Drug-Resistant Gonorrhea: Epidemiology, Management, and Future Treatment



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Financial Relationships With Ineligible Companies (Formerly Described as Commercial Interests by the ACCME) Within the Last 2 Years

Dr Adamson reported no relevant financial relationships with ineligible companies. (Updated April 30, 2025)

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Learning Objectives

After attending this presentation, learners will be able to:

- Identify current recommended and alternative treatment options for gonococcal infections
- Explain principles and clinical application of resistance-guided therapy for gonorrhea
- List factors that make pharyngeal infections more difficult to eradicate
- Describe scenarios in which a cephalosporin treatment failure should be suspected
- List 2 future treatments for gonorrhea

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Case

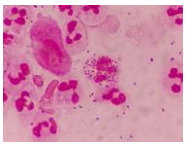
- A 42-year-old heterosexual male presents to the clinic with 4-day history of urethral discharge and dysuria
- Three days prior to symptoms, he reports having sexual intercourse with a female
- He recently returned from Thailand, where he reported having sexual intercourse with a female

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Case: Exam, Lab Results, and Treatment

- Exam: purulent urethral discharge
- Smear showing 3+ inflammatory cells and Gram-negative diplococci
- Treatment:
  - ceftriaxone 1g IM once
  - doxycycline 100mg BID for 7 days
- Urine positive for *N. gonorrhoeae* by NAAT
- Urethral culture grew *N. gonorrhoeae*
- Antibiotic susceptibility testing was performed…



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Case: Antibiotic susceptibility testing

Antibiotic	Minimum inhibitory concentration (MIC)	Interpretation
Penicillin	1 mg/L	Intermediate susceptible
Ciprofloxacin	> 32 mg/L	Resistant
Tetracycline	32 mg/L	Resistant
Azithromycin	> 256 mg/L	High-level resistant
Ceftriaxone	0.5 mg/L	Resistant
Cefixime	2 mg/L	Resistant
Spectinomycin	8 mg/L	Susceptible

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Case: Follow-up

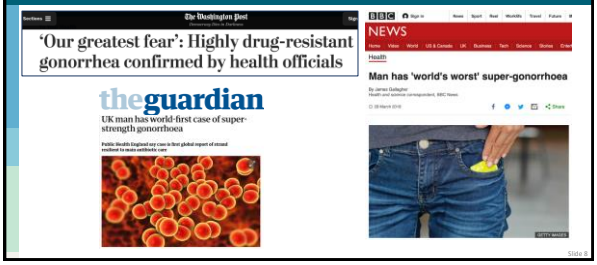
- Day 13: recalled to clinic, symptoms resolved, received spectinomycin 2g IM, urine NG NAAT (-)
- Day 33: Pharyngeal swab culture positive for NG, same antibiotic susceptibility profile
  - Denied sexual contact after treatment
  - Received ertapenem 1g IV for 3 days
- Day 54: NAAT and culture of urethral and pharyngeal swabs were negative
  - Unable to contact Thai partner

Eyre et al. Eurosurveillance, 2018

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The Clap Heard 'Round the World



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Drug-resistant *N. gonorrhoeae* is a global health threat

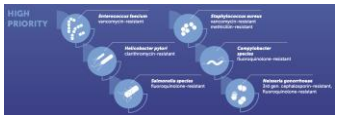
CDC

Threat Level: URGENT



World Health Organization

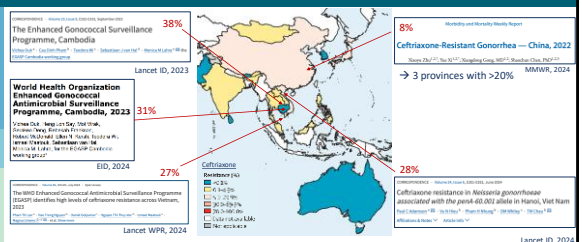
High Priority Pathogen List



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Ceftriaxone is under threat in Asia Pacific



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Ceftriaxone-resistant strains in Europe



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Multi-drug resistant gonorrhea in the US



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Massachusetts MDR case

Novel strain of multidrug non-susceptible *Neisseria gonorrhoeae* in the USA

Jennifer L Reimche ✉ • Cau D Pham • Sandeep J Joseph • Shelby Hutton • John C Cartee • Yuheng Ruan • et al.

