

TREATMENT AND MANAGEMENT OF OCULAR INFECTION: SYSTEMIC ANTIBIOTICS IN EYE CARE

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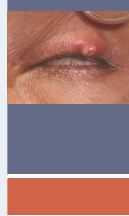
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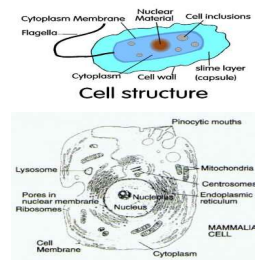
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Principles of Antimicrobial Therapy

- 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

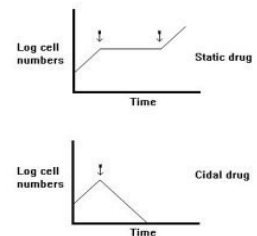
- Selection of an appropriate antimicrobial requires:
 - knowledge of the organisms identity,
 - its susceptibility,
 - site of infection,
 - patient factors,
 - safety of agent and
 - cost of therapy.
- Often, the organism is not conclusively identified, and the treatment is empirical.
- Children 12 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)



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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.

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MRSA

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



MRSA

- Risk factors for infection due to HA-MRSA include:
 - antibiotic use,
 - prolonged hospitalization,
 - intensive care,
 - invasive devices,
 - hemodialysis,
 - MRSA colonization, and
 - proximity to others with MRSA colonization or infection.



MRSA

- Additional risk factors for CA-MRSA infection include:
 - skin trauma (eg, lacerations, abrasions, tattoos, injection drug use),
 - cosmetic body shaving,
 - incarceration,
 - HIV infection, and
 - sharing equipment that is not cleaned or laundered between users.



ARMOR

- Antibiotic Resistance Monitoring in Ocular Microorganisms (ARMOR)
- Approximately 42% of isolates were determined to be MRSA
- Newer fluoroquinolones have better activity than earlier generations
- 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



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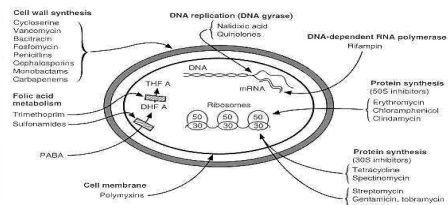
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1 million patients seen in the system from 2000-2004, with 3460 confirmed MRSA infections
- of the total MRSA infections, 1.3% if them were ocular

Ophthalmic Infection	Percent of Cases
Preseptal cellulitis	42%
Conjunctivitis	21%
Corneal ulcers	10%
Endophthalmitis	8%
Orbital cellulitis	2%
Other: e.g. dacryocystitis	10%

Sites of Antimicrobial Actions

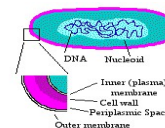
- Antibiotics can be classified by their chemical structure, the organisms they are effective against or by their site of action.



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 ½ 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.

Penicillins: Cloxacillin (Apo-Cloxi[®])

- Oral: 250 to 500 mg every 6 hours (maximum adult dose: 6 g/day)
- Oral: available 250 and 500 mg
 - ▣ Also available for IM and IV administration
- Administer with water 1 hour before or 2 hours after meals
- Treatment of bacterial infections including endocarditis, pneumonia, bone and joint infections, skin and soft-tissue infections, and sepsis that are caused by susceptible strains of penicillinase-producing staphylococci.



Penicillins

- This group includes the following commonly used members:
 - ▣ **Amoxicillin** (250/500 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: Clavulin (Augmentin)

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



Penicillins: Clavulin (Augmentin)

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



Penicillins: Clavulin (Augmentin)

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



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.



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Stevens-Johnson Syndrome

- medical emergency that usually requires hospitalization.
- treatment focuses on eliminating the underlying cause, controlling symptoms and minimizing complications.
- recovery can take weeks to months, depending on the severity.
- if it was caused by a medication, the patient will need to permanently avoid that drug and others closely related to it.

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Penicillins: Clavulin (Augmentin).

