Systemic Antibiotic Management of Infection and Ocular Disease

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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.
  – the choice of agents in the absence of confirmatory testing maybe guided by known association of a particular organism with an infection in a given clinical setting

Principles of Antimicrobial Therapy

• Adequate levels of the antibiotic must reach the site of infection.
  – different tissues have variable permeability to the drug.
  – 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,
  - i.e. 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 bodies normal flora (and result in superinfections)

Preventing Resistance

- Just one organism, methicillin-resistant Staphylococcus aureus (MRSA), kills more Americans every year (~19,000) than emphysema, HIV/AIDS, Parkinson’s disease, and homicide combined.
  - most serious MRSA infections, an estimated 85%, are associated with a healthcare exposure, but nearly 14% of the infections are community-associated.
- Almost 2 million Americans per year develop hospital-acquired infections (HAIs), resulting in 99,000 deaths the vast majority of which are due to antibiotic-resistant pathogens.
- CDC: Get Smart: Know When Antibiotics Work
  - teaches both the provider and the patient when antibiotics should be used.
- 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.

Shortage of New Antibiotics

- In 2010, in recognition of the need for creative, new ideas to address the antibiotic pipeline problem and a measurable goal by which to gauge progress, IDSA (Infectious Diseases Society of America) launched the “10 × ’20 initiative”.
  - The 10 × ’20 initiative calls for the development of 10 novel, safe and effective, systemic antibiotics by 2020.
New Class of Antibiotics

- Fidaxomycin (Dificid) is the first of a new class of antibiotics called macrocycles and was approved by the FDA in May 2011;
  - Optimer Pharmaceuticals
  - it’s a narrow-spectrum drug aimed specifically at *Clostridium difficile*,
    - the bacterial, toxin-producing, potentially fatal infection of the gut that occurs when broad-spectrum antibiotics have killed off the other populations of bacteria that normally live in the intestines
  - Fidaxomycin’s existing competition is vancomycin
    - as compared against vancomycin, fidaxomycin was "noninferior," in industry jargon

Ocular Trust 3

- Antimicrobials tested represent six classes of drugs:
  - fluoroquinolones (ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin);
  - dihydrofolate reductase inhibitors (trimethoprim);
  - macrolides (azithromycin);
  - aminoglycosides (tobramycin);
  - polypeptides (polymyxin B); and
  - β-lactams (penicillin).
- Staphylococci were classified as methicillin-resistant (MRSA) or methicillin-susceptible (MSSA) based on susceptibility to oxacillin.

Ocular Trust 3: Ongoing Longitudinal Surveillance of Antimicrobial Susceptibility in Ocular Isolates

- Background:
  - Ocular TRUST is an ongoing annual survey of nationwide antimicrobial susceptibility patterns of common ocular pathogens.
  - To date, more than 1,000 isolates from ocular infections have been submitted to an independent, central laboratory for in vitro testing.
  - Ocular TRUST, now in its third year, remains the only longitudinal nationwide susceptibility surveillance program specific to ocular isolates.

Ocular Trust 3: Results

- most antimicrobials, except penicillin and polymyxin B, continue to be highly active against MSSA (azithromycin shows only moderate activity)
- with the exception of trimethoprim and tobramycin, less than one-third of MRSA strains are susceptible to ophthalmic antimicrobials
- susceptibility profiles remain virtually identical for the fluoroquinolones, regardless of methicillin phenotype
- S. aureus is more susceptible to the fluoroquinolones than to macrolides, as represented by azithromycin

OPHTHALMIC MRSA INFECTIONS IN THE PARKLAND HEALTH AND HOSPITAL SYSTEM, 2000 – 2004

<table>
<thead>
<tr>
<th>Ophthalmic MRSA Infections</th>
<th>Percent of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preseptal cellulitis</td>
<td>42%</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>21%</td>
</tr>
<tr>
<td>Corneal ulcers</td>
<td>10%</td>
</tr>
<tr>
<td>Endophthalmitis</td>
<td>6%</td>
</tr>
<tr>
<td>Orbital cellulitis</td>
<td>2%</td>
</tr>
<tr>
<td>Other e.g. dacrocystitis</td>
<td>10%</td>
</tr>
</tbody>
</table>

1 million patients seen in the system from 2000 to 2004, with 3460 confirmed MRSA infections
- of the total MRSA infections, 0.5% if them were ocular

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

- 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:
  - β-lactam antibiotics and
  - vancomycin.

