Hypertension

Hypertension affects nearly 50 million people in the US and one billion people worldwide.

It is the leading indication for physician's office visits and one of the leading causes of cardiovascular morbidity and mortality. It is a major factor for renal disease and greatly increases the risk of stroke.

In 2010, elevated blood pressure was found to be the leading risk factor for death and disability-adjusted life-years lost.

Essential hypertension

Exact cause is unknown:

- Male sex
- Increased age
- Family history
- Smoking
- Sedentary lifestyle

Costs of Hypertension

• The total costs attributed to high blood pressure in 2011 in the US were $46 billion dollars in healthcare, medications and lost days of work.
Renin-angiotensin system

- Renin-angiotensin-aldosterone system
  - Hormone system that regulates blood pressure and fluid balance.
  - When renal blood flow is reduced (low BP), the kidney secretes renin into circulation.
  - Renin then converts angiotensinogen (released by the liver) into angiotensin I.

Angiotensin II is then converted to angiotensin II by converting enzyme (found in the lungs).
Angiotensin II is a vasoconstrictor and causes the blood vessels to constrict, which increases BP.

Angiotensin II also stimulates the release of aldosterone from the adrenal cortex.
This causes the tubules of the kidney to increase re-absorption of sodium and water into the blood and causes the excretion of potassium.
This increases the extracellular fluid of the body which increases blood pressure.

Secondary Hypertension

- Linked to a specific cause:
  - Birth control use increases activity of renin-angiotensin system - rare
  - Chronic kidney disease
  - Adrenal tumors – pheochromocytoma
  - Chronic steroid use
  - Sleep apnea

Sympathetic over-activity

- Another cause of HTN
  - Increased heart rate
  - Increased ventricular contraction strength
  - Decreases duration of systolic contraction
  - Increased vasoconstriction causing increased BP
Complications of Hypertension

**Heart:**
- Coronary artery disease
- Atherosclerosis
- Left ventricular hypertrophy
- Heart failure
- Angina
- MI
- Sudden death

**Brain:**
- CVA
- Encephalopathy

**Kidneys:**
- Renal artery stenosis
- Renal insufficiency

Atherosclerosis

- Invasion and accumulation of macrophages (foam cells), and proliferation of smooth muscle cell causing a fibrofatty plaque.
- Plaques build up inside the arteries.
- The plaques are made up of cholesterol, lipid, cellular waste and fibrin.
- Plaques may partially or totally block the blood flow through the arteries.
- Plaques may break loose (embolus) or cause a blood clot to form (thrombus).

Left Ventricular Hypertrophy

- A result of prolonged hypertension
- Significant risk of morbidity and mortality
- With greater peripheral resistance from HTN, the left ventricle must work harder to push blood out of the heart.
- The left ventricle undergoes hypertrophy of the muscle and this causes an increased demand for oxygen to the left ventricle.
- Failure to meet this oxygen demand manifests as angina, MI or sudden death.

Heart Failure

- If the arterial pressure is high, the left ventricle may not pump out its full load.
- Some blood remains in the heart and oxygen does not get to body tissues.
- Blood cannot get into the ventricle from the left atrium because the ventricle is already full.
- This backs blood up to the pulmonary vein and possibly to the vena cava (right side of heart)
- Patients may experience dyspnea, and low cardiac output.

Cardiovascular accident

- HTN and atherosclerosis are responsible for the majority of CVAs
- Cause hemorrhagic, thrombotic or embolic event.
- 40% of all CVAs are attributable to systolic HTN greater than 140 mmHg.
Kidney Disease

- Prolonged hypertension can lead to chronic kidney disease from renal artery stenosis
- Low flow to the kidneys from renal artery stenosis makes the body think it is dehydrated
- This starts the renin-angiotensin system and blood pressure is further elevated.

Diagnosis of Hypertension

- Diagnosed if BP readings are consistently 140/90 or above
- Usually factor in the results of 2-3 BP readings before HTN or pre-HTN is diagnosed.
- Some patients have 'white coat' syndrome and have elevated readings in the office. They may be asked to obtain home readings and bring in a BP log.

SPRINT research group

- 9361 patients with systolic BP of 130 mmHg or higher and an increased risk of cardiovascular disease, but not diabetes
- Separated into two groups:
  1) Systolic BP of less than 120 mmHg (intensive group)
  2) Target of less than 140 mmHg (standard therapy)

Results:
There was a significant reduction in mortality in the intensive treatment group, there were significantly less: MI, stroke, heart failure, death from cardiovascular causes.

Treatments for Hypertension

- Lifestyle modifications are critical for the prevention of high BP and its management
- Adoption of the DASH (Dietary Approach to Stop Hypertension) diet
  This diet is rich in potassium and calcium, and incorporates dietary sodium restrictions
- Increased physical activity, ~30 minutes per day
- Moderate alcohol consumption (2 per day, men ~ 1 per day, women)
Treatments for Hypertension

Medical therapies:
- Diuretics
- Beta-blockers
- ACE inhibitors
- Calcium channel blockers
- Angiotensin II antagonists
- Aldosterone receptor blockers

Diuretics
- Thiazide diuretics are the most effective
- Block re-absorption of sodium at the distal tubule of the nephron.
- This causes the body to excrete more water and lower the fluid volume in the body, reducing blood pressure.

