Neisseria gonorrhea, the Next Super Bug: Coming to a Clinic Near You

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Learning Objectives:
1. Understand the resistance pattern of *N. gonorrhea* over time
2. Explain the rationale behind first line therapy guidelines
3. Identify barriers to routine culture and susceptibility testing in clinical settings
4. Evaluate the evidence supporting alternative treatments
I. Introduction
   A. Gonorrhea is one of oldest known human illnesses
      i. Referenced in biblical Old Testament (Leviticus) and other works of antiquity
      ii. Galen (130 AD), a physician introduced the term *gonorrhea* “flow of seeds”
   B. Organism was first described by Neisser in 1879 and cultivated in 1882
   C. Effective treatment wasn’t available until the advent of sulfonamides in 1930 and penicillin in 1943

II. Epidemiology
   A. Transmission
      i. Main route of transmission is via sexual contact
      ii. Vertical transmission via exposure to infected cervical exudate at birth
      iii. Nonsexual transmission of ocular infection among children in tropical settings
   B. Remains the second most commonly reported bacterial sexually transmitted disease (STD)
   C. In 2010, a total of 309,341 cases reported in the US yielding 100.8 cases per 100,000 population
      i. Statistics likely represent significant underestimate
      ii. True incidence was estimated to be 700,000 cases
      iii. Rates are highest among adolescents and young adults
         a. In 2010, the highest rate observed was among women aged 15-19 years and 20-24 years

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**Figure 1.** Gonorrhea rates by county, United States 2010. Adapted from the Centers for Disease Control and Prevention STD Surveillance 2010: National Profile. Available at [http://www.cdc.gov/std/stats10/figures/18.htm](http://www.cdc.gov/std/stats10/figures/18.htm)
III. Clinical Presentation

A. Uncomplicated urogenital infection
   i. Incubation period is 2 – 5 days
   ii. Men
      a. Acute urethritis is the predominant clinical manifestation
      b. Accompanied by urethral discharge and dysuria
   iii. Women
      a. Usually asymptomatic or have minor symptoms
      b. Pathogen can be recovered from the endocervix, urethra, or rectum

B. Pharyngeal infection
   i. Almost all infections are asymptomatic
   ii. Some treatment regimens have decreased efficacy against pharyngeal infections compared to urogenital infections

C. Pelvic inflammatory disease (PID) and disseminated gonococcal infection (DGI)
   i. PID: estimated to occur in 10-20% of women
      a. Fallopian tube obstruction causes infertility
      b. Infertility occurs in 15-20% of women after a single episode and 50-80% after ≥ 3 episodes
   ii. DGI
      a. Results from bacteremic dissemination
      b. Most common presentation is arthritis-dermatitis syndrome

IV. Etiology and Microbiology

A. *N. gonorrhoea* is a nonmotile, non-spore forming, gram negative coccus

B. All strains have complex growth requirements
   i. Chocolate agar with enriched with glucose is a satisfactory medium
   ii. Requires selective media containing antimicrobials to inhibit commensal species

V. Diagnosis

A. Culture and isolation have been the historical standard for diagnosis
   i. Ninety-five percent sensitive for urethral specimens and 80-90% for endocervical infections
ii. Inexpensive and is the only validated diagnostic test for rectal and pharyngeal infection
iii. Preserves an isolate for susceptibility testing
iv. Unable to distinguish *N. meningitidis* from *N. gonorrhea*
v. Only used in designated sentinel clinics for susceptibility surveillance

B. Nucleic Acid Amplification Tests (NAAT)
i. Have replaced culture in most clinical settings
ii. Ninety-nine percent specificity and 95% sensitivity for cervical or urethral specimens
iii. Retains sensitivity when testing voided urine or vaginal swabs
iv. Cannot test for susceptibility

VI. Gonococcal Isolate Surveillance Project (GISP)
   A. A national sentinel surveillance system established in 1986
   B. Reference labs that test sample isolates for susceptibility
   C. Monitor trends in antimicrobial susceptibilities of *N. gonorrhea*
   D. Data collected from selected STD clinics at 25-30 GISP sentinel sites from 4-5 regional laboratories

