Putting the Pieces Together: Approaches in the Investigation and Management of Outbreak Infections

Elmer Y. Tu, MD
Professor of Clinical Ophthalmology
University of Illinois eye and Ear Infirmary
Chicago, IL USA

Disclosures: None

Off-label use of drugs and devices will be discussed
Big Data
England in the 1800’s
European Pandemics

- Bubonic Plague
- Cholera
Transmission of Disease

- Miasmatic Theory
  - Disease is transmitted through exposure to “bad air”
  - Usually foul or rotting organic matter
  - Held throughout history
  - Disease is transmitted through breathing, not direct contact or ingestion
    - Bubonic plague (Black Death), Cholera, etc…
Cholera Outbreak

- Sporadic outbreaks of Cholera in London, England in the 1800’s
Interventions

- Miasmatic theory of transmission
  - City began directing human waste away from homes into the river Thames
John Snow

• Skeptic of the Miasmatic theory of disease transmission
• Previously written on his theory of the origin of cholera outbreaks (1849)
  • Identified a particular water company supplying South London
    • Over 50% of deaths in all of London

http://johnsnow.matrix.msu.edu/
Soho Outbreak

- August, 1854
  - 127 dead within three days of the initial case
  - 500 dead within the first 10 days of the outbreak
    - ~13% of all people contracting the disease died
Reverend Henry Whitehead

- Self titled “Mythbuster”
- Miasmatic theorist
- Met John Snow through local commission to investigate cholera
  - Set out to disprove John Snow’s theories
- After interviewing local residents - believed Snow
Investigation

http://www.ph.ucla.edu/epi/snow.html
Broad Street Tap

- Public Health Disease
  - Limited understanding of transmission, mechanism of disease, treatment
- Episodic outbreaks
  - Large numbers of cases
  - Respected geography
  - Allowed study

- Established infrastructure
  - John Snow’s thoughts and writings
  - Henry Whitehead’s understanding of the community
- Clinical Understanding of Disease
  - Ask appropriate questions
- Collaboration
Birth of Epidemiology

• More than statistics
  • Brings together expertise from multiple disciplines
    • Physicians
      • Understanding of mechanisms of human disease
      • Generation of patient and population data
    • Epidemiologists
      • Investigate patterns of disease from data based on the disease characteristics
    • Biostatisticians
      • Complex data manipulations

• Small, well designed study
  • Appropriate questions based on an understanding of the disease

• Benefits
  • Eventual demise of the Miasmatic theory
  • Example of how to approach other human disease
Putting the Pieces Together

Atypical Corneal Infections
Atypical Corneal Infections

- May be bacterial, viral, fungal or parasitic
- Characteristics
  - Rare or uncommon diseases
  - Difficult to diagnose
  - Unresponsive to commonly available medications
  - Infections often unique to the eye
- Offer both the greatest challenge, but also the greatest opportunity.
ACANTHAMOEBA

- Free-living protozoa, found in most sources of water, soil
  - Seasonal variation
- First identified as an eye pathogen in 1973
Challenge and Opportunity

- Traditionally a rare disease
  - Incidence ~ 2 cases per million contact lens wearers per year
- Easily Traceable
  - Special diagnostic modalities
  - Specialized, compounded medications
- Primarily a disease of the eye
  - Rarely described as an encephalitis, cutaneous or visceral disease
  - Little help from the systemic medical literature
History of Acanthamoeba Outbreaks

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1st Association with CL Wear

>100

349
Question: Who is at greatest risk for contracting *Acanthamoeba* Keratitis?

- A. Soft Contact Lens Wearers who wear their lenses only during the day
- B. Soft Contact Lens Wearers who wear their lenses overnight
- C. Gas Permeable Contact Lens Wearers who wear their lenses only during the day
- D. Gas Permeable Contact Lens Wearers who wear their lenses overnight
Question: How often is contact lens related Acanthamobea Keratitis bilateral?

- A. Never
- B. 1% of cases
- C. 10% of cases
- D. 25% of cases
Who gets Acanthamoeba Keratitis?

