

From DoxyPEP to Drug Resistance: The Changing Face of STIs



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

Dr Ghanem reported no relevant financial relationships with
ineligible companies. (Updated November 11, 2025)

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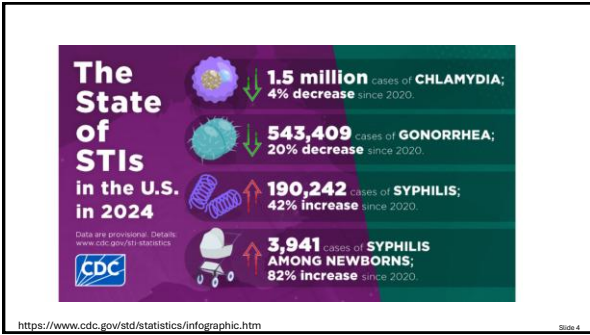
Learning Objectives

After attending this presentation, learners will be able to:

- Describe key management strategies for syphilis, gonorrhea, and *Mycoplasma genitalium*
- Describe emerging trends in antimicrobial resistance among sexually transmitted infections
- Summarize new evidence on the clinical impact of doxycycline postexposure prophylaxis (doxyPEP)

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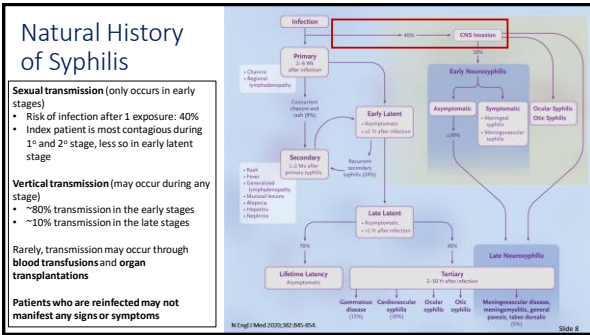
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Syphilis

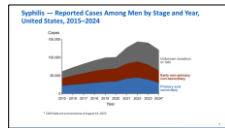
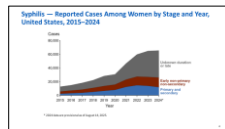
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Syphilis Epidemiology 2024

- Comparing 2023 to 2024 syphilis cases by stage among men:
 - Syphilis (all stages) **decreased** 14.1% (140,392 to 120,567)
 - P&S syphilis **decreased** 24.5% (39,188 to 29,575)
 - Early latent syphilis **decreased** 17.5% (40,486 to 33,401)
- Comparing 2023 to 2024 syphilis cases by stage among women:
 - Syphilis (all stages) **increased** 1.0% (64,795 to 65,460)
 - P&S syphilis **decreased** 13.8% (13,763 to 11,859)
 - Early latent syphilis **increased** 7.9% (13,036 to 14,061)



CDC STI Surveillance Report 2024 cdc.gov

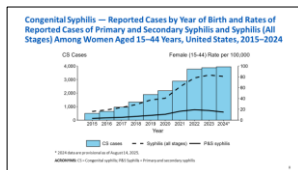
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Congenital Syphilis 2024

- Congenital Syphilis in the U.S.
- 1 year (2023 to 2024) - CS cases **increased** 1.6% (3,878 to 3,941)
 - 5 years (2020 to 2024) - CS cases **increased** 81.8% (2,168 to 3,941)
 - 10 years (2015 to 2024) - CS cases **increased** 696.2% (495 to 3,941)

- Among women aged 15 to 44 years comparing rates of P&S syphilis:
- 1 year (2023 to 2024) - rates **decreased** 16.9% (17.7 to 14.7 per 100,000)
 - 5 years (2020 to 2024) - rates **increased** 37.4% (10.7 to 14.7 per 100,000)
 - 10 years (2015 to 2024) - rates **increased** 359.4% (3.2 to 14.7 per 100,000)



CDC STI Surveillance Report 2024 cdc.gov

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Therapy for Syphilis

- Parenteral penicillin G is the drug of choice for all stages of syphilis
- It is the **ONLY** therapy with documented efficacy for syphilis during pregnancy

