#### Oral Pharmaceuticals in Anterior Segment Disease

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#### Disclosures

#### Paid consultant for:

Maculogix: Honoraria-Advisory Board Sun: Honoraria: Advisory Board



#### 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)



#### Herpes Simplex Keratitis

- Epithelial Keratitis:
  - 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-byherpes-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



#### **Anti-Viral Medication**

| Drug                    | Mechanism of Action  | Bioavailability   | Dosing  | Side Effects   |
|-------------------------|--|---|---|--|
| Acyclovir               | Acyclovir interferes with<br>DNA synthesis inhibiting<br>viral replication   | 10-30% gets<br>absorbed<br>Short ½ life<br>*Metabolized in<br>kidneys           | Simplex:<br>400 mg 5x/day<br>Zoster:<br>800 mg 5x/day | Overall very safe<br>Nausea, vomiting,<br>headaches,<br>dizziness, confusion |
| Valacyclovir            | Acyclovir pro-drug<br>Equivalent to acyclovir but<br>better for pain<br>management   | 95% converted to<br>acyclovir*<br>Better bioavailability<br>and longer 1/2 life | Simplex:<br>500 mg tid<br>Zoster:<br>1 g tid          | Same as acyclovir  |
| Famciclovir<br>(Famvir) | Inhibits DNA chain<br>elongation<br>It is metabolized to<br>penciclovir where it is<br>active 10-20x as long as<br>acyclovir | Superior to<br>acyclovir*   | Simplex:<br>250 mgTID<br>Zoster:<br>500 mg TID        | Same as acyclovir<br>11  |

#### **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



## 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:
  - Zirgan 5x/day until the ulcer heals, then 3x/day for one week
  - 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



#### Herpes Simplex Keratitis

- Prophylactic Treatment:
  - Reduces the rate of recurrence of epithelial and stromal keratitis by  $\approx 50\%$ 
    - 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 longterm ACV prophylaxis predisposes to ACV-refractory disease due to the emergence of corneal ACVR HSV-1.



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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-precived 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 comeal 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 2.0%, p = 0.761) or pensistent 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.

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# Pain Management: Oral Analgesics

- Conditions potentially requiring us of oral analgesics:
  - Corneal ulcers
  - Herpes simplex/zoster
  - Post-surgical
  - Trauma
  - Thermal burns



#### Acetaminophen



- Mechanism of Action is not well understood.
  - Possibly some <u>CNS</u> 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



#### 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.

## Ibuprofen

- Adult analgesic dose: 200-400mg q4hours
  - Maximum Dosage: 2400 mg/day for pain (approved for 3200 mg/day in arthritis treatment)
- OTC: 200 mg tabs
- Rx: 300, 400, 600, 800mg tabs
- 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<sup>R</sup>)
- Rx: 550 mg tablets (Anaprox<sup>R</sup> and Crysanal<sup>R</sup>)
- Adult Dose:
  - OTC: 1 tablet every 8-12 hours (can use two tablets on first dose)
  - Rx: 550 initial dose, followed by 275 (half tablet) every 6-8 hours.
    - Maximum Dose: 1375mg/day.



#### Indoleacetic Acids: Indomethacin

- Adult Dosage: 25-50 mg TID
- Rx Only: 10mg 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.



#### **Cox-2** Inhibitors

- Selective agents for only COX-2 designed to protect the GI system from the side effects seen with NSAID's.
- 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.
- It is approved for the treatment of osteoarthritis and rheumatoid arthritis.
  - Dosage: 100 mg BID or 200 mg daily



## **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: 1200 mg/day OTC and up to 3200 mg/day prescription (for RA)
  - Naproxen: 1250/day
  - Naproxen sodium: 1375/day
  - Codeine: 360 mg/day



## **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 alleve pain



#### **Opioids Information**

- Drug of first choice for the treatment of <u>severe</u> 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.
- Often administered in combination with acetaminophen or aspirin to enhance the analgesic effect.
  - FDA recommended in 2011 that all prescription narcotics containing acetaminophen standardize and limit the dosage to 325 mg.
    - This is to be slowly phased in over three years (just required in January 2014).