Show all authors

- August 2022: heterosexual male, presented to primary care with urethral discharge
- Urine culture performed, grew NG
- Resistance to ceftriaxone, cefixime, and azithromycin
- Cured with ceftriaxone 500mg IM x 1
- Retrospective analysis identified one additional NG case with resistance

Reimche et al, Lancet ID, 2024

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How did we get here?

How it started



CDC 1944

How it's going

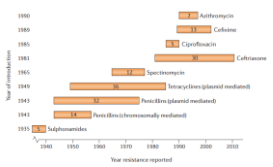


CDC 2023

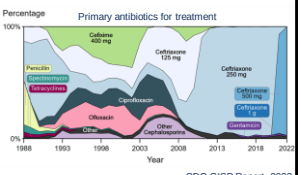
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Antibiotics used for gonorrhea



Goire et al, Nat Rev Micro, 2014

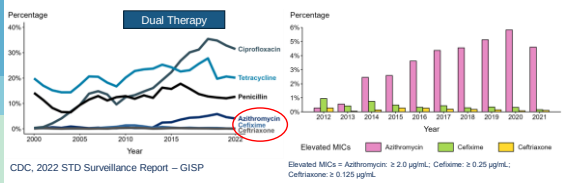


CDC GISP Report, 2022

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AMR increasing in *N. gonorrhoeae* in US



CDC, 2022 STD Surveillance Report – GISP

Elevated MICs = Azithromycin: ≥ 2.0 µg/mL; Cefixime: ≥ 0.25 µg/mL; Ceftriaxone: ≥ 0.125 µg/mL

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CDC Treatment Guidelines

Uncomplicated Gonococcal Infection – urethral, cervical, rectal

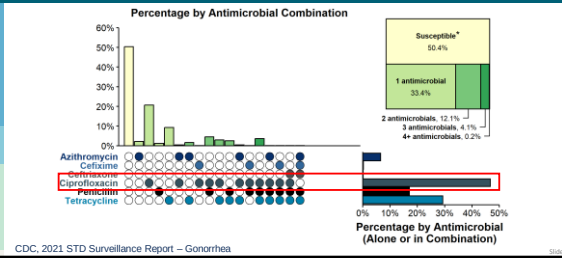
- Ceftriaxone 500 mg intramuscular once for persons weighing <150 kg
- Alternatives:
  - Cefixime 800mg PO once
  - Gentamicin 240 mg IM once PLUS Azithromycin 2 g PO once
- If chlamydia has not been excluded: doxycycline 100 mg PO BID x 7 days
- Partner treatment
- Retesting at 3 months

CDC STI Treatment Guidelines, 2021

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Half of *N. gonorrhoeae* are susceptible

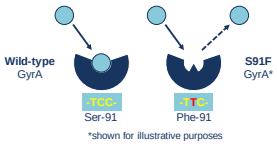


CDC, 2021 STD Surveillance Report – Gonorrhea

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Ciprofloxacin resistance and Gyrase A



*shown for illustrative purposes

Wild-type gyrA associated with susceptibility to ciprofloxacin

- 98.2% sensitive
- 98.6% specific[1]

[1]Allan-Blitz, *STD*, 2017

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Ciprofloxacin for the treatment of gonorrhea

- Multi-site, prospective trial, 2016-2018
- Used gyrA PCR test (Ser-91) to evaluate the efficacy of ciprofloxacin 500mg PO once to treat *N. gonorrhoeae*
- Follow-up microbiological cure 5-10 days post-treatment
- Enrolled 211 participants through gyrA testing and culturing prior to treatment

[1]Klausner, JD et al., CID, 2020

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Ciprofloxacin for the treatment of gonorrhea

