Oral Pharmaceuticals in Anterior Segment Disease

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Disclosures:

- Maculogix: advisory board
- Sun Pharmaceuticals: speakers bureau,
- Avellino: advisory board,
- Dompe: advisory board,
- RVL Pharmaceuticals: advisory board

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Expected Learning Outcomes

- Needs Assessment:
  - To enable optometrists to provide care for patients who require the use of oral pharmaceuticals in the treatment of their anterior segment disease

- At the end of the presentation, attendees should be able to:
  - know diagnostic criteria for herpes zoster ophthalmicus and the appropriate oral and topical treatments
  - the diagnostic criteria for HSV keratitis and the appropriate oral and topical treatments
  - familiar with the common oral medications used in the management of ocular pain
  - know the diagnostic criteria for lid/periocular tissue disease (e.g. hordeola, preseptal cellulitis) and appropriate oral treatments
  - diagnostic criteria for recurrent corneal erosion and appropriate oral and topical treatments

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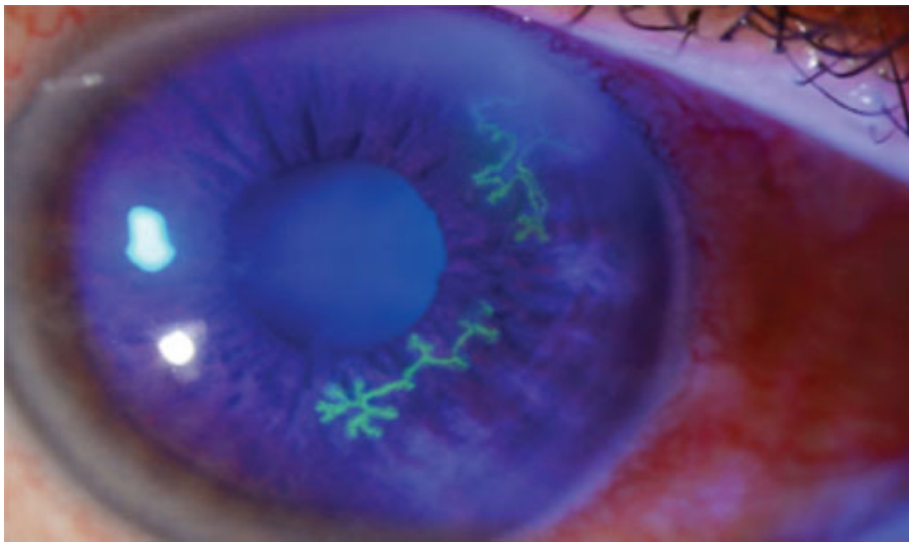
Case

- 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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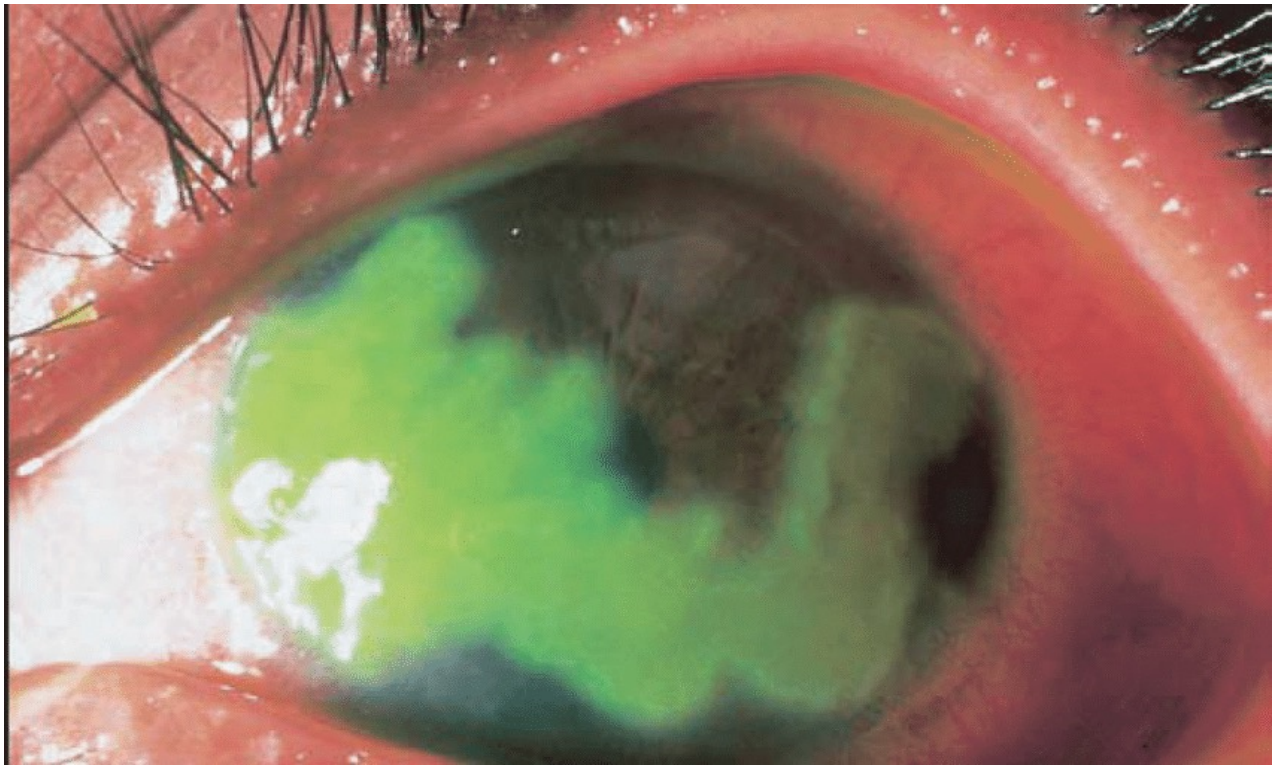
Herpes Simplex Keratitis