Beta Blockers
- Block beta receptors in the heart, kidney and CNS
  - Kidney:
    - B1 receptors are blocked. This inhibits the release of renin.
  - Heart:
    - Block B1 receptors to decrease cardiac contractility.
  - Central and peripheral nervous system:
    - Decreases sympathetic nervous system activity

ACE inhibitors
- Acts to suppress the renin-angiotensin-aldosterone system
- Inhibit ACE, which usually converts angiotensin I to angiotensin II
- This causes vasodilation and decreases blood volume.

Calcium channel blockers
- Inhibit calcium influx into smooth muscle cells by blocking calcium channels in the cell membrane
- This causes a vasodilation effect which decreases blood volume and lowers blood pressure.

Ocular side effects of hypertension
- Retinal:
  - Vasoconstriction
  - Sclerosis
  - Exudation
  - Complications of sclerosis
- Optic Nerve Vasculature:
  - Bilateral ONH edema
  - Exudation
- Choroidal Vasculature:
  - Elschng spots
  - Siegrist spots
  - Serous RD
Retinal vasculature
- Regulated by autoregulation
- Initial reaction to hypertension is vasoconstriction
- Best appreciated beyond the second branch of the central retinal artery.
- Over time, hypertension causes thickening of the arterial walls. This is seen as attenuated arterials and nicking banking at A/V crossing (sclerotic phase)

Choroidal vasculature
- Not auto-regulated, controlled by sympathetic innervation.
- Majority of cases of hypertensive choridopathy are in young patients with acute HTN.
- Elschnig spot – focal necrosis of the RPE corresponding to the choriocapillaris.
- Siegrist spot/streak - focal RPE loss in the equator.

Retinal pathologies from the sclerotic phase of hypertension

Vein Occlusions
- Arterial compression of the vein → Leads to turbulent blood flow in the retina → Causes intravascular thrombus formation
- This interrupts venous flow and retinal ischemia can result downstream from the occlusion → Rapid increase in VEGF and this causes a breakdown of the blood-retina barrier which can then cause CME.

Central retinal artery occlusion
- Caused by an occlusion (embolic, thrombotic, inflammatory or traumatic) of the central retinal artery.
- Risk factors include atherosclerosis, cardiac disease, coagulopathy, collagen vascular disease.
Retinal pathologies from the sclerotic phase

Retinal artery macroaneurysm
- Acquired, focal dilation of the retinal arterial branches
- Prognosis generally good. Vision loss can occur from macular edema, arteriolar occlusion from thrombosis or rupture of aneurysm.
- Caused by local ischemia from focal embolic damage to the arterial walls from vascular disease. Causes increased permeability of vessels.

Grading hypertensive retinopathy
Keith-Wagner-Baker classification:
- Stage 1: Mild retinal vascular changes (arteriolar narrowing)
- Stage 2: Moderate to severe vascular changes (a/v crossing)
- Stage 3: Stage 1 and 2 plus CWS, retinal hemorrhages, exudates
- Stage 4: Stage 3, plus optic nerve swelling and macular star

Other ocular manifestations of HTN

Case
59 yo white male presents for a routine examination
- Chief complaint: Patient states the vision in his left eye has diminished.
- Ocular history: Past CRAO OD with resultant macular scarring and severely decreased BCVA
- BCVA:
  - OD: 20/400
  - OS: 20/20
- Pupils: ERRL (+) APD OD
- Dilated exam:
Impression:
- New onset BRVO OS with CME
- h/o CRVO OD with resultant macular scarring and severely decreased BCVA

Plan:
- With a BCVA of 20/20, monitor for now.

Eligibility
1) BRVO 3 to 18 months.
2) VA 20/40 or worse from CME
3) Sufficient clearing of heme.
4) FA confirms leakage involving fovea (ME). NOT NONPERFUSION.

BRVO study
Multicenter study to answer the following:
- Can grid laser improve CME and VA worse than 20/40?
- Can laser prevent NV?
- Can laser prevent VH?
Methods

139 patients
- Average follow up: 3.1 years
- Assigned to either grid macular laser photoagulation or no laser treatment.

Results

<table>
<thead>
<tr>
<th>Criteria Measured</th>
<th>Treatment Group</th>
<th>Controls</th>
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</thead>
<tbody>
<tr>
<td>% gaining 2 lines</td>
<td>65%</td>
<td>37%</td>
</tr>
<tr>
<td>% having decrease in VA</td>
<td>12%</td>
<td>17%</td>
</tr>
<tr>
<td>&lt;20/40 at 3.1 years</td>
<td>63%</td>
<td>26%</td>
</tr>
<tr>
<td>Avg. VA 20/40 to 20/70</td>
<td>12%</td>
<td>23%</td>
</tr>
<tr>
<td>Avg. Line Gain</td>
<td>1.33</td>
<td>0.23</td>
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</tbody>
</table>

This study established grid laser as the standard of care for CME from a BRVO.

