

Simplifying Systemic Antibiotics

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Disclosures:

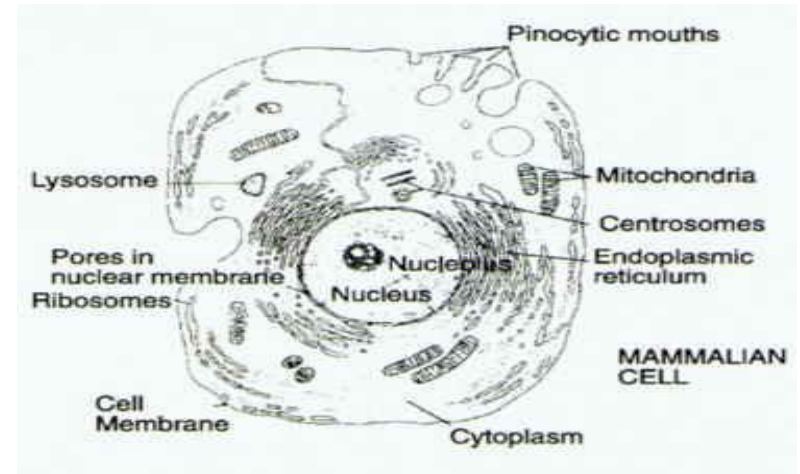
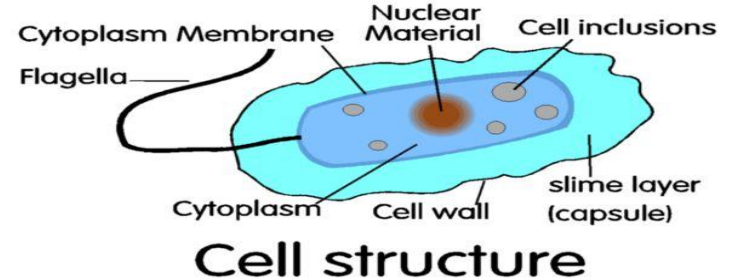
- Sun Pharmaceuticals: speakers bureau,
- Dompe: advisory board,
- RVL Pharmaceuticals: advisory board:
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Principles of Antimicrobial Therapy

- Structural and biochemical differences exist between humans and microorganisms.

Antimicrobial therapy takes advantage of these differences, e.g.

- Bacterial cell wall
- Bacterial ribosomes

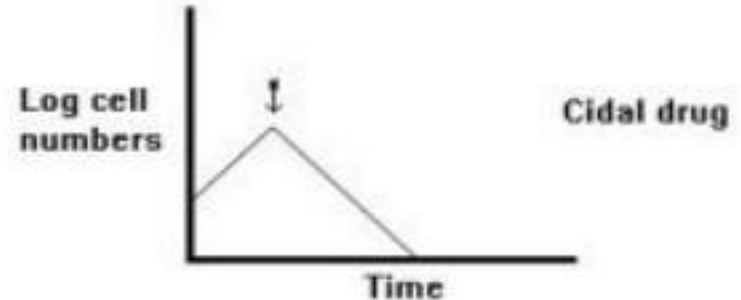
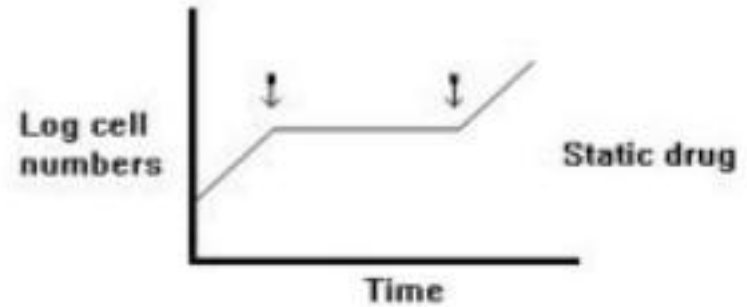


Principles of Antimicrobial Therapy

- Selection of an appropriate antimicrobial requires:
 - knowledge of the organism's identity,
 - its susceptibility,
 - site of infection,
 - patient factors,
 - safety of agent and
 - cost of therapy.
- Often, the organism is not conclusively identified, and the treatment is empirical.
- Children 12 years and older can be dosed as an adult unless special considerations

Principles of Antimicrobial Therapy

- Bacteriostatic vs. Bactericidal drugs:
 - **bacteriostatic** drugs “arrest” the growth and replication of bacteria thus limiting the spread of infection while the body attacks.
 - **bactericidal** drugs kill bacteria at serum concentration levels



Principles of Antimicrobial Therapy

- Adequate levels of the antibiotic must reach the site of infection.
 - different tissues have variable permeability to the drugs.
 - natural barriers to drug delivery exist, such as prostate, CNS, brain and vitreous.
- Patient factors are crucial in drug selection. For example:
 - the status of patient's immune system,
 - kidneys, liver, circulation,
 - age, gender, pregnancy, breast feeding,
 - allergies, etc.

Principles of Antimicrobial Therapy

- many of the antibiotics are minimally toxic
 - such as penicillins as they interfere with a site unique to bacteria growth
- others are reserved for life-threatening infections because of potential for serious toxicity
 - e.g. chloramphenicol
- cost of therapy also needs to be considered,
 - ie. if similar efficacy is achieved with a generic or less expensive medication (or combo of meds) that may increase compliance.

Chemotherapeutic Spectra

- **Narrow-spectrum antibiotics:**
 - act only on a single or a limited group of microorganisms, e.g. isoniazid active only against mycobacteria.
- **Extended-spectrum antibiotics:**
 - effective against gram + and significant number of gram - bacteria, e.g. ampicillin.
- **Broad-spectrum antibiotics:**
 - effective against wide variety of microbial species (e.g. tetracycline and chloramphenicol).
 - their use can drastically alter the body's normal flora (and result in superinfections)

Antibiotic Resistance

- Microorganism that was originally in the spectrum of activity is no longer susceptible to the drug.
- **Mechanisms of Resistance Include:**
 - Producing an enzyme capable of destroying or inactivating the antibiotic.
 - Altering the target site receptor for the antibiotic so as to reduce or block its binding.
 - Preventing the entry of the antibiotic into the bacterial cell or actively transporting the antibiotic out.

Avoiding Resistance

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

Preventing Resistance

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

MRSA

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

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



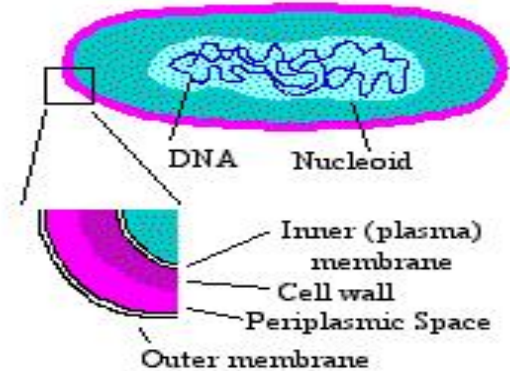
ARMOR

- Antibiotic Resistance Monitoring in Ocular Microorganisms (ARMOR)
- Approximately 39% of isolates were determined to be MRSA
- Newer fluoroquinolones have better activity than earlier generations
- Increased resistance to tobramycin
- Besivance has the lowest MIC values of all the fluoroquinolones
- Vancomycin is drug of choice if MRSA present
- Azithromycin had very poor activity against Staph

Inhibitors of Cell Wall Synthesis

Inhibitors of Cell Wall Synthesis

- Human cells do not possess a cell wall like bacteria do
 - it is a very selective way to interfere with bacterial growth.
- To be maximally effective, the inhibitors require actively proliferating bacteria
 - they are ineffective against non-dividing bacteria.
- The most important members of this group are:
 - **B-lactam antibiotics and**
 - **vancomycin.**



