Oral Pharmaceuticals in Primary Eyecare

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Disclosures:

- Sun Pharmaceuticals: speakers bureau,
- Dompe: advisory board, speakers bureau
- AbbVie: advisory board
- Thea: advisory board
- Apellis: speakers bureau

- All financial relationships have been mitigated.

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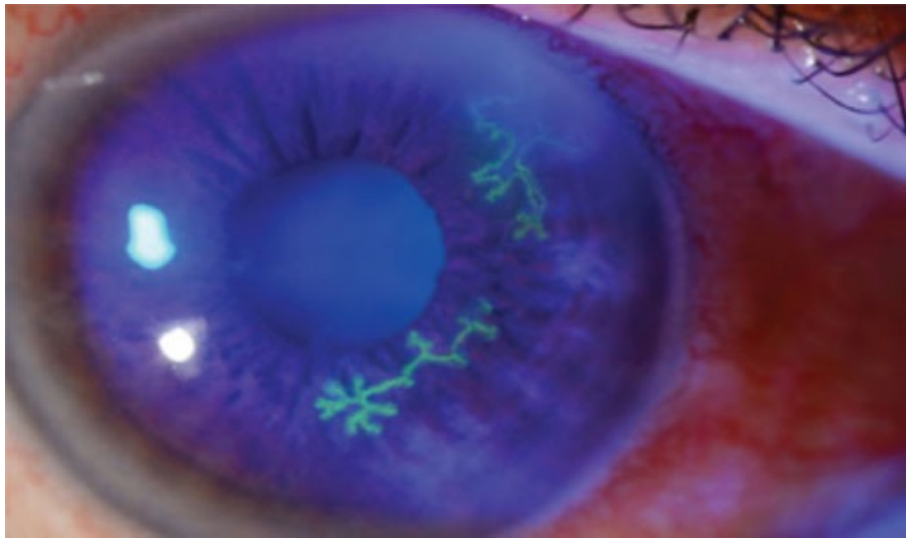
Case

- 20 year old male presents with a red painful eye
  - Started that morning when he woke up
  - reports a watery discharge, no itching, and is not a contact lens wearer
- SLE:
  - See attached image with NaFl stain



Herpes Simplex Virus (HSV) Keratitis: Clinical Features

- Characterized by primary outbreak and subsequent reactivation
  - Primary outbreak is typically mild or subclinical (90% of people are asymptomatic)
  - Most clinical ocular infections are manifestations of virus reactivation; ocular involvement occurs in fewer than 5% of primary infections
- After primary infection, the virus becomes latent in the trigeminal ganglion or cornea
  - The majority of ophthalmic HSV cases are unilateral, with recurrences affecting the same eye. Bilateral disease (not necessarily concurrent) occurs in 1-12% of cases and is more common in patients with atopy or other immune abnormalities
- Stress, UV radiation, and hormonal changes can reactivate the virus
- Lesions are common in the immunocompromised (i.e. recent organ transplant or HIV patients)

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Herpes Simplex Virus Keratitis

- **<u>Epithelial Keratitis:</u>**
  - Symptoms:
    - Ocular irritation, redness, photophobia, watering, blurred vision
  - Signs:
    - Swollen opaque epithelial cells arranged in a course punctate or stellate pattern
    - Central desquamation results in a dendrite***
      1. Central ulceration
      2. Terminal end bulbs
    - ***Corneal sensation is reduced***

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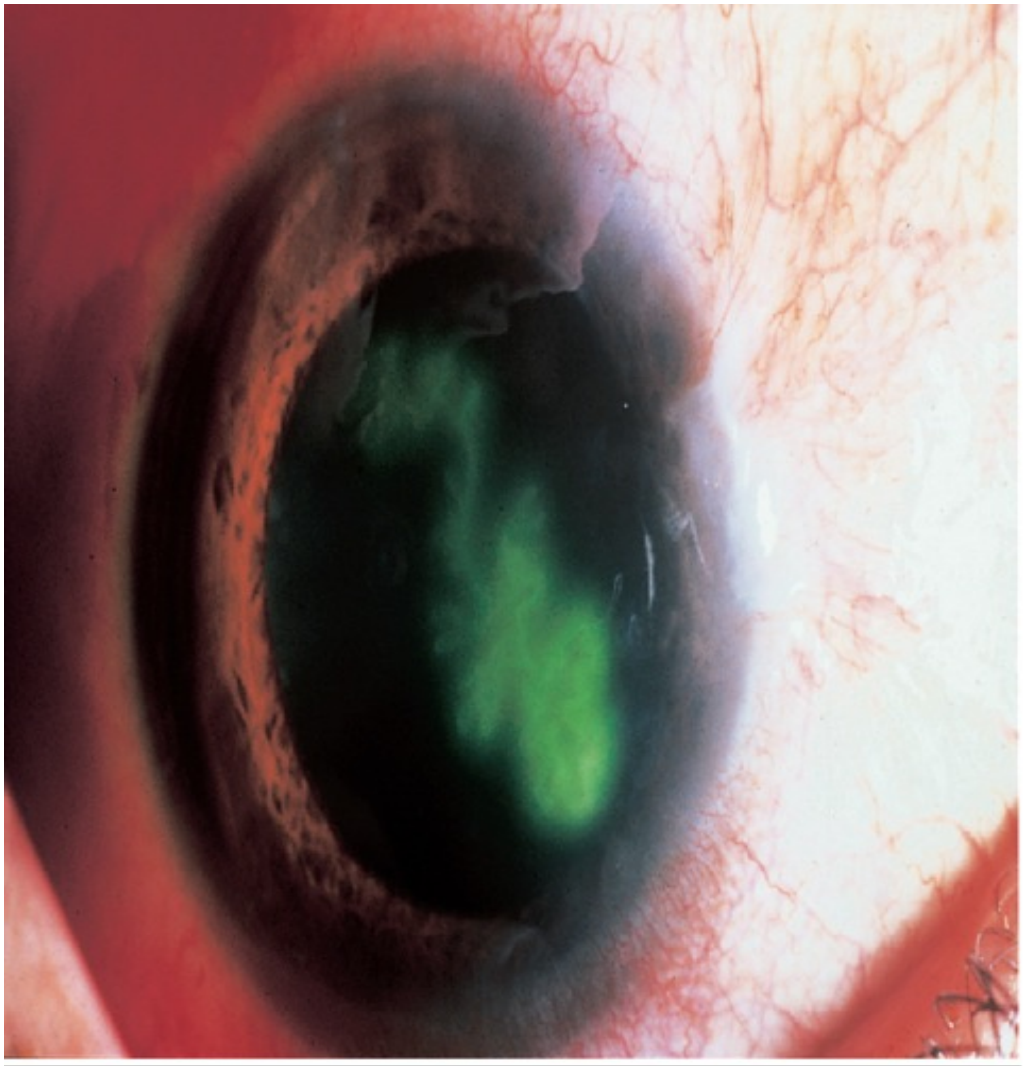
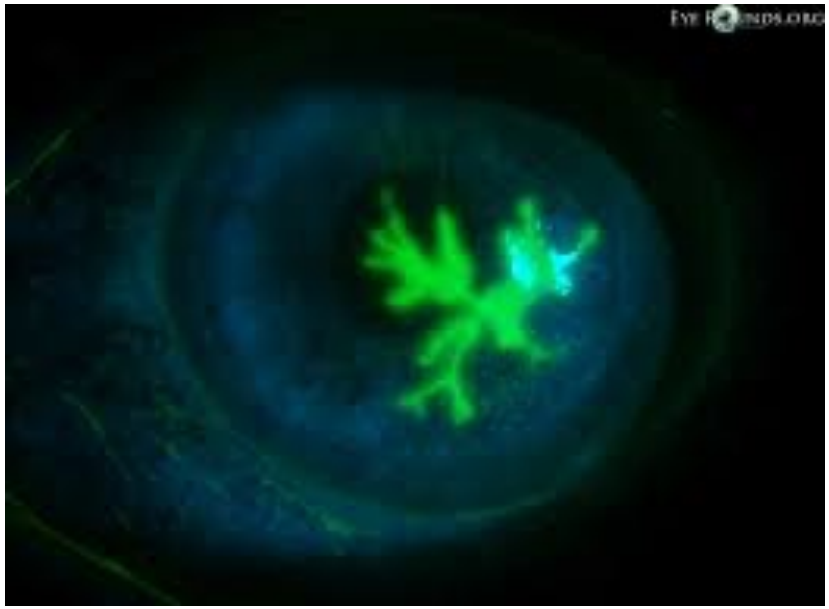
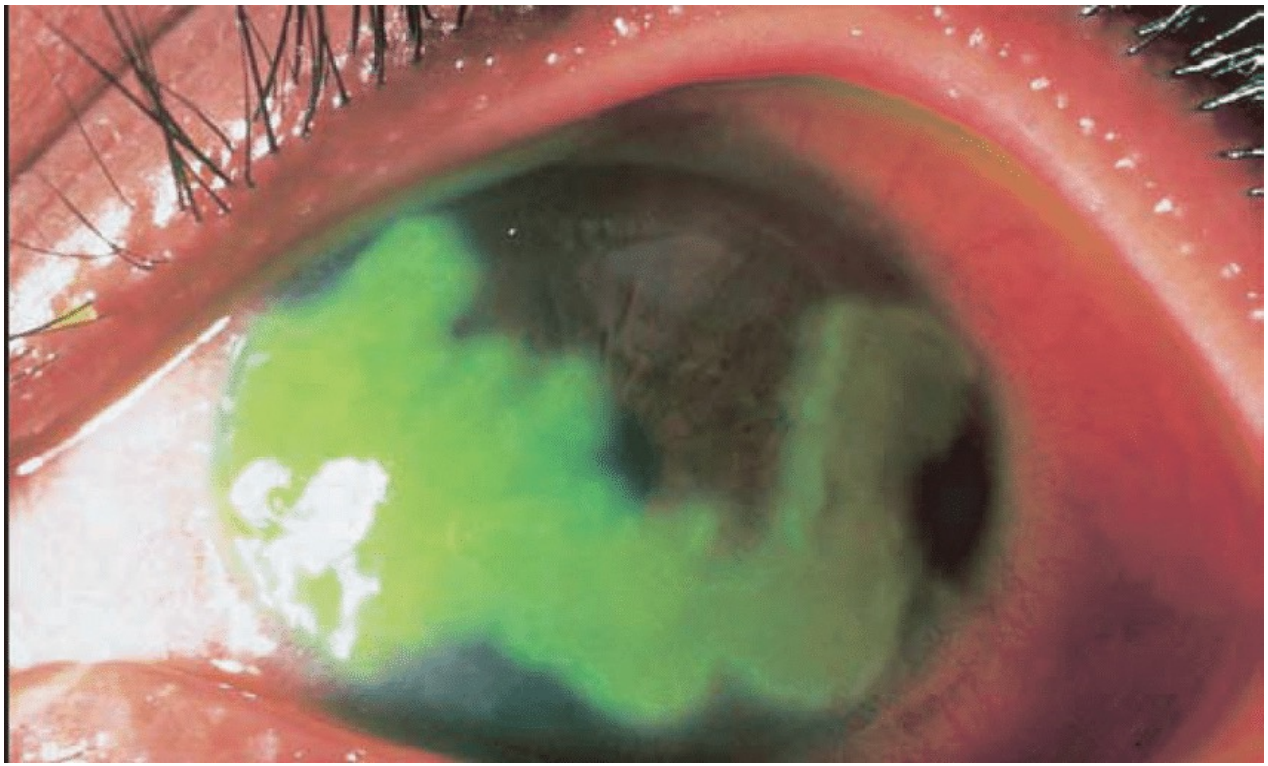
Dendritic Ulcers





HSV Geographic Ulcer



https://www.researchgate.net/figure/Geographic-corneal-ulcer-caused-by-herpes-simplex-virus-keratitis_fig1_26730111

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Pediatric HSV Keratitis

- pediatric herpes simplex keratitis has an 80% risk of recurrence, a 75% risk of stromal disease, and a 30% rate of misdiagnosis
- 80% of children with herpes simplex keratitis develop scarring, mostly in the central cornea
  - results in the development of astigmatism
  - 25% of children have more than 2 D of astigmatism, most of which is irregular
- consider pediatric HSV when a patient has unilateral recurrent disease in the anterior segment

Herpes Simplex Virus Keratitis Management

- Topical:
  - Viroptic (trifluridine) q 2h until epi healed then taper down for 10-14 days.
    - Viroptic is toxic to the cornea.
  - Zirgan (ganciclovir) available, use 5 times a day until epi healed then 3 times for a week (US only)