<table>
<thead>
<tr>
<th>Treatment Timeline</th>
</tr>
</thead>
</table>

I. Resistance = Persistence: Treatment Throughout the History
   A. Sulfonamides were the first effective agents against gonorrhea in mid 1930s, resistance developed a decade later
   B. Penicillin was the drug of choice in 1943
      i. Served as the mainstay treatment of choice for several decades
      ii. During the pre-penicillin era nearly all isolates had MICs of <0.0125 mg/L
      iii. By 1974, 11-23% of isolates in some US regions were resistant (MIC > 0.5 mg/L)
         1. Resistance mechanisms involved altered penicillin binding protein (PBP) and penicillinase
   C. Tetracycline resistance emerged in the 1970s along with penicillin resistance
   D. Fluoroquinolones became widely available in the 1980s
      i. Highly effective against *N. gonorrhea* at all anatomic sites and required one oral dose
      ii. In 1993, ciprofloxacin was the first line therapy recommended by the Centers for Disease Control and Prevention (CDC)
      iii. Resistance patterns worldwide
         1. By 1992, 40% of isolates were ciprofloxacin resistant in Japan
         2. Resistant strains spread from Asia to North America and Europe via travelers
         3. United States resistance rates were highest along the West Coast, Hawaii and California
         4. In 2007, CDC no longer recommended ciprofloxacin as a first line agent

II. The New Superbug
   A. Ability to cause repeated infection in the same host
   B. Propensity to develop resistance against all clinically useful antibiotics
   C. Multiple mechanisms to cope with the innate and adaptive host immunity
Figure 3. History of antibiotic treatment of gonorrhea and evolution of resistance in the United States

First Line Therapy

I. Current CDC guideline recommendation

Table 1: Uncomplicated Gonococcal Infections of the Cervix, Urethra, and Rectum

<table>
<thead>
<tr>
<th>Recommended</th>
<th>Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Ceftriaxone 250 mg intramuscular (IM) single dose PLUS • Azithromycin 1 g orally (PO) single dose • Doxycycline 100 mg twice daily (BID) for 7 days</td>
<td>• Cefixime 400 mg orally single dose PLUS azithromycin 1 g PO single dose /doxycycline 100 mg BID for 7 days • AND Test-of-cure in one week OR (for Cephalosporin allergic patients) • Azithromycin 2 g PO single dose • AND Test-of-cure in one week</td>
</tr>
</tbody>
</table>

Table 2: Gonococcal Infections of the Pharynx

• Ceftriaxone 250 mg IM single dose PLUS • Azithromycin 1 g PO single dose or • Doxycycline 100 mg PO BID for 7 days

II. The Current Clinical Laboratory Standards Institute (CLSI) susceptible breakpoints

A. Cefixime = 0.25 μg/mL and Ceftriaxone = 0.25 μg/mL
I. Criteria for Selecting Effective Treatment
   A. Efficacy: first line agents
      i. The definition of efficacy has not been easily delineated or strongly supported by evidence
      ii. In 1992, treatment with > 95% cure and a lower 95% CI ≥ 90%
         a. Supported by the World Health Organization (WHO) and the United States
      iii. In 1995, Moran et al. recommended a more stringent criteria
         a. There was a wide variety of antimicrobial agents with overall cure rates >95%
         b. A change was made to increase the lower 95% CI to > 95%
         c. Use a dose that is twice as high as the therapeutic reserve
            1. Therapeutic reserve: difference between the dose used and the minimal dose expected
to cure an acceptable percentage of infections
      d. Rationale for stringent criteria
         1. Reduce the risk of therapeutic failure
         2. Prevent continued transmission of gonorrhea
         3. Limit development of antimicrobial resistance
      iv. Again a change in the 2005 STD guidelines allowed for alternative regimens
         a. Increasing rate of ciprofloxacin resistance
            1. Began limiting the number of active antimicrobial agents
            2. A need for alternative regimen
         b. Decreased the lower 95% CI to > 90%, a less stringent criteria
II. Threshold of Antimicrobial Resistance for Abandoning a Therapy Regimen
   A. The WHO suggested that an antimicrobial agent not be used when resistance rate is > 5%
      i. Based off in vitro susceptibility data
III. Pharmacokinetic Determinants of Penicillin Cure of Gonococcal Urethritis
     A. Study was initially conducted in 1964, data reanalyzed using "modern" techniques
     B. 47 male inmates received intraurethral inoculation of 15 x 10^19 CFU of N. gonorrhea
     C. After 2 days of urethritis subjects were divided into 6 groups to receive:
        i. Procaine penicillin G (PAM): group 1 = 0.9 x 10^6 U, group 2 = 1.2 x 10^6 U, group 3 = 2.4 x 10^6 U
        ii. Aqueous procaine penicillin G: group 4 = 1.2 x10^6 U, group 5 =2.4 x 10^6 U, group 6 = 1.0 x 10^6 U
           followed by 0.4 x 10^6 U 3 hours later
        iii. Serum penicillin concentrations were obtained at 1, 2, 4, 6, 12, 18, 24, 36, 48, and 72 h
     D. Statistical analysis
        i. Serum penicillin parameters calculated by the grafted polynomial method
        ii. Parameters were analyzed for correctly classifying cures or failures using discriminant analysis
     E. Results