B-Lactam Antibiotics

- This group includes:
  - penicillins,
  - cephalosporins,
  - carbapenems and monobactams.
- β-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: Dicloxacillin

- Dicloxacillin (250-500 mg)
  - penicillinase resistant, used in penicillin resistant staph
  - administer orally at least 1 hour before or 2 hours after meals
  - Dosing:
    - Children<40kg: 12.5-25 mg/kg daily divided
    - Children>40kg: 125-250 mg q 6 hours
    - Adults: 250 mg q 6 hours
Penicillins

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

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

Penicillins: Augmentin

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

Penicillins: Augmentin

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

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.
  - medullary 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.
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 102 degrees 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
- Augmentin 250/500 TID for 5-7 days for adults, 10-14 days for children

Penicillins: Hordeola:

- **Internal** are secondary to 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.
- Standard treatment includes:
  - good lid hygiene with warm compresses and lid washes
  - Dicloxacillin 250 mg po QID for 7-10 days.
  - may consider topical AB ung on external hordeolum.

Penicillins: Hordeola:

- 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

- **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.
- Standard treatment includes:
  - good lid hygiene with warm compresses and lid washes
  - Dicloxacillin 250 mg po QID for 7-10 days.
  - may consider topical AB ung on external hordeolum.

Penicillins: Dacryocystitis

- Dacryocystorhinostomy (DCR)
  - surgical procedure of choice.
  - allows for the bypassing of the lacrimal duct apparatus as long as the canalicular apparatus is intact.
  - Punctal dilation and nasolacrimal irrigation is contraindicated in the acute stage due to the increased risk of peri orbital cellulitis.

Penicillins: Dacryocystitis

- Treatment includes:
  - Augmentin 500/125 mg (500 mg amoxicillin/125 mg clavulanic acid) TID
  - or 875/125 mg BID for 7-10 days
  - Dicloxacillin 250 mg po QID.

Penicillins: Dacryocystitis

- Infection and inflammation located anterior to the orbital septum and limited to the superficial periorbital tissues and eyelids.
  - usually follows peri orbital trauma or dermal infection (suspect staph sp in trauma).
  - eyelid swelling, redness, ptosis, pain and low grade fever.
- Tx:
  - Augmentin 500/125 mg TID
  - or 875/125 mg BID for 7-10 days or
  - if moderate to severe IV Fortaz (ceftriaxone) 1-2 g q8h.
Cephalosporins

- Closely related structurally and functionally to the penicillins,
  - have the same mode of action,
  - tend to be more resistant to β-lactamases.
- Classified as 1st, 2nd, 3rd, and 4th generation based largely on their bacterial susceptibility patterns and resistance to β-lactamases.
- Should be avoided or used with caution in patients who are allergic to penicillin (approx 10% x-reaction with penicillin allergy has been reported but thought to be much closer to the 1-2%),
- Allergic response without allergy to penicillin is 1-2%.
- Typically administered IV or IM, poor oral absorption.

Cephalosporins: 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.

Chlamydia: Treatment

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

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 nonspecific 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.

Gonorrhea Treatment

- **Adult cervical/urethral infection:**
  - **Ceftriaxone (Rocephin)** IM injection of 250 mg in a single dose.
  - If not an option then:
  - **Cefixime (Suprax)** 400 mg oral in a single dose.
  - Alternative treatments include:
  - Azithromycin 1 gram single dose.
  - Doxycycline 100 mg BID 7-10 days.
  - **Neonatal**: 25-50 mg/kg up to 125 mg IV/IM ceftriaxone daily for 7 days.
  - Syphilis, gonorrhea, chlamydia, chancroid, HIV infection, and AIDS are reportable diseases in every state.