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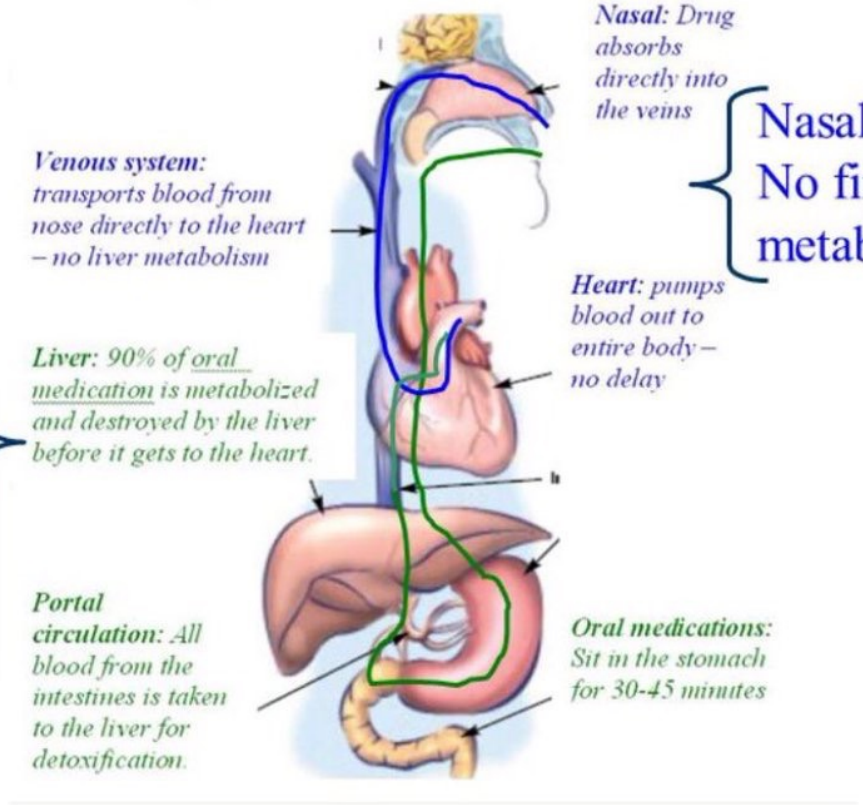
First pass metabolism



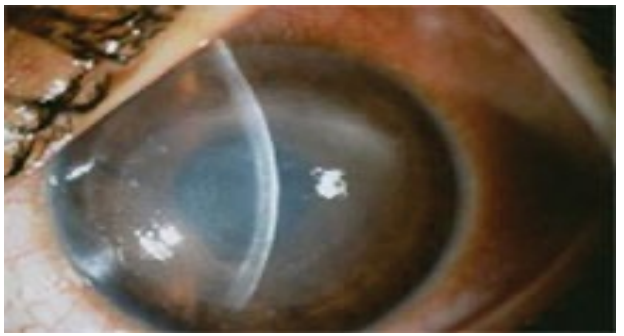
Nasal Mucosa: No first pass metabolism

Gut mucosa: Subject to first pass metabolism

Anti-Viral Medication

Drug	Mechanism of Action	Bioavailability	Dosing	Side Effects
Acyclovir	Acyclovir interferes with DNA synthesis inhibiting viral replication	10-30% gets absorbed Short ½ life *Metabolized in kidneys	Simplex: 400 mg 5x/day Zoster: 800 mg 5x/day	Overall very safe Nausea, vomiting, headaches, dizziness, confusion
Valacyclovir	Acyclovir pro-drug Equivalent to acyclovir but better for pain management	95% converted to acyclovir* Better bioavailability and longer 1/2 life	Simplex: 500 mg tid Zoster: 1 g tid	Same as acyclovir
Famciclovir	Inhibits DNA chain elongation It is metabolized to penciclovir where it is active 10-20x as long as acyclovir	Superior to acyclovir*	Simplex: 250 mgTID Zoster: 500 mg TID	Same as acyclovir

HSV Stromal Disease



- HSV Stromal disease is an immune-mediated disease
  - Stromal involvement is rarely an initial ocular finding, accounting for fewer than 2% of initial presentations but for 20 – 60% of recurrent corneal disease
- Increased risk of scarring and high risk of poor visual prognosis
- Requires corticosteroids (HEDS: corticosteroid reduced risk of progression by 68%)
  - Without epithelial defect: corticosteroids and prophylactic anti-viral dosage
  - With epithelial defect: active infection anti-viral dosage with judicious corticosteroids

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How much to dose steroid?

- HEDS used QID of *prednisolone phosphate*
- Current Recommendations:
  - Mod – severe (especially with neo): 1% Prednisolone or Lotemax QID to 6x/day
  - Want the lowest dose needed to control the inflammation
  - AAO EBM Treatment Guideline 2014
    - Topical steroid for 10 weeks (this is based on HEDS results) with oral antiviral

HSV Epithelial Keratitis

- Treatment Regimen:
    - Zirgan (ganciclovir) available, use 5 times a day until epi healed then 3 times for a week OR
    - Oral Valtrex 500 mg 3x/day for 7-10 days
  - Artificial tears

  - L-Lysine 2 grams daily?
    - Proven to “slow down” and retard the growth of the herpes virus and inhibit viral replication
  - Debride the ulcer?
    - Prior to topical antiviral therapy debridement was treatment of choice
    - Generally try to avoid use of sharp instruments and use of cotton swab and anesthetic

- RTC 1 day, 4 days, 7 days

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Herpes Simplex Keratitis

- Prophylactic Treatment:
  - Reduces the rate of recurrence of epithelial and stromal keratitis by ≈ 50%
    - Acyclovir 400 mg BID
    - Valtrex 500 mg QD
    - Famvir 250 mg QD
    - L-lysine 1 gram/day:
      - Proven to “slow down” and retard the growth of the herpes virus and inhibit viral replication
    - Frequent debilitating recurrences, bilateral involvement, or HSV infection in a monocular patient

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Epithelial (Anterior) Basement Membrane Dystrophy (EBMD or ABMD)

- Primary features of this "dystrophy" are:
  - abnormal corneal epithelial regeneration and maturation,
  - abnormal basement membrane
- Often considered the most common dystrophy, but may actually be an age-related degeneration.
  - large number of patients with this condition,
  - increasing prevalence with increasing age, and
  - its late onset support a degeneration vs. dystrophy.

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Epithelial (Anterior) Basement Membrane Dystrophy (EBMD or ABMD)

- Not all patients are symptomatic
- Most common symptom is mild FB sensation which is worse in dry weather, wind and air conditioning
- Blurred vision from irregular astigmatism or rapid TBUT
- Pain is usually secondary to a RCE (recurrent corneal erosion) in apprx 10%

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Epithelial (Anterior) Basement Membrane Dystrophy (EBMD or ABMD)

- Easy to overlook:
  - typically bilateral though often asymmetric,
  - females>males,
  - often first diagnosed b/w ages of 40-70

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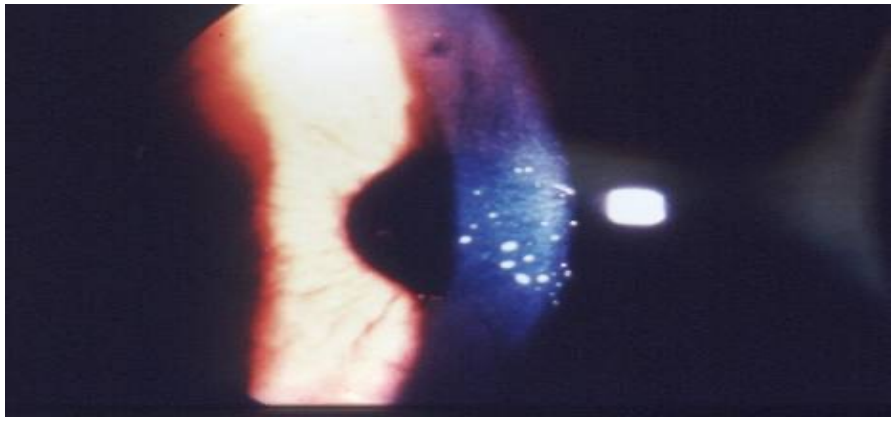
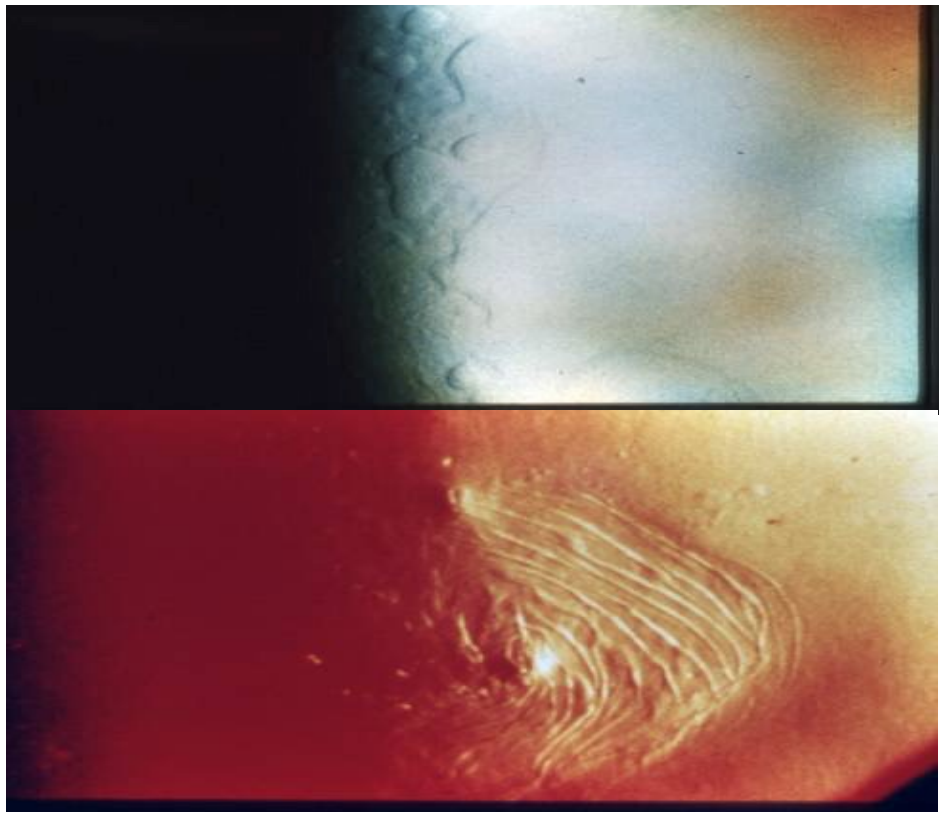
Epithelial (Anterior) Basement Membrane Dystrophy (EBMD or ABMD)

- Most common findings are:
  - chalky patches,
  - intraepithelial microcysts, and
  - fine lines (or any combination) in the central 2/3rd of cornea

