Gonorrhea Treatment Strategies: Needs & Emerging Data to Address Future Challenges

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FDA/NIH/CDC Meeting on Gonorrhea
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Update to CDC’s Treatment Guidelines for Gonococcal Infection, 2020

Ceftriaxone 500 mg IM in a single dose

BOX. CDC recommended regimens for uncomplicated gonococcal infections, 2020

Regimen for uncomplicated gonococcal infections of the cervix, urethra, or rectum:

Ceftriaxone 500 mg IM as a single dose for persons weighing <150 kg (330 lb)

- For persons weighing ≥150 kg (330 lb), 1 g of IM ceftriaxone should be administered.
- If chlamydial infection has not been excluded, providers should treat for chlamydia with doxycycline 100 mg orally twice daily for 7 days. During pregnancy, azithromycin 1 g as a single dose is recommended to treat chlamydia.

Alternative regimens for uncomplicated gonococcal infections of the cervix, urethra, or rectum if ceftriaxone is not available:

Gentamicin 240 mg IM as a single dose plus azithromycin 2 g orally as a single dose OR

Cefixime 800 mg orally as a single dose. If treating with cefixime, and chlamydial infection has not been excluded, providers should treat for chlamydia with doxycycline 100 mg orally twice daily for 7 days. During pregnancy, azithromycin 1 g as a single dose is recommended to treat chlamydia.

Recommended regimen for uncomplicated gonococcal infections of the pharynx:

Ceftriaxone 500 mg IM as a single dose for persons weighing <150 kg (330 lb)

- For persons weighing ≥150 kg (330 lb), 1 g of IM ceftriaxone should be administered.
- If chlamydia coinfection is identified when pharyngeal gonorrhea testing is performed, providers should treat for chlamydia with doxycycline 100 mg orally twice a day for 7 days. During pregnancy, azithromycin 1 g as a single dose is recommended to treat chlamydia.
- No reliable alternative treatments are available for pharyngeal gonorrhea. For persons with a history of a beta-lactam allergy, a thorough assessment of the reaction is recommended.
- For persons with an anaphylactic or other severe reaction (e.g., Stevens Johnson syndrome) to ceftriaxone, consult an infectious disease specialist for an alternative treatment recommendation.

Abbreviation: IM = intramuscular.
Gaps & Challenges

• Clinical trials generally emphasize urogenital outcomes, but pharyngeal infection represents a major reservoir and AMR mechanism
• No universal option for oral therapy; parenteral therapy required
• No practical regimen for CTX alternative
• IDSA, other groups have focused on AMR; limited success
  – No new antibiotics FDA approved since 2019!
• PASTEUR act: a good first step
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Acinetobacter baumannii, carbapenem-R</td>
<td>Critical</td>
<td>Critical</td>
<td>Urgent (carbapenem-R)</td>
<td>Serious (MDR)</td>
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<td>Serious (MRSA)</td>
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<td>Serious (drug-R)</td>
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<td>Streptococcus pneumoniae, penicillin-NS</td>
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<td>Serious (drug-R)</td>
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<td>Shigella spp., fluoroquinolone-R</td>
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<td>Urgent</td>
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<td>Urgent (C. glabrata)</td>
<td>Serious (Drug-resistant)</td>
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<td>M. tuberculosis</td>
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<td>Serious (drug-R)</td>
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<td>Group A Streptococcus</td>
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<td></td>
<td>Concerning (erythro-R)</td>
<td>Concerning (erythro-R)</td>
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<tr>
<td>Group B Streptococcus</td>
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<td>Concerning (clinda-R)</td>
<td>Concerning (clinda-R)</td>
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<td>Aspergillus fumigatus</td>
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<td></td>
<td>Watch (azole-R)</td>
<td>Watch (clinda-R)</td>
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<td>Mycoplasma genitalium</td>
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<td></td>
<td>Watch (drug-R)</td>
<td>Watch (clinda-R)</td>
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<tr>
<td>Bordetella pertussis</td>
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<td></td>
<td>Watch (drug-R)</td>
<td>Watch (clinda-R)</td>
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</table>

*Note that the Indian PPL sometimes differs slightly from WHO in terms of precise patterns of qualifying R.
What’s new?
Pew Development Pipeline December 2020

• 43 New antibiotics in development
  — > 95% small companies; > 70% pre-revenue
  — 15 phase 1 - Not a good sign!
  — 13 phase 2
  — 13 phase 3
    — 60% likely to make it to FDA approval
• 19 + potential to treat G- ESKAPE pathogens
  — 15/19 + potential activity against carbapenem-R organisms
• 10 + potential to treat *N. gonorrhoeae* or *C. difficile*
• 1 in 4 = novel drug class or mechanism of action
• Initial indications: cUTI, cIAI, ABSSSI

Focus on systemically available antibiotics in phase 2 or beyond

PASTEUR Act

Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (PASTEUR) Act

• Goals:
  — Support the development of new antibiotics and promote appropriate use of existing ones
  — Limit increase and spread of resistant infections
  • Good stewardship
PASTEUR Act

• Subscription program to provide federal payments for critically needed new antibiotics
• Payments delinked from sales —provides predictable return on investment that aligns with appropriate use goals
• Establishes a new HHS committee to determine details of subscription contracts (including preferred characteristics of drugs that should receive subscription payments); input from advisory group of non-government experts
• Payments made after drug’s approval over a period of up to 10 years
• Establishes new HHS grant program to support hospital implementation of antibiotic stewardship programs and hospital reporting of antibiotic use/resistance data to CDC National Healthcare Safety Network
PASTEUR Act

• Bipartisan leadership:
  – Senators Bennet (D-CO) and Young (R-IN)
  – Reps. Doyle (D-PA) and Ferguson (R-GA)

• Supported by 40+ organizations, including: IDSA, AdvaMedDx, ASM, BIO Cystic Fibrosis Foundation, Research!America, Society of Critical Care Medicine, Society of Hospital Medicine, Society of ID pharmacists, The Joint Commission, multiple academic centers

• Reflects consensus recommendations from multiple expert bodies and reports: PACCARB, UK AMR Review, Duke Margolis Center for Health Policy, PCAST, DRIVE-AB
*N. gonorrhoeae* and *N. meningitidis* are genetically similar, with NHBA and OMV antigens present in both pathogens.