Back to our patient...

2 months later...

Chief compliant:
- Increased haze in the left eye
- BCVA:
  - OD: 20/400
  - OS: 20/50 ~ 2 PH: NI

OCT: Increased cystoid macular edema OS

Retina visit

Impression:
- BRVO with macular edema OS, decreased acuity and increased edema

Plan:
- Intravitreal Avastin OS

BRAVO study

Study design: Multicenter, randomized sham-controlled study on the efficacy and safety of Lucentis for macular edema from BRVO.

Inclusion criteria:
- Macular thickness of 250 μ or greater
- Vein occlusion within 12 months. (mean time 3.5 months)
**BRAVO study**

397 patients initially, 392 completed 6 months of the study.

Patients were assigned to:
- 0.3 mg injections monthly x 6 months (n = 134)
- 0.5 mg injections x 6 months (n = 131)
- Sham injections monthly x 6 months. (n = 132)

Patients were eligible for laser if no improvement at 3 months.

**Results**

Mean letter gain at 6 months:
- 16.6 letters in 0.3 mg group
- 18.3 letters in 0.5 mg group
- 7.3 letters in sham

By month 6, more than half of treated patients reached 3 lines of better acuity.

After 6 months, sham patients were allowed to get injections (now sham/0.5mg group) on a PRN basis. Others were given injections on a PRN basis.

**CRVO study (CVOS)**

- Multicenter study
- 725 patients were followed q 4 months x 3 years.
- Eyes with non-perfusion at baseline were followed monthly for at least 6 months.

**Take away points – BRVO**

- After the BRVO study, grid laser was the standard of care for CME from BRVO.
- The BRAVO study showed Lucentis to be very effective in the treatment of CME from BRVO. Lucentis is now FDA approved for CME from a RVO.

**Our patient**

Last visit 10/2014
- s/p Avastin OS x 8, focal laser OS

- BCVA:
  - OD: 20/400
  - OS: 20/25+
### Outcome measures
- Presence of:
  - NVI
  - NVG
- Final visual acuity

### Visual acuity, natural history without treatment
- 65% of patients with 20/40 or better maintained good acuity.

<table>
<thead>
<tr>
<th>Visual acuity range</th>
<th>Improvement</th>
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</thead>
<tbody>
<tr>
<td>20/50-20/200 vision</td>
<td>19% improved to better than 20/50</td>
</tr>
<tr>
<td></td>
<td>44% stayed the same</td>
</tr>
<tr>
<td></td>
<td>37% had worse VA (20/200)</td>
</tr>
</tbody>
</table>

  In patients with acuity <20/200:
  - 80% stayed the same level.

### Non-perfusion
- Developed fastest in the first 4 months.
- NVI and/or NVA developed in 16% of eyes.
- Strongest predictors of NVI/NVA were initial visual acuity and the amount of non-perfusion on angiography.

### Recommended management (CVOS)
- Pay close attention to VA at first exam
- Return for f/u every 1-2 months for the first 6 months.
- If NV present, refer for PRP.
- Initial acuity will help manage patients.

### Laser for CME from CRVO?
- Is this a good idea?
  - No difference in treated acuity vs. untreated acuity.
  - Observation: 20/125 baseline, 20/160 final at 3 years
  - Treatment: 20/160 baseline, 20/100 final at 3 years
- What benefits were found?
  - Macular appearance was clinically flatter, but no improvement in BCVA

### Back to our patient
**Retina visit:**
**Impression:**
- Non-ischemic CRVO OD with CME and decreased BCVA

**Plan:**
- Intravitreal Avastin OD
CRUISE Study

Methods: 6 monthly injections followed by 6 months of observation/PRN injections. Multicenter, randomized, sham injection controlled study

Purpose: Compared six, monthly 0.3 mg or 0.5 mg injections to observation of macular edema from CRVO

Primary outcome:
- Mean BCVA change from baseline.

Inclusion criteria:
- Central thickness of 250 u or more on OCT.
- BCVA 20/40 – 20/320

Results:
- At 6 months:
  - 12.7 letters gained 0.3 mg Lucentis group
  - 14.9 letters gained 0.5 mg Lucentis group
  - 0.8 letters gained Sham group

At 12 months:
- 13.9 letters gained 0.3 mg group
- 13.9 letters gained 0.5 mg group
- 7.3 letters gained sham/0.5 mg group

Percent gaining 15 letters:
- 46.2% 0.3 mg Lucentis group
- 47.7% 0.5 mg Lucentis group
- 16.9% Sham group

SCORE 2 – Hot off the Press!

Question: Is Avastin’s off-label use non-inferior to Eylea in management of visual acuity in eyes with macular edema from a CRVO or HRVO?

Methods: 362 patients were randomized to receive either an injections of Avastin or Eylea every 4 weeks for 6 months.
### Herpes Simplex

- **One of the most common infections for humans.**
- Herpes simplex virus is split into two subtypes (HSV1 and HSV2)
  - HSV1 is usually responsible for infections above the waist
  - HSV2 is usually responsible for infections below the waist.