B-Lactam Antibiotics

- This group includes:
 - penicillins,
 - cephalosporins,
 - carbapenems and monobactams.
- All PCN's have short $\frac{1}{2}$ lives
- **B-lactamase inhibitors are sometimes added in combination to reduce a bacteria's ability to overcome the activity of the antibiotic**
 - E.g potassium clavulanate (clavulanic acid)

Penicillins

- Among the most widely effective and least toxic
 - increased resistance has limited their use
 - they are bactericidal
- Interfere with the last step of bacterial wall synthesis, resulting in cell lysis.
- Therapeutic application in gram (+) cocci and bacilli, gram (-) cocci, anaerobic, spirochetes (syphilis).
- The most common side effects include hypersensitivity and diarrhea
 - Antibiotic associated diarrhea (AAD)

Antibiotic Associated Diarrhea (AAD)

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

AAD and Probiotics

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

5 Facts About Penicillin Allergy

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

Penicillins

- This group includes the following commonly used members:
 - **Amoxicillin** (250 tid, 500 bid or tid, 875 mg bid or extended release 775mg qd)
 - May be taken with food
 - treatment of otitis media, sinusitis, and infections caused by susceptible staph/strept involving upper and lower respiratory tract, skin and urinary tract; prophylaxis of infective endocarditis
 - Pediatric dosing:
 - <3 months: oral 20-30 mg/kg/day divided q 12 hrs
 - >3 months: oral 20-50 mg/kg/day divided 8-12 hrs
 - >12 yrs: extended release 775 mg daily

Penicillins

Name	Treatment for	Administration
Penicillin G and V	All stages and forms of syphilis	Via IM or IV injection
Ampicillin	Prophylactic use in dental surgery patients Active against haemophilus and salmonella	Adults: - 250-500 mg every 6 hours
Nafcillin	Osteomyelitis, septicemia, endocarditis and CNS infections	IM/IV Adults: - 500 mg every 4-6 hours

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 effect).

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.

Stevens-Johnson Syndrome

- Stevens-Johnson syndrome is a rare, serious disorder of the skin and mucous membranes.
 - reaction to a medication or an infection
 - begins with flu-like symptoms, followed by a painful red or purplish rash that spreads and blisters. Then the top layer of the affected skin dies and sheds.
 - medical emergency that usually requires hospitalization.



Penicillins: Augmentin (Clavulin)

Adults:

- 250 mg 3x/day
- 500 mg bid or tid
- or 875 mg q 12hr (bid)
- also available in chewable tablets and suspension

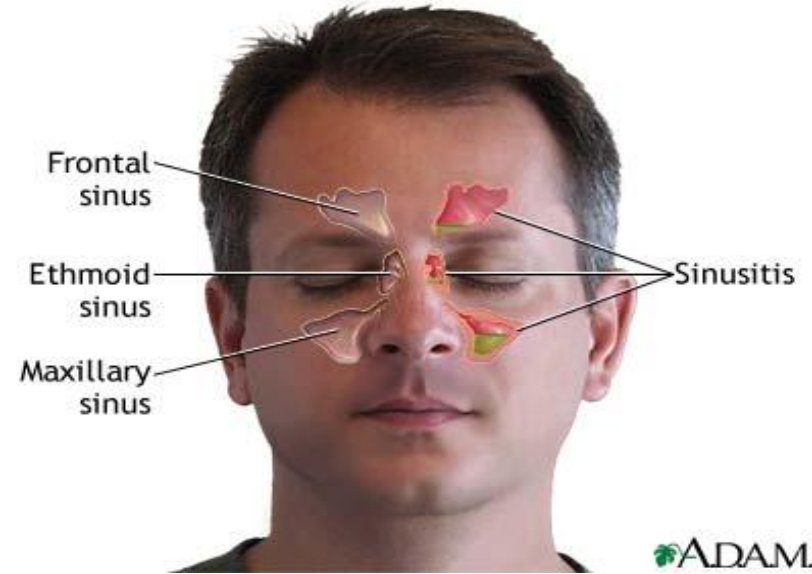
Peds: <3 mos 30mg/kg/day divided q12hrs using suspension

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



Sinusitis Red Eye

- Sinus infections (rhinosinusitis), are an inflammation of the nasal and sinus passages that can cause uncomfortable pressure on either side of the nose and last for weeks
- The increase in mucus creates pressure in the sinuses that leads to pain.
- Most develop during or after a cold or other upper respiratory infection, but allergens and environmental irritants may also trigger them



Sinusitis Treatment

- The majority of sinus infections are VIRAL (>90%)
- Acute rhinosinusitis accounts for 1 in 5 antibiotic prescriptions for adults, making it the fifth most common reason for an antibiotic prescription
- The infection is likely bacterial and should be treated with antibiotics if:
 - symptoms last for 10 days without improvement, or
 - include fever of 38.9 degrees C (102 degrees F) or higher,
 - nasal discharge and facial pain lasting three to four days
- Because of increasing resistance to the antibiotic amoxicillin – the current standard of care – the ISDA recommends Augmentin (Clavulin)
- Augmentin (Clavulin) 500 TID (or 875 bid) for 5-7 days for adults, 10-14 days for children

Penicillins: Hordeola:

- **Internal** are secondary to a staph infection of the meibomian glands (often considered low grad preseptal cellulitis)
- **External** are an infection of the Zeis or Moll glands
 - Patients present with tenderness and swelling of affected area.
- **Treatment includes:**
 - hot compresses (with masks versus washcloth)
 - topical antibiotics (?)
 - **possibly systemic antibiotics**
 - Augmentin (Clavulin) 875 mg BID x 7days
 - Keflex 500 mg TID-QID x 7 days
- Treat concurrent blepharitis



Penicillins: Dacryocystitis

- infection of the lacrimal sac usually secondary to an obstruction.
- in pediatric patients:
 - the obstruction usually resolves by age 9-12 months.
 - many pediatric ophthalmologists will wait until after this age to probe the ducts to free the obstruction.



Penicillins: Dacryocystitis

- Treatment includes:
 - Augmentin (Clavulin) 875 mg BID x 7 days
 - Keflex 500 mg TID-QID x 7 days
- Recommend referral to oculo-plastics for silicone tube intubation or DCR (dacryocystorhinostomy)



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



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

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)
- Keflex, Ceclor, Omnicef (all orally administered) are effective against most gram positive pathogens and especially good for skin and soft tissue infections.



