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

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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

- 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

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
Methicillin-Resistant Staphylococcus Aureus (MRSA)

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

Staphylococcus Aureus 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

Staphylococcus Aureus 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

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

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

- Prolonged 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 fluoroquinolones 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

**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

**4th Gen FQ Resistant Bacterial Keratitis after Refractive Surgery**


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

**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

**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**

- 53.4%
- 23.1%
- 7.7%
- 7.7%
- Unknown, 1 (bilateral)/13 patients

**Ocular Involvement of MRSA**
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

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

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

Tracking Resistance

Culture Positive Rates BPEI 2011-2013

- % Culture Positive Rate

<table>
<thead>
<tr>
<th></th>
<th>Culture Positive Rate</th>
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<tbody>
<tr>
<td>All Ocular (N=3020)</td>
<td>49.8</td>
</tr>
<tr>
<td>Anterior Chamber (N=241)</td>
<td>29.2</td>
</tr>
<tr>
<td>Vitreous/Wash (N=234)</td>
<td>35.8</td>
</tr>
<tr>
<td>Cornea (N=2279)</td>
<td>41.5</td>
</tr>
<tr>
<td>Conjunctiva (N=1173)</td>
<td>47.8</td>
</tr>
</tbody>
</table>

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

- Growth (N=153) 61.9%
- No Growth (N=185) 55.9%

- First and last quarter-2013, Significant differences, p<0.001
- 64.7%-Monotherapy
**Presenting Monotherapy Choice**  
N=119/184 (64.7%)

<table>
<thead>
<tr>
<th>Monotherapy-Presenting</th>
<th>Presenting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Others (N=233)</td>
<td>99.3%</td>
</tr>
<tr>
<td>Steroids (N=5)</td>
<td>4.2%</td>
</tr>
<tr>
<td>Antimalarials (N=2)</td>
<td>5.7%</td>
</tr>
<tr>
<td>Antifungals (N=9)</td>
<td>7.6%</td>
</tr>
<tr>
<td>Aminoglycosides (N=20)</td>
<td>16.8%</td>
</tr>
<tr>
<td>Fluoroquinolones (N=51)</td>
<td>40.9%</td>
</tr>
<tr>
<td>Polytrim (N=9)</td>
<td>7.6%</td>
</tr>
</tbody>
</table>

**Impact of Prior Therapy—Detection Time (N=153)**

![Chart showing impact of prior therapy detection time.](chart)

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

![Graph showing trends in organism group frequency.](graph)

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

**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
  - 1,169 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

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

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

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.

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.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MSSA (%S) N=190</th>
<th>MRSA (%S) N=84</th>
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</thead>
<tbody>
<tr>
<td>Cefazolin</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>98</td>
<td>43</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>100</td>
<td>85</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>93</td>
<td>25</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>91</td>
<td>31</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>99</td>
<td>92</td>
</tr>
</tbody>
</table>

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 breakthrough 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

<table>
<thead>
<tr>
<th></th>
<th>1990</th>
<th>1998</th>
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<tbody>
<tr>
<td>Bact Keratitis</td>
<td>196</td>
<td>137</td>
</tr>
<tr>
<td>Resistance to Staph Aures</td>
<td>11% Cipro and Oflox</td>
<td>28 % Cipro and Oflox</td>
</tr>
<tr>
<td>Resistance to Pseudomonas</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Staph aures Pseudomonas</td>
<td>(27) 29%</td>
<td>(32) 48%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

**Resistance to FQ’s**

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

1053 Isolates from 825 Cases 1993 to 1997

<table>
<thead>
<tr>
<th></th>
<th>1993</th>
<th>1997</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bact Keratitis</td>
<td>284</td>
<td>75</td>
</tr>
<tr>
<td>Resistance to Staph Aures</td>
<td>5.8% Cipro 4.7% Oflox</td>
<td>35% Cipro 35% Oflox</td>
</tr>
<tr>
<td>Resistance to Strep</td>
<td>51%</td>
<td>50%</td>
</tr>
<tr>
<td>Gram + Gram -</td>
<td>81.8%</td>
<td>51.4%</td>
</tr>
<tr>
<td></td>
<td>18.2%</td>
<td>48.6%</td>
</tr>
</tbody>
</table>

**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\(^2,3\)

**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

**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

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Gatifloxacin and Moxifloxacin
Comparison of In Vitro Efficacy

Fourth-Generation Fluoroquinolones Far More Effective Than Third-Generation Fluoroquinolones
Isolates From Bacterial Endophthalmitis Resistant to Ciprofloxacin, Ofloxacin, and Levofloxacin

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

![Bar chart showing endophthalmitis rates for different medications over 10 years.]

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

Four-Year Retrospective Comparison of Endophthalmitis after Cataract Surgery

![Bar chart showing endophthalmitis rates for different medications over 4 years.]

Ophthalmic Solutions of Fourth-Generation Fluoroquinolones

<table>
<thead>
<tr>
<th></th>
<th>ZyMar®</th>
<th>Vigamox®</th>
<th>Besivance™</th>
<th>Zymaxid™</th>
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<tbody>
<tr>
<td>Approval year</td>
<td>2003</td>
<td>2003</td>
<td>2009</td>
<td>2010</td>
</tr>
<tr>
<td>Indication</td>
<td>Bacterial conjunctivitis</td>
<td>Bacterial conjunctivitis</td>
<td>Bacterial conjunctivitis</td>
<td>Bacterial conjunctivitis</td>
</tr>
<tr>
<td>Active ingredient</td>
<td>Gatifloxacin 0.3%</td>
<td>Moxifloxacin 0.5%</td>
<td>Besifloxacin 0.6%</td>
<td>Gatifloxacin 0.5%</td>
</tr>
<tr>
<td>Preservative</td>
<td>0.005% BAK</td>
<td>No preservative</td>
<td>0.01% BAK</td>
<td>0.005% BAK</td>
</tr>
<tr>
<td>Package size/mean drops</td>
<td>5 mL/152 mean drops per bottle</td>
<td>3 mL/82 mean drops per bottle</td>
<td>5 mL*</td>
<td>2.5 mL/83 mean drops per bottle</td>
</tr>
</tbody>
</table>

*BAK = benzalkonium chloride.
*Mean drops not yet calculated.