2021 Update to the Sexually Transmitted Infections (STI) Treatment Guidelines

Ashley Yeh, PharmD, PGY-2 Emergency Medicine Pharmacy Resident

Robert Wood Johnson University Hospital | Rutgers University

Preceptor: Deepali Dixit, PharmD, BCPS, BCCCP, FCCM

Clinical Associate Professor at Rutgers University Ernest Mario School of Pharmacy

Speaker Disclosures

Neither the presenter nor her preceptor have conflicts of interests related to this presentation

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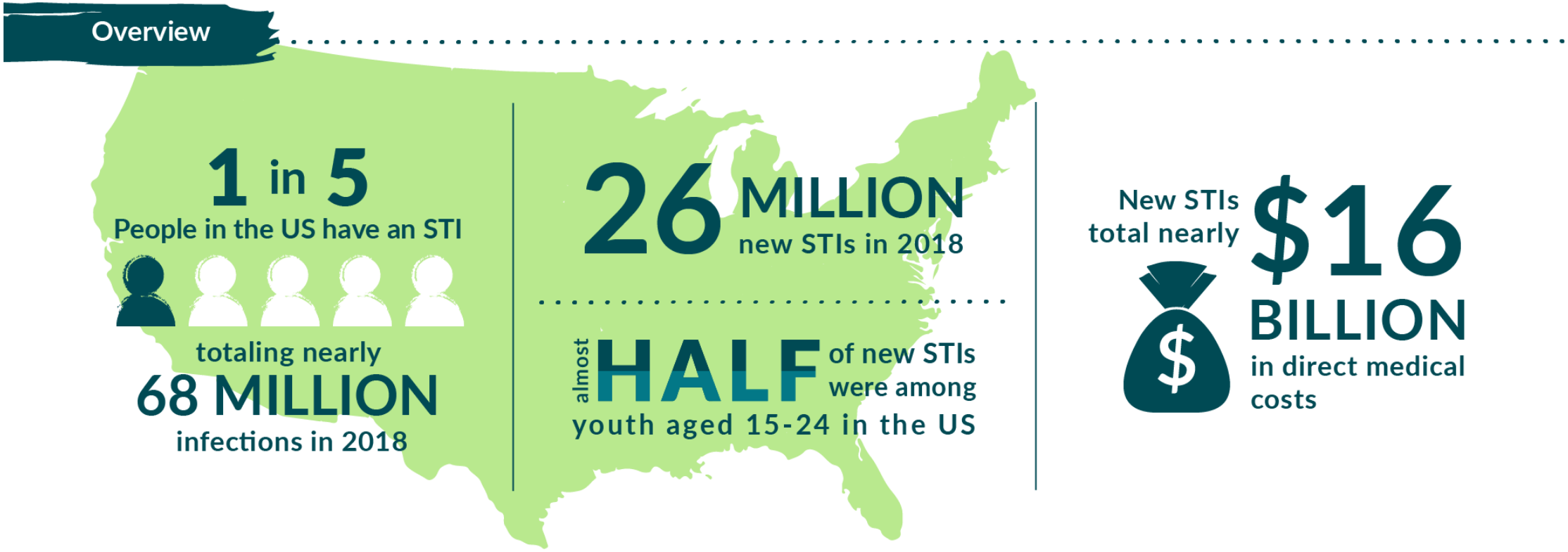
Learning Objectives

1. List available drugs for the treatment of common sexually transmitted infections
2. Recommend appropriate pharmacologic therapy and medication dosing depending on indication
3. Explain key counseling points including drug adverse reactions for pharmacologic therapy

