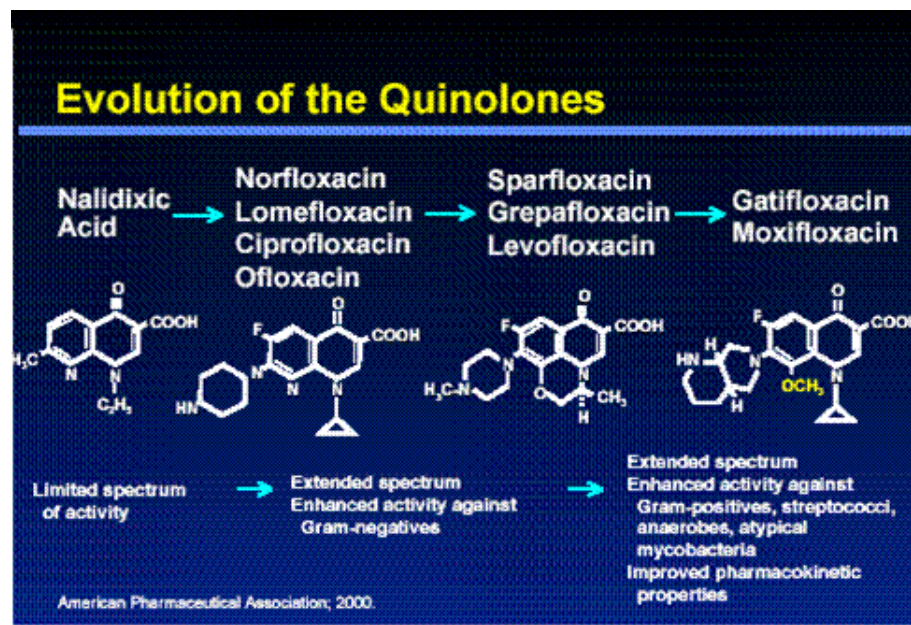


Moxifloxacin eye drops (Apdrops - Ajanta Pharma)

This promotional topic was presented to the JDOS audience by Mr. Suvir Tiwari of Ajanta Pharma Limited.



Gaps in current generation fluoroquinolones coverage of:

| Agent | 248 gm +ve isolates | Streptococcus (from corneal ulcer) |
|---------------|---------------------|------------------------------------|
| Ciprofloxacin | 66% | 67% |
| Ofloxacin | 64% | 78% |
| Levofloxacin | 67% | 90% |

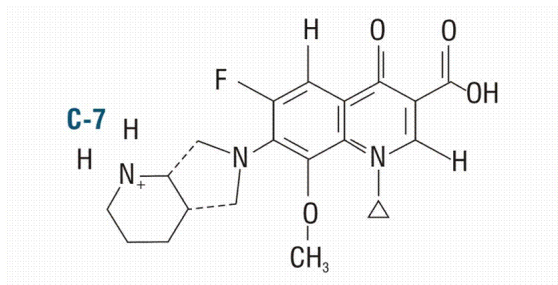
Concern for the ophthalmic surgeon:

Staphylococcus, Streptococcus and Pseudomonas occurring on ocular natural flora

Atypical (Mycobacterium- non tuberculous) introduced during surgery.

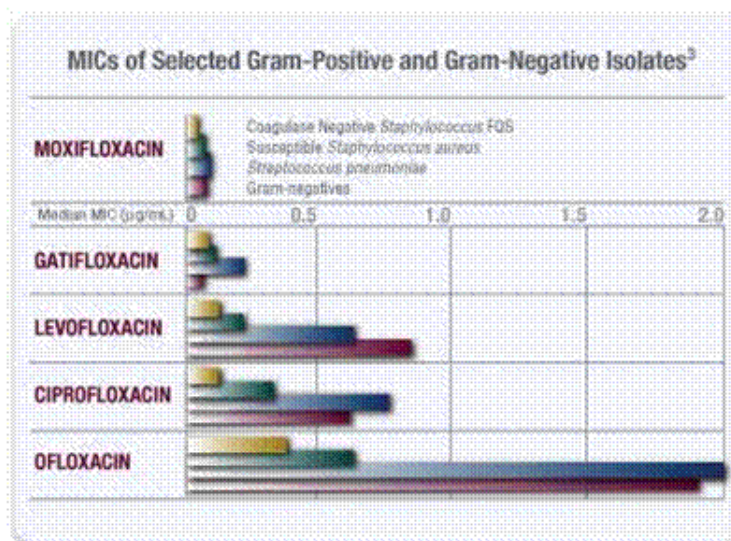
Coverage of both required.

30% of Gr + Ve organisms are insensitive to current fluoroquinolone.