## **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.



#### **Opioid Side Effects**

- GI Side Effects:
  - Nausea and Vomiting (more common in ambulatory pts.)
  - Constipation
    - Opioids inhibit intestinal trace motility.
    - Very commonly found side effect.
      - Can be relieved by OTC docusate sodium (Colace).



## **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<sub>2</sub>
  - 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.



#### **Patient Education**

- Avoid all depressants especially using along with alcohol.
- Must educate all patients of risks of these symptoms and caution them for driving or operating dangerous machines.
- Stomach upset can be helped by consuming the medication with food.
- Watch for signs of breathing difficulty or changes in blood pressure.



#### 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<br>Oxycodone + APAP = Percocet or Tylox<br>Oxycodone + ASA = Percodan<br>Oxycodone + NSAID = Combunox<br>Hydromorphone (Dilaudid)<br>Codeine Sulfate = Codeine Generic<br>Meperidine (Demerol)<br>Hydrocodone + APAP = Lortab or Vicodin<br>Hydrocodone + Ibuprofen = Vicoprofen |  |
| Ш        | 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)<br>Propoxyphene with APAP = Darvocet<br>(Removed from Market in November 2010).<br>Pentazocine + APAP (Talacen)<br>Tramadol   |  |
| V        | Very limited abuse potential. May be OTC in some states.                           | Acetaminophen   |  |

# Schedule III Opioids: Codeine

- Prodrug that relies on the cytochrome P-450 system to be metabolized to active drug morphine.
  - Schedule II medication if prescribed alone (Codeine Sulfate 15, 30, 60 mg generic.)

- Analgesic effect occurs within 20 minutes of ingestion and reaches a maximum at 1 – 2 hours.
  - Ceiling effect occurs.



#### Schedule III Opioids: Codeine

- Usually administered in combination with .
  - Tylenol 3 = Codeine 30 mg and Acetamenophin 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.



# Schedule II 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.



# Schedule II 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


# Schedule II 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.



# Schedule II 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



# Schedule IV: Tramadol (Ultram)

- Central acting narcotic
  - Synethetic 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



## 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



- 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.



- 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%



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



- 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

### Acute Treatment of RCE



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



# 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



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



## 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



#### Case Example

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



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Case courtesy of Dr. Tammy Than

# Minocycline?

- Proposed mechanisms
  - Anti-inflammatory
  - Reduction in microglial activation
  - $-\downarrow$  MMPs
  - Nitric oxide production
  - Inhibition of apoptotic cell death



# 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



| 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   |
|              |           |       |        |        |

randomized clinical trials. J Neurol. 2018 Aug;265(8):1871-1879



#### 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



#### Shortly after TX







# 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



# 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
  - <u>doxycycline 50 mg po BID for 2-3 months</u>
    <u>Alternative treatment:</u>
  - <u>Azythromycin 500 mg/day for 3 days for</u> <u>three- four weeks</u>





## 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 <u>Oracea (40 mg</u> in morning) or
  - doxycycline 50 mg po or minocycline 100 mg po for 4-12 wks.
  - <u>NOTE:</u> Oracea is subantimicrobial <u>therapy</u>
  - 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 500 mg bid-tid
    - Doxycycline 100 mg bid
- Treat concurrent blepharitis





by Dipl.-Med. Frank Wiegleb zt fuer Allgemeinmedizin, Siebigerode



#### **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 Bactrim/Septra


## Penicillins: Augmentin

- <u>Augmentin is amoxicillin with potassium</u> <u>clavulanate (clavulanic acid 125 mg).</u>
- 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 <u>*low*</u>:
  - GI upset,
  - allergic reaction and anaphylaxis.
- Serious complications include:
  - anemia,
  - pseudomembranous colitis and
  - Stevens-Johnson syndrome.



## Penicillins: 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</li>
- 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, 4<sup>th</sup> and now 5th generation based largely on their bacterial susceptibility patterns and resistance to Blactamases.
- Typically administered IV or IM, <u>poor oral</u> <u>absorption</u>.



# Side Effects and Contraindications

- Hypersensitivity Reactions are common.
  - Risk of cross sensitivity with PCN's is higher for 1<sup>st</sup> 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
- <u>Omnicef, Keflex, Ceclor</u> (all orally administered) are effective against most gram positive pathogens and especially good for skin and soft tissue infections.