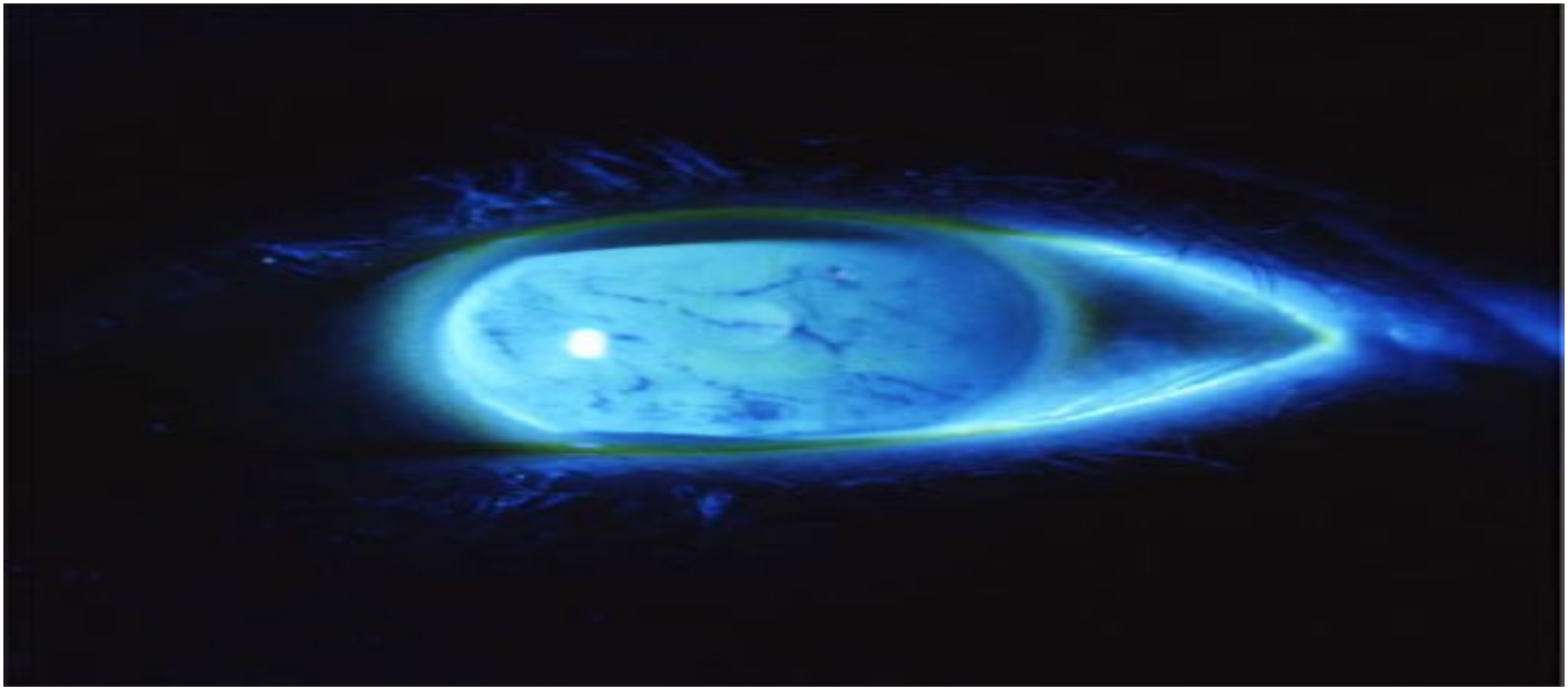


Epithelial (Anterior) Basement Membrane Dystrophy (EBMD or ABMD)

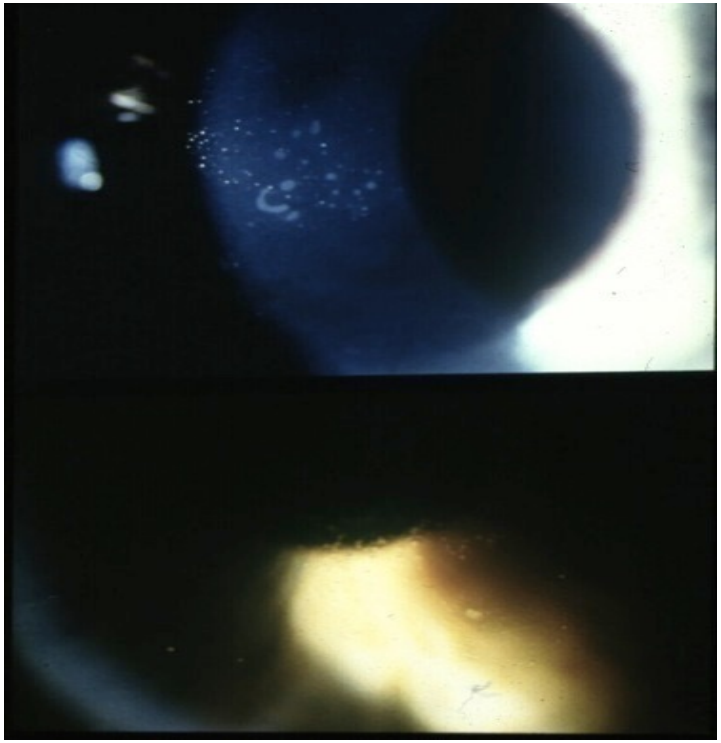
- Often referred to as:
  - maps,
  - dots or
  - fingerprints



EBMD-Negative Staining

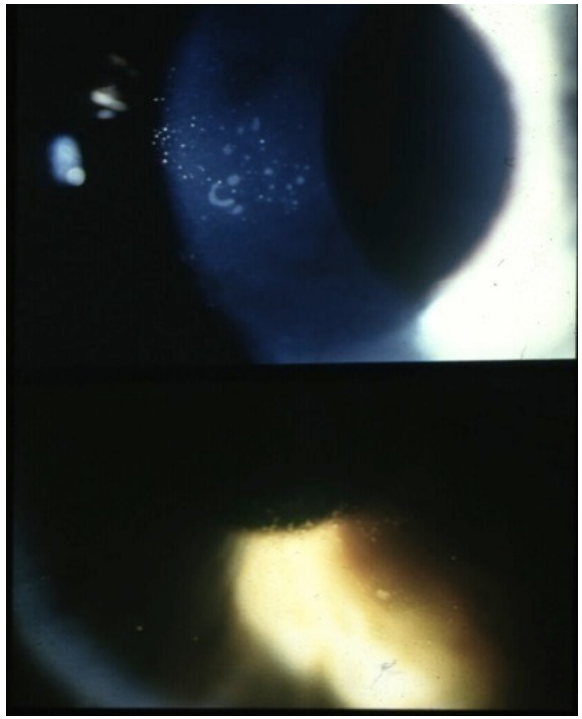


Epithelial (Anterior) Basement Membrane Dystrophy (EBMD or ABMD): Treatment



- Typically directed towards preventing RCE
- If RCE's develop:
  - awake with painful eye that improves as day wears on
  - chalky patches/dots in lower 2/3rd of cornea

Acute Treatment of RCE: Dr Greenwood, MD



- use of hyperosmotic ointment at bedtime
- bandage contact lens
- Frequent lubrication
- Plugs
- Topical meds
- No ceiling fans
- Nighttime ointment
- PTK

Recurrent Corneal Erosion: Treatment

- If severe enough to cause vision loss or repeated episodes:
    - oral doxycycline with/without topical corticosteroid
        - Doxy 50 mg bid and FML tid for 4-8 weeks
        - both meds inhibit key metalloproteinases important in disease pathogenesis
    - debridement,
    - Debridement + diamond burr polishing
    - stromal puncture (not commonly done anymore)
    - PTK
    - Latest development: amniotic membrane transplant e.g. Prokera typically after debridement

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CORNEAL DEBRIDEMENT

- Soften epithelium
- 1-2 gtt topical anesthetic q 15-30 seconds for 2-3 minutes
- Use cotton swab, spatula, spud or jewelers forceps
- Remove flaps by pulling edges toward center
- Don't pull directly up or out
- Remove flaps down to tight, firm edges.
- Tx abrasion (>50-100%)
  - Recurrence Rate 18%

Pictured: Kimura Platinum Spatula

Diamond Burr Polishing

- Removes abnormal basement membrane
- Provides smooth surface for cells to grow

Vo, et al (2014): epithelial debridement with diamond burr polishing was 95% effective after single treatment in preventing recurrence for an average of 32 months follow up time

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Academic Emergency Medicine
Official Journal of the Society for Academic Emergency Medicine

ORIGINAL CONTRIBUTION

Topical Tetracaine Used for 24 Hours Is Safe and Rated Highly Effective by Patients for the Treatment of Pain Caused by Corneal Abrasions: A Double-blind, Randomized Clinical Trial

Neil Waldman, MD, FACEM, Ian K. Densie, and Peter Herbison, DSc

Abstract

Objectives: The objective of this study was to test the hypothesis that topical tetracaine would be safe to use for 24 hours and would not affect corneal healing, that patients would experience more pain relief, and that patients would perceive tetracaine to be more effective than saline eye drops for the treatment of pain caused by corneal abrasions.

Methods: The study was a 12-month, prospective, double-blind, randomized trial of tetracaine versus saline set in the emergency department (ED) of a regional tertiary care teaching hospital. A total of 116 patients presenting with uncomplicated corneal abrasions were included in this study. The intervention was either undiluted, preservative-free, topical tetracaine hydrochloride 1% or saline, applied up to every 30 minutes while awake for 24 hours. Main safety outcome measures were repeat ED examinations at 48 hours with fluorescein staining and slit-lamp examination, 1-week and 1-month telephone interviews with additional examinations as needed, and monitoring of charts for complications. Secondary outcome measures were 100-mm visual analogue scale (VAS) pain scores recorded every 2 hours while awake for 48 hours and patient-perceived overall effectiveness using a numeric rating scale (NRS) of 0 to 10 obtained during telephone interviews.

Results: At least one follow-up encounter was completed on each of the 116 patients. No complications specifically attributed to topical anesthetic use occurred in the 59 patients in the tetracaine group, and the binomial probability confidence interval (CI) of this occurring is 0 to 6.1. There was no significant difference in corneal healing as measured by the percentage of patients with persistent fluorescein uptake at 48 hours between the two groups (23.9% vs. 21.3%, difference = 2.6%, 95% CI = –14% to 20%, $p = 0.761$) or persistent symptoms at 48 hours (21.7% vs. 21.3%, difference = 0.4%, 95% CI = –16% to 17%, $p = 0.957$). There was no clinical difference in VAS pain scores between the groups. Patients in the tetracaine group rated the study drugs' overall effectiveness significantly higher on the NRS (7.7 vs. 3.9) compared to patients in the saline group (difference = 3.9, 95% CI = 2.4 to 5.3, $p < 0.0005$).

Conclusions: Topical tetracaine used for 24 hours is safe, and while there was no significant difference in patient VAS pain ratings over time, patient surveys on overall effectiveness showed that patients perceived tetracaine to be significantly more effective than saline.

ACADEMIC EMERGENCY MEDICINE 2014;21:374–382

Systemic NSAID's

- NSAID's are the drug of choice for treating mild to moderate ocular pain.
  - Very beneficial for treating systemic inflammation as well.
- All NSAID's are rapidly absorbed from the GI tract, highly bound in the plasma, and capable of crossing the blood-brain barrier.
- Exhibit a "ceiling effect" – there is a dosage beyond which no further analgesia occurs.
  - Produce no tolerance or dependence, increasing their safety profile.
- Variability exists in patient responses to NSAID's
  - No definitive recommendation on treatment can be given.
    - If one NSAID does not work – TRY ANOTHER.

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OTC NSAIDs

- Ibuprofen:
  - Adult analgesic dose: 200-400mg q4hours
  - Maximum Dosage: 1200 mg/day OTC for pain (approved for 3200 mg/day in arthritis treatment)
  - OTC: 200 mg tabs (US) 400 mg and 600 mg (Canada)
  - Most renal toxic of all the NSAID's
- Naproxen sodium:
  - OTC: 220 mg (Aleve^{R})
  - OTC: 1 tablet every 8-12 hours (can use two tablets on first dose)

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Prescription NSAIDs

- Indomethacin:
  - Adult Dosage: 25-50 mg TID
- Mainly used as a short-term anti-inflammatory especially for conditions that do not respond to less toxic NSAIDS.
  - Indomethacin has a very high level of intolerance compared to other NSAID's.
  - Oral NSAID most widely used in Tx of ocular inflammation.
- Celebrex:
- It is approved for the treatment of osteoarthritis and rheumatoid arthritis.
  - Dosage: 100 mg BID or 200 mg daily

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Contraindications to NSAIDs

- Avoid in:
  - Pregnancy (especially the late trimesters)
  - Active Peptic Ulcer Disease
  - Cross Sensitivity to ASA
  - Previous Hypersensitivity to NSAIDs
  - Chronic Renal Insufficiency

- At Risk Patients Include:
  - Dehydration
  - HTN or CHF
    - Use of ACE Inhibitors, diuretics and B-blockers
    - Higher doses of NSAIDs and chronic therapy extending beyond a week will be more likely to increase BP
  - Advanced Age

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NSAID-related ulcers

- COX-2 inhibitors such as celecoxib (Celebrex) are less likely to cause ulcers than aspirin
- Proton pump inhibitors (e.g. Losec^{R} Prevacid® or Prilosec ®) help to offset the risk of NSAID-related stomach ulcers
  - patients should be treated with concomitant proton pump inhibitors once daily, which results in ulcer healing rates of approximately 80% at 8 weeks in patients continuing to take NSAIDs

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Acetaminophen

- Mechanism of Action is not well understood.
  - Possibly some CNS component
  - Very weak inhibitor of prostaglandin synthesis

- One of the most commonly used analgesics for mild to moderate pain.
  - Equal analgesic properties to ASA unless associated with inflammation, where it is less effective.

Take home: Good for pain; Good for fever;
No effect on inflammation

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Dangers of Acetaminophen

- Acetaminophen overdose is the leading cause of liver failure in the U.S.
  - It sends 56,000 people to the emergency room annually and causes approximately 400 deaths yearly.

