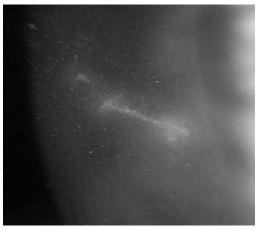
ORAL PHARMACOLOGY IN ANTERIOR SEGMENT DISEASE

Blair Lonsberry, MS, OD, MEd
Professor of Optometry
Pacific University College of Optometry
blonsberry@pacificu.edu

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

- Most common virus found in humans
  - 60-99% are infected by 20 years old
- Double stranded DNA virus
  - HSV type 1 (HSV-1)
  - HSV type 2 (HSV-2)
- Primary infection
  - Occurs in childhood via droplet exposure
  - Subclinical infection in most
- Secondary infection (recurrence)

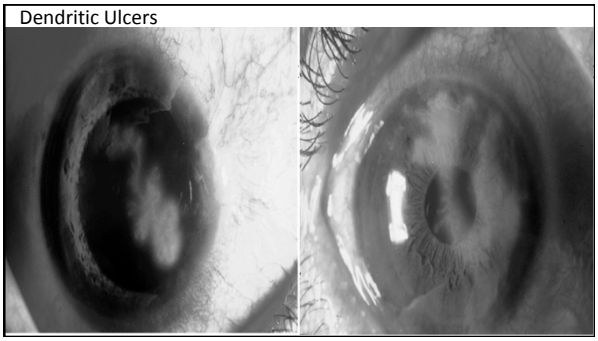
Herpes Simplex

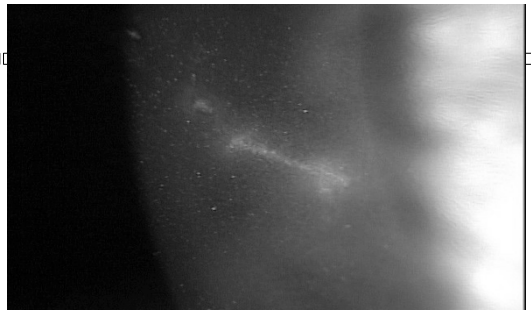
- Recurrent infection:
  - After primary infection the virus is carried to the trigeminal ganglion where a latent infection is established.
  - Latent virus is incorporated in host DNA
  - Stress (trauma, UV light, fever, hormonal changes, finals week, etc) causes reactivation of the virus

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





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

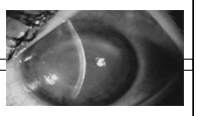
Herpes Simplex Keratitis Management

- 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)

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:
  - 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

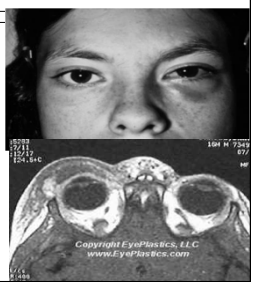
- Prophylactic Treatment:
  - Reduces the rate of recurrence of epithelial and stromal keratitis by ≈ 50%
    - Acyclovir 400 mg BID
    - Valtrex 500 mg QD
    - Famvir 250 mg QD
    - L-lysine 1 gram/day:
      - Proven to "slow down" and retard the growth of the herpes virus and inhibit viral replication
    - 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.

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.



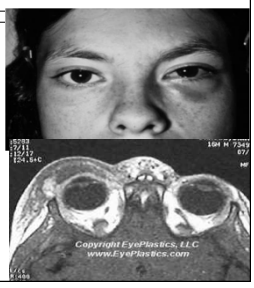
Differentiating Orbital vs. Preseptal

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:
  - ***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 (Clavulin)

- **Augmentin (Clavulin) 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).

Penicillins: Augmentin (Clavulin)

- **Augmentin (Clavulin) 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 (Clavulin)

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

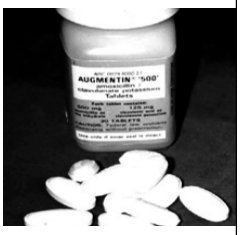
Penicillins: Augmentin (Clavulin).

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 5th generation based largely on their bacterial susceptibility patterns and resistance to B-lactamases.
- Should be avoided or used with caution in patients who are allergic to penicillin **(apprx 10% x-reaction with penicillin allergy has been reported but thought to be much closer to the 1-2%)**
  - allergic response without allergy to penicillin is 1-2%.
- Typically administered IV or IM, **poor oral absorption**.

Cephalosporins

- 1st generation: **cefadroxil, cefazolin (Ancef), cephalexin (Keflex)**, and cephalothin
- 2nd generations: **cefaclor (Ceclor)**, cefprozil, **cefuroxime**, cefotetan, cefoxitin
- 3rd generation: **cefdinir (Omnicef)**, cefixime, **cefotaxime (Claforan)**, **ceftazidime (Fortaz)**, ceftibuten, ceftizoxime, **ceftriaxone (Rocephin IM, IV)**.
- 4th generation: cefepime
- *Keflex, Ceclor, and Omnicef* (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)

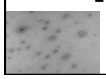
- Resistance is more difficult because has to develop resistance to both drugs.
- Adverse effects include:
  - severe potential for dermatologic reactions,
  - GI upset,
  - blood disorders, and
  - drug potentiation.