Study Population and Statistics	Cervical/Urethral	Rectal	Pharyngeal	All Anatomic Sites
Intent-to-treat[a]				
Number of infections with microbiological cure, n	38	81	35	154
Number of infections, n	39	89	40	168
Microbiological cure, %	974	91	875	917
95% CI, %	90.4–100.0	85.0–100.0	77.0–100.0	87.6–100.0
Microbiological intent-to-treat[b]				
Number of infections with microbiological cure, n	33	74	14	121
Number of infections, n	34	79	16	129
Microbiological cure, %	971	93.7	875	93.8
95% CI, %	89.1–100.0	88.0–100.0	69.5–100.0	89.6–100.0
Per-protocol[c]				
Number of infections with microbiological cure, n	30	73	14	117
Number of infections, n	30	73	14	117
Microbiological cure, %	100	100	100	100
95% CI, %	90.5–100.0	96.0–100.0	80.7–100.0	97.5–100.0

[1]Klausner, JD et al., CID, 2020

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Resistance-guided therapy for gonorrhea



- Use for other pathogens and antibiotics
  - *S. aureus* – methicillin, vancomycin
  - Gram negatives - extended-spectrum beta lactamases, carbapenemases
  - *M. tuberculosis*

- Gonorrhea typically diagnosed by NAATs
- Allows for oral treatment option and cost-saving
- Potentially conserve last-line therapy

Allan-Blitz et al, CID 2022

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Guidelines for treating gonorrhea with ciprofloxacin

- Permissive use of ciprofloxacin in the US, United Kingdom, and Australia

2021 CDC Treatment Guidelines:
"If a patient is asymptomatic and the treating facility is able to perform gyrase A (gyrA) testing to identify ciprofloxacin susceptibility (wild type), oral ciprofloxacin 500 mg in a single dose can be administered."

- Commercial assays are available in some regions
  - Allows for simultaneous detection of NG + gyrA

- Laboratory developed tests in the US
  - Reflex testing, takes ~1 day to result
  - No FDA cleared assay



SpeeDx

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CDC Treatment Guidelines

Uncomplicated Gonococcal Infection – pharynx

- Ceftriaxone 500 mg intramuscular once for persons weighing <150 kg
  - 1g for persons weighing >150 kg
- No alternative treatments
- **Test-of-cure: 7–14 days after initial treatment using either culture or NAAT**

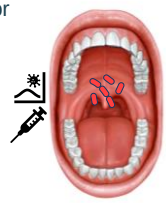
CDC STI Treatment Guidelines, 2021

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Pharyngeal Infections

- Harder to eradicate than urogenital or rectal infections
- Presence of commensal *Neisseria* species in the mouth can be a reservoir for resistance
- Poor penetration of antibiotics into the site
- Common site of reported treatment failures



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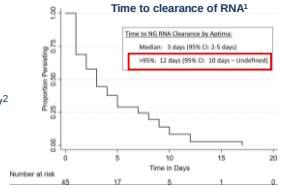
Test of Cure

Purpose: to identify asymptomatic persistent infections, identify resistant infections, and reduce transmission

Challenges:

- Getting people to return for TOC
  - <50% return for TOC when recommended
- Timing of TOC
- Positive tests – 5-10% in CDC study[2]
  - Remnant DNA – ~33%[2]
  - Re-infection - ~33%[2]
  - Treatment failure – 15%[2] (no cephalosporin resistance)

Time to clearance of RNA[1]



[1] Barbee et al, JCM, 2022; [2]Quilter et al, STD, 2025

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Cephalosporin treatment failure

- **Definition:** persistence of *N. gonorrhoeae* infection despite cephalosporin treatment
- **When to suspect:**
  - If symptoms persist despite treatment → rule-out/treat other infections
  - No ongoing sexual contact
  - Positive NAAT 7-10 days* after treatment without sexual contact
  - Culture positive at test-of cure

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Suspected Treatment Failure

- Confirm history (sexual, travel, treatment, etc)
- Obtain swabs (urethral, rectal, pharyngeal) for NAAT and gonococcal culture + AST ← IMPORTANT!
- CDC Treatment Guidelines:
  - Ceftriaxone 500mg IM once (repeat or if initially treated with alternative regimen)
  - Single dose gentamicin 240mg IM plus azithromycin 2g orally

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The New York Times

A Federal Lab That Tracked Rising S.T.I.s Has Been Shuttered

The United States can no longer keep tabs on drug-resistant gonorrhea, among other infections, scientists said.



