The Battle of Resistance: Treating Infections in the Age of Resistance

Mark T. Dunbar, O.D., F.A.A.O.
Bascom Palmer Eye Institute
University of Miami, Miller School of Med
Miami, FL

The Age of Modern Medicine

- Prior to Penicillin, the # 1 war-time killer was infection
- Began being mass produced in 1943
  - Physicians were finally able to treat many diseases and childhood infections
  - This marked a new era in modern medicine
- Within 4 yrs of its release, resistance to penicillin began popping up and grew at an alarming rate

Mark Dunbar: Disclosure

- Optometry Advisory Board for:
  - Allergan
  - Carl Zeiss Meditec
  - ArticDx
  - Sucampo

Mark Dunbar does not own stock in any of the above companies

The Age of Modern Medicine

- By the mid-1940s and early 1950s streptomycin, chloramphenicol, and tetracycline had been discovered and the age of antibiotic therapy was underway
- These new antibiotics were very effective against a number of different pathogens including Gram-(+) and gram (-) bacteria, intracellular parasites, and tuberculosis.
- The mass production of antimicrobials provided a temporary advantage in the struggle with microorganisms
  - Despite these rapid advances resistance quickly followed

The Age of Modern Medicine

- He discovered penicillin more than 70 years ago
  - Considered to be one of the most significant medical breakthroughs of the twentieth century
- Ernest Duchesne was the 1st to describe the antibiotic properties of *Penicillium sp.* 1897

How Resistance Develops

Bacterial Resistance

- Bacterial become resistant when a mutation occurs in the DNA that protects the bacteria from a chemical
  - Mutation is only significant if the bacteria colony is exposed to the drug
- "Survival of the fittest" dictates survival occurs in only those capable of mutating

Factors Implicated in Growing Rates of Antibiotic Resistance

- Microbiological
  - Antibiotic misuse
- Environmental Factors
  - Aging population
  - Social behavior
  - AIDS
  - International travel
- Technical Factors
  - Increasing surgical intervention
  - Organ replacement
  - Life support systems

Resistant Bacteria

- For any given bacterial population, random mutations will arise
- With strong external selection pressures these mutations will be favored resulting in resistant bacteria
- American Academy of Microbiology
  - 17.8 million pounds of antibiotics are used in animals each year
  - Human exposure of these antibiotics is significant

Susceptibility of Multidrug-Resistant Bacteria

- 256 bacterial strains isolated from 164 patients undergoing intraocular surgery b/w 1/2002 10/2002
- 124 (76%) coagulase-negative *Staphylococci*
- High level of resistance to penicillin, aminoglycosides, macrolides, ciprofloxacin,ofloxacin
- Gatifloxacin and moxifloxacin had the lowest resistance frequency in the fluoroquinolones antibiotic group
- Newer-generation fluoroquinolones provide excellent broad-spectrum coverage against bacterial flora isolated from conj, despite the high % of multidrug-resistant bacteria

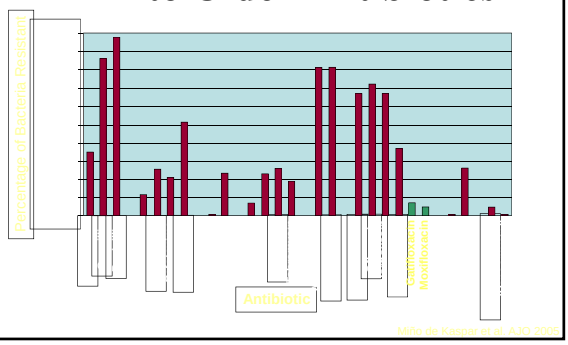
Bacterial Resistance

The problem is….