### Herpes Simplex 1

- HSV-1 is contracted through oral secretions.
- Acquired during childhood and is asymptomatic or may have an upper respiratory infection
- Signs include lesions and vesicles of the intraoral membranes, lips and facial area

### Results:
At 6 months, the Avastin group gained an average of 18.6 letters. The Eylea group gained an average of 18.9 letters.

### Conclusion:
Among patients with macular edema due to CRVO or HRVO, Avastin was non-inferior to Eylea with respect to visual acuity at 6 months.
Herpes Simplex 1

Trigger factors for reactivation:
- Sun exposure
- Wind
- Fever
- Local trauma
- Menstruation
- Emotional stress
- Decreased immunity
Treatment of Herpes Simplex

- Most often, symptoms of HSV 1 and HSV 2 are self-limiting and benign.
- Can be life threatening in immunocompromised individuals.
- Anti-viral therapy is the mainstay of herpes treatment.

Oral or intravenous acyclovir is used for the treatment of HSV 1 infections as well as to course or prevent genital HSV 2 infections.

Oral Acyclovir 200 MG 5x/day

Other preventative measures: sunblock on lips, condoms to prevent spread of HSV 2, C-section to prevent neonatal infection when the mother has HSV 2.

Ocular manifestations of Herpes Simplex

- Primarily due to HSV 1 infection, but can sometimes be associated with an HSV 2 infection.
- Ocular herpes can occur from a primary infection or as a result of a recurrent non-ocular infection (cold sores) which later spread to the eye.

Epithelial keratitis:
- Begins with punctate lesions caused by actively replicating virus.
- Lesions increase in size to form the classic dendritic ulcer.
- Dendritic ulcer has a classic branching pattern and terminal end blubs.
- Usually heal in 5-12 days, but can progress to large, slow, geographic ulcers.

Stromal keratitis:
- Infection may extend to the stroma causing a hypersensitivity reaction to the viral particles in the stroma.
- Disciform keratitis is a round area of stromal edema underneath an intact epithelium.
- Interstitial keratitis presents with areas of stromal infiltration from inflammatory cells and is more chronic.
Ocular manifestations of Herpes Simplex

Stromal keratitis:
- Complications are vascularization, necrosis, scarring, stromal thinning, perforation which can result in blindness.
- Symptoms: photophobia, blurred vision, increased tearing, and pain.

Ocular manifestations of Herpes Simplex

Neurotrophic cornea/ulcers:
- Cornea after a herpetic infection may lose its sensation and a neurotrophic ulcer can result
- Ulcer is sterile and results from disruption to the basement membrane
- Symptoms: Decreased corneal sensation, tearing, some pain upon awakening, foreign body sensation.

Ocular manifestations of Herpes Simplex

Uveitis:
- Can occur as a sequela to stromal and endothelial inflammation
- Can be present as a recurrence of the HSV infection without corneal involvement
- May be mild-severe in presentation and may be a cause of uveitic glaucoma.

Diagnosis of ocular herpes simplex keratitis

Diagnosed by clinical examination
- Signs:
  - Unilateral lid vesicles
  - Dendrites on the epithelium
  - Follicular conjunctivitis
  - Neurotrophic ulcers
  - Reduced corneal sensation

Treatment of herpes simplex blepharoconjunctivitis

- Often self-limiting and may require no treatment
- If needed, oral antivirals can be used to shorten the course of the infection.
  - Acyclovir 400 MG 5x/day PO x 7-10 days
  - Valtrex 500 mg TID PO x 7-10 days

Treatment of Epithelial HSV

There are two topical agents available for treatment of herpes simplex:
- Trifluoridine (viroptic)
  - Used for herpes epithelial keratitis up to 9x/day (usually dosed Q2H)
  - Toxic to the corneal epithelium
- Ganciclovir gel (tigan)
  - Applied 5x/day until epithelium is healed and then TID x 7 days
  - Only affects the herpes virus, not the corneal epithelium.
### Treatment of epithelial HSV

**Oral agents:**
- Acyclovir 400 mg 5x/day x 7-10 days
- Valacyclovir 500 mg TID x 5-7 days
- Avoid steroid use with an active dendritic lesion

### Treatment of Herpes Simplex stromal keratitis

- Topical steroids are a MUST for treating stromal keratitis (Pred Forte at least 1 gtt QID OU)
- Oral acyclovir is added to shorten the course of the infection (400mg 5x/day)
- After the infection has resolved, keep the patient on a maintenance dose of acyclovir 400 mg BID to avoid recurrence

### Herpetic eye disease study 1

- To evaluate the efficacy of topical corticosteroids in treating stromal keratitis in conjunction with topical trifluridine
- To evaluate the efficacy of oral acyclovir in treating stromal keratitis
- To evaluate the efficacy of oral acyclovir in treating iridocyclitis with topical steroid and trifluridine

### Oral acyclovir for herpes stromal keratitis

- Patients were randomized to a 10 week course of oral acyclovir (400mg 5x/day) vs. placebo
- All patients received a standard regimen of topical pred forte/viroptic.
- There was no significant benefit of oral acyclovir for visual acuity, time to treatment failure, proportion whose keratitis resolved.