ASTDA Position Paper: Alternatives to Benzathine Penicillin G for the Treatment of Syphilis During Pregnancy

Sexually Transmitted Diseases • Volume 91, Number 4, April 2015

- Data on doxycycline are more limited but suggest excellent efficacy in adults who are not pregnant with early (14 days) and late latent infections (28 days)
- Ceftriaxone is a recommended alternative to IV penicillin for CNS complications

For primary and secondary syphilis in nonpregnant adults, including HIV-infected adults:

Penicillin G benzathine, 2.4 million units in a single IM dose

Doxycycline, 100 mg orally twice a day for 14 days (first alternative)

Ceftriaxone, 1-2 g daily, IM or IV, for 10-14 days (second alternative)

For latent syphilis in nonpregnant adults, including HIV-infected adults:

Early latent: penicillin G benzathine, 2.4 million units total, administered in 3 IM doses of 2.4 million units each at 1-week intervals

Late latent: penicillin G benzathine, 7.2 million units total, administered in 3 IM doses of 2.4 million units each at 1-week intervals

For late syphilis (gummas and cardiovascular manifestations) but not neurosyphilis:

Penicillin G benzathine, 7.2 million units total, administered in 3 IM doses of 2.4 million units each at 1-week intervals

For neurosyphilis and ocular syphilis:

Aqueous crystalline penicillin G, 18-24 million units per day, administered as 6 IM doses of 3-4 million units every 4 hr or as a continuous infusion, for 10-14 days

Penicillin G procaine, 2.4 million units in a single IM dose daily, plus procaine, 100 mg administered orally four times a day, both for 10-14 days (alternative)

For primary and secondary syphilis in pregnancy:

Penicillin G benzathine, 2.4 million units in a single IM dose

For latent syphilis in pregnancy:

Early latent: penicillin G benzathine, 2.4 million units in a single IM dose

Late latent: penicillin G benzathine, 7.2 million units total, administered in 3 IM doses of 2.4 million units each at 1-week intervals

* Treatment guidelines are from the Centers for Disease Control and Prevention (Workowski and Bolan¹). IM denotes intramuscular, and IV intravenous.

† Some experts recommend an additional IM dose of 2.4 million units of penicillin G benzathine, given 1 week later. N Engl J Med 2020;382:840-854.

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Point of Care & At-Home Testing

- 2 FDA cleared POC tests and 1 at-home test all assess for the presence of treponemal antibodies- **you still need an RPR titer to manage these patients appropriately**



NOWDiagnostics First To Know® Syphilis Test Receives FDA De Novo Marketing Authorization for Over-the-Counter Use
First and only rapid syphilis test with in-home results to receive addressing growing epidemic

On 8/18/20, the U.S. Food and Drug Administration granted marketing authorization to NOWDiagnostics for the First To Know Syphilis Test.

The First To Know® Syphilis Test is a qualitative rapid membrane immunoassay for the detection of *Treponema pallidum* (syphilis) antibodies in human whole blood (capillary). This test is intended for over the counter (OTC) consumer use in individuals suspected of syphilis. Positive test results with the First To Know® Syphilis Test alone are not sufficient to diagnose syphilis infection and must be followed by additional laboratory testing through a health care provider to confirm a diagnosis of syphilis.

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How do you interpret a treponemal antibody-only test? [point of care tests or at-home tests]

- The POC test reveals a **non-reactive** treponemal antibody result
 - The patient does not have syphilis
 - Early syphilis
- The POC test reveals a **reactive** treponemal antibody result
 - A false positive treponemal antibody result
 - Treated syphilis
 - Untreated syphilis

CLINICAL CHALLENGE: A pregnant patient presents to your clinic and results obtained today demonstrate a treponemal CIA that is reactive and a reactive RPR with a titer of 1:8. The patient states that she was diagnosed with syphilis one year ago based on a point of care test performed when she was at her PCP's office, and she was treated with a dose of BPG. Now, what do you do? What will you do with the infant after delivery?

