THE GROWING THREAT OF MULTIDRUG-RESISTANT GONORRHEA

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Molecular Basis of *N. gonorrhoeae* Resistance to Antimicrobials

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New Tools to Combat Multidrug Resistance

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What Public Health Can Do Now and in the Future
Neisseria gonorrhoeae Infections and the Emergence of Antimicrobial Resistance

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Disclosure

- Receive grant support for clinical trials from Cepheid, Becton Dickinson, Roche Molecular GenProbe, and Cempra Pharmaceuticals
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Outline

- *N. gonorrhoeae* (gonococcus) infections
- Evolution of antimicrobial treatment
- Surveillance for antimicrobial resistance
- Current treatment recommendations
- The emerging threat of cephalosporin-resistant *N. gonorrhoeae*
Burden of Gonococcal Disease in the United States

- >300,000 cases reported in 2010
  - Approximately 50% underestimation
- The spectrum of gonococcal infections
  - Uncomplicated local disease (urethrititis/cervicitis)
  - Complications disproportionately impact women
Complications of Untreated Gonorrhea

- Pelvic inflammatory disease (PID) leads to scarring and:
  - Infertility
  - Ectopic pregnancy
  - Chronic abdominal pain

- Disseminated gonococcal infection
- Childhood blindness (neonatal infection)
- Increased risk for HIV transmission and acquisition
Gonorrhea Case Report Rates
United States, 1941–2010

Gonorrhea Case Report Rates by County, 2010

Rate per 100,000 population

- ≤19.0 (n = 1,408)
- 19.1–100.0 (n = 1,107)
- >100.0 (n = 627)

Gonorrhea Case Report Rates by Race/Ethnicity, 2001–2010

Treatments for Gonorrhea Before 1937 Were Ineffective and/or Toxic
Sulfonamides and Penicillin for Treatment of Gonorrhea

- **1937**: Sulfonamide therapy introduced
- **1940s**: Penicillin proved effective
  - Sulfonamide resistance in 34% of patients
- **1972**: Penicillin dosage increased; probenicid added
- **1989**: Penicillin no longer drug of choice
Antimicrobials Previously Recommended for Treatment of Gonorrhea

- Sulfonamides
- Penicillin
- Macrolides
- Tetracyclines
- Aminoglycosides
- Spectinomycin
- Fluoroquinolones
The Gonococcal Isolate Surveillance Project (GISP)

- CDC-supported U.S. sentinel surveillance since 1987
- Monitors trends in *N. gonorrhoeae* susceptibility to antimicrobials
- 30 STD clinic sites

**Methods**

- Urethral *N. gonorrhoeae* isolates obtained from the first 25 men per site each month
- Susceptibility testing conducted by 5 regional laboratories
  - Minimum inhibitory concentrations (MICs) by agar dilution
- Confirmatory testing by CDC
GISP, Gonococcal Isolate Surveillance Project
Antimicrobial Options for Treatment of Gonorrhea in 2006

ONE OF THE FOLLOWING

- Ceftriaxone 125 mg IM
- Cefixime 400 mg PO
- Ciprofloxacin 500 mg PO*
- Ofloxacin 400 mg PO*
- Levofloxacin 250 mg PO*

AND

Azithromycin 1 g single dose or doxycycline 100 mg twice a day for 7 days if chlamydial infection is not ruled out

* Not for MSM or travelers

CDC. Sexually Transmitted Disease Treatment Guidelines, 2006. MMWR 2006; Volume 55 (RR-11)
IM, intramuscularly
PO, by mouth
MSM, men who have sex with men

GISP, Gonococcal Isolate Surveillance Project, 1990–2008
Resistant isolates have ciprofloxacin MICs ≥1 μg/ml. Isolates with intermediate resistance have ciprofloxacin MICs of 0.125 - 0.5 μg/ml
Susceptibility to ciprofloxacin was first measured in GISP in 1990

GISP, Gonococcal Isolate Surveillance Project, 1990–2007
Resistant isolates have ciprofloxacin MICs ≥1 µg/ml
Ciprofloxacin Resistance in *N. gonorrhoeae*, by Sex of Sex Partner, United States, 1999-2007

- **MSM**: men who have sex with men
- **MSW**: men who have sex exclusively with women