Cephalosporins

- **Keflex (cephalexin) 1st Generation:**
 - 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
 - Available:
 - 250 mg
 - 500 mg
 - 750 mg (pricey)
 - Typically a BID dosing
 - Not commonly used

Cephalosporins

- Cefaclor (Ceclor) (2nd generation):
 - Immediate-release: 250 to 500 mg every 8 hours
 - Extended-release: 500 mg every 12 hours
- Mild preseptal cellulitis = 250-500 mg TID in adults and 20-40 mg/kg/day in three divided doses for children

Cephalosporins

- Cefdinir (Omnicef no longer available in the US, available as generic)
 - Used in the treatment of community acquired pneumonia, acute flare ups of chronic bronchitis, acute maxillary sinusitis and tonsilitis.
 - Adult dosing:
 - comes in 300 mg capsules and recommended dosing is 600 mg per day (single dose is equivalent to 300 every 12 hours)

Cephalosporins: Hyperacute Conjunctivitis

- Hyperacute conjunctivitis:
 - usually secondary to gonorrhoea (possibly chlamydia).
 - profuse purulent discharge,
 - pain,
 - redness,
 - chemosis,
 - papillae,
 - positive nodes



Chlamydia and Gonorrhea: Diagnosis and Treatment

- NAATs (nucleic acid amplification **test**) are the most sensitive tests and are recommended for detecting chlamydia and gonorrhea infections

Gonorrhea Recommended Management

- *N. gonorrhoeae* is classified as an URGENT THREAT on the CDC's list of Antibiotic Resistance Threat Reports
- For uncomplicated gonococcal infections of the cervix, urethra, and rectum
 - **Ceftriaxone 500 mg*** IM in a single dose for persons weighing <150 kg
 - If chlamydial infection has not been excluded, treat for chlamydia with doxycycline 100 mg orally 2 times/day for 7 days.
 - * For persons weighing ≥150 kg, 1 g ceftriaxone should be administered.
- Should be tested for other STIs
- Sexual partners must be tested and treated
- Report to state or local health department

Gonorrhea Recommended Management

- Alternative Regimens if Ceftriaxone Is Not Available
 - **Gentamicin** 240 mg IM in a single dose
 - PLUS
 - **Azithromycin** 2 g orally in a single dose
 - OR
 - **Cefixime (Suprax) 800 mg* orally in a single dose**
 - * If chlamydial infection has not been excluded, providers should treat for chlamydia with doxycycline 100 mg orally 2 times/day for 7 days.
 - An 800-mg oral dose of cefixime should be considered only as an alternative cephalosporin regimen because it does not provide as high, nor as sustained, bactericidal blood levels as a 500-mg IM dose of ceftriaxone.

Recommended Management for Ocular Infection

- Lavage infected eye with saline solution once
- **Adult and children ≥ 45 kg: Ceftriaxone 1 g IM in 1dose**
- Children: Ceftriaxone 25-50 mg/kg IV or IM in 1dose, not to exceed 125 mg
 - Hospitalize infants to watch for disseminated infection
 - Treat mother and mother's sexual partners
- Possible topical fluoroquinolone treatment?
- **NOTE: Topical antibiotic therapy alone is inadequate and unnecessary if systemic treatment is administered**

Ophthalmia Neonatorum Prophylaxis

- Prophylaxis has traditionally been done on all newborns shortly after birth to prevent gonococcal/chlamydial conjunctivitis
- However, erythromycin ointment has on occasion become in short supply and so availability has to be constantly re-assessed
 - Alternative available ophthalmic antibiotics have not been tested for safety nor efficacy for prophylaxis in newborns.
 - Recommended Regimen
 - Erythromycin (0.5%) ophthalmic ointment in a single application

Chlamydia Management

- Anogenital and conjunctival chlamydia
 - Non-pregnant and non-lactating adults
 - Doxycycline 100 mg PO bid X 7 days
 - Alternative treatment:
 - **Azithromycin** 1 g orally in a single dose
 - OR
 - **Levofloxacin** 500 mg orally once daily for 7 days

Chlamydia Management

- Anogenital and conjunctival chlamydia
 - Previously a single gram dose of azithromycin was considered standard of care however doxycycline is now the new recommended standard:
 - A meta-analysis and a Cochrane systematic review evaluated data from randomized clinical trials of azithromycin versus doxycycline for treating urogenital chlamydial infection determined that microbiologic treatment failure among men was higher for azithromycin than for doxycycline.
 - Observational studies have also demonstrated that doxycycline is more efficacious for rectal *C. trachomatis* infection for men and women than azithromycin.
 - A randomized trial for the treatment of rectal chlamydia infection among MSM reported microbiologic cure was 100% with doxycycline and 74% with azithromycin
 - Sexual partners must be tested and treated
 - Report to state or local health department

Chlamydia Management

- Adult Inclusion Conjunctivitis
 - Treat systemically
 - Erythromycin ung bid to tid X 3 w (????)
 - Clinical signs may take 2 - 3 m to resolve and recurrence is possible
- Neonatal inclusion conjunctivitis
 - Neonatal ocular prophylaxis with erythromycin is ineffective against chlamydial ophthalmia
 - Oral erythromycin 500 mg/kg/d X 2 weeks

Cephalosporins

- **Dacryocystitis Tx:**
 - Keflex 250-500 mg po QID,
 - In febrile cases:
 - IV cefazolin (Ancef) 1g q8h or
 - IV cefuroxime (Zinacef) 1.5g q8h.
- **Preseptal cellulitis:**
 - Mild:
 - Ceclor (cefaclor) 250-500mg q8h
 - Moderate to severe:
 - IM Rocephin (ceftriaxone) 1-2 grams/day or
 - IV Fortaz (ceftazidime) 1-2 g q8h.

Cephalosporins: Orbital Cellulitis

- infection and inflammation within the orbital cavity producing orbital S&S.
- most commonly secondary to ethmoid sinusitis.
- **Staph and Strept most common isolates.**
- Signs and Symptoms include:
 - decreased VA,
 - pain,
 - red eye,
 - HA,
 - diplopia,
 - bulging eye,
 - APD,
 - EOM restriction,
 - lid swelling and
 - fever (generally 102 degrees F or higher)



Cephalosporins: Orbital Cellulitis

Treatment

Vancomycin: 40-60 mg/kg IV per day every 8 to 12 hours

PLUS: (one of the following)

- Ceftriaxone (Rocephin): 2 g IV every 24 hours **or**
- Cefotaxime: 2 g IV every four hours **or**

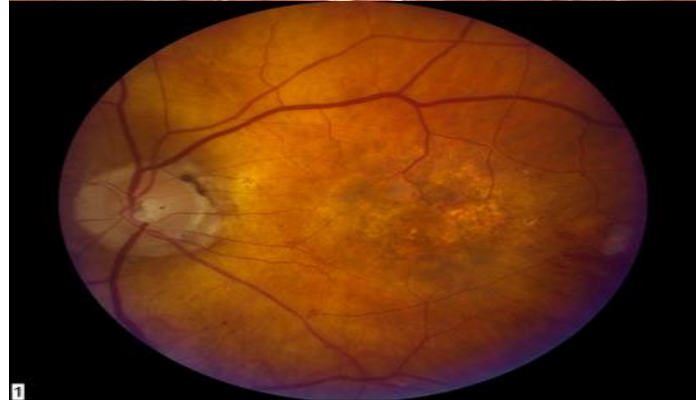
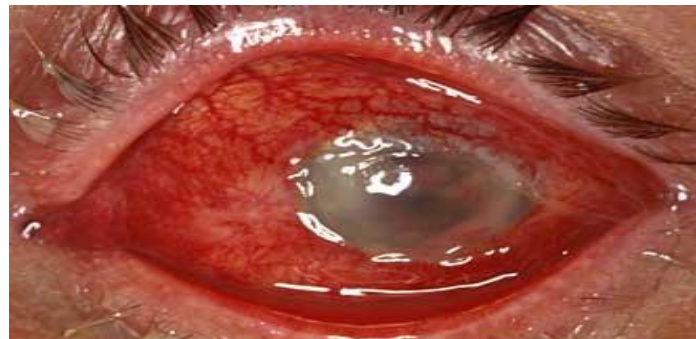


Orbital Cellulitis

- IV therapy continued until improvement noticed (minimum 3-5 days)
- Switch to oral antibiotics (2-3 weeks):
 - Clindamycin 300 mg every 8 hours
 - Clindamycin or Bactrim/Septra PLUS
 - Augmentin 875 mg every 12 hours **or**
 - Cefpodoxime 400 mg every 12 hours **or**
 - Cefdinir 300 mg twice daily