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**OMV**

22 core proteins comprise >90% of OMV content

**Nm OMV protein antigens**

16 proteins

% ID to *Ng*

- >90%
- >80%
- <80%

2 proteins

2 proteins

2 proteins

No *Ng* homologue identified

**NHBA**

*Nm NHBA* (present in Bexsero)

Share 67% identity

*Ng NHBA*

- **Surface exposed**
- Highly **conserved** in *N. gonorrhoeae* strains (>93% identity)
- Recognised by **human serum** samples from people vaccinated with Bexsero

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*Ng, N. gonorrhoeae; NHBA, Neisseria heparin binding antigen; Nm, N. meningitidis; OMV, outer membrane vesicle*

In New Zealand studies, young adults vaccinated with MeNZB were less likely to have or be hospitalised with gonorrhoea.

Mass MenB immunisation programme using MeNZB (2004–2006, 3+0 schedule)\(^1\)

- Of population aged ≤20 years, 81% received doses (~1 million individuals had 3 doses)\(^1\)
- Population included residents born 1984–1999, residing in NZ from 2004 until at least 2015\(^1\)

Two retrospective studies investigated MeNZB effectiveness against gonorrhoea and associated hospitalisation (2004–2015/16)

- Confirmed gonorrhoea diagnoses were assessed in a case-control study, using data from sexual health clinics\(^1\)
  - 1241 cases (gonorrhoea only)
  - 12487 controls (chlamydia only)
- Gonorrhoea-associated hospitalisation was assessed in a cohort study, using hospital diagnostic coding data\(^2\)
  - 935,496 cohort members were included

MeNZB showed 31% effectiveness against gonorrhoea in 15-30yoa (95% CI: 21–39%)

MeNZB showed 24% effectiveness against gonorrhoea-associated hospitalization in 15-30yoa (95% CI: 1–42%)

CI, confidence interval; NZ, New Zealand

A Phase II proof of concept study aims to demonstrate the efficacy of Bexsero against gonococcal infection.

**Study design**
Phase II, randomised, observer-blind, placebo-controlled trial (USA and Thailand)

**Primary objective**
Bexsero efficacy in preventing urogenital and/or anorectal gonococcal infection

Subjects at risk of *N. gonorrhoeae* infection
N=2200, aged 18–50 years

Recruiting | estimated completion Aug 2023

Randomised 1:1
Bexsero
Placebo

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15 months</th>
</tr>
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</table>

**Key:**
- Treatment dose
- Phone call to assess safety
- Clinic visit

"STI" Immunizations

- Hepatitis A/B
- Either 9vHPV or 4vHPV vaccination through age 26 years if vaccinated previously (catch-up); shared clinical decision-making for persons 27 through 45 years
- Meningococcal vaccine in HIV+
  - MenACWY-D (Menactra) or MenACWY-CRM (Mencevo)

### TABLE 1. Evidence of increased risk for meningococcal disease among HIV-infected persons compared with HIV-uninfected persons — seven study populations, 1996–2013

<table>
<thead>
<tr>
<th>Period</th>
<th>Study site</th>
<th>Age group</th>
<th>No. of cases</th>
<th>Increase in meningococcal disease rate among HIV-infected compared with HIV-uninfected persons</th>
<th>Serogroups</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990–1999</td>
<td>Australia</td>
<td>All ages</td>
<td>60</td>
<td>3-fold</td>
<td>B, C</td>
</tr>
<tr>
<td>1990–2000</td>
<td>London</td>
<td>All ages</td>
<td>2,000</td>
<td>14-fold</td>
<td>B, C</td>
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<tr>
<td>1988–1993</td>
<td>Atlanta, Georgia</td>
<td>18–45 years</td>
<td>132</td>
<td>24-fold</td>
<td>B, C, Y</td>
</tr>
<tr>
<td>2003–2007</td>
<td>South Africa</td>
<td>All ages</td>
<td>504</td>
<td>11-fold</td>
<td>A, B, C, W, Y</td>
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<tr>
<td>2000–2011</td>
<td>New York City</td>
<td>15–64 years</td>
<td>203</td>
<td>10-fold</td>
<td>C, Y</td>
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<tr>
<td>2011–2013</td>
<td>United Kingdom</td>
<td>All ages</td>
<td>2,253</td>
<td>3-fold</td>
<td>A, B, C, W, Y</td>
</tr>
</tbody>
</table>

Abbreviations: ABCs = Active Bacterial Core surveillance; HIV = human immunodeficiency virus.
Challenges in GC Diagnosis

• Many GC infections are asymptomatic or have atypical symptoms; routine screening performance remains suboptimal, especially in HIV care settings & at sites not diagnosed by urine
  – Diagnosis often depends on presentation of clinical syndromes
• Limited availability of culture; practical barriers
• Slow uptake of point of care testing, encouraging developments in last year
THANK YOU

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