GISP, Gonococcal Isolate Surveillance Project, 1990–2007
Resistant isolates have ciprofloxacin MICs ≥1 µg/ml
MSM, men who have sex with men
MSW, men who have sex exclusively with women
Changes in Gonorrhea Treatment, 2007

ONE OF THE FOLLOWING

- Ceftriaxone 125 mg IM
- Cefixime 400 mg PO
- Ciprofloxacin 500 mg PO*
- Ofloxacin 400 mg PO*
- Levofloxacin 250 mg PO*

AND

Azithromycin 1 g single dose or doxycycline 100 mg twice a day for 7 days

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CDC. Sexually Transmitted Disease Treatment Guidelines, 2006. MMWR 2006; Volume 55 (RR-11)
IM, intramuscularly
PO, by mouth
MSM, men who have sex with men
Antimicrobial Options for Treatment of Gonorrhea, 2010

Ceftriaxone 250 mg IM

OR

Cefixime 400 mg PO

AND

Azithromycin 1 g single dose

OR

Doxycycline 100 mg twice daily for 7 days

CDC. Sexually Transmitted Disease Treatment Guidelines, 2010. MMWR 2010; Volume 59 (RR-12)
IM, intramuscularly
PO, by mouth
Elevated Cefixime and Ceftriaxone MICs in *N. gonorrhoeae*

- Elevated cefixime MICs ≥ 0.25 μg/ml
- Elevated ceftriaxone MICs ≥ 0.125 g/ml

GISP, Gonococcal Isolate Surveillance Project

* Cefixime susceptibility not tested in 2007 and 2008

**Prevalence, %**

Year

- 2006
- 2007
- 2008
- 2009
- 2010
- 2011*

MIC, minimum inhibitory concentration
Percentage of Gonococcal Isolates with Elevated Cefixime MICs (≥0.25 µg/ml), 2005–2011*

MSM, men who have sex with men; MSW = men who have sex exclusively with women
MIC, minimum inhibitory concentration
Possible Changes in Treatment Recommendations

- **Recommended**
  - Ceftriaxone 250 mg PLUS
  - Azithromycin 1 g single dose or doxycycline 100 mg twice a day for 7 days

- **Oral therapy as alternative** ("second-line")
Molecular Basis of *N. gonorrhoeae* Resistance to Antimicrobials

William Shafer, PhD  
*Professor of Microbiology and Immunology*  
Emory University  
Atlanta, Georgia
Outline

- Resistance mechanisms expressed by the gonococcus
- Culture-based antimicrobial susceptibility testing
- Detection of antimicrobial resistance markers using molecular assays
Genetic Basis of Antimicrobial Resistance of the Gonococcus

- The gonococcus mutates rapidly
- Resistance results from mutations and acquisition of new genes
- Resistance is promoted by selection pressure
  - Antimicrobials kill susceptible strains, but allow resistant strains to survive
  - Resistance genes then spread to other strains of the gonococcus
Resistance of Gonococci to Penicillin and Ciprofloxacin

- Importance of mechanisms by which the gonococcus developed resistance to penicillin and ciprofloxacin
  - Persistence of resistance genes
  - Some of the same systems are making the gonococcus less susceptible to ceftriaxone and cefixime, which are the main antimicrobials used to cure gonorrhea today
Genetic Basis of Penicillin Resistance

- **Low level resistance is the result of multiple mutations that**
  - Reduce penicillin influx (entry into the bacterial cell)
  - Increase penicillin efflux (exit from the bacterial cell)
  - Reduce ability of penicillin to bind to enzymes that synthesize the cell wall (penicillin binding proteins 1 and 2: PBP 1 and PBP 2)

- **High level resistance identified in 1976**
  - Acquisition of gene that encodes beta lactamase (enzyme that destroys penicillin)

By 1987, penicillin was discontinued
Genetic Basis of Ciprofloxacin Resistance

- Ciprofloxacin binds to bacterial enzymes involved in maintaining DNA structures necessary for viability of gonococcus
  - The genes that code for these enzymes are called gyrA and parC
- Early 1990s: Resistance developed first by a mutation in gyrA and then parC
- Intermediate resistance: Mutation in gyrA
- High level resistance: Mutations in gyrA and parC