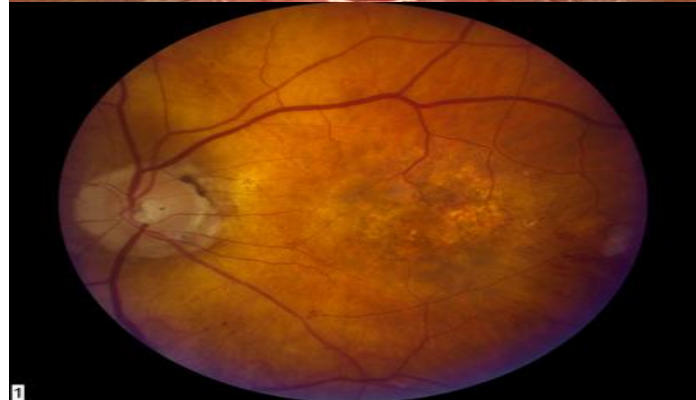
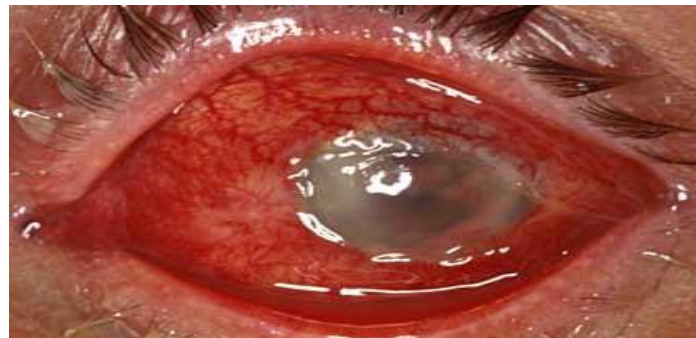
Endophthalmitis

- intraocular infection involving anterior/posterior segments usually secondary to postoperative infection, intravitreal injection or trauma.
 - 95% gram +ve bacteria including
 - staph (80%), strept (10%) with about 6% gram –ve organisms (these infections to be more virulent and have worse prognosis)



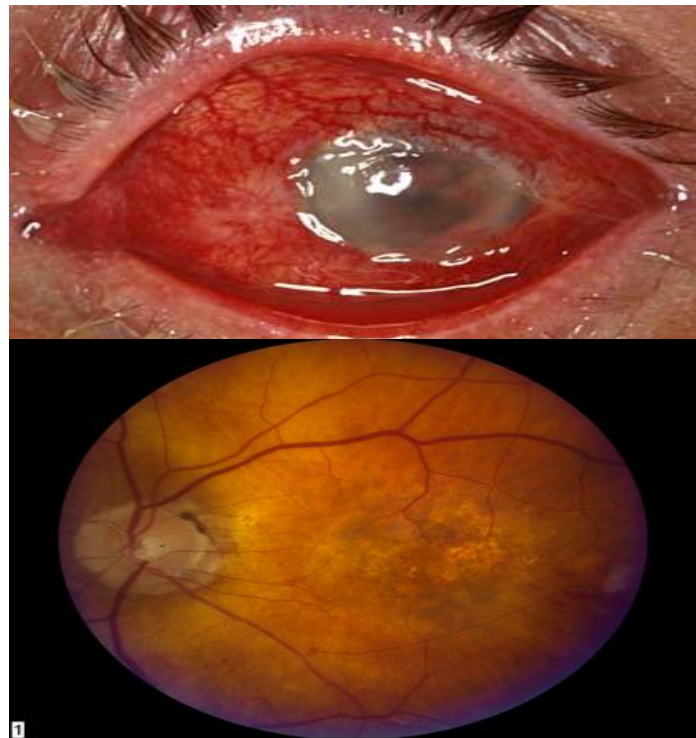
Endophthalmitis

- Signs/symptoms typically present:
 - Post-trauma: 12-24 hours
 - Post –surgery: occurs within six weeks of surgery, typically within a few days
 - Post-intravitreal injection: 24 hours to 26 days (average: 4 days)
- While post-cataract surgery endophthalmitis was the most common type of endophthalmitis reported in most series prior to 2005, **post-injection endophthalmitis cases now exceed post-cataract surgery endophthalmitis** cases at many centers that perform both procedures



Endophthalmitis

- Patients' present with:
 - decreased VA (95%)
 - pain (75%),
 - red eye (80%),
 - hypopyon (>80%)
 - discharge, proptosis,
 - corneal edema, injection,
 - KP' s,
 - vitritis, photophobia,



Post-operative Endophthalmitis

Treatment

Post-operative endophthalmitis:

- Endophthalmitis Vitrectomy Study (EVS), vitrectomy decreased the rate of severe vision loss from 47% (tap group) to 20% (vitrectomy group) in patients who presented with the worst vision (light perception only)
- Intravitreal:
 - vancomycin 1 mg/0.1ml and ceftazidime (Fortaz) 2.25 mg/0.1 ml (or amikacin)
 - if no improvement after 48 hours a repeat injection of either vancomycin or Fortaz (but not amikacin secondary to retinal toxicity issues)
 - Intravitreal steroids maybe considered

Vancomycin/Bacitracin

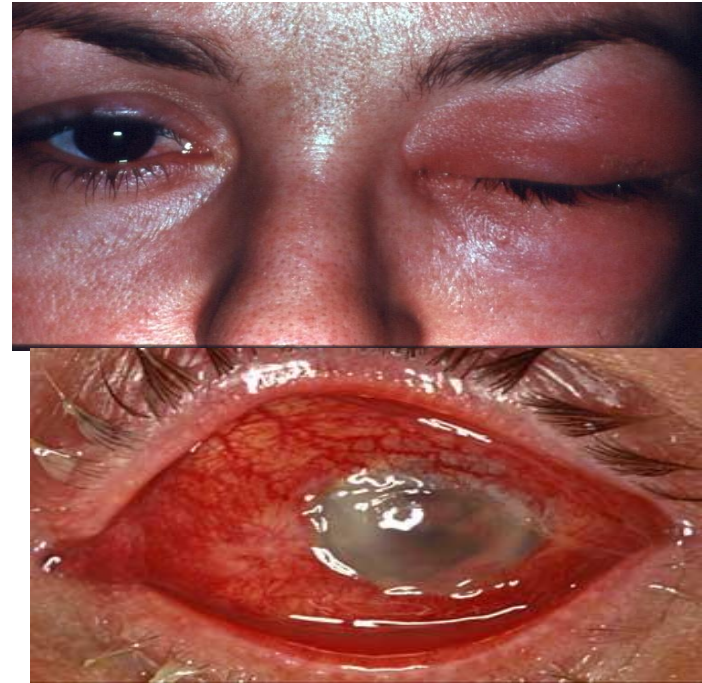
- Vancomycin and bacitracin both inhibit cell wall synthesis.
- **Vancomycin is increasingly important as it is effective against multiple drug-resistant organisms (such as MRSA/MRSE and enterococci)**
 - used in patients who have penicillin allergies
 - often considered the drug of last resort, though overuse has brought about resistance.
- **Bacitracin is active against a wide variety of gram (+) organisms**
 - restricted to topical use due to its potential for nephrotoxicity.