85-100% are contact lens wearers
• 7.7-12% Rigid lens wearers

Rates (per million CL users/year)
• United Kingdom
  • SCL 21.14 - 31 cases
  • RCL 17.53 – 27 cases

Orthokeratology
• Literature review 2001-2007
  • 123 cases
    • 52% Pseudomonas
    • 33% Acanthamoeba

Bilateral Disease
• 7-11% of cases

Non-Contact Lens Wearers
• 1.13-1.26 cases per million adults/year

Watt KG, Swarbrick HA

Acanthamoeba: Geographic Variation

- AK patients in counties with flooding
  - RR = 10.83 (95% CI, 1.48-79.49) P < .003
- Other risk factors
  - Municipal water

Previous Outbreaks

- Geographic Variation
- Water quality
  - 3x greater risk in hard water households
  - Development of hard water scale is associated with higher bacterial contamination rates
    - Biofilm formation

Acanthamoeba

- 27 Acanthamoeba keratitis cases
  - Multiple samples of domestic water taps
  - 8/27 (30%) Acanthamoeba positive
    - 6/8 genetic profiles identical to keratitis specimens
  - Water storage tanks/ Rooftop cisterns

UIC Cornea Service

- Confocal Microscopy
  - Obtained a slit-scanning confocal microscope in 1999-2000
    - Developed a working expertise with the instrument and made the service available to the community
  - Quickly developed into a regional referral center for imaging
  - 1999-2003 – 0-3 cases of Acanthamoeba keratitis per year.
Incidence of AK in the U.S.

- 1989 OMIG/ CDC
  - 208 cases
- 1985-1987 Estimate
  - 1.65-2.01 cases per million contact lens wearers/ year
- Baseline incidence
  - Fraction of 1 case per million contact lens users/ year.

Acanthamoeba Keratitis

- Increasing number of cases after 2003
- Referral patterns in place

### TABLE 5. Diagnosed Acanthamoeba Keratitis Cases and Rate Ratios Per Time Period

<table>
<thead>
<tr>
<th>Time Period</th>
<th>No. of Cases Diagnosed</th>
<th>Rate Ratio 95% Confidence Limit</th>
<th>χ²</th>
<th>P Value</th>
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<tr>
<td>June 1, 2003 to November 30, 2005</td>
<td>40</td>
<td>6.67 3.05 17.52 18.78</td>
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<td>&lt;.0001</td>
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<tr>
<td>June 1, 2000 to November 30, 2002</td>
<td>6</td>
<td>1.00 1.00</td>
<td></td>
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</table>

*Based on US Census 2000 population data.

### Epidemiological Characteristics of a Chicago-area Acanthamoeba Keratitis Outbreak

CHARLOTTE J. JOSHIN, OD, ELAIS Y. SU, MD, TIMOTHY T. MAEYEN, OD, DOUG J. PASSMORE, MD, MPH, LEISL T. TAGGNER, MD, PHD, AND JON SUGAR, MD

- **Burden**: To characterize Acanthamoeba keratitis (AK) cases and analyze the geographical distributions within the Chicago/ Evanston metropolitan area, Chicago, Illinois, USA.
- **Methods**: Retrospective, population-based case study.
- **Results**: All AK cases diagnosed at the University of Illinois at Chicago-Coombe Children's Hospital, June 1, 2000, to November 30, 2005, were included in analyses. Patients with limbus involvement were included in case through clinical documentation, and matched controls were selected from the same time period. Patients' charts were reviewed to confirm whether AK cases were auto- and manually distributed. County population data were extracted from US Census 2000 data, and sites were standardized to Cook County. Poisson regression analysis was used to estimate the age-standardized rate ratio (SSR) between 2000 cases and control of each county. Current cases (June 1, 2000 to November 30, 2005) were compared with historical cases (June 1, 2000 to November 30, 2005) to determine if the current rate of AK diagnosis differed from historical rates.
- **Discussion**: June 1, 2003, 2004, and 2005, the average age of patients with AK was 26.8 ± 11.5 years, 13-35 years, 52.5% were men, and 95.0% were contact lenses. Retained ER measures demonstrated increased rates for all counties relative to Cook, and were significant for Cook County (IRR 1.35; 95% confidence interval [CI] 1.44, 1.36) and 91% for Illinois (IRR 1.33; 95% confidence interval [CI] 1.44, 1.35) ER measures. The increase in SSR was significant in Cook County (IRR 1.35; 95% confidence interval [CI] 1.44, 1.36) and 91% for Illinois (IRR 1.33; 95% confidence interval [CI] 1.44, 1.35).

- **Conclusion**: The incidence of AK appears to be increasing in Cook County, and the increased rate is significantly higher than the historical rates (IRR 1.44; CI 1.36-1.52). The increased rate is significantly higher than the historical rates (IRR 1.44; CI 1.36-1.52).