Antibiotics are used extensively

- Topically
- Systemically
- Agriculturally as a growth stimulant
  - Most significant use of fluoroquinolones

Widespread Resistance to Older Antibiotics



MRSA

Methicillin-Resistant Staphylococcus Aureus

Staphylococcus Aures Pharmacology

- Methicillin was an antibiotic used many years ago to treat patients with Staphylococcus aureus infections
- It is now no longer used except as a means of identifying this particular type of antibiotic resistance

Staphylococcus Aureus

- Common bacteria usually found on the skin or in the nose
- Can cause a range of illnesses from minor skin infections such as pimples, impetigo, boils, cellulitis and abscesses…
- To life-threatening diseases such as pneumonia, meningitis, endocarditis, and septicemia
- There are many different types of staphylococcus aureus

MRSA

- 1st outbreak identified in 1960 ‘s
- Predominantly seen in hospitals, chronic care facilities and parenteral drug abusers
- The prevalence of MRSA isolates in hospitals in the US has risen steadily, such that now about ¼ nosocomial isolates are methicillin resistant

Staphylococcus *Aures* Pharmacology

- MRSA is a particular strain of staphylococcus aureus that does not respond (is resistant) to many antibiotics
- *S aureus* was sensitive to penicillin when the drug was 1st introduced, but resistance developed almost immediately as the organism acquired a β-lactamase enzyme that was capable of inactivating drug

MRSA

- Community-acquired MRSA is becoming a significant problem, with the prevalence of MRSA among community isolates expected to reach as high as 25% in the next decade

Reasons for Rise of MRSA

- More powerful strains of MRSA developing
- An increased number of very sick people in hospital
- More complex medical treatments
  - The use of central lines and catheters
- Patients move within and between hospitals more often
- High workloads which result in less compliance with routine hand washing

Risk Factors for MRSA

- Proloned hospital stays
- Prior surgery
- Seriously ill in intensive care
- Immunocompromised

Multi-Drug Resistant Bacteria

- Emerging resistance of *S aureus* has also been demonstrated for streptomycin, tetracycline, chloramphenicol, erythromycin and third-generation fluoroquinolones. T
- The topical 4th Generation fluoroquinolonesare are more potent against MRSA than prior generation fluoroquinolones
  - They inhibit both DNA gyrase and topoisomerase IV, requiring two genetic mutations for the bacteria to become resistant

2005: Deaths from MRSA Surpassed AIDS

- In 2005, AIDS killed 17,011 Americans
- CDC reports > 90,000 get the potentially deadly "superbug" infections annually
- Recent JAMA surveillance study, only about ¼ of MRSA infections involved hospitalized patients
  - More than half were in the health care system
    - People who had recently had surgery or were on kidney dialysis
    - Open wounds and exposure to medical equipment are major ways the bug spreads.

MRSA

- About 1/3 of people carry MRSA on their skin or in their nose without knowing it
- These people are said to be 'carriers' of MRSA
  - The bacteria are present on the body but don't cause any harm
  - This is also referred to as being 'colonised' with MRSA
- Most people who carry MRSA in this way don't go on to develop an infection

MRSA Facts

- MRSA has evolved into a multitude of genetically distinct strains that vary widely in drug resistance, transmissibility and virulence

MRSA Facts

- Non-healthcare workers are now just as likely as healthcare workers to carry MRSA on the conjunctiva and lid margin

4th Gen FQ Resistant Bacterial Keratitis after Refractive Surgery

Moshirfar M, J Cataract Refract Surg 2006; 32:515-518

2 Cases of Bacterial Keratitis resistant to 4th Gen FQ

- 1st pt – Pseudomonas following PRK -> had been treated with Vigamox
- 2nd pt – MRSA following LASIK treated with Zymar…and Vigamox
- Culture susceptibilities resistance to both 4th Gen FQ

MRSA Fact

- While CA-MRSA strains tend to be less multi-drug resistant, some strains are associated with unusually invasive infections of the eye and orbit
  - USA300 clone – CA-MRSA with the PVL virulence marker

13 Cases of MRSA Following Refractive Surgery

- Multicenter, retrospective chart review of 13 cases of MRSA keratitis following refractive surgery
  - 9 were either healthcare workers or exposed to a hospital surgical setting
- 7 pts were prescribed 3rd generation FQ, 1 pt prescribed tobramycin, 1 pt was prescribed erythromycin and 3 were prescribed a 4th generation FQ

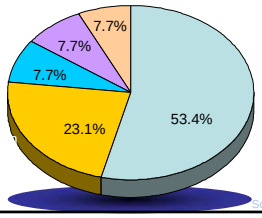
Solomon. *Am J Ophthalmol.* 2007.