Vancomycin

- Vancomycin is typically administered systemically as an infusion due to its poor oral absorption
 - complications are minimized when it is administered at less than 10 mg/min
 - topical fortified vancomycin can be compounded (25-50 mg/ml) (Vancocin HCl 2.5% Ophthalmic Drops)
- Complications include:
 - anaphylaxis (hypotension, wheezing, dyspnea, urticaria, pruritis),
 - upper body flushing,
 - pain secondary to muscle spasm, nausea, diarrhea, headache.
 - typically the most serious complication is nephrotoxicity but it is an infrequent complication

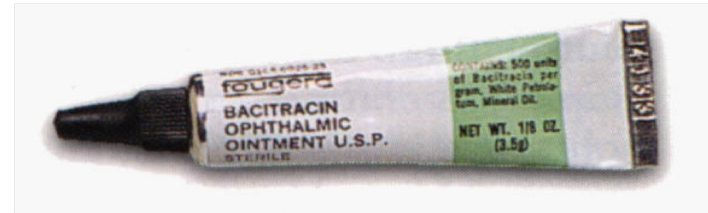
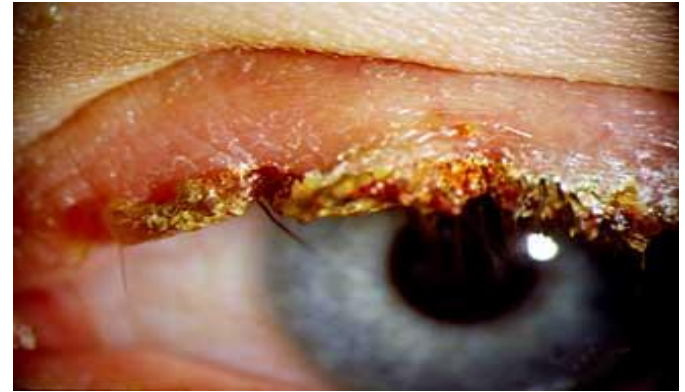
Vancomycin

- Treatment:
 - Orbital Cellulitis
 - Endophthalmitis



Bacitracin

- Due to nephrotoxicity, *bacitracin not used as a systemic med.*
- Bacitracin useful for bacterial lid disease (staph blepharitis)
 - has a low rate of allergy and toxicity.
- Primarily gram + activity so usually found in combination with a gram - compound
 - e.g. polymixin B (Polysporin).



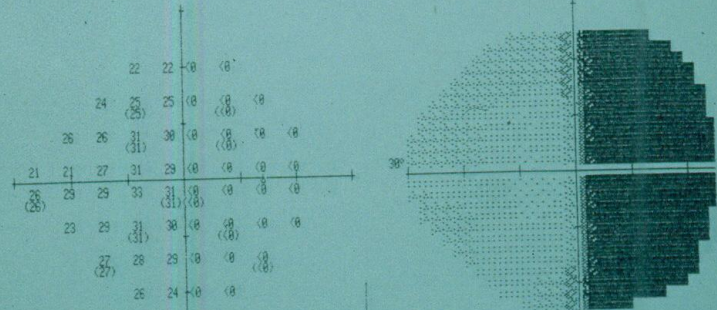
Case Example

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

AC

FT

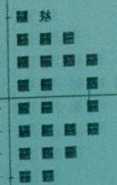
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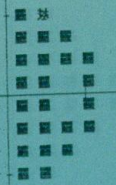
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PATTERN DEVIATION



PROBABILITY SYMBOLS
 □ P < 5%
 ■ P < 2%
 ■ P < 1%
 ■ P < 0.5%



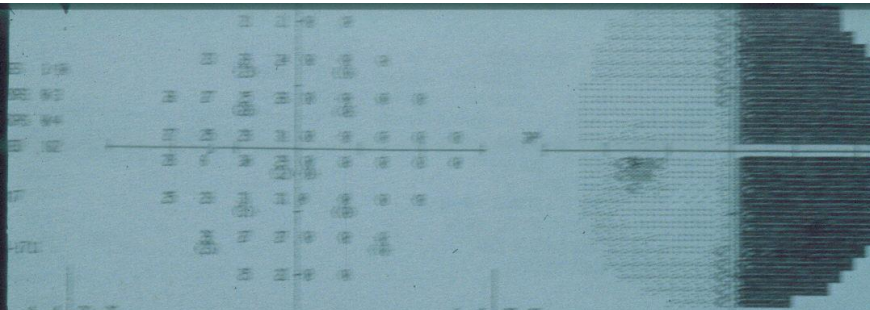
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 GPSD 15.87 DB P < 0.5%

GRAYTONE SYMBOLS

REV 9.1

8	2.5	8	25	79	251	794	2512	7943	2
.1	1	3.2	10	32	100	316	1000	3162	10000
41	36	31	26	21	16	11	5	1	50
50	40	35	30	25	20	15	10	5	50

HUMPHREY INSTRUMENTS
 A CARL ZEISS COMPANY

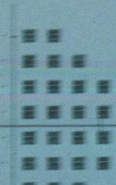


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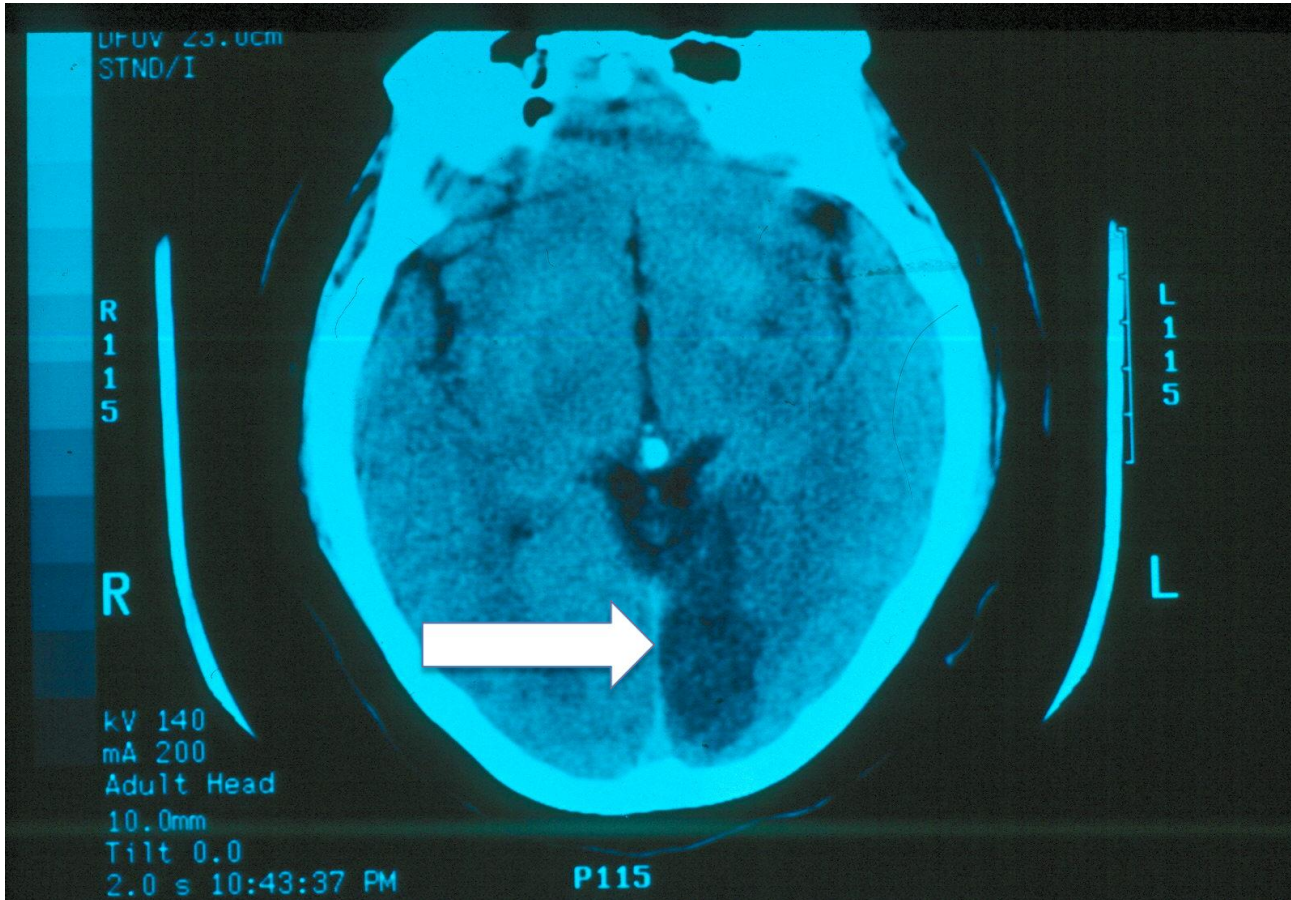


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Case courtesy of Dr. Tammy Than

Minocycline?

