Does this baby have congenital syphilis?

- 19 yo, presents for delivery
- G4P0030, diagnosed with syphilis Jan 2024
- Jan 2024 titers 1:256
- Dose #1 Bicillin is 7/18/2024
- Dose #2 Bicillin, no date documented
- Dose #3 8/22/24
- 11/12/24 RPR 1:2 (GC/CT negative, HIV negative)
- 12/9/24 RPR 1:4, FTA +

POLL: Was the mother adequately treated?

1. Yes, she received 3 shots and her titer went down 4-fold
2. Yes, she was overtreated as she had early syphilis
3. No, although she got 3 shots, they were not at the appropriate intervals, even if the RPR decreased by 4-fold
4. I can't tell as we didn’t get her history of previous titers.
5. No, she should have been treated with doxycyline 100mg BID x 28 days

General Screening for Syphilis

Population	Recommendations
Men who have sex with men	• At least annually if sexually active, and every 3-6 months based if increased risk*
Patients taking PrEP	• At initiation and every 3-6 months based if increased risk*
Persons living with HIV	• At diagnosis and at least annually if sexually active, and every 3-6 months if increased risk*
Non-pregnant Women (Cis-gender) and Non-MSM Men	• **No national recommendation for routine screening** • Screening at least annually is recommended in sexually active persons if increased risk*
Pregnant Women	• **First prenatal encounter plus third trimester (28 weeks) and at delivery if increased risk or in a community with increased prevalence*** **

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US Preventive Services Task Force, Curry SJ, Krist AH, Owens DK, Barry MJ, Caughey AB, Davidson KW, Doubeni CA, Epling JW Jr, Kemper AR, Kubik M, Kurth AE, Landefeld CS, Mangione CM, Phipps MG, Silverstein M, Simon MA, Tseng CW, Wong JB. Screening for Syphilis Infection in Pregnant Women: US Preventive Services Task Force Reaffirmation Recommendation Statement. JAMA. 2018 Sep 4;320(9):911-917. doi: 10.1001/jama.2018.11785. PMID: 30193283.

US Preventive Services Task Force (USPSTF), Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW Jr, García FA, Gillman MW, Harper DM, Kemper AR, Krist AH, Kurth AE, Landefeld CS, Mangione CM, Phillips WR, Phipps MG, Pignone MP. Screening for Syphilis Infection in Nonpregnant Adults and Adolescents: US Preventive Services Task Force Recommendation Statement. JAMA. 2016 Jun 7;315(21):2321-7. doi: 10.1001/jama.2016.5824. PMID: 27272583

NEW YORK CITY STD HIV PREVENTION TRAINING CENTER

Intervals between Bicillin injections: Pregnancy

- How many days between injections is acceptable for latent syphilis?
  - **General Population**
    - "If a person receives a delayed dose of penicillin in a course of weekly therapy for late latent syphilis or syphilis of unknown duration, the course of action that should be recommended is unclear"
    - Interval of 7–9 days **preferred**
    - An interval of 10–14 days between doses of benzathine penicillin for latent syphilis "**might**" be acceptable before restarting the sequence of injections
      - **Check with local health departments for their policies**

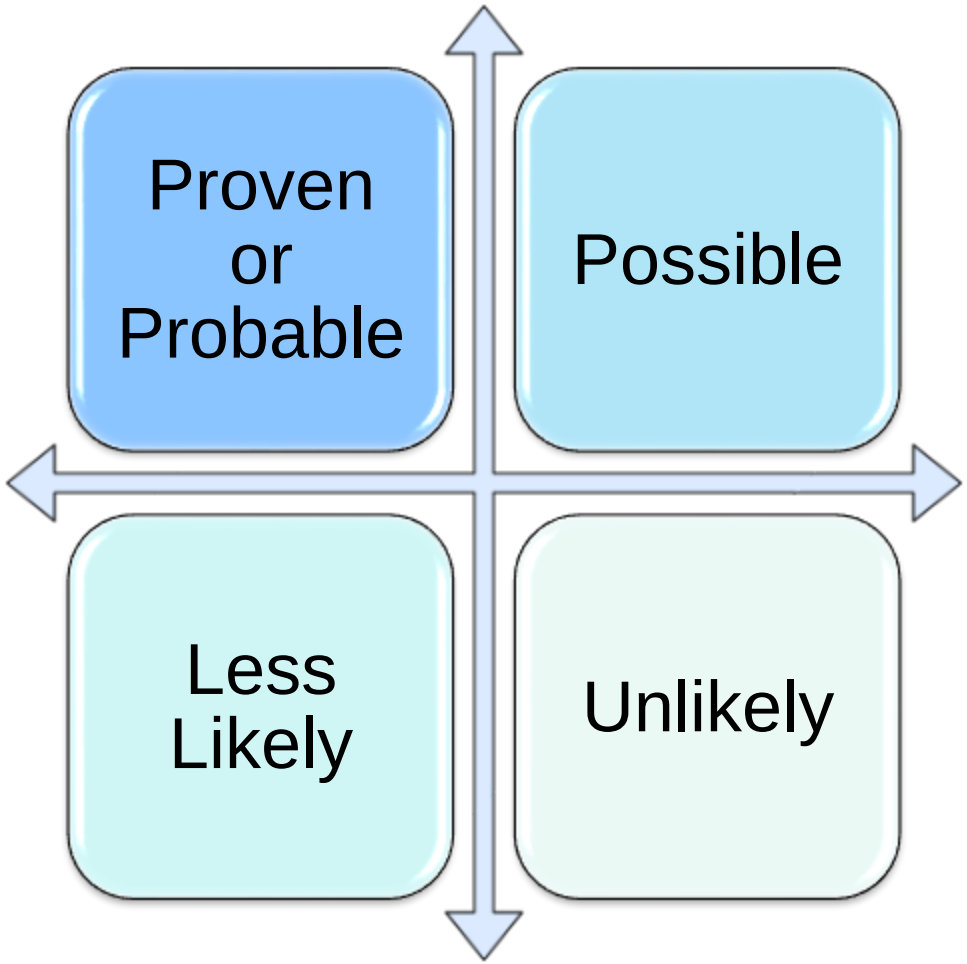
  - **Pregnant women**
    - Optimal Interval is 7 days
    - Missed doses >9 days between doses are **not acceptable**
    - Missed doses = repeat the full course of therapy

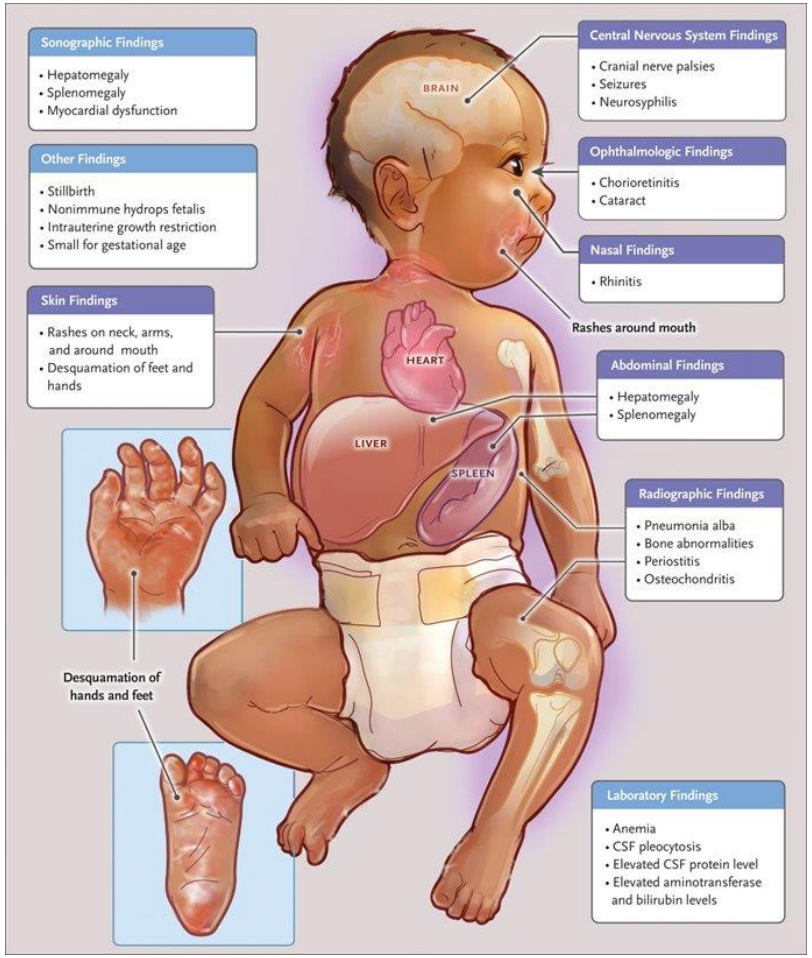
Treating Syphilis in Pregnancy

Stage	Treatment	Alternative
Incubation	Benzathine penicillin G 2.4 million units intramuscular injection once	**"Pregnant women who have a history of penicillin allergy should be desensitized and treated with penicillin"**
Primary		
Secondary		
Early latent		
Late latent	Benzathine penicillin G 2.4 million units intramuscular injection 3 times at one week intervals	
Late of unknown duration		
Neurosyphilis, Ocular, or Otic Syphilis	Aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units intravenously every 4 hours, or by continuous infusion, for 10–14 days	
Tertiary		

- Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015 Jun 5;64(RR-03):1-137. Erratum in: MMWR Recomm Rep. 2015 Aug 28;64(33):924. PMID: 26042815; PMCID: PMC5885289.