Gonorrhea Conjunctivitis Treatment

- For patients with gonorrhea conjunctivitis:
  - Single 250 mg IM injection Ceftriaxone (Rocephin) or:
  - Cefixime (Suprax) 400 mg oral in a single dose.
  - Concurrent use of ophthalmic lavage and topical fluoroquinolone.
  - E.g., ciproflaxin/loxin/levo/levo.

Cephalosporins: Dacryocystitis

- Dacryocystitis Tx:
  - Keflex 250-500 mg po QID.
- In febrile cases:
  - IV cefazolin (Ancef) 1g q8h or
  - IV cefuroxime (Zinacef) 1.5g 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.
- Tx:
  - Keflex (cephalexin) 250-500 mg po QID.
  - For more severe cases IV cefazolin (Ancef) 200mg/kg divided into 3 doses.
Cephalosporins: Preseptal Cellulitis

- Infection and inflammation anterior to the orbital septum and limited to the superficial periorbital tissues and eyelids.
- Signs and symptoms include:
  - Eyelid swelling,
  - Redness,
  - Ptosis,
  - Pain, and
  - Low-grade fever.

Cephalosporins: Preseptal Cellulitis Treatment

- Tx:
  - Mild:
    - Ceclor (cefaclor) 250-500mg q8h
  - Moderate to severe:
    - IM Rocephin (ceftriaxone) 1-2 grams/day or
    - IV Fortaz (ceftazidime) 1-2g q8h.

Cephalosporins: Orbital Cellulitis

- Infection and inflammation within the orbital cavity producing orbital signs.
- Most commonly secondary to ethmoid sinusitis.
- Staph and Strept most common isolates.
- Signs and symptoms include:
  - Decreased VA,
  - Pain,
  - Red eye,
  - Discharge,
  - Bulging eye,
  - Diplopia,
  - Lid swelling,
  - Fever (generally 102 degrees F or higher).

Cephalosporins: Orbital Cellulitis Treatment

- IV Antibiotics for 7-10 days:
  - IV Ceftriaxone (Rocephin) 50 mg/kg Q12h/day
  - IV Cefotaxime (Claphoran) 50 mg/kg Q6h/day
- PLUS
  - IV clindamycin 40 mg/kg/day in 3 doses
  - IV vancomycin 30 mg/kg/day in 3 doses infused over 90 minutes if patient has a penicillin allergy

- Oral treatment 2-3 weeks post IV:
  - Amoxicillin/clavulananate 875 mg/125mg PO q8h or
  - Cefpodoxime 200 mg PO q12h or
  - Cefdinir 600 mg/day PO q12h

Cephalosporin: Endophthalmitis

- Endophthalmitis:
  - Intraocular infection involving anterior/posterior segments usually secondary to postoperative infection.
  - About 90% gram +ve bacteria including:
    - Staph (80%), strept (10%) with about 5% gram -ve organisms.
- Patients’ present with:
  - Pain, photophobia,
  - Discharge, red eye,
  - Decreased VA, proptosis,
  - Corneal edema, injection,
  - KP, AC reaction,
  - Vitritis, etc.

Endophthalmitis Treatment

- Intravitreal:
  - Vancomycin 1mg/0.1ml and ceftazidime (Fortaz) 2.25mg/0.1ml or amikacin
- Subconjunctival:
  - Vancomycin 25mg and ceftazidime (Fortaz) 100mg (gentamicin) and dexamethasone 12-24mg
- Topical:
  - fortified vancomycin (Vanocin HCI 2.5% Ophthalmic) and ceftazidime (Fortaz) 10mg/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).
  
  - Vancomycin 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

- Orbital Cellulitis: Infection and inflammation within the orbital cavity producing orbital S&S.
  - decreased VA, pain, red eye, HA, diplopia, bulging eye, AFD, IOM restriction, lid swelling and fever.
- IV ceftriaxone (Rocephin) 50 mg/kg/ Q12h/day
- IV ceftaxime (Claforan) 50 mg/kg/ Q6h/day
- IV vancomycin 30 mg/kg/day in 3 doses infused over 90 minutes (penicillin allergy) or IV clindamycin 40 mg/kg/day in 3 doses.