- **Implications**: All cases are increasing in frequency. The increased rate in Cook County is significantly higher than the historical rates (IRR 1.44; CI 1.36-1.52). Further research is warranted to better understand the increased and unusual geographical distribution. (Am J Ophthalmol 2006;142: 312-317, © 2006 by Elsevier Inc. All rights reserved.)

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**Editorial**: The University of Illinois at Chicago College of Medicine, Illinois Eye and Ear Infirmary, Chicago, IL 60612, USA. Printed in USA. For reprint permission, contact the publisher, Elsevier Inc.
Acanthamoeba Keratitis 2003-2005

- Wills Eye Institute
  - Nov 2005 – 19 cases

- University of Illinois Eye and Ear Infirmary
  - Aug 2006- 40 cases

Number of AK cases reported

- Non-culture confirmed cases
- Culture confirmed cases

Year

1999 2000 2001 2002 2003 2004 2005 2006

Yoder CDC
Acanthamoeba Outbreak Cases

[Bar chart showing the number of cases over time, with categories for No Rub, Silicone Hydrogels, and AMO-CMP.]

[Graph showing environmental data such as daily air temperature and water temperature over months.]
Contact Lens Solution Association

- CDC - MMWR May, 2007
- AJO, August 2007
  - AMO Complete Moisture Plus
  - OR 16.67
- Hygiene
  - Solution reuse
  - Infrequent rubbing of lenses
  - Showering with lenses
- Recall of AMO-CMP

**CONCLUSIONS:** AMO Complete MoisturePlus Multi-Purpose Solution use is independently associated with AK among soft contact lens users. However, it does not explain all cases, suggesting additional factors. Further
Risk factors

- Contact lens wear
- AMO Complete Moisture Plus OR 16.67
- Solution Reuse
- Infrequent rubbing of lenses
- Showering with lenses
- Recent contact lens initiation

The Association of Contact Lens Solution Use and Acanthamoeba Keratitis

CHRISTINE L. JOHN, IRIS V. TE, SHAYA N. SIVAK, GREGORY C. BOGGS, PAUL A. PEITZ, JANET E. MURPHY, ROBERT L. ANDERSON, JAMES A. MYDLOVICH, BILL E. SUGAR, JAN E. HAMANN, AND ISMAIL T. YAMIR

Purpose: To investigate Acanthamoeba keratitis (AK) risk factors. Diagnosis of AK, a rare but serious corneal infection, has recently increased significantly at the University of Illinois at Chicago (UIC) Eye Service.

Methods: Retrospective case-control study.

Results: Fifty-six AK cases with contact lens use were diagnosed between May 1, 2007, and September 30, 2009. Case-matched controls with contact lens use were recruited. Subjects completed surveys targeting lens hygiene, contact lens solution use, and lens exposure.

Conclusion: AMO Complete Moisture Plus OR 16.67 and solution reuse were the most significant risk factors for AK. Although other solutions were also significantly associated with AK, AMO Complete Moisture Plus OR 16.67 was a major risk factor.

National Outbreak of Acanthamoeba Keratitis Associated with Use of a Contact Lens Solution, 2002

Jennifer R. Vaez, Satirica L. Lons, Jennifer S. Yoder, Michael J. Oster, Christopher R. Brandt, Jacqueline M. Robles, Craig S. Conover, Sue Chen, Keatessa A. McCollum, Douglas C. Chang, Benjamin L. Park, Dar S. Jones, Gerardo S. Venesiano, and Herbert L. Roy, for the Acanthamoeba Keratitis Investigative Team

Acanthamoeba keratitis (AK) is a serious fungal infection of the cornea that usually causes visual loss or even corneal scarring. Although rare, AK is a serious concern for contact lens users. A large outbreak of AK was identified in the United States in 2002, which was associated with the use of a specific contact lens solution (AMO Complete Moisture Plus OR 16.67). This study aimed to investigate the epidemiology of the outbreak and identify risk factors associated with AK among contact lens users.

Methods: A case-control study was conducted to identify risk factors associated with AK. Cases were identified through a retrospective review of medical records at the University of Illinois at Chicago Eye Service. Controls were matched by age, sex, and type of contact lens solution used. The study included 60 cases and 60 controls.