Table 3: Parameters of the serum penicillin concentration curve as predictors of treatment result

<table>
<thead>
<tr>
<th>Parameter</th>
<th>R²</th>
<th>Mean of parameters for:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cures, Mean (SD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Failures, Mean (SD)</td>
</tr>
<tr>
<td>Time above 4 x MIC</td>
<td>0.85</td>
<td>6.9 h (3.8)</td>
</tr>
<tr>
<td>Peak concentration</td>
<td>0.72</td>
<td>6.2 U/mL (4.1)</td>
</tr>
<tr>
<td>Total area under curve</td>
<td>0.67</td>
<td>45.6 (20.1)</td>
</tr>
<tr>
<td>Time above MIC</td>
<td>0.53</td>
<td>30 h (21.7)</td>
</tr>
</tbody>
</table>

* standard deviations
F. Cure of gonococcal urethritis is most likely to occur when penicillin levels is 4 x MIC for 7 to 10 h

G. Discussion
   i. Strengths
      a. Direct human pharmacokinetic parameters correlating with clinical cure
      b. Used various doses, formulations, and dosing intervals of penicillin
      c. Applicable to other β-lactam antibiotics
   ii. Weaknesses
      a. Small and homogenous sample size
      b. May not be applicable to pharyngeal infection

IV. Characteristics of First Line Agent
   A. High clinical efficacy >95%
   B. Lower 95% CI ≥ 95% for uncomplicated infection at all anatomical sites
   C. Low rate of resistance <5%
   D. Preferably single dose

V. Other Cephalosporin Therapies Studied
   A. Active agents against N. gonorrhoea
   B. Did not meet first line therapy criteria treating uncomplicated gonococcal as a single dose

Table 4: Efficacy and PK parameters of other cephalosporins

<table>
<thead>
<tr>
<th>Antimicrobial agent dose and route, site of infection</th>
<th>No. evaluable patients/No. cured, % cure (95% CI)</th>
<th>Half Life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefoxitin 2 g IM SS+ MU</td>
<td>187/197, 94.9 (91.9 to 98.9)</td>
<td>0.5 – 1</td>
</tr>
<tr>
<td></td>
<td>353/366, 96.4 (94.6 to 98.3)</td>
<td></td>
</tr>
<tr>
<td>Cefotetan 1 g IM SS+ MU</td>
<td>94/98, 95.9 (89.9 to 98.9)</td>
<td>3 – 5</td>
</tr>
<tr>
<td></td>
<td>3/3, 100 (29.2 to 100)</td>
<td></td>
</tr>
<tr>
<td>Cefotaxime 1 g IM SS+ PH</td>
<td>603/609, 99 (98.2 to 99.8)</td>
<td>1 – 1.5</td>
</tr>
<tr>
<td></td>
<td>17/20, 85 (62 to 96.8)</td>
<td></td>
</tr>
<tr>
<td>Cefpodoxime 200 mg PO SS+ PH</td>
<td>274/284, 96.5 (94.3 to 98.6)</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>15/19, 78.9 (54.4 to 94)</td>
<td></td>
</tr>
<tr>
<td>Cefuroxime 1 g PO SS+ PH</td>
<td>454/469, 96.8 (95.2 to 98.4)</td>
<td>1-2</td>
</tr>
<tr>
<td></td>
<td>16/29, 55.2 (37.1 to 73.3)</td>
<td></td>
</tr>
<tr>
<td>SS = single urogenital site, PH = pharynx, MU = multiple or unspecified sites</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

VI. Third Generation Cephalosporins: Ceftriaxone
   A. Extensively studied in the 1980-1990s for the treatment gonorrhoea
      i. Ceftriaxone’s long half-life and bioavailability translates to more favorable pharmacodynamics

Table 5: Pharmacokinetic parameters of ceftriaxone

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Ceftriaxone IM10,11,12</th>
<th>Cefixime PO13,14</th>
</tr>
</thead>
<tbody>
<tr>
<td>VL, volume of distribution (L)</td>
<td>14.7 ± 4.9</td>
<td>19.0 ± 3.0</td>
</tr>
<tr>
<td>F_w, unbound fraction</td>
<td>0.05</td>
<td>0.35</td>
</tr>
<tr>
<td>F, bioavailability</td>
<td>1.0</td>
<td>0.45 ± 0.045</td>
</tr>
<tr>
<td>T_1/2, half-life (h)</td>
<td>8.45</td>
<td>3.4</td>
</tr>
</tbody>
</table>
B. Ceftriaxone 250 mg single IM injection clinical efficacy\textsuperscript{15}
   i. Cured 99.2% uncomplicated urogenital and anorectal infections (95% CI, 97.9%-99.8%)
   ii. Cured 98.9% of pharyngeal infections
C. Cefixime 400 mg orally single dose\textsuperscript{15}
   i. Cured 97.5% uncomplicated urogenital and anorectal infections (95% CI, 95.7%-98.9%)
   ii. Cured 92.3% of pharyngeal infections

