“Super Gonorrhea”, Emerging Antimicrobial Resistance in Neisseria Gonorrhoeae and Implications for Management

Satellite Conference and Live Webcast
Tuesday, December 4, 2018
9:00 – 10:30 a.m. Central Time

Produced by the Alabama Department of Public Health
Video Communications and Distance Learning Division

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Disclosures
Grant/Research Support: NIH, CDC, WHO, GlaxoSmithKline, Becton Dickinson, Cepheid, Hologic, Roche Molecular, Cempra, Entasis

Consultant: Hologic

Speakers Bureau: None

Neisseria Gonorrhoeae Presentation Overview

Epidemiology
Diagnosis
Treatment/Antimicrobial Resistance
Control Measures

Current WHO Estimates of Global Gonorrhea Prevalence
106 Million cases Annually

THE U.S. IS EXPERIENCING STEEP, SUSTAINED INCREASES IN SEXUALLY TRANSMITTED DISEASES

Combined diagnoses of chlamydia, gonorrhea, and syphilis increased sharply over the past five years

For more information, visit
ncidc.gov/std/stats/sexuallytransmitteddiseases.html
Gonorrhea — Rates of Reported Cases by Year, United States, 1941–2016

Gonorrhea—Rates of Reported Cases by Sex, United States, 2000–2016

Male +22.2%
Total +18.5%
Female +13.8%

Gonorrhea — Rates of Reported Cases by Age Group and Sex, United States, 2016

Gonorrhea — Rates of Reported Cases by State, United States and Outlying Areas, 2016

NOTE: The total rate of reported cases of gonorrhea for the United States and outlying areas (Guam, Puerto Rico, and Virgin Islands) was 144.4 per 100,000 population.

Gonorrhea — Rates of Reported Cases by Region, United States, 2007–2016

Gonorrhea — Rates of Reported Cases by Race/Ethnicity, United States, 2012–2016

**Note:** Data collection for gonorrhea began in 1941; however, gonorrhea became nationally notifiable in 1944. Refer to the National Notifiable Disease Surveillance System (NNDSS) website for more information: [https://wwwn.cdc.gov/nndss/conditions/gonorrhea/](https://wwwn.cdc.gov/nndss/conditions/gonorrhea/)

*AI/AN* = American Indians/Alaska Natives; *NHOPI* = Native Hawaiians/Other Pacific Islanders.

Features of US Gonorrhea Epidemiology

- Incidence in non-whites 10 times greater than in whites
- Urban residence
- Lower socioeconomic status
- Early coital debut
- Single People
- Past history of gonorrhea
- Increasing focus on extra-genital infections and antimicrobial resistance

HIV-1 RNA in Blood and Semen of Urethritis Patients
(median values)

Effect of STD Treatment on HIV-1 RNA in Semen of Urethritis Patients

Neisseria Gonorrhoeae
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Gonorrhoea Detection

Gram’s Stain
Culture
Antigen Detection
Nucleic Acid Detection
Nucleic Acid Amplification
Changing Paradigms For Urogenital Specimen Collection

Pre-NAAT’s: Specimen Quality Critical
- Endocervical Or Urethral Swabs
- Swab Order Impacts Test Results
  - Culture > Non-Amplified Nucleic Acid Detection > Antigen Detection

NAAT’s: More Forgiving Specimen Collection
- Vaginal Swab > Endocervical Swab > Initial Void Urine

Impact of NAATs Testing for STDs – Alabama

Cumulative Reported Infections as of:

<table>
<thead>
<tr>
<th></th>
<th>Oct 1, 2005</th>
<th>Sept 30, 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. gonorrhoeae</td>
<td>6,698</td>
<td>7,110</td>
</tr>
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<td>C. trachomatis</td>
<td>11,638</td>
<td>15,314</td>
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Impact of NAATs Testing for STDs – Alabama


Performance of NAATs for Diagnosis of Pharyngeal N. Gonorrhoeae and Infections

<table>
<thead>
<tr>
<th>Pharyngeal Gonococcal Infection By Site</th>
<th>No (%) Individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td></td>
</tr>
<tr>
<td>Genital and Oral</td>
<td>23 (28%)</td>
</tr>
<tr>
<td>Genital Only</td>
<td>28 (34.1%)</td>
</tr>
<tr>
<td>Oral Only</td>
<td>31 (37.8%)</td>
</tr>
<tr>
<td>Total Genital or Oral</td>
<td>82 (100%)</td>
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</tbody>
</table>

