CLINICAL DECISION MAKING IN MICROBIAL KERATITIS

Gregory M. Schultz, O.D., F.A.A.O.
Eye Center of Virginia
Williamsburg and Gloucester Virginia
The Questions we will answer:
GOALS OF THIS COURSE:
QUESTIONS WE WILL ANSWER

• Do I have an “infectious” corneal ulcer?
• How do I determine if this infiltrate/ulcer is “sterile” vs. infection?
• Do I have to culture?
  • How do I maximize my yield if I culture?
• How aggressive must I be with my treatment?
• When do I modify my treatment plan?
QUESTIONS WE WILL ANSWER:

• The Standard of Care: What is my liability here?
  • Is a fourth generation Fluoroquinolone enough?
• What is the recommended dosing regimen?
• Do I keep my patient up through the night?
• Should I use drops, ointments or both?
• When or should I employ a steroid?
GOALS OF THIS COURSE

• When would I use fortified antibiotics?
• If I treat with commercially available AB, do I use a 2\textsuperscript{nd}, 3\textsuperscript{rd}, or a fourth generation fluoroquinolone
• What about besifloxacin, is it the best?
• New treatments of bacterial keratitis
INFECTIOUS KERATITIS

• Infectious keratitis is a potentially blinding eye disease
• 30,000 cases each year
  • Bacterial, fungal, Acanthamoeba (Pepose, JS et al AJO 1992)

• If appropriate antimicrobial treatment is delayed only 50% of eyes gain reasonably good visual recovery

• * AAO Preferred Practice Patterns for bacterial keratitis
PREDISPOSING FACTORS: BACTERIAL KERATITIS

- Contact lens wear/ EW, homemade soln. /use of tap water
  - DW 1 case / 2,500 per year
  - EW 1 case / 150-300 / year
- Ocular surface disease (MGD, DES)
- Previous HSK
  - Corneal anesthesia
- Exposure/ lagophthalmus
- Bullous Keratopathy
- trauma
PREDISPOSING FACTORS: BACTERIAL KERATITIS

- Immuno-compromised host
  - Debilitating illness (DM, Cancer/chemo)
- Recent ocular surgery
  - LASIK / LASEK, PK, PRK
- Dry eye/ OSID
- Lid deformities/ trichiasis, entropion/ectropion
- Chronic use of topical steroids
- Contact lens wear and or abuse
Virtually anything that will put a chink in the armor!
HOWEVER THERE ARE A FEW BUGS THAT CAN PENETRATE AN INTACT CORNEAL EPITHELIUM

Neisseria species
Cornybacterium diphtheriae
Haemophilus species, Aegyptius
Listeria species
SYSTEMIC CONDITIONS THAT PREDISPOSE TO BACTERIAL KERATITIS

- Diabetes
- Vitamin A deficiency
- Collagen vascular diseases
- Gonococcal infection with conjunctivitis
INFECTIOUS KERATITIS

The hallmark of Corneal infection is Corneal Leukocytic infiltration!
BACTERIAL KERATITIS: SIGNS/ SYMPTOMS

- Mild to severe ocular pain
- Photophobia
- Decreased vision
- Tearing with discharge
- Mild to severe conjunctival inflammation

- Focal white opacity in the stroma
  - (infiltrative lesion)
- Stromal edema
- Corneal ectasia
- Liquifactive necrosis
- Mild to severe hypopyon, A/C reaction
- Lid edema
PSEUDOMONAS INFECTION
# Differentiating Infectious from Sterile Keratitis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Infectious</th>
<th>“Sterile”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Significant</td>
<td>Little to none</td>
</tr>
<tr>
<td>Onset</td>
<td>Acute onset/ 24 hours or &lt;</td>
<td>More indolent course</td>
</tr>
<tr>
<td>Location</td>
<td>Central / para-central</td>
<td>Peripheral/mid-periph</td>
</tr>
<tr>
<td>Injection</td>
<td>Significant: grade 3-4+</td>
<td>Trace to 1+</td>
</tr>
<tr>
<td>Discharge</td>
<td>excessive</td>
<td>Minimal to none</td>
</tr>
<tr>
<td>Visual Acuity</td>
<td>Typically reduced</td>
<td>Often unaffected</td>
</tr>
<tr>
<td>A/C reaction</td>
<td>2-4+</td>
<td>trace</td>
</tr>
</tbody>
</table>
THE RULE OF 2