Mechanism of Resistance to fluoroquinilone

- o Current FQ binds to
 - DNA gyrase - Gr +ve
 - DNA gyrase and topoisomerase IV to Gr -Ve
- o Moxifloxacin binds to both topoisomerase
- o C7 side chain impedes efflux



Potency of Fluoroquinolones for Gram-Positive Pathogens⁴

| POTENCY BY RANK ¹ | PATHOGEN |
|---|---|
| Mox > Gat > Lev = Cip > Ofx | FQS ² <i>Staphylococcus aureus</i> , <i>Streptococcus viridans</i> group, <i>Streptococcus pneumoniae</i> , <i>Enterococcus</i> |
| Mox > Gat > Cip = Lev > Ofx | β-hemolytic <i>Streptococcus</i> FQS CoagNeg ² <i>Staphylococcus</i> |
| Mox > Gat > Lev > Cip = Ofx | Resistant <i>Staphylococcus aureus</i> |

Potency of Fluoroquinolones for Gram-Negative Pathogens⁴

| POTENCY BY RANK | PATHOGEN |
|---------------------------------------|----------------|
| Mox = Gat = Lev = Cip > Ofx | Gram-Negatives |

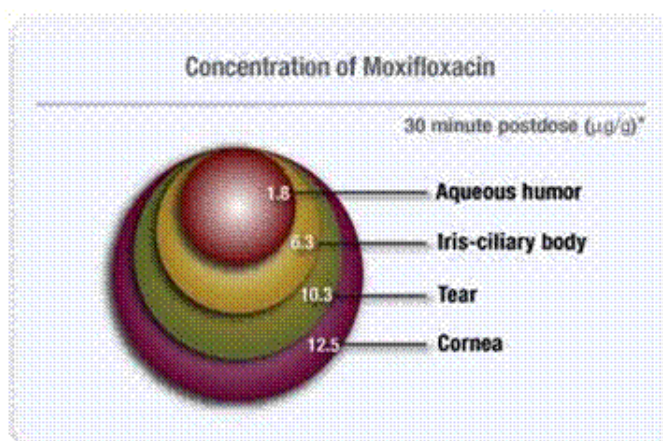
The median MICs (µg/mL) of 93 bacterial endophthalmitis isolates to ciprofloxacin (CIP), ofloxacin (OFX), levofloxacin (LEV), gatifloxacin (GAT), and moxifloxacin (MOX)

| | N | CIP | OFX | LEV | GAT | MOX | Potency by rank (P = .05) |
|------------------------------|----|------|------|------|------|------|-----------------------------|
| Resistant <i>S. aureus</i> | 8 | 64 | 64 | 12 | 3.5 | 1.75 | mox > gat > lev > cip = ofx |
| Susceptible <i>S. aureus</i> | 6 | 0.32 | 0.63 | 0.22 | 0.11 | 0.06 | mox > gat > lev = cip > ofx |
| Coag-neg staph FQR | 10 | 64 | 64 | 38 | 2.0 | 2.5 | mox = gat > lev = cip = ofx |
| Coag-neg staph FQS | 10 | 0.13 | 0.38 | 0.13 | 0.09 | 0.05 | mox > gat > cip = lev > ofx |
| <i>S. pneumoniae</i> | 10 | 0.75 | 2.0 | 0.63 | 0.22 | 0.09 | mox > gat > lev = cip > ofx |
| <i>S. viridans</i> | 10 | 0.87 | 2.0 | 0.75 | 0.25 | 0.13 | mox > gat > lev = cip > ofx |
| Beta-hemolytic strep | 5 | 0.5 | 1.5 | 0.75 | 0.25 | 0.13 | mox > gat > cip = lev > ofx |
| <i>Enterococci</i> spp. | 9 | 0.75 | 2.0 | 0.75 | 0.38 | 0.19 | mox > gat > lev = cip > ofx |
| <i>Bacillus</i> spp. | 9 | 0.13 | 0.38 | 0.13 | 0.09 | 0.09 | mox = gat > lev = cip > ofx |
| Gram negatives | 16 | 0.06 | 0.19 | 0.08 | 0.06 | 0.08 | cip = gat = lev = mox > ofx |

FQR indicates resistant to ciprofloxacin and ofloxacin as determined by disk diffusion; FQS indicates susceptible to ciprofloxacin and ofloxacin as determined by disk diffusion. ">" indicates significantly greater potency; "=" indicates equal potency; Resistant *S. aureus* indicates *Staphylococcus aureus* resistant to ciprofloxacin and ofloxacin as determined by disk diffusion. Susceptible *S. aureus* indicates *Staphylococcus aureus* susceptible to ciprofloxacin and ofloxacin as determined by disk diffusion. Adapted from Mather E, et al. *Am J Ophthalmol* 2002;133:463-6.