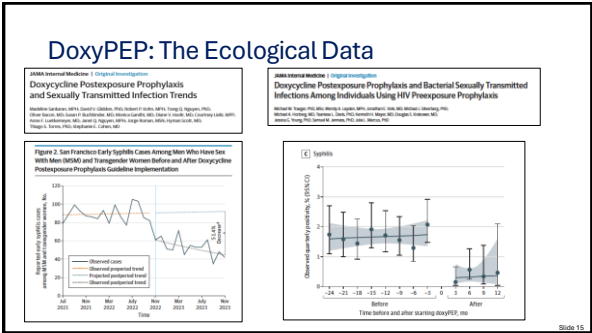
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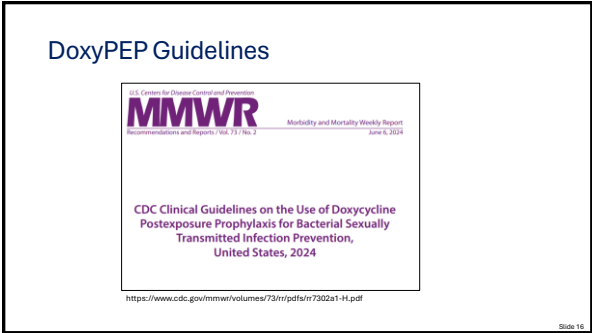
Biomedical Prevention of Syphilis (and Chlamydia): **DoxyPEP**

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The Impact of DoxyPEP on GC Antimicrobial Resistance

- In a follow-up study nested within the DOXYVAC trial: MSM on HIV PrEP randomized to DoxyPEP (n=362) or no-PEP (n=183) arms were tested for GC at baseline and every three months thereafter, by culture (N=78) and NAAT (N=233)
 - Increase in rate of high-level tetracycline GC resistance in the DoxyPEP arm than in the no-PEP arm (35.5 vs. 12.5%, p=0.043)
 - Decreased susceptibility to cefixime more frequent in the DoxyPEP arm than the no-PEP arm (32.3% vs 10.0%, p=0.033)
 - The MICs of ceftriaxone, fluoroquinolones and azithromycin were similarly distributed in the DoxyPEP and no-PEP arms

Bercoff B, et al. Clinical Infectious Diseases, 2025 (in press)

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The Impact of DoxyPEP on Syphilis Clinical Presentation and Serologies

- 1777 patients on HIV PrEP in Seattle (91% male, 52% white, 36% DoxyPEP use; 25% prior history of syphilis)
- 59 syphilis cases in 56 patients (24% on DoxyPEP)
- **CLINICAL:** Higher proportion of symptomatic P&S syphilis among non DoxyPEP users (88%) than DoxyPEP users (12%)
- **SEROLOGICAL:** Median RPR titer of DoxyPEP users is 1:8 vs. 1:32 in non DoxyPEP users

These preliminary data suggest that DoxyPEP significantly impacts early clinical and serological manifestations of syphilis

Cannon et al. ISSTD July 2025 Montreal, Canada: Evaluation of RPR Titer Differences at Early Syphilis Diagnosis in DoxyPEP Users vs. Non-Users

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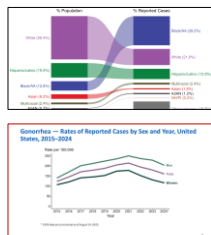
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Gonorrhea

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Gonorrhea



In 2024, the total rate of reported gonorrhea in the United States was 159.8 per 100,000 population.

Comparing rates of gonorrhea:

1 year (2023 to 2024):

- Men: 11.1% decrease (228.3 to 203.0 per 100,000)
- Total: 11.0% decrease (179.5 to 159.8 per 100,000)
- Women: 11.4% decrease (130.7 to 115.8 per 100,000)

5 years (2020 to 2024):

- Men: 13.5% decrease (234.8 to 203.0 per 100,000)
- Total: 21.9% decrease (204.5 to 159.8 per 100,000)
- Women: 33.4% decrease (173.8 to 115.8 per 100,000)