A corneal ulcer is less likely to be infectious when:

- It is < 2 mm in diameter
- There is < 2+ cells in the anterior chamber
- The lesion is > 2mm from the visual axis
## DISTRIBUTION OF CAUSATIVE ORGANISMS IN MONOMICROBIAL KERATITIS

LEVY SB ET AL. CORNEA. 1997; 16:383-386

<table>
<thead>
<tr>
<th>Organism</th>
<th>Percent of Infections</th>
<th>Gram+/-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus epidermidis</td>
<td>47%</td>
<td>+</td>
</tr>
<tr>
<td>Pseudomonas Aeruginosa</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>13.2%</td>
<td>+</td>
</tr>
<tr>
<td>Serratia</td>
<td>5.3%</td>
<td></td>
</tr>
<tr>
<td>Streptococcus pneumonia**</td>
<td>5.3%</td>
<td>+</td>
</tr>
</tbody>
</table>
BACTERIAL FLORA IN THE NORMAL EYE

- Staph epidermidis 75-90%
- Diptheroida 20-33%
- Staphylococcus aureus 20-25%
- Hemophilus influenzae 3% or >
- Streptococcus pneumoniae 1-3%
- Gram negative rods 1%
- Psuedomonas 0-5%
GRAM (+) COCCI
(EYE PATHOGENS)

- Staphylococcus Aureus/ epidermidis
- Micrococcus Species
- Streptococcus pneumonia
- Streptococcus pyogenese
- Streptococcus viridans
GRAM (+) BACILLI (EYE PATHOGENS)

- Cornybacterium
- Propionibacterium Acnes (P. Acnes)
- Clostidium
- Listeria
GRAM (-) COCCI (EYE PATHOGENS)

- Neisseria gonorrhoeae
- Moraxella
- Proteus
- Serratia Marcesens
GRAM (-) BACILLI (EYE PATHOGENS)

- Pseudomonas aeruginosa
- H. influenzae
- Moraxella lacunata
- Proteus
- Serratia Marcescens
PSEUDOMONAS AERUGINOSA

- Ubiquitous gram (-) rod
- Most virulent corneal pathogen
- Can **not** penetrate an intact corneal epithelium
- Can perforate a cornea in 24 hours
THESE BACTERIA CAUSE RAPID TISSUE DESTRUCTION

Pseudomonas

Streptococcus pneumoniae
gonococcus
RESULTS OF BACTERIAL KERATITIS

• Corneal scarring
  • Visual morbidity
• Corneal perforation
• Endophthalmitis
In 1996-1999, 12% of all cases were related to CL wear.

In 1999-2002, 30% of all cases were related to CL use.

43% of CL related infections related to daily wear, frequent replacement soft CL’s.
BACTERIA, FUNGI, PROTOZOA AND VIRUSES CAN ALL INFECT THE CORNEA.

How do we know what we are dealing with?
DIFFERENTIAL DIAGNOSIS

• Must differentiate from:
  • Herpetic ulcers
    • Hypoesthesia, geographic lesions, dendritic lesions
    • Disciform lesions of stroma / ring immune infiltrate
  • Fungal ulcers
    • Characteristic “feathery” appearance
    • Poor response to antibiotic therapy
    • History of vegetative trauma
HSK

Geographic ulcer

Dendritic ulcer
EPITHELIAL WITH STROMAL DISEASE
FUNGAL KERATITIS
DIAGNOSIS

• Clinical suspicion, corneal scraping, superficial keratectomy

• Diagnostic stains: Gram stain, Giemsa stain, PAS, acridine orange, calcofluor white

• Culture media: Sabouraud’s dextrose agar, blood agar

• Confocal microscopy
MOST COMMON FUNGAL KERATITIS

- Aspergillus, filamentous fungi
- Fusarium, filamentous fungi,
- Yeast (candida albicans)
  - There are 40 different genera that cause keratomycoses
  - Nation wide about 300 cases per year

Treatment:
- Natamycin 5% (Natacyn)
- Amphotericin B 0.15%
TREATMENT OF FUNGAL KERATITIS