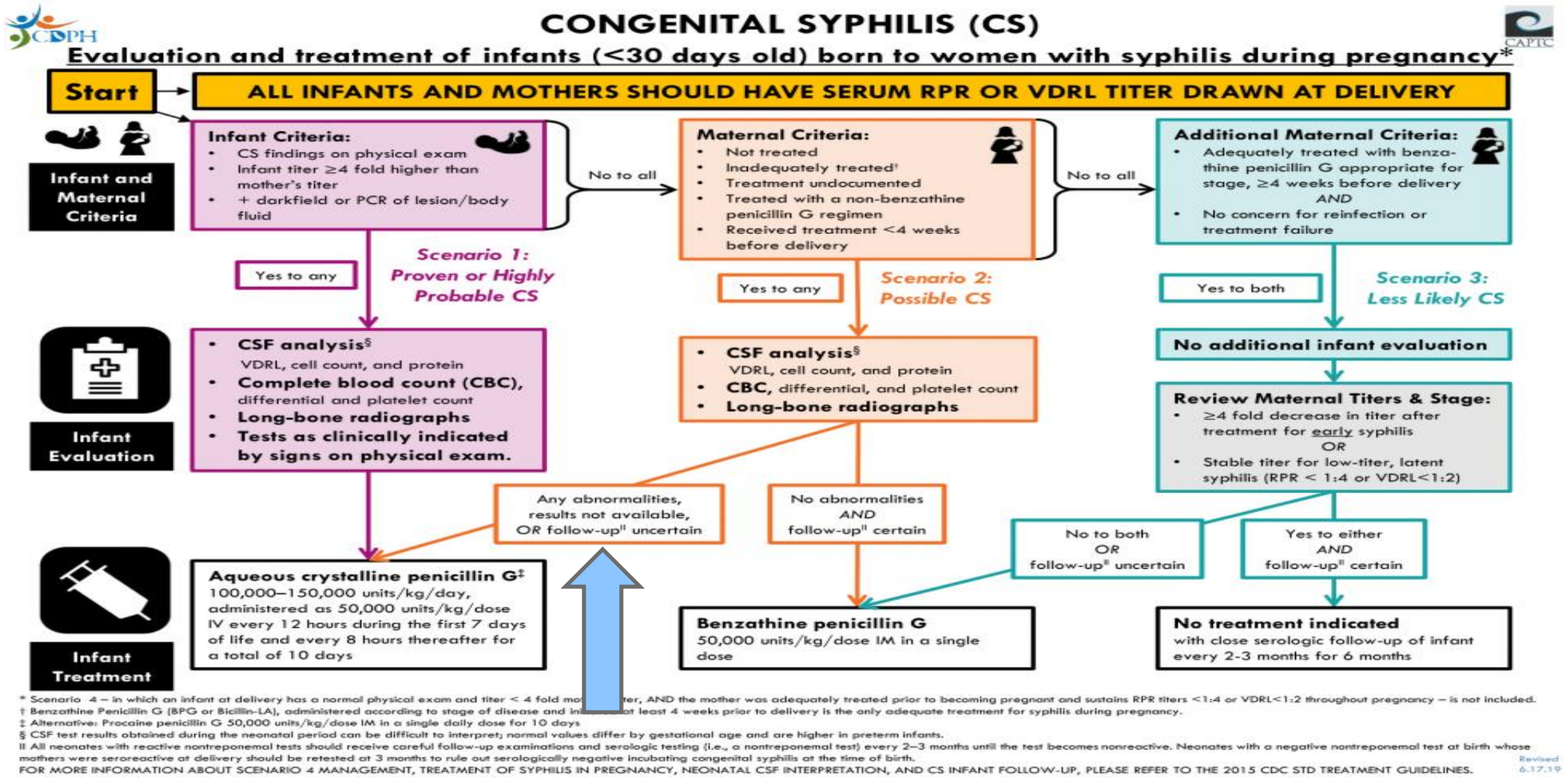
Congenital Syphilis





Stafford IA, Workowski KA, Bachmann LH. Syphilis Complicating Pregnancy and Congenital Syphilis. N Engl J Med. 2024 Jan 18;390(3):242-253. doi: 10.1056/NEJMra2202762. PMID: 38231625.

Infant Evaluation



Congenital Syphilis Management of Neonates Born to Women with Reactive Serologic Tests for Syphilis during pregnancy (Modified from the CDC 2021 STD Treatment Guidelines1)

Confirmed or Highly Probable Congenital Syphilis:

Neonatal Criteria	Neonatal Evaluation	Recommended Treatment
Abnormal physical examination consistent with congenital syphilis OR, Nontreponemal titer that is ≥ fourfold the maternal nontreponemal titer at delivery OR, Positive darkfield microscopy test or PCR of placenta, cord, lesions, blood, CSF OR, Positive immunohistochemistry or silver stain of placenta/cord	-CSF analysis for VDRL, cell count, protein -Complete blood count with differential and platelet count -Long-bone radiographs -Any other clinically indicated test (liver function test, auditory brain stem response, ophthalmologic exam	Aqueous crystalline PCN G 100,000–150,000 units/kg/day as 50,000 units/kg/dose IV every 12 hrs during the first 7 days and every 8 hrs thereafter for a total of 10 days OR, Procaine PCN G 50,000 units/kg/dose IM in a single daily dose for 10 days

*Evaluation is not necessary if a 10-day course of therapy is given.

Julie

- Julie is a 30 year old cis woman who presents for primary care follow up after an urgent care visit last week.
- She had presented for one week thin, white vaginal discharge, and vaginal itching. No pelvic pain, genital ulcers or erythema, or systemic symptoms. Has a prior history of vulvovaginal candidiasis, and thought this might be a recurrence.
- Sexual hx: History of trichomonas 2 years ago, tx w/ metronidazole complicated by nausea. 2 new male sex partners in the last 6 months. Uses condoms consistently with one partner, but not the other. Reports oral sex (gives and receives) and vaginal sex.
- Urgent care performed a multiplex vaginitis panel, and prescribed her one dose of empiric oral fluconazole given the history of VVC
- Today she notes that her discharge is unchanged
- The multiplex PCR panel comes back: + trichomonas, +BV, +M genitalium

Poll: What treatment would you offer Julie?

1. Metronidazole gel 0.75% intravaginally x 5 days
2. Azithromycin 1 g x 1, then 500 mg daily x 3 days
3. Doxycycline 100 mg BID x 7 days followed by moxifloxacin 400 mg daily x 7 days
4. Metronidazole 500 mg BID x 7 days
5. Tinidazole 2 grams once daily x 2 days
6. Concurrent doxycycline->moxifloxacin + metronidazole

Julie returns

- Julie comes back four weeks later. Her symptoms have improved slightly, but are ongoing
- You revisit her history, and she notes no sexual contact since her initial urgent care visit. However, mentions that she's a little concerned because it's been 6 weeks since her last period.
- Exam reveals some thin white vaginal discharge, no CMT, slightly erythematous cervix.
- Urine HCG at that visit is positive
- Trichomonas NAAT, G/C NAAT, Nugent score, and KOH wet prep are negative. (As is HIV ab/ag and RPR!). Mgen NAAT is positive, no reflex to susceptibility is available

Poll: What therapy would you offer Julie now?

1. Doxycycline 100 mg BID x 7 days followed by moxifloxacin 400 mg daily x 7 days
2. Doxycycline 100 mg BID x 7 days followed by azithromycin 1 gram, then 500 mg daily x 3 days
3. Azithromycin 1 gram, followed by 500 mg daily x 3 days
4. Moxifloxacin 400 mg daily x 14 days
5. No treatment

Julie's course

- You opt to treat Julie with azithromycin only
- Her symptoms resolve, and she delivers her child without complication
- You recommend that both of her sex partners are tested/treated for Mgen – one of them is seen by you, tests positive, and treated with doxy-moxi
- Julie develops symptom recurrence 6 months after delivery, tests positive for Mgen only, and is treated with doxy-moxi at that time with good resolution