**Surveillance and Susceptibility**

I. Susceptibility in the United States\textsuperscript{2}
   A. In 2010, overall 27.2% of GISP isolates were resistant to penicillin, tetracycline, ciprofloxacin, or some combination of these antibiotics
   B. Ceftriaxone
      i. 2009-2010 proportion of isolates with MICs = 0.06 µg/ml and 0.125 µg/ml did not change
      ii. 2009-2010 proportion of isolates MICs = 0.25 µg/ml increased from 0% to 0.05% (n = 3)
      iii. 2010 four reported isolates with MIC = 0.5 µg/ml, none >0.5 µg/ml

\[\text{Figure 3 and 4. Percent of GISP Isolates with elevated cefixime (MIC \geq 0.25 \mu g/ml) and ceftriaxone (MIC_\text{90} \geq 0.125 \mu g/ml), US 2006 – August 2011. Adapted from the CDC STD Surveillance 2010: National Profile.}\textsuperscript{16}\]

C. Cefixime\textsuperscript{2}
   i. Testing begin in 1992, was discontinued in 2007 and restarted in 2009
   ii. Increase in percent of isolate with MIC \geq 0.25 µg/ml reported from 2006-2009
      1. Particular among isolates in the West coast and in men who have sex with men (MSM)
      2. Increased proportion of isolates with MICs of 0.125 µg/ml (1.4% to 1.6%), 0.25 µg/ml (0.7% to 1.2%), and 0.5 µg/ml (0.1% to 0.2%)
      3. Since 2000, 20 isolates had MIC = 0.5 µg/ml, in 2010 88.9% of these isolates were from MSM

II. Significant Cephalosporin MIC Creep Around the World
   A. In the UK, 99.3% of gonococci isolates were susceptible to cefixime at \leq 0.06 µg/ml and to ceftriaxone at \leq 0.03 µg/ml\textsuperscript{19}
      i. From 2004 to 2008, isolates with cefixime MIC \geq 0.25 µg/ml increased 0% to 1.5% (p=0.002)
      ii. From 2003 to 2008, geometric means of ceftriaxone MICs rose by 33% (p<0.001)
Table 6: Cefixime MIC distributions by year

<table>
<thead>
<tr>
<th>MIC µg/ml</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.008</td>
<td>524.4</td>
<td>322.3</td>
<td>198.8</td>
<td>387.8</td>
<td>400.5</td>
</tr>
<tr>
<td>0.015-0.03</td>
<td>716.4</td>
<td>774.6</td>
<td>108.3</td>
<td>256</td>
<td>243.2</td>
</tr>
<tr>
<td>0.06-0.125</td>
<td>59</td>
<td>185.9</td>
<td>18.5</td>
<td>36.6</td>
<td>31.0</td>
</tr>
<tr>
<td>0.25</td>
<td>0</td>
<td>0</td>
<td>1.2</td>
<td>2.1</td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>2045</td>
<td>1680</td>
<td>1599</td>
<td>1309</td>
<td>1253</td>
</tr>
</tbody>
</table>

Table 7: Ceftriaxone MIC distributions by year

<table>
<thead>
<tr>
<th>MIC µg/ml</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
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<tbody>
<tr>
<td>0.008</td>
<td>87.5</td>
<td>116.3</td>
<td>116.2</td>
<td>157.3</td>
<td>146.5</td>
</tr>
<tr>
<td>0.015-0.3</td>
<td>25.8</td>
<td>98.1</td>
<td>37.3</td>
<td>181.4</td>
<td>105.4</td>
</tr>
<tr>
<td>0.06-0.125</td>
<td>0</td>
<td>11.0</td>
<td>3.7</td>
<td>7</td>
<td>11.5</td>
</tr>
<tr>
<td>0.25</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.1</td>
</tr>
<tr>
<td>Total</td>
<td>2045</td>
<td>1680</td>
<td>1599</td>
<td>1309</td>
<td>1253</td>
</tr>
</tbody>
</table>

B. Japan
i. Case reports of cefixime treatment failures at the beginning of 2000
ii. As of 2006, cefixime was no longer a first line therapy of gonorrhea
iii. 2011, the first high-level ceftriaxone-resistant gonococcal strain (H041) was isolated from the pharynx of a female commercial sex worker in Kyoto, Japan