• Topical: natamycin 5 % suspension
  • Q1h for 24-48 hrs

• Amphotericin-B 0.1-0.5%
  • Q 15-20 minutes for 24-48 hours

• Miconazole 1% - very toxic
  • Q1h

• Oral therapy
  • Ketoconazole (Nizoral) or Fluconazole (Diflucan) 100-200 mg /day
FUNGAL KERATITIS
DIFFERENTIAL DIAGNOSIS

- Endophthalmitis does not follow bacterial keratitis without corneal perforation
  - Unlike fungal keratitis

- Therefore A/C and vitreous taps are not necessary when perforation is absent in bacterial keratitis!
ACANTHAMOEBA KERATITIS: COURSE

- Pain, photophobia, and tearing that is out of proportion with the clinical picture
- Often starts as non-specific keratitis
- Epithelial micro-erosions, micro-cystic edema and perineural infiltrates in radial pattern
- Proceeding to a classic ring infiltrate
ACANTHAMOEBA KERATITIS: PROTOZOAN

- A ubiquitous protozoan feeds on other microbes not human tissue
  - Seven species infect the eye
  - Explains indolent course
- Has the ability to encyst when food supply is low
- Most have a history of CL wear with bad hygiene habits
- Unsanitary water conditions; lakes pools hot-tubs
- 10% are not CL wearers
ACANTHAMOEBA KERATITIS
ENCYSTED ORGANISM: ACANTHAMOEBA
ACANTHAMOEBA KERATITIS: TREATMENT

- Brolene 0.1%
- Polyhexamethylene Biguanide (PHMB) 0.2%
  - DESTROYS cysts and trophozoites

Alternate therapies include:
- Neomycin
- Clotrimazole
- Chlorhexidine
- Baquacil
TREATMENT OF ACANTHAMOEBA

USE ONE FROM THE BIOCIDES/CATIONIC ANTISEPTIC GROUP PLUS ONE OR MORE OF THE FOLLOWING

Polyhexamethylene biguanide (PHMB, Baquasil, Cosmocil)
chlorhexidine digluconate
TREATMENT OF ACANTHAMOEBA

- Antibiotic / Aminoglycoside
  - Paromomycin (Humatin)/ neomycin
- Antifungal
  - Clotrimazole, ketoconazole, itraconazole, miconazole, fluconazole (Diflucan)
- Anti-parasitic
  - Propamidine isethionate (Brolene)
DIFFERENTIAL DIAGNOSIS

- Non-infectious stromal inflammation may be associated with CL wear (EWCL)
- Systemic diseases such as collagen vascular disorders (RA, SLE)
- Vasculitic disorders – polyarteritis nodosa
- Wegener’s granulomatosis
- Sarcoid
- Severe rosacea
- Atopy/ limbal vernal
CORNEAL PERFORATIONS
CORNEAL CULTURING AND SCRAPINGS

A must in severe bacterial keratitis!
INDICATIONS FOR CORNEAL CULTURING

CORNEAL SCRAPING IS A MUST IN SEVERE/SERIOUS INFECTIOUS KERATITIS

• Central location
• Large lesions (>2mm)
• Painful lesions
• Post-op corneal infections
• Suspected fungal infection
WHEN YOU NEED TO CULTURE

- Depth of infiltrate **middle to deep stroma**
- Simultaneous presence of significant A/C reaction, fibrin or hypopyon
- Poor vision
- Presence of corneal abscess
- Unresponsive to broad spectrum therapy!
HOW TO CULTURE
AND OBTAIN RELIABLE RESULTS

MAXIMIZING YOUR YIELD
CULTURING: WHAT IS OUR GOAL

• The culture guided approach to managing bacterial keratitis involves taking a sample of corneal tissue (by scraping) and performing microbiological tests to determine the type of bacterial organisms and their sensitivities.