# 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



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





- 2. Reactivation Shingles (Herpes Zoster)
  - More often in the elderly and immunosuppressed (AIDS)
    - Systemic work-up if Zoster in someone < 40</li>
  - 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



- 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



- 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



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





- Associated factors include increasing age, immune deficiency and stress.
- Only people who had natural infection with wildtype 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.



- 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.



- 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<sup>R</sup>

- August 22<sup>nd</sup>, 2018 the FDA approved Oxervate for the treatment of neurotrophic keratitis (first ever approved treatment)
- Oxervate<sup>R</sup> (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



# 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 (<u>Zostavax®</u>) to prevent shingles and related complications
- the preferred vaccine for preventing shingles and related complications



## Case

- 30 BF presents with eye pain in both eyes for the past several days
  - Severe pain (8/10)
  - Never had eye exam before
- PMHx:
  - Has chronic bronchitis
  - Rash on legs
  - Has recently lost weight and has a fever
  - Taking aspirin for pain



# Ocular Health Assessment

- VA: 6/9 (20/30) OD, OS
- PERRL
- FTFC
- EOM"s: FROM with eye pain in all quadrants
- SLE:
  - 3+ injection,
  - 3+ cells and trace flare,
  - deposits on endo (see photo)
- IOP: 18, 18 mmHg
- DFE:
  - see attached fundus image and fluorescein angiography.



## Sarcoid Diagnosis

| Lab Test                            | Findings   |
|-------------------------------------|--|
| CBC with differential               | Anemia/thrombocytopenia/leukopenia                 |
| Serum calcium/24 hour calcium       | Hypercalcemia                                      |
| Liver/Kidney function tests         | AST/ALT/BUN/Creatinine elevated in hepatic disease |
| ACE (angiotensin converting enzyme) | Elevated in 60% of patients                        |
| Pulmonary x-rays                    | Hilar adenopathy                                   |



# **Blood Chemistry**

- Angiotensin-Converting Enzyme (ACE)
  - Found mainly in lung and liver
  - Serum elevations are found in patients with sarcoidosis, and significant levels are achieved in pulmonary sarcoid
  - Cirrhosis of the liver may produce elevated ACE levels
  - Active tuberculosis infection of the lung does NOT produce elevated ACE levels



# Diagnosis: Radiographic

- Radiographic involvement is seen in almost 90% of patients.
- Chest radiography is used in staging the disease:
  - Stage I disease shows bilateral hilar lymphadenopathy (BHL).
  - Stage II disease shows BHL plus pulmonary infiltrates.
  - Stage III disease shows pulmonary infiltrates without BHL
  - Stage IV disease shows pulmonary fibrosis.



# Diagnosis: Radiographic

- CT and MRI scans may be useful in finding granulomas in other organ systems
- Gallium scan-gallium 67 has been found to accumulate in active sarcoidal tissue



# Stages of Syphilis

#### Table 1. Stages of Syphilis

| Stage <sup>a</sup>           | Clinical Presentation  |
|------------------------------|--|
| Primary syphilis             | Single firm, round, small, and painless<br>sore (chancre)  |
| Secondary syphilis           | Nonitchy, reddish-brown skin rash and<br>mucous membrane lesions +/- systemic<br>symptoms (fever, pharyngitis, headache,<br>arthralgias) |
| Tertiary syphilis            | Gumma formation (nonspecific granulomatous lesion that may infiltrate the skin, bone, or any organ or tissue)                            |
| Latent syphilis <sup>b</sup> | Positive serologic test, but no symptoms   |



# Syphilis Diagnosis

- Typical diagnosis is with blood tests using nontreponemal and/or treponemal tests.
  - Nontreponemal test are used initially and include:
    - venereal disease research laboratory (VDRL)
    - rapid plasma reagin (RPR)
    - chemiluminescent microparticle immunoassay (CMIA)\*\*\*

\*\*\* primary screening test for patients suspected of being exposed to syphilis



# Syphilis Diagnosis

- False positives can occur with some viral infections such as (varicella and measles), as well as with lymphoma, tuberculosis, malaria, endocarditis, connective tissue disease, pregnancy
- confirmation is required with a treponemal test such as:
  - treponemal pallidum particle agglutination (TPPA) or
  - fluorescent treponemal antibody absorption test (FTA-Abs)
    - The FTA-ABS test checks for antibodies to the bacteria that cause syphilis and can be used to detect syphilis except during the first 3 to 4 weeks after exposure to syphilis bacteria..