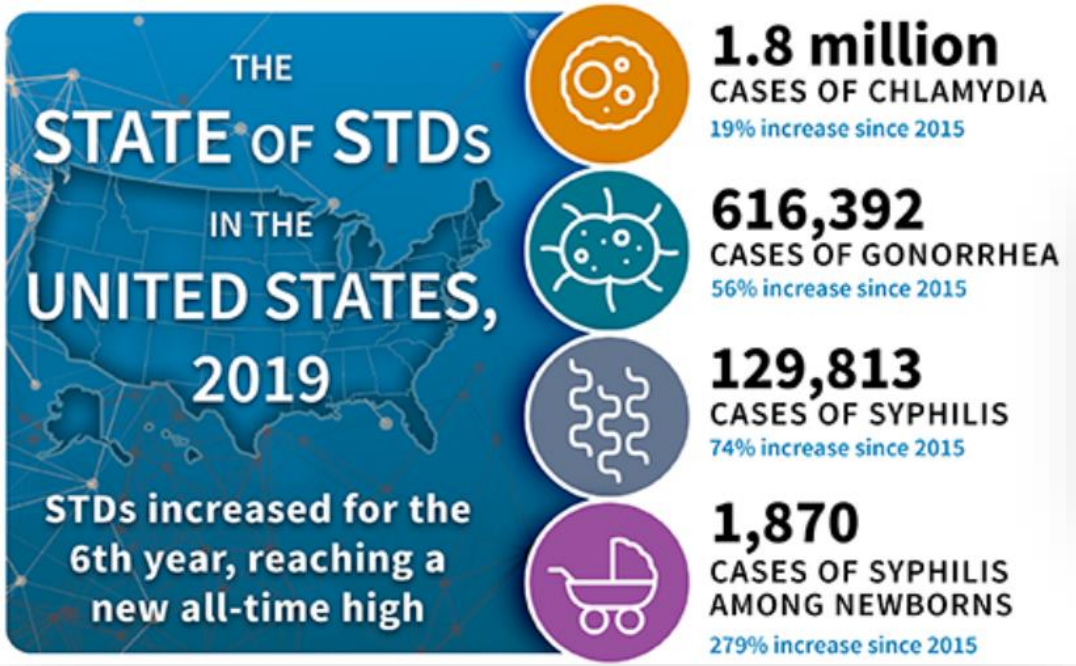
Outline

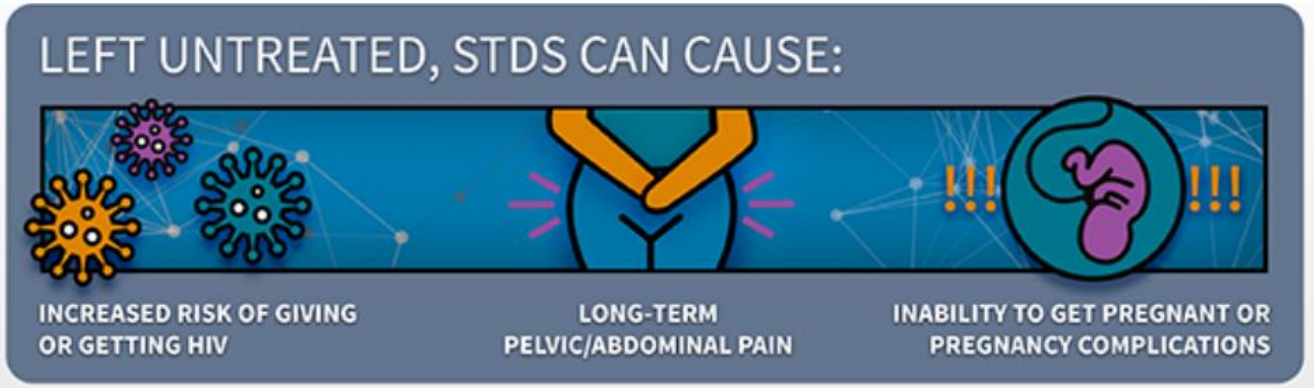
- Background
- Sexually Transmitted Infections
  - Chlamydia trachomatis
  - Neisseria gonorrhoeae
  - Trichomoniasis
  - Syphilis
  - Bacterial vaginosis
  - Pelvic inflammatory disease
  - Mycoplasma genitalium
- Summary

Background



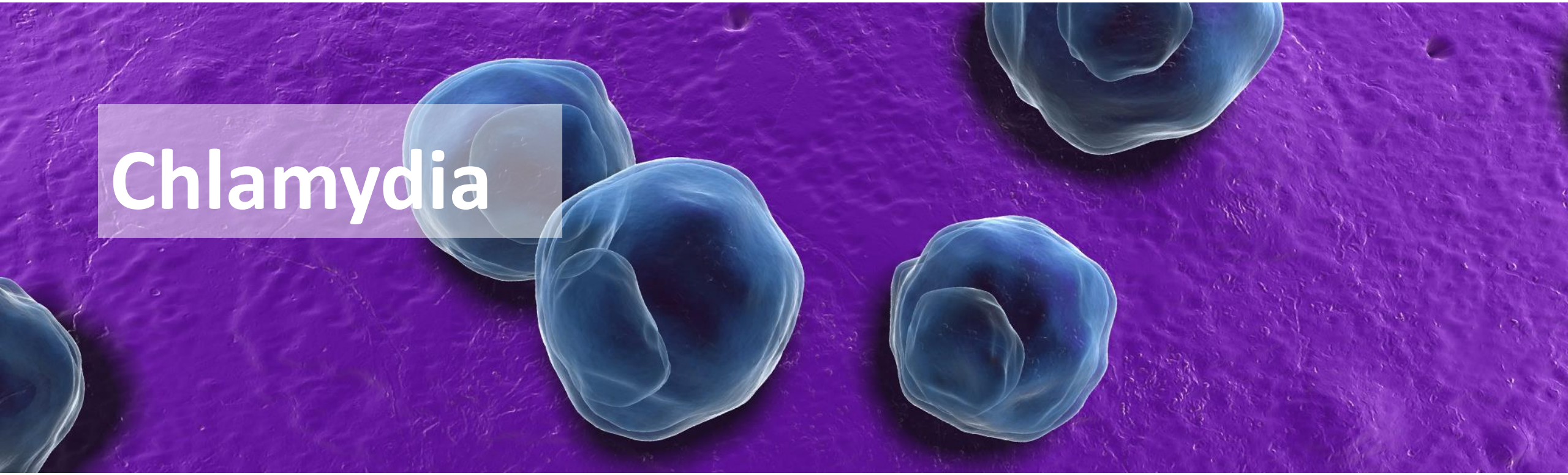
Source: https://www.cdc.gov/std/statistics/prevalence-2020-at-a-glance.htm





Sources: https://www.cdc.gov/std/statistics/2019/images/stateofSTDs-sm-1200x659-1.png
https://www.cdc.gov/std/statistics/2019/images/stateofSTDs-sm-1200x675-2.png

Chlamydia



Source: https://www.cdc.gov/std/chlamydia/default.htm

Chlamydia trachomatis

- Most frequently reported bacterial infectious disease in the United States
- Prevalence is highest among persons aged ≤24 years
- Potential complications:
  - Pelvic inflammatory disease, ectopic pregnancy, and infertility
- Counseling Points
  - Abstain from sexual intercourse for 7 days after single-dose therapy or until completion of a 7 day regimen

CDC. *MMWR Recomm Rep* 2021;70(4):1-192.