Results: The risk factors identified in this study included AMO Complete Moisture Plus OR 16.67 solution use, solution reuse, and recent contact lens initiation. The outbreak strain of Acanthamoeba was identified as Acanthamoeba castellanii serotype D.

Conclusion: This study provided valuable insights into the epidemiology of AK and identified specific risk factors associated with the outbreak. These findings can help in the development of strategies to prevent future outbreaks and improve contact lens user education.

GME ACTIVITY

Research:

- Acanthamoeba keratitis, a rare, potentially blinding, corneal infection, was estimated to affect over 1,000 people in the United States in 2007. Cases were often diagnosed late, and the infection was frequently underdiagnosed.
- Risk factors associated with Acanthamoeba keratitis include contact lens use, especially with extended wear lenses, and exposure to contaminated water or solutions.
- The outbreak strain of Acanthamoeba in the United States was identified as Acanthamoeba castellanii serotype D.

Policy:

- The Food and Drug Administration (FDA) issued a recall of the affected contact lens solution (AMO Complete Moisture Plus OR 16.67) to prevent further infections.

Education:

- Public health campaigns were launched to educate contact lens users about the risks of Acanthamoeba keratitis and the importance of proper lens care.

Implementation:

- Enhanced surveillance systems were implemented to monitor the incidence of Acanthamoeba keratitis and other contact lens-related infections.

Evaluation:

- Follow-up studies were conducted to assess the effectiveness of the intervention strategies and to identify any areas for improvement.

The response to this outbreak highlighted the importance of ongoing research in contact lens hygiene and the need for improved contact lens solutions to prevent future infections.
Acanthamoeba Keratitis

- AMO Complete MoisturePlus
  - Use in only ~50% of patients in both studies
    - ~50% reported no use of AMO products
      - Chicago – 5 x greater number of cases than was estimated in the 1980’s.
Chicago Acanthamoeba Outbreak

- Non-Random Distribution of Cases
- Collar Counties

### Epidemiological Characteristics of a Chicago-area Acanthamoeba Keratitis Outbreak

**CHARLOTTE L. BRYNE, MD, EI-HAB Y. TU, MD, TIMOTHY T. NINSON, MD, JOSEPH J. PROUDFOOT, MD, AND JAY C. STREIT, MD.**

**Legend**
- Population Density Per Census Tract 2003 Census, Per Square Mile
  - 0 - 3,050
  - 3,051 - 6,365
  - 6,366 - 15,141
  - 15,142 - 104,627

- Cumulative Annual Incidence Rate Per 100,000 People
  - 0.01 - 1.00
  - 1.01 - 3.00
  - 3.01 - 7.00

**Map:**
- Cook County
- Will County
- DuPage County
- McHenry County
- Lake County
- Kane County
- Kendall County
- Will County

**Table:**
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<td>Kane County</td>
<td>7,200</td>
<td>6,365</td>
<td>1.01 - 3.00</td>
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<td>Lake County</td>
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<td>McHenry County</td>
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<td>DuPage County</td>
<td>7,200</td>
<td>104,627</td>
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**Footnote:**
- Contact the author for a more detailed description of the methodology and findings.
Will County
Cook County
Kane County
Lake County
McHenry County
Dupage County
Kendall County

Cumulative Annual Incidence, 6/03 - 6/07.

Legend
Population Density
2003 Census, Per Square Mile
0 - 3,050
3,051 - 6,365
6,366 - 15,141
15,142 - 104,627

Cumulative Annual Incidence Rate
Per 100,000 People
0.01 - 1.00
1.01 - 3.00
3.01 - 7.00
Acanthamoeba Outbreak Cases

- Chicago Cases
- CDC Survey
- CDC Case Control

EPA Rule Changes

- No Rub

Year:
- 2000
- 2002
- 2004
- 2006
Chicago area chlorine free residual levels (mg/L) pre- and post-compliance with EPA Stage 1 Disinfection Byproduct Rule regulations. Mean and 95% confidence intervals calculated from laboratory bench sheet data publicly available online through the DuPage Water Commission.[104]

<table>
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<th>Water Treatment System</th>
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¹ Student’s t-test between groups: $P < 0.10$

² Student’s t-test between groups: $P < 0.05$
Shifting Distribution of Chicago-Area Acanthamoeba Cases

Mean distance between the patients’ residence and UIC:

2003-2005  22.90 miles
2005-2007  17.81 miles  \( P=.04 \)

