### Treatment Options for Ocular Infection

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www.eyeupdate.com

### Antibacterial Medications

- Sulfa Preparations
- Erythromycin
- Bacitracin
- Bacitracin / Polymyxin B
- Bacitracin / Polymyxin B / Neomycin
- Chloramphenicol
- Gentamicin
- Tobramycin
- Trimethoprim / Polymyxin B
- Fluoroquinolones
- Azithromycin
- Oral antibiotics

### Off label

- “An estimated 50 percent of medications used routinely in ophthalmic practice are used off-label.”
- “Clinical practice should be guided by the best interest of the patient.”
- “In many instances, off-label treatments may be the best, or the only, available treatment, and withholding treatment would be unethical.”


### Are Generics OK?

“The more recent (since 1992) ophthalmic generics are approved according to strict criteria for sameness and are expected to behave in the same manner as the innovator.”

Reference: Ophthalmology, June 2012. Editorial by W. Chambers, MD of the FDA

### Trimethoprim with Polymyxin B

- Trimethoprim, a non-antibiotic antibacterial
- Bacteriostatic and broad spectrum
- Inhibits bacterial dihydrofolate reductase
- Effective against most common ocular pathogens, except pseudomonas species
- Excellent for bacterial infections in children
- Haemophilus influenzae and streptococcus pneumoniae
- Polymyxin B is a highly effective gram – bactericidal drug
- Available as a 10 ml solution (Polytrim and generic)

### Financial Disclosure

Dr. Ron Melton and Dr. Randall Thomas are consultants to, on the speakers bureau of, on the advisory committee of, or involved in research for the following companies: Allergan, Icare, Shire, and Valeant.
Azithromycin 1% Ophthalmic Solution

- Topical eyedrop solution of azithromycin
- Only macrolide eyedrop formulation
- Spectrum coverage is similar to erythromycin
- Good tissue penetration; viscous vehicle
- Dosage: BID for 2 days then QD for 5 days
- Avoid use if patient is allergic to erythromycin
- Pregnancy category B; approved down to age 1
- Marketed as AzaSite 1% ophthalmic solution in a 2.5 ml opaque bottle by Akorn

Implications of Azithromycin and Fluoroquinolone Use

- “The repeated use of azithromycin or fluoroquinolone antibiotics significantly alters the composition of conjunctival flora by increasing the percentage of S. epidermidis.”
- “Resistant strains of S. epidermidis emerge rapidly after antibiotic exposure and possess co-resistance to other classes of antibiotics.”
- “The high percentage (75%) of baseline resistance to azithromycin may have allowed resistant S. epidermidis strains to readily out-compete other flora.”
- “The practice of long-term or repeated use of azithromycin for blepharitis may therefore select for not only azithromycin-resistant but also doxycycline-resistant strains of S. epidermidis.”

Oph. May 2013

Aminoglycosides

- Bactericidal
- Inhibits protein synthesis
- Effective against most commonly encountered gram positive and gram negative bacteria
- Available in both solution and ointment form
- Gentamicin - toxic/allergic reactions do occasionally occur. Pregnancy category C.
- Tobramycin - resistance, toxic and allergic reactions rare (Pregnancy category B)

Drugs and Antibiotic Resistance

- Study: 200 patients - 90% Gm+, 10% Gm –
- Least susceptible: penicillins (17%) and erythromycin (48%)
- Highest susceptible: gentamicin (94%), tobramycin (90%), tetracycline (91%)
- Intermediate susceptible: moxifloxacin and gatifloxacin (75%)
- About half of Gm+ were methicillin resistant
- “The fluoroquinolones are failing to cover 20% or more potential pathogens; additionally, we found that fluoroquinolones may cover 1 but not all CNS strains present in a patient. One should therefore entertain alternatives to fluoroquinolones. Indeed, given the overall 90-plus percent susceptibility rate, one should perhaps consider instead the aminoglycosides.”

Reference: AJO, January 2013

Gatifloxacin 0.5%

- Inhibits topoisomerase types 2 and 4
- Highly effective against Gram+ and Gram− bacteria
- FDA-approved for bacterial conjunctivitis
- Pregnancy category C; pediatric to age 1
- BAK preserved
- Available from Allergan as 0.5% Zyomaxid
- Systemically: Tequin (removed from market)

Moxifloxacin 0.5%

- Actions: Inhibits topoisomerase type 2 (DNA gyrase) and topoisomerase type 4
- Highly effective against G+ and G− bacteria
- Pregnancy category C
- Pediatric indication:
  - Vigamox - age 1
  - Moxeza - age 4 months
- Xanthan gum prolongs ocular surface contact time, thus a decreased dosing frequency
- Dosing:
  - Vigamox 0.5% tid x 7 days (pH 6.8)
  - Moxeza 0.5% bid x 7 days (pH 7.4)
- Vigamox and Moxeza 3ml – available by Alcon
- Systemically available as Avelox
Antimicrobial Resistance

- Staph. Epi. was the most common pathogen in this study
- 97% of all isolates were sensitive to gentamicin
- Fluoroquinolone resistance ranged from 32% to 40%
- “The high prevalence of fluoroquinolone-resistant organisms among ocular and nasal flora in our patient population raises concern with regards to the usefulness of topical fluoroquinolones as the best first-line agent in the setting of ophthalmic prophylaxis and for empiric use in acute ophthalmic infectious processes.”