By 2007, ciprofloxacin was no longer recommended for treatment of gonorrhea
Emergence of Resistance to Cephalosporins

- **1980s:** Cephalosporins (ceftriaxone and cefixime) were found to kill gonococci by a mechanism similar to that of penicillin
- **2007:** Cephalosporins became the antimicrobials of choice for empiric treatment of gonorrhea
- **2009:** Gonococcus began showing reduced susceptibility to cephalosporins due to 2 mutations
  - Acquired a new *penA* gene that encodes PBP-2 from other bacteria
    - Remodeled PBP-2 has a lower affinity for penicillin and cephalosporins
  - Overproduction of an efflux pump that exports antimicrobials, including penicillin and ceftriaxone

PBP, penicillin binding protein
The Importance of the \textit{mtrCDE} Efflux Pump

- Removes hydrophobic molecules from bacterial cell
- Needed for sustained lower genital infection in mice
- Confers bacterial protection against host innate immunity system that consists of antimicrobial peptides and other compounds that bathe mucosal surfaces

Enhanced pump gene expression contributes to penicillin resistance, decreased ceftriaxone susceptibility, and resistance to innate host defenses

Shafer WM et al. PNAS 1998;95(4):1829-33  
Increased Expression of the MtrCDE Efflux Pump and Decreased Antibiotic Susceptibility

- Mutations in genes that normally repress pump genes
- High level resistance to antimicrobials
  - Single nucleotide change near the promoter responsible for pump gene expression
  - Detected in clinical gonococcus isolates with decreased susceptibility to ceftriaxone
Genetic Basis for Persistence of Antimicrobial Resistance in the Gonococcus

- Resistance persists even after antimicrobial is no longer used for treatment of gonorrhea

- **Hypothesis**
  - Resistance mutation provides “fitness advantage” even without selection pressure

Conducted experiments with infected female mice to study survival and fitness of gonococci that overexpress the pump or are resistant to ciprofloxacin*

*Collaboration with Dr. A Jerse, Uniformed Services University of the Health Sciences
Antimicrobial Resistance Systems Can Increase Fitness During Infection

- Overexpression of the efflux pump
  - Increased fitness: Competitive Index (CI) of 100-1000

- Mutation in *gyrA*: Intermediate resistance to ciprofloxacin
  - Increased fitness: CI of 50

- Mutations in both *gyrA* and *parC*: High level ciprofloxacin resistance
  - Slightly decreased fitness: CI of 0.5

- Mutation that results in overexpression of the efflux pump and mutations in *gyrA* and *parC*:
  - Increased fitness: CI of 50
Implications of Survival Advantage of Resistant Gonococcus Strains

- Mutations conferring resistance can actually improve survival of bacteria, even without antimicrobial use
- Resistance mutations can persist among bacteria
- Previously recommended antimicrobials cannot be reintroduced for routine use
Antimicrobial Susceptibility Testing

- Laboratory testing to detect whether antimicrobials can kill a certain strain and at what antimicrobial concentration
  - Disk diffusion, Etest, Agar dilution
- Requires culturing live organisms
  - The gonococcus is fragile and difficult to grow
- Critical for detection and monitoring of resistance

If a patient fails cephalosporin therapy, culture and antimicrobial susceptibility testing should be done so appropriate antimicrobial therapy can be instituted
Gonococcus Antimicrobial Susceptibility Testing

Dicker et al. STD 2004;31(5):259-264
Dicker et al. STD 2007; 34(1):41-46
Molecular Assays for Detection of Resistance Markers in Gonococci

- **For clinical diagnosis of gonorrhea**
  - Nucleic Acid Amplification Tests (NAATS) have largely replaced culture
  - Highly sensitive, convenient, and noninvasive

- **For detection of known resistance mutations**
  - Not yet available, but scientists are working to develop them
Summary

- The gonococcus mutates rapidly
  - Can acquire resistance genes from other bacteria
  - Genetic changes can spread among strains of the gonococcus

- Resistance mutations can persist even when the antimicrobials are no longer routinely prescribed

- Declining laboratory capacity to culture gonococci hinder detection and response to cephalosporin resistance and other antimicrobials used in the future

- Molecular tests can help in surveillance, but cannot now replace culture-based testing for resistance
New Tools to Combat Multidrug Resistance