C. France
i. 2010, high-level cefixime and ceftriaxone strain F89
ii. Isolated from a 50-year old man who had sex with men (MSM) at test-of-cure
   1. After receiving cefixime 200 mg PO for two doses 6 hours apart

III. Resistance Determinants of Multidrug Resistant (MDR) N. gonorrhoea

A. Alteration of penA gene encoding for penicillin binding protein (PBP-2): the lethal β-lactam target
   i. Decreases affinity for cephalosporin
   ii. Acquisition of a penA mosaic allele
   iii. Specifically: single amino acid alterations of A501 in PBP2

B. mtrR mutation: overexpression of the MtrC-MtrD-MtrE efflux pump

C. porB1b mutation: alteration in the PorB1b porin causing decrease intake of cephalosporin

In Search for Alternative Therapies

I. Monte Carlo Simulation: Best Pharmacodynamics Predictor Next to Prisoner

<table>
<thead>
<tr>
<th>Objective</th>
<th>Pharmacodynamic analyses to predict efficacy against N. gonorrhoea strains with raised cephalosporin MICs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>• PK/PD parameter correlating with cure: free drug concentration above MIC ($fT_{\text{MIC}}$) after various single-dose regimens were estimated&lt;br&gt;• Monte Carlo simulation for single dose of cefixime (400 mg PO), ceftriaxone (250mg IM), and ceftriaxone (1 g IM)</td>
</tr>
<tr>
<td>Results</td>
<td>• $fT_{\text{MIC}}$ values (h) for various regimens based on mean PK parameter values</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MIC mg/L</th>
<th>Cefixime</th>
<th>Ceftriaxone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>400 mg</td>
<td>2x 200 mg 6 h apart</td>
</tr>
<tr>
<td>0.015</td>
<td>29.2</td>
<td>33.1</td>
</tr>
<tr>
<td>0.03</td>
<td>25.7</td>
<td>29.5</td>
</tr>
<tr>
<td>0.06</td>
<td>22.2</td>
<td>26.1</td>
</tr>
<tr>
<td>0.125</td>
<td>18.8</td>
<td>22.6</td>
</tr>
<tr>
<td>0.25</td>
<td>15.3</td>
<td>19.0</td>
</tr>
<tr>
<td>0.5</td>
<td>11.7</td>
<td>15.2</td>
</tr>
<tr>
<td>1</td>
<td>7.8</td>
<td>7.1</td>
</tr>
<tr>
<td>2</td>
<td>1.4</td>
<td>0</td>
</tr>
</tbody>
</table>

: Dark shading <10 h above MIC, light shading 10-20 h above MIC, no shading >20 h above MIC
• For isolates with cefixime and ceftriaxone MIC < 0.06 and < 0.125, respectively the $f_{T_{>MIC}}$
  for cefixime 400 mg and ceftriaxone 250 mg were ≥ 22.2 h and ≥ 24.3 h.
• $f_{T_{>MIC}}$ became markedly shorter as the MIC increased, this was even more pronounced
  in ceftriaxone especially at the higher MIC.
• $f_{T_{>MIC}}$ values (h) for various regimens based Monte Carlo Simulation

<table>
<thead>
<tr>
<th>MIC (mg/L)</th>
<th>Cefixime 400 mg</th>
<th>Ceftriaxone 250 mg IM</th>
<th>Ceftrixone 1 g IM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Lower 95% CI</td>
<td>Median</td>
</tr>
<tr>
<td>0.015</td>
<td>28.3</td>
<td>23.6</td>
<td>49.9</td>
</tr>
<tr>
<td>0.03</td>
<td>24.9</td>
<td>20.8</td>
<td>41.4</td>
</tr>
<tr>
<td>0.06</td>
<td>21.5</td>
<td>17.9</td>
<td>32.8</td>
</tr>
<tr>
<td>0.125</td>
<td>18</td>
<td>14.9</td>
<td>24.1</td>
</tr>
<tr>
<td>0.25</td>
<td>14.5</td>
<td>11.8</td>
<td>15.4</td>
</tr>
<tr>
<td>0.5</td>
<td>10.9</td>
<td>8.3</td>
<td>6</td>
</tr>
<tr>
<td>1</td>
<td>6.8</td>
<td>3.8</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0.25</td>
<td>0.25</td>
<td>0</td>
</tr>
</tbody>
</table>

• For some patients $f_{T_{>MIC}}$ will be considerably shorter than the “average” values
  o Monte Carlo simulation may reflect a more realistic pharmacodynamic accounting
    for interpersonal variabilities
  o The greater differential between median and the lower 95% CI in ceftriaxone may
    be due to the varying elimination rate in the population