Vancomycin

- Endophthalmitis: Intracocular infection involving anterior/posterior segments usually secondary to postoperative infection.
  - Present with pain, photophobia, discharge, red eye, decreased VA, proptosis, corneal edema, injection, KP’s, AC reaction, vitritis, etc.
- Intravitreal vancomycin 1 mg/0.1 ml and ceftazidime 2.25 mg/0.1 ml (or amikacin).
- Subconj vancomycin 25 mg and ceftazidime 100 mg (gentamicin) and dexamethasone 12-24 mg.
- Topical fortified vancomycin and ceftazidime 50 mg/ml/hr, topical steroid and cycloplegic.

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).

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 include gastric discomfort, phototoxicity, effects on calcified tissues, vestibular problems, pseudotumor.

Acne Rosacea Treatments

<table>
<thead>
<tr>
<th>OTC Medications</th>
<th>Prescriptions</th>
<th>Non-Prescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythromycin</td>
<td>Benzamycin (Clindamycin 1%/ benzil peroxide 5%)</td>
<td>Rosacea-Ltd III</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>BenzaClin (Clindamycin 2%/ benzil peroxide 5%)</td>
<td>Erythromycin 1% &amp; benzoyl peroxide 5%</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>BenzaMycin (Erythromycin 3%/ benzil peroxide 5%)</td>
<td>Neo Therapy</td>
</tr>
<tr>
<td>Minocycline</td>
<td>retin-A</td>
<td>Kinerase</td>
</tr>
<tr>
<td></td>
<td>Clindamycin 1% lotion</td>
<td>Rosacea</td>
</tr>
<tr>
<td></td>
<td>Plexion Cleanser/Lotion (Sulfa 10% &amp; sulfur 5%)</td>
<td>Rosacea</td>
</tr>
</tbody>
</table>

www.internationalrosaceafoundation.org

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.
- Mainstay oral Tx is Oracea (40 mg in morning) or
  - tetracycline 500 mg po BID or doxycycline 100 mg po BID for 4-12 wks.
  - NOTE: Oracea is subantimicrobial therapy

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

- If left untreated, resolves spontaneously in 6-18 months
- can be treated topically with tetracycline, erythromycin, and fluoroquinolones
- due to the high prevalence of concomitant genital tract infection, systemic antibiotic therapy is recommended
- Mainstay oral treatment is:
  - Doxycycline 100 mg po BID for 7-10 days.
  - Topical AB therapy is done concurrently.

Recent Case

21 yo Hispanic female
- Chief Complaint: Red eye
- Quality: Painful irritation; progressing in severity
- Duration: Started that same morning
- Location: OD only
- Relief: OTC allergy drop provides no relief (pt believed it to be allergies)
- Associated symptoms: Throbbing pain, watering, no light sensitivity, no pain with blinking
- Severity: 7/10
- PMHx: Asthma diagnosed 7-8 yrs prior. Inhaler PRN, usually once a month. Heart murmur diagnosed at birth, without causing any complications.
- Allergies: NKDA
- Medications: IUD for birth control

Examination

Aided VAs: OD 20/25 +1 OS 20/20 OU 20/20
OD SLE
- Lid/Lashes: slight ptosis of UL, with swelling; mild mucous discharge
- Palpebral Conjunctiva: 2+ follicles (inf), 1+ papillary rxn (sup + inf)
- Anterior Chamber: Deep and quiet
- IOP: OD: 18 OS: 21
- Posterior pole unremarkable

Assessment/Plan

379.91 Pain In or Around Eye
- Photophobia, follicles, and papillary rxn
- Mild mucous discharge, inferior fornix OD
- Plan
  - 1 gtt Durezol OU in-office
  - Pt education of iritis, symptoms, and course of treatment
  - Dispensed sample of Tobradex ST q2h OU x 2-3 days
  - Rx Z-pak
  - RTC 1 – 2 days for red eye follow-up

Tetracyclines: Hordeola

- Internal are secondary to a staph infection of the meibomian glands, while external are an infection of the Zeis or Moll glands. Px present with tenderness and swelling of affected area.
- Standard treatment includes:
  - good lid hygiene with warm compresses and lid scrubs in conjunction with
  - doxycycline 50-100 mg po BID for 2-3 weeks
  - may consider topical AB ung on external hordeolum.