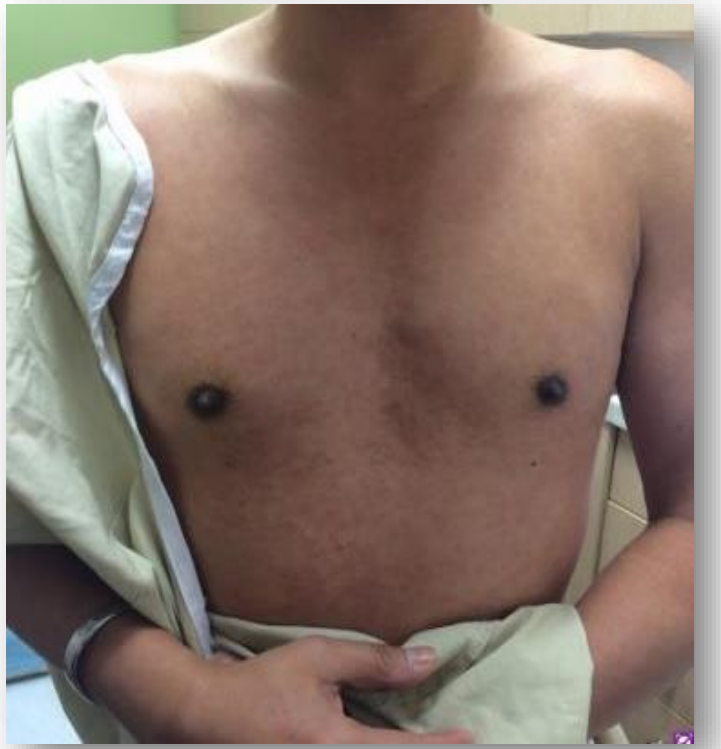
Mgen in the pregnant patient

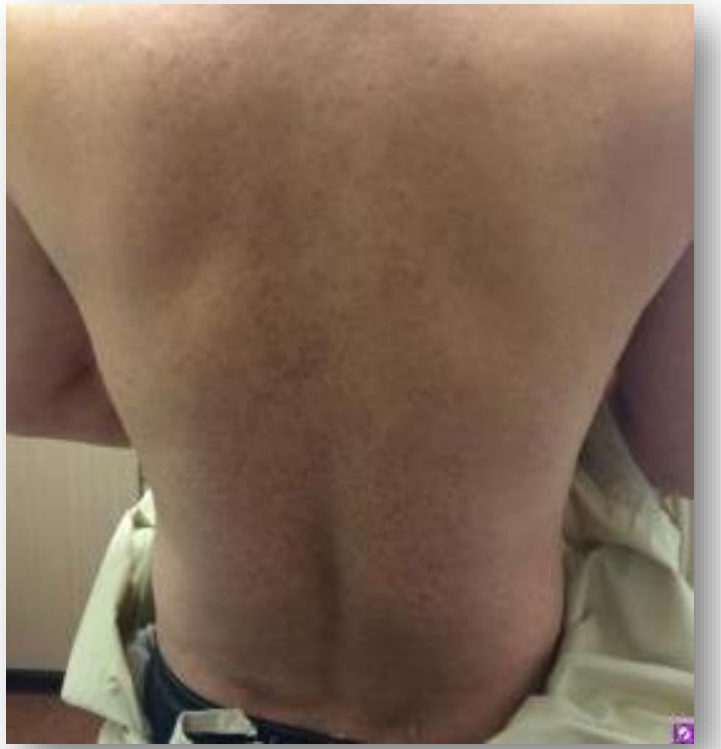
- Moxifloxacin and doxycycline not routinely recommended for use during pregnancy
- Given lack of clear evidence for harms, reasonable to defer therapy if no sxs
- For patients with symptoms, azithromycin is the only drug routinely recommended for use
  - In this group, reasonable to send macrolide resistance testing if this is available
    - If macrolide-susceptible, can treat with azithromycin 4-day course
    - If resistant, risk-benefit conversation with patient, then potential treatment after delivery

Jack

- In March, at the start of the COVID outbreak, he went to urgent care with a “rash” and rectal pain
- “STI testing” was sent but he is not sure exactly what was sent, and he never received his results
- Treated with on-site Ceftriaxone and Azithromycin

Physical Exam





Jack's Course

2 months later

- Jack felt like he was having a hard time hearing the TV
- Went to the ED where he was seen by ENT
  - "Asymmetric hearing loss, please get MRI"
  - MRI unremarkable
  - Told to follow-up outpatient

Jack's Course

2 months later

- Jack felt like he was having a hard time hearing the TV
- Went to the ED where he was seen by ENT
  - "Asymmetric hearing loss, please get MRI"
  - MRI unremarkable
  - Told to follow-up outpatient

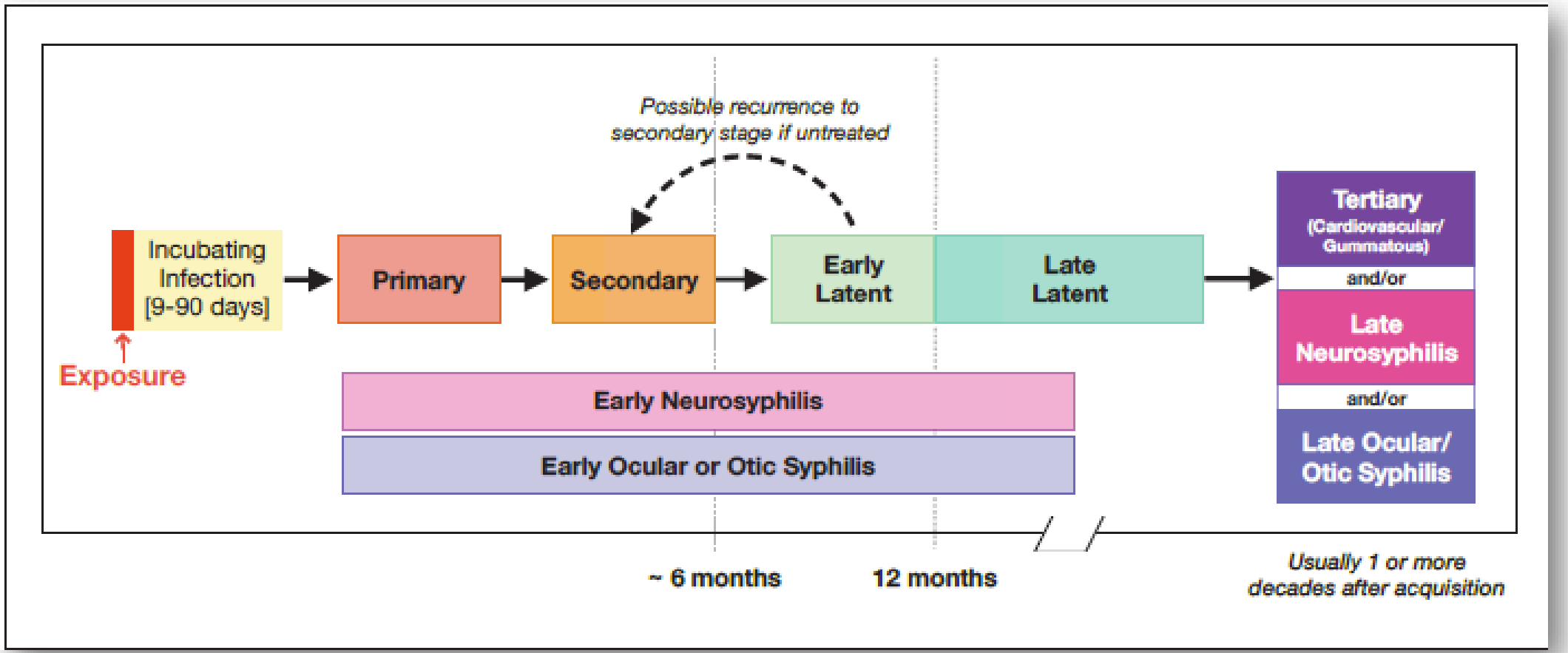
1 month later

- Jack felt like he was having a hard time seeing the TV
- Went to the ED where he was seen by Optho
  - "Panuveitis"
  - "**Send panuveitis work-**up"
  - Told to follow-up outpatient

Poll: For Panelists

- What are you thinking?

Syphilis


Possible recurrence to secondary stage if untreated
Incubating Infection [9-90 days]
Exposure
Primary
Secondary
Early Latent
Late Latent
Tertiary (Cardiovascular/ Gummatous)
and/or
Late Neurosyphilis
and/or
Late Ocular/ Otic Syphilis
Early Neurosyphilis
Early Ocular or Otic Syphilis
~ 6 months
12 months
Usually 1 or more decades after acquisition

Enhanced Clinical Descriptions of Ocular and Otic Manifestations

Ocular Syphilis

- Often presents as panuveitis
- Can involve any structure in the anterior and posterior segment of the eye including:
  - Conjunctivitis
    - Red eye/Pain
  - Anterior uveitis
  - Posterior interstitial keratitis
  - Optic neuropathy
  - Retinal vasculitis
- Can lead to **permanent** vision loss

Otosyphilis

- Typically presents with cochleo-vestibular symptoms including
  - Tinnitus
  - Vertigo
  - Sensorineural hearing loss
    - Unilateral/Bilateral
    - Have a sudden onset
    - Progress Rapidly
- Can result in **permanent** hearing loss