- **<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***

Dendritic Ulcers

HSV Geographic Ulcer



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

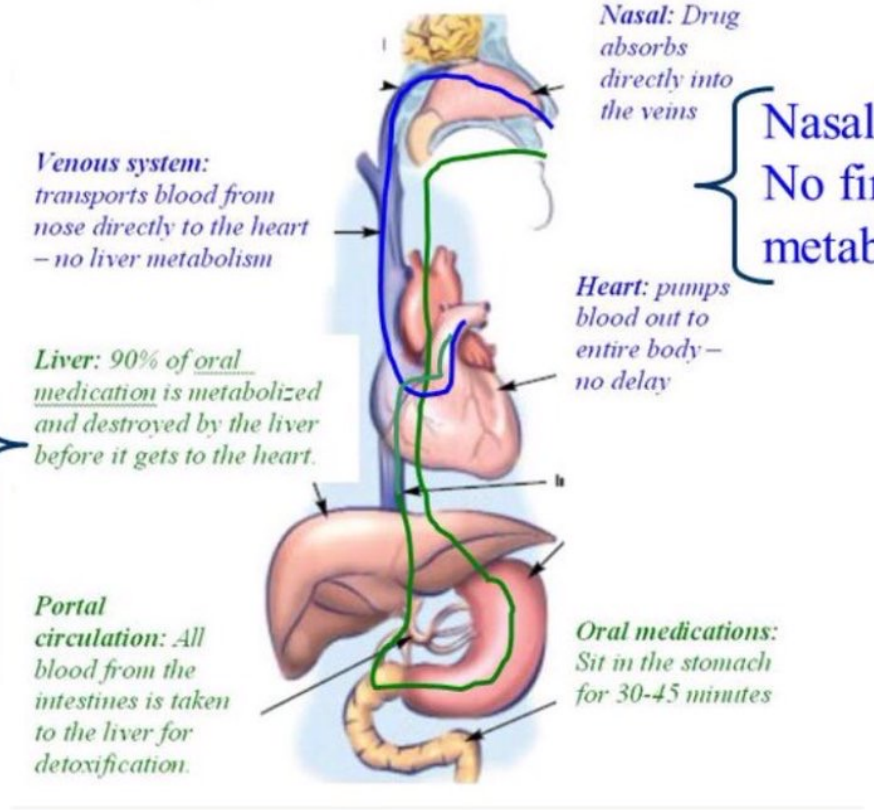
Pediatric HSV Keratitis

- 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 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)

First pass metabolism



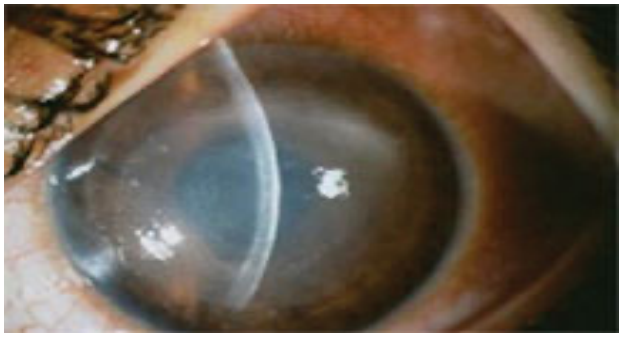
Nasal Mucosa: No first pass metabolism

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 (Famvir)	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
- 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

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

Herpes Simplex Epithelial Keratitis

- Treatment Regimen:
  - Oral Valtrex 500 mg 3x/day for 7-10 days
  - If topical Zirgan 5 times per day until epi has healed then 3 times per day for another week
  - 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

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

Prophylaxis??

- **Pitfalls to Prophylaxis**:
  - Reduction of recurrence does not persist once drug stopped
  - Resistance????
    - van Velzen, et. al., (2013) demonstrated that long-term ACV prophylaxis predisposes to ACV-refractory disease due to the emergence of corneal ACVR HSV-1.

Academic Emergency Medicine
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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

Pain Management: Oral Analgesics

- Conditions potentially requiring use of oral analgesics:
  - Corneal ulcers
  - Herpes simplex/zoster
  - Post-surgical
  - Trauma
  - Thermal burns
  - Periorbital infections (preseptal/dacryocystitis)

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Oral Analgesics: Guidelines

- Make the proper diagnosis first (ie. Don't prescribe without knowing what you are prescribing for!)
- Treat the underlying cause for the pain
- Treat the pain at presentation..don't wait!
- Treat pain continuously over a 24-hour schedule
- Non-prescription drugs should be first choice and tend to be low cost
- Treat patients with the simplest and safest means to aleve pain

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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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Aspirin (ASA)

- Weak organic acid.
- Oldest non-opioid analgesic available today.
- Very good anti-inflammatory and antipyretic properties.
  - Adult Dosage: 325 – 650 mg every 4 hours
    - Do not exceed 4 g/day.
  - Most Common use of ASA: Inhibit platelet aggregation in patients with history of heart attacks and heart surgery.
    - Most common dosing is 81 mg/day
- Largely replaced as treatment for pain associated with inflammation by the other classes of NSAID's due to the frequent side effects.
  - GI Distress: Inhibit prostaglandin synthesis and the production of a mucous lining on the stomach leading to increased gastric acid secretion.