Tetracyclines: 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
- Erythromycin ung (Ilotycin) can also be used externally.
Tetracyclines: Recurrent Corneal Erosion

- RCE:
  - repeated, spontaneous disruption of corneal epi.
  - patient experiences foreign body sensation, photophobia, blepharospasm, decreased VA and lacrimation upon waking.
  - History of trauma usually reported or EBMD

Tetracyclines: Recurrent Corneal Erosion

- Standard treatment includes:
  - bandage contact lens, hyperosmotics
  - treat with doxycycline 50 mg po BID for 2-3 months
    - include use of topical steroid bid-tid for 6-8 weeks.
  - if recurrence still happen, consider stromal puncture of affected area.

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, clindamycin.
- 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

Aminoglycosides: Ocular Indications

- Systemic aminoglycosides not commonly indicated for ocular conditions
  - amikacin has been used for endophthalmitis IV and intravitreal
- Topical preparations are widely used as single agent preparations, in combination with other antibiotics as well as in combination with steroids.

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

Azithromycin (Z-pak) is active against respiratory infections due to H. influenzae and Moraxella.
- It is 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.

Recent New Report

- A study published in a recent addition of the New England Journal of Medicine, found patients prescribed Z-Pak were more likely to die than those prescribed amoxicillin.
- The results were especially pronounced for those who died of heart attacks.
- Patients on azithromycin had two and a half times the odds of dying from a cardiovascular than did patients on amoxicillin.
- FDA Recommendation: those patients on azithromycin should continue taking their medication.

Macrolide: Hyperacute Conjunctivitis

- Hyperacute conjunctivitis:
  - Usually secondary to gonorrhea or chlamydia.
  - Profuse purulent discharge, pain, redness, chemosis, positive nodes.
- Tx: Azithromycin (Zithromax)
  - 1 gram single oral dose.

Macrolide: Adult Inclusion Conjunctivitis

- Adult Inclusion Conjunctivitis:
  - Occurs in sexually active adults presenting with ocular irritation, watering, mucopurulent discharge and positive nodes.
  - Follicles inferior fornix, mixed papillary/follicular on upper lid, subepithelial infiltrates, SPK.
- Inclusion conjunctivitis:
  - Azithromycin 20 mg/kg (1 gram for adults) in a single dose or
  - 500 mg first day then 250 mg daily for 4 days.
  - Erythromycin 250 mg po QID for 14 days.

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
  - Ilotycin
  - for treatment of superficial infections
    • blepharitis and prophylaxis of ophthalmia neonatorum

AzaSite

- Azithromycin ophthalmic solution 1%
- Indicated for the treatment of bacterial conjunctivitis
- Delivery vehicle is DuraSite which forms a gel-like matrix which enhances contact time to the ocular surface
  - results in high drug concentration in a variety of ocular tissues
  - drug concentration levels remain high for a sustained period of time even after dosing stopped

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.

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.
- Norfloxacin was the first member of this group and has been rapidly followed by newer generations of drugs which offer greater potency, a broader spectrum and a better safety profile.
  - 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.

• 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.

• Ciprofloxacin is the most frequently used fluoro in the US.
  – effective against many systemic infections, with the exception of serious infections caused by methicillin-resistant Staph aureus, 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.

• The fluoro are generally very well tolerated though some of the most common adverse reactions include:
  – GI upset,
  – CNS problems (HA and dizziness),
  – phototoxicity,
  – liver toxicity, nephrotoxicity, and
  – connective tissue problems
    • should be avoided in pregnancy, nursing mothers and children under age of 18

Ocular Indications

• Hyperacute conjunctivitis (chlamydia): 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.