Discussion
• This study based the general clinical efficacy of β-lactams on $f_{T_{>MIC}}$ for 10 hours
• However, Jaffe et al correlated penicillin efficacy with serum levels 4 x MIC for 10 h
• Correlating with reported clinical efficacy of cefixime 2 x 200mg
  o 100% cure rate in organisms were only susceptible up to MIC 0.06
  o Efficacy may in actuality follow an $f_{T_{>MIC}}$ of 20-24h rather than 10 h
• Modifying existing antibiotic dosing regimens to overcome resistance and slow its
  accumulation and clinical practicability of altered regimens
  o Higher doses of ceftriaxone
  o Administer ceftriaxone at the clinic followed by oral cefixime for several days
  o Adopt laboratory-guided patient-individualized treatment based on susceptibility
  o Using cephalosporins with another active drug against N. gonorrhea
Clinical Efficacy of Alternative Regimens Against Decreased Susceptible Strains

I. Ceftriaxone 1g IM or IV for Gonorrhea has Already Been in Use in Asia

II. Single Dose 1 g Ceftriaxone

Objective
Evaluate the efficacy of 1 g ceftriaxone in the treatment of urethritis, cervicitis, and pharyngeal infections caused by N. gonorrhea

Background
• Report of oral third generation cephalosporin such as cefixime treatment failure in genitourinary gonococcal infections
• Attributed to a new multi-drug resistant strain, cefozopran (fourth generation cephalosporin)-resistant N. gonorrhea (CZRNG: MIC of cefozopran ≥1 mg/L)
  o Extended resistance to fluoroquinolones, tetracyclines, and macrolides
  o Mechanism of resistance to β-lactams by dynamic alterations of the PBP-2

Design
• Outpatients with uncomplicated gonorrhea either symptomatic, known gonorrhea, and urine sediment

Outcomes
• Efficacy: eradication of N. gonorrhea based on post-treatment culture results
  o Efficacy was evaluated only in patients who returned for examination and culture between 3 and 14 after treatment
• Safety assessment, antimicrobial susceptibility, and PBP-2 alteration

Results
• Baseline characteristics: 67 patients enrolled, 56 were evaluable for efficacy

<table>
<thead>
<tr>
<th>Age (yr) mean ± SD</th>
<th>Male (n=27)</th>
<th>Female (n=40)</th>
<th>Total (n=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>31.4 ± 10.8</td>
<td>26 ± 8.6</td>
<td>28.1 ± 9.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Isolated site (evaluable)</th>
<th>Urogenital</th>
<th>Pharynx</th>
<th>Simultaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male (n=20)</td>
<td>Female (n=36)</td>
<td>Eradication (%)</td>
</tr>
<tr>
<td>Urethra</td>
<td>20</td>
<td>28</td>
<td>20/20 (100)</td>
</tr>
<tr>
<td>Cervix uteri</td>
<td>28</td>
<td>28/28 (100)</td>
<td></td>
</tr>
<tr>
<td>Pharynx</td>
<td>2</td>
<td>23</td>
<td>25/25 (100)</td>
</tr>
</tbody>
</table>

• Efficacy: eradication of N. gonorrhea, according to sex and site of infection

• Antimicrobial susceptibility
  o 58 and 28 strains isolated from the urogenital and the pharynx, respectively
  o Proportion of high resistant isolates to penicillin (≥ 2 µg/mL), ciprofloxacin (≥1 µg/mL), and tetracycline (≥ 2 µg/mL) were 24%, 79%, and 61% respectively
  o Ceftriaxone and cefixime inhibited the growth of all isolates at <0.25 µg/mL

• PBP-2 alteration: susceptibility with wild type PBP-2 (WT) and chimeric PBP-2

<table>
<thead>
<tr>
<th>WT PBP-2 (n=47)</th>
<th>Chimera PBP-2 (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
</tr>
<tr>
<td>PCN</td>
<td>0.06-4</td>
</tr>
<tr>
<td>Cefixime</td>
<td>0.004-0.03</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>0.004-0.6</td>
</tr>
<tr>
<td>TET</td>
<td>0.13-4</td>
</tr>
<tr>
<td>CIP</td>
<td>0.002-64</td>
</tr>
</tbody>
</table>

#: % of susceptible isolates with MIC less than its breakpoints. PCN: penicillin, TET: tetracycline, CIP: ciprofloxacin. Breakpoints: PCN=0.06 µg/mL, cefixime=0.25 µg/mL, ceftriaxone=0.25 µg/mL, TET=0.25 µg/mL, CIP=0.06 µg/mL
All CZRNG isolates had chimera PBP-2
- The ratio of CIP high-resistant isolates with chimera PBP-2 were significantly higher than WT PBP-2 (97.4% vs. 63.8%; p<0.01)
- MIC patterns of PCN, cefixime, and ceftriaxone had poor correlation to PBP-2
- Multidrug resistant strains with chimera PBP-2 accounted for 41.9%