Chlamydia trachomatis

Preferred Treatment:

- **Doxycycline** 100mg PO BID x 7 days

Alternative Regimens:

- **Azithromycin** 1g PO x 1
- **Levofloxacin** 500mg PO daily x 7 days

CDC. *MMWR Recomm Rep* 2021;70(4):1-192.

Clinical Pearl

Doxycycline vs. azithromycin

- Geisler WM, et al. *N Engl J Med* 2015;373:2512-2521
  - Efficacy of azithromycin was 97% and doxycycline was 100% for treatment of urogenital chlamydia
  - Noninferiority of azithromycin was not established in this setting
- Dombrowski JC, et al. *Clin Infect Dis* 2021;73(5):824-831
  - Randomized, double-blind, placebo-controlled trial
  - Microbiologic cure, defined as CT-negative NAAT at 4 weeks, was higher with doxycycline than azithromycin in the ITT population (91% [80 of 88] vs 71% [63 of 89]; absolute difference, 20%; 95% CI, 9–31%; P < .001)

Geisler WM, et al. *N Engl J Med*2015;373:2512-2521.
Dombrowski JC, et al. *Clin Infect Dis* 2021;73(5):824-831.

Chlamydia trachomatis

Special Populations – pregnancy

- Rate of transmission from an untreated mother to a neonate is ~50%
- Doxycycline is contraindicated during 2nd and 3rd trimester – tooth discoloration risk

Preferred Treatment

- **Azithromycin** 1g PO x1
- **Amoxicillin** 500mg PO TID x 7 days

CDC. *MMWR Recomm Rep* 2021;70(4):1-192.

Medication Counseling Points

Drug	Counseling Points
Doxycycline	**Pediatric**: tooth discoloration – not preferred in children ≤8 years of age **Dietary**: avoid taking with calcium containing products **Dermatologic**: photosensitivity
Azithromycin	**Gastrointestinal**: nausea, vomiting, diarrhea
Amoxicillin	**Gastrointestinal**: nausea, vomiting, diarrhea **Dermatologic**: maculopapular rash - Relatively benign, not a contraindication to subsequent use

Gonorrhoeae

Source: https://www.cdc.gov/std/gonorrhea/default.htm

Neisseria gonorrhoeae

- Second highest reported bacterial sexually transmitted infection
- Known for ability to rapidly develop antibiotic resistance
  - Potential harm to the microbiome → reduced benefits of maintaining dual therapy
- Antibiotics
  - Isolates demonstrating reduced susceptibility to azithromycin has increased almost tenfold, to 5.1% in 2019
  - Decreased susceptibility to ceftriaxone or cefixime remains low

CDC. *MMWR Recomm Rep* 2021;70(4):1-192.

Neisseria gonorrhoeae

Preferred Treatment:

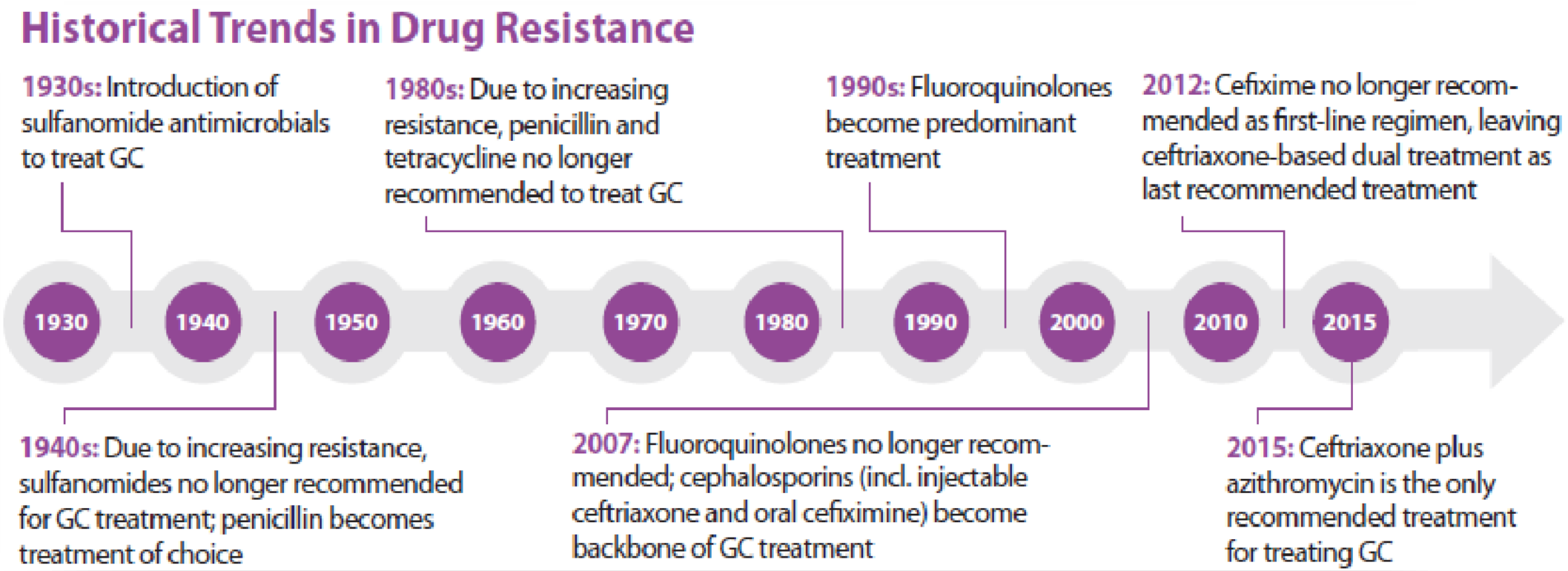
- **Ceftriaxone** 500mg IM x 1 if <150kg
- **Ceftriaxone** 1g IM x 1 if ≥150kg

Alternative Regimens:

- **Gentamicin** 240mg IM x1 *plus* **Azithromycin** 2g PO x 1
- **Cefixime** 800mg PO x 1

CDC. *MMWR Recomm Rep* 2021;70(4):1-192.

