye too short, needs a lens to correct.
- Astigmatism: Irregular curvature of the cornea, different refractive power in different areas.
- Presbyopia: Age-related impaired accommodation focusing on near objects, primarily due to lens elasticity changes. Needs reading glasses.
Conjunctivitis: “Pink Eye”

Symptoms
- Pink or red color of the sclera resulting from swollen and dilated blood vessels
- Swelling of the conjunctiva and/or eyelids
- Increased tear production
- Foreign body sensation
- Itching, irritation, and/or burning
- Discharge (pus or mucus)
- Crusting of eyelids or lashes, especially in the morning
- Contact lens discomfort

Conjunctivitis: “Pink Eye”

Bacterial Conjunctivitis
- Caused by Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae
- Usually caused by the same bacteria that cause respiratory tract infections
- More common in kids than adults
- Common in winter months (Dec – Apr)

Viral Conjunctivitis
- Caused by a number of different viruses, such as adenoviruses
- Very contagious

Allergic Conjunctivitis
- Reaction to allergens: pollen; dust mites; molds; pets; medicines, or cosmetics
- Not contagious
- Occurs more frequently among people with other allergic diseases
- Often seasonally

Conjunctivitis Caused by Irritants
- Caused by irritation from a foreign body in the eye or contact with chemicals, fumes, smoke, or dust
- Not contagious

Diagnosis and treatment

<table>
<thead>
<tr>
<th>Cause</th>
<th>Diagnosis</th>
<th>Course</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial</td>
<td>Occurs together with ear infection; occurs shortly after birth; discharge is thick rather than watery (pus)</td>
<td>Mild cases often spontaneously resolve in 2-3 days; more severe cases may take up to 2 weeks</td>
<td>In more severe cases, treat with topical antibiotics</td>
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<tr>
<td>Vernal</td>
<td>Usually caused by common cold or respiratory tract infection; watery discharge</td>
<td>Mostly mild cases; typically resolve in 1-2 weeks, but can take up to three weeks</td>
<td>Treat with topical antihistamines if suspected herpes simplex or varicella zoster infection; antibiotics are ineffective</td>
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<tr>
<td>Allergic</td>
<td>Occurs seasonally; eyes itch/internally; bilateral; occurs together with other allergic disease; watery eyes and mucus discharge</td>
<td>Mild to severe; remove allergen; limit exposure; treat with topical antihistamines and vasoconstrictors</td>
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Uveitis
- Inflammation of uvea: three types
  - Anterior uveitis: iritis
  - Intermediate uveitis
  - Posterior uveitis: choroiditis and/or retinitis.
- Symptoms:
  - Typically unilateral
  - Red eye, with or without pain
  - Photophobia
  - Blurry vision, floaters
- May have hypopyon (accumulation of pus in anterior chamber) or conjunctival redness.
- Associated with systemic inflammatory disorders (e.g., sarcoidosis, rheumatoid arthritis, juvenile idiopathic arthritis, HLA-B27–associated conditions).
- Mainstay therapy: corticosteroids

Cataract
- Painless opacification of the lens
- Often bilateral

Signs and symptoms:
- Vision blurring
- "Rainbow" color vision
- "Halos" and glare at night

Leading cause of blindness worldwide
- 20.5 million (17.2%) Americans aged 40 years and older have cataract in one or both eyes
- 6.1 million (5.1%) have had their lens removed operatively
- Total number of people with cataract estimated to increase to 30.1 million by 2020.

Cataract
- Acquired risk factors:
  - Age, smoking, excessive alcohol use, excessive sunlight, prolonged corticosteroid use, diabetes mellitus, trauma, infection;
- Congenital risk factors:
  - Classic galactosemia, galactokinase deficiency, trisomies (13, 18, 21), ToRCHs infections (e.g., rubella), Marfan syndrome, Alport syndrome, myotonic dystrophy, neurofibromatosis 2.
Cataract

Treatment: “cataract surgery”, e.g. phacoemulsification and IOL replacement

Procedure (simplified):

- corneal incision (1.9-2.75 mm)
- capsulorrhexis and capsulotomy
- phacoemulsification
- aspiration
- lens insertion

Glaucoma

- Optic neuropathy
- Characteristic optic disc atrophy, “cupping”
- Often associated with increased intraocular pressure (IOP)
- Progressive peripheral visual field loss
Open Angle Glaucomas

- Primary open angle glaucoma
- Secondary open angle glaucoma

- Primary open angle glaucoma:
  - Age-related
  - Increased risk in African Americans and individuals with family history and normal tension glaucoma
  - Unknown cause
  - Leading cause of irreversible blindness