Adults:

- 250-500 mg tab q 8hr (tid) (also available in chewable tablets and suspension)
- or 875 mg q 12hr (bid)

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

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

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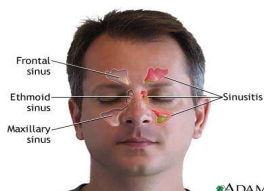
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Sinusitis Red Eye

- 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.
- The sinuses surround the ocular region
 - pressure from sinuses may feel like eye pressure.
 - swollen sinuses and nasal membranes can push against ocular nerves resulting in pain.
- Most develop during or after a cold or other upper respiratory infection, but allergens and environmental irritants may also trigger them



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Sinusitis Treatment

- 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 Clavulin (Augmentin)
- Clavulin (Augmentin) 250/500 TID for 5-7 days for adults, 10-14 days for children

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Penicillins: Hordeola:

- **Internal** are secondary to a staph infection of the meibomian glands
- **External** are an infection of the Zeis or Moll glands
 - ▣ Patients present with tenderness and swelling of affected area.
- **Treatment includes:**
 - hot compresses (e.g. Bruder)
 - topical antibiotics (?)
 - possibly systemic antibiotics
 - Augmentin (Clavulin) 875 mg BID x 7 days
 - 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 oculoplastics for DCR (dacryocystorhinostomy)



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Preseptal Cellulitis

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




Differentiating Orbital vs. Preseptal

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

Treatment: Orals for Preseptal, Often IV for Orbital



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Preseptal Cellulitis

Tx:

- 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/Septa



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Cephalosporins

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



Side Effects and Contraindications

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



Cephalosporins

- 1st generation: cefadroxil (Duricef), cefazolin (Ancef), cephalexin (Keflex), and cephalothin
- 2nd generations: cefaclor (Cecel), cefprozil, cefuroxime (Zinacef), cefotetan, cefoxitin
- 3rd generation: cefdinir (Omnicef), cefixime, cefotaxime (Claforan), ceftazidime (Fortaz), ceftibuten, ceftizoxime, ceftriaxone (Rocephin IM/IV).
- 4th generation: ceftepime
- 5th generation: Ceftaroline is a novel fifth-generation cephalosporin, which exhibits broad-spectrum activity against Gram-positive bacteria, including MRSA and extensively-resistant strains, such as vancomycin-intermediate S. aureus (VISA), heteroresistant VISA (hVISA), and vancomycin-resistant S. aureus (VRSA)
- Omnicef, Keflex, Cefclor (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

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

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Cephalosporins

- Cefaclor (Ceclor):
 - Mild preseptal cellulitis = 250-500 mg TID in adults and 20-40 mg/kg/day in three divided doses for children

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Cephalosporins: Hyperacute Conjunctivitis

- Hyperacute conjunctivitis:
 - **usually secondary to gonorrhea or chlamydia.**
 - profuse purulent discharge,
 - pain,
 - redness,
 - chemosis,
 - papillae,
 - positive nodes



Chlamydia

- Chlamydia is the most frequently reported bacterial sexually transmitted disease in the United States
- Chlamydia is known as a "silent" disease because the majority of infected people have no symptoms
 - if symptoms do occur, they usually appear within 1 to 3 weeks after exposure
- women who have symptoms might have an abnormal vaginal discharge or a burning sensation when urinating
- men with signs or symptoms might have a discharge from their penis or a burning sensation when urinating
 - men might also have burning and itching around the opening of the penis.

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Chlamydia: Treatment

- Recommended Treatment Regimens:
 - **Azithromycin** 1 g orally in a single dose
 - OR
 - **Doxycycline** 100 mg orally twice a day for 7 days
- Alternative Treatment Regimens:
 - Erythromycin base 500 mg orally four times a day for 7 days
 - OR
 - Erythromycin ethylsuccinate 800 mg orally four times a day for 7 days
 - OR
 - Levofloxacin 500 mg orally once daily for 7 days
 - OR
 - Ofloxacin 300 mg orally twice a day for 7 days

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Chlamydia: Treatment

- **Azithromycin versus doxycycline:**
 - for the treatment of genital chlamydial infection treatments were equally efficacious
- Azithromycin should always be available to treat patients for whom compliance with multiday dosing is uncertain.
- Levofloxacin and ofloxacin are effective treatment alternatives but are more expensive and offer no advantage in the dosage regimen.
 - other quinolones either are not reliably effective against chlamydial infection or have not been evaluated adequately

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Gonorrhea

- Some men with gonorrhea **may have no symptoms at all**
 - signs or symptoms appear 1 to 14 days after infection
 - signs and symptoms include a burning sensation when urinating, or a white, yellow, or green discharge from the penis
 - sometimes men with gonorrhea get painful or swollen testicles.
- In women, **the symptoms of gonorrhea are often mild, but most women who are infected have no symptoms.**
 - symptoms can be so non-specific as to be mistaken for a bladder or vaginal infection.
 - initial symptoms and signs in women include a painful or burning sensation when urinating, increased vaginal discharge, or vaginal bleeding between periods.
 - risk of developing serious complications from the infection, regardless of the presence or severity of symptoms.