Ocular Involvement of MRSA

Methicillin-Resistant *Staphylococcus aureus* Infectious Keratitis Following Refractive Surgery

- A retrospective chart review of cases occurring between May 2002 and February 2005 in 10 referral cornea and refractive disease practices

Prophylactic Antibiotics



Solomon. *Am J Ophthalmol.* 2007.

Infectious Keratitis in Refractive Eye Care

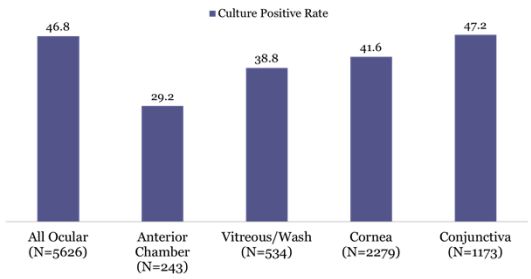
- Clinicians must be alert to the postop patient with signs and symptoms of possible post-LASIK and post-PRK infectious keratitis.
- PRK: Corneal scrapings, cultures, and sensitivities of all cases of focal infiltrates
- LASIK: Lifting the flap, scraping, culturing, and obtaining sensitivities on all cases of focal infiltrates

Tracking Resistance

Precautions for Healthcare Workers

- Patients exposed to healthcare facilities who are at higher risk of infection from nosocomial MRSA, prophylactically treat blepharitis with lid hygiene and hot compresses preoperatively
- Consider a nasal swab for MRSA carriage
- Consider bacitracin or a fourth-generation fluoroquinolone or bacitracin for preoperative prophylaxis

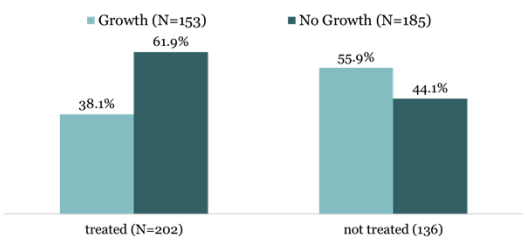
Culture Positive Rates BPEI 2011-2013



Treatment of MRSA s/p LASIK

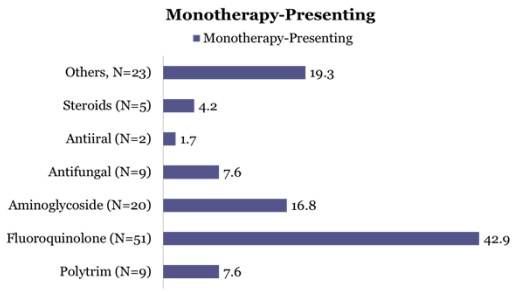
- Irrigating under the flap with fortified vancomycin (50 mg/ml)
- Antibiotics to include better coverage for MRSA-fortified vancomycin every 30 minutes, alternating with topical 4th Gen q 30 min
- Bacitracin ointment or Neosporin ointment to the eyelids qid

Impact of Prior Therapy (59.8%)- Pathogen Recovery 2013*, N=338,

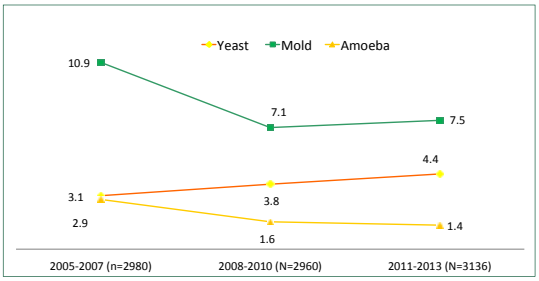


- *First and last quarter-2013, Significant differences, p=0.001*
- *64.7%-Monotherapy*