High solubility

- o Solubility and penetration are interdependent
- o Moxifloxacin is stable at physiological pH
 - Prevents precipitation
 - Facilitates penetration
 - Increase bioavailability



Moxifloxacin Ophthalmic Solution 0.5%: Solubility

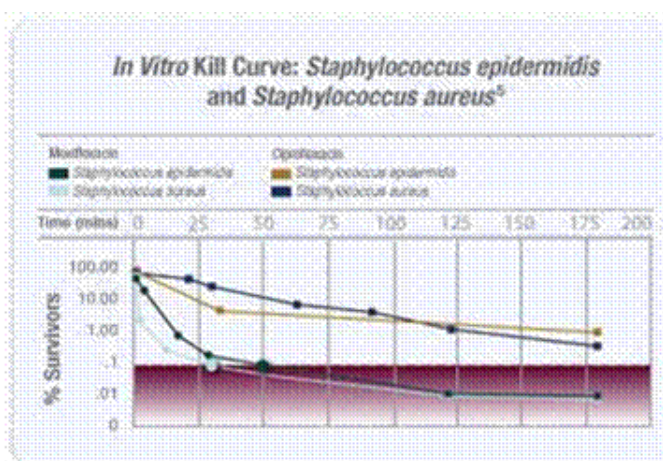
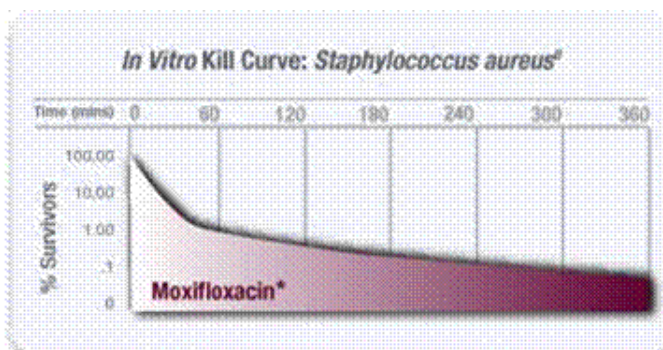
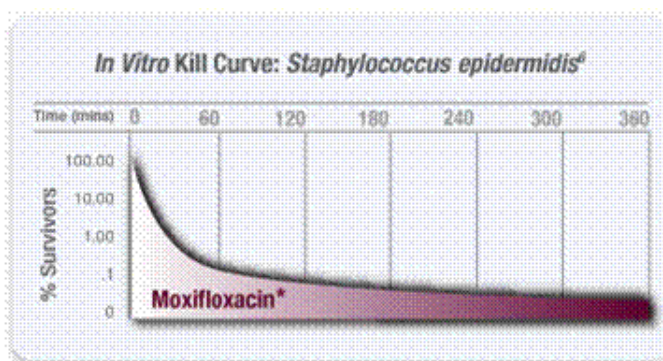
- Moxifloxacin is highly soluble at a neutral pH (7.0)¹
 - 300 times more soluble than ciprofloxacin at physiologic pH
- No precipitates form with moxifloxacin
- Moxifloxacin formulated at near-neutral pH of 6.8
- Gatifloxacin formulated at pH of 6.0

1. Alcon Laboratories, Inc. Data on file.

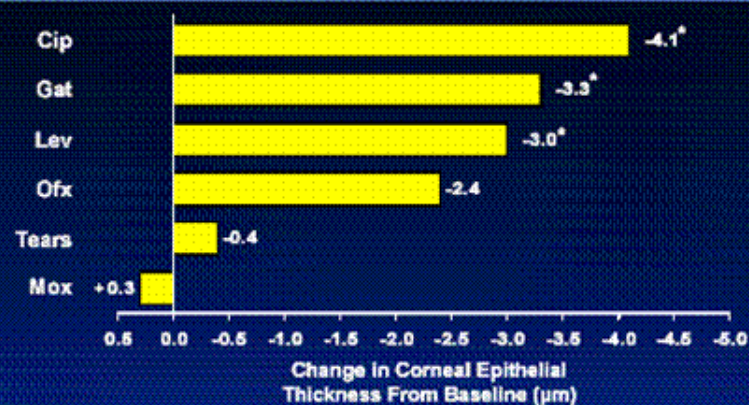
Fluroquinolones are concentration dependent.

Higher conc. = More killing.

Moxifloxacin - 0.5 % concentration with excellent tissue penetration.