• Avoiding contamination and false positives!
WHAT YOU WILL NEED: SUPPLIES

- Kimura Spatula
- Heat sterilization method
- Culture media
  - Blood agar
  - Chocolate agar
  - Thioglycolate broth
  - Sabaraud’s dextrose agar
  - Access to calcofluor white
<table>
<thead>
<tr>
<th>Culture media</th>
<th>Growth of Isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood agar</td>
<td>Aerobic and facultative anaerobic bacteria</td>
</tr>
<tr>
<td></td>
<td>P. aeruginosa, S. aureus, S.epidermidis, S.pneumonia</td>
</tr>
<tr>
<td>Chocolate Agar</td>
<td>H. influenza, N. Gonorrhea, bartonella species</td>
</tr>
<tr>
<td>Thioglycolate broth</td>
<td>Aerobic and facultative anaerobic bacteria</td>
</tr>
<tr>
<td>Sabaraud's dextrose agar</td>
<td>Fungi</td>
</tr>
</tbody>
</table>
## SUPPLEMENTAL CULTURE MEDIA

<table>
<thead>
<tr>
<th>Culture media</th>
<th>Growth of Isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaerobic Blood agar</td>
<td>P. Acnes, streptococcus</td>
</tr>
<tr>
<td>Lowenstein-Jensen</td>
<td>Mycobacterium species</td>
</tr>
<tr>
<td>Middlebrook agar</td>
<td>Mycobacterium species</td>
</tr>
<tr>
<td>Thayer- Martin Agar</td>
<td>Pathogenic Neisseria</td>
</tr>
</tbody>
</table>
WHAT YOU WILL NEED: SUPPLIES

- Sterile cotton swabs
- Glass microscopic slides for gram staining and smears
CULTURING SUPPLIES
KIMURA SPATULA
HOW TO CULTURE: TECHNIQUE

- Instill topical anesthetic! (better if preservative free)
  - This helps with patient cooperation
  - Yield may improve if PF anesthetics are used
  - Culturing only the purulent material often yields inadequate sample
    - Grab stroma!
  - Inoculate directly onto culture media
  - Consider the CL case, the CL and solutions!
HOW TO CULTURE: TECHNIQUE

• Consider culturing when ulcer presents with features that are suggestive of fungal, amoebic or mycobacterial keratitis

• Culture when the history is suspicious
  • Trauma
  • Vegetative injury
  • CL hx. In lakes, pools, or hot tubs
  • Post LASIK
SPECIALIZED CULTURES

- Fungal
- Acanthamoeba
- Moraxella
- Proteus
CULTURING TECHNIQUES
CULTURING TECHNIQUES
# Diagnostic Stains

<table>
<thead>
<tr>
<th>Diagnostic Stain</th>
<th>Organisms Visualized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram Stain</td>
<td>Best for bacteria, can visualize fungi and Acanthamoeba</td>
</tr>
<tr>
<td>Giemsa Stain</td>
<td>Bacteria, fungi, chlamydia, Acanthamoeba</td>
</tr>
<tr>
<td>Acid fast</td>
<td><strong>Mycobacterium</strong>, nocardia</td>
</tr>
<tr>
<td>Acridine Orange</td>
<td>Bacteria, fungi, Acanthamoeba</td>
</tr>
<tr>
<td>Calcofluor White</td>
<td>fungi, Acanthamoeba</td>
</tr>
</tbody>
</table>
GRAM STAINING

Flow Through Procedure

1. Wipe bottom of biofilm slide clean
2. Clean top edges of slide about 2mm

3. Build up a ridge of petroleum jelly on the top and bottom of a cover slip
4. Cover slip with petroleum jelly
5. Biofilm on slide held in place by petroleum jelly

6. Add crystal violet-wait 30 sec.
7. Wash with water
8. Add Grams Iodine-wait 1.5 min.

9. Decolorize with alcohol
10. Wash with water
11. Stain with Safranin dye-wait 30 sec.

12. Wash with water
13. Examine under oil immersion through the cover slip
GRAM STAIN PROCEDURE

Crystal Violet

Iodine

Alcohol

Safranin

All purple

All purple

G+ = purple

G- = colorless

G+ = purple

G- = red
STAINING PROPERTIES OF BACTERIA

GRAM +
- Peptidoglycan
- Membrane

GRAM -
- Peptidoglycan
- Membrane
- Periplasm
- Lipopolysaccharide & protein
INVITRO VIEW
TREATMENT OF BACTERIAL KERATITIS