Presenting Monotherapy Choice N=119/184 (64.7%)

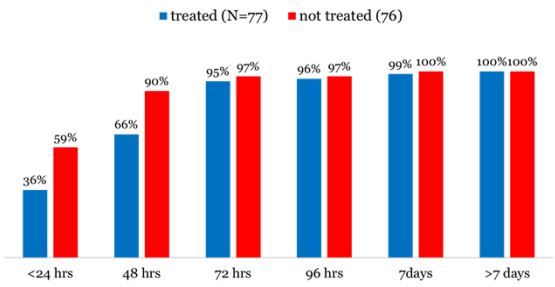


Trends in Organism Group Frequency (%) Nonbacterial (N=417, 13.3%)



Significant, decline in nonbacterial pathogens from 2005 to 2013, p=0.00016

Impact of Prior Therapy-Detection Time (N=153)



Original Investigation

Antibiotic Resistance Among Ocular Pathogens in the United States

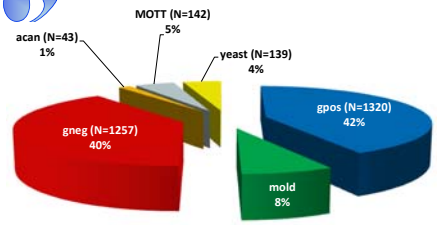
Five-Year Results From the Antibiotic Resistance Monitoring in Ocular Microorganisms (ARMOR) Surveillance Study

Penny A. Asbell, MD, MBA; Christine M. Sanfilippo, PhD; Christopher M. Pillar, PhD; Heleen J. DeCory, PhD; Daniel F. Sahm, PhD; Timothy W. Morris, PhD

JAMA Ophthalmology 2015

- **ARMOR study was initiated in 2009 to survey antibiotic resistance among S. aureus, Co.NS, S. pneumoniae, H. influenzae, and Pseudomonas isolates from ocular infections**

Update on Epidemiology and Anti-Microbial Resistance in South Florida



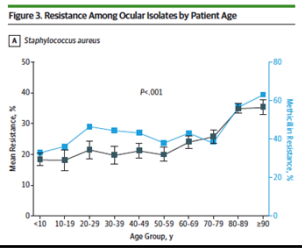
Organism group-Distribution Ocular Pathogens 2011-2013

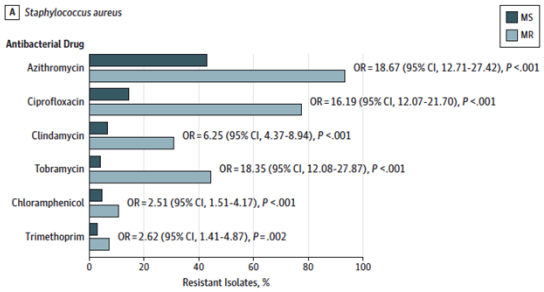
ARMOR

- **A total of 3,237 ocular isolates were obtained from 72 centers**
  - **1169 S aureus**
  - **992 CoNS**
  - **330 S pneumoniae**
  - **357 H influenzae**
  - **389 P aeruginosa)**
- **Methicillin resistance was found among 493 S aureus isolates (42.2%) and 493 CoNS isolates (49.7%)**
- **Methicillin-resistant (MR) isolates had a high probability of concurrent resistance to fluoroquinolones, aminoglycosides, or macrolides**
- **There was "multidrug resistance" to at least 3 additional antibiotic classes was found in MR cases**
- **All staphylococcal isolates were susceptible to vancomycin**

MRSA Trends

- Staphylococcal isolates from elderly patients were more likely to be MR, as were S aureus isolates obtained from the southern United States