Clinical Pearl

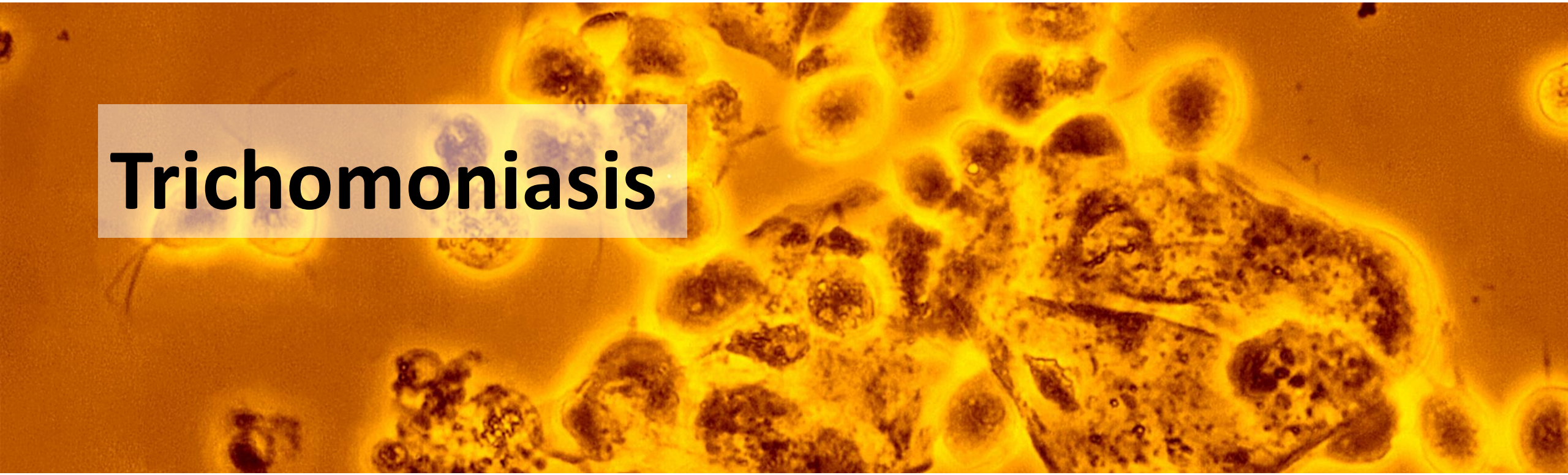


Source: https://www.cdc.gov/nchhstp/newsroom/docs/factsheets/drug-resistant-gonorrhea.pdf

Medication Counseling Points

Drug	Counseling Points
Ceftriaxone	**Gastrointestinal**: nausea, vomiting, diarrhea **Hypersensitivity**: maculopapular rash
Gentamicin	**Neuro**: cochlear and vestibular toxicity – caution in patients with use of other neurotoxic drugs **Renal**: caution in patients with preexisting renal impairment or nephrotoxic meds
Azithromycin	**Gastrointestinal**: nausea, vomiting, diarrhea

Trichomoniasis



Source: https://www.cdc.gov/std/trichomonas/default.htm

Trichomoniasis

- Estimated to be the most prevalent nonviral STI worldwide
- Prevalence rates are as high among women aged >24 years as they are for women aged <24 years
- Increased risk for cervical cancer and causes reproductive morbidity
  - Associated with a 1.4x greater likelihood of preterm birth, premature rupture of membranes, and infants who are small for gestational age

CDC. *MMWR Recomm Rep* 2021;70(4):1-192.

Trichomoniasis

Preferred Treatment:

- Women: **metronidazole** 500mg PO BID x 7 days
- Men: **metronidazole** 2g PO x 1

Alternative Regimens:

- **Tinidazole** 2g PO x 1

CDC. *MMWR Recomm Rep* 2021;70(4):1-192.