### Iritis

- Patients with active HSV iridocyclitis were randomized to either 400 mg 5x/day for 10 weeks or placebo.
  - They also received topical pred forte (8 drops/day x 7 days and gradually decreasing over 10 weeks)
Herpetic eye disease study 1
• Trial was too small for statistically conclusive results, but trend was toward less treatment failure in acyclovir group.

Herpetic eye disease study 2
• To determine whether early treatment using oral acyclovir of herpes simplex of the epithelium prevents progression to stromal keratitis and iridocyclitis, no benefit was found.
• To determine the efficacy of low dose acyclovir in preventing recurrent HSV eye infections.

Herpetic eye disease study 2
• Assigned 703 immunocompetent patients who had ocular HSV within the last year to 400 mg acyclovir BID PO vs. placebo.
• Study outcome: the rate of development of ocular or non-ocular HSV within the 12 month treatment period and 6 month observation period.

Herpes Zoster
• The cumulative probability of a recurrence of ocular HSV during the 12 month period was significantly lower in the acyclovir than placebo group.
• Stromal keratitis was observed in 8 percent of the treatment vs 13 percent of the observation group.
Herpes Zoster

- Caused by the Varicella virus, a viral infection known as the chickenpox, that is usually acquired during childhood
- After a primary infection, the virus remains dormant and in the sensory ganglia until later in life it is re-activated as shingles

Herpes Zoster

- Primarily affects older individuals as they have an attenuated immune system
- Patients with HIV/AIDS are more susceptible to infection
- Patients undergoing chemotherapy or radiation are more susceptible as well as those on chronic steroid therapy.

Herpes Zoster

Three phases to varicella re-activation:
- Prodromal
- Acute
- Postherpetic

Prodromal phase:
- May precede the acute phase by hours to days
  - Malaise, headache, fever, tingling, burning, redness, chills, pain

Herpes Zoster

Acute phase:
- Grouped skin lesions which follow a particular dermatome
- Lesions are almost always unilateral
- Skin hypersensitivity results and the skin can scar in the areas of vesicle formation
- Acute inflammation and pain can occur and last 8-14 days

Herpes Zoster

Postherpetic phase:
- A serious complication of a herpes zoster infection
- Commonly affects the thoracic dermatome and the ophthalmic nerve
- Persistent, boring pain that follows the acute infectious phase.
- Severe pain usually lasts 1-3 months, but for some, this may be chronic.

Herpes Zoster

Disseminated disease:
- Very rare
- Can affect multiple organ systems
- Can cause: cerebral angitis, myelitis, meningencephalitis and lead to death
Diagnosis of Herpes Zoster

- Typically based on clinical presentation, history
- Patients will have unilateral skin lesions distributed along a single dermatome.
- In a younger patient with a HZ infection, you MUST rule out an HIV infection.

Treatment of Herpes Zoster

- Acyclovir 800 mg 5x/day PO for 7-10 days
- Valtrex 1g TID PO x 7-10 days
- Acute pain: analgesics, narcotics if necessary
- ***Antivirals should be given within the first 72 hours of the appearance of skin vesicles. This greatly reduces the chance of post herpetic neuralgia***

Ocular manifestations of herpes zoster

- Eye involvement stems from the ophthalmic division of the trigeminal nerve (V1).
- Occasionally V2 may be affected (maxillary nerve).
- Classified by unilateral skin lesions that do not cross the midline.

Ocular manifestions of herpes zoster

- Ocular structures are affected by direct viral invasion, secondary inflammation or autoimmune reactions in the eye.
- Ocular complications are:
  - Lid involvement (~28%)
  - Cornea (~55%)
  - Uveitis (~43%)
  - Postherpetic neuralgia (~17%)

Lids:
- Vesicles found in HZO are small and numerous
- Acute inflammation may affect the skin lesions.
- Nasociliary nerve involvement and a good predictor for ocular involvement is a Hutchinson's sign (vesicles at the tip of the nose)

Conjunctivitis:
- Common ocular manifestation that usually resolves without treatment
- Dr. Di Mattina usually uses a topical steroid to manage this.

Cornea:
- Can be split into:
  - Early manifestations (2-4 weeks)
  - Late manifestations
Ocular manifestations of herpes zoster

Early corneal manifestations:
- Punctate epithelial keratitis
- Zoster pseudodendrites

Late corneal manifestations:
- Disciform keratitis
- Serpiginous ulcers
- Neurotrophic keratopathy

Ocular manifestations of herpes zoster

Punctate epithelial keratitis:
- Area of swollen, elevated epithelial cells.
- Usually multiple and peripheral in the cornea.
- Self-limiting and possibly an early form of a pseudodendrite.

Pseudodendrites:
- Composed of peripherally located swollen epithelial cells with a gray-white dendritic pattern.
- Pseudodendrites are self-limiting and resolve in days up to a month.
- Dr. Di Mattina treats them with topical steroids.