- Secondary open angle glaucoma:
  - Obstruction of the trabecular meshwork by:
    - White blood cells (e.g., uveitis)
    - Red blood cells (e.g., vitreous hemorrhage)
    - Retinal debris (retinal detachment)
    - Exfoliation material (exfoliation glaucoma – most common form of secondary OAG)
    - Extracellular matrix (steroid-induced glaucoma)

- Management:
  - Pharmacologic
  - Surgical

Glaucoma

Pharmacologic agents:

- Prostaglandin analogs (e.g., latanoprost)
- Beta-blockers (e.g., timolol)
- Alpha-2 agonists (e.g., brimonidine)
- Carbonic anhydrase inhibitors (e.g., dorzolamide)
- M3 agonists (e.g., pilocarpine)

New pharmacologic agents recently approved for POAG and OHT:

- Latanoprostene bunod: nitric oxide donating prostaglandin receptor agonist
  - FDA approval: Nov 2, 2017
  - Bausch & Lomb: Vyzulta

- Netarsudil: Rho kinase inhibitor
  - FDA approval: Dec 18, 2017
  - Aerie Pharmaceuticals: Rhopressa

Angle closure glaucoma

Acute angle closure:

- IOP increases in forward angle closure.
- Very painful
- Red eye
- Sudden vision loss
- Halos around lights
- Fixed and mid-dilated pupil
- True ophthalmic emergency

Treatment of acute angle closure glaucoma:

- Pilocarpine (M3 agonist)
- Do not give epinephrine because of its mydriatic effect

Primary angle closure glaucoma:

- Exposure or forward displacement of iris against central iris (pupil margin) leading to the obstruction of normal aqueous flow through the pupil.
- Fluid builds up behind iris, pushing peripheral iris against cornea and impeding flow through the trabecular meshwork.

Secondary angle closure glaucoma:

- Hypoplasia of the angle or iris configuration leading to the obstruction of normal aqueous flow through the pupil.
- Fluid builds up behind iris, pushing peripheral iris against cornea and impeding flow through the trabecular meshwork.

Chronic closure is often asymptomatic with progressive damage to the optic nerve and loss of peripheral vision.
Age-Related Macular Degeneration (AMD)

Dry ("non-exudative")
- > 80%
- Deposition of yellowish extracellular material between Bruch membrane and retinal pigment epithelium ("Drusen") with gradual loss of vision.
- Prevent progression with multivitamin and antioxidant supplements
- Age-Related Eye Disease Study 2 (AREDS2)

Wet ("exudative")
- 10 – 15%
- Accounts for > 90% of all cases of severe vision loss
- Rapid vision loss due to hemorrhage 2° to choroidal neovascularization
- Treatment: anti-VEGF antibody
  - bevacizumab (Avastin)
  - ranibizumab (Lucentis)
  - aflibercept (Eylea)

Diabetic eye disease
- Diabetic eye disease comprises a group of eye conditions that affect people with diabetes:
  - diabetic retinopathy (DR)
  - diabetic macular edema (DME)
  - cataract
  - glaucoma
- Adults with diabetes are 2-5 times more likely than those without diabetes to develop cataract.
- In adults, diabetes nearly doubles the risk of glaucoma.
Diabetic retinopathy (DR)

- **Mild nonproliferative retinopathy.** Microaneurysms may leak fluid into the retina.
- **Moderate nonproliferative retinopathy.**
  - More than just microaneurysms (with or without cotton-wool spots, venous beading, or intraretinal microvascular abnormality, IRMA) but less than the 4:2:1 rule.
  - More than "mild" but less than "severe."
- **Severe nonproliferative retinopathy.**
  - Any of the following (4:2:1 rule):
    - 20 or more intraretinal hemorrhages (dot blot hemorrhages) in each of all four quadrants.
    - Definite venous beading in 2 or more quadrants.
    - Prominent intraretinal microvascular abnormality (IRMA) in 1 or more quadrants.
  - More than "mild" but less than "severe."
- **Proliferative diabetic retinopathy (PDR).**
  - Definite neovascularization, or
  - Proliferation of vitreous hemorrhage.