Carolyn Deal, PhD
Chief, Sexually Transmitted Diseases Branch
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Development of Antimicrobial Resistance

Selective pressure by use of antimicrobial drugs
- Overprescribing by physicians
- Use of broad-spectrum vs. narrow-spectrum drugs
- Noncompliance by patients
- Over-the-counter availability

Source: AS Fauci, NIAID Director
Resistant Bacteria: Here and Abroad

- **Hospital pathogens**
  - Vancomycin-Resistant Enterococci (VRE)
  - Methicillin-resistant *Staphylococcus aureus* (MRSA)
  - ESBL-producing *Enterobacteriaceae* (*E. coli, Klebsiella, Enterobacter*)
  - *Acinetobacter baumanii*
  - *Pseudomonas aeruginosa*
  - *Clostridium difficile*

- **Respiratory pathogens**
  - *Streptococcus pneumoniae*, MDR/XDR TB

- **Sexually transmitted pathogens**
  - *Neisseria gonorrhoeae*

Elemam, et al.. CID 2009; 49; 271-4.; Hidron AI et al. Infectin Control and Hospital Epidemiology. 2008; 29(11)996-1011
Tapsall J. Expert Review of Anti-infective Therapy. 2006; 4(4) 619
National Institute of Allergy and Infectious Diseases Research Agenda

Promotion of Rational Use of Antimicrobials

Surveillance

Strategies to Address Antimicrobial Resistance

Infection Control

Biomedical Research

Peters, NK; et al. J Infect Dis. 2008 Apr 15; 197(8): 1087-93
Strategy: Biomedical Research

NIH Antimicrobial Research

- Microbial Pathogenesis
- Research Resources
- Mechanisms of Resistance
- Immunology
- Diagnosis & Rapid Detection
- Drugs & Novel Therapeutics
- Vaccines & Preventive Strategies
- Genetics & Genomics
- Biochemistry

Source: AS Fauci, NIAID Director
NIAID Sponsored Gonococcal Research

- Current support for 137 research grants on gonorrhea
- **Basic research**
  - Bacterial pathogenesis
  - Molecular basis of antigenic variation
  - Immunologic response to infection
- **Translational research**
  - Identifying vaccine candidates
  - Development of new diagnostics
  - Identifying targets for antimicrobial development
Identifying vaccine candidates
- Cell surface components
- Lipooligosaccharides
- Peptides

Development of new diagnostics
- Markers specific for the gonococci
- Reducing the size and cost of instrumentation
- Increasing the sensitivity and specificity of tests

Identifying targets for antimicrobial development
- Inhibition of Lipid A biosynthesis, protein synthesis, and DNA replication
Clinical Research Example

- Clinical trial to evaluate efficacy
  - Regimen 1: Gentamicin and azithromycin
  - Regimen 2: Gemifloxacin and azithromycin
- Outcome: Treatment of uncomplicated urogenital gonorrhea
- Principal Investigator: Robert D. Kirkcaldy, CDC
NIAID Antibacterial Development
Exploiting Old and Exploring New Targets

Peptidoglycan synthesis

Modification of membrane lipids

Inner membrane

Periplasm

Outer membrane protein

Anti-cell wall MAbs

Signal pathways

Biosynthetic pathways

DNA replication

Transcription

Protein synthesis

Ribosomes

Efflux pump

b-Lactamases
Antimicrobial Pipeline

- Basic Research
- Target Identification and Preclinical Development
- Clinical Evaluation
- Safety Evaluation
- Manufacturing and post-licensure evaluation

Variable ~ 6 Years ~ 9 Years

Antimicrobial Pipeline

Total cost: $3.7B to $11.8B per new drug

Total time: 15 or more years

Biomedical Research: Diagnostics

- **Next generation diagnostics**
  - Miniaturization of devices by incorporating new technology
  - Identification of the pathogen in a point-of-care setting

- **New ways to look at the use of diagnostics**
  - Identification of antibiotic resistance markers in the clinical sample
  - Use this knowledge to guide treatment
Prevention of Infection by Vaccines or Microbicides

- **Challenges to development of vaccines or antimicrobials**
  - Antigenic variation of bacterial surface components
  - Gonococci can induce antibodies that block the binding of effective antibodies
  - It is unclear what immunological response is protective