Screening for Neurosyphilis

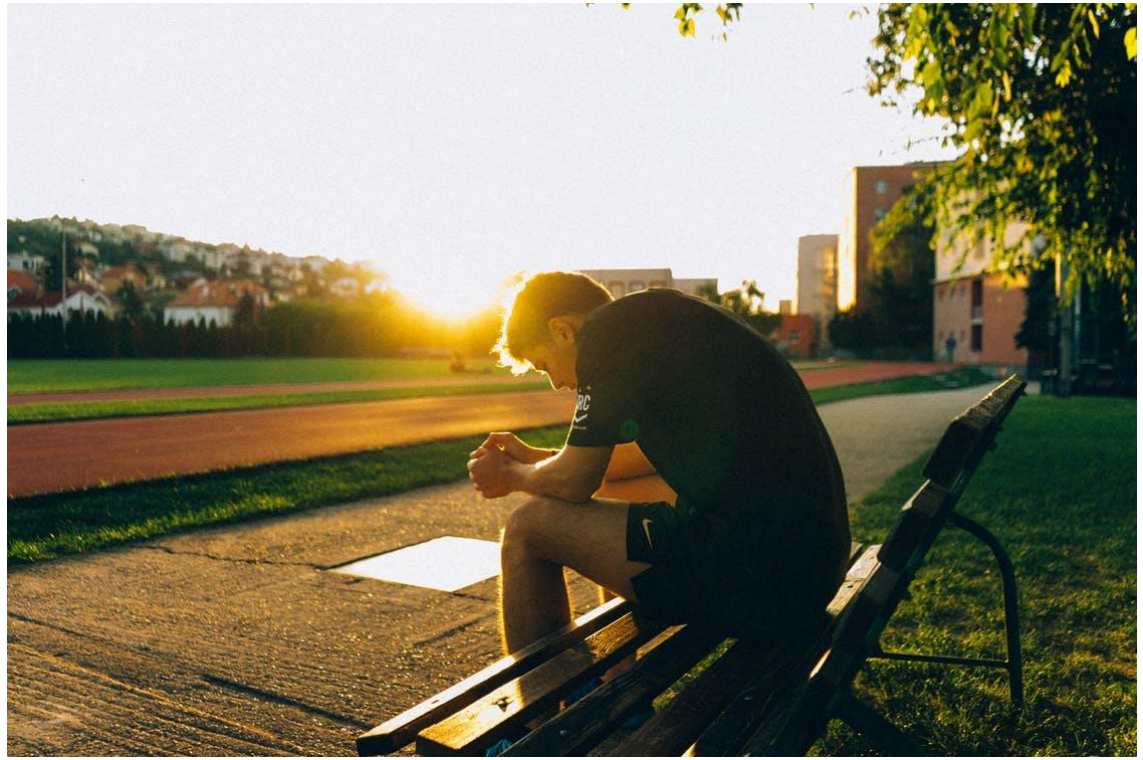
Screening Questions for Neurosyphilis (Including Ocular and Otosyphilis)

Questions	
Symptoms of Otosyphilis	
1) Have you recently had new trouble hearing?	☐ Yes – refer to ENT ☐ No
2) Do you have ringing in your ears?	☐ Yes – refer to ENT ☐ No
Symptoms of Ocular syphilis	
3) Have you recently had a change in vision?	☐ Yes – refer to ophthalmology ☐ No
4) Do you see flashing lights?	☐ Yes – refer to ophthalmology ☐ No
5) Do you see spots that move or float by in your vision?	☐ Yes – refer to ophthalmology ☐ No
6) Have you had any blurring of your vision?	☐ Yes – refer to ophthalmology ☐ No
Symptoms of neurosyphilis	
7) Are you having headaches?	☐ Yes ☐ No
8) Have you recently been confused?	☐ Yes ☐ No
9) Has your memory recently gotten worse?	☐ Yes ☐ No
10) Do you have trouble concentrating?	☐ Yes ☐ No
11) Do you feel that your personality has recently changed?	☐ Yes ☐ No
12) Are you having a new problem walking?	☐ Yes ☐ No
13) Do you have weakness or numbness in your legs?	☐ Yes ☐ No

- http://www.kingcounty.gov/healthservices/health/communicable/hiv.aspx

Jack's Diagnosis

- RPR returned 1:128
- Called by the DOH
- Came into STD clinic



Poll: Does Jack Need an LP?

- Yes
- No

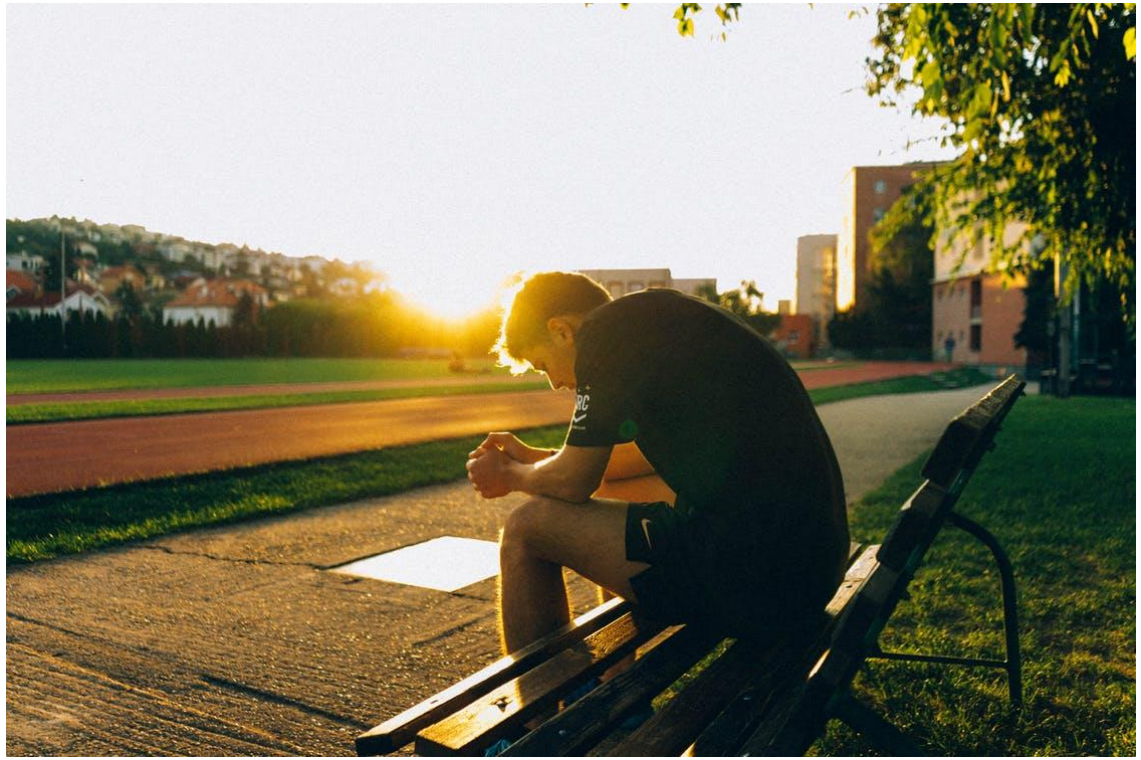
Syphilis Management

No – Updated Guidelines Recommend Fewer Lumbar Punctures

- Neuro syphilis
  - No repeat CSF exam at 6 months with adequate RPR response (HIV - and HIV+/ART)
- Isolated ocular symptoms and no cranial nerve dysfunction
  - CSF exam is not necessary
- Otic syphilis
  - CSF exam is not necessary

Jack's Diagnosis

- RPR returned 1:128
- Called by the DOH
- Came into STD clinic



Poll: How Would You Treat Jack?

- 2.4 million units IM PCN G x 1
- 2.4 million units IM PCN G weekly x 3 weeks
- Aqueous crystalline penicillin G 18–24 million units per day IV for days
- Procaine penicillin G 2.4 million units IM once daily *PLUS* Probenecid 500mg 4 times daily for 10 days