Acanthamoeba keratitis (AK) is a rare contact lens-related infection with significant morbidity. Acanthamoeba are ubiquitous, free living, and believed to infect the cornea through contaminated water. Risk factors include poor hygiene, swimming while wearing contact lenses, tap water contamination, and use of certain contact lens solutions. A statistically significant increase in cases began in June 2003 in Chicago, Illinois. Self-reported use of COMPLETE MoisturePLUS multipurpose solution (Advanced Medical Optics, Inc, Santa Ana, California) was strongly associated with AK in 2 studies, leading to a product recall on May 25, 2007. Nevertheless, only 55% to 80% of patients with AK reported exposure to COMPLETE MoisturePLUS, while approximately 40% did not. Although Acanthamoeba are resistant to multipurpose solutions, generalized outbreaks have not occurred since introduction. In Chicago, cases continue despite the recall (11 cases were diagnosed from June 1, 2003, to May 31, 2004; 21 cases were diagnosed from...
Chicago Acanthamoeba Outbreak

Complete MoisturePlus Multipurpose Solution Recall

Total AK Cases by Solution

Acanthamoeba Year (June 01 - May 31)

Figure 1: Cases of *Acanthamoeba keratitis* diagnosed at 13 ophthalmology centers and laboratories, by year: 1999 – 2009 (n=875)

*Cases confirmed by other diagnostic methods (e.g., histopathology, confocal microscopy)*
Evidence suggests increased pressure on current contact lens disinfection systems
- Increased environmental “load” of Acanthamoeba
  - 18% - Chicago water supply (ARVO 2007)
    - Non-random sampling
  - 2.8% - Fort Lauderdale
  - 7.7% - Seoul Korea
  - 10% - Hong Kong (PCR)
  - 30% - UK (Patient homes)
Summary

- Acanthamoeba keratitis is a rare infection
  - Contact lens wear is the primary risk factor
  - Amplified by deviations in water quality

- Environmental risk factors may not be modifiable
  - Daily disposable lenses
  - New contact lens solution guidelines (FDA)
    - Efficacy testing against Acanthamoebae

- The surge in Acanthamoeba keratitis may reflect changes in risk factors that may have an effect not only on other ocular infections but also on the general public health.
Putting the Pieces Together
Approaches in the Management of Atypical Corneal Infections
Small Data

Big Data
Small Data
Atypical Infections

• Difficult to diagnose
• Poorly responsive to available medications
• Limited clinical experience with ophthalmic medical therapy
• Limited experience with systemic medical therapy
Approach to Atypical Infections

• Diagnosis
  • History, Examination
  • Microbiologic sampling
  • Imaging
  • Goal: Identify the Causative Pathogen
    • Genus, Species

• Empiric Therapy
  • Antibacterials
  • Avoid steroids
  • Goal: Avoid rapid, catastrophic loss
    • Best guess therapy
Approach to Atypical Infections: Failure of Initial Therapy

Pathogen Identified

- Determine specific therapy
  - Based on historical antimicrobial clinical ophthalmic efficacy
  - If none exists or it fails—look harder
    - Changes in nomenclature
      - (drfungus.org)
    - Systemic agents and laboratory studies
    - Polymicrobial infections
      - Herpes, Acanthamoeba
  
- Surgery

Pathogen Unidentified

- Further empiric therapy
  - Based on history, examination, testing

- Further Diagnostics
  - Molecular microbiologic methods
  - Corneal biopsy

- Remains unidentified
  - Empiric therapy
    - Herpes, Acanthamoeba
  - Non-infectious
  - Surgery
Advances in the Clinical Management
Diagnostic Techniques for Acanthamoeba Keratitis

• “Clinical Characteristics”
  • History, clinical presentation

• Microbiologic methods
  • Culture – Charcoal yeast, Non-nutrient Agar with E. aerogenes (35-50%)
  • Histologic smears – KOH, Giemsa, Acridine Orange, H&E
  • Pathology – Corneal transplant button, corneal biopsy
  • PCR detection – ubiquitous organism, validation

• Imaging – Confocal microscopy
Confocal Microscopy
• 53 patients were diagnosed with AK
  • 53/53 examined by confocal
  • 42/53 cultured
    • Corneal scrapings only
  • 41/53 Diff-Quik smears
  • 5/53 received PKPs
    • 1/5 was performed for optical reasons after completing tx
How did Confocal Microscopy fare?
Question: What is the most important presenting prognostic factor for a patient’s visual outcome who has acanthamoeba keratitis?