Review of Standard of Care
And New Treatment Alternatives
GOALS OF THERAPY

- Preserve the globe
- Minimize stromal scar formation
- Minimize inducement of irregular astigmatism
- Vision rehabilitation
  - PTK
  - CL’s or PK
  - Collagen cross linking
“MOST CASES OF COMMUNITY ACQUIRED BACTERIAL KERATITIS RESPOND TO EMPIRICAL TREATMENT WITH BROAD SPECTRUM ANTIBIOTICS”

Preferred Practice Guidelines on bacterial keratitis, AAO
KEYS TO SUCCESSFUL THERAPY

• RAPID RECOGNITION
• TIMELY INSTITUTION OF THERAPY
• APPROPRIATE FOLLOW-UP
MEDICAL TREATMENT

• Broad spectrum topical antibiotics
• Fluoroquinolones
  • 2nd generation….. Ciloxan, Ocufox
  • 3rd generation……Quixin
  • 4th generation………Vigamox, Zymar, Besivance
• Fortified Antibiotics: When to use them
• Judicious Use of Corticosteroids
PROCEDURAL TREATMENT

• Cultures and smears
  • Cultures and sensitivities
  • Gram/ geimsa staining
• Deeper tissue corneal biopsy
• TISSUE GLUE
• Collagen cross linking
• PDT
• PTK
• PKP
BROAD SPECTRUM ANTIBIOTICS ARE THE MAINSTAY OF TREATMENT

PREFERRED TREATMENT IN NON-SEVERE CASES
BROAD SPECTRUM ANTIBIOTICS
THE FLUOROQUINOLONES

2\textsuperscript{nd} generation: ciprofloxacin, ofloxacin

3\textsuperscript{rd} generation: levofloxacin

4\textsuperscript{th} generation: moxifloxacin, gatifloxacin, besifloxacin
THE FLUOROQUINOLONES:
SOME INTERESTING POINTS

• Some clinical trials have shown 4th generation Fluoroquinolones to be as effective/potent as combined fortified antibiotics against the common pathogens that cause bacterial keratitis
  • The Ofloxacin Study Group, Ophthalmology 1997
• There are still concerns with resistance (2nd and 3rd gen)
• No difference in clinical efficacy or overall time to cure
# TOPICAL FLUOROQUINOLONES: CLINICAL INDICATIONS

<table>
<thead>
<tr>
<th>Drug / concentration</th>
<th>Indications</th>
<th>Rec. treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin 0.3%</td>
<td>Conjunctivitis, Corneal ulcers</td>
<td>7 days, 14 days</td>
</tr>
<tr>
<td>Ofloxacin 0.3%</td>
<td>Conjunctivitis, Corneal ulcers</td>
<td>7 days, 9 days</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; gen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levofloxacin 0.5%</td>
<td>Bacterial conjunctivitis, Corneal ulcers</td>
<td>7 days</td>
</tr>
<tr>
<td>4&lt;sup&gt;th&lt;/sup&gt; gen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin 0.5%</td>
<td>Bacterial conjunctivitis</td>
<td>7 days TID</td>
</tr>
<tr>
<td>Gatifloxacin 0.3%</td>
<td>Bacterial conjunctivitis</td>
<td>Days 1-2 q2h, Days 3-7 QID</td>
</tr>
</tbody>
</table>
THE MECHANISM OF ACTION OF FLUROQUINOLONES

- Fluoroquinolones inhibit bacterial DNA gyrase (topoisomerase II), topoisomerase IV OR BOTH.
  - These are the key enzymes in bacterial DNA replication and transcription
- 2nd generation FQ inhibit DNA gyrase
- 3rd generation FQ inhibits DNA gyrase
- 4th generation FQ inhibit both enzymes
- Inhibition of these enzymes will result in bacterial cell death
THE FLUOROQUINOLONES: MOA

• Topoisomerase IV is the main target for most gram + organisms
• DNA gyrase (topoisomerase II) is the main target for most gram negatives
• 4\textsuperscript{th} Generation FQ inhibit both
  • Gatifloxacin, Moxifloxacin, besifloxacin
• 2\textsuperscript{nd} generation FQ inhibit / target DNA gyrase (topoisomerase II)
  • Ciprofloxacin, ofloxacin
Mechanism of action of fluoroquinolones: the basics...
Mechanism of Action of Fluoroquinolones

Fluoroquinolones bind to two nuclear enzymes, inhibiting DNA replication.