At a Glance

- Data on antibiotic resistance of common ocular bacterial pathogens are needed.
- In all, 3237 ocular isolates (1169 *Staphylococcus aureus*, 992 coagulase-negative staphylococci [CoNS], 330 *Streptococcus pneumoniae*, 357 *Haemophilus influenzae*, and 389 *Pseudomonas aeruginosa* isolates) were collected from 72 centers in the United States from January 1, 2009, through December 31, 2013, as part of the ongoing Antibiotic Resistance Monitoring in Ocular Microorganisms study.
- Methicillin resistance was found among 493 *S aureus* isolates (42.2%) and 493 CoNS isolates (49.7%), and methicillin-resistant (MR) isolates had a high probability of concurrent resistance to fluoroquinolones, aminoglycosides, or macrolides (*P* < .001).
- Multidrug resistance to 3 or more additional antibiotic classes continues to be a challenge and was found in 428 MR *S aureus* isolates (86.8%) and 381 MRCoNS isolates (77.3%).

Trends in Infectious Keratitis

- 73% of MRSA strains are resistant to multiple antibiotics
- 23% of ALL staphylococci strains are resistant to at least 3 ocular antibiotics commonly used to treat

The US ARMOR study compared results available from surveillance in 2013 to results from 2012. By the time of this analysis, ARMOR study investigators from 27 US sites had collected a total of 239 isolates of *Streptococcus pneumoniae*, *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS), *Pseudomonas aeruginosa*, and *Haemophilus influenzae*, all organisms frequently implicated in bacterial infections of the eye, and tested them for susceptibility to as many as 16 available ophthalmic antibiotics.[1]

Study authors reported that, from 2012 to 2013, antibiotic resistance rates increased among isolates of already problematic strains of staphylococci and *P aeruginosa*. For example, preliminary results suggest that nonsusceptibility of *P aeruginosa* to the antibiotics ciprofloxacin and imipenem may have doubled from the previous year to 14% and 21%, respectively. Nonsusceptibility of isolates of *S aureus* and CoNS also increased slightly year over year, exceeding 50%

ARMOR: 5 Year Results

CONCLUSIONS:

- Resistance to 1 or more antibiotics is prevalent among ocular bacterial pathogens.
- Current resistance trends should be considered before initiating empiric treatment of common eye

In vitro Susceptibility for Select/Common Ocular Drugs.

Antibiotic	MSSA (%S) N=190	MRSA (%S) N=84
Cefazolin	100	0
Erythromycin	98	43
Gentamicin	100	85
Gatifloxacin	93	25
Moxifloxacin	91	31
Trimethoprim -sulfa	99	92

Ophthalmic Antibiotics: Fluoroquinolones

- The first safe broad-spectrum ophthalmic agents
- Revolutionized treatment of severe corneal infections
- Very low sensitization rate
- Excellent safety profile
- Comfortable
- No reports of systemic effects

Our Arsenal of Antimicrobial Therapy

Fluoroquinolones

- 1st released for ophthalmic use in early 1990's
- Represented an important break-through for clinicians
- For the 1st time strong commercially available antibiotics available to treat bacterial conjunctivitis and ulcerative keratitis
- Broad spectrum including pseudomonas

The Arsenal

- Fluoroquinolones
  - Ciprofloxacin
  - Levofloxacin
  - Gatifloxacin
  - Moxifloxacin
- Aminoglycosides
  - Tobramycin
  - Gentamycin
- Macrolides
  - Erythromycin
  - Bacitracin
  - Azithromycin
- Dihydrofolate reductase inhibitors
  - Trimethoprim
- Polypeptides
  - Polymixin B

Fluoroquinolones

Ophthalmology July 1999; 106 (7): 1313-8

- The BIG problem with the fluoroquinolones has been bacterial resistance!
  - 1993 – 5.8% resistance
    - 2 yrs after release of fluoroquinolones
  - 1997 – 35% bacterial resistance
  - 2001 – 100% resistance to staph aureus isolates cultured in endophthalmitis
    - Resistance to cipro, oflox, levoflox