- No patients had adverse events after treatment

<table>
<thead>
<tr>
<th>Authors’ Conclusions</th>
<th>High dose ceftriaxone might be useful not only to eradicate <em>N. gonorrhoea</em> strains including CZRNG from the pharynx of patients with gonococci, but also to prevent emerging newer resistant mutants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discussion</td>
<td>Close to 40% of multidrug resistant strains also have the chimera PBP-2 mutation. PBP-2 mutation correlated to an increase in resistance to ciprofloxacin, but not ceftriaxone or cefixime. Ceftriaxone 1 g was effective in eradicating all gonococcal infections regardless of site of infections as well as multidrug resistant strains with chimera PBP-2 mutation. Safe to administer 1 g ceftriaxone in uncomplicated gonococcal infections</td>
</tr>
</tbody>
</table>

### III. Azithromycin 2 g Orally

<table>
<thead>
<tr>
<th>Objective</th>
<th>To compare the efficacy and tolerability of single-dose treatment of uncomplicated gonorrhea with azithromycin, 2 g orally, and ceftriaxone 250 mg IM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Prospective, multicenter, open, randomized control trial in 10 public STD clinics</td>
</tr>
<tr>
<td>Patient Population</td>
<td>Patient included: isolation of <em>N. gonorrhoea</em> at enrollment. Specimens were collected from the urethra and pharynx in men, and from the rectum if there is a history of MSM. Specimens were obtained from the cervix, urethra, rectum, and pharynx in women</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary outcome: eradication of gonorrhoea based on cultures at the first follow-up (f/u) visit (1 week between 5-9 days after treatment). Secondary endpoints: safety and tolerability assessed by open-ended and directed questions at follow-up visits (1 week and subset of second f/u visit at 2 weeks after treatment)</td>
</tr>
<tr>
<td>Methods</td>
<td>Patients were enrolled into 2:1 ratio. Patients received azithromycin 2 g orally or ceftriaxone 250 mg IM. Isolation and identification of <em>N. gonorrhoea</em> were performed by carbohydrate utilization reactions or immunochemical identification. Isolates were tested for β-lactamase by chromogenic cephalosporin methods</td>
</tr>
<tr>
<td>Statistics</td>
<td>Dichotomous outcomes were analyzed by chi-square analysis or the two-tailed Fisher exact test. Continuous variables were analyzed by Student’s t test</td>
</tr>
</tbody>
</table>
# Results

- 724 patients enrolled and randomized, 548 evaluable for efficacy
  - 176 not assessed for efficacy: 88 in whom *N. gonorrhoea* was not isolated at enrollment, 81 had no f/u, 5 received systemic antibiotic, 2 violated protocol
- Baseline characteristics were not significantly different (age, sex, race/ethnicity)
- Primary outcome: Eradication of *N. gonorrhoea*

<table>
<thead>
<tr>
<th>Sex</th>
<th>Site of infection</th>
<th>No. cured/ No. Evaluable (%)</th>
<th>Azithromycin</th>
<th>Ceftriaxone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Urethra</td>
<td>236/237 (99.6)</td>
<td>110/112 (98.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rectum</td>
<td>4/5 (80)</td>
<td>4/4 (100)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>Cervix/urethra</td>
<td>134/137 (97.8)</td>
<td>61/64 (96.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rectum</td>
<td>22/22 (100)</td>
<td>13/13 (100)</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>Pharynx</td>
<td>19/19 (100)</td>
<td>15/15 (100)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>370/374 (98.9)</td>
<td>171/175 (97.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>95% CI (%)</td>
<td>97.9-100</td>
<td>95.5-99.9</td>
<td></td>
</tr>
</tbody>
</table>

- Of the patients who returned for second f/u 100% remained culture negative in the azithromycin group vs. 99% in the ceftriaxone group
- 14.2% of patients had stains of *N. gonorrhoea* positive for β-lactamase, 13% in the azithromycin vs. 17.1% in the ceftriaxone group (p-value not significant)
- Safety and tolerability
  - Most frequently reported adverse effects were GI-related
  - 35% (95% CI 30.7-39.8%) of patients given azithromycin had ≥1 gastrointestinal symptoms vs. 2.4% of patients given ceftriaxone (P<0.001)
  - 87% of adverse effects were mild and all resolved spontaneously

# Authors' Conclusions

- Single 2 g dose of azithromycin is highly effective against uncomplicated gonorrhea
- Frequency of GI intolerance are higher than those of alternative therapies, which may limit the routine use of this regimen

# Discussion

- Appears to work for β-lactamase positive *N. gonorrhoea* strains
  - Study did not assess other mechanisms of resistance such as *mtr* gene associated with erythromycin resistance
- A different class of antibiotics that is active against *N. gonorrhoea*, which may work synergistically with cephalosporins for treatment of multidrug resistant stains

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IV. Ertapenem for MDR Gonorrhea?