- A. Duration of symptoms
- B. Prior steroid treatment
- C. Depth of corneal involvement
- D. Prior antibiotic treatment
Prognostic Factors

- 72 eyes of 65 patients
  - Final visual acuity 61/65 patients (93.8%)
  - Age 13-70
  - Contact Lens Wear 62/65
  - Soft Contact Lenses 58/65
  - GPHCL 4/65
- Prior Treatment
  - HSV 26/60 patients (43%)
  - Steroids 50/61 patients (82%)

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Prognostic Factors Affecting Visual Outcome in Acanthamoeba Keratitis

Objective: To identify clinical and demographic factors associated with worse visual outcome in Acanthamoeba keratitis (AK).

Design: Retrospective case-control study.

Patient Sample: A total of 72 eyes of 65 patients with AK were diagnosed at the University of Illinois Eye and Ear Infirmary between May of 2005 and May of 2007 with treatment complete by October of 2007. The final visual acuity was analyzed in bilateral cases.

Methods: Patients were divided into three groups based on demographic characteristics, treatment methods, and final visual outcome: group A (Prognosis Factors), group B (not Prognosis Factors), and group C (no visual outcome data available). Wilcoxon rank-sum test was used for continuous variables, and chi-square test was used for categorical variables. Multivariable analysis was performed using logistic regression.

Results: AK was confirmed through microbiologic evidence in 48 of 65 eyes (73.8%) or with corneal microscopy in 6 of 65 eyes (9.2%). Final visual acuity data were available in 51 of 65 eyes (78.5%), of these 51 eyes, 40 (78.4%) achieved a final visual acuity of 20/60 or better. In multivariable analysis, deep stromal involvement at presentation was independently associated with worse visual outcomes (OR, 4.32; 95% confidence interval [CI], 2.08-8.93). Multivariable analysis failed to confirm associations with initial visual outcome (OR, 2.35; 95% CI, 0.98-5.64), and univariate analysis failed to confirm associations with initial visual outcome (OR, 0.92; 95% CI, 0.51-1.67).

Conclusions: Multivariable analysis of patients who presented with a ring corneal opacity was highly predictive of worse outcomes, allowing the identification of patients who might benefit from more aggressive medical or surgical intervention. While previous reports of symptoms before treatment was not reliable in predicting the final visual result in our series.
Duration and Visual Outcome

- Duration of Symptoms
  - > 3 weeks = Deeper Disease
    - (OR, 4.43; 95% CI, 0.99 –19.83)
  - No correlation with visual outcome
Disease Stage at Presentation

• Disease stage at presentation
  • Good Prognosis
    • Epitheliitis with or without radial neuritis
    • Anterior stromal disease
  • Guarded Prognosis
    • Deep stromal keratitis
    • Ring infiltrate
    • Extracorneal Inflammation
  • > 10 times more likely to have a worse visual outcome (20/30 or worse)
    • (OR: 10.27; 95% CI: 2.91 – 36.17)
Question: Does having Acanthamoeba keratitis confer immunity against future infections?

• A. Yes
• B. No
Re-infection in Acanthamoeba Keratitis

- 16 year old male
  - 2 acanthamoeba keratitis episodes one year apart
  - Two genotypically distinct isolates
  - Contracted 900 miles apart

Tu EY, Joslin CE, Shoff ME, Lee JA, Fuerst PE. Eye (Lond). 2009 Nov 27. [Epub ahead of print]
Sequential corneal infection with two genotypically distinct Acanthamoebae associated with renewed contact lens wear.
Question: Which of the following have been identified as Co-pathogens with Acanthamoeba keratitis?

- A. Bacteria
- B. Herpes Simplex
- C. Mold
- D. Other Ameoba
- E. All of the Above
Polymicrobial Keratitis: Acanthamoeba and Infectious Crystalline Keratopathy

ELMER Y. TU, CHARLOTTE E. JOSLIN, LISA M. NJIM, ROBERT S. FEDER, SANDEEP JAIN, AND MEGAN E. SHOFF

Courtesy Dr. Sandeep Jain
Polymicrobial Acanthamoeba Keratitis

- Acanthamoeba keratitis Co-pathogens
  - Herpes simplex
  - Fungal pathogens
  - Bacterial pathogens
  - Other protozoa
    - Hartmanella
    - Vahlkampfia

Polymicrobial Acanthamoeba Keratitis

• UIC Series
  • 111 patients with Acanthamoeba keratitis
  • 5 (4.5%) patients demonstrated co-isolates
    • The widespread availability of broad spectrum antibacterial agents
  • UIC cases were consistent with previously understood disease definition
  • Availability of broad spectrum antibiotics had either no effect or potentially reduced detected cases.