Resistance to FQ's

Alexandrakis et al, Ophthalmology August 2000; 107: 1497-1502

9 yr period: 2920 cultures; 1468 (50%) recovered

	1990	1998
Bact Keratitis	196	137
Resistance to Staph Aures	11% Cipro and Oflox	28 % Cipro and Oflox
Resistance to Pseudomonas	0%	0%
Staph aures Pseudomonas	(27) 29% (51) 54%	(32) 48% (32) 46%

Fluoroquinolones: Resistance

- In vitro tests that compare moxifloxacin with other fluoroquinolones suggest that moxifloxacin is less likely to
  - Be affected by genetic mutations[1,2]
  - Select for resistance[2,3]

1. Tankovic J, et al. *J Antimicrob Chemother.* 1999;43(suppl B):19-23. 2. Schedletzky H, et al. *J Antimicrob Chemother.* 1999;43(suppl B):31-37. 3. Balfour JAB, Lamb HM. *Drugs.* 2000;59:115-139.

Resistance to FQ's

Goldstein et al. Ophthalmology July 1999; 106 (7): 1313-8

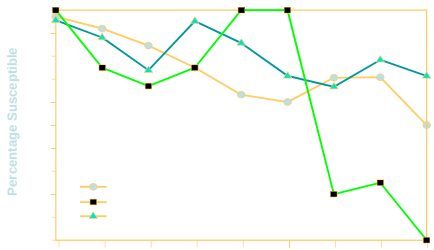
1053 Isolates from 825 Cases 1993 to 1997

	1993	1997
Bact Keratitis	284	75
Resistance to Staph Aures	5.8% Cipro 4.7% Oflox	35% Cipro 35% Oflox
Resistance to Strep	51%	50%
Gram + Gram -	81.8% 18.2%	51.4% 48.6%

4th Generation Fluoroquinolones

- Developed to address the issues of resistance
- Developed to allow for broader coverage for both gram (+) and gram (-) organisms
  - Better gram (+) coverage is needed as the growing trend towards more gram (+) infections

Widespread Decline in Susceptibility to 3rd-Generation Fluoroquinolones



Kowalski et al. *Ophthal Clinics of N. America.* 2003.

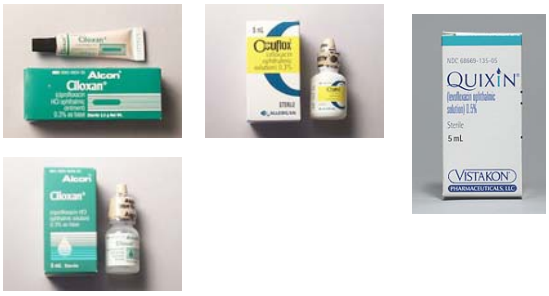
Mechanism of Action: Fluoroquinolones

- Cause lethal breaks in the bacterial chromosome at their target site
- Targets of 3rd-generation FQs
  - DNA gyrase in Gram-negatives
  - Topo IV in Gram-positives
- Targets of 4th-generation FQs are dual binding
  - DNA gyrase AND topo IV in both Gram-positives and Gram-negatives

Gatifloxacin and Moxifloxacin

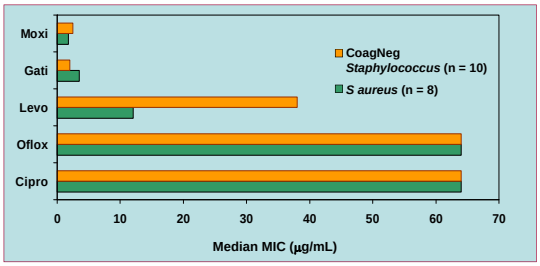
Comparison of In Vitro Efficacy

3rd Generation FQ's



Fourth-Generation Fluoroquinolones Far More Effective Than Third-Generation Fluoroquinolones

Isolates From Bacterial Endophthalmitis Resistant to Ciprofloxacin, Ofloxacin, and Levofloxacin