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

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



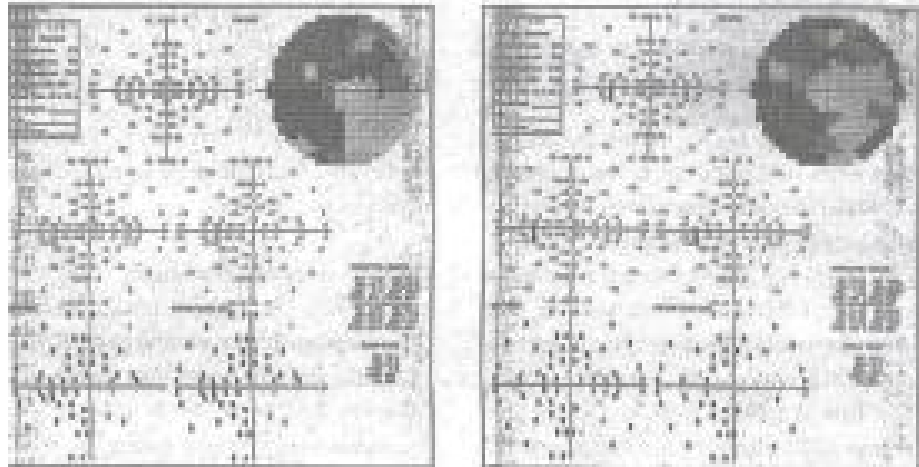
Total NIH Stroke Scale Score	
1a - Level of Consciousness:	1
1b - LOC Questions:	1
1c - LOC Commands:	1
2 - Best Gaze:	0
3 - Visual Fields:	0
4 - Facial Palsy:	2
5a - Left Motor Arm:	2
5b - Right Motor Arm:	0
6a - Left Motor Leg:	1
6b - Right Motor Leg:	0
7 - Limb Ataxia:	0
8 - Sensory:	1
9 - Best Language:	0
10 - Dysarthria:	1
11 - Extinction and Inattention:	0
Total NIHSS Score: 10	
Home Reset All	

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

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

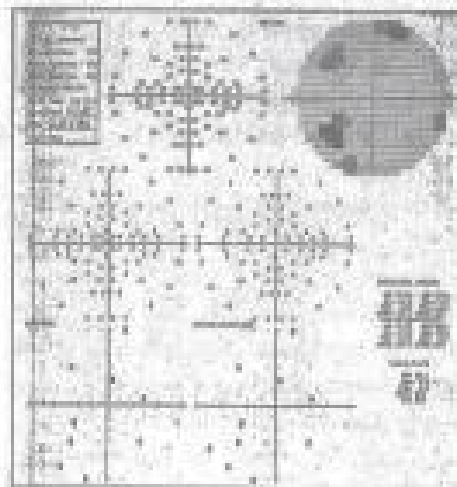
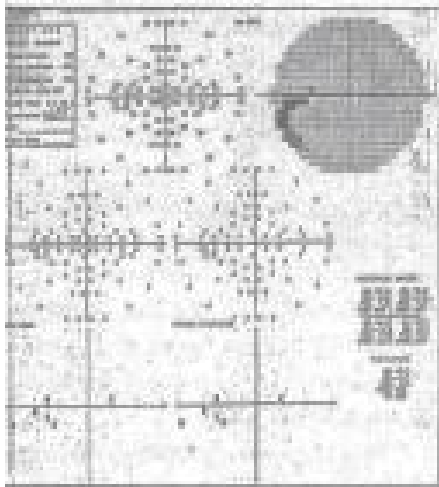
Case Report

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

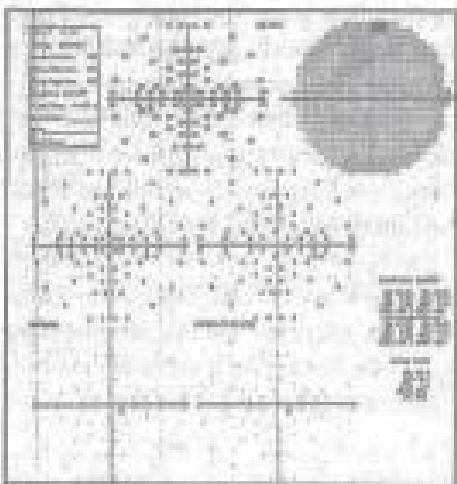
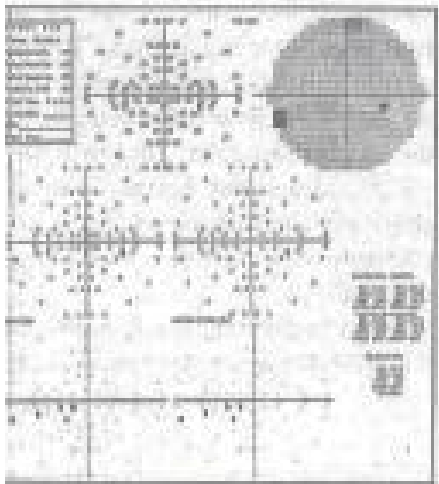


Mark Tomsik, OD and Marlene Skulskie, OD

Shortly
after TX



1 Year
Later



PROTEIN SYNTHESIS INHIBITORS

Protein Synthesis Inhibitors

- These antibiotics work by targeting the bacterial ribosome.
 - they are structurally different from mammalian ribosomes,
 - in higher concentrations many of these antibiotics can cause toxic effects.
- This group includes:
 - (a) tetracyclines, (b) aminoglycosides, (c) macrolides,
 - (d) chloramphenicol, (e) clindamycin, (f) quinupristin/dalfopristin and (g) linezolid

Side Effects of Tetracyclines

- Side effects include gastric discomfort, phototoxicity, effects on calcified tissues, vestibular problems, IHH.
- 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



Tetracyclines

- Drug of choice for Rocky Mountain Spotted Fever, Cholera, Lyme disease, mycoplasma pneumonia, and chlamydial infections
 - Rocky mountain spotted fever: tick born disease that can potentially be fatal. Doxycycline is drug of choice.
 - 2021 CDC STI Guidelines: doxycycline 100 mg BID for 7 days is the new recommended treatment for chlamydia over azithromycin 1 gram.
- Side effects include gastric discomfort, effects on calcified tissues, vestibular problems.