Nummular keratitis:
- Anterior stromal infiltrates
- An early form of stromal keratitis and often associated with pseudodendrites or PEK
- Usually resolve without treatment and if they scar, often do not affect vision.

Disciform keratitis:
- Results from stromal keratitis weeks to months after initial onset.
- Focal, well demarcated area of stromal infiltration with stromal edema
- May lead to interstitial keratitis with neovascularization and scarring

Serpiginous ulcers:
- Crescent shaped
- Peripherally located
- Can potential lead to corneal thinning and perforation.
### Ocular manifestations of herpes zoster

**Neurotrophic keratopathy:**
- Caused by loss of corneal sensation
- Can lead to pannus, scar formation
- Ulceration can cause decreased vision, perforation or loss of an eye.

**Uveitis:**
- Inflammation, particularly anterior uveitis
- Usually mild, but can be severe.
- IOP can be increased by the inflammation (long term), posterior synechiae, debris in the trabecular meshwork

**Iris:**
- Localized ischemic changes can result in a distorted pupil
- Sympathetic innervation problems can cause a Horner’s syndrome
- Ciliary ganglion issues can cause a Adie’s pupil. (dilated pupil with near/light dissociation)

**EOMS:**
- Can occur days to weeks after involvement
- The third cranial nerve is the most commonly affected, followed by the sixth or the fourth nerve
- Usually resolves on its own by 2 months

**Late cicatricial phase**
- Retinal holes and tears occur at the junction of normal and atrophic retina.
- Leads to retinal detachment in 50-75% of untreated eyes.

**Retina and optic nerve:**
- Generally rare.

**Acute retinal necrosis:**
- Split into two phases:
  - Acute herpetic phase: episcleritis or scleritis, uveitis and vitreous opacification, inflammation of retina and retinal arteries, optic neuropathy can occur
Ocular manifestations of herpes zoster

Progressive outer retinal necrosis:
- Usually present in immunocompromised patients.
- A silent, minimally inflammatory retinitis without a vitritis (unlike ARN)
- Necrosis progresses circumferentially to affect the entire retina
- Optic nerve involvement and retinal detachment are very common.

Diagnosis of Herpes Zoster Ophthalmicus

- Typically based on clinical presentation
- Characteristic skin lesions and distribution
- Staining patterns to pseudodendrites.
  - Poor staining with fluorescein, better staining with rose Bengal.

Treatment of Herpes Zoster Ophthalmicus

- Epithelial keratitis:
  - Debridement, topical lubricants, topical steroids.
- Stromal keratitis:
  - Topical steroids
- Neurotrophic keratitis:
  - Lubricants, topical antibiotic to prevent infection.

Treatment of Acute Retinal Necrosis

- Referral to retina. Pt will need to be hospitalized and monitored by retina and an ID doctor.

Ocular Side Effects of Systemic Medications

- Antimalarial Agents
  - Chloroquine (Aralens)
  - Hydroxychloroquine (Plaquenil)
  - Commonly used to treat rheumatoid arthritis, systemic lupus erythematosus, and other connective tissue diseases
  - Ocular toxicity
    - Incidence: 0% to 4%
    - Binds to melanin in the RPE and affects retinal metabolic activity
Plaquenil mechanism of action

• Proposed mechanism of action is interference with the “antigen processing” in macrophages and other antigen-presenting cells.
• Results in down-regulation of the immune response against autoantigenic peptides.

Antimalarial Agents: potential side effects

• Punctate or verticillata corneal deposits
• Decreased visual acuity
• Difficulty with night vision (nyctalopia)
• Reduced color vision (especially blue/yellow)

Antimalarial Agents: risk factors for toxicity

- Cumulative dosage
- Duration of treatment
- Renal/liver function
- Age
- Concomitant retinal disease

<table>
<thead>
<tr>
<th>Low risk</th>
<th>High risk</th>
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</table>
2011 monitoring Guidelines
- Dilated fundus exam at baseline, not for screening
- No longer recommend color vision or amsler grid testing
- 10-2 SS VF still recommended
- When possible: FAF, mERG or macular OCT.
- Watch when cumulative dosage is >1000g.
- Annual screening recommended after 5 years of the medication.

Newest Guidelines - 2016
- Updated again based on higher than previously believed prevalence of toxicity in long-term users.
- Risk is highly dependent on the daily dose by weight.
- Also, “bull’s eye” pattern of maculopathy is infrequent in Asian patients.

Newest Guidelines - 2016
- New data suggests that patients taking 4.0 – 5.0 mg/kg real weight had markedly reduced levels of toxicity than higher doses.

Newest Guidelines - 2016
- The annual incremental risk is lower than 1% for the first 10 years of therapy for the <= 5.0 mg/kg group and increases to only 4% after 20 years.