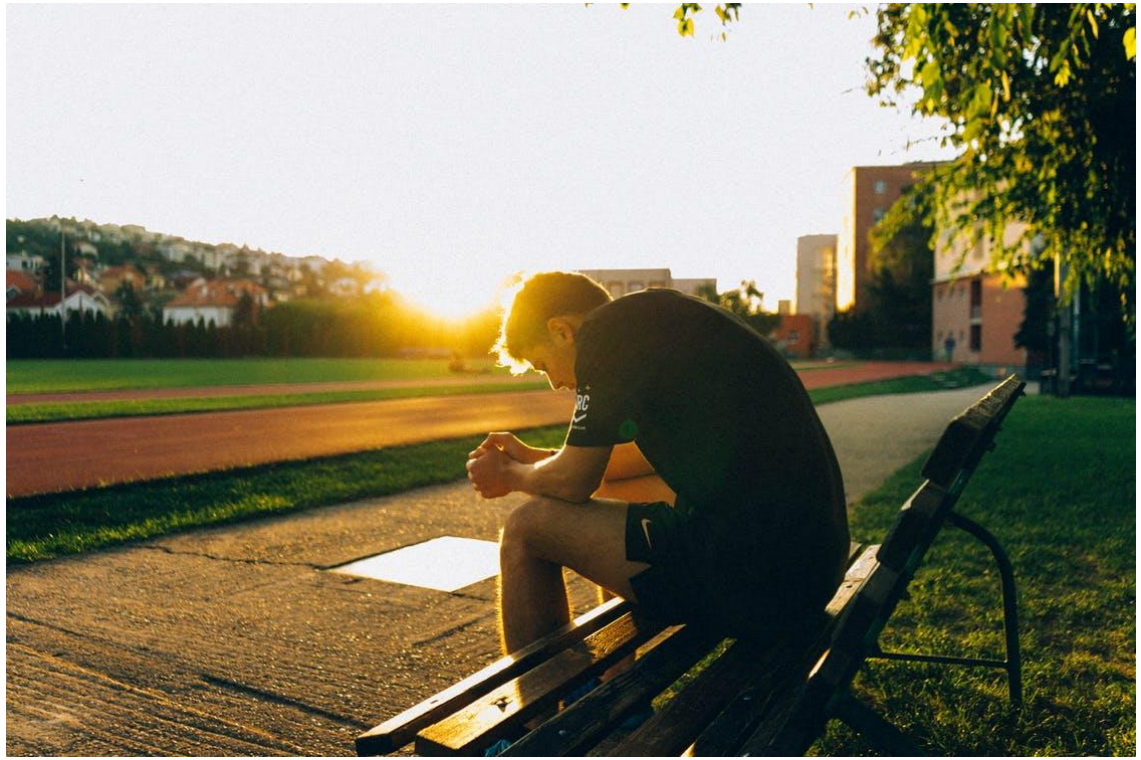
Recommended Options for Treating Syphilis

Stage	Treatment	Alternative
Incubation	**Benzathine penicillin** G 2.4 million units intramuscular injection once	**Doxycycline** 100mg twice daily for 14 days
Primary		
Secondary		
Early latent		
Late latent	**Benzathine penicillin** G 2.4 million units intramuscular injection 3 times at one week intervals	**Doxycycline** 100mg twice daily for 28 days
Syphilis of unknown duration		
Tertiary (non-neuro)		
Neurosyphilis, Ocular, or Otic Syphilis	**Aqueous crystalline penicillin** G 18–24 million units per day, administered as 3–4 million units intravenously every 4 hours, or by continuous infusion, for 10–14 days	**Procaine penicillin** G 2.4 million units IM once daily *PLUS* Probenecid 500mg 4 times daily for 10–14 days

• Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015 Jun 5;64(RR-03):1-137. Erratum in: MMWR Recomm Rep. 2015 Aug 28;64(33):924. PMID: 26042815; PMCID: PMC5885289.

Jack's Diagnosis

- RPR returned 1:128
- Called by the DOH
- Came into STD clinic
  - PICC placed at home
  - Improved with 14 days of IV PCN



Jasmine

- Jasmine is a 28 year old cis woman presenting to re-establish primary care after her prior PCP retired 1 year ago
- No acute complaints today, but notes that about 9 months ago she an “uncomfortable vaginal rash.” She’d had a similar rash 2 years ago while travelling internationally, which was treated with acyclovir. This time, a covering doctor from her old practice sent her a prescription for valacyclovir, which seemed to help speed her recovery. She reports that no one has ever taken a specimen from her rash, though she recalls being told she had herpes.
- Sexual history notable for one cis-male partner for the past year. They are monogamous, and do not use condoms. She has no other STI history, and tested negative for HIV, syphilis, and gonorrhea/chlamydia 2 years ago. She is not currently using any other form of contraception.
- She requests another prescription for valacyclovir so that she can have this available if the rash comes back

Poll: What should we do for Jasmine?

1. Tell her to come back if the rash recurs so that we can evaluate and send testing at that time
2. Send a serum HSV-1/HSV-2 IgG
3. Prescribe valacyclovir 500 mg BID x 3 days to be taken at the first symptom of a rash
4. Send a vaginal swab for HSV-1/HSV-2 PCR
5. Prescribe valacyclovir 1 gram daily to prevent future recurrences

Jasmine's results

- Her HSV-2 IgG is positive (HSV-1 IgG negative, as is comprehensive HIV/STI screening!)
- Since she's only had 2 outbreaks, you prescribe Jasmine valacylovir to keep on hand for episodic therapy and ask her to let you know about future outbreaks
- You also counsel her that she should inform her partner about her diagnosis. He subsequently visits his PCP, and also tests positive for HSV-2 IgG
- Several years later, Jasmine comes back to your office and lets you know that she's 24 weeks pregnant. She already established with OB/GYN at another practice, and is getting all recommended prenatal care. She hasn't had any recurrences of genital herpes since you met her. On further questioning she realizes she forgot to tell her OB-GYN about the herpes since it was so long ago

Poll: What needs to happen for Jasmine?

(Besides making sure her OB finds out this important information)

1. Start suppressive valacyclovir now
2. Tell her to expect delivery by C-section
3. Tell her she'll need to start suppressive valacyclovir at 36 weeks
4. Make sure she still has the valacyclovir you originally prescribed, and tell her to take it only if she develops symptoms
5. No need for any treatment since she's never had another recurrence

Jasmine's course

- With Jasmine's consent, you share her HSV-2 diagnosis and treatment history with her OB-GYN
- She self-monitors for symptoms suggestive of recurrence, but remains asymptomatic
- She is started on suppressive acyclovir at 36 weeks and delivers via NSVD without incident

Guideline updates – serologic HSV testing

- Useful
  - Recurrent or atypical genital symptoms or lesions with a negative HSV PCR or culture result
  - Clinical diagnosis of genital herpes without laboratory confirmation
  - 12 weeks after suspected recent acquisition
  - Patient's partner has genital herpes

- Might be useful
  - Persons at higher risk for infection (presenting for STI evaluation—10 or more lifetime sex partners)
  - Persons with HIV

- Not useful
  - Screening of the general population

Two-Step Serologic Testing

Step 1: EIA Assay (IgG)* (often falsely positive at low index value (<3.0)

Positive EIA

Step 2: Confirm with a second test that uses a different antigen (Biokit/Western blot)

*IgM is not recommended for serologic testing

Preventing Transmission

- Daily valacyclovir lowers the risk of HSV-2 transmission from HIV-negative people with symptomatic genital herpes (approx. 50%)
  - Unknown if this is true for those without a history of symptoms. Not effective/recommended for people with HIV not on ART
- Condom use can decrease, but not eliminate, the risk for HSV-2 transmission
- Male medical circumcision
- Caution against HSV acquisition during pregnancy – avoid genital and/or oral sex with partners who have history of orolabial or genital herpes in 3rd trimester, monitor closely peri-delivery
- Pregnant people with a history of genital herpes should be offered suppression starting at 36 weeks to decrease risk of recurrence during delivery, c-section rate, and asymptomatic shedding

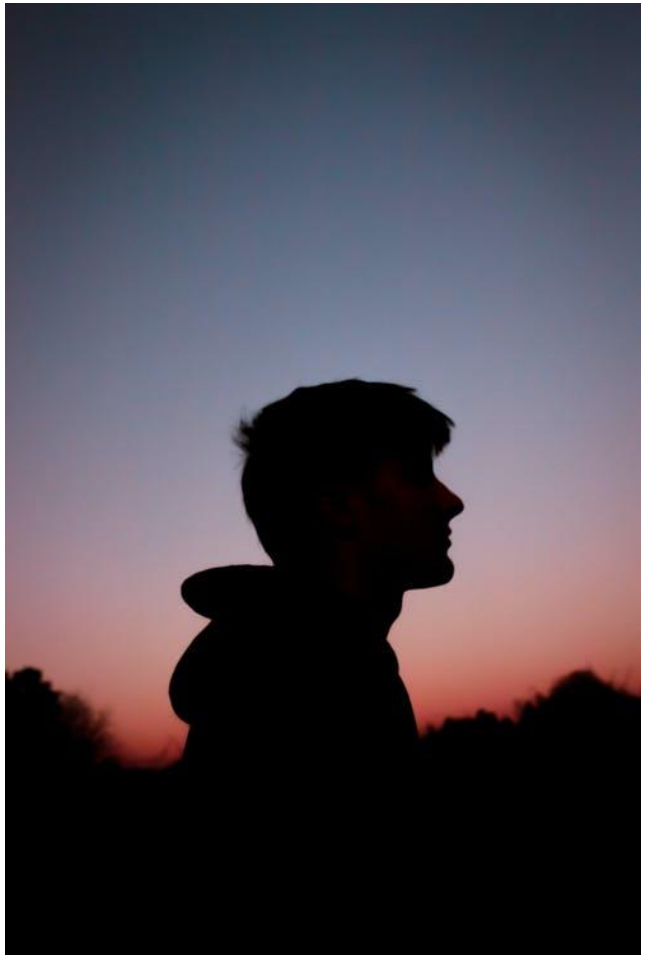
- Corey L, Wald A, Patel R, Sacks SL, Tyring SK, Warren T, Douglas JM Jr, Paavonen J, Morrow RA, Beutner KR, Stratchounsky LS, Mertz G, Keene ON, Watson HA, Tait D, Vargas-Cortes M; Valacyclovir HSV Transmission Study Group. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. N Engl J Med. 2004 Jan 1;350(1):11-20
- Urato AC. ACOG Practice Bulletin No. 220: Management of Genital Herpes in Pregnancy. Obstet Gynecol. 2020 Oct;136(4):850-851