Neisseria Gonorrhoeae
Presentation Overview

Epidemiology

Diagnosis

Treatment/Antimicrobial Resistance

Control Measures

DR. READ EUREKA TONIC
SYPHILORRHOEA
Emerging Gonococcal Antimicrobial Resistance – Deja Vu

Pre-1937
- Antiseptic Irrigation With Potassium Permanganate, Silver Salts, Mercurochrome

1937
- Sulfonamide Therapy

1943
- Penicillin Therapy (Mahoney et al)

1944
- 35% Treatment Failure With Sulfonamides

1972
- Penicillin Regimen Increased to 4.8 Million Units Plus Probenecid

GONORRHEA THERAPY – HISTORICAL PERSPECTIVE

- Previously Recommended Medications For Gonorrhea Therapy
  - Sulfonamides
  - Penicillins
  - Macrolides
  - Tetracyclines
  - Aminoglycosides
  - Spectinomycin
  - Fluroquinolones

Gonococcal Antimicrobial Resistance: Determinants and Mechanisms

Gonorrhea Therapy: The Shrinking Pipeline

Location of Participating Sentinel Sites and Regional Laboratories, Gonococcal Isolate Surveillance Project (GISP), United States, 2016

NOTE: Austin is a regional laboratory only.
Neisseria gonorrhoeae — Distribution of Isolates with Penicillin, Tetracycline, and/or Ciprofloxacin Resistance, Gonococcal Isolate Surveillance Project (GISP), 2016

Gonococcal Isolate Surveillance Project (GISP) - Percent of Neisseria gonorrhoeae isolates with resistance or intermediate resistance to ciprofloxacin, 1990–2008

Emergence of Fluoroquinolone-Resistant N. gonorrhoeae (QRNG) in the US, 1989–2007

2006 CDC STD TREATMENT GUIDELINES
Uncomplicated Gonorrhea

Ceftriaxone 125 mg IM or
Cefixime 400 mg PO or
Ciprofloxacin 500 mg PO or
Ofloxacin 400 mg PO or
Levofoxacin 250 mg PO

PLUS IF CHLAMYDIAL INFECTION IS NOT RULED OUT
Azithromycin 1.0 g Single Dose or
Doxycycline 100 BID x 7d

2010 CDC STD TREATMENT GUIDELINES
Uncomplicated Gonorrhea

Ceftriaxone 250 mg IM or
Cefixime 400 mg PO
PLUS
Azithromycin 1.0 g Single Dose or
Doxycycline 100 BID x 7d

"Those who cannot remember the past are condemned to repeat it."
George Santayana
Decreased Cephalosporin Susceptibility

1999: Japan: 0% isolates have MICs to cefixime ≥ 0.5 µg/ml
2001: Japan: Possible treatment failure with cefdinir
2002: Japan: 30% isolates have MICs to cefixime ≥ 0.5 µg/ml
2003: Japan: 8 (12%) of men with GC in study unsuccessfully treated with cefixime
2007: Hong Kong: 4 treatment failures with cefixime
2008-2009: Increasing MICs to cephalosporins reported in Australia, Europe, and US
2010: Japan: Isolate with Ceftriaxone MIC of 2 µg/ml (female CSW) treated with cefixime
2016

N. Gonorrhoeae Treatment Failures to Cefixime, Toronto, Canada

Rx failure overall – 6.8% (95% CI – 3.1-12.5%)
  If cefixime MIC ≥0.12 – 25%(95% CI 10.7-44.9%)
  If cefixime MIC <0.12 – 1.9% (95% CI 0.23-6.7%)
Treatment failures:
  4 of 76 urethral (5.3%)
  2 of 7 pharyngeal (28.6%)
  3 of 39 rectal (7.7%)

2015 CDC STD TREATMENT GUIDELINES
Uncomplicated Gonorrhea

Ceftriaxone 250 mg IM
PLUS
Azithromycin 1.0 g Single Dose or
Doxycycline 100 BID x 7d
Even if chlamydia negative