Reference: AJO, December 2011

2009 ARMOR Surveillance
All S. aureus (n = 200)

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<th>Antibiotic</th>
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39% of ocular S. aureus isolates were MRSA
38% of ocular S. aureus isolates were FQ-resistant

Haas et al. Presented at ARVO, Fort Lauderdale, FL, May 2-6, 2010. Abstract #D965. % resistance based on oxacillin and ciprofloxacin breakpoints.

A Novel Fluoroquinolone - Besifloxacin

- A unique bi-halogenated quinolone
- New chemical entity: An 8-chloro- fluoroquinolone
- NOT used systemically – relative resistance-proof
- FDA-approved medication: Bacterial conjunctivitis
- FDA-approved treatment protocol: tid for 7 days
- Pediatric approval: ages 1 and older
- Preserved with 0.01% BAK (Durasite vehicle)
- Marketed as Besivance 0.6% ophthalmic suspension by B&L Pharmaceuticals – 5 ml

Antibiotic Susceptibilities

- “The efficacy of aminoglycosides has been well-documented in endophthalmitis.”
- As the use of topical fluoroquinolones has increased, so have the number of reports documenting an increase in bacterial resistance.
- “The 4th generation fluoroquinolones evaluated did not provide much greater coverage than the earlier generation fluoroquinolones.”
- To guard against resistance, eye doctors are discouraged from using antibiotics with EKC, and prophylactic use before intravitreal injections.

Reference: Ophthalmology, August 2014

Perspective on Besivance in Corneal Ulcer Treatment

“Corneal infectious keratitis and ulceration are ocular emergencies that require topical antibiotics at a therapeutic mainstay. At the initial examination, it is unclear whether we are dealing with one or more organisms, and if any resistance to antibiotics exists. Hence, a shotgun approach is preferred with a broad-spectrum antibiotic that covers both gram-positive and gram-negative organisms. Newer fluoroquinolones, such as besifloxacin, can be used as a monotherapy with frequent applications around the clock, depending on the severity of the corneal infection.”

CDC Reports Keratitis Hardship Stats

- 930,000 outpatient visits and 58,000 emergency room visits each year for keratitis or contact lens conditions
- 76.5% of visits - Rx given for antimicrobial drug
- 250,000 hrs or more of clinician time spent in keratitis visits
- $175 million in direct health expenditures for keratitis and contact lens conditions
- $58 million and $12 million expenditures attributed to Medicare and Medicaid patients


Chloramphenicol Revisited

- More than 50% of the world uses chloramphenicol as a first-line agent in the treatment of conjunctivitis
- It is OTC in many countries
- Approximately a one in 2 million chance of blood dyscrasia
- “If American medicine continues to tilt towards more socialized care and some medications are not available based on cost alone, drugs like chloramphenicol eye drops could be considered as a viable treatment option.”

Reference: AJO, September 2013

Antibiotics - Systemic

- Penicillins
- Cephalosporins
- Tetracyclines
- Macrolides
- Fluoroquinolones

www.drugfacts.com

The Numbers Behind Antibiotic Use

- "More than 8 in 10 Americans received antibiotic prescriptions in 2011
- “A total of 262.5 million courses of outpatient antibiotics were prescribed in 2011
- Rate of 842 prescriptions per 1000 persons
  - For infants (age < 2 years), children (age 3-9) and older adults (age > 65) rates actually exceeded 1000 prescriptions per 1000 persons
  - Amoxicillin was the most commonly prescribed antibiotic among children and teenagers
  - Azithromycin was the antibiotic most commonly prescribed among young adults
  - Women were almost twice as likely as men to receive antibiotics
  - Antibiotic prescribing rates were considerably higher in the South
  - Per-physician prescribing rates were highest among dermatologists, family practitioners and pediatricians”

Abigail Zuger, MD. Clinical Infectious Diseases; Open Forum Infectious Diseases. May 2015.