Igor

- 29-year-old male
- Takes HIV PrEP for HIV prevention
- Sexually active with men
  - Four condomless partners since his last visit
  - Is a walks in to clinic between quarterly visits with 2 days of green penile discharge

- **Routine testing for HIV, syphilis, and three-site gonorrhea/chlamydia testing performed**

- **Treated empirically with Ceftriaxone and Doxycycline**



Igor's Results

Lab results:

HIV Ab/Ag – non-reactive

Urine GC/CT – GC positive

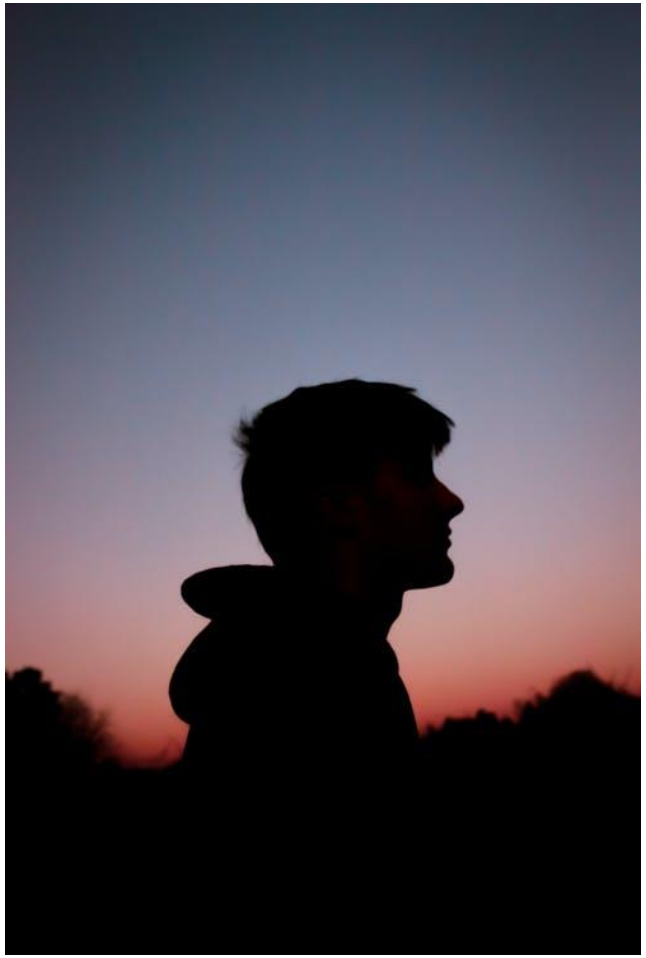
Pharyngeal GC/CT – GC positive

Rectal GC/CT – GC positive

RPR – Negative

Igor

- Returned 6 weeks later saying that, **“I got totally better but now it hurts again when I pee”**
  - Seven condomless partners since his last visit
  - Confident that his regular partners were treated for gonorrhea and syphilis
  - Repeat routine testing for HIV, syphilis, and three-site gonorrhea/chlamydia testing was performed
  - Treated empirically (again) with Ceftriaxone and Doxycycline
  - Started on Doxy-PEP



Igor's Results

Lab results:

HIV Ab/Ag – non-reactive

Urine GC/CT – Negative

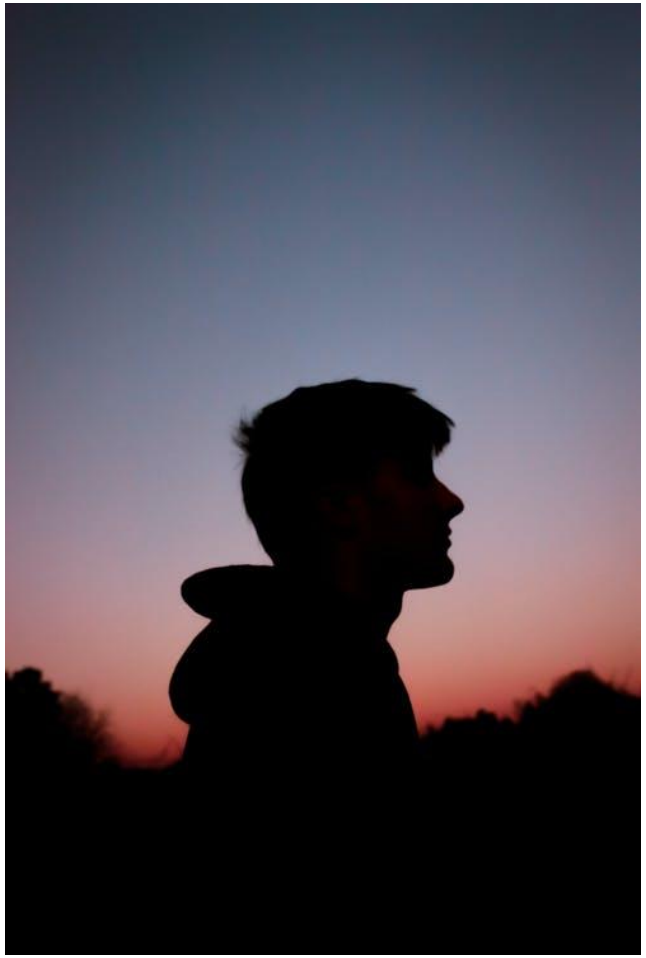
Pharyngeal GC/CT – GC positive

Rectal GC/CT – GC positive

RPR – Negative

Igor

- Returned 3 weeks later saying that, **“I never got totally better but now it hurts really bad again when I pee”**
  - One condomless partner since his last visit
  - Confident that this partner was treated for gonorrhea and syphilis



Poll: What Would You Do Next?

1. Retreat with Ceftriaxone and Doxycycline
2. Treat with Gentamicin and Azithromycin
3. Get a urine culture
4. Get a gonorrhea culture

Gonorrhea Resistance

Rising Gonorrhea Resistance

First case of super-resistant gonorrhea reported

The Commonwealth of Massachusetts
Executive Office of Health and Human Services
Department of Public Health
Bureau of Infectious Disease and Laboratory Sciences
305 South Street, Boston, MA 02130

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Commissioner

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www.mass.gov/dph

CLINICAL ALERT
January 19, 2023

MULTI-DRUG NON-SUSCEPTIBLE GONORRHEA IN MASSACHUSETTS

- A novel strain of multidrug-non-susceptible *Neisseria gonorrhoeae* with reduced susceptibility to ceftriaxone, cefixime, and azithromycin, and resistance to ciprofloxacin, penicillin, and tetracycline, has been identified in a Massachusetts resident. Although ceftriaxone 500 mg IM was effective at clearing infection for this case, this is the first isolate identified in the United States to demonstrate resistance or reduced susceptibility to all drugs that are recommended for treatment.
- Enhanced surveillance has identified a second isolate that, based on its genome, likely has similarly reduced susceptibility to ceftriaxone and cefixime.

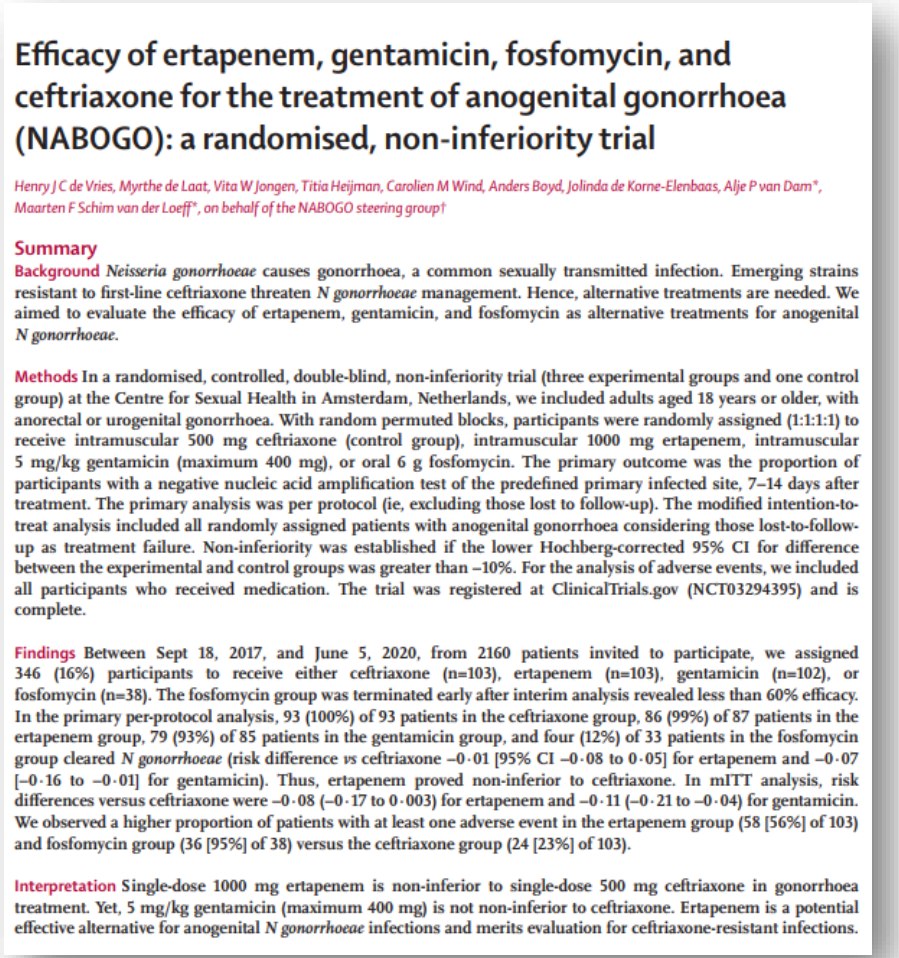
V STUDY RAISING ALARMS ABOUT "SUPERBUGS"

Video Ad Feedback

How bugs become superbugs

00:58 · Source: CNN

What Could Be Our Next Option?