Clinical Pearl

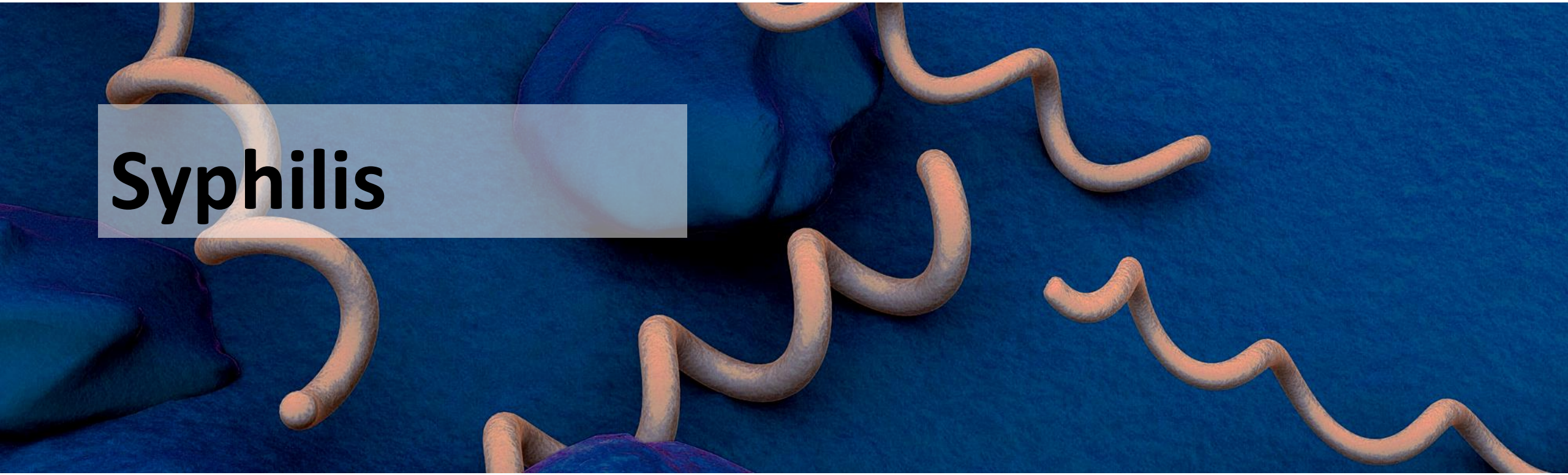
- Nitroimidazoles are the only class of medications with clinically demonstrated efficacy against T. vaginalis infections
- Tinidazole
  - More expensive
  - Reaches higher levels in serum and the genitourinary tract
  - Longer half-life
  - Fewer gastrointestinal side effects

CDC. *MMWR Recomm Rep* 2021;70(4):1-192.

Medication Counseling Points

Drug	Counseling Points
Metronidazole	**Gastrointestinal**: nausea **Genitourinary**: vaginitis **Nervous system**: headache
Tinidazole	**Gastrointestinal**: metallic bitter taste, nausea, vomiting

Syphilis



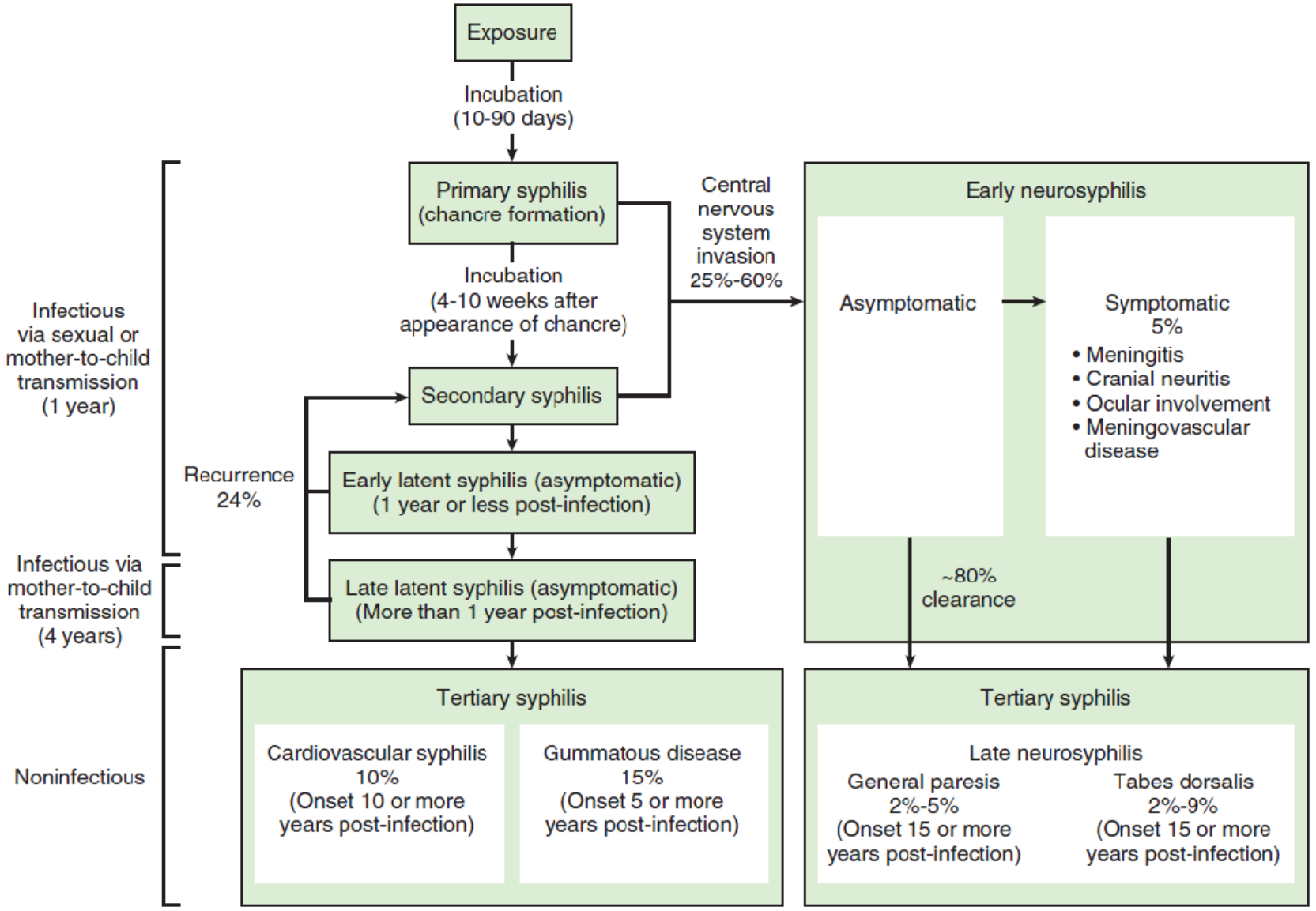
Source: https://www.cdc.gov/std/syphilis/default.htm

Syphilis

- Caused by the *Treponema pallidum* bacterium
- Thin, tightly coiled spirochete, microaerophilic bacteria
- Spread: sexual contact with infected mucous membranes or lesions
- Sites of infection: external genitalia, perianal region, mouth → multisystem involvement secondary to infection spread
  - Can reside in sites (CNS and aqueous humor) that are poorly accessed by some forms of penicillin

CDC. *MMWR Recomm Rep* 2021;70(4):1-192.