DNA gyrase

Topoisomerase IV
TOPICAL 4\textsuperscript{TH} GENERATION FQ ARE GOOD ALTERNATIVES TO COMBINATION FORTIFIEDS
THE 4TH GEN FLUOROQUINOLONES

• Highly soluble with excellent tissue penetration
• BAK free........self preserved! (Vigamox)
• Formulated at near neutral (6.8) pH = comfort
• Less likely to select for resistance
4TH GENERATION FLUOROQUINOLONES

- Several controlled studies have shown both gatifloxacin and moxifloxacin performed at least as well as standard therapy with fortified cefazolin and tobramycin.
- Both 4th gen fluoroquinolones are not approved for treatment of bacterial keratitis by the FDA.
  - Any use in this regard is “off label”
  - So what is the standard of care?
THE 4\textsuperscript{TH} GEN FLUOROQUINOLONES

- The 4\textsuperscript{th} generation FQ’s are more effective against Gram + organisms while maintaining adequate coverage against Gram (-)
- One FQ resistant organism is atypical mycobacterium
4^TH GEN FLUOROQUINOLONES: STUDIES SUPPORTING USE

- Parmar et al compared gatifloxacin 0.3% to ciprofloxacin 0.3% in treatment of bacterial keratitis (ulcers > 2mm).
- Looked at the susceptibility to bacterial isolates
  - Dosing q1h for bacterial ulcers
  - Found susceptibility to gram +
    - was 96% to gatifloxacin, 60% to ciprofloxacin
  - Found susceptibility to gram –
    - Was 93% to gatifloxacin
    - Was 86% to ciprofloxacin
4th GEN FLUOROQUINOLONES: STUDIES SUPPORTING USE

- Shah et al looked at bacterial corneal ulcers >2mm and randomized their treatment to:
  - Moxifloxacin 0.5%, q1h for 48-72 hours
  - Gatifloxacin 0.3% q1h for 48-72 hours
  - Fortified AB (5% Cefazolin, 1.3% Tobramycin) or (10.4% Cefazolin with 5.2% Tobramycin) both q1h
- Cure rates for Fortifieds was 90%
- Cure rates Gatifloxacin/moxifloxacin group was 95%
MIC 90’S

- MIC 90 for Gram +’s is lower for 4\textsuperscript{th} generation FQ than 2nd or 3\textsuperscript{rd}
  - Especially for FQ resistant staph aureus
- MIC 90 for Gram –’s is better with the 2\textsuperscript{nd} generation than 4\textsuperscript{th} gen. FQ

- Of the 4\textsuperscript{th} generation FQ
  - Moxifloxacin has a lower MIC 90 for most gram +
  - Gatifloxacin has a lower MIC 90 for most gram –
- One interesting fact is ciprofloxacin (2\textsuperscript{nd} gen.) had lower MIC 90’s than both the 4\textsuperscript{th} generation FQ against gram –’s (esp pseudomonas species)
TOPICAL FLUOROQUINOLONES

- Current treatment of choice in non-severe bacterial keratitis
- Treatment is broken down into 2 critical phases each with a clear endpoint for clinical review and decision making
  - Sterilization Phase
    - Clinical signs may not indicate when sterilization has occurred after starting intensive therapy
    - Sterilization often precedes both epithelialization and resolution of inflammatory signs
  - Healing phase
DOSING OF THE FLUOROQUINOLONES IN SUSPECTED BACTERIAL KERATITIS

- Dosing needs to be aggressive early on in treatment
  - Q 5-15 min to start for several hours
  - Q 30 min through the first day
  - Q 1-2 hours through the night
- Checking for improvement daily or every other day
DOSING IN LESS SEVERE KERATITIS

- Q2h, q3h with loading dose hs
- Cycloplegics for pain and synechiae prevention.
SEVERE BACTERIAL KERATITIS
SEVERE BACTERIAL KERATITIS
FOLLOW-UP PROTOCOL

• Frequent initially every day until clinical improvement is seen

• Frequency of re-evaluation
  • depends on extent of disease

• Then follow-up appointments can be spaced according to level of improvement and practitioner comfort level
NIGHT TIME THERAPY: DO I HAVE TO HAVE MY PATIENT GET UP DURING THE NIGHT?