A. Objective:
   - *In vitro* activity of ertapenem against *N. gonorrhoea*
   - Effects of resistance determinants on ertapenem

B. Methods:
   - Total of 257 clinical strains from (Australia and Sydney)
   - Two strains of clinical high-level resistance to all extended spectrum cephalosporins (ESC)
     - H041 from Japan (cefixime MIC = 8 µg/mL, ceftriaxone MIC = 2 µg/mL)
     - F89 from France (cefixime MIC = 4 µg/mL, ceftriaxone MIC = 1 µg/mL)

C. Results:
   - In general, MICs of ertapenem and ceftriaxone were similar
     - Ertapenem MIC$_{50}$ = 0.032 µg/mL and MIC$_{90}$ = 0.064 µg/mL
     - Ceftriaxone MIC$_{50}$ = 0.032 µg/mL and MIC$_{90}$ = 0.125 µg/mL
Table 8: Corresponding ertapenem MICs to specific high cefixime and ceftriaxone MICs strains

<table>
<thead>
<tr>
<th>Strain Type</th>
<th>Cefixime MIC (µg/mL)</th>
<th>Ceftriaxone MIC (µg/mL)</th>
<th>Ertapenem MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone Resistant (n=4)</td>
<td>–</td>
<td>0.5 to 4</td>
<td>0.016 to 0.064</td>
</tr>
<tr>
<td>H041 Strain</td>
<td>8</td>
<td>2</td>
<td>0.064</td>
</tr>
<tr>
<td>F89 Strain</td>
<td>4</td>
<td>1</td>
<td>0.016</td>
</tr>
<tr>
<td>Cefixime treatment failure (n=3)</td>
<td>0.25-1</td>
<td>0.125 to 0.5</td>
<td>0.064 to 0.125</td>
</tr>
<tr>
<td>Ceftriaxone treatment failure (n=1)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ii. Prevalence of resistance determinants (n=257)
   a. 249 (91%) porB1b, 242 (88%) mtrR, 101 (37%) penA mosaic allele, and 71 (25.9%) alteration of A501 in PBP2

iii. Resistance determinants and ertapenem MICs
   a. Presence of a penA mosaic allele was associated with increase in MICs
   b. Isolates with penA mosaic allele, mtrR, and porB1b had the highest ertapenem MIC

D. Discussion
   i. Ertapenem had no apparent in vitro advantage for low ceftriaxone MIC isolates
   ii. For all isolates with resistance to ceftriaxone (MIC 0.5 to 4 µg/mL), ertapenem MICs were low (0.016 to 0.064 µg/mL)
   iii. Further research regarding the effects of different penA mosaic alleles and other penA alterations and its implications to ceftriaxone and ertapenem susceptibility is warranted

Conclusion

I. Increasing Resistance Against Third Generation Cephalosporins Worldwide
II. Limitations to Treatment and Barriers to Disease Management
   A. Lack of new antimicrobials in the development
   B. Culture and susceptibility testing not routinely done
      i. No current standard protocol in most clinical laboratories
      ii. Slow turn-around time for diagnosis
III. Alternative Therapies
   A. Modifying dosing regimen of existing antibiotics
      i. Increase dose or frequency of doses
   B. Using combination antibiotic classes for synergy against multidrug resistant strains
   C. Other potential active agents
      i. Corresponding ertapenem MICs were low for ceftriaxone resistant strains
      ii. However, there is no clinical data at this point in time
IV. Case and Recommendations
   A. RH is a 20 y/o male who recently traveled to Japan and received ceftriaxone 250 mg IM single dose for uncomplicated gonorrhea. He returns to clinic with persistent urethritis and repeatedly denies having had sexual contact between the time he was treated to this clinic visit
      i. Administer ceftriaxone 1 g IM single dose and azithromycin 2 g PO single dose
      ii. Obtain fluid sample for culture and susceptibility
      iii. Have RH return to clinic within one week for test-of-cure
      iv. Consider patient delivered partner treatment
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23 Tapall JW. Implications of current recommendations for third-generation cephalosporin use in the WHO Western Pacific Region following the emergence of multiresistant gonococci. Sex Transm Infect. 2009; 85:256-258.

24 Muratani T, Inatomi H, Ando Y et al. Single dose 1 g ceftriaxone for urogenital and pharyngeal infection caused by \textit{Neisseria gonorrhoea}.