Syphilis – Natural Course



Source: Radolf JD, Tramont EC, and Salazar JC. *Syphilis (Treponema pallidum).* In: *Principles and Practice of Infectious Diseases.* 8th Ed. Bennet JE, Dolin R, Blaser MJ, et al., eds. Philadelphia, PA: Saunders;2015.

Primary/Secondary Syphilis

Preferred Treatment:

- **Benzathine penicillin G** 2.4 million units IM x1

Alternative Regimens:

- **Doxycycline** 100mg PO BID x14 days
- **Tetracycline** 500mg PO four times daily x14 days
- **Ceftriaxone** 1-2g daily IM or IV x 10-14 days*

*limited to observational studies, optimal dose and duration not defined

Ghanem KG, et al. *N Engl J Med* 2020;382:845:854.
CDC. *MMWR Recomm Rep* 2021;70(4):1-192.

Latent Syphilis

Positive serologic test for syphilis but no visible signs or symptoms

Goal: prevent complications and transmission during pregnancy

Early Latent (<1 year)

- **Benzathine penicillin G** 2.4 million units IM x1

Late Latent (>1 year)

- **Benzathine penicillin G** 2.4 million units IM weekly x 3 weeks (7.2 million units total)

Penicillin Allergy

- **Doxycycline** 100 mg PO BID x 28 days
- **Tetracycline** 500 mg PO four times daily x 28 days

Ghanem KG, et al. *N Engl J Med* 2020;382:845:854.
CDC. *MMWR Recomm Rep* 2021;70(4):1-192.

Tertiary Syphilis

Severe infection affecting organ systems (neurosyphilis, ocular syphilis, etc…)

Primary Treatment:

- **Aqueous crystalline penicillin G** 18–24 million units per day, administered as 3–4 million units IV every 4 hours OR continuous infusion, for 10–14 days

Alternative Regimens:

- **Procaine penicillin G** 2.4 million units IM daily *plus* **Probenecid** 500 mg PO four times daily, each x10-14 days

Ghanem KG, et al. *N Engl J Med* 2020;382:845:854.
CDC. *MMWR Recomm Rep* 2021;70(4):1-192.

Clinical Pearl

Jarisch-Herxheimer Reaction

- Occurs ~2-4 hrs after antibiotic treatment of spirochetal infections
- Acute febrile reaction that is frequently associated with fever, chills, myalgias, headache, vasodilatation with flushing, exacerbated skin rash, or mild hypotension
  - Reaction to treatment, NOT allergic reaction to penicillin
- Most frequently in early syphilis → higher bacterial burden
- Often self-limiting and resolves spontaneously
- Antipyretics for symptom management

Davis LE, et al. *Jama Neurol* 2013;70(8):1060-1064.
Yang C, et al. *Clin Infect Dis* 2010;51(8):976-979.
CDC. *MMWR Recomm Rep* 2021;70(4):1-192.

Syphilis

Special Populations – pregnancy

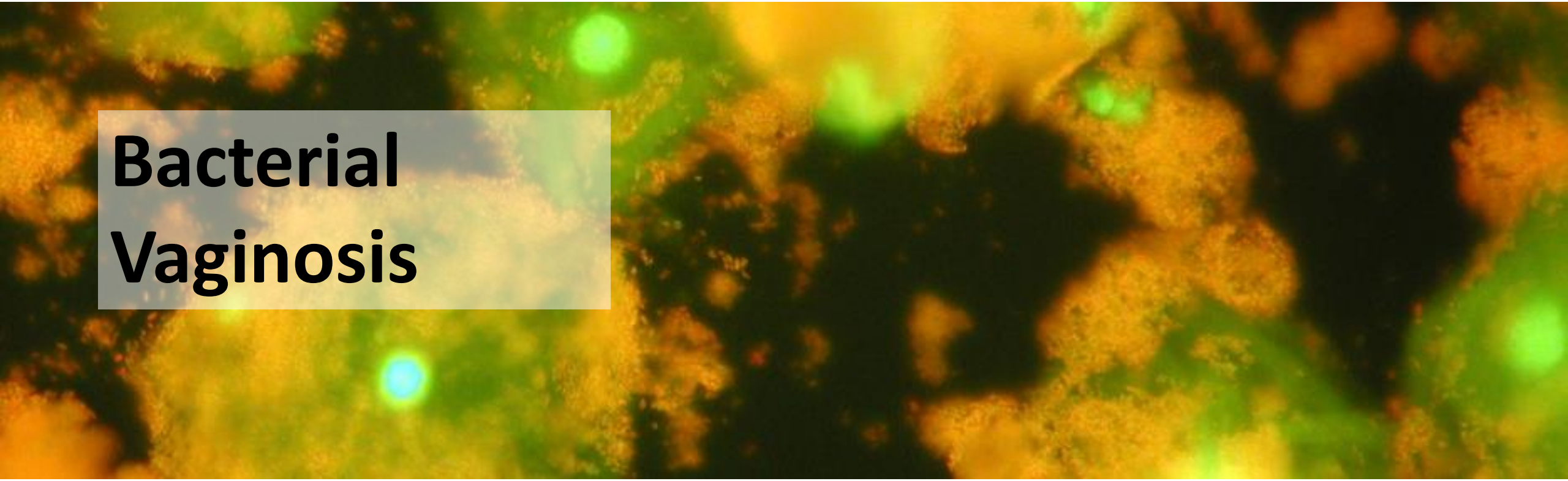
- **Data to support use of alternative therapies is limited**
  - Recommend desensitization strategies with patients who report penicillin allergies
- Pregnant patients should be tested and treated
  - Penicillin is first line, alternative therapies pose risks
  - Baby may develop serious problems

CDC. *MMWR Recomm Rep* 2021;70(4):1-192.