- Acetaminophen is used in so many products, people are often unaware that they are taking it, leading to more overdoses.
  - Combined with agents to get wide range of symptom coverage.
    - Antihistamines such as diphenhydramine – Tylenol PM
    - Diuretics such as Pyrilamine maleate – Midol Complete
    - Cough Suppressants such as Dextromethorphan - Nyquil

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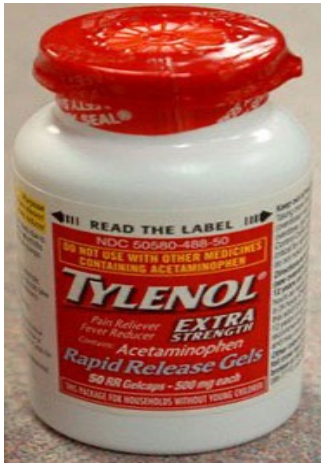
Consider Combining APAP with NSAID's for Mild to Moderate Pain Relief

1:00 pm: Two 325mg acetaminophen

3:00 pm: Two 200mg Ibuprofen

5:00 pm: Two 325mg acetaminophen

7:00 pm: Two 200mg Ibuprofen



Alternated every 2 hours while awake

- Each medication is q 4 hours.

Oral Analgesics: Guidelines

- Never exceed maximum recommended dosages:
  - ASA: 8 grams/day
  - Acetaminophen: 4 grams/day (newer data suggest should be closer to 3-3.2 grams/day)
  - Ibuprofen: 2400 mg/day OTC and up to 3200 mg/day prescription (for RA)
  - Naproxen: 1250/day
  - Naproxen sodium: 1375/day
  - Codeine: 360 mg/day

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Gabapentin (Neurontin^{R})

- Classified as an anticonvulsant drug
- Additionally, used in the treatment of patients with chronic pain
- Gabapentin has primarily been studied and found effective for the treatment of postherpetic neuralgia and painful diabetic neuropathy; evidence for efficacy in other types of neuropathic pain is limited
  - The transition of gabapentinoids into a first-line pain medication is in part due to an intentional marketing strategy by the pharmaceutical industry without adequate studies.

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Gabapentin (Neurontin^{R})

- Treatment with gabapentin should be initiated at a low dose with gradual increases until pain relief or dose-limiting adverse effects are achieved.
- Dosage:
  - Day 1 single 300 mg dose
  - Day 2 600 mg dose
  - Day 3 900 mg dose
  - Can be tittered up all the way to 1800 mg/day

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Gabapentin (Neurontin^{R})

- Gabapentinoids have significant risks despite their reputation as safe drugs.
  - Central nervous system effects such as sedation, dizziness, gait instability, and feeling intoxicated are quite common; as many as one in three patients taking therapeutic doses will experience dizziness or somnolence

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Opioids Information

- Drug of first choice for the treatment of **severe** acute pain.
- Block the body's natural protective mechanism for protecting areas in pain – thus never prescribe unless you know the direct cause of the pain.

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Opioids vs 1000mg Acetaminophen and 400 mg Ibuprofen

- **Ibuprofen Plus Acetaminophen Equals Opioid Plus Acetaminophen for Acute Severe Extremity Pain.** **Am Fam Physician. 2018;97(5):348**

- Effect of a Single Dose of Oral Opioid and Nonopioid Analgesics on Acute Extremity Pain in the Emergency Department: A Randomized Clinical Trial. JAMA. 2017;318(17):1661-1667.
  - no statistically significant or clinically important differences in pain reduction at 2 hours among single-dose treatment with ibuprofen and acetaminophen or with 3 different opioid and acetaminophen combination analgesics

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SIGNS OF AN OPIOID OVERDOSE. B.L.U.E.

BREATHING — Breathing during an overdose is shallow, gurgling, erratic, or completely absent.

LIPS — Lips and fingertips are blue, due to decreased oxygen throughout the body.

UNRESPONSIVE — The victim will not respond to verbal or physical stimulation.

EYES — Pupils are pinpoint, as the opioids constrict the pupils to an unusally small size.

Opioid Overdose: Management
Naloxone (Narcan^{R})

- Opioid antagonist
- Available routes of administration include IV (preferred), IM, SubQ, and intranasal
- For the initial treatment of an opioid-associated life-threatening emergency, the American Heart Association recommends, after initiation of CPR, the use of intranasal or IM naloxone with a repeat dose as needed.
- If there is an initial patient response (ie, purposeful movement, regular breathing, moan or other response) but the patient then stops responding, begin CPR and repeat naloxone dose.
- If no initial response, continue CPR and use AED as appropriate

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Opioid Overdose: Management
Naloxone (Narcan^{R})

- 4 mg (contents of 1 nasal spray) as a single dose in one nostril; may repeat every 2 to 3 minutes in alternating nostrils until medical assistance becomes available

Opioid Side Effects

- Side Effects are very hard to predict because opioids can cause CNS depression or stimulation.
- CNS Side Effects
  - Dizziness, lightheadedness, sedation, and drowsiness are the most common.
  - Mood elevation (euphoria) and disorientation can occur in some patients.
  - Visual symptoms such as blurry vision, miosis, and diplopia can occur.
- Constipation
  - Opioids inhibit intestinal trace motility.
- Respiratory Depression
  - Most serious side effect of the opioids

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Opioids: Codeine

Note: Tylenol 3 and 4 no longer available as Brand name

- Analgesic effect occurs within 20 minutes of ingestion and reaches a maximum at 1 – 2 hours.
  - Ceiling effect occurs.
- Usually administered in combination with acetaminophen .
  - Tylenol 1 (222): codeine 8 mg, 300 mg acetaminophen and 15 mg caffeine (Canada)
  - Tylenol 3 = Codeine 30 mg and Acetaminophen 300 mg
    - Dosage: 1-2 tablets every 4 hours.
  - Tylenol 4 = Codeine 60 mg and Acetamenophin 300 mg
    - Dosage: 1 tablet every 4 – 6 hours

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Codeine

- Also available as generic with 15, 30, or 60 mg of Codeine with 300 mg of Acet. or elixer of 12 mg codeine + 120 mg Acet. per 5 mL.
  - Elixer can be used in children for pain management if >3 years.
- Serious side effects:
  - Respiratory depression: caution in patients with asthma, COPD
  - Caution in patients taking sedative medications (Xanax/Valium), muscle relaxants or other pain medications
  - No alcohol consumption

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Opioids: Hydrocodone and Oxycodone

- Hydroxycodone:
  - Approximately 6X more potent than codeine.
  - Milder Side Effects than Codeine: Less constipation and sedation.
  - Clinically believed to cause more euphoria than codeine, but this is not backed by clinical studies.
- Oxycodone:
  - Approximately 10-12X more potent than codeine
  - Lower level of side effects in comparison to morphine, but high level of euphoria produced, thus higher level of abuse risk.

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Tramadol

- Central acting narcotic
  - Synthetic analogue of codeine.
  - Binds to mu receptors and inhibits norepinephrine and serotonin reuptake.
  - Potential for abuse is very low, but has occurred.

- Available as 50 mg tablets.

- Dosage: 50 – 100 mg q4 – 6 hours.
  - Analgesia occurs after 1 hour.
  - Maximum dose: 400 mg/day

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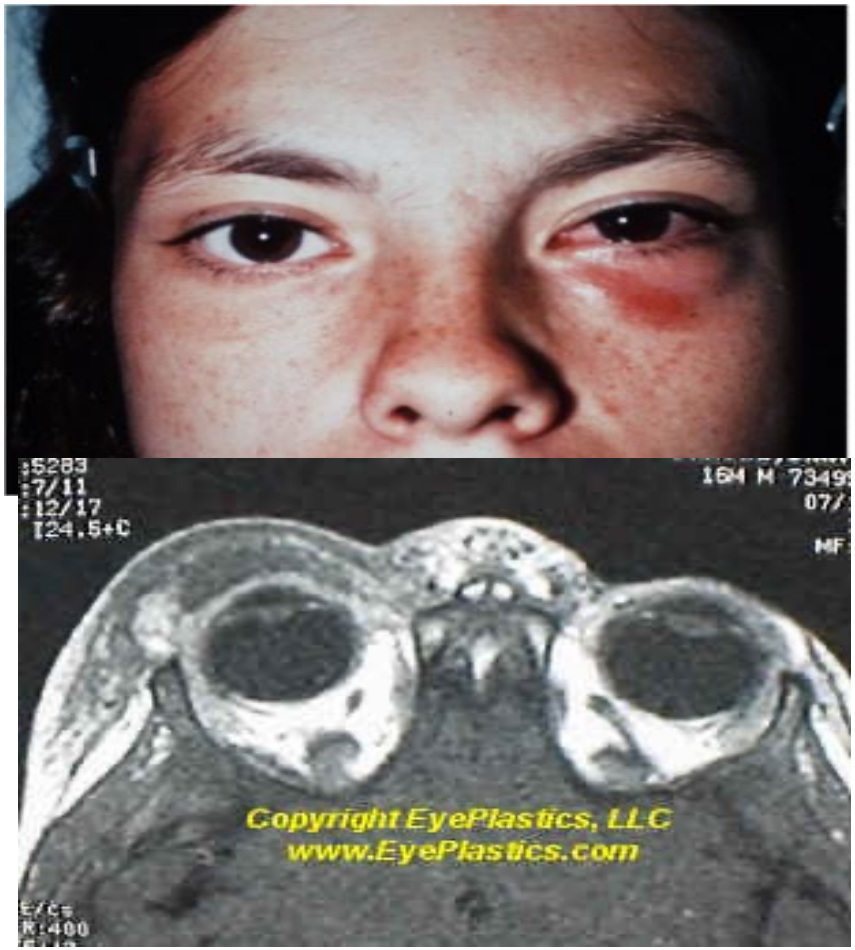
Preseptal Cellulitis

- Infection and inflammation located anterior to the orbital septum and limited to the superficial periorbital tissues and eyelids.
- Usually follows sinus infection or internal hordeolum (possibly trauma)
- Eyelid swelling, redness, ptosis, pain and low grade fever.



Differentiating Orbital vs. Preseptal

FINDING	ORBITAL	PRESEPTAL
Visual Acuity	Decreased	Normal
Proptosis	Marked	Absent
Chemosis and Hyperemia	Marked	Rare/Mild
Pupils	RAPD	Normal
Pain and Motility	Restricted and Painful	Normal
IOP		Normal
Temperature	102 - 104	Normal/mild elevation
HA and Assoc. Symptoms	Common	Absent

Treatment: Orals for Preseptal, Often IV for Orbital

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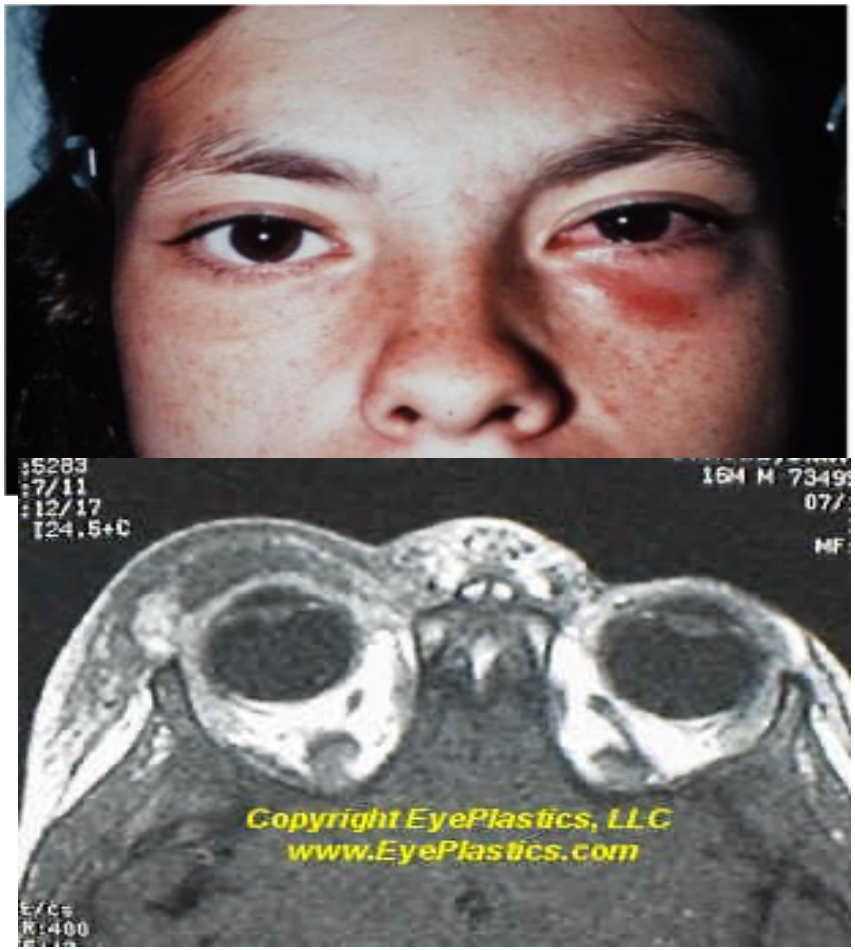
Preseptal Cellulitis

- Tx:
  - ***Augmentin (Clavulin) 500 mg TID or 875 mg BID for 5-7 days***
  - ***Keflex 500 mg QID 5-7 days***
  - or if moderate to severe IV Fortaz (ceftazidime) 1-2 g q8h.
  - If MRSA possible, consider Bactrim/Septra



Antibiotic Resistance

- Microorganism that was originally in the spectrum of activity is no longer susceptible to the drug.