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Gonorrhea Conjunctivitis Treatment

- For patients with uncomplicated gonorrhea conjunctivitis:
 - Single 250 mg IM injection Ceftriaxone (Rocephin) for the treatment of the gonococcal infection PLUS
 - Azithromycin (1g) for possible additional activity against gonorrhea plus possible chlamydia co-infection



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: Dacryoadenitis

- An inflammation or infection of the lacrimal gland.
 - S&S include:
 - swelling of lid,
 - pain in area of swelling,
 - excess tearing or discharge and swelling of lymph nodes.
- maybe secondary to viral or bacterial infection or an inflammatory condition (e.g. sarcoid or Graves disease)



Cephalosporins: Dacryoadenitis

Tx:

- Most cases are viral and self resolving (supportive measures)
- If bacterial:
 - Keflex (cephalexin) 250-500mg po QID,
 - for more severe cases IV cefazolin (Ancef) 200mg/kg divided into 3 doses.
- If the enlargement does not subside after 2 weeks, consider lacrimal gland biopsy.



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Cephalosporins: Orbital Cellulitis

- infection and inflammation within the orbital cavity producing orbital SSS
- most commonly secondary to ethmoid sinusitis.
- Staph and Strep 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: 5 to 20 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**
- Ampicillin-sulbactam: 3 g IV every six hours



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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

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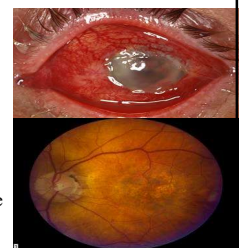
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Endophthalmitis

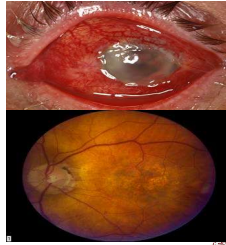
- intraocular infection involving anterior/posterior segments usually secondary to postoperative infection (0.1% risk post-op cataract).
 - 95% gram +ve bacteria including
 - staph (80%), strept (10%) with about 6% gram -ve organisms (these infections to be more virulent and have worse prognosis)



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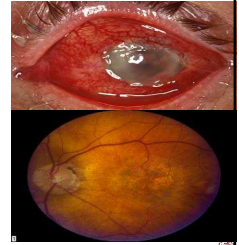
Endophthalmitis

- Signs/symptoms typically present:
 - Post-trauma: 12-24 hours
 - Post-surgery: day 2 (or later)
 - Post-intravitreal injection: 1-6 days (av 3.4 days)



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

Post-traumatic Endophthalmitis Treatment

Post-traumatic endophthalmitis: (in addition to intravitreal)

- Subconjunctival:**
 - vancomycin 25mg and ceftazidime (Fortaz) 100mg (gentamicin) and dexamethasone 12-24mg,
- Topical:**
 - fortified vancomycin (Vancocin HCl 2.5% Ophthalmic) and ceftazidime (Fortaz) 50mg/ml/hr, topical steroid and cycloplegic,
- controversial IV systemic AB.

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.

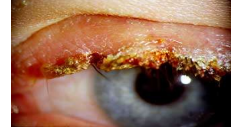
Vancomycin

- Treatment:
 - Orbital Cellulitis
 - Endophthalmitis



Bacitracin (Bacitin)

- 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. polymyxin B (Polysporin).



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

Tetracyclines

- Nonresistant strains concentrate this antibiotic intracellularly resulting in inhibition of protein synthesis.
- Broad spectrum, bacteriostatic,
 - ▣ effective against gram (+) and (-) bacteria and against non-bacterial organisms
 - ▣ widespread resistance has limited their use.
- Drug of choice for Rocky Mountain Spotted Fever, Cholera, Lyme disease, mycoplasma pneumonia, and chlamydial infections.