- **Candidates that give optimism for the future**
  - Major outer membrane proteins
  - Transferrin (iron) binding proteins
  - Peptide mimics of lipo-oligosaccharide (LOS) antigens
  - Compounds that inhibit attachment to cervical/vaginal cells
A Delicate Balance

Extraordinary capability of microbial pathogens to persist and develop resistance

Public health measures, biomedical research, development of new antimicrobials

Source: AS Fauci, NIAID Director
Gonococci are one of many organisms with emerging resistance to antimicrobials

Biomedical research
- Increases our understanding of the mechanisms of bacterial pathogenesis
- Identifies prospects for antimicrobials, vaccines, and microbicides

Challenges of time scale and economics

Grounds for optimism include promising vaccine and microbicide candidates
What Public Health Can Do Now and in the Future

Robert D. Kirkcaldy, MD, MPH
Medical Epidemiologist
Division of STD Prevention
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention
Everyone Can Contribute to the Response

- **Public Health**
  - CDC
  - US Government partners
  - Health departments

- **Clinicians**

- **Laboratories**

- **Sexually active adolescents and adults**
What CDC Can Do Now

- Continue to closely monitor resistance trends
  - Use of and investment in GISP
- Update treatment guidelines based on best available data
- Support local surveillance and laboratory capacity
  - Training and education
  - Reference testing
  - National response plan
- Study genetic basis for resistance
What CDC Can Do Now

- Enhance international collaboration and surveillance of multidrug-resistant gonococci
- Provide scientific basis for need for culture capacity and development of new antimicrobials
What U.S. Government Partners Can Do Now

- Study effectiveness of available antimicrobials
- Support antimicrobial and vaccine development and approval - new antimicrobials are urgently needed
What Local and State Health Departments Can Do Now

- Strengthen local gonorrhea control efforts
- Enhance surveillance for resistant gonococci
- Ensure persons diagnosed with gonorrhea and their partners are treated appropriately
- Remain vigilant for treatment failures
- Promote access to culture and antimicrobial susceptibility testing
What Clinicians Can Do Now

- **Screen**
  - Sexually active women at increased risk
    - Under 25, prior gonococcal infection, other STDs, new or multiple partners, inconsistent condom use, sex work, or drug use
  - Sexually active MSM at all exposed anatomic sites at least annually


CDC. Sexually Transmitted Diseases Treatment Guidelines, 2010

MSM, men who have sex with men
What Clinicians Can Do Now

**Screen**
- Sexually active women at increased risk
- Sexually active MSM at all exposed anatomic sites annually

**Treat**
- With ceftriaxone 250 mg AND azithromycin 1 g OR doxycycline 100 mg twice daily for a week
- Patient’s partners from prior 2 months

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CDC. Sexually Transmitted Diseases Treatment Guidelines, 2010
## What Clinicians Can Do Now

| Screen | - sexually active women at increased risk  
| Treat  | - sexually active MSM at all exposed anatomic sites annually  
| Report | - with ceftriaxone 250 mg AND azithromycin 1 g OR doxycycline 100 mg twice daily for a week  
|        | - patient’s partners from prior 2 months  
|        | - suspected treatment failures to local or state health department and CDC |
What Laboratories Can Do Now

- Maintain capacity to culture for gonococcus
- Promptly inform clinician and health department of elevated cephalosporin MICs
- Store isolates with elevated cephalosporin MICs or from unsuccessfully treated patients

MIC, minimum inhibitory concentration
What Sexually Active Adolescents and Adults Can Do Now

- Abstain from sex
- Commit to safer sex
  - Monogamy with uninfected partner
  - Consistent and correct condom use
- Seek medical care for symptoms
- If infected, notify all your partners
- Notify your health care provider if symptoms do not resolve
The Growing Threat of Multidrug-Resistant Gonorrhea: Summary

- Gonorrhea is a major preventable cause of infertility
- Gonococcal antimicrobial resistance threatens treatment and prevention of gonorrhoea
- Continued surveillance for gonococcal resistance is vital
- Action is needed by public health officials, clinicians, laboratories, and those at risk
  - Clinicians urged to treat with ceftriaxone and either azithromycin or doxycycline
- New treatment options are urgently needed