Medication Counseling Points

Drug	Counseling Points
Natural Penicillins	**Gastrointestinal**: nausea, vomiting, diarrhea **Hypersensitivity**: maculopapular rash **Neurologic**: seizures – dose dependent, very high doses required **Administration of benzathine or procaine PCN G by IV route has led to seizures and death

Bacterial Vaginosis



Source: https://www.cdc.gov/std/bv/default.htm

Bacterial Vaginosis

- Results from replacement of normal hydrogen peroxide and lactic-acid–producing Lactobacillus species in the vagina with high concentrations of anaerobic bacteria
  - Gardnerella vaginalis, Prevotella species, Mobiluncus species, Atopobium vaginae, and other BV-associated bacteria
- Appearance of a polymicrobial biofilm on vaginal epithelial cells
- Women with BV are at increased risk for obtaining STIs

CDC. *MMWR Recomm Rep* 2021;70(4):1-192.

Bacterial Vaginosis

Preferred Treatment:

- **Metronidazole** 500mg PO BID x 7 days
- **Metronidazole** gel 0.75% one full applicator (5g) intravaginally once daily x 5 days
- **Clindamycin** cream 2% one full applicator (5g) intravaginally once daily x 7 days

Alternative Regimens:

- **Clindamycin** 300mg PO BID x 7 days
- **Clindamycin** ovules 100mg intravaginally QHS x 3 days
- **Secnidazole** 2g oral granules PO x 1
- **Tinidazole** 2g PO once daily x 2 days
- **Tinidazole** 1g PO once daily x 5 days

CDC. *MMWR Recomm Rep* 2021;70(4):1-192.

Clinical Pearl

Alcohol/metronidazole interaction

- Fjeld H, et al. *Tidsskr Nor Laegeforen* 2014;134(17):1661-1663.
  - Literature review
  - No clinically relevant interaction between ethanol and metronidazole
  - Concern was based on lab experiments where reported reactions were likely to have been caused by alcohol alone or by adverse effects of metronidazole

Fjeld H, et al. *Tidsskr Nor Laegeforen* 2014;134(17):1661-1663.
CDC. *MMWR Recomm Rep* 2021;70(4):1-192.

Bacterial vaginosis

Special Populations – pregnancy

- Symptomatic BV is associated with adverse pregnancy outcomes:
  - premature rupture of membranes, preterm birth, intra-amniotic infection, and postpartum endometritis
- Newer data demonstrate that vaginal clindamycin is safe
- Metronidazole is secreted in breast milk, but case series show no evidence of metronidazole-associated adverse effects

Lamont RF, et al. *Am J Obstet Gynecol* 2011;205(3):177-190.
Erickson SH, et al. *Obstet Gynecol* 1981;57:48-50.
CDC. *MMWR Recomm Rep* 2021;70(4):1-192.

Medication Counseling Points

Drug	Counseling Points
Metronidazole	**Gastrointestinal**: nausea **Genitourinary**: vaginitis **Nervous system**: headache
Clindamycin	**Gastrointestinal**: nausea, vomiting, DIARRHEA
Secnidazole	**Gastrointestinal**: nausea, vomiting, diarrhea **Genitourinary**: vulvo-vaginal candidiasis
Tinidazole	**Gastrointestinal**: metallic bitter taste, nausea, vomiting

Pelvic Inflammatory Disease

Source: https://www.cdc.gov/std/gonorrhea/default.htm

Pelvic Inflammatory Disease

- Serious complication of gonorrhea and chlamydia
- Clinical syndrome that results from microorganisms moving upward from the cervix and vagina to upper genital tract/reproductive organs
  - Spectrum of inflammatory disorders of the upper female genital tract – endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis
- Complications:
  - Infertility
  - Chronic pelvic pain
  - Ectopic pregnancy

CDC. *MMWR Recomm Rep* 2021;70(4):1-192.

Pelvic Inflammatory Disease

Preferred Treatment:

- **Ceftriaxone** 1g IV q24h *plus* **Doxycycline** 100mg PO/IV q12h *plus* **Metronidazole** 500mg PO/IV q12h

Alternative Regimens:

- **Ampicillin-sulbactam** 3g IV q6h *plus* **Doxycycline** 100mg PO/IV q12h
- **Clindamycin** 900mg IV q8h *plus* **Gentamicin** 2mg/kg IV load, then 1.5mg/kg IV q8h

CDC. *MMWR Recomm Rep* 2021;70(4):1-192.

Clinical Pearl

- IM or PO therapy can be considered for mild-to-moderate acute PID
  - Clinical outcomes among women treated with IM/PO regimens are similar to those treated with IV therapy

- IV/PO doxycycline and metronidazole provide similar bioavailability
- After clinical improvement with parenteral therapy, transition to oral therapy
  - **Doxycycline** 100 mg PO and **Metronidazole** 500 mg PO BID x 14 days with **Ceftriaxone** 500 mg IM x 1

CDC. *MMWR Recomm Rep* 2021;70(4):1-192.