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2019 Aspirin Recommendations

- American College of Cardiology:
  - *Aspirin should be used infrequently in the routine primary prevention of ASCVD because of lack of net benefit.*
  - low-dose aspirin should not be routinely given as a preventive measure to adults 70 years and older or to any adult who has an increased risk of bleeding
    - Just updated (2021): no longer recommended for patients 60 and older, and for patients aged 40-59 it should be on a case to case basis.

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Ibuprofen

- Mild to moderate pain, fever
- Adult analgesic dose: 200-400mg q4-6 hours
  - Maximum Dosage: 2400 mg/day for pain (approved for 3200 mg/day in arthritis treatment)
- OTC: 200 mg tabs (US) 400 mg and 600 mg (Canada)
- Rx: 300, 400, 600, 800mg tabs
  - Can prescribe 800 mg q8hrs
- Peak levels 1-2 hours
- Most renal toxic of all the NSAID's
- Brand Names: Motrin, Advil, and Nuprin

Naproxen Sodium

- OTC: 220 mg (Aleve^{R})
- Rx: 550 mg tablets (Anaprox^{R} and Crysanal^{R})
- For mild to moderate pain

- Adult Dose:
  - OTC: 2 tablets first dose, then 1 tablet 8-12 hours (max dose 1250 mg)
  - Rx: 550 initial dose, followed by 275 (half tablet) every 6-8 hours.
    - Maximum Dose: 1375mg/day.

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NSAIDS Black Box Warning

- BLACK BOX WARNING:
  - May increase the risk of serious thrombotic events, MI, and stroke.
  - Increase risk of serious GI adverse effects such as bleeding, ulcer, and perforation.

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Indomethacin (Indocin)

- used to treat moderate to severe osteoarthritis, rheumatoid arthritis, gouty arthritis, or ankylosing spondylitis.
- Usual Adult Dosage for Pain: 25-50 mg two to three times/day
- Rx Only: 25, 50 and 75mg capsules
- 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
  - E.g. Scleritis treatment 75 mg BID

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Cox-2 Inhibitors

- Selective agents for only COX-2 designed to protect the GI system from the side effects seen with NSAID's.
- It is approved for the management of the signs and symptoms of osteoarthritis, rheumatoid arthritis, JRA (in patients >2), ankylosing spondylitis and acute pain
- Major agent available on the market is Celecoxib (Celebrex).
  - Other agents Valdecoxib (Bextra) and Rofecoxib (Vioxx) were removed from the market due to increased risk of heart attacks and strokes.
- Available: 50, 100, 200 and 400 mg capsules
- Osteoarthritis Dosage: 100 mg BID or 200 mg single dose daily
- RA: 100 to 200 mg BID 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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Acetaminophen

- Typical Adult Dosage (FDA Based):
  - 650 mg every 4 - 6 hours for Regular Strength (2 X 325)
    - Cannot take more than 10 caplets in 24 hours.
  - 1000 mg every 6 hours for Extra Strength (2 X 500)
    - Cannot take more than 6 caplets in 24 hours.
  - 1300 mg every 8 hours for Extended Release (2 X 650)
    - Cannot take more than 6 capsules in 24 hours.
- Daily dose of Extra Strength Tylenol should not exceed 3 grams!
  - This has been recently changed from 4000 mg which can be done with doctor approval.
- Should only be used for short term therapy
- Exhibits a ceiling effect, like NSAIDs and ASA.

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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 Tylenol

3:00 pm: Two 200mg Ibuprofen

5:00 pm: Two 325mg Tylenol

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: 4 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**, is not currently classified as a **controlled substance** in most states, however, its abuse potential is still being investigated.
  - Kentucky, Michigan, Tennessee, West Virginia ??, Virginia ??, and Ohio ?? have reclassified **gabapentin** as a Schedule V **controlled substance**.

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Gabapentin (Neurontin^{R})

- 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
- 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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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 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.
  - Exacerbated if used in combination with alcohol, depression medications such as tricyclic antidepressants, anticholinergics, antihistamines, anti-seizure medications, or muscle relaxants, etc.
  - Visual symptoms such as blurry vision, miosis, and diplopia can occur.

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Opioid Side Effects

Respiratory Side Effects:

- Respiratory Depression
  - Most serious side effect of the opioids
  - Opioids suppress the brainstem respiratory centers
    - Alter tidal volume, respiratory rate, rhythmicity, and responsiveness to CO_2
  - Does not commonly occur at therapeutic doses in healthy patients, but must use caution in patients with pulmonary disease.
- Cardiovascular Side Effects:
  - Peripheral vasodilation can result in orthostatic hypotension, decreased BP, and changes in pulse rate.

- Others Include: Urinary retention, cough suppression, headaches, rashes, itching.

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Scheduled Medications – Most Opioids

Schedule	Description	Optometric Medications
I	Not commercially available; no approved indication	
II	Very addictive medications that are accepted for medicinal use	Oxycodone = OxyContin, OxyFast Oxycodone + APAP = Percocet or Tylox Oxycodone + ASA = Percodan Oxycodone + NSAID = Combunox Hydromorphone (Dilaudid) Codeine Sulfate = Codeine Generic Meperidine (Demerol) **Hydrocodone + APAP = Lortab or Vicodin** **Hydrocodone + Ibuprofen = Vicoprofen**
III	Significant abuse risk, but less potent than I or II. May still contain narcotics.	Codeine + APAP = Tylenol 3 and Tylenol 4
IV	Relatively low abuse potential and limited risk	Propoxyphene (Darvon) Propoxyphene with APAP = Darvocet (Removed from Market in November 2010). Pentazocine + APAP (Talacen) Tramadol
V	Very limited abuse potential. May be OTC in some states.	Cough medicine with codeine

Opioids: Codeine

- 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
  - 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.