• Depends on severity of disease
  • If the patient has a central ulcer with reduced VA --- YES!
  • Any features consistent with severe keratitis — Yes!
  • If the lesion is mid-peripheral and less ominous consider
    • Ointment HS (as cover hs)
    • Loading Dose HS
  • Avoid using ointments in patients with severe keratitis!
FEATURES OF SEVERE INFECTIOUS KERATITIS

- Significant pain
- Dense central infiltrates
- Large Ulcers
- Hypopyon/ fibrin in AC
- Suppurative lesions/ liquifactive necrosis
  - The stroma turns to soup!
- Unresponsive to initial therapy with 4\textsuperscript{th} gen FQ
FEATURES OF SEVERE INFECTIOUS KERATITIS

• Infection extending into sclera
  • May require injected sub-conjunctival AB

• Heavy mucous discharge

• Impending perforation

• Gonococcal keratitis
  • Requires systemic therapy
  • Oral Azithromycin or Doxycycline 100 mg BID X 7 days
FEATURES SUGGESTIVE OF POSITIVE RESPONSE TO TREATMENT

- Decreased pain
- Decreased discharge
- Lessened eyelid edema
- Decreased density of stromal infiltrate
- Reduced stromal edema
FEATURES SUGGESTIVE OF POSITIVE RESPONSE TO TREATMENT

• Consolidation and sharper demarcation of stromal infiltrates perimeter
• Reduced A/C reaction, fibrin, hypopyon
• Re-epithelialization, reduced epithelial defect
  • Measure it !!!
POSITIVE RESPONSE TO TREATMENT: SERRATIA
MODIFICATION OF THERAPY:

- Efficacy of treatment judged on clinical response to empirical treatment
- If condition improving therapy need not be adjusted on basis of lab results
- Dual AB therapy may not be necessary
- Modify the treatment plan if the eye shows a lack of response / improvement after 48-72 hours
- Culture results may have an impact on the modification of therapy
  - Especially when the response has been poor
WHAT ABOUT RESISTANCE: CAN IT HAPPEN?

2 concomitant mutations are necessary for the development of resistance to the 4th generation fluoroquinolones.
EMERGING CHALLENGES:
BACTERIAL RESISTANCE TO FQ

- Already widespread resistance to 3rd generation FQ
- Studies have shown increasing resistance to 2nd generation FQ
  - Prashant et al Ophthalmology July 1999
  - Studied cultured proven pseudomonas keratitis
  - 1991 6.2% were ciprofloxacin resistant
  - 1998 23% were ciprofloxacin resistant
THE MECHANISMS RESISTANCE TO FQ

• Mutation of target enzymes
• Formation of gyrase protecting proteins
• Reduction in cell permeability
• Increases in drug efflux
  • Despite all this still a relatively low incidence of resistance to 4th gen FQ
Resistance to fluoroquinolones: the basics

- Decreased permeability
- Efflux pump
- Mutation of the enzymes
NEW KIDS ON THE BLOCK: THE LATEST PLAYERS

• **Zymaxid 0.5%**, gatifloxacin, Zymar 0.3%
• **Moxeza 0.5%**, moxifloxacin with xanthan gum vehicle
  • Prolongs contact time with the ocular tissues
  • Increases tissue penetration
• **Besivance 0.6%**, besifloxacin ophthalmic suspension formulated with Durasite vehicle
  • Good broad spectrum FQ
  • Should have increased contact time and better tissue penetration as a result of Durasite
  • No FDA labeling for bacterial keratitis, only bacterial conjunctivitis
  • Novel fluoroquinolone without a systemic counterpart
BESIVANCE : BESIFLOXACIN

- Only dual halogenated fluoroquinolone AB
- Effective treatment in studies for:
  - MRSA *(previous FQ have shown to be poorly effective)*
  - MRSE
  - *Pseudomonas aeruginosa* *(FDA approval) on its labeling*
- Potent balanced inhibition
  - DNA gyrase inhibition - hits gram -’s
  - Topoisomerase IV inhibition – hits gram +’s
- Bactericidal drug
- Uses the same Durasite muco-adhesive vehicle as Azasite
MODIFYING THERAPY IN SEVERE DISEASE
MODIFICATION OF AB THERAPY: SEVERE DISEASE

- Every 5-15 minutes in the 1st few hours
- Every 15 minutes to 1 hour around the clock
  - Patient sets alarm to get up during night!
- Cycloplegia
  - pain from ciliary spasms
  - reduce posterior synechia
WHAT IF THINGS ARE GOING BADLY........?