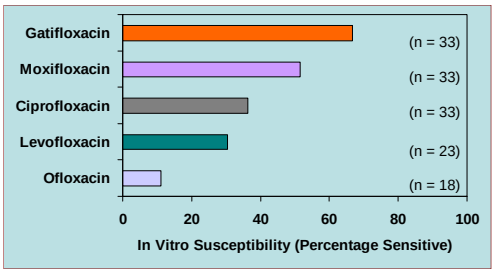


Mather et al. *Am J Ophthalmol*. 2002;

4th Generation Fluoroquinolones

Fourth-Generation Fluoroquinolones More Effective Than Older-Generation Fluoroquinolones

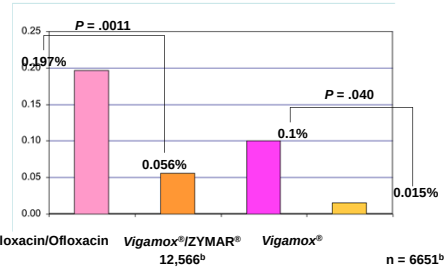
Staphylococcal Endophthalmitis Isolates More Susceptible to Fourth Generation Fluoroquinolones than to Older Fluoroquinolones



Rate of Endophthalmitis: Third- vs Fourth-Generation Fluoroquinolones

- A retrospective, cross-sectional (prevalence) study of patients who had phacoemulsification at a university eye center over a 10-year period.
- The main outcome measure was the occurrence of endophthalmitis after cataract surgery.
  - Third-generation fluoroquinolones (ciprofloxacin, ofloxacin) were used as prophylactic antibiotics from January 1997 to August 2003.
  - Fourth-generation fluoroquinolones (gatifloxacin, moxifloxacin) were used as prophylactic antibiotics from September 2003 to December 2007.
- A nosocomial infectious reporting database was used to report endophthalmitis occurrences.
- Prospectively collected data were retrospectively analyzed to establish endophthalmitis rates.

Ten-Year Retrospective Comparison of Endophthalmitis after Cataract Surgery

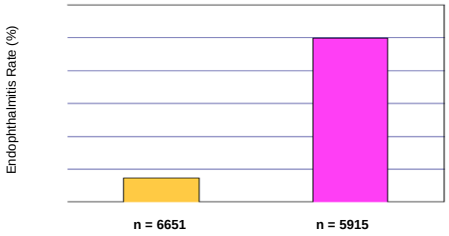


[a]During the period of 1997 to 2003.
[b]During the period of 2003 to 2007.

Jensen et al. *J Cataract Refract Surg*. 2008.

Four-Year Retrospective Comparison of Endophthalmitis after Cataract Surgery

7 Cases of Endophthalmitis out of 12,566 Cataract Surgeries (0.056%)



The rate of 0.015% with Zymar® is the lowest rate of endophthalmitis ever recorded in cataract surgery patients using perioperative antibiotics.

Ophthalmic Solutions of Fourth-Generation Fluoroquinolones

	ZYMAR®	*Vigamox*®	*Besivance*™	ZYMAXID™
Approval year	2003	2003	2009	2010
Indication	Bacterial conjunctivitis	Bacterial conjunctivitis	Bacterial conjunctivitis	Bacterial conjunctivitis
Active Ingredient	Gatifloxacin 0.3%	Moxifloxacin 0.5%	Besifloxacin 0.6%	Gatifloxacin 0.5%
Preservative	0.005% BAK	No preservative	0.01% BAK	0.005% BAK
Package size/ mean drops	5 mL/132 mean drops per bottle	3 mL/82 mean drops per bottle	5 mL[a]	2.5 mL/83 mean drops per bottle

BAK = benzalkonium chloride.
[a] *Besivance*™ mean drops not yet calculated.

Besivance™ [package insert]. 2009; Jensen and Fiscella. *Am J Health Syst Pharm*. 2006; *Vigamox*® [package insert]. 2003; ZYMAR® [package insert]. 2004; ZYMAXID™ [package insert]. 2010.