Alternative GC Treatment 2015 CDC STD Treatment Guidelines

Cefixime 400mg po x 1
Plus
Azithromycin 1gm po x 1
TOC in 1 week 14d


Gonorrhea Treatment - What’s Next

Salvage Therapy:
  Gentamicin 240 IM/ Azithromycin 2.0g PO
    (IM Administration/Toxicity)
  Gemifloxacin 340 mg/Azithromycin 2.0g PO
    (GI Toxicity)
On The Horizon:
  Solithromycin (??)
  Delafloxacin
  AZ D0914 (Zolfioodacin)
  BTZ116576 (Gepotidacin)
  Others
**ETX0914 Urogenital Microbiological Per Protocol Cure Rates**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Confirmed Infections</th>
<th>Cures</th>
<th>Micro. Cure Rate %</th>
<th>Micro. Cure % 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETX0914 2g</td>
<td>49</td>
<td>48</td>
<td>97.96</td>
<td>89.15, 99.95</td>
</tr>
<tr>
<td>ETX0914 3g</td>
<td>47</td>
<td>47</td>
<td>100.00</td>
<td>92.45, 100.00</td>
</tr>
<tr>
<td>Ceftriaxone 500 mg</td>
<td>21</td>
<td>21</td>
<td>100.00</td>
<td>83.89, 100.00</td>
</tr>
</tbody>
</table>

**ETX0914 Pharyngeal Microbiological Per Protocol Cure Rates**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Confirmed Infections</th>
<th>Cures</th>
<th>Micro. Cure Rate %</th>
<th>Micro. Cure % 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETX0914 2g</td>
<td>6</td>
<td>4</td>
<td>66.67</td>
<td>22.28, 95.67</td>
</tr>
<tr>
<td>ETX0914 3g</td>
<td>9</td>
<td>7</td>
<td>77.78</td>
<td>39.99, 97.19</td>
</tr>
<tr>
<td>Ceftriaxone 500 mg</td>
<td>4</td>
<td>4</td>
<td>100.00</td>
<td>39.76, 100.00</td>
</tr>
</tbody>
</table>

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**A New Model for STD Treatment Trials**

Collaborative, multinational trial of Zoliflodacin, a candidate antibiotic for treatment of uncomplicated gonorrhea.

- Led by GARDP (Global Antibiotic Research and Development Partnership)
- Collaborators: Entasis Pharmaceuticals, NIAID, WHO
- Study sites in: U.S, Thailand, South Africa, E.U.
- Goal: Approval of a non-beta-lactam antibiotic effective vs. resistant gonorrhea

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**Gonorrhea Treatment Research Key Questions**

1. Origins of resistance
   - Selection resulting from antimicrobial use
   - Acquisition of resistance from other organisms
2. Optimal strategies to slow further development of resistance
   - New drugs
   - Combination therapy
   - Multi-dose therapy
3. How important is pharyngeal gonorrhea as a source of development of resistance &/or a public health problem
4. How can whole genome sequencing help answer continuing questions

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**Neisseria Gonorrhoeae Presentation Overview**

**Epidemiology**

**Diagnosis**

**Treatment/Antimicrobial Resistance**

**Control Measures**
Reasons for STD Treatment Failure

- Reinfection
- Wrong Therapy
  - Wrong diagnosis
  - Wrong dosage/duration
  - Self medication
- Resistant Organisms
- Other

STD Incidence Modifiers - GC

\[ R = BcD \]

- \( R \): Reproductive Rate
- \( B \): Infectivity: GC biologic characteristics, Condoms, (Vaccine)
- \( C \): Sexual Partner Selection (rate and variability) and Notification Parameters
- \( D \): Duration of Infectivity: Expedient Detection and Effective Treatment (AMR)

After Anderson, RM and May RM; Nature 1988;333:323-320

Gonorrhea Prevention

Current:
- Expeditious Diagnosis and Therapy
  - Behavior Change
  - Condoms
  - Antimicrobial Prophylaxis

Future:
- Vaccines (New Hope, New Energy)
- Microbicides