Co-Trimoxazole (Bactrim/Septra)

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

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

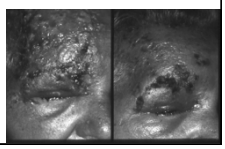


Herpes Zoster

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

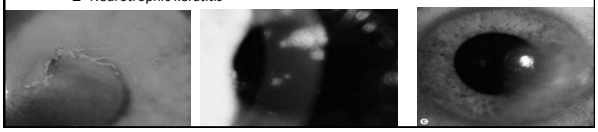
Herpes Zoster

- 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

- 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).

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

AAO Recommendations (2015)

- The AAO recommends vaccination for 50-59
  - Highest efficacy in this group
  - Decreasing age of disease onset
  - higher risk of ocular and systemic complications
  - Greatest number of cases
- Vaccination in this earlier age group would reduce the economic burden (work productivity) and morbidity

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

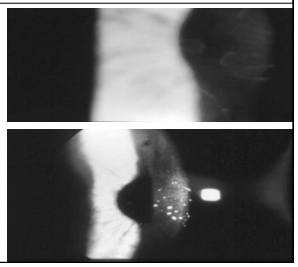
- Abnormal basement membrane production
- Not all patients are symptomatic (range 10-69%)
- Most common symptom is mild FB sensation which is worse in dry weather, wind and air conditioning
- Blurred vision from irregular astigmatism or rapid TBUT
- Pain is usually secondary to a RCE (recurrent corneal erosion) in apprx 10%

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

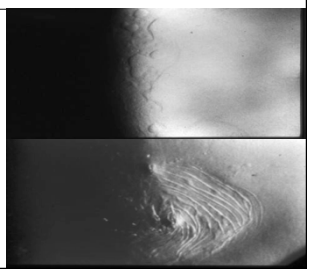
Epithelial (Anterior) Basement Membrane Dystrophy (EBMD or ABMD)

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

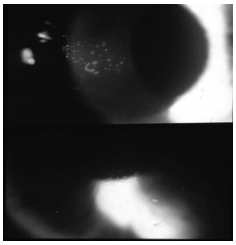


Epithelial (Anterior) Basement Membrane Dystrophy (EBMD or ABMD)

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

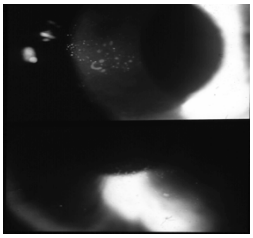


Epithelial (Anterior) Basement Membrane Dystrophy (EBMD or ABMD): Treatment



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

RCE: Treatment



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

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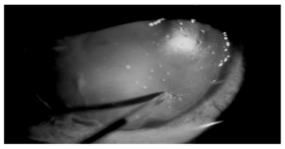
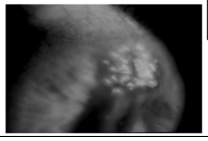
Recurrent Corneal Erosion: Treatment

- 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
    - Azasite (topical azithromycin)
  - debridement,
  - stromal puncture, or
  - PTK
  - Latest development: amniotic membrane transplant e.g. Prokera

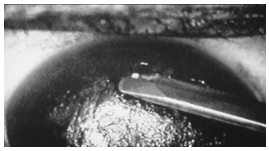
Stromal Puncture





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%



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

ProKera

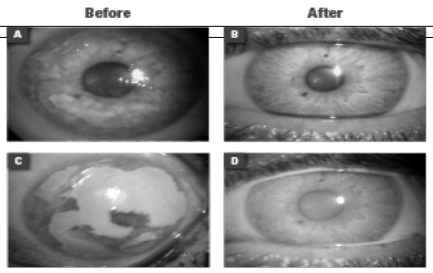
ProKera Clear:

- has a trephinated 6mm aperture allowing some visual potential
- best suited for chronic inflammatory cases with the limbus being the targeted area of biologic boost and healing e.g. KCS

ProKera

- ProKera
- ProKera Slim:
  - ComfortRing™ Technology was designed with a slim profile that contours to the ocular surface, moves with the eye, and maximizes amniotic membrane contact with the cornea, limbus, and limbal stem cells, providing clinical benefits and maximizing patient comfort
- ProKera Plus:
  - incorporates multiple layers of amniotic membrane that make it suitable for therapeutic applications requiring longer biologic action and durability on the ocular surface. It is recommended for use in severe indications such as chemical burns, Stevens Johnson Syndrome, and severe corneal ulcers.

Recurrent Corneal Erosion



http://www.biotissue.com/products/prokera/prokera-indications/recurrent-corneal-erosion-ppv

AmbioDisk

- ~~AmbioDisk™ Amniotic Membrane from IOP Ophthalmics~~
- AmbioDisk™ is a 4th generation amniotic membrane (AM) technology - a sutureless, overlay AM disk for the office-based or surgical treatment of the ocular surface.
- **Conventional Uses**
  - Non-Healing Epithelial Defects
  - Neurotrophic Ulcerations
  - Corneal Erosions
  - Acute Chemical/Thermal Burns
  - Post-Infectious Keratitis (herpetic, vernal, bacterial)

Diamond Burr Polishing

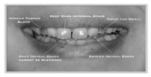
- Removes abnormal basement membrane
- May also promote scarring

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**

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.**
    - Erythomycin ung (Ilotycin) can also be used externally.