- Mechanisms of Resistance Include:
  - Producing an enzyme capable of destroying or inactivating the antibiotic.
  - Altering the target site receptor for the antibiotic so as to reduce or block its binding.
  - Preventing the entry of the antibiotic into the bacterial cell or actively transporting the antibiotic out.

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Avoiding Resistance

- Bacterial resistance is a natural result of mutation.

- Antibiotics cause a faster rate of selection against these resistant bacteria if not prescribed correctly.
  - Avoid prescribing for non-bacterial infections.
  - Avoid sublethal doses (attack to kill all).
  - Avoid intermittent use.
  - Always complete the full dosage for an appropriate length of time.
  - NEVER TAPER AN ANTIBIOTIC below recommended dosing schedule!

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Preventing Resistance

- **The IDSA suggests five to seven days is long enough to treat a bacterial infection** without encouraging resistance in adults, though children should still get the longer course
  - this is different than previous guidelines of treating infections from 10-14 days.

Antibiotic Associated Diarrhea (AAD)

- The most common side effects of antibiotics are gastro-intestinal, such as nausea and diarrhea
- AAD arises when the antibiotic disrupts the ecology of the intestinal microbiota, by altering the diversity and numbers of bacteria in the gut.
- Diarrhea is most frequently associated with the use of broad-spectrum antibiotics (e.g amoxicillin)

Agamennone, V., Krul, C.A.M., Rijkers, G. et al. A practical guide for probiotics applied to the case of antibiotic-associated diarrhea in The Netherlands. BMC Gastroenterol 18, 103 (2018

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AAD and Probiotics

- The core benefit of probiotics is exercised by contributing to the maintenance of a balanced microbiota and therefore by creating a favorable gut environment
- The efficacy of probiotics in preventing AAD depends on the dose.
  - A daily intake of at least 5 × 10^9 CFU is associated with significant efficacy for AAD and it has been shown that higher probiotic dose is linked to greater efficacy
  - Example: The probiotic content of yogurt products can range from 90 to 500 billion CFU per serving

Agamennone, V., Krul, C.A.M., Rijkers, G. et al. A practical guide for probiotics applied to the case of antibiotic-associated diarrhea in The Netherlands. BMC Gastroenterol 18, 103 (2018

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5 Facts About Penicillin Allergy

- Approximately 10% of all U.S. patients report having an allergic reaction to a penicillin class antibiotic in their past.
  - When evaluated, fewer than 1% of the population are truly allergic to penicillins.
- Approximately 80% of patients with IgE-mediated penicillin allergy lose their sensitivity after 10 years.
- Broad-spectrum antibiotics are often used as an alternative to penicillins. The use of broad-spectrum antibiotics in patients labeled "penicillin-allergic" is associated with higher healthcare costs, increased risk for antibiotic resistance, and suboptimal antibiotic therapy.
- Correctly identifying those who are not truly penicillin-allergic can decrease unnecessary use of broad-spectrum antibiotics.

https://www.cdc.gov/antibiotic-use/community/pdfs/penicillin-factsheet.pdf

Penicillins: Augmentin (Clavulin)

- **Augmentin is amoxicillin with potassium clavulanate (clavulanic acid 125 mg).**
- Clavulanate is a B-Lactamase inhibitor which reduces a bacteria's ability to negate the effect of the amoxicillin by inactivating penicillinase (enzyme that inactivates the antibiotic affect).
  - Dicloxacillin can also be used in infections due to penicillinase-producing staph.

Penicillins: Augmentin

- **Augmentin is very effective for skin and skin structure infections** such as:
    - dacryocystitis,
    - internal hordeola,
    - pre-septal cellulitis.
  - Treatment of:
    - otitis media,
    - sinusitis,
    - lower respiratory and urinary infections.
  - Given prophylactically to dental surgery patients.

Penicillins: Augmentin

- It has ***low***:
  - GI upset,
  - allergic reaction and anaphylaxis.
- Serious complications include:
  - anemia,
  - pseudomembranous colitis and
  - Stevens-Johnson syndrome.

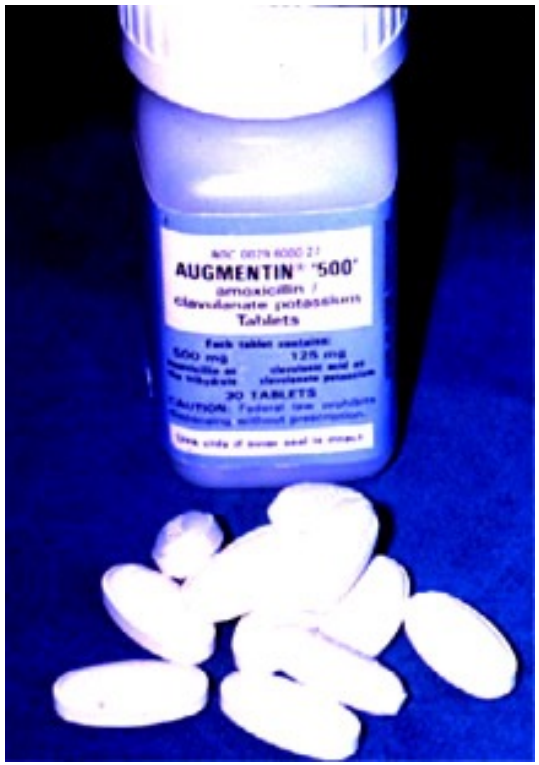
Penicillins: Augmentin.

Adults:

- **250 TID, 500 mg tab BID-TID depending on what you are treating** (also available in chewable tablets and suspension)
- or **875 mg q 12hr (bid)**
- 1000 mg XR: q12 hr and not for use in children <16

Peds: <3 mos 30mg/kg/day divided q12hrs using suspension

- >3 mos 45-90mg/kg/day divided q12hrs (otitis media 90mg for 10 days)

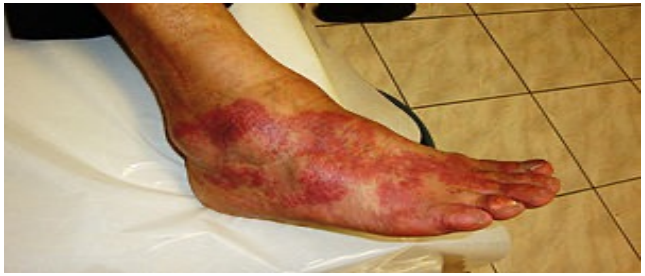


Cephalosporins

- Closely related structurally and functionally to the penicillins,
  - **have the same mode of action,**
  - affected by the same resistance mechanisms.
  - tend to be more resistant to B-lactamases.
- classified as 1st, 2nd, 3rd, 4th and now 5th generation based largely on their bacterial susceptibility patterns and resistance to B-lactamases.
- Typically administered IV or IM, **poor oral absorption**.

Side Effects and Contraindications

- Hypersensitivity Reactions are common.
  - Risk of cross sensitivity with PCN's is higher for 1st generation, but often overestimated for later medications.
  - Used to state the cross sensitivity was ~10%, but now believed to be closer to 3%.



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Cephalosporins

- 1st generation: **cefadroxil (Duricef)**, **cefazolin (Ancef)**, **cephalexin (Keflex)**, and cephalothin
- 2nd generations: **cefaclor** (Ceclor), cefprozil, **cefuroxime (Zinacef)**, cefotetan, cefoxitin
- 3rd generation: , cefixime, **cefotaxime (Claforan)**, **ceftazidime (Fortaz)**, ceftibuten, ceftizoxime, **ceftriaxone (Rocephin IM/IV)**.
- 4th generation: cefepime
- 5th generation: Ceftaroline is a novel **fifth-generation cephalosporin**, which exhibits broad-spectrum activity against Gram-positive bacteria, including MRSA and extensively-resistant strains, such as vancomycin-intermediate S. aureus (VISA), heteroresistant VISA (hVISA), and vancomycin-resistant S. aureus (VRSA)
- *Keflex, Ceclor are* (all orally administered) are effective against most gram-positive pathogens and especially good for skin and soft tissue infections.

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Cephalosporins

- **Keflex (cephalexin):**
  - treatment of respiratory, GI, skin and skin structure, and bone infections as well as otitis media
  - Adults: 250-1000 mg every 6 hours
    - **- typical dosing 500 every 6 hours**
  - Children: 25-100 mg/kg/day divided 6-8 hours

Cephalosporins

- Cefaclor (Ceclor) (2nd generation):
  - Immediate-release: 250 to 500 mg every 8 hours
  - Extended-release: 500 mg every 12 hours

Note: An extended-release tablet dose of 500 mg twice daily is clinically equivalent to an immediate-release capsule dose of 250 mg 3 times daily; an extended-release tablet dose of 500 mg twice daily is **NOT** clinically equivalent to 500 mg 3 times daily of other cefaclor formulations.

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MRSA

- Healthcare-associated methicillin-resistant *Staphylococcus aureus* (HA-MRSA) is associated with severe, invasive disease in hospitalized patients
- Community-associated methicillin-resistant *S. aureus* (CA-MRSA) is most often associated with skin and soft tissue infections in young, healthy individuals with no recent healthcare exposure

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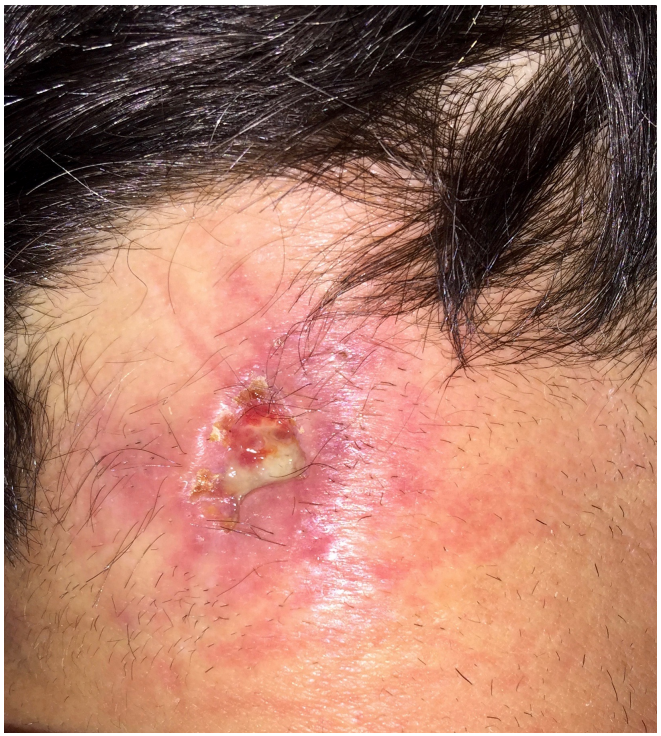
Consider Covering for MRSA

1. Hx of non-response to amoxicillin or Augmentin
2. Hx of previous MRSA infections
3. Infection did not start at lid margin like a regular hordeolum but more superior like near the eyebrow area
4. Hx of recent incarceration or hospitalization or in nursing home
5. health care worker
6. pain outside clinical presentation



Co-Trimoxazole (Bactrim)

- Combination of trimethoprim and sulfamethoxazole
  - shows greater antimicrobial activity than equivalent quantities of either drug alone.
- Has broader spectrum of action than the sulfa's and is effective in treating:
  - UTIs and respiratory tract infections
  - often considered for treatment of MRSA skin infections

Co-Trimoxazole (Bactrim)

- Available:
  - **Bactrim tablets**:
    - contains 80 mg trimethoprim and 400 mg sulfamethoxazole
    - dosing **2 tablets every 12 hours**
  - **Bactrim DS (Double Strength)**
    - contains 160 mg trimethoprim and 800 mg sulfamethoxazole
    - Dosing **1 tablet every 12 hours**