Diabetic retinopathy (DR)

- **Treatment**
  - anti-VEGF
    - bevacizumab (Avastin)
    - ranibizumab (Lucentis)
    - aflibercept (Eylea)
  - peripheral retinal photocoagulation – Laser surgery
    - seal leaky blood vessels
    - reduce swelling
  - surgery – vitrectomy

Central retinal artery occlusion (CRAO)

- Presentation: sudden, painless, complete loss of vision
- Funduscopic exam:
  - May be cloudy normal, followed by cloudy swelling and subsequent whitening (corresponding to focal necrosis of retina)
  - Cotton-wool spot on the fovea
  - Retinal hemorrhage and venous engorgement, edema in affected area.
- Evaluate for embolic source (eg., carotid artery atherosclerosis, cardiac vegetations, patent foramen ovale)
- Emboli can be directly visualized in 20% of cases.
- **Acute treatment**
  - dilation of the central retinal artery by rebreathing expired carbon dioxide, breathing carbogen (5% carbon dioxide with 95% oxygen), or sublingual nitroglycerin
  - gentle massage through a closed lid may dislodge the embolus distally
  - vitreous aspiration or manipulative, anterior chamber paracentesis, and trabeculectomy to control IOP.
Central retinal vein occlusion (CRVO)

- Presentation: sudden, painless, monocular loss of vision
- Funduscopy exam:
  - non-ischemic CRVO
    - dilated tortuous veins, retinal hemorrhages, cotton wool spots, retinal edema, disc swelling
  - classic 'blood and thunder' appearance from widespread hemorrhages that obscure most fundal details
  - Neovascularization
- Management:
  - Anti-VEGF, intravitreal triamcinolone, dexamethasone implant
- Branch retinal vein occlusion: only affects a sector of the retina corresponding to the distribution of the affected branch. Visual loss is limited to a segment of the visual field.

Retinal detachment (RD)

- Pathological progression of RD:
  1. separation of neurosensory layer of retina (photoreceptor layer) from retinal pigment epithelium (RPE)
  2. degeneration of photoreceptors
  3. vision loss.
- May be 2° to retinal breaks, diabetic traction, inflammatory effusions.
- Funduscopy exam and diagnosis:
  - crinkling of retinal tissue
  - changes in vessel direction.
- Breaks more common in patients with high myopia and/or history of head trauma.
- Often preceded by posterior vitreous detachment
- Eventual monocular loss of vision
- Surgical emergency

Central serous chorioretinopathy or central serous retinopathy (CSR)

- Sporadic disease of unknown etiology
  - approx. 1 in 22,000
  - Gender: male > female 6:1
  - Race: Whites and Asians > Blacks
- blister-like serous detachment of the retina and RPE
- Characteristic “smokestack” on FA
- “central” refers to visual symptoms due to serous detachment in the macular region
- Presents with blurred vision and a central, positive scotoma, unilateral metamorphopsia and/or micropsia, etc.
- May be associated with pigment epithelial detachment (PED)
- Relative preservation of functional vision
- Linked to corticosteroid use
- Women: pregnancy, systemic lupus erythematosus
Central serous chorioretnopathy or central serous retinopathy (CSR)

- **Course and outcome:**
  - Usually self-limiting: 90% cases show spontaneous recovery within a few months.
  - Recurrence: 50% in first year.
  - RPE atrophy, CNV (up to 6%), transformation into polypoidal chorioidal vasculopathy.

- **Management:**
  - **Non-drug Treatments:**
    - Reduce stress.
    - Reduce caffeine.
    - Avoid cortisone treatments.
  - **Pharmacologic approaches:**
    - Ketoconazole.
    - Anti-VEGF.
  - **Surgical:**
    - Photodynamic therapy (PDT).

Retinitis pigmentosa (RP)

- Genetic retinal disease.
- More than 50 known genetic loci.
- 1:4,000.
- Onset: childhood to young adulthood.

- Manifests with impaired night vision first (rods affected first), and impaired peripheral vision.
- Characteristic dark pigment deposits ("Bone spicule-shaped" deposits around macula).
- No general treatment for RP.

Retinitis pigmentosa (RP)

- **Diagnosis:**
  - Genetic testing.
  - Electroretinography.
  - Visual field testing.
  - OCT.

- **Disease progression:**
  - Rod outer segment.
  - Rod inner segment.
  - Outer nuclear layer.
  - Cones.

- Intertinal vessels can make contact with the RPE, migration of RPE cells along the intraretinal vessels, loss of tight junctions of the RPE, "recreated" retinal blood barrier, bone spicule-shaped deposits.
Luxturna (voretigene neparvovec-rzyl)

- First FDA approved gene therapy for any retinal or inherited genetic disorder
- Approved for RP with a confirmed bi-allelic RPE65 mutation
- Adeno-associated virus vector-based
- Requirement for existing viable retinal cells
- APPROVED: 12/19/2017

Luxturna (voretigene neparvovec-rzyl)

- Subcutaneous injection method

**Q&A**