Newest Guidelines - 2016
- No longer recommended:
  - Fundus examination for screening
  - Bull’s eye macula is a late stage sign
  - Time-domain OCT
  - FFA
  - Full field ERG
  - Amsler Grid
  - Color vision

Visual fields:
- 10-2 SS VF is good for central macular field, but 24-2 and 30-2 are recommended for Asian patients in whom toxicity manifests outside the macula.
- The most common initial visual field loss will be superonasal.
Antimalarial agents: management of toxicity
• No effective treatment
• Discontinue med in conjunction with patient’s internist or rheumatologist
• Drug clears slowly from the body = ocular changes may continue after cessation of treatment
• F/u every 3 months until ocular findings stabilize, then annually

Anti-Arrhythmic medications

Anti-Arrhythmic medications
• Amiodarone: benzofuran derivative
• Normal dose: 600-800 mg QD x 1 month, then 400 mg QD thereafter

Amiodarone mechanism of action
• Inhibits inward sodium and calcium channels.
• Results in suppression of excitability and conductivity of cardiac tissues

Amiodarone: potential side effects
• Superficial punctate opacities (69-100%)
• Corneal edema
• Whorl-like (vortex) keratopathy
• Lipophilic drug attaches to the basal stem cells at the limbus and is carried to the center of the cornea until the cells differentiate and desquamate
• Photophobia (57%)

Amiodarone: potential side effects
• Anterior subcapsular yellow-white punctate opacities
• Optic neuropathy (1.8%)
• Drug-induced lipid storage disease
• Accumulation of intracytoplasmic lamellar inclusions in the optic nerve axons; impairs axoplasmic flow and causes optic disc edema
• Predisposing risk factors: DM, HTN
**Toxic Neuropathy vs NAION**

<table>
<thead>
<tr>
<th></th>
<th>Amiodarone-induced Optic Neuropathy</th>
<th>NAION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of visual loss</td>
<td>Insidious (months)</td>
<td>Rapid (days to weeks)</td>
</tr>
<tr>
<td>Degree of vision loss</td>
<td>20/20 to 20/200</td>
<td>20/20 to NLP</td>
</tr>
<tr>
<td>Ocular involvement</td>
<td>Usually simultaneous</td>
<td>Rarely simultaneous</td>
</tr>
<tr>
<td>Resolution of disc edema</td>
<td>Within weeks</td>
<td>Within weeks/months</td>
</tr>
</tbody>
</table>

**Amiodarone: baseline examination (AOA guideline)**
- Complete eye exam including DFE
- Screening visual field
- Amsler grid
- Color vision (red/green, blue/yellow)

**Amiodarone: management of ocular toxicity**
- Report adverse side effects to cardiologist and/or PCP
- Protective sunwear for photophobia
- Discontinue medication in conjunction with the prescribing doctor if optic neuropathy develops

**Amiodarone: one more thing...**
- Can cause thyroid dysfunction
  - Inhibits peripheral conversion of T4 to T3
  - Hypothyroidism or hyperthyroidism
  - Tx: decrease dosage

**Digoxin: mechanism of action**
- Digoxin: cardiac glycoside
  - Normal dose: 0.125 mg – 0.25 mg
  - Used for treatment of heart failure and chronic atrial fibrillation
  - Works by inhibiting subunits of ATPase. This promotes sodium-calcium exchange and increases the force of myocardial contractions.

**Digoxin: potential side effects**
- Xanthopsia (yellow vision)
- Decreased IOP
- Inhibits Na⁺-K⁺-ATPase = impaired cone function and reduced aqueous secretion
- Management/follow-up: same as for amiodarone
Antineoplastic drugs

Tamoxifen (Nolvadex)
- Nonsteroidal anti-estrogen agent used for long-term, preventative therapy after breast cancer surgery
- Normal dosage: 20 – 40 mg QD
- Retinal findings more common at dosages of 180 mg QD

Tamoxifen: mechanism of action
- Binds to the Estrogen receptor.
- Strongly anti-estrogenic on the mammillary epithelium
- Lowers the circulating levels of insulin-like growth factor (IGF-1) in breast cancer patients. IGF-1 may stimulate the growth of breast cancer cells.

Tamoxifen ocular side effects
- Crystalline retinopathy (incidence: 6%)
- Refractile bodies in the inner retina; may be product of axonal degeneration
- Macular edema
- Optic neuritis

Tamoxifen ocular side effects
- Keratopathy (subepithelial calcium map-dot changes)
- Cataracts
Management: Follow-up annually unless retinopathy noted, then q3 months

Anti-psychotic medications
- Phenothiazines
- Chlorpromazine (Thorazine)
- Thioridazine (Mellaril)
- Trifluoperazine (Stelazine)
Anti-psychotic medications

Ocular side effects
- Decreased accommodation (anticholinergic properties)
- Dry eye
- Anterior subcapsular (ASC) cataracts
- Corneal endothelial pigment deposits
- Pigmentary retinopathy

Interferon

- For treatment of Hepatitis C
- Pegasys (peginterferon alfa-2a)
- Interferon is an anti-inflammatory, anti-tumour, antiviral, and immunomodulatory cytokine

Interferon mechanism of action

- Interferon is a natural protein, usually produced by WBCs to fight off infection.
- By injecting additional interferon, the medication assists the immune system in fighting off the hepatitis C virus.

Hepatitis C

- Health care workers (such as nurses, lab technicians and doctors) can get these infections if they are accidentally stuck with a needle that was used on an infected patient.