Tetracyclines

- Traditional wisdom is that all tetracyclines should not be used in children under the age of 8 due to discoloration of teeth.
 - Six studies assessed tooth discoloration in at least 338 patients exposed to doxycycline before 8 years of age.
 - Six patients had potential discoloration, but studies consistently found no difference in tooth discoloration between exposed patients and controls.
 - Recommendations have changed stating doxycycline, but not other tetracyclines, can be used for short courses (<21 days) regardless of age.
 - Clinicians should be aware of these data because doxycycline use may extend to disease states apart from tick-borne illnesses in pediatric patients.
 - Stultz JS, Eiland LS. Doxycycline and Tooth Discoloration in Children: Changing of Recommendations Based on Evidence of Safety. *Annals of Pharmacotherapy*. 2019;53(11):1162-1166.

Tetracyclines

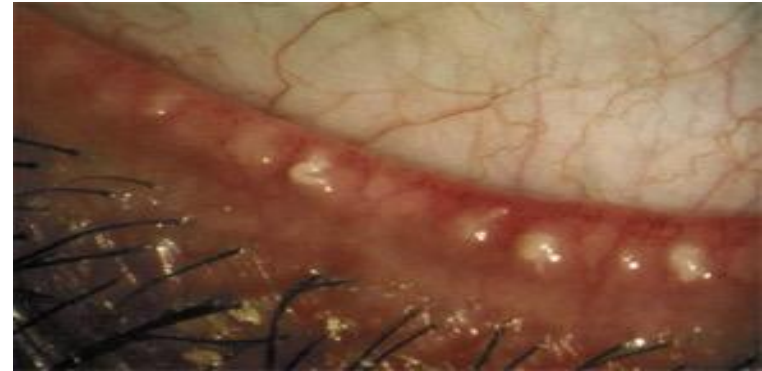
- **MRSA: methicillin resistant staph aureus**
 - Infections with MRSA occur in three specific groups of people: (1) persons currently in the hospital (hospital-associated MRSA), (2) persons with recent hospitalization or ongoing contact with medical clinics, dialysis units, or those undergoing complex outpatient treatments, such as chemotherapy (health care-associated MRSA), and (3) persons in the community (community-associated MRSA).
 - Treatment of MRSA at home usually includes a 7- to 10-day course of an antibiotic (by mouth) such as trimethoprim-sulfamethoxazole (brand name: Bactrim), clindamycin, **minocycline**, linezolid, or **doxycycline**.
 - Minocycline: 200 mg orally once, then 100 mg orally twice daily
 - Doxycycline: 100 mg orally twice daily

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

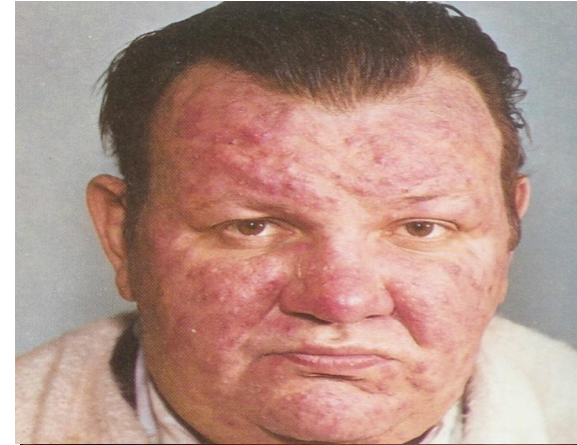
Alternative treatment:

- **Azithromycin: discussed later**



Tetracyclines: 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.



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 Management

- Traditionally, treatment for acne/ocular rosacea has focused on symptom suppression to improve patient quality of life and to help manage the disease.
 - avoidance of triggers including gentle skin care, sun-protection and avoiding the use of cosmetic products known to cause flushing.
- Treatment should be initiated even in patients with mild disease, as early intervention can be key in minimizing both the progression of rosacea and its effects on symptoms and visual function.

Acne Rosacea Management

- Nonpharmacologic interventions:
 - Treatment options for ocular rosacea include omega-3 fatty acids (FAs) and gamma linolenic acid (GLA), lipid-based artificial tears, lid hygiene with a mild cleanser, hypochlorous acid, and warm compresses.
 - Omega-3 FAs and GLA supplements have been shown to reduce symptoms, lid margin inflammation, and meibomian gland dysfunction (MGD).
 - Hypochlorous acid products contain antiinflammatory and antibacterial properties that decrease the signs and symptoms of ocular irritation that occur when there is an excessive quantity of bacteria on the lids
 - use a tea tree oil-based soap to wash the entire face in order to get the Demodex under control.

Acne Rosacea Management

- Tetracycline, doxycycline, and minocycline have been used for many years for the management of rosacea. These agents are most useful for improving inflammatory papules and pustules, and may also reduce erythema
 - Since no definitive microbial cause of rosacea has been identified, the efficacy of oral antibiotics in rosacea is often attributed to their anti-inflammatory properties

Acne Rosacea Management

- The pharmacologic agent with the strongest evidence for efficacy for persistent facial erythema in rosacea is topical brimonidine (brimonidine tartrate gel 0.33% (Brand name: Mirvaso))
 - Effects can be seen as quickly as 30 minutes after application
 - MIRVASO topical gel is for topical use only and not for oral, ophthalmic, or intravaginal use.
 - **NOT CHEAP: Good Rx Price: 530 dollars**
- Topical metronidazole, azelaic acid, and topical ivermectin are also considered first-line therapies in mild to moderate facial disease

Acne Rosacea Management

- Laser and light-based therapies, which have been used extensively for the treatment of a variety of vascular lesions, have also been used for the vascular features of rosacea, especially telangiectasias.
 - The mechanism of actions are well known and include immunomodulation of the inflammatory burden, destruction of Demodex, decrease of the bacterial load, photomodulation of mitochondrial activity and rejuvenation of collagen production.

Tetracyclines: Ocular Conditions

- Hordeola:
 - doxycycline 50-100 mg po BID for 2-3 weeks.
 - may consider topical AB ung on external hordeolum.
- Meibomian Gland Dysfunction:
 - good lid hygiene with warm compresses and lid scrubs in conjunction with
 - doxycycline 50 mg po for 2-3 months.
- Recurrent Corneal Erosion
 - treat with doxycycline 50 mg po BID for 2-3 months
 - include use of **topical steroid** bid-tid for 6-8 weeks.



Aminoglycosides

- Previously were mainstay treatment for infections due to aerobic gram (-) bacilli.
 - due to serious associated toxicities, they have been replaced by safer antibiotics such as 3rd gen cephalosporins, fluoroquinilones, cilastin.
- Effective in the treatment of infections suspected of being due to aerobic gram (-) bacilli including Pseudomonas.
 - usually combined with B-lactam or vancomycin for anaerobic bacteria. They are bacteriocidal!
- Can have severe adverse effects including ototoxicity, nephrotoxicity, delay in nerve conduction, and skin rash.

Aminoglycosides

- This group includes:
 - Gentamicin
 - Neomycin
 - Streptomycin
 - Tobramycin
 - Amikacin

Macrolides

- Erythromycin was the first of these drugs, as an alternative to penicillin. Bacteriostatic though at [higher] maybe cidal
- Macrolides bind to the bacterial ribosome and inhibit protein synthesis.
 - have same spectrum of action as penicillins so are used in those patients who are allergic to that group.
- **Resistance to erythromycin is becoming a serious clinical problem.**
- Adverse effects include:
 - epigastric distress, jaundice, ototoxicity and contraindicated in patients with hepatic disease.