CONSIDER FORTIFIED ANTIBIOTICS!

FOR SEVERE INFECTION OF EYES UNRESPONSIVE TO TREATMENT WITH SINGLE AGENTS
<table>
<thead>
<tr>
<th>Drug</th>
<th>Effective against</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefazolin</td>
<td>• Gram +</td>
<td>50mg/ml</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>• Gram +</td>
<td>15mg/ml 25mg/ml 50mg/ml</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>• Gram -</td>
<td>14mg/ml</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>• Gram -</td>
<td>14mg/ml</td>
</tr>
</tbody>
</table>
FORTIFIED ANTIBIOTICS
THE LONGSTANDING STANDARD OF CARE

- Probably the best choice in the eyes of the law
- Have withstood the test of time
TREATMENT PEARLS:
SEVERE BACTERIAL KERATITIS

- Bandage CL’s and Collagen shields are risky in treatment of severe bacterial keratitis
  - They can become dislodged interrupting AB therapy
  - May actually impair AB penetration into the ulcer bed
- Subconjunctival AB therapy in cases of scleral extension, systemic infection
- Steer away from ointments at night, the drops are more potent and these interfere with penetration of fortifieds or 4th FQ
- Instead dose through the night!
When to pull the trigger!
CORTICOSTEROID USE FOR INFECTIOUS KERATITIS

• Many believe steroids have a place in treatment of bacterial keratitis

• **Judicious use of steroids can reduce ocular morbidity**

• Suppresses inflammation and subsequent scarring leading to better visual outcomes

• **Ideally should not be used until culture results return or positive response to therapy**
CORTICOSTEROID USE FOR INFECTIOUS KERATITIS

• In order to have success with steroid therapy
  • Use the minimal amount of steroid required to control inflammation
  • Optimal timing: AB response, C/S results, not fungal
  • Careful dose regulation
    • use adequate and appropriate concomitant AB
    • Close follow up, monitor IOP
IN TREATMENT OF SEVERE BACTERIAL KERATITIS INVOLVING THE VISUAL AXIS

General Rule of Thumb
After 2-3 days of steady improvement with topical AB’s safe to introduce a steroid
DISADVANTAGES WITH STEROID TREATMENT

- Recurrence of infection
- Local immunosuppression
- Inhibition of collagen synthesis predisposing to corneal melts
- No conclusive evidence that steroids alter the clinical outcome in bacterial keratitis
- Closer follow-up is necessary
  - Optimal timing and dose regulation
TREATMENT IN COMPLICATED CASES

Perforations, progressive unresponsive disease, Endophthalmitis
ADJUVANT THERAPY

- Collagenase inhibitors
  - EDTA, Tetracyclines, Doxycycline
- Steroids?
- NSAIDS
- Tissue adhesives
- Debridement/ biopsy
- Bandage lenses/ collagen shields
- Therapeutic / tectonic PK
Collagen cross-linking (CXL) is a technique that uses riboflavin (B2) and Ultraviolet-A irradiation to cause a strengthening effect in corneal tissue which enhances its rigidity. The interactive effect of riboflavin with UV-A irradiation strengthens formation of chemical bonds between collagen fibrils in the corneal stroma and helps in increasing resistance against enzymatic digestion.
Collagen cross-linking may be considered in treatment-resistant infectious keratitis or as an adjunct to antibiotics therapy.
COLLAGEN CROSS-LINKING

• Three patients with *Acanthamoeba* keratitis were successfully treated with a topical application of 0.1% riboflavin solution and 30 minutes of UV irradiation focused on the corneal ulcer. \[^2\]
TREATMENT IN COMPLICATED CASES

Perforation

Tissue glue
THERAPY IN COMPLICATED CASES

- Thin Corneas
- Impending perforation
  - Tissue adhesives
  - PK
  - Lamellar PK
- Endophthalmitis
THANKS FOR YOUR ATTENTION
• Gregory M. Schultz, O.D., F.A.A.O.
• Eye Center of Virginia
• Williamsburg VA
• Email: gschultz31@cox.net