- Most people don’t feel sick when they are first infected with hepatitis C. Instead, the virus stays in their liver and causes chronic liver inflammation

- You are also at a higher risk if you got a blood transfusion or an organ transplant before 1992 (improvements in blood-screening technology were made in 1992).

- Hepatitis C is usually spread through contact with blood products. People who use intravenous (IV) drugs can get hepatitis C when they share needles with someone who has the virus.
### Interferon retinopathy

- Damage to the small blood vessels.
- Leads to:
  - cotton wool spots
  - retinal hemorrhages
  - optic neuropathy.

### Interferon retinopathy

- Retinopathy usually has little-to-no effect on vision, but can cause severe vision loss.
- Should discontinue medication once retinopathy noted.

### Topamax (topiramate)

- Used to treat seizures and now for the prevention of headaches.
- Anticonvulsant
- Adverse effect usually (85%) occurs in the first 2 weeks.

### Topiramate mechanism of action

- Precise mechanism of action is unknown
- Inhibits voltage gated sodium channels and high voltage gated calcium channels.
- Also inhibits some subtypes of carbonic anhydrase.

### Topiramate Ocular Side Effects

- Manifests as an atypical angle closure glaucoma with a narrow anterior chamber, acute myopia and a quiet eye.
- LPI is ineffective in this condition.

### Topamax (topiramate) angle closure

- Bilateral presentation, (regular angle closure is very rarely bilateral).
- Mechanism: ciliochoroidal effusion causing a forward rotation of the lens-iris diaphragm. This causes a narrow anterior chamber and acutely elevated IOP.
Topamax (topiramate) Angle Closure

• Acute myopia is presumably due to ciliary body edema, which causes relaxation of the zonules and induced myopic shift in refraction.
• Treatment: d/c topiramate, anti-glaucoma meds, Atropine.

Ethambutol

• Used in the treatment of Tuberculosis and MAC (M. avium and M. intracellulare)
• Usually given in combination with Isoniazid, rifampicin and pyrazinamide.

Ethambutol Mechanism of Action

• Bacteriostatic mechanism
• Works by obstructing the formation of the cell wall.
• Dose: 15 mg/kg orally, once daily.

Ethambutol Ocular Side Effects

• Can cause toxic optic Neuropathy.
  • Subacute, painless, bilateral central vision loss
  • Color desaturation
  • “stocking and glove” peripheral neuropathy

Ethambutol Ocular Side Effects Signs:

• Papillomacular bundle preferentially affected
• Visual fields demonstrate bilateral central or cecocentral scotomas
• Pupils sluggish, but no APD
• Optic discs first normal or hyperemic and then eventually pale.

Ethambutol Monitoring

• Monitoring: (AOA guidelines)
  • Baseline: comprehensive exam, screening visual field, amsler grid, color vision, fundus photography
  • Recommended follow-up: monthly visual acuity, screening visual field, amsler grid, color vision. Central visual field when optic neuropathy suspected. Repeat fundus exam/photographs when indicated.
Ethambutol monitoring
• Report adverse effects to the infectious disease doctor prescribing the medication so they can change the treatment regimen.
• There is some evidence of visual acuity improving slowly over many months with the discontinuation of ethambutol.

Contraceptives
Estrogen and/or progesterone.
• Two female sex hormones
• Work by preventing ovulation and change the lining of the uterus to prevent pregnancy.

Female Fertility cycle
Estrogen: Causes growth of the uterine lining, inhibits FSH. Stimulates LH and the release of the egg.
Progesterone: Maintains the lining of the uterus, inhibits LH after ovulation.

Leutinizing Hormone (LH):
Stimulates the release of the egg (ovulation). Stimulates estrogen and progesterone production.

Follicle Stimulating Hormone (FSH):
Stimulates egg development and release of estrogen.

Contraception effect on fertility cycle
• Estrogen inhibits secretion of FSH through negative feedback in the anterior pituitary.
• Progesterone inhibits secretion of LH and prevents ovulation.
• Estrogen and progesterone work together to alter the endometrium to discourage egg implantation.

Contraceptives effects on the eyes
• Papilledema
• Venous sinus thrombosis.
• Idiopathic intracranial hypertension
• Retinal artery occlusions
• Dry eye?
• Conflicting data.
Erectile dysfunction medications

- Phosphodiesterase type 5 inhibitor (PDE5 inhibitor)
- Blocks PDE5 in the smooth muscle cells lining the blood vessels supplying the corpus cavernosum of the penis.
- Widely used medications in the US

Erectile dysfunction medication ocular side effects

- Vision can have a “blue hue”
- Sudden, painless loss of vision (NAION) has been found to be two-fold the risk in patients who take PDE5 inhibitors in some studies. Others show no link to NAION.

Lithium

- Used for mental illness including bipolar, depression and schizophrenia. Used for eating disorders: anorexia and bulimia.
- It has been shown to reduce suicide rates in people with major depressive disorders.

Lithium side effects

- Diplopia
- Keratitis Sicca
- Blurred vision
- Downbeat Nystagmus