## Tuberculosis

- Difficult to culture the slow-growing organism in the laboratory (it may take 4 to 12 weeks for blood or sputum culture).
- A complete medical evaluation for TB must include:
  - a medical history,
  - a physical examination,
  - a chest X-ray,
  - microbiological smears,
  - and cultures.
- It may also include a tuberculin skin test, a serological test.
  - The interpretation of the tuberculin skin test depends upon the person's risk factors for infection and progression to TB disease, such as exposure to other cases of TB or immunosuppression



#### Tuberculosis

- Currently, latent infection is diagnosed in a non-immunized person by a tuberculin skin test, which yields a delayed hypersensitivity type response to an extract made from M. tuberculosis.
- Those immunized for TB or with past-cleared infection will respond with delayed hypersensitivity parallel to those currently in a state of infection, so the test must be used with caution, particularly with regard to persons from countries where TB immunization is common



## Tuberculosis

- The newer interferon release assays (IGRAs) overcome many of these problems.
  - IGRAs are in vitro blood tests that are more specific than the skin test.
  - IGRAs detect the release of interferon gamma in response to mycobacterial proteins
  - These are not affected by immunization or environmental mycobacteria, so generate fewer false positive results.



# Uveitis

- Uveitis frequently is nonspecific but can be associated with:
  - systemic disease,
  - occur following trauma, or
  - be the result of a primary ocular disorder such as:
    - Fuchs's heterochromic iridocyclitis or
    - glaucomatocyclitic crisis (Possner-Schlossman syndrome)



# **Classification of Uveitis**

- 4 main questions we need answered
  - Where is the inflammation located?
  - Is disease acute or chronic?
  - Granulomatous or non-granulomatous?
  - Unilateral or bilateral?



# **Classification of Uveitis**

- Secondary Questions:
  - Demographics of the patient
  - Has this happened before? If so did it respond to treatment?
- Systemic questions:
  - Lung /breathing problems?
  - Rashes/skin problems?
  - Joint problems or low back pain?
  - Urination issues?
  - Digestive problems diarrhea? Bloody stools? Cramps?
  - Have you been out of the country recently?
  - Have you been in a wooded area? Ticks?
  - Any other systemic/autoimmune diseases?


### Classification

- Classification is the key to the proper diagnosis and management of the uveitic patient
- Most common classifications
  - Anterior vs. Intermediate vs. Posterior vs. Panuveitis
  - Acute vs. Chronic/Recurrent
  - Granulomatous vs. Non-granulomatous
  - Infectious vs. Autoimmune



### Anterior Uveitis Classification

- Acute, unilateral (or bilateral), non- granulomatous anterior uveitis
  - Idiopathic, HLA-B27, Herpetic, Behcet's
- Chronic, bilateral (or unilateral), non-granulomatous anterior uveitis
  - JIA, Fuch's Heterochromic, Idiopathic, Herpetic
- Chronic, bilateral (or unilateral), granulomatous anterior uveitis
  - TB, Sarcoid, Syphilis, VKH



# Helpful Mnemonic

- Mnemonic for acute forms of non-granulomatous uveitis: BLAIR G
  - **B**: Behcet's disease
  - L: Lyme disease
  - A: Ankylosing spondilitis
  - I: Inflammatory bowel disease (Crohns/ulcerative colitis)
  - **R**: Reactive arthritis
  - G: Glaucomatocyclitic crisis



## Uveitis

- The clinical features of anterior uveitis are readily recognizable
  - complaints of:
    - photophobia,
    - pain,
    - blurred or variable vision
- A change in the blood-aqueous barrier results in the liberation of protein and cellular matter into the anterior chamber and the vitreous.