Macrolides

- This group includes:
 - Erythromycin (125 or 250 mg cap, enteric coated)
dosing 250mg q 6h or 500 q12h
 - Clarithromycin
 - *Azithromycin (Z-pak) (500mg first day, then 250 mg for next 4 days)*
 - Telithromycin

Macrolides

- Azithromycin (Z-pak):
 - Azithromycin is used to treat certain bacterial infections, such as **bronchitis;** **pneumonia;** sexually transmitted diseases (STD); and infections of the ears, lungs, sinuses, skin, throat, and reproductive organs.
 - Z-pak: 500 mg first day and then 250 for the next 4 days



Meibomian Gland Dysfunction

Alternative treatment:

- **Azithromycin 500 mg/day for 3 days for three- four weeks or from a recent study: 1 gram single dose once a week for 3 weeks**
 - Recent study: single Z-pak treatment was more effective than 30 day doxy treatment
 - Another study: A 3-week course of weekly oral azithromycin was equivalent to a 6-week course of oral doxycycline.



<https://www.healio.com/news/ophthalmology/20230412/azithromycin-shows-equal-efficacy-to-doxycycline-in-meibomian-gland-dysfunction-treatment>

Azithromycin

- MGD/Blepharitis:
 - 500 mg/day for 3 days for three-four weeks
 - e.g. M/T/W then off for next 4 days and then again M/T/W and do that 2 more times



Macrolides: Ocular Indications

- Azithromycin (Z-pak) can be used as alternative treatment in patient with:
 - internal hordeola,
 - pre-septal cellulitis,
 - dacryocystitis
- remember high incidence of staph resistance.



Chloramphenicol

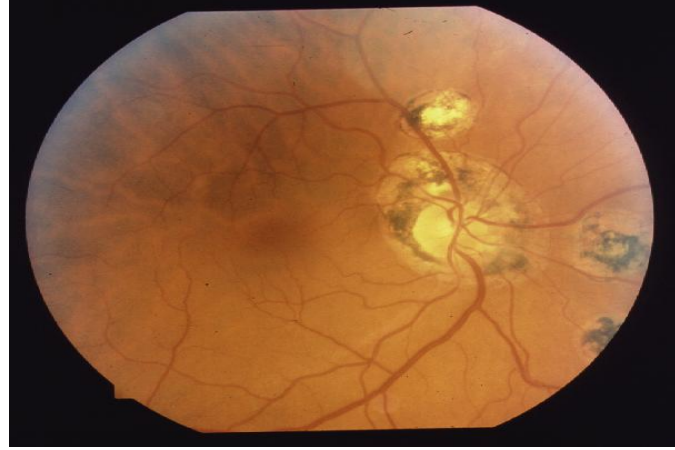
- Active against a wide range of gram (+) and (-) organisms.
 - because of its toxicity, its use is restricted to life-threatening infections for which no alternative exists.
 - It is reserved for severe infections, such as rickettsial diseases, meningitis caused by Haemophilus Influenza, Neisseria meningitidis, or Streptococcus pneumoniae, or in typhoid fever caused by Salmonella enterica serotype Typhi and cholera
- Adverse effects include hemolytic and aplastic anemia.

Chloramphenicol: Ocular Indications

- Available in solution 0.5% and ointment 1% (Chloroptic)
- Indications for its use include superficial eye infections (bacterial conjunctivitis), and otitis externa
 - generally not used in the US but commonly used abroad (Europe and Australia).

Clindamycin

- Inhibits protein synthesis by binding to a portion of the 50S ribosome subunit.
- Available IV, IM, and orally.
- High levels of side effects such as serious pseudomembranous colitis and superinfections have limited use.



Clindamycin

- Occasionally used in the treatment of Ocular Toxoplasmosis but not FDA approved.
- Another option for use in the treatment of MRSA ocular infections:
 - 450 mg TID for Adults
 - 10 – 30 mg/kg/day in three doses for kids
- Main use is in patients allergic to Sulfa drugs.

Inhibitors of Nucleic Acid Synthesis/Function

Inhibitors of Nucleic Acid Synthesis/Function.

- they enter the bacterium via passive diffusion and once inside the cell **inhibit the replication of bacterial DNA** by interfering with the action of DNA gyrase and topoisomerase IV during bacterial growth and reproduction.
- unfortunately, their overuse has already led to the emergence of resistant strains.

Ciprofloxacin

- used to treat anthrax infection after inhalational exposure
- used to treat and prevent plague
- used to treat urinary tract infections, including acute uncomplicated pyelonephritis.

Rifampin

- **Treatment of tuberculosis**, there are three preferred regimens, chosen for effectiveness, safety and high treatment completion rates, **are rifamycin-based**. They are
 - three months of once-weekly isoniazid plus rifapentine for adults and children older than age 2, regardless of HIV status;
 - four months of daily rifampin; or
 - three months of daily isoniazid plus rifampin

Rifampin

- Rifampin:
 - the most commonly used rifamycin for treatment of nontuberculous mycobacterial diseases, in combination with other agents.
 - It is also used for treatment of tuberculosis (active disease and latent infection), for prophylaxis following exposure to *Neisseria meningitidis* or *Haemophilus influenzae*, and as an adjunctive agent for treatment of select deep-seated staphylococcal infections.

Rifampin

- Rifampin:

- The usual adult dose of rifampin for treatment of tuberculosis is 10 mg/kg (maximum 600 mg daily) given daily or three times weekly by directly observed therapy.
- Patients should be advised that rifampin typically causes an orange or red-orange discoloration of body fluids (including urine, sweat, saliva, and tears).
- The potential for drug-drug interactions with rifamycins is high for individuals taking the following drugs: warfarin, oral or other hormonal contraceptives, some antihypertensives, some antiarrhythmics, some antidepressants, some anticonvulsants, methadone, and the protease inhibitor class of antiretroviral drugs.

Inhibitors of Nucleic Acid Synthesis/Function

- The most common adverse reactions include:
 - GI upset,
 - CNS problems (HA and dizziness),
 - phototoxicity,
 - liver toxicity,
 - nephrotoxicity
 - Tendonitis/tendon rupture
 - Peripheral neuropathy

Inhibitors of Metabolism

Inhibitors of Metabolism

- Folic acid is required for the synthesis of precursor molecules for RNA, DNA and other compounds necessary for cellular growth.
 - in the absence of folic acid, cells cannot grow or divide.
- (a) Sulfonamides and (b) trimethoprim are folic acid antagonists and interfere with an infecting bacteria's ability to divide.
- Compounding the two has made a synergistic compound used for effective treatment of a variety of bacterial infections.

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 SS (standard strength):**
 - 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

Co-Trimoxazole (Bactrim/Septra)

- **Contraindication!!!!**
 - **Methotrexate (MTX)** is a folic acid antagonist used for the treatment of many autoimmune diseases (e.g. rheumatoid arthritis, JIA, lupus etc)
 - TMP-SMX is an inhibitor of folic acid metabolism and can cause **bone marrow suppression**.
 - TMX-SMX is also known to decrease the renal excretion of MTX.
 - When used in combination, the potential for toxicity is substantial.
- **Drink plenty of fluids to prevent kidney stones.**
 - Interacts with diuretics and ACE inhibitors
- **Exposure to sunlight**, even for brief periods of time, may cause severe sunburn or skin rash, redness, itching, or discoloration.

Inhibitors of Cell Membrane Function

V: Inhibitors of Cell Membrane Function

- **Isoniazid** is one of the most potent of the anti-tubercular drugs and interferes with the production of mycobacterial cell walls.
- Mycobacteria is a slow growing organism and treatment is often required from 6 months to several years.
 - due to poor compliance, resistance has developed and therefore treatment is never given as a single agent.
- Multi-drug therapy is given and maybe changed on a regular basis in order to effectively treat the patient.

Thank You!!!