Effect of Topical Ophthalmic Fluoroquinolone Solutions on Corneal Epithelial Thickness

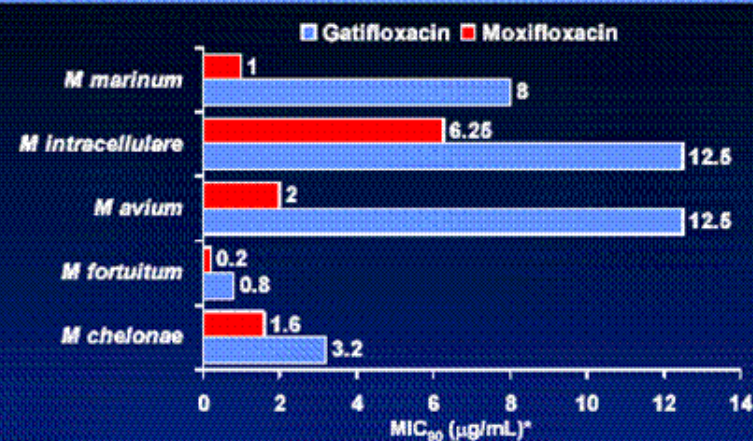


Mox=moxifloxacin; Ofx=ofloxacin; Lev=levofloxacin; Gat=gatifloxacin; Cip=ciprofloxacin.
 * P< .05 from baseline.
 Kim AS, et al. Poster presented at Annual Meeting of the Association for Research in Vision and Ophthalmology, May 5, 2003.

BAC free (Preservative Free)

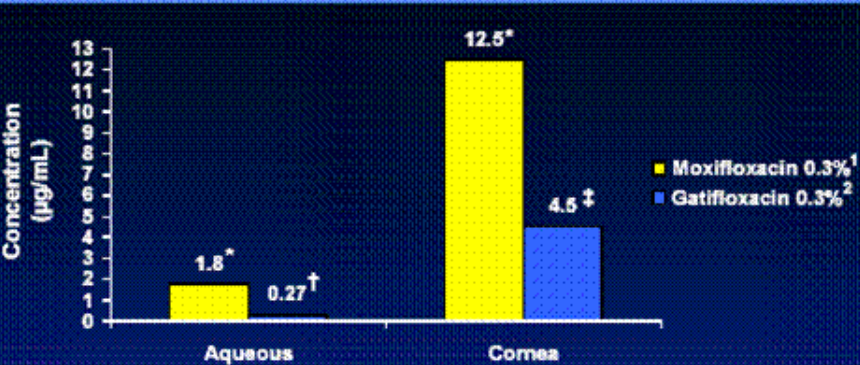
- o Less toxicity to cornea
- o Least epithelial thinning
- o Maintain health and integrity of ocular surface - esp. following refractory surgery.
- o Fewer problems such as dry eyes, irritation, foreign body sensation.

Moxifloxacin vs Gatifloxacin Against Atypical Mycobacteria



*MIC=minimum inhibitory concentration.
 Alcon Laboratories, Inc. Data on file.

Penetration of Newer-Generation Fluoroquinolones in Rabbit Models



* Concentration at 30 min.
 † Maximum concentration (C_{max}) at 1 h.
 ‡ C_{max} at 30 min.
 1. Robertson SM, et al. Poster presented at Annual Meeting of the Association for Research in Vision and Ophthalmology, May 5, 2003. 2. Baltoosingh AL, et al. Presented at Annual Meeting of the Association for Research in Vision and Ophthalmology, May 6, 2003.

Overview: Fourth-Generation Fluoroquinolones

| Agent (Concentration) | Indication | Treatment Duration | Dosing | BAK Concentration* |
|-----------------------|--------------------------|----------------------|--------------|--------------------|
| Gatifloxacin (0.3%) | Bacterial conjunctivitis | Days 1-2 Days 3-7 | Q 2 H QID | 0.005% BAK |
| Moxifloxacin (0.5%) | Bacterial conjunctivitis | 7 days | TID | None |

* BAK=benzalkonium chloride.

Moxifloxacin in the Spectrum of Ocular Fluoroquinolones

HAROLD R. KATZ, MD

| Drug | Generation | Concentration | Preservative | Time of treatment for bacterial conjunctivitis | Highly effective against gram-positives, including strep, and organisms resistant to 3rd-generation fluoroquinolones |
|---------------|------------|---------------|--------------|--|--|
| Moxifloxacin | 4th | 0.5% | none | 4 days (in clinical trials) | yes |
| Gatifloxacin | 4th | 0.3% | BAK | 5 days (in clinical trials) | yes |
| Levofloxacin | 3rd | 0.5% | BAK | 7 days (PDR) | no |
| Ciprofloxacin | 2nd | 0.3% | BAK | 7 days (PDR) | no |
| Ofloxacin | 2nd | 0.3% | BAK | 7 days (PDR) | no |

BAK - Benzalkonium chloride