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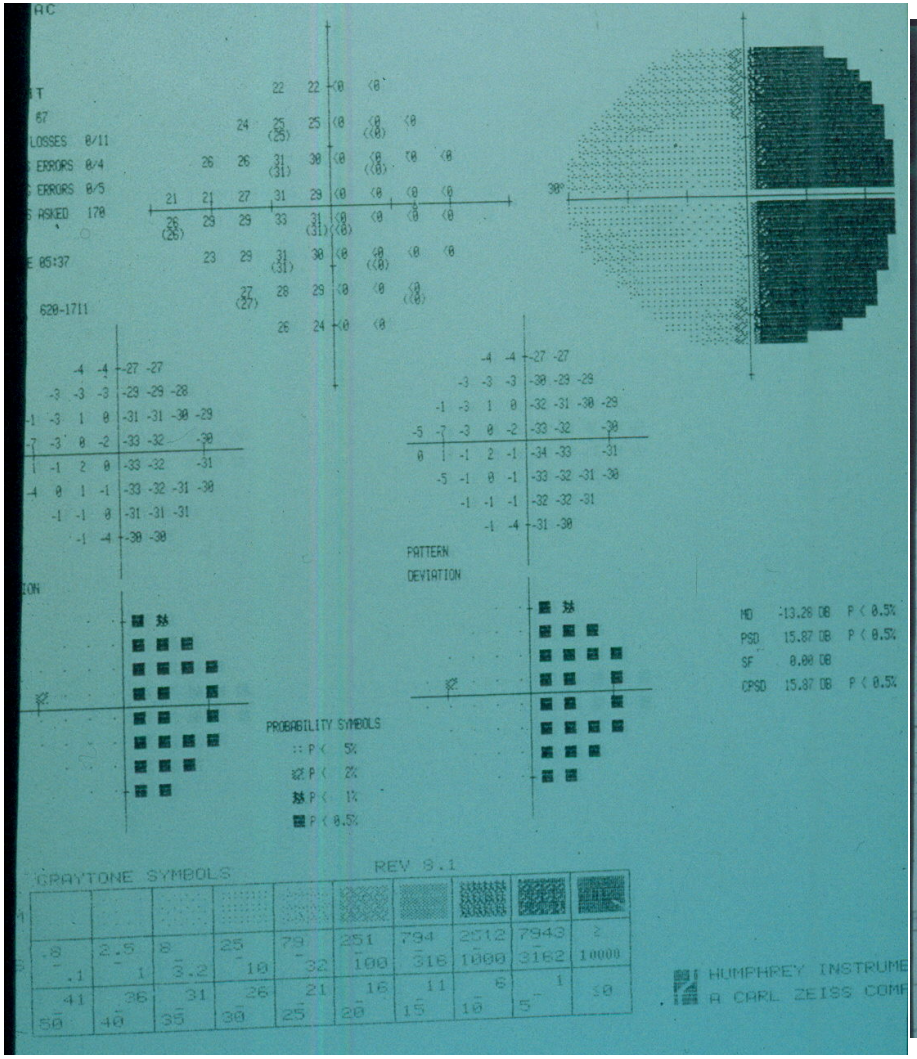
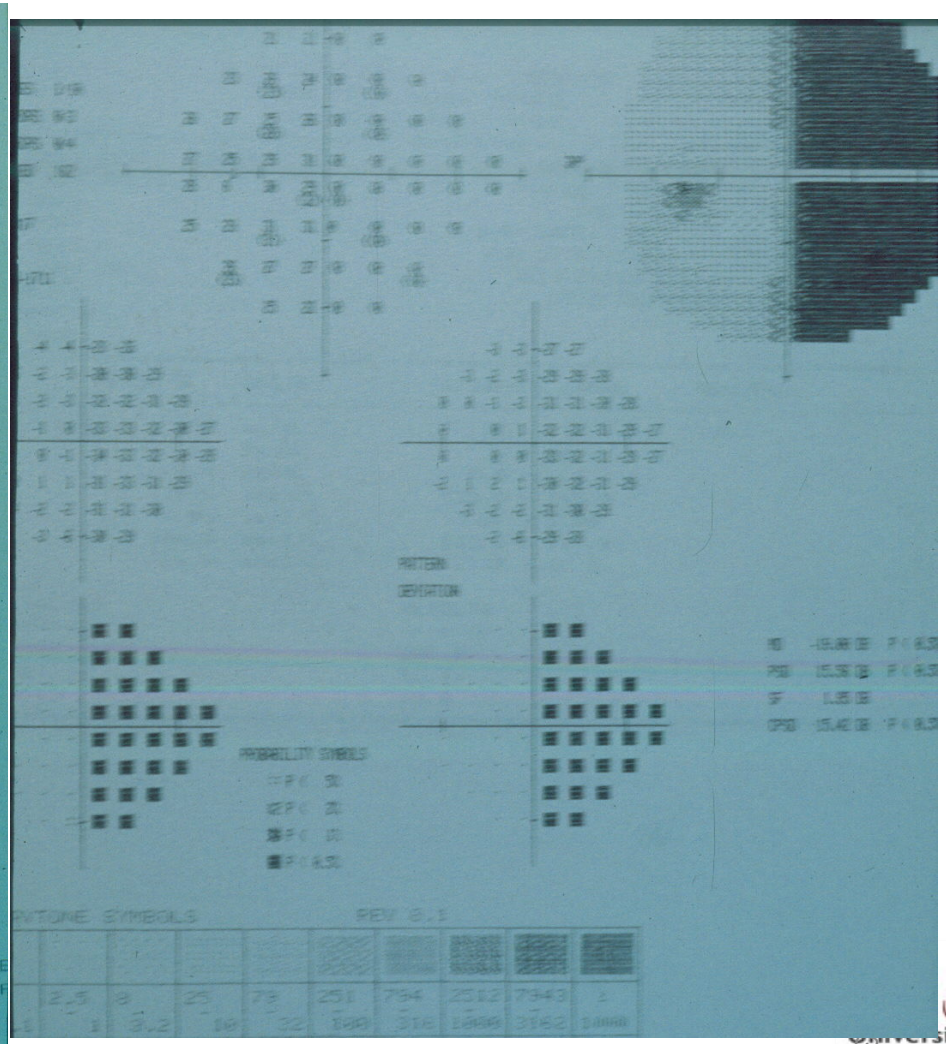
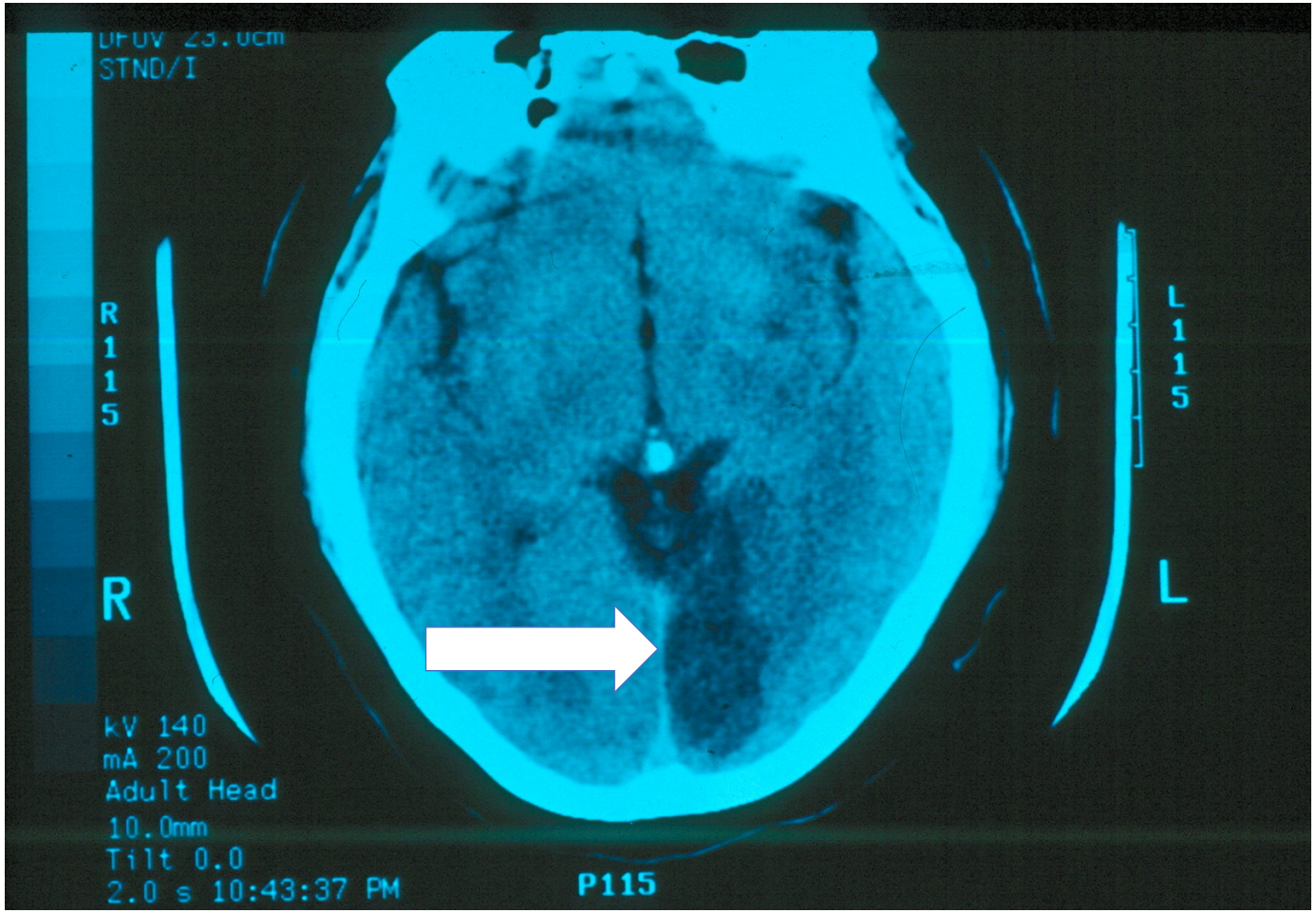
Case Example

- 67 YOF
- HA and vision loss x 2 days
- OHx: unremarkable
- LEE: 3 days ago!
- MHx: unremarkable

Case courtesy of Dr. Tammy Than


LOSSES 0/11
ERRORS 0/4
ERRORS 0/5
ASKED 170
620-1711
PATTERN
DEVIATION
MD -13.28 DB P < 0.5%
PSD 15.87 DB P < 0.5%
SF 0.00 DB
CPSD 15.87 DB P < 0.5%
PROBABILITY SYMBOLS
P < 5%
P < 2%
P < 1%
P < 0.5%
GRAYTONE SYMBOLS
REV 8.1
HUMPHREY INSTRUME
A CARL ZEISS COMP


PATTERN
DEVIATION
PROBABILITY SYMBOLS



Case courtesy of Dr. Tammy Than

Minocycline?