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



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 doxy comes in 100 mg tablets (Apo-Doxy, Novo-Doxilin and Vibra-Tabs)
 - Apprilon (30 mg doxy + 10 mg slow release doxy)



Tetracyclines

- 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
 - ▣ Recommend sun protection



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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



Tetracyclines: Acne Rosacea

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



Treatments for Demodex

Table 1 Summary of lid cleansers for Demodex

Cleanser	Manufacturer	Active Ingredients
Ciradex [®] and Ciradex [®] Light (towelettes and foam)	Bio-Tissue, Inc.	4-Terpaeol (14%)
OUST [™] Demodex [®] Swabsticks [™] and OUST [™] Demodex [®] Cleanser (premoistened pads)	OCuSOFT [®]	50% tea tree oil, 40% sea buckthorn oil, and 10% caprylic acid
OCuSOFT [®] Lid Scrub Plus (premoistened pads, Swabsticks)	OCuSOFT [®]	1,2-Octanediol and detergents
Avenova [®]	NovaBay [®] Pharmaceuticals	Pure 0.01% hypochlorous acid

Fromstein, S. R., Harthan, J. S., Patel, J., & Opitz, D. L. (2018). Demodex blepharitis: clinical perspectives. Clinical optometry, 10, 57–63. doi:10.2147/OPTO.S142708

Acne Rosacea Treatments

Oral Antibiotics	Topical Treatments	Non-Prescription
Erythromycin	metronidazole (Metrogel)	Rosacea-Lid III
Tetracycline	BenzaClin (Clindamycin 1% & benzoyl peroxide 5%)	ZenMed
Doxycycline	BenzaMycin (Erythromycin 3% & benzoyl peroxide 5%)	Neova Therapy
Minocycline	tretinoin (Retin-A)	Kinerase
	Clindamycin 1% lotion/gel	Rosacare
	Plexion Cleanser/Lotion (Sulfa 10% & sulfur 5%)	

www.internationalrosaceafoundation.org

Tetracyclines: Adult Inclusion Conjunctivitis



- occurs in sexually active adults
- women are more susceptible than men.
- usually transmitted through hand-to-eye spread of infected genital secretions.
- incubation period is one to two weeks
- Signs and Symptoms:
 - ▣ ocular irritation, watering, mucopurulent discharge and positive nodes
 - ▣ often a unilateral disease but can involve both eyes
 - ▣ follicles inferior fornix, mixed papillary/follicular on upper lid, subepithelial infiltrates, SPK.

Tetracyclines: Adult Inclusion Conjunctivitis Treatment

- Mainstay oral treatment is:
 - ▣ **Doxycycline 100 mg po BID for 7 days.**
- Or
- ▣ **Azithromycin 1 gram single dose**
- ▣ Topical AB therapy is done concurrently.



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, fluoroquinolones, 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



Clarithromycin (Biaxin)

- Derivative of Erythromycin that is more stable in gastric acid with a ½ life that is nearly twice that of Erythromycin.
- Used for respiratory and skin infections as well as the treatment of H. Pylori ulcers, but can be used for Chlamydia if needed.
- BIAxin is available as immediate-release tablets, extended-release tablets, and granules for oral suspension.



Macrolides

- Azithromycin (Z-pak) is active against respiratory infections due to H. influenzae and Moraxella.
 - ▣ It was a costly medication (generic now available),
 - ▣ now a preferred therapy for urethritis by chlamydia.
 - ▣ excellent for soft tissue infections.
 - ▣ use with caution in patients with impaired liver function and no controlled studies for use in pregnancy.



Azythromycin

- Hyperacute conjunctivitis:
 - ▣ Secondary to Chlamydia or Gonorrhea
- Adult inclusion conjunctivitis
 - ▣ Secondary to chlamydial infection
- **MGD/Blepharitis:**
 - ▣ 500 mg/day for 3 days for three- four weeks



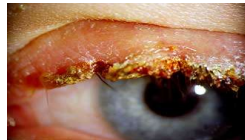
Macrolides: Ocular Indications

- Erythromycin can be used as alternative treatment in patient with:
 - ▣ internal hordeola,
 - ▣ pre-septal cellulitis,
 - ▣ dacrocystitis
- remember high incidence of staph resistance.



Macrolides: Ocular Indications

- Erythromycin available in topical ointment form
 - EURO-Erythromycin
 - Odan-Erythromycin
 - PDP-Erythromycin
- ▣ for treatment of superficial infections
 - blepharitis and prophylaxis of ophthalmia neonatorum



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.
- Bacteriocidal and bacteriostatic depending on the organism.
- Adverse effects include hemolytic and aplastic anemia.

Chloramphenicol: Ocular Indications

- Systemic treatment rarely used for ocular conditions.
- Available in solution 0.5% and ointment 1% (Chloroptic)
 - ▣ generally not used in the US but commonly used abroad (Europe and Australia).
- Effective against most ocular bacterial infections but because of potentially fatal complications should only be used as a last resort.

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.

- The fluoroquinolones are the main group of antibiotics that act in this fashion.
 - ▣ 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.



Inhibitors of Nucleic Acid Synthesis/Function.

- Rifampin is the other major member of this group and is an inhibitor of RNA synthesis
- Bactericidal
- Is a broad spectrum antibiotic but is used mostly in the treatment of TB
 - ▣ resistance is common
 - ▣ Rifampin is typically used in combination with other anti-TB meds
 - ▣ has a new role in treatment of MRSA in combination with fusidic acid.



Inhibitors of Nucleic Acid Synthesis/Function.

- All the fluoro are bactericidal, with activity becoming more pronounced as the serum [drug] increases.
 - ▣ in general, they are effective against gram(-) bacteria including pseudomonas and haemophilus, and have good activity against some gram (+) organisms such as strept.
- Common practice to classify the fluoro into “generations” with nalidixic acid being 1st generation.



Inhibitors of Nucleic Acid Synthesis/Function.

- Ciprofloxacin is the most frequently used fluoro in the US.
 - ▣ effective against many systemic infections, with the exception of serious infections caused by MRSA, the enterococci and pneumococci.
 - ▣ it is used in treating infections caused by enterobacteria (ex. travelers diarrhea) and drug of choice for anthrax prophylaxis.
 - ▣ has good activity against pseudomonas, and may have synergistic activity with B-lactams.
- Resistance has developed due to mutations in both gyrase and topoisomerase.



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 Nucleic Acid Synthesis/Function.

- ▣ connective tissue problems:
 - strongly associated with Achilles tendinopathy and tendon rupture
 - Achilles tendinopathy was stronger among individuals who were >60 years old and female
 - The median duration of fluoroquinolone use before the onset of tendon injury is eight days
- ▣ should be avoided in pregnancy, nursing mothers and children under age of 18 and patient >60



May 2016

- The US Food and Drug Administration (FDA) states that unless they lack other treatment options, patients with uncomplicated infections should not receive fluoroquinolones, given the risk for disabling and potentially permanent adverse events.
- The FDA will update the labels to state that the serious risks posed by fluoroquinolones generally outweigh their benefits for patients with sinusitis, bronchitis, and uncomplicated urinary tract infections that are treatable by other means.



December 2018

- The FDA has issued a safety alert warning that systemic (oral, injectable) fluoroquinolone use can increase the occurrence of aortic dissections or ruptures. The use of systemic fluoroquinolones should be avoided in patients with an existing aortic aneurysm or in patients at an increased risk for developing an aortic aneurysm, including patients with peripheral atherosclerotic vascular diseases, hypertension, genetic disorders involving blood vessel changes (eg, Marfan syndrome, Ehlers-Danlos syndrome), and the elderly, unless there are no other treatment options available.

4/22/2020



July 2018

- In response to a recent review, the FDA is strengthening current warnings in the prescribing information for systemic fluoroquinolone antibiotics regarding significant hypoglycemia and certain mental health side effects. In addition to current warnings regarding blood sugar disturbances, including high blood sugar and low blood sugar, the FDA is requiring the addition that low blood sugar levels can lead to coma; and the mental health side effects to be added or updated across all fluoroquinolones are disturbances in attention, disorientation, agitation, nervousness, memory impairment, and serious disturbances in mental abilities called delirium.

4/22/2020



Levofloxacin

- It is most commonly used to treat infections of the bladder, kidney, prostate, sinus, skin, and lung.
- This medication may be taken with or without food.
- Levofloxacin should be taken at least 2 hours before or 2 hours after taking antacids containing calcium, magnesium, or aluminum; sucralfate; or vitamin and mineral tablets containing calcium, iron, or zinc.
- Make sure to drink plenty of fluids each day while taking levofloxacin.

4/22/2020



Levofloxacin

- Available in 250, 500 and 750 mg
- Typical adult dosing is 500 or 750 mg daily for 7 days
 - ▣ ACT Levofloxacin
 - ▣ APO-Levofloxacin
 - ▣ Auro-Levofloxacin
 - ▣ PMS-Levofloxacin
 - ▣ SANDOZ Levofloxacin
 - ▣ TEVA-Levofloxacin

4/22/2020



Ciprofloxacin (Cipro)

- Tablet, Oral, as hydrochloride [strength expressed as base]:
 - ▣ Cipro: 500 mg
 - ▣ Generic: 100 mg, 250 mg, 500 mg, 750 mg
- Tablet Extended Release 24 Hour, Oral, as base and hydrochloride [strength expressed as base]:
 - ▣ Cipro XL: 500 mg, 1000 mg
 - ▣ Generic: 500 mg

4/22/2020



Ciprofloxacin (Cipro)

- May administer with most foods to minimize GI upset; avoid antacid use; maintain proper hydration and urine output.
- Avoid concomitant administration with dairy products (eg, milk, yogurt) or calcium-fortified juices alone
- Dosing: 500 mg bid or 750 once daily

4/22/2020



Moxifloxacin

- Tablet, Oral:
 - ▣ Avelox: 400 mg
 - ▣ Generic: 400 mg
- Dosing: 400 mg every 24 hours
- Oral: Administer without regard to meals. Administer at least 4 hours before or 8 hours after products containing magnesium, aluminum, iron, or zinc, including antacids, sucralfate, multivitamins, and didanosine (buffered tablets for oral suspension or the pediatric powder for oral solution).

4/22/2020



Ocular Indications

- Hyperacute conjunctivitis (gonococcal): Oral or IM fluoroquinolone (only indicated if unable to use cephalosporin)
- Cat Scratch Disease: ciprofloxacin 500-750 mg po q 12h for 10-14 days.
- Orbital cellulitis: IV ciprofloxacin
- Majority of the use of fluoroquinolones in ocular use is in the form of topical drops and ointments. Used in all forms of infections and prophylaxis in ocular surgeries.



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.



Sulfonamides

- Sulfa drugs are seldom prescribed alone except in the developing countries, where they are used because of their low cost and efficacy in certain infections such as trachoma.
- With the combination with trimethoprim, co-trimoxazole there was a renewed interest in the sulfa drugs.
- Sulfa drugs are bacteriostatic,
 - active against selective enterobacteria in the urinary tract.
 - resistance exists in those bacteria that don't synthesize folic acid and in any PABA producing bacteria (purulent producing bacteria).



Sulfonamides

- Adverse effects include:
 - hypersensitivity reactions such as rashes,
 - angioedema,
 - Stevens-Johnson syndrome are fairly common.
 - may also result in nephrotoxicity, hemolytic anemia,
 - drug potentiation
 - Ex. increased effect of hypoglycemic effect of tolbutamide or anticoagulant of warfarin



Trimethoprim and Pyrimethamine

- Similar antibacterial spectrum as sulfonamides, though has a 20-50 fold more potent effect than the sulfonamides.
- Trimethoprim maybe used on its own to treat acute UTI's and in the treatment of bacterial prostatitis (fluor preferred though) and vaginitis
 - been found to be an effective treatment option for MRSA
- Pyrimethamine is used for prophylaxis and Tx of malaria.
- Resistance does exist, and adverse effects include several blood anemias which can be reversed by administering folic acid.



Trimethoprim: Ocular Indications

- Combined with sulfa (Bactrim/Septra) indicated for MRSA suspected infections
- Trimethoprim is found in combination with polymyxin B in a topical eye drop.
 - Trimethoprim has both gram +/- activity but not effective against pseudomonas so Polymyxin B is added.
- Low rate of allergic and toxic reactions, and approved for children >2 months.



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:
 - ▣ 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



INHIBITORS OF CELL MEMBRANE FUNCTION

Drugs Affecting the Cell Membrane

- Interact with the phospholipids of the cell membrane causing increased permeability and disruption of the osmotic gradient.
- Bactericidal in nature.
- Two Main Drugs:
 - ▣ Polymyxin B
 - ▣ Gramicidin



V: Inhibitors of Cell Membrane Function

- Isoniazid is 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!!!

4/22/2020