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Opioids: Hydrocodone

- 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.

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Opioids: Hydrocodone

- Used in combination with APAP and Ibuprofen.
  - Lortab: Hydrocodone 5, 7.5, and 10 mg with APAP 325 mg
    - Dosage: 1-2 tablet every 4-6 hours
  - Lortab Elixer: Hydrocodone 10 mg with APAP 300 / 15 mL
    - Dosage: 3 tsp every 4-6 hours
  - Vicodin: Hydrocodone 5 mg with Acetaminophen 300 mg
  - Vicodin HP: Hydrocodone 10 mg with Acetaminophen 300 mg
    - Dosage: 1 tablet every 4-6 hours
  - Vicodin ES: Hydrocodone 7.5 mg with Acetaminophen 300 mg
    - Dosage: 1 tablet every 4 – 6 hours
  - Vicoprofen: Hydrocodone 7.5 mg with Ibuprofen 200 mg
    - Dosage: 1 tablet every 4-6 hours
  - Norco: Hydrocodone 5, 7.5, and 10 with 325 mg APAP

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Opioids: Oxycodone

- Approximately 10-12X more potent than codeine
  - As potent as parenteral morphine when given orally.
- 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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Opioids: Oxycodone

- Available in combination with APAP, ASA, or Ibuprofen.
  - Percocet Tablets
    - 2.5, 5, 7.5 or 10 mg Oxycodone with 325 mg Acetaminophen
    - Dosage: 1 tablet every 6 hours
  - Tylox Capsules
    - 5 mg Oxycodone with 300 mg Acetaminophen
    - Dosage: 1 tablet every 6 hours
  - Percodan Tablets
    - 4.5 mg Oxycodone HCl
    - 0.38 mg Oxycodone terephthalate
    - 325 mg Aspirin
    - Dosage: 1 tablet every 6 hours
  - Combunox
    - 5 mg Oxycodone with 400 mg Ibuprofen
    - Dosage: 1 tablet daily to QID

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Tramadol (Ultram)

- 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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Tramadol + APAP (Ultracet)

- Combination of:
  - 325 mg of APAP
  - 37.5 mg of Tramadol
- Dosage: 2 tablets every 4 – 6 hours
- Max: 8 tablets daily

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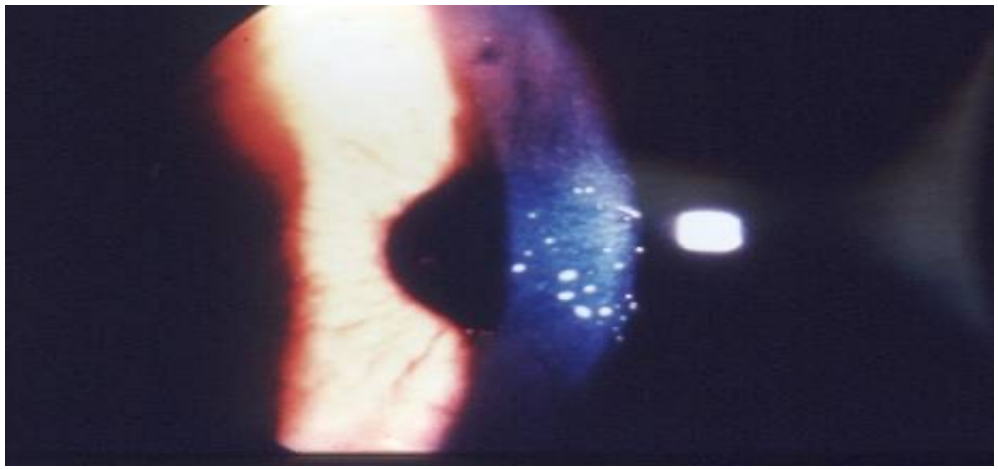
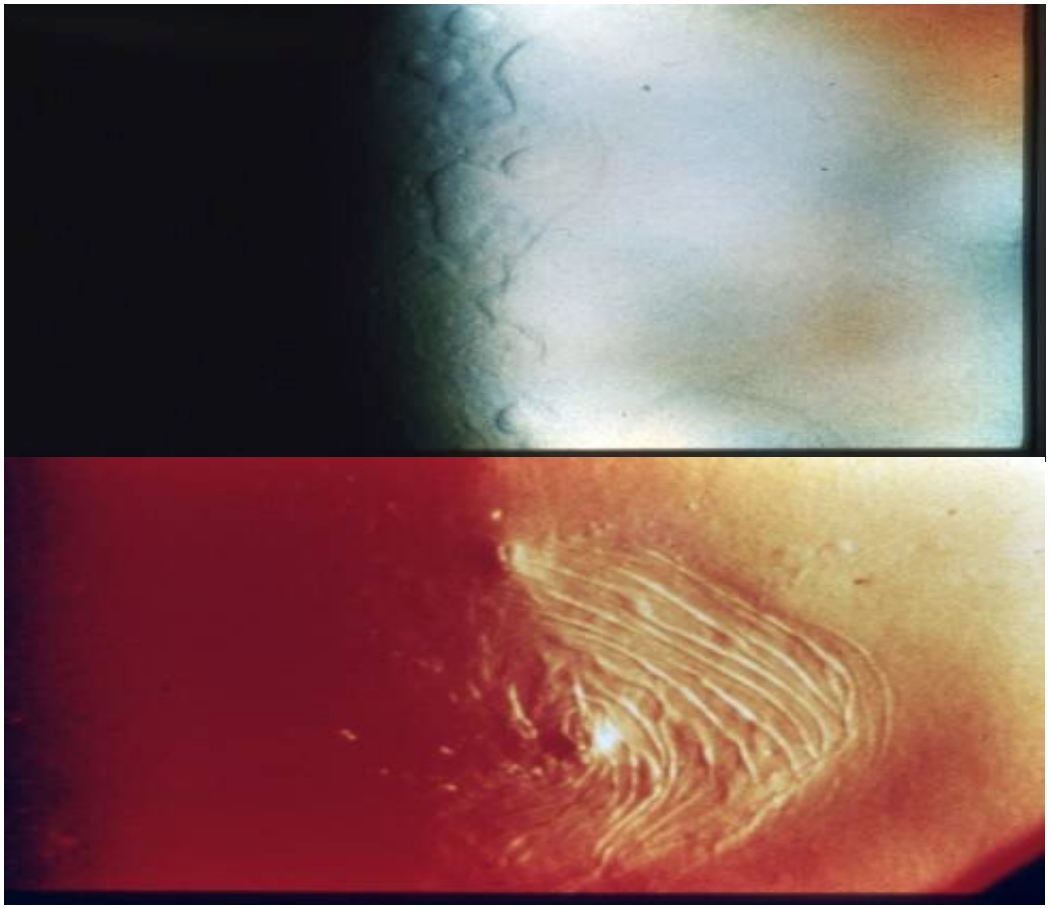
Epithelial (Anterior) Basement Membrane Dystrophy (EBMD or ABMD)