Efficacy of ertapenem, gentamicin, fosfomycin, and ceftriaxone for the treatment of anogenital gonorrhoea (NABOGO): a randomised, non-inferiority trial

Henry J C de Vries, Myrthe de Laat, Vita W Jongen, Titia Heijman, Carolien M Wind, Anders Boyd, Jolinda de Korne-Elenbaas, Alje P van Dam*, Maarten F Schim van der Loeff*, on behalf of the NABOGO steering group†

Summary

Background *Neisseria gonorrhoeae* causes gonorrhoea, a common sexually transmitted infection. Emerging strains resistant to first-line ceftriaxone threaten *N gonorrhoeae* management. Hence, alternative treatments are needed. We aimed to evaluate the efficacy of ertapenem, gentamicin, and fosfomycin as alternative treatments for anogenital *N gonorrhoeae*.

Methods In a randomised, controlled, double-blind, non-inferiority trial (three experimental groups and one control group) at the Centre for Sexual Health in Amsterdam, Netherlands, we included adults aged 18 years or older, with anorectal or urogenital gonorrhoea. With random permuted blocks, participants were randomly assigned (1:1:1:1) to receive intramuscular 500 mg ceftriaxone (control group), intramuscular 1000 mg ertapenem, intramuscular 5 mg/kg gentamicin (maximum 400 mg), or oral 6 g fosfomycin. The primary outcome was the proportion of participants with a negative nucleic acid amplification test of the predefined primary infected site, 7–14 days after treatment. The primary analysis was per protocol (ie, excluding those lost to follow-up). The modified intention-to-treat analysis included all randomly assigned patients with anogenital gonorrhoea considering those lost-to-follow-up as treatment failure. Non-inferiority was established if the lower Hochberg-corrected 95% CI for difference between the experimental and control groups was greater than –10%. For the analysis of adverse events, we included all participants who received medication. The trial was registered at ClinicalTrials.gov (NCT03294395) and is complete.

Findings Between Sept 18, 2017, and June 5, 2020, from 2160 patients invited to participate, we assigned 346 (16%) participants to receive either ceftriaxone (n=103), ertapenem (n=103), gentamicin (n=102), or fosfomycin (n=38). The fosfomycin group was terminated early after interim analysis revealed less than 60% efficacy. In the primary per-protocol analysis, 93 (100%) of 93 patients in the ceftriaxone group, 86 (99%) of 87 patients in the ertapenem group, 79 (93%) of 85 patients in the gentamicin group, and four (12%) of 33 patients in the fosfomycin group cleared *N gonorrhoeae* (risk difference *vs* ceftriaxone –0·01 [95% CI –0·08 to 0·05] for ertapenem and –0·07 [–0·16 to –0·01] for gentamicin). Thus, ertapenem proved non-inferior to ceftriaxone. In mITT analysis, risk differences versus ceftriaxone were –0·08 (–0·17 to 0·003) for ertapenem and –0·11 (–0·21 to –0·04) for gentamicin. We observed a higher proportion of patients with at least one adverse event in the ertapenem group (58 [56%] of 103) and fosfomycin group (36 [95%] of 38) versus the ceftriaxone group (24 [23%] of 103).

Interpretation Single-dose 1000 mg ertapenem is non-inferior to single-dose 500 mg ceftriaxone in gonorrhoea treatment. Yet, 5 mg/kg gentamicin (maximum 400 mg) is not non-inferior to ceftriaxone. Ertapenem is a potential effective alternative for anogenital *N gonorrhoeae* infections and merits evaluation for ceftriaxone-resistant infections.

- Randomized, controlled, double-blind, non-inferiority trial
- 346 randomly assigned
  - 103 – Ceftriaxone
  - 103 – Ertapenem
  - 102 – Gentamicin
  - 38 - Fosfomycin

Teker B, de Vries H, Heijman T, van Dam A, Schim van der Loeff M, Jongen VW. Spontaneous clearance of asymptomatic anogenital and pharyngeal *Neisseria gonorrhoeae*: a secondary analysis from the NABOGO trial. *Sex Transm Infect*. 2023;99(4):219-225. doi:10.1136/sextrans-2022-055488

What Could Be Our Next Option?

	Ceftriaxone group	Ertapenem group	Gentamicin group	Fosfomycin group	Ertapenem vs ceftriaxone		Gentamicin vs ceftriaxone		Fosfomycin vs ceftriaxone	
					Risk difference*	p†	Risk difference*	p†	Risk difference*	p†
Primary analysis per protocol*										
Clearance (7–14 days)	93/93 (100%; 96 to 100)	86/87 (99%; 94 to 100)	79/85 (93%; 85 to 97)	4/33 (12%; 3 to 28)	−0·01 (−0·08 to 0·05)	0·0089	−0·07 (−0·16 to −0·01)	0·37	−0·88 (−0·95 to −0·72)	1·000
Secondary analysis modified intention-to-treat‡										
Clearance (7–14 days)	93/93 (100%; 96 to 100)	86/93 (92%; 85 to 97)	79/89 (89%; 80 to 94)	4/35 (11%; 3 to 27)	−0·08 (−0·17 to 0·003)	0·64	−0·11 (−0·21 to −0·04)	1·000	−0·89 (−0·96 to −0·74)	1·000
Secondary analysis per protocol§										
Clearance (7–28 days)	93/93 (100%; 96 to 100)	87/88 (99%; 94 to 100)	82/88 (93%; 86 to 97)	4/33 (12%; 3 to 28)	−0·01 (−0·08 to 0·05)	0·0084	−0·07 (−0·16 to −0·003)	0·32	−0·88 (−0·95 to −0·72)	1·000
Secondary analysis strict per protocol¶										
Clearance (7–14 days)	81/81 (100%; 96 to 100)	78/79 (99%; 93 to 100)	75/81 (93%; 85 to 97)	3/28 (11%; 2 to 28)	−0·01 (−0·09 to 0·05)	0·015	−0·07 (−0·17 to −0·001)	0·44	−0·89 (−0·96 to −0·72)	1·000

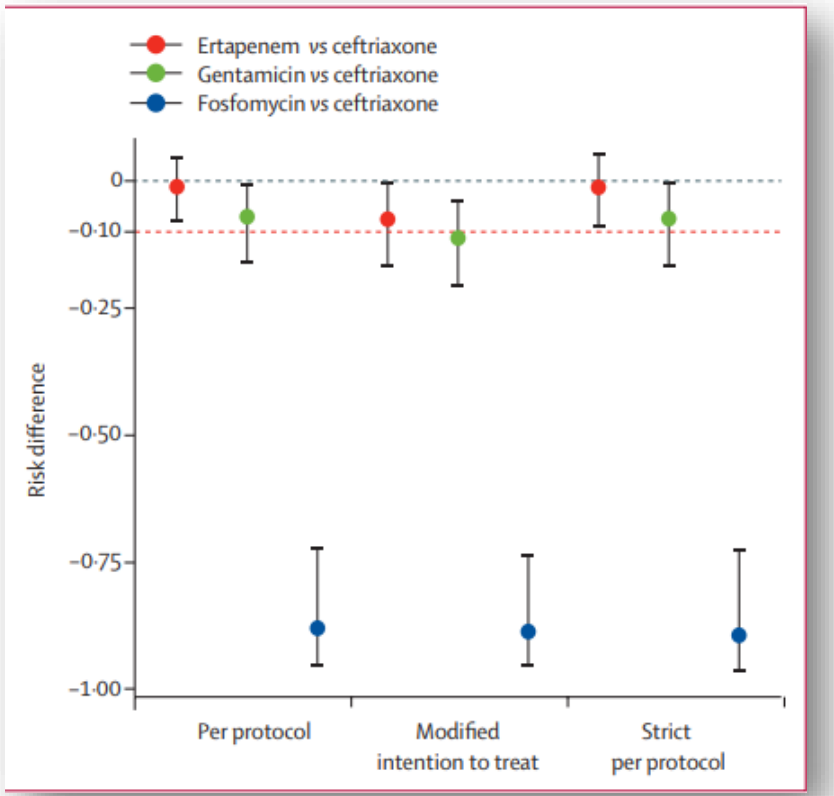
Efficacy

- Ceftriaxone 100%
- Ertapenem 99%
- Gentamicin 93%

- Teker B, de Vries H, Heijman T, van Dam A, Schim van der Loeff M, Jongen VW. Spontaneous clearance of asymptomatic anogenital and pharyngeal *Neisseria gonorrhoeae*: a secondary analysis from the NABOGO trial. *Sex Transm Infect*. 2023;99(4):219-225. doi:10.1136/sextrans-2022-055488