<https://www.cdc.gov/sti-statistics/annual/index.html>

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Treatment of Gonorrhea

- The treatment of uncomplicated gonorrhea is **500 mg of intramuscular ceftriaxone**; if chlamydia is present or is not ruled out, add one week of 100 mg of oral doxycycline taken twice daily
 - Alternate regimens for **urogenital or rectal infections** include oral cefixime 800 mg; intramuscular gentamicin 5mg/kg plus 2 g oral azithromycin
- Patients with pharyngeal gonorrhea should be treated with ceftriaxone- **no alternate regimens are recommended**; a **test-of-cure** should be performed one to two weeks later
- A reported history of penicillin allergy should prompt clinicians to obtain more information about the nature of that allergy; a majority of these patients may be safely treated with ceftriaxone
- Re-screen all persons diagnosed with gonorrhea in 3 months
- Treat all sex partners in the preceding 60 days of index patients diagnosed with gonorrhea**

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What's to be done if a patient reports an allergy to penicillin?

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STOP!

DON'T ABANDON

CEFTRIAXONE JUST YET

GET MORE

INFORMATION ABOUT

THE NATURE OF THE

PATIENT'S PENICILLIN

ALLERGY

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JHH Department of Antimicrobial Stewardship

Newsletter – August 2023



Keep in mind: ~80 percent of patients with IgE-mediated penicillin allergy have lost the sensitivity after 10 years

New guidelines from the American Academy and College of Allergy, Asthma, and Immunology for cephalosporin use in patients with penicillin allergy¹

- Patients with a history of anaphylaxis to penicillin can receive cephalosporins (which is a non-cross-reactive cephalosporin) without skin testing or a test dose.
 - Avoid cefazolin with history of Stevens Johnson Syndrome, toxic epidermal necrolysis, or DRESS.
- Patients with a non-anaphylactic penicillin allergy can receive any cephalosporin without skin testing or a test dose.
 - For example, patients with a history of urticaria to a penicillin can receive any cephalosporin without testing/test dose.
- Patients with a history or susceptibility to penicillin should undergo allergy consult/skin testing prior to receiving a non-cefazolin cephalosporin.

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Extended-spectrum cephalosporin resistant gonorrhea- the coming plague...

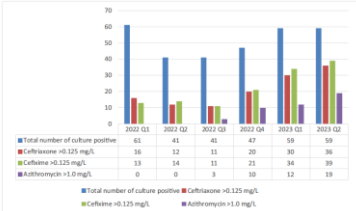
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While extended-spectrum cephalosporin resistance is still exceedingly rare in the United States...

High prevalence of ceftriaxone-resistant and XDR *Neisseria gonorrhoeae* in several cities of Cambodia, 2022–23: WHO Enhanced Gonococcal Antimicrobial Surveillance Programme (EGASP)

V. Dha¹, L. Eng Hong², M. Simal³, S. Seng⁴, M. M. Loh⁵, B. Pheasant⁶, S. Krasak⁷, R. McDowell⁸, M. Kach⁹, M. Simeon¹⁰, L. BPT and J. Mouton¹¹ on behalf of the EGASP Cambodia Working Group



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The IAS–USA Annual Virtual Course Update: Emerging Challenges in HIV Medicine, December 4, 2025

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Suspected Cephalosporin Treatment Failures

- Treatment failure should be considered for persons whose symptoms do not resolve within 3–5 days after recommended treatment and report no sexual contact during the post-treatment follow-up period and persons with a positive test of cure (i.e., positive culture >72 hours or positive NAAT >7 days after receiving recommended treatment) when no sexual contact is reported during the posttreatment follow-up period.
- In cases in which reinfection is unlikely and treatment failure is suspected, before retreatment, relevant clinical specimens should be obtained for culture (preferably with simultaneous NAAT) and antimicrobial susceptibility testing if *N. gonorrhoeae* is isolated. All isolates of suspected treatment failures should be sent to CDC for antimicrobial susceptibility testing store isolates for possible further testing if needed.
- For persons with suspected cephalosporin treatment failure, the treating clinician should consult an infectious disease specialist, the National Network of STD Clinical Prevention Training Center clinical consultation line (<https://www.stdcn.org/render/Publicexternal/icon>), the local or state health department STI program, or CDC (telephone: 800-232-4636) for advice about obtaining cultures, antimicrobial susceptibility testing, and treatment. Suspected treatment failure should be reported to CDC through the local or state health department <24 hours after diagnosis.