## Uveitis

- Clinical findings of:
  - circumlimbal hyperemia,
  - cells and flare in the aqueous and anterior vitreous, and
  - keratic and trabecular precipitates





### **Uveitis: Treatment**

- "Classical treatment":
  - Pred forte: prednisolone acetate 1% formulation which allows penetration through cornea to anterior chamber
  - dependent upon the severity of the uveitis
  - In severe uveitis an aggressive treatment may require a drop every 15-30 minutes (for 6-8 hours) then every hour (while awake) until the follow up exam
  - Mild to moderate: every 1-3 hours while awake until follow up exam
- "Newer" treatment option:
  - Durezol



### **Treatment Options**

- Durezol:
  - Difluprednate
    - only difluorinated steroid
  - Steroid emulsion
  - BAK free
  - Increased "potency" so dosing needs to be less than "classical treatment" with Pred Forte
    - rough recommendation is 1/2 dosing of Pred Forte





# Cycloplegics

- Common cycloplegic agents include:
  - cyclopentolate 1-2% tid for mild-to-moderate,
  - homatropine 5% BID
  - scopolamine 0.25%
  - atropine 1% bid-tid for moderate-to-severe inflammation
- most common is the use of Homatropine 5% bid (though challenging to find due to manufacturing)
- be careful using atropine as there is potential for severe systemic side effects
  - also makes the iris essentially immobile



# Cycloplegics

- Cycloplegia:
  - used for reduction of pain,
  - break/prevent the formation of posterior synechiae
  - also functions in the reduction of inflammation
- Cycloplegics may not be enough to break existing synechiae
  - Consider adding a sympathomimetic drug such as phenylephrine which activates the iris dilator muscles and may break the synechiae
  - 2.5% is commonly used as part of "routine" dilation but 10% is also available and is primarily used for breaking synechiae
    - Word of caution: 10% is contraindicated in patients with hypertension or thyrotoxicosis and children under the age of 1.
    - Cardiovascular effects which have been seen primarily in hypertensive include marked increase in blood pressure, syncope, myocardial infarction, tachycardia, arrhythmia and subarachnoid hemorrhage



- Topical administration is most common though periocular injections and systemic meds are useful for posterior uveitis and difficult cases
- Dosing is dependent upon severity of the inflammation
  - typically you want to hit the uveitis hard and fast!
    - E.g In severe uveitis an aggressive treatment may require a drop every 15-30 minutes (for 6-8 hours) then every hour (while awake) until the follow up exam
    - Mild to moderate: every 1-2 hours while awake until follow up exam
    - Dosing should continue until the inflammation is gone (i.e. no cells or flare noted in the anterior chamber) before steroid tapering
    - If you have a minimal anterior chamber reaction then steroid may not be necessary at all (e.g. traumatic iritis)



- NOTE: it is crucial to taper your steroid treatment!
  - You will have a rebound inflammation if you simply remove your patient from their steroids...especially if the anterior chamber is not completely resolved.
    - Consider beginning taper a day or two after you have seen resolution of the anterior chamber reaction to ensure no residual inflammation



- The taper will be dependent upon how long you have had them on the steroid to get rid of the inflammation!
- Typically, a slow taper is better in order to prevent rebound inflammation
- If the patient has been on the steroid for less than a week a faster taper can be considered.
- Important to inform patient that they may be receiving steroid treatment for a significant time period (weeks to months) and important to not stop treatment even if feeling better.



• NSAIDs:

 do not play an important role in the treatment of an acute uveitis

- Topical NSAID's may have a possible role as adjunctive therapy in reducing inflammation and potentially treat CME associated with the uveitis
- Oral NSAIDs may reduce the chance of recurrence and reduce the total cumulative dose of steroids
  - Note: this has to be balanced with the side effects of chronic oral NSAID use



## Follow-up

- Every 1-7 days in acute phase depending upon severity and every 1-6 months when stable.
- On each f/u visit the AC reaction and IOP should be evaluated
  - DFE should be performed for flare-ups, when VA affected, or every 3-6 months.



# Follow Up

- If AC reaction improving, then steroid drops can be slowly tapered.
  - cycloplegia can also be tapered as the AC reaction improves.
  - slow taper recommended for chronic granulomatous uveitis.