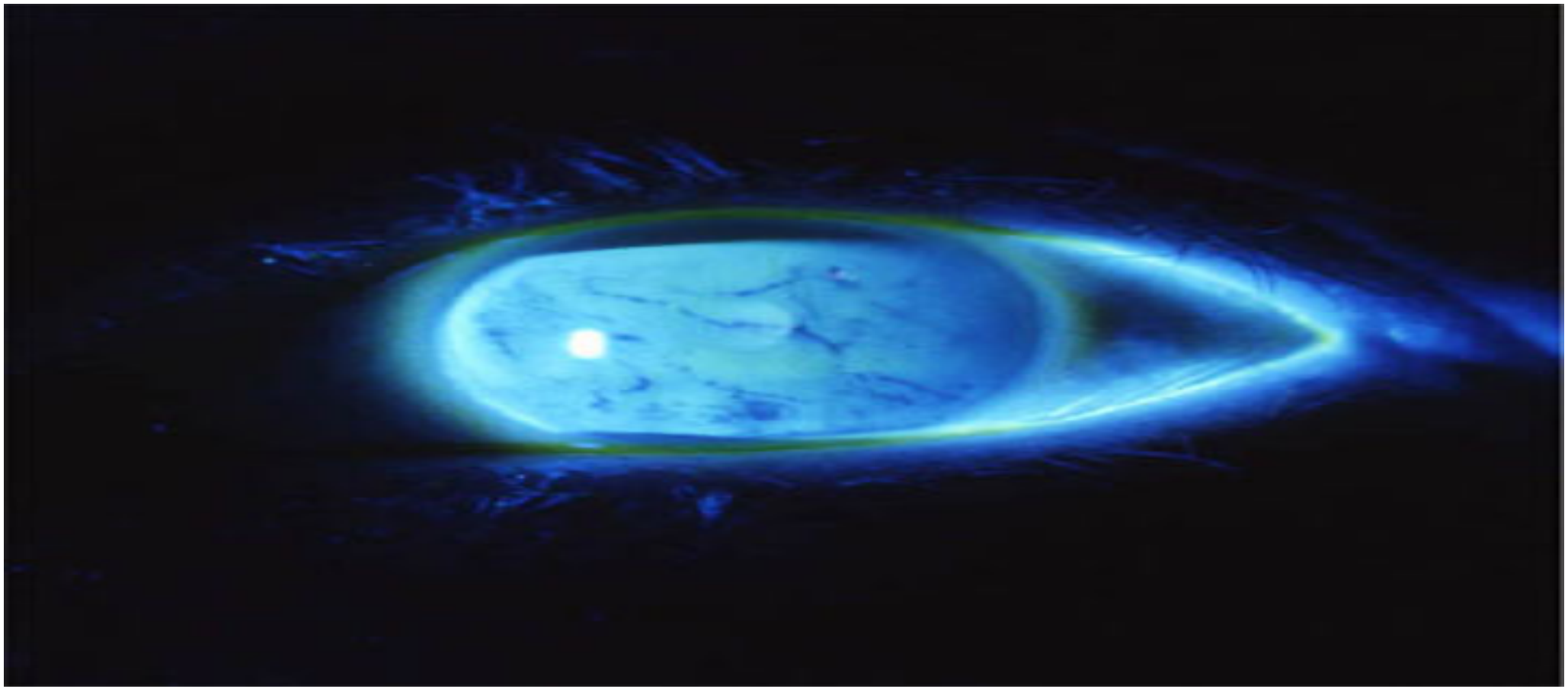
- Most common findings are:
  - chalky patches,
  - intraepithelial microcysts, and
  - fine lines (or any combination) in the central 2/3rd of cornea