NY Times, April 4, 2025

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Suspected Treatment Failure

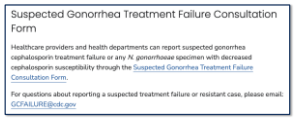
- Send cultures for antibiotic susceptibility testing
  - Quest and LabCorp can perform Etest method
  - County/State Public Health labs
- National Network of STD Clinical Prevention Training Center clinical consultation line (https://www.stdccn.org/render/Public)
- Report to public health department/CDC

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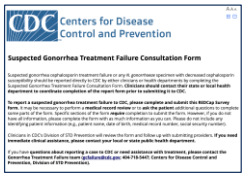
Suspected Treatment Failure

CDC Gonorrhea Treatment Failure Consultation Form


Suspected Gonorrhea Treatment Failure Consultation Form

Healthcare providers and health departments can report suspected gonorrhea cephalosporin treatment failure or any *N. gonorrhoeae* specimen with decreased cephalosporin susceptibility through the Suspected Gonorrhea Treatment Failure Consultation Form.

For questions about reporting a suspected treatment failure or resistant case, please email: GCFAILURE@cdc.gov


CDC Centers for Disease Control and Prevention

Suspected Gonorrhea Treatment Failure Consultation Form

https://airc.cdc.gov/surveys/?s=JACPEYPPAJ3T779W

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New Treatments - Gepotidacin

Hot Off The Press

Oral gepotidacin for the treatment of uncomplicated urogenital gonorrhoea (EAGLE-1): a phase 3 randomised, open-label, non-inferiority, multicentre study

Jonathan D C Ross, Janet Wilson, Kimberly A Workowski, Stephanie N Taylor, David A Lewis, Sally Gatsi, William Flight, Nicole E Scangarello-Oman, Charles Jakielaszek, Dan Lythgoe, Marcy Powell, Salim Janmohamed, Judith Alisalon, Caroline Perry

Lancet, April 2025

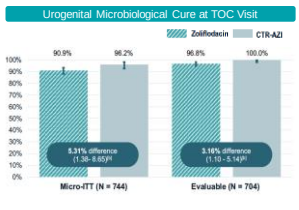
- First-in-class triazaacenaphthylene
- Dose – 3g PO x 2 (10-12 hrs) for urogenital gonorrhea
- Non-inferiority (10% margin) to ceftriaxone 500mg + azithromycin 1g
- Microbiologic intention to treat – 92.6% (vs. 91.2%)
- Resistance in Phase 2 trial; higher dose in Phase 3 and no mutations found
- FDA approved for uncomplicated UTIs (Mar '25), avail in US Summer 2025*

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New Treatments - Zoliflodacin

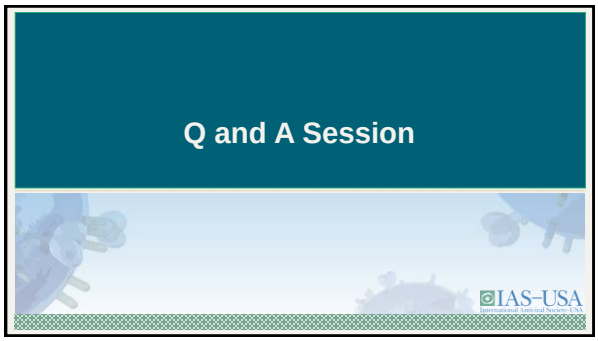
- First-in-class spiropyrimidinetrione
- Dose – 3g PO once for urogenital NG infections
- Non-inferiority trial (12% margin) to ceftriaxone 500mg + azithromycin 1g
- Microbiologic intention to treat – 90.9% vs 96.2%[1]
- FDA Fast Track status – anticipated approval in 2025



[1]ESCMID Global 2024

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