## Larger Series Reporting Microbiologic Co-Isolates

<table>
<thead>
<tr>
<th>Acanthamoeba keratitis series</th>
<th>Number of Cases</th>
<th>Initial Sample</th>
<th>Subsequent Sample</th>
<th>Positive Cases Total</th>
<th>Presumed Contaminants*</th>
<th>Non-Contaminant positives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacon, et al. 1993&lt;sup&gt;3&lt;/sup&gt;</td>
<td>72</td>
<td>14 Fungal (3) Bacterial (13)</td>
<td>11 Fungus (1) Bacterial (11)</td>
<td>20 (28%) Fungus (3) Bacterial (20)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mathers, et al. 1996&lt;sup&gt;5&lt;/sup&gt;</td>
<td>43</td>
<td>NA</td>
<td>NA</td>
<td>17 (40%) Bacterial (17)</td>
<td>11</td>
<td>6 (14%)</td>
</tr>
<tr>
<td>Duguid et al., 1997&lt;sup&gt;10&lt;/sup&gt;</td>
<td>111</td>
<td>NA</td>
<td>NA</td>
<td>11 (10%) Bacterial (11)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>UIC, 2009</td>
<td>111</td>
<td>7</td>
<td>5</td>
<td>12 (11%) Bacterial (12)</td>
<td>7 (5 broth, 2 non-active AK)</td>
<td>5 (4.5%)</td>
</tr>
<tr>
<td>Microbiology-Based Survey</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Srinivasan et al., 1997&lt;sup&gt;14&lt;/sup&gt;</td>
<td>3 (297 cases)</td>
<td>NA</td>
<td>NA</td>
<td>0 (0%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Bharathi et al. 2002&lt;sup&gt;13&lt;/sup&gt;</td>
<td>8 (1618 keratitis cases)</td>
<td>NA</td>
<td>NA</td>
<td>0 (0%)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Tu EY, et al. Polymicrobial Acanthamoeba Keratitis. IOVS; 50:ARVO E-Abstract 5936
### Acanthamoeba

#### Keratitis Co-Pathogens
- Herpes simplex
- Bacteria
- Fungi
- Protozoa

#### Endosymbionts
- Legionella
- Mycobacterium
- E.coli
- Salmonella
- Pseudomonas
- Vibrio cholerae
- Heliobacter pylori
- Listeria
- Shigella
- Pasteurella
- Campylobacter
- Cytophagia
- HSV
Acanthamoebal Endosymbionts

- 37/38 Acanthamoeba keratitis isolates
- Endosymbionts 59.4%
  - Legionella (3)
  - Pseudomonas (13)
  - Mycobacterium (5)
  - Chlamydia (1)
- Enhanced Cytopathic Effects
- Reflective of environmental bacterial prey

Detection of Bacterial Endosymbionts in Clinical Acanthamoeba Isolates

Pathogenicity of Acanthamoeba with Legionella Endosymbionts

- Clinical Acanthamoeba isolates from the Chicago Acanthamoeba Outbreak
  - Infected with L. pneumophilia
- C57BL/6 mice
  - Corneal injection of Acanthamoebae, L. pneumophilia alone or Acanthamoebae with L.pneumophilia endosymbionts
- Results
  - Qualitatively more severe corneal disease in endosymbiont-containing Acanthamoebae

Yen C. Hsia, Sixto M. Leal, Jr., Gregory C. Booton, Charlotte E. Joslin, Nicholas P. Cianciotto, Elmer Y. Tu, Eric Pearlman.
5794/D1079 Abstract Title: Acanthamoeba Keratitis Is Exacerbated In The Presence Of Intracellular Legionella Pneumophila
Onchocerca volvulus

• River blindness
  • Nematode source
  • Hematogenous spread to the peripheral cornea with centripetal migration
  • Severe inflammatory keratitis ensues \textit{after} initiation of anti-nematode therapy
    • Originally thought to be secondary to antigenic release from dying Onchocerca

• Endosymbiont
  • \textit{Wolbachia sp.}
    • Host’s death leads to release of the bacteria in the corneal stroma stimulating Toll-like receptors and the inflammatory cascade.
Concomitant Antimicrobial Therapy?