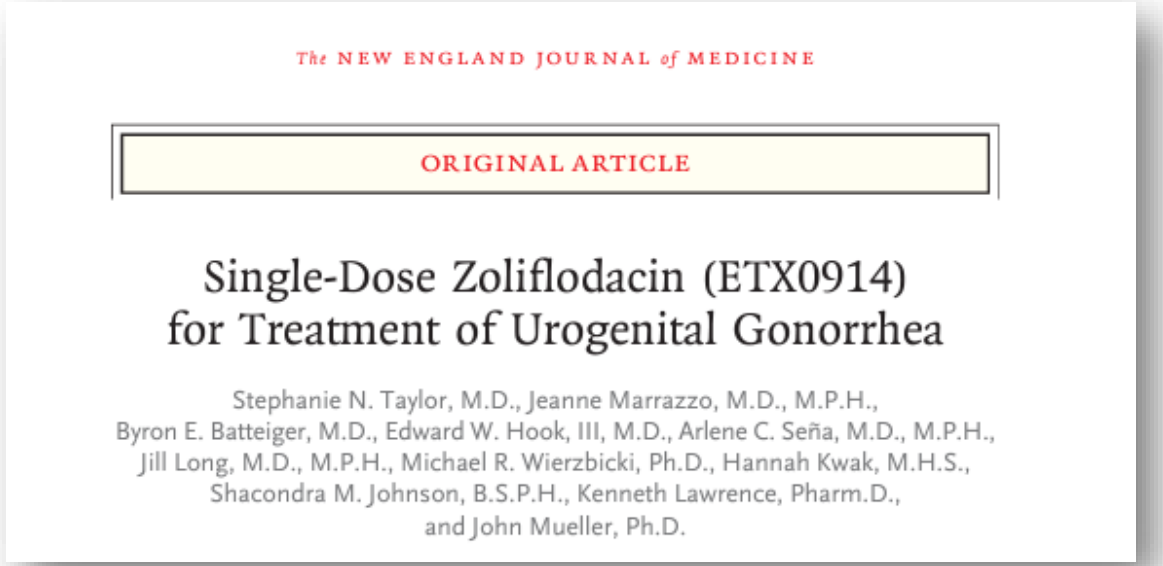
What Could Be Our Next Option?

- Single-dose ertapenem 1000 mg **is non-inferior** to single-dose ceftriaxone 500 mg for uncomplicated anogenital gonorrhea
- Single-dose 5 mg/kg gentamicin (max 400mg) is **not non-inferior** to ceftriaxone
- Single-dose oral fosfomycin was ineffective



- Teker B, de Vries H, Heijman T, van Dam A, Schim van der Loeff M, Jongen VW. Spontaneous clearance of asymptomatic anogenital and pharyngeal *Neisseria gonorrhoeae*: a secondary analysis from the NABOGO trial. *Sex Transm Infect*. 2023;99(4):219-225. doi:10.1136/sextrans-2022-055488

What Could Be Our Next Option?



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Single-Dose Zoliflodacin (ETX0914) for Treatment of Urogenital Gonorrhea

Stephanie N. Taylor, M.D., Jeanne Marrazzo, M.D., M.P.H., Byron E. Batteiger, M.D., Edward W. Hook, III, M.D., Arlene C. Seña, M.D., M.P.H., Jill Long, M.D., M.P.H., Michael R. Wierzbicki, Ph.D., Hannah Kwak, M.H.S., Shacondra M. Johnson, B.S.P.H., Kenneth Lawrence, Pharm.D., and John Mueller, Ph.D.

New gonorrhea antibiotic shows promise in pivotal phase 3 trial

Chris Dall, MA, *November 2, 2023*

Topics: Antimicrobial Stewardship , Gonorrhea

SHARE

A desperately needed new antibiotic for gonorrhea infections could soon be on the way.

In a phase 3 trial conducted in five countries, the investigational oral antibiotic zoliflodacin met its primary end point, demonstrating statistical non-inferiority in curing patients who had uncomplicated urogenital gonorrhea infections compared with the standard treatment of intramuscular ceftriaxone and oral azithromycin. Zoliflodacin was also found to be well tolerated by patients, with no serious adverse events or deaths recorded.

A first-in-class antibiotic with a novel mechanism of action,

iLexx / iStock

- Taylor SN, Marrazzo J, Batteiger BE, et al. Single-Dose Zoliflodacin (ETX0914) for Treatment of Urogenital Gonorrhea. *N Engl J Med*. 2018;379(19):1835-1845. doi:10.1056/NEJMoa1706988

Igor's Results

Lab results:

HIV Ab/Ag - Negative

Urine GC/CT – GC positive

Pharyngeal GC/CT – GC positive

Rectal GC/CT – negative

RPR – 1:4

Igor's Gonorrhea Culture

Lab results:

Azithromycin – susceptible (MIC 0.125)

Ciprofloxacin – resistant (MIC 1)

Ceftriaxone – susceptible (MIC 0.016)

Cefixime – Susceptible (48mm)

Tetracycline – resistant (MIC 12)

Is there anything else you can offer me?

17-year-old with medication intolerance

- 17 yo presented to ED 48 hrs after a sexual assault; history of running away, depression, anxiety, oppositional defiant behavior and self-harm
- ED evaluation included:
  - GC/CT NAAT (urine, pharnyeal, and rectal)
  - Review of immunization history Hep B
  - Blood testing for HIV, HCV, and syphilis, HepB; also creatinine, Liver function tests
  - Medication treatment (STI treatment and HIV PEP):
    - ceftriaxone 500 mg IM, doxycycline 100 mg po BID x 7 days, metronidazole 500 mg BID x 7 days
    - Truvada 300 mg /emtricidibine 200 mg daily + raltegravir 400 mg BID
- Returns 1 week later, complaining of abdominal pain and vomiting, low grade fever per report

POLL: What are you concerned about?

1. Medication toxicity such as renal disease
2. Development of pelvic inflammatory disease
3. Medication toxicity such as liver dysfunction
4. Pregnancy
5. Intolerance to HIV medication due to nausea
6. CNS issue e.g. intracranial hypertension due to doxycycline
7. None of the above

ED follow up visit

Non-toxic appearing but distressed

- Vitals: Temp 38, BP 110/70, RR 20
- Exam: lower abdominal tenderness, pelvic exam- no discharge, but cervical motion tenderness, no adenxal fullness
- Labs: GC/CT NAAT negative (all three sites), RPR non-reactive, HIV negative, Hep B Ab+ , Hepatitis C negative, WBC 8K, 75% pmn; CRP 10, ESR 30.

Poll: what would you do now?

1. Restart all medications (antibiotics and PEP) oral
2. Restart PEP first and then other medications
3. Start her on IV zidovudine
4. Start IV azithromycin, ceftriaxone and metronidazole and previous PEP medications (tenofovir/emtricidibine + raltegravir)
5. Start IV azithromycin, cefotaxime and metronidazole and change PEP to biktarvy
6. Phone the PEP hotline

Follow up

- ID consulted, discussed treatment for PID
- Team agreed to trial changing of some medications to IV e.g. metronidazole and azithromycin for a few days
- Changed the PEP regimen to biktarvy
- She tolerated all of this and was discharged to psychiatric facility

CDC recommended prophylaxis for STIs in Sexual Assault

Recommended Regimen for Adolescent and Adult Female Sexual Assault Survivors

Ceftriaxone 500 mg* IM in a single dose

PLUS

Doxycycline 100 mg 2 times/day orally for 7 days

PLUS

Metronidazole 500 mg orally 2 times/day orally for 7 days

* For persons weighing ≥150 kg, 1 g of ceftriaxone should be administered.

Recommended Regimen for Adolescent and Adult Male Sexual Assault Survivors

Ceftriaxone 500 mg* IM in a single dose

PLUS

Doxycycline 100 mg 2 times/day orally for 7 days

* For persons weighing ≥150 kg, 1 g of ceftriaxone should be administered.

Concern for PID due to symptoms

- Mild to moderate pelvic inflammatory disease (PID). No new information on the definition of this condition.

- Clinical diagnostic criteria (minimum 3 criteria)
  - Temperature >38.3C
  - Abnormal mucopurulent cervical discharge
  - WBC in vaginal saline microscopy (wet prep)
  - Elevated ESR and CRP
  - + test for GC/CT

PID Treatment

- Ceftriaxone **500** mg IM x 1
  for persons weighing <150kg*

Ceftriaxone 1g Q24 hours

Doxycycline 100 mg PO twice daily x 14 days

Doxycycline 100 mg PO twice daily x 14 days