Medication Counseling Points

Drug	Counseling Points
Ceftriaxone	**Gastrointestinal**: nausea, vomiting, diarrhea **Hypersensitivity**: maculopapular rash
Doxycycline	**Pediatric**: tooth discoloration – not preferred in children ≤8 years of age **Dietary**: avoid taking with calcium containing products **Dermatologic**: photosensitivity
Metronidazole	**Gastrointestinal**: nausea **Genitourinary**: vaginitis **Nervous system**: headache
Ampicillin-sulbactam	**Gastrointestinal**: nausea, vomiting, diarrhea **Hypersensitivity**: maculopapular rash
Clindamycin	**Gastrointestinal**: nausea, vomiting, DIARRHEA
Gentamicin	**Neuro**: cochlear and vestibular toxicity – caution in patients with use of other neurotoxic drugs **Renal**: caution in patients with preexisting renal impairment or nephrotoxic meds

Mycoplasma genitalium

Source: https://www.cdc.gov/std/treatment-guidelines/mycoplasmagenitalium.htm

Mycoplasma genitalium

- Causes approximately 15-20% of nongonococcal urethritis
  - Co-infection with chlamydia is common
  - Higher prevalence seen in women with pelvic inflammatory disease
- Lacks cell wall – antibiotics such as penicillins and cephalosporins that target the cell-wall are ineffective
- Resistance-guided therapy demonstrated cure rates of >90%, but requires macrolide-resistance testing

CDC. *MMWR Recomm Rep* 2021;70(4):1-192.

Mycoplasma genitalium

Preferred Treatment:

- **Macrolide sensitive** – doxycycline 100mg PO BID x 7 days, then azithromycin 1g PO x 1, then azithromycin 500mg PO once daily x 3 days
- **Macrolide resistance** – doxycycline 100mg PO BID x 7 days, then moxifloxacin 400mg PO once daily x 7 days

CDC. *MMWR Recomm Rep* 2021;70(4):1-192.

Medication Counseling Points

Drug	Counseling Points
Doxycycline	**Pediatric**: tooth discoloration – not preferred in children ≤8 years of age **Dietary**: avoid taking with calcium containing products **Dermatologic**: photosensitivity
Azithromycin	**Gastrointestinal**: nausea, vomiting, diarrhea
Moxifloxacin	Gastrointestinal, QTc prolongation, Photosensitivity, Tendon rupture/tendonitis (FDA black box warning), Cartilage and/or bone deformities in young children, Glycemic control abnormalities, Exacerbate muscle weakness with myasthenia gravis (FDA black box warning)

Summary

1. Pharmacists play a huge role in providing appropriate medication therapy and dosing for STI treatment
2. High rates of increasing antibiotic resistance and treatment failures – pharmacists play a role in providing patient specific treatment alternatives
3. Pharmacists are key to counseling patients on drug adverse reactions for different pharmacologic therapies

Assessment Question #1

Which penicillin preparation is used in the treatment of syphilis?

A. Penicillin G benzathine (Bicillin L-A) 2.4 million units IM x1

B. Penicillin G procaine 600,000 units IM x1

C. Penicillin V postassium 2.4 million units PO x1

D. Penicillin benzathine-procaine (Bicillin C-R) 7.2 million units IM x1

Assessment Question #1: Correct Response

Which penicillin preparation is used in the treatment of syphilis?

A. Penicillin G benzathine (Bicillin L-A) 2.4 million units IM x1

B. Penicillin G procaine 600,000 units IM x1

C. Penicillin V postassium 2.4 million units PO x1

D. Penicillin benzathine-procaine (Bicillin C-R) 7.2 million units IM x1

Assessment Question #2

What is the best agent for treatment of chlamydia in a pregnant patient?

A. Doxycycline 100mg PO BID x7 days

B. Azithromycin 1g PO x1

C. Azithromycin 2g PO x1

D. Ceftriaxone 500mg IM x1

Assessment Question #2: Correct Response

What is the best agent for treatment of chlamydia in a pregnant patient?

A. Doxycycline 100mg PO BID x7 days

B. **Azithromycin 1g PO x1**

C. Azithromycin 2g PO x1

D. Ceftriaxone 500mg IM x1

Assessment Question #3

Which of the following is NOT a counseling point for a patient on doxycycline?

A. Avoid excessive sun exposure

B. If diarrhea worsens, patient should contact physician

C. Allow 2-3 hours before ingesting foods high in calcium

D. Caution for increased risk of arrhythmias and QT prolongation

Assessment Question #3: Correct Response

Which of the following is NOT a counseling point for a patient on doxycycline?

A. Avoid excessive sun exposure

B. If diarrhea worsens, patient should contact physician

C. Allow 2-3 hours before ingesting foods high in calcium

D. **Caution for increased risk of arrhythmias and QT prolongation**

References

1. CDC. *MMWR Recomm Rep* 2021;70(4):1-192.
2. Geisler WM, Uniyal A, Lee JY, et al. Azithromycin versus doxycycline for urogenital chlamydia trachomatis infection. *N Engl J Med*2015;373:2512-2521.
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Deepali Dixit, PharmD, BCPS, BCCCP, FCCM

Clinical Associate Professor Ernest Mario School of Pharmacy

Robert Wood Johnson University Hospital

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Ashley Yeh, PharmD

Ashley.yeh@rwjbh.org

PGY-2 Emergency Medicine Pharmacy Resident

Robert Wood Johnson University Hospital | Rutgers University