- Proposed mechanisms
  - ↓ MMPs (MMP-9)
    - Increase in MMP-9 disrupt blood brain barrier and are linked to poor functional recovery
  - Anti-inflammatory
  - Reduction in microglial activation
    - **microglial activation** is believed to play a central role **in** neuroinflammation and pathological progression of ischemic tissue
  - Nitric oxide (NO) production
    - NO plays a neuroprotective role in **acute ischemic stroke**.
  - Inhibition of apoptotic cell death
    - **Apoptosis** may contribute to a significant proportion of neuron death following acute brain **ischemia**

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Acute Stroke Management

- N=152
- Open-label, evaluator masked study
- Minocycline 200 mg QD x 5 d or placebo
- Evaluated on NIH Stroke Scale
  - 0-1 complete/nearly complete improvement
  - 2-7 – mild
  - 8-14 – moderate
  - >15 – severe
  - Day 30: 1.8 versus 7.1

Lampl Y, Boaz M, Gilad R, Lorberboym M, Dabby R, Rapoport A, et al. Minocycline treatment in acute stroke. Neurology. 2007;69(14):1404–10

TEST	Admission	Day 7	Day 30	Day 90
NIHSS - Min	7.5	6.5	1.8	1.6
NIHSS – Cont	7.6	8.1	7.3	6.5
mRS – Min	2.8	1.5	1.1	0.9
mRS – Cont	2.0	3.1	2.7	2.1
BI – Min	70.0	85.9	90.6	94.9
BI – Cont	63.9	61.9	68.5	77.6

Minocycline for acute stroke treatment: a systematic review and meta-analysis of randomized clinical trials. J Neurol. 2018 Aug;265(8):1871-1879

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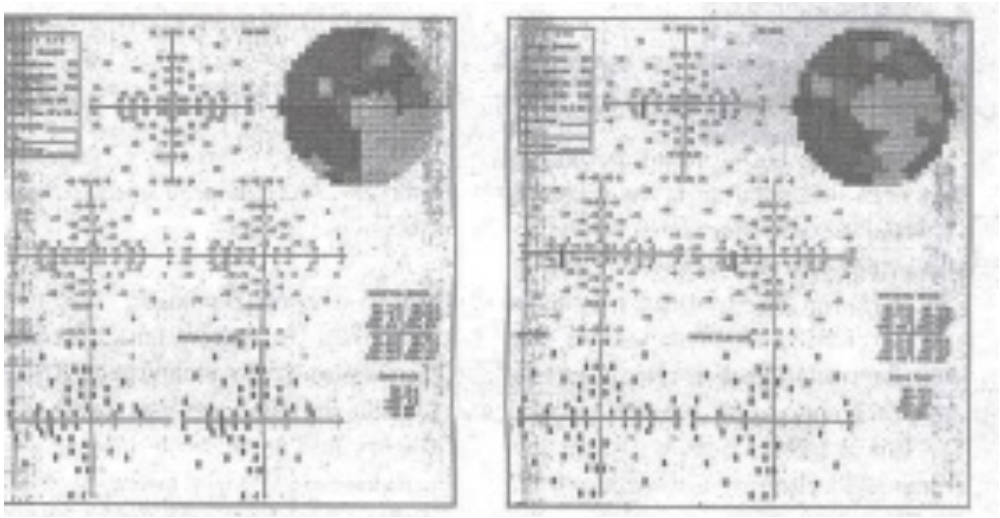
Case Report

- 77 YOM
- Right occipital infarct
- 3 weeks post stroke
  - Minocycline 100 mg BID x 5 days



Mark Tomsik. OD and Marlene Skulskie. OD

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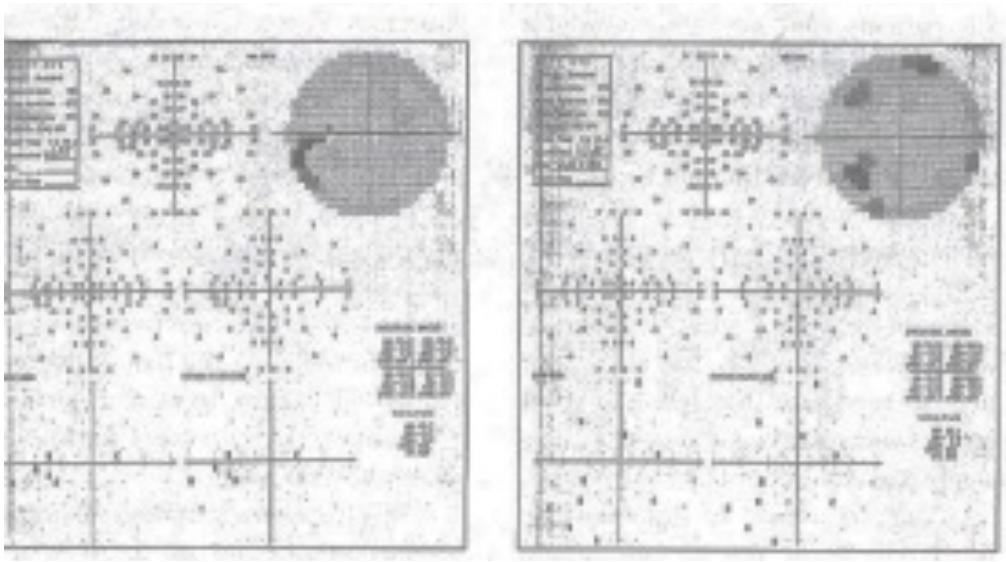
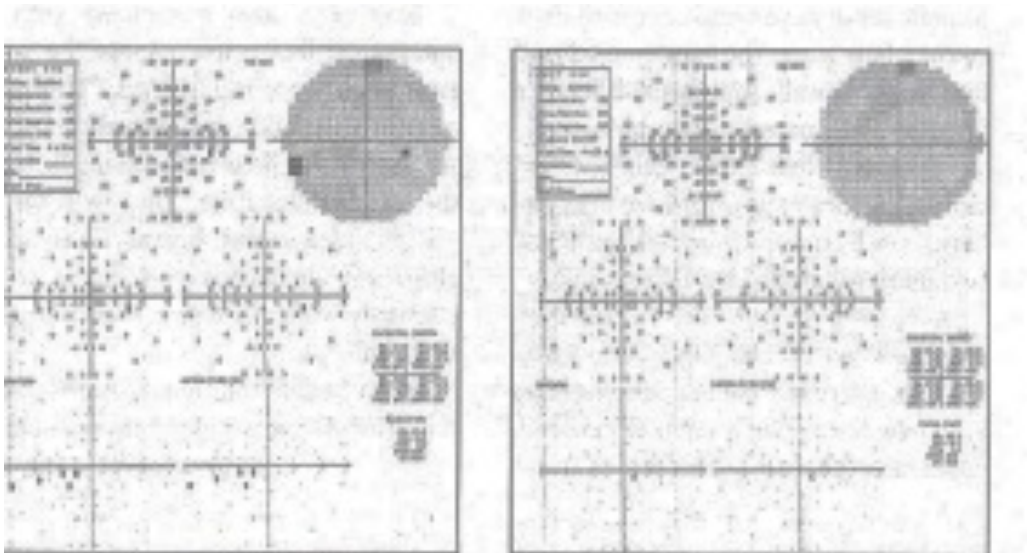
Shortly after TX



1 Year Later



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Tetracyclines

- This group includes:
  - Tetracycline (250mg - 500 mg cap BID-QID) needs to be taken 1 hour before or 2 hours after a meal.
  - Minocycline (100 mg cap BID)
  - **Doxycycline (20mg - 100 mg cap or tab BID)**
    - **In Canada: Apprilon (30 mg doxy + 10 mg slow release doxy)**
- **Rules of Thumb with Doxy:**
  - **Do not take before lying down (>2 hours before)**
  - **Do not take with calcium and avoid antacids**
  - **Do not take with dairy**
  - **Do take with food**
  - **Do educate on sun protection**

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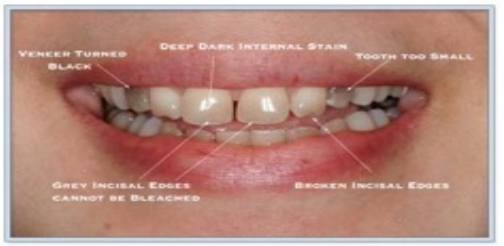
Side Effects of Tetracyclines

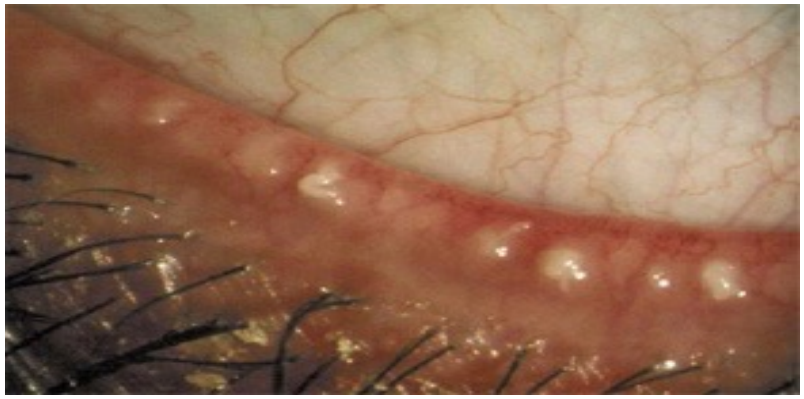
- Side effects include gastric discomfort, phototoxicity, effects on calcified tissues, vestibular problems, pseudotumor.
- Pregnancy Category D.
  - Tetracyclines are attracted to embryonic and growing bone tissue.
    - Depress growth of long bones in pregnant women/children.
    - Cause changes in both deciduous and permanent teeth during the time of tooth development (Includes discoloration and increased cavities)
- Contraindicated in:
  - Women in the last half of pregnancy
  - Lactating women
  - Children under 8 years of age



Meibomian Gland Dysfunction

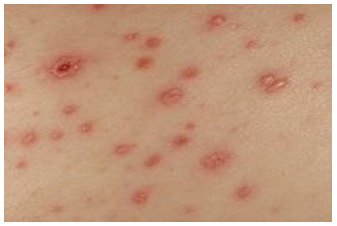
- Meibomian gland dysfunction:
  - also referred to as meibomitis and patients experience dry eye problems secondary to increased evaporation of the tears.
  - signs include noticeable capping of the glands and frothing of tear film.
- Standard treatment includes:
  - good lid hygiene with warm compresses and lid scrubs in conjunction with
  - **doxycycline 50 mg po BID for 2-3 months**

  Alternative treatment:
  - **Azythromycin 500 mg/day for 3 days for three- four weeks**
    - **Recent study used single Z-pak treatment**



Herpes Zoster

1. Primary infection – Chicken pox (Varicella)
   - Usually in children
   - Highly contagious***
   - Very itchy maculopapular rash with vesicles that crust over after ≈ 5 days
   - 96% of people develop by 20 years of age
   - Vaccine now available



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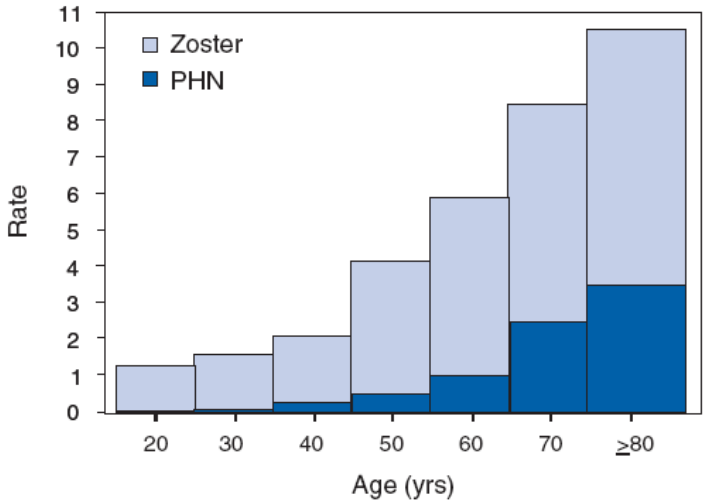
Herpes Zoster

Reactivation – Shingles (Herpes Zoster)

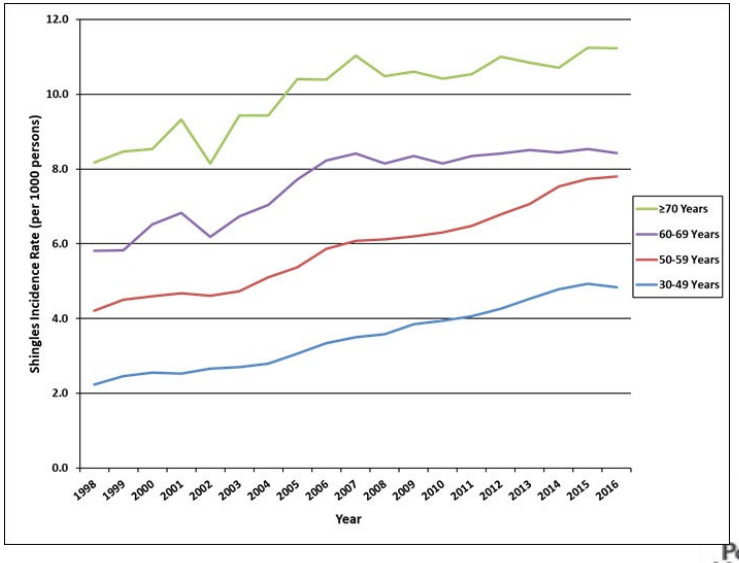
- More often in the elderly and immunosuppressed (AIDS)
  - Systemic work-up if Zoster in someone < 40
- Can get shingles anywhere on the body
- Herpes Zoster Ophthalmicus (HZO)
  - Shingles involving the dermatome supplied by the ophthalmic division of the CNV (trigeminal)
    - 15% of zoster cases

Herpes Zoster

- Associated factors include increasing age, immune deficiency and stress.
  - Traditionally thought to only affect patients over the age of 60 and those patients under 60 should be worked up for immune deficiency
  - Increasing trend to affect patients of younger age who are not immunocompromised