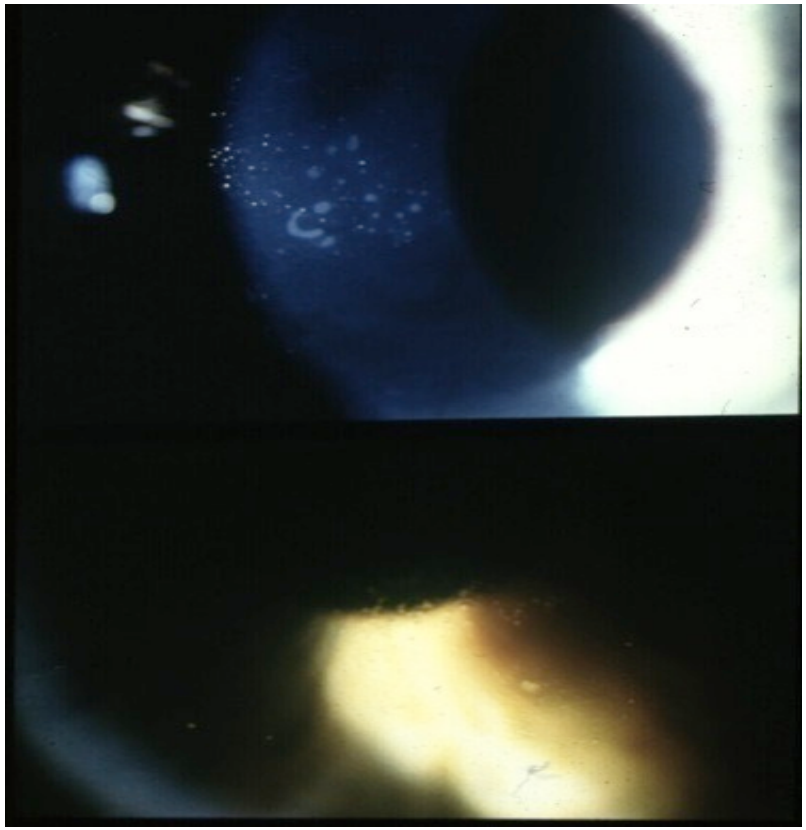


- Often referred to as:
  - maps,
  - dots or
  - fingerprints



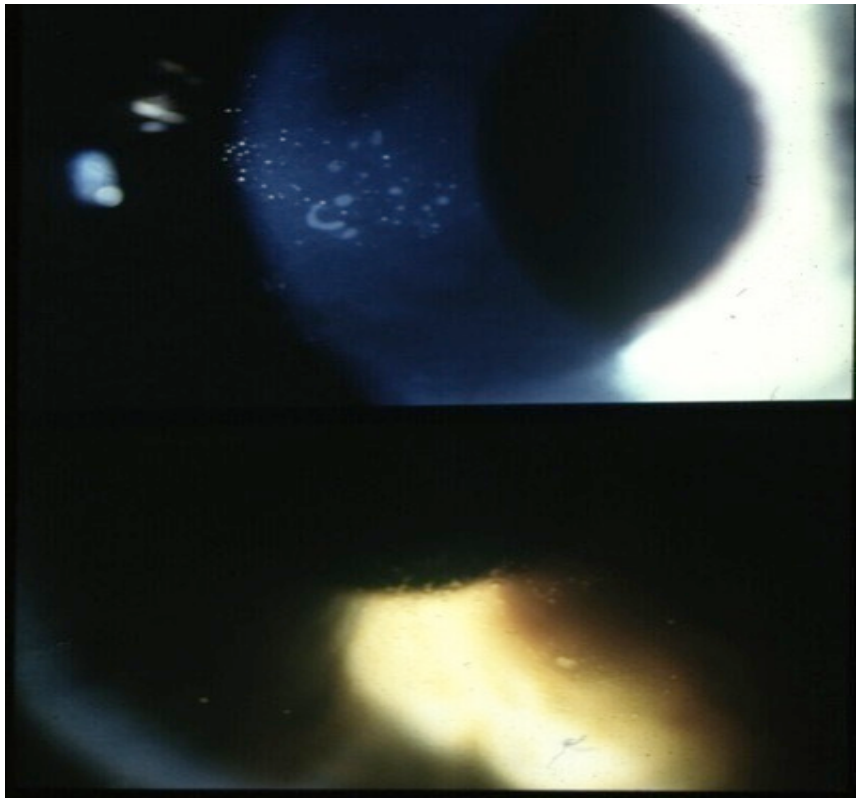
EBMD-Negative Staining





- 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

RCE: Treatment



- Initial treatment includes:
  - use of hyperosmotic ointment at bedtime,
  - bandage contact lens and
  - lubrication.

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
        - topical azithromycin off label use
    - debridement,
    - stromal puncture, or
    - PTK
    - Latest development: amniotic membrane transplant e.g. Prokera