Amoxicillin/Clavulanic Acid (Augmentin)

- Clavulanic acid enables amoxicillin to be bactericidal against common gram positive pathogens
- Useful in treating soft tissue infections
- Cannot use if patient is allergic to penicillin
- Tx: 250, 500 & 875 (generic) or 1000 mg (branded only) tablet q 12 hrs x 7-10 days
- Can be taken with meals

Cephalexin (Keflex)

- Cephalexin - 1st generation cephalosporin
- Effective against most gram positive pathogens
- Some earlier generation cephalosporins share about a 1% cross-allergenicity to PCN
- Usual dosage: 500 mg bid x 1 week
- Useful in soft tissue staph infections, such as internal hordeola, preseptal cellulitis, etc.
**Allergic Reactions to Cephalosporins**

- Widely used to treat outpatient infections
- 19 of “more than a million” patients experienced allergic reactions
- “Almost 66,000 patients who received cephalosporins had previously documented allergies to penicillin, and 3,300 had previous reports of cephalosporin allergies.”
- “Cross reactivity between cephalosporins and penicillin has long been a concern; however, in recent studies, almost all penicillin-allergic patients have received cephalosporins safely.”

Reference: J. Allergy and Clinical Immunology. March 15, 2015.

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**Options for True Penicillin Allergy Patients**

- 2nd or 3rd generation cephalosporin such as cefuroxime (Ceftin) or cefpodoxime (Vantin)
- Sulfamethoxazole/trimethoprim (Bactrim or Septra)
- A fluoroquinolone (Levofloxacin)
- Doxycycline
- Erythromycin

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**The Tetracyclines**

- Tetracycline, doxycycline, minocycline
- Doxycycline most commonly used
- Advantages over tetracycline
  - Maintenance dose 20-100 mg daily
  - Can be taken without regard to meals
  - Contraindicated in pregnancy, nursing mothers, under age 8; photosensitivity warning
  - Indications in primary eye care
    - Meibomianitis (chronic inspissated glands)
    - Adult inclusion conjunctivitis (chlamydia)
    - Recurrent corneal erosion

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**Oracea**

- Doxycycline 30 mg immediate release and 10 mg delayed release beads (once daily 40 mg capsule)
- First and only oral therapy approved by FDA to treat rosacea
- Works by controlling inflammation
- Recommended to take in morning with a full glass of water
- Contraindications and side effects similar to tetracyclines (photosensitivity and yeast infections not observed in clinical trials).
- Marketed by Galderma

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**Minocycline, MGD, and Dry Eye**

- “Lid hygiene plus minocycline showed significant improvements in clinical signs and remarkable changes in fatty acid composition.”
- “There is no agreement on the ideal dosage of minocycline.”
- “Our study showed remarkable benefit with 50 mg oral minocycline twice daily for two months without any fatal complications.”
- “To obtain meaningful patient satisfaction and favorable clinical results we should consider minocycline as a first-line therapy for the treatment of moderate and severe MGD.”

AJO, December 2012

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**Medical Approach to RCE**

- Small study – limited follow-up
- 100 mg doxycycline per day for 1 month and Lotemax q.i.d. for 1 month
- Results: Curative in almost all cases
- An alternative (or adjunctive) to ASP or conventional therapies
Oral Doxycycline and Pterygial Angiogenesis

- UV light is a known trigger for pterygenesis and progression
- Doxycycline (and corticosteroids) can inhibit neovascularization
- Perhaps pterygium management can be augmented with 50 mg P.O. doxycycline daily for many weeks or many months after (or concurrent with) topical loteprednol q.i.d. for 1 month, the b.i.d. for 2 months


Azithromycin - (Zithromax)

- Used for soft tissue infection; heavy prescribing has resulted in much resistance
- Drug of choice for chlamydial infections
- Dosage for chlamydial eye infection - four 250 mg capsules or two 500 mg capsules for one day or a single dose of a 1,000 mg suspension
- Zmax is a 2,000 mg oral suspension (but rarely used)

Doxycycline versus Azithromycin for MGD

- Patients (110) with MGD received oral azithromycin (500mg day one, then 250 mg/d 4 days) vs one month oral doxycycline (200 mg/day) x 1 month
- After 2 months both groups significant improvement; % of clinical improvement significantly better for azithromycin; less GI SE with azithromycin (4% vs 26%); azithromycin less expensive.


Bactrim or Septra

- Drug of choice for MRSA infections
- Combination of 160 mg of trimethoprim and 800 mg of sulfamethoxazole
- Rule out true sulfa allergy
- Sig: Take 1 or 2 DS tabs p.o. bid x 7-10 days
- Note that the standard strength of these drugs is “double strength” (DS)
- If sulfa-allergic, then doxycycline 100 mg used bid for 7-10 days
- Both are old, generic, and highly-effective