Shingles and Postherpetic Neuralgia† Rates* by Age, United States



Shingles Rates in Adults 30 and Older, 1998-2016

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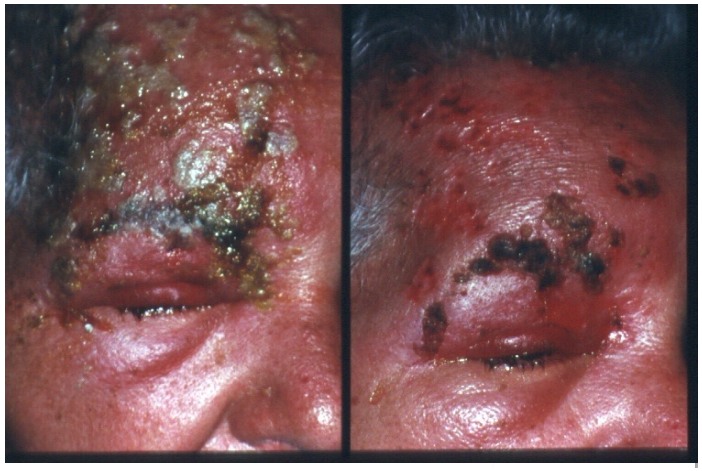
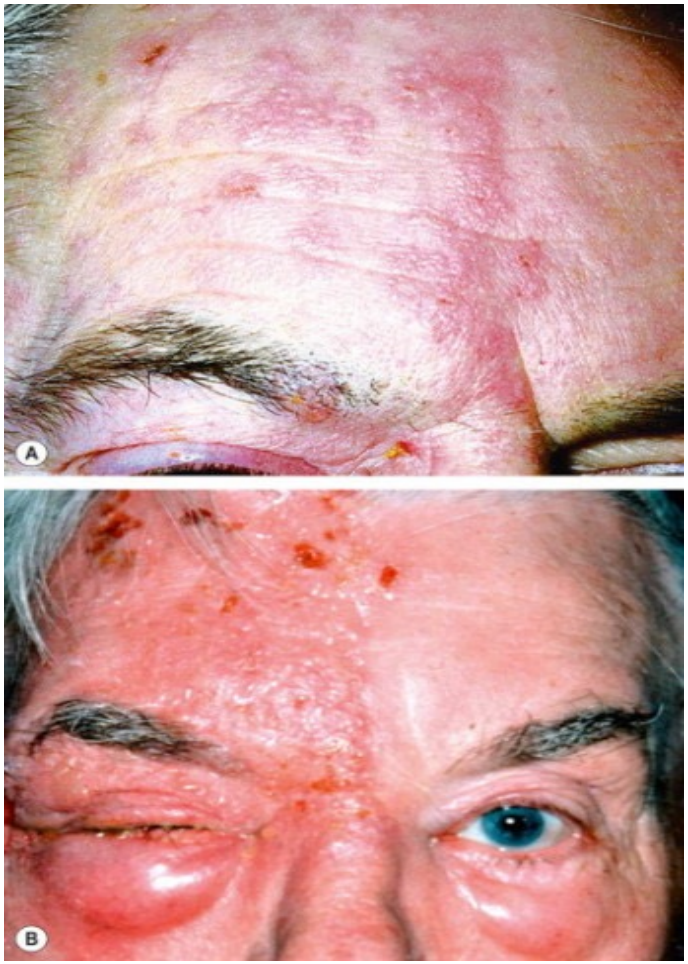
Herpes Zoster

- Symptoms:
  - Generalized malaise, tiredness, fever
  - Headache, tenderness, paresthesias (tingling), and pain on one side of the scalp
    - Will often precede rash
  - Rash on one side of the forehead
  - Red eye
  - Eye pain & light sensitivity



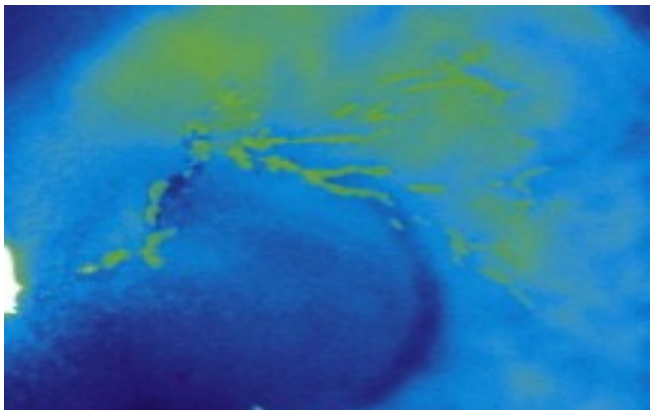
Herpes Zoster

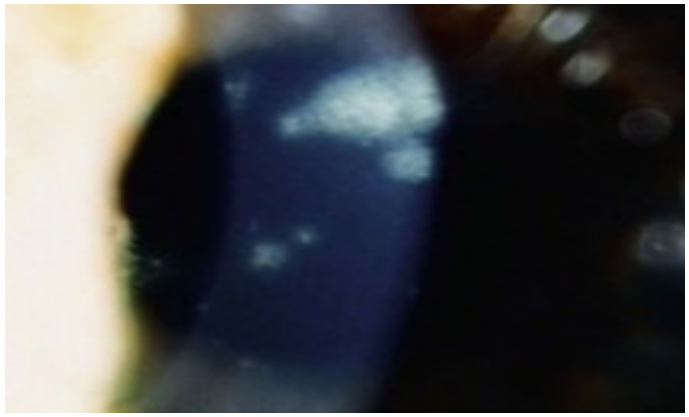
- Signs:
  - Maculopapular rash -> vesicles -> pustules -> crusting on the forehead
  - Respects the midline***
  - Hutchinson sign
    - rash on the tip or side of the nose***
  - Classically does not involve the lower lid
  - Numerous other ocular signs

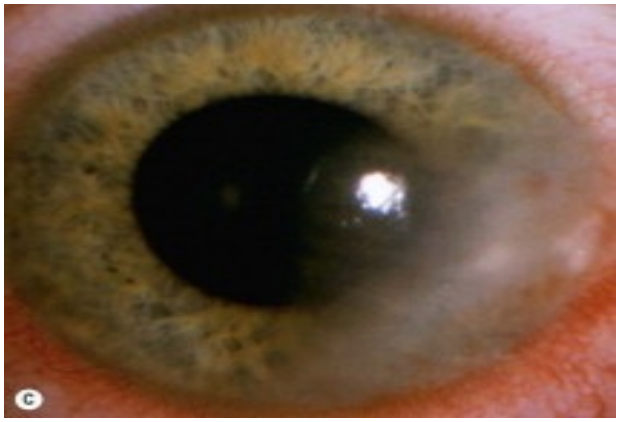


Herpes Zoster

- Other Eye Complications (Acute):
  - Anterior uveitis (most common ocular manifestation)
  - Acute epithelial keratitis (pseudodendrites)
  - Conjunctivitis
  - Stromal (interstitial) interstitial keratitis
  - Endotheliitis (disciform keratitis)
  - Neurotrophic keratitis







Herpes Zoster

- Associated factors include increasing age, immune deficiency and stress.
- Only people who had natural infection with wild-type VZV or had varicella vaccination can develop herpes zoster.
- Children who get the varicella vaccine appear to have a lower risk of herpes zoster compared with people who were infected with wild-type VZV.

Herpes Zoster

- A person's risk for herpes zoster increases sharply after 50 years of age.
- Almost 1 out of 3 people in the United States will develop herpes zoster during their lifetime.
- A person’s risk of developing post-herpetic neuralgia also increases sharply with age.

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Herpes Zoster

- Management includes:
  - oral antivirals:
    - 800mg acyclovir 5x/day
    - valacyclovir (Valtrex) 1g TID,
    - famciclovir (Famvir) 500 mg TID
  - effectiveness of therapy is best started within 72 hours
  - oral steroids (clinical trials show variable results but often prescribed with antiviral to reduce pain)
  - management of pain (capsaicin, tricyclic antidepressants, gabapentin).
  - If ocular complications, consider topical steroids (Pred Forte QID).

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Purpose of ZEDS

- To find out whether or not 12 months of low dose valacyclovir treatment, compared with placebo, delays time to development of new or worsening of specific eye disease manifestations of Herpes Zoster Ophthalmicus(HZO)

- Secondary objective: To find out whether there is persistent treatment benefit at 18 months, 6 months after cessation of treatment

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ZEDS Guidance for Evidence-based Clinical Practice

- Evidence supports suppressive valacyclovir treatment 1000 mg daily for one year to reduce new or worsening keratitis or iritis in immunocompetent, non pregnant adults with good renal function
- Pre-specified analysis of primary endpoint did not show overall benefit at 12 months, but did at 18 months (secondary endpoint)
  - Evidence supports suppressive valacyclovir treatment to reduce multiple episodes of keratitis or iritis

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ZEDS Guidance for Evidence-based Treatment of PHN/Pain

- Recommend 1 year of suppressive valacyclovir in HZO patients
  - HZO Onset < 60 years, chronic stratum
- Significantly lower pain scores at 12(p=0.05), 18months (p=0.02)
- HZO Overall
  - Significant decrease pain duration at 18months (p=0.05)

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Shingrix HZ Vaccine

- Approved in US/Canada as of October 2017
- non-live antigen, to trigger a targeted immune response, with a specifically designed adjuvant to enhance this response and help address the natural age-related decline of the immune system
- Shingrix is 97% effective against shingles for people between the ages of 50 and 69 and 91% effective for people 70 or older.
- It is 91% effective against postherpetic neuralgia for people 50 and older.
- These rates are based on evidence presented to the committee from clinical trials with over 38,000 total participants.

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Shingrix HZ Vaccine

- recommended for healthy adults aged 50 years and older to prevent shingles and related complications
- recommended for adults who previously received the current shingles vaccine (Zostavax®) to prevent shingles and related complications
- the preferred vaccine for preventing shingles and related complications

Systemic Corticosteroids

- Prednisone
  - Available as Oral: 1, 2.5, 5, 10, 20, 50 mg tablets and 1 and 5 mg/mL solution and syrup

- Ocular Treatment Guidelines:
  - Mild to Moderate: Initial dose of 20-40 mg
  - Moderate to Severe: 40 – 60 mg
  - Severe: Begin with 60 mg and increase if necessary
  - Specific Conditions: Giant Cell Arteritis
    - 80-100 mg Prednisone
    - Consider IV Methylprednisolone 250 mg IV q6hours for 12 doses

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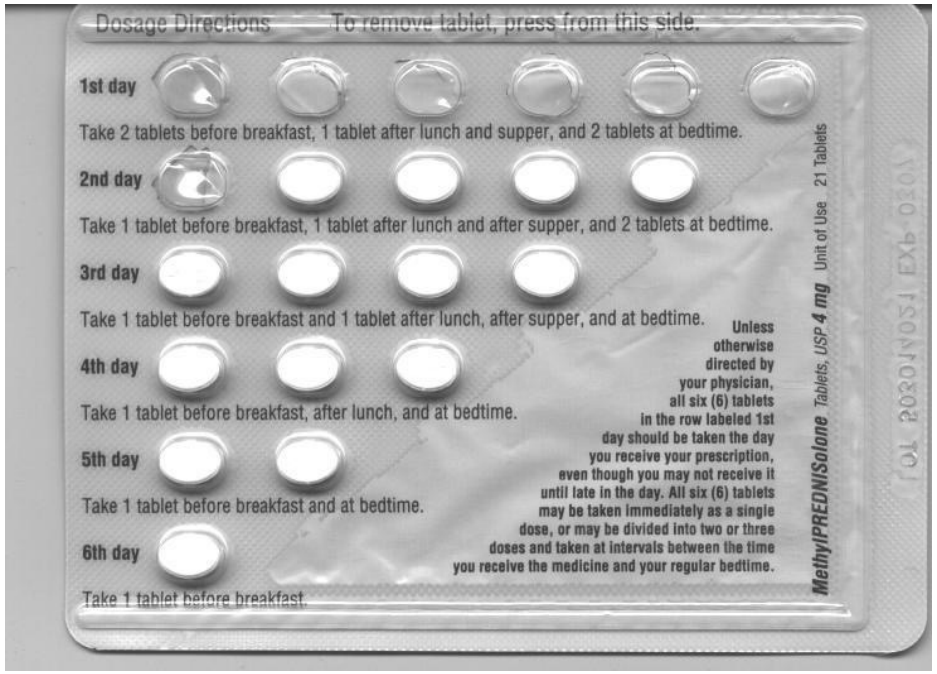
Tapering Systemic Medications

- Medrol Dose Pack (Methylprednisolone) – 4 mg pills
  - Provided with dosage for 6 days of treatment.



In Optometry, generally if we do an oral to a level that requires a taper we want dosages of higher than 24 mg to start and treatment for longer than 6 days.

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CORTICOSTEROIDS
Side Effects