Fluoroquinolone: Hyperacute Conjunctivitis

Tx:
• Gonorrhea: CDC in 2007 took floros off potential treatment due to resistance. They may be used in cases of proven resistance to cephalosporins
• Chlamydia: can use as alternative therapy after azithromycin and doxycycline
  • Eg. Ofloxacin: 500 mg orally twice a day for 7 days or Levofloxacin 500 mg orally once daily for 7 days
  – concurrent use of oral tetracycline and topical fluoroquinolone (e.g. cipro//min/bril/parlfloucin qid bid).
Fluoroquinolone: Cat-Scratch Disease

- Cat-scratch disease (Parinaud’s): infection with Bartonella
  - resulting in granulomatous conjunctivitis with associated preauricular lymphadenopathy,
  - neuroretinitis,
  - focal chorioretinitis.
- Tx: e.g. oral ciprofloxacin 500 mg or gatifloxacin or moxifloxacin 400mg,
  - IV fluoroquinolone.
  - concurrent use of ocular lavage and topical fluoroquinolone (e.g. cipro//moxi/gatifloxacin q1-2 hrs).

Ocular Fluoroquinolones

- Commonly used in optometry for treatment of bacterial conjunctivitis and keratitis
  - standard of care for the treatment of bacterial keratitis
  - FDA approved are Ciloxan, Ocuflox, Iquix
    - most practitioners utilize newer generation Vigamox, Zymar, Besivance, Iquix (levofloxacin 1.5%)
    (3rd gen though increased concentration from previous Quixin 0.5% levofloxacin)

- Besivance (besifloxacin 0.6%) is strictly an ophthalmic preparation with no systemic counterpart
  - thought to possibly reduce chance of resistance development
  - has DuraSite as vehicle so forms a gel-like liquid on the eye increasing contact time
  - animal data has shown possible increased activity for MRSA

- Allergan released a concentrated form of gatifloxacin
  - Zymar is gatifloxacin 0.3% (currently discontinued)
  - Zymaxid is gatifloxacin 0.5%
    - Indicated for bacterial conjunctivitis
  - Alcon has released Moxeza which is same concentration of moxifloxacin as Vigamox but with an added ingredient to increase ocular contact time
    - Vigamox is 0.3% moxifloxacin

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, cotrimoxazole 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

Sulfonamides: Ocular Indications

- No common indications for systemic sulfonamides (sulfadiazine is sometimes used as adjunct therapy in toxoplasmosis Tx) though topical preparations do exist.
- Sulfa’s have limited use due to resistance and allergic reactions
  - used more by non-ophthalmic providers.
- Available in combination with steroids
  - ex. Blephamide

Trimethoprim and Pyrimethamine

- Similar antibacterial spectrum as sulfonamides, though has a 20-50 fold more potent affect than the sulfonamides.
- Trimethoprim maybe used on its own to treat acute UTI’s and in the treatment of bacterial prostatitis (fluox 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 affects include several blood anemias which can be reversed by administering folinic acid.

Trimethoprim: Ocular Indications

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

Pyrimethamine: Ocular Indications

- Toxoplasmosis chorioretinitis (acquired) presents with:
  - decreased VA,
  - photophobia, floaters,
  - vascular sheathing,
  - full-thickness retinal necrosis,
  - fluffy, yellow-white retinal lesion adjacent to old scars,
  - overlying vitreous reaction (headlights in fog), and
  - anterior chamber reaction.
Treatment

• Pyrimethamine 25 mg po 1-2 times/day (loading dose 75mg) and
  – sulfadiazine 1 g po 6hrs and clindamycin 300 mg po 6hrs.

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.

Case

• 25 WF presents to ER with swollen and painful RUL
  – started 2 days previously
  – medical and ocular history unremarkable.
  – VA normal, EOM’s unrestricted, pupils normal, CVP full, CT or orbit reveals swelling anterior to orbital septum.

Inhibitors of Cell Membrane Function
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!!!