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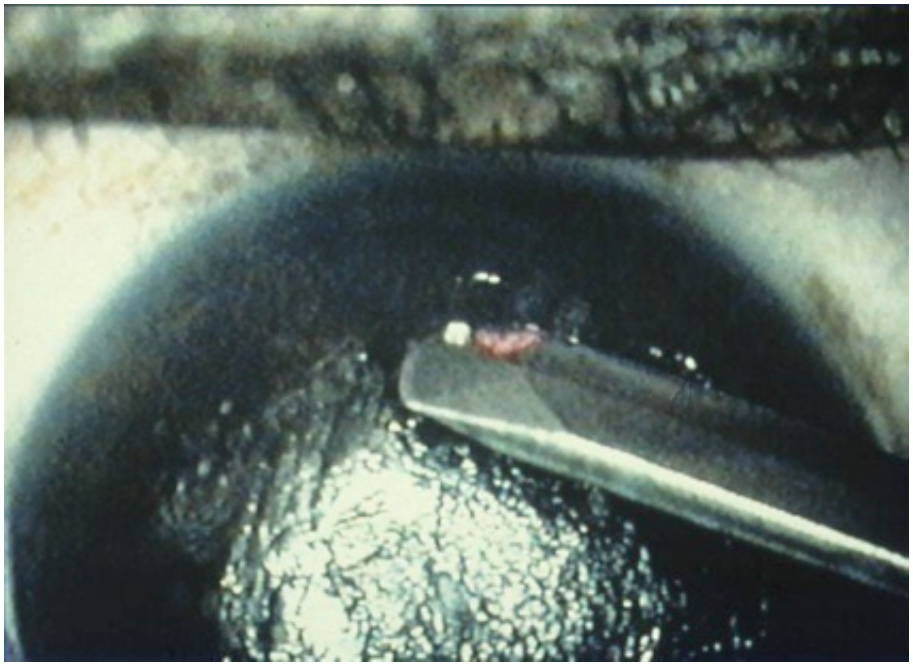
CORNEAL DEBRIDEMENT

- 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%



Diamond Burr Polishing

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

https://www.katena.com/pterygium-burr-3-5mm-w-chuck-k2-4913

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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Amniotic Membrane Transplant

- Amniotic membrane is a biologic tissue with:
  - antiangiogenic,
  - antiscarring,
  - antimicrobial, and
  - anti-inflammatory properties that promotes healing of the ocular surface
- Amniotic membrane grafts have been used for a variety of ocular conditions including:
  - Corneal burns
  - Neurotrophic ulcers
  - Stem cell damage
  - Persistent epithelial defects

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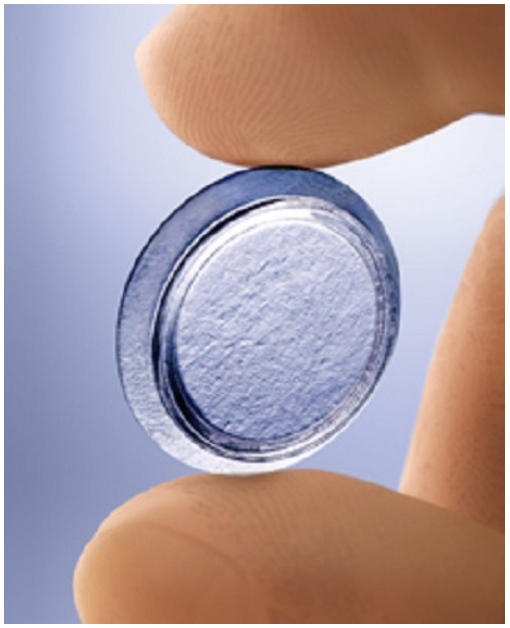
Amniotic Membrane Grafts (AMG)

Biotissue- Prokera, Prokera Slim, Prokera Clear, Amniograft, & Amnioguard



http://www.biotissue.com/products/prokera.aspx

IOP Ophthalmics- Ambiodisk

http://www.iopinc.com/store/ambiodisk/

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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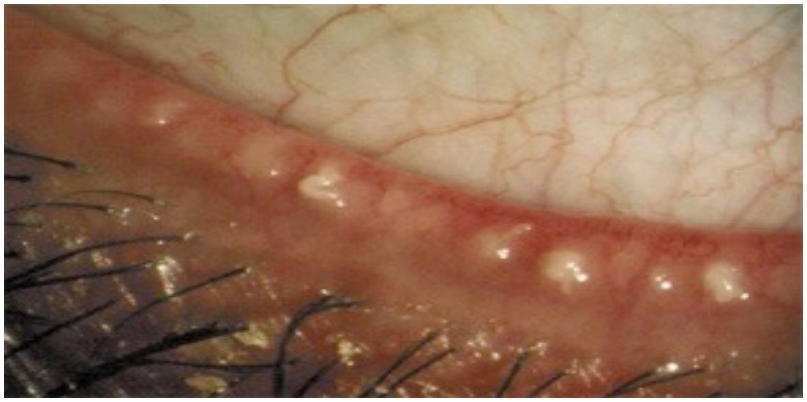
Side Effects of Tetracyclines

- 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**



Acne Rosacea

- Acne rosacea:
  - affects females>males after 30 with peak incidence 4-7th decade of Celtic/Northern European descent. Males more disfigured.
- 4 subtypes with classic signs of flushing, papules or pustules usually in crops, telangiectasia.
  - secondary ocular complications (85% of patients) and often precede other skin manifestations include erythema, itching and burning.
  - Lipases secreted by bacteria on the skin metabolize sebum and produce metabolites that result in inflammation of the skin

Acne Rosacea and Demodex

- Demodex is a natural part of human microbiome
- *Demodex folliculorum* live in hair follicles, primarily on the face, as well as in the meibomian glands of the eyelids;
- *Demodex brevis* live in the sebaceous glands of the skin.