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: <https://www.cdc.gov/std/treatment-guidelines/gonorrhea-adults.htm>

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

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Testing for Gonorrhea

Anatomical Site	Specimen type	GC Gram's stain (sensitivity)	GC Culture (Sensitivity)	GC/CT NAATs (Sensitivity)
Male urethra	Swab	Symptomatic: 89-94% Asymptomatic: 40-60%	Symptomatic: 90-95% Asymptomatic: 65-85%	>95% (symptomatic and asymptomatic)
Urine	First catch	Not appropriate specimen	Not appropriate specimen	87-95% overall Preferred specimen for men
Endocervical	Swab	37-70% overall (lower for asymptomatic); specificity is poor	Symptomatic: ~85% Asymptomatic: 65-80%	>95% (symptomatic and asymptomatic)
Vaginal	Swab	Not appropriate specimen	Not appropriate specimen	>95% (symptomatic and asymptomatic) Preferred specimen for women
Throat	Swab	Not appropriate specimen	~50%	>95% (symptomatic and asymptomatic)
Rectal	Swab	Not appropriate specimen	~50%	>95% (symptomatic and asymptomatic)

Goodhart ME Sex Transm Dis. 1982; Schink K J Reprod Med. 1985; Goh BT Sex Transm Dis. 1985; Tabrizi SN / Clin Microbiol. 2011; Doernberg SR Clin Infect Dis. 2009

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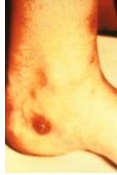
In the meantime, keep in mind...

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Disseminated gonococcal infection (DGI)

- DGI frequently results in petechial or pustular acral skin lesions (< 12 lesions and usually tender), tenosynovitis, and asymmetrical arthralgia, or (oligoarticular) septic arthritis
- The infection is occasionally complicated by perihepatitis and rarely by endocarditis or meningitis.
- Strains of *N. gonorrhoeae* that cause DGI may cause **minimal genital inflammation**
- Risk factor for DGI: terminal complement deficiency (acquired form often seen in SLE) and complement inhibitors (e.g. **Eculizumab**)
- Differential diagnosis: meningococemia, RMSF, dengue, endocarditis, Reiter's
- **Test all mucosal surfaces using NAATs and culture (genital, rectal, pharyngeal). Culture is less sensitive but it allows for antimicrobial resistance testing**
- **Treatment: Start with IV ceftriaxone and once clinical status improves, de-escalate to oral regimen based on antimicrobial susceptibility testing. Short courses (i.e. <7 days) are adequate except for meningitis, endocarditis, and septic arthritis.**



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Mycoplasma genitalium

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Mycoplasma genitalium

- **Clinical Associations:**
 - Strong association with (NGU) [~ 10-25% of cases] and **~40% of cases of persistent/recurrent urethritis**
 - Also associated with **persistent cervicitis**
 - Associations with PID and infertility are still not strong
- **Diagnosis:** NAAT test-test men with recurrent/refractory NGU and women with recurrent/refractory cervicitis; testing may be considered in women with PID who do not respond to standard therapy.
- **Antimicrobial activity**
 - Doxycycline poorly effective at eradication but effective at decreasing bacterial load
 - Azithromycin resistance in US 44-90%
 - Moxifloxacin resistance in US 0%-15%
 - If resistance to both azithromycin and moxifloxacin consider minocycline 100 mg PO BID

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Mycoplasma genitalium: Testing and Treatment

- NAATs now FDA-cleared
- **Test men with persistent urethritis and women with persistent cervicitis**
- CONSIDER testing women with PID that does not respond to standard therapy
- Do NOT routinely test extragenital sites
- **PLEASE: Do NOT screen asymptomatic men or women*******
- **Partners:** If you can test partners, treat those who are positive; if you cannot, consider treating the partner with the same regimen used to treat

Two-stage therapy approaches, (ideally using resistance-guided therapy) are recommended for treatment:

Recommended Regimens if *M. genitalium* Resistance Testing is Available

If macrolide sensitive: Doxycycline 100 mg orally 2 times/day for 7 days, followed by azithromycin 1 g orally single dose, followed by 500 mg orally daily for 3 additional days (2.5 g total)

If macrolide resistant: Doxycycline 100 mg orally 2 times/day for 7 days, followed by moxifloxacin 400 mg orally once daily for 7 days

Recommended Regimen if *M. genitalium* Resistance Testing is Not Available

If *M. genitalium* is detected by an FDA-cleared NAAT: Doxycycline 100 mg orally 2 times/day for 7 days, followed by moxifloxacin 400 mg orally once daily for 7 days

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What to do if patients fail fluoroquinolone therapy?

- No FDA approved drugs. Regimens that have been used and that are available in the United States:

Efficacy of Minocycline for the Treatment of *Mycoplasma genitalium*

Bailey J, Clarke R, Lewis A, Hooton T, et al. (2015) *Journal of Clinical Microbiology* 53(12):3500-3504

Minocycline 100 mg orally twice daily for 14 days

Successful Treatment of *Mycoplasma genitalium* Urethritis With High-Dose Tinidazole

Christina Luciwsky, MD, Ashley Lippin, MD, and Jose A. Baeza, DO

Tinidazole 2 g orally daily for 7 days

Efficacy and tolerability of the combination of minocycline and metronidazole for macrolide-resistant *Mycoplasma genitalium*

Bailey J, Clarke R, Lewis A, Hooton T, et al. (2015) *Journal of Clinical Microbiology* 53(12):3500-3504

Minocycline 100 mg + metronidazole 400 mg orally twice daily for 14 days (enhanced cure with doxycycline 100 mg PO BID twice daily for a week preceding the minocycline + metronidazole)

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The NNPTC provides:

- Clinical training
- STD clinical consultations
- Resources and tools for STD treatment

Visit: www.nnptc.org

GOT A TOUGH STD QUESTION?

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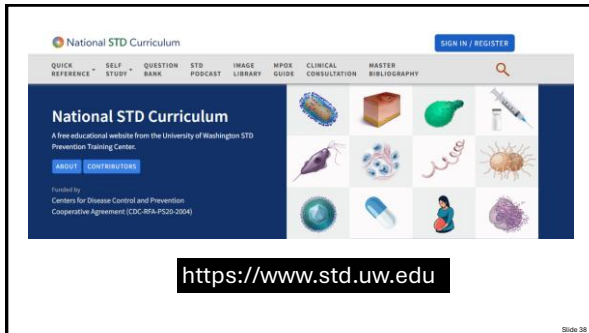
Ask your question

National STD experts review

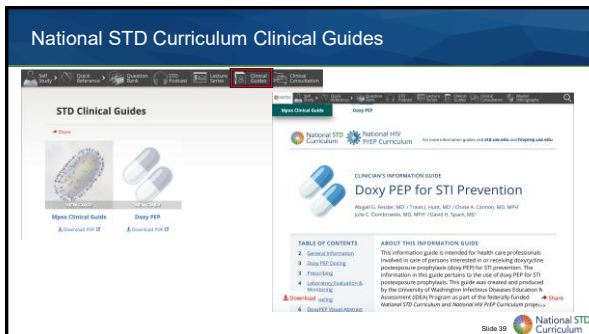
Response within 6-8 business days, depending on urgency

Log on to www.STDCCH.org for medical professionals nationwide

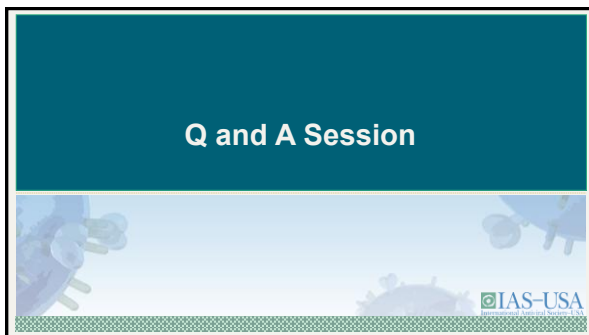
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