- Bacterial Co-pathogens are the most common
- Other classes of organisms are uncommon or rare
- Prognostic Factors
  - Prior Therapy
  - Use of non-benzalkonium chloride containing antibiotic prior to presentation resulted in a poorer outcome (OR: 3.50; 95% CI 1.02-12.03)
    - Univariate analysis
What is benzalkonium chloride?

- Hotly debated role in ophthalmic drugs
- Anti-infectives
- Surface toxicity
- Improves penetration through the epithelium

Fluoroquinolones and acanthamoeba

- Acanthamoeba castellanii (CDC V-568, isolate T4)
- $10^4$ trophozoites incubated
  - Amoeba saline
  - H2O2 3%
  - Moxifloxacin (Parenteral) 0.5%
- Rinsed in Dey Engley Broth
  - 5 time intervals
- Enumeration by MPN method
- No significant reduction of acanthamoeba growth

Adapted from: Elmer Y. Tu, Megan E. Shoff, Charlotte E. Joslin. 5830/D1115 - The Addition Of Benzalkonium Chloride To Moxifloxacin Confers Anti-acanthamoebal Activity In An In Vitro Model, ARVO 2011
Moxifloxacin + BAK
Acanthamoeba Outbreak Cases

- Chicago Cases
- CDC Survey
- CDC Case Control
Advances in Medical Therapy
Standard Medical Treatment

- Mechanical Debridement
  - Debulk organism load
  - Diagnosis confirmation
- Combination meds (Tapered according to response)
  - Propamidine Q1 hour (trophozoites, inhibits encystment)
    - First month of therapy
  - Biguanide-Chlorhexidine 0.02% Q1 hour (also cysticidal)
- Add systemic meds as indicated
- Steroids are eliminated or reduced at diagnosis
Overall Visual Results

- IOWA 1993-4
- UK 1992-9
- Wills 2007
- IEEI

Legend:
- Blue: Less than 20/100
- Orange: 20/50-20/100
- Green: 20/40 or better

Bar chart showing visual results across different studies.
ANTI-ACANTHAMOEBAL Clinical Resistance

• Up to 5% may remain persistently culture positive with therapy
  • Perez-Santonja et al Ophthalmology 2002
Voriconazole

- High Bioavailability
  - Oral and IV form
  - Nearly equal tissue levels
  - 200 mg Q12 hours
  - Extensively studied for use in endophthalmitis

- Clinical activity against Acanthamoeba

- Mixed results of in vitro sensitivity testing


Voriconazole and Acanthamoeba Keratitis

• Previously described as topical, adjunctive therapy (Bang, et al.)
• 3 eyes of two patients with chronic culture-proven stromal keratitis
  • Resolution with sole use after several months of therapy (200mg Q12h)

Successful Treatment of Chronic Stromal Acanthamoeba Keratitis With Oral Voriconazole Monotherapy

Elmer Y. Tu, MD,* Charlotte E. Joslin, OD, PhD,** and Megan E. Shoff, MS, PhD†


Other Agents

- Miltefosine
  - Anti-leishmaniasis drug with anti-acanthamoebal activity
  - Low toxicity drug used widely in developing countries
  - Significant inhibitory effect on Acanthamoeba with cidal activity above 40 micrograms/ml
Miltefosine
Summary

• Big Data > Small Data > Really Small Data
• Good, clean data is more important
  • Team approach to planning, gathering and analyzing data
  • Take time to generate new hypotheses
• Medical Treatment of Recalcitrant, Atypical Keratitides
  • Accurate identification and isolation
  • Valid susceptibility testing
  • Safety and efficacy of topical ophthalmic application for compounded anti-infectives
Summary

• Acanthamoeba keratitis is a rare infection
  • Contact lens wear is the primary risk factor
  • Amplified by deviations in water quality
• Environmental risk factors may not be modifiable
  • Daily disposable lenses
  • New contact lens solution guidelines (FDA)
    • Efficacy testing against Acanthamoebae
• The surge in Acanthamoeba keratitis may reflect changes in risk factors that may have an effect not only on other ocular infections but also on the general public health.
Summary

• Increase in cases of Acanthamoeba keratitis have led to innovation in treatments
  • Alternative topical and systemic medications
  • Surgical intervention
  • Immunosuppression
• Advancing testing methods for current and future contact lens disinfection systems
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