Acne Rosacea and Demodex

- *Demodex folliculorum* frequently occur in greater numbers in those with rosacea and this overabundance is thought to trigger an immune response or possibly certain bacteria associated with the Demodex

Acne Rosacea

- Mainstay oral Tx is **Oracea (40 mg** in morning) or
  - **doxycycline 50 mg po** or minocycline 100 mg po for 4-12 wks.
  - **NOTE: Oracea is subantimicrobial therapy**
  - **May want to consider Tea Tree oil wipes/foam for the face and lids to try and reduce the role Demodex plays**

Hordeola

- Acute purulent inflammation
  - Internal occurs due to obstruction of MG
  - External (stye) from infection of the follicle of a cilium and the adjacent glands of Zeiss or Moll
- Painful edema and erythema,

Hordeola

- Typically caused by Staph and often associated with blepharitis
- Treatment includes:
  - hot compresses (e.g. Bruder)
  - topical antibiotics (?)
  - possibly systemic antibiotics
    - Augmentin (Clavlulin) 500 mg bid-tid
    - Doxycycline 100 mg bid
    - Keflex 500 mg tid
- Treat concurrent blepharitis

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

Preseptal Cellulitis

- Tx:
  - **Clavulin** (***Augmentin) 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 adding Bactrim/Septra
    - If allergic to sulfa: Clindamycin

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

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Penicillins: Clavulin (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.

5 Facts About Penicillin Allergy (Type 1, Immunoglobulin E (IgE)-mediated)

- 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

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Penicillins: Clavulin (Augmentin)

- **Clavulin (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: Clavulin (Augmentin)

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

Penicillins: Clavulin (Augmentin)

Adults:

- **250-500 mg tab q 8hr (tid)** (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%.

Cephalosporins

- 1st generation: **cefadroxil (Duricef)**, **cefazolin (Ancef)**, **cephalexin (Keflex)**, and cephalothin
- 2nd generations: **cefaclor (Ceclor)**, cefprozil, **cefuroxime (Zinacef)**, cefotetan, cefoxitin
- 3rd generation: cefdinir **(Omnicef)**, 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)
- *Omnicef, Keflex, Ceclor* (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

Co-Trimoxazole (Bactrim/Septra)

- 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/Septra)

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

Herpes Zoster

2. 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

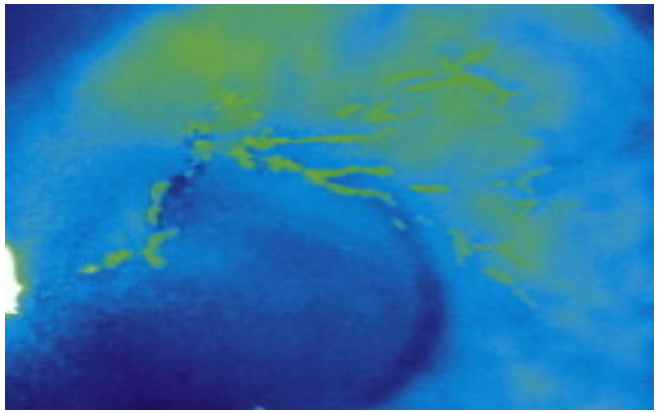
- Symptoms:
  - Generalized malaise, tiredness, fever
  - Headache, tenderness, paresthesias (tingling), and pain on one side of the scalp
    - Will often precede rash
  - Rash on one side of the forehead
  - Red eye
  - Eye pain & light sensitivity

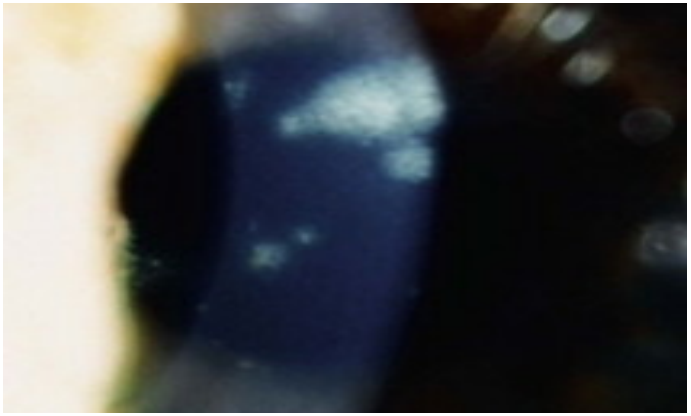
Herpes Zoster

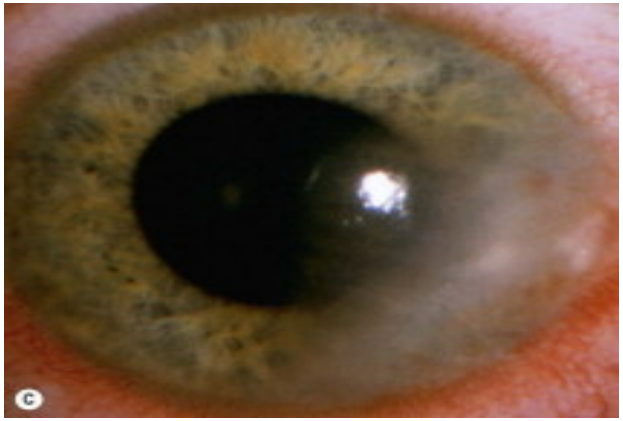
- Signs:
  - Maculopapular rash -> vesicles -> pustules -> crusting on the forehead
  - Respects the midline***
  - Hutchinson sign
    - rash on the tip or side of the nose***
  - Classically does not involve the lower lid
  - Numerous other ocular signs

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.

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).

Oxervate®

- August 22nd, 2018 the FDA approved Oxervate for the treatment of neurotrophic keratitis (first ever approved treatment)
- Oxervate® (cenegermin): recombinant human nerve growth factor
- The safety and efficacy of the topical eye drop was studied in 151 patients with neurotrophic keratitis in two 8-week, randomized, controlled, multi-center, double masked studies. In both studies, patients were given the drops six times daily in the affected eyes for 8 weeks. Across both studies, 70% of patients treated with Oxervate experienced complete corneal healing in 8 weeks compared with 28% of patients who were not treated with the active ingredient, cenegermin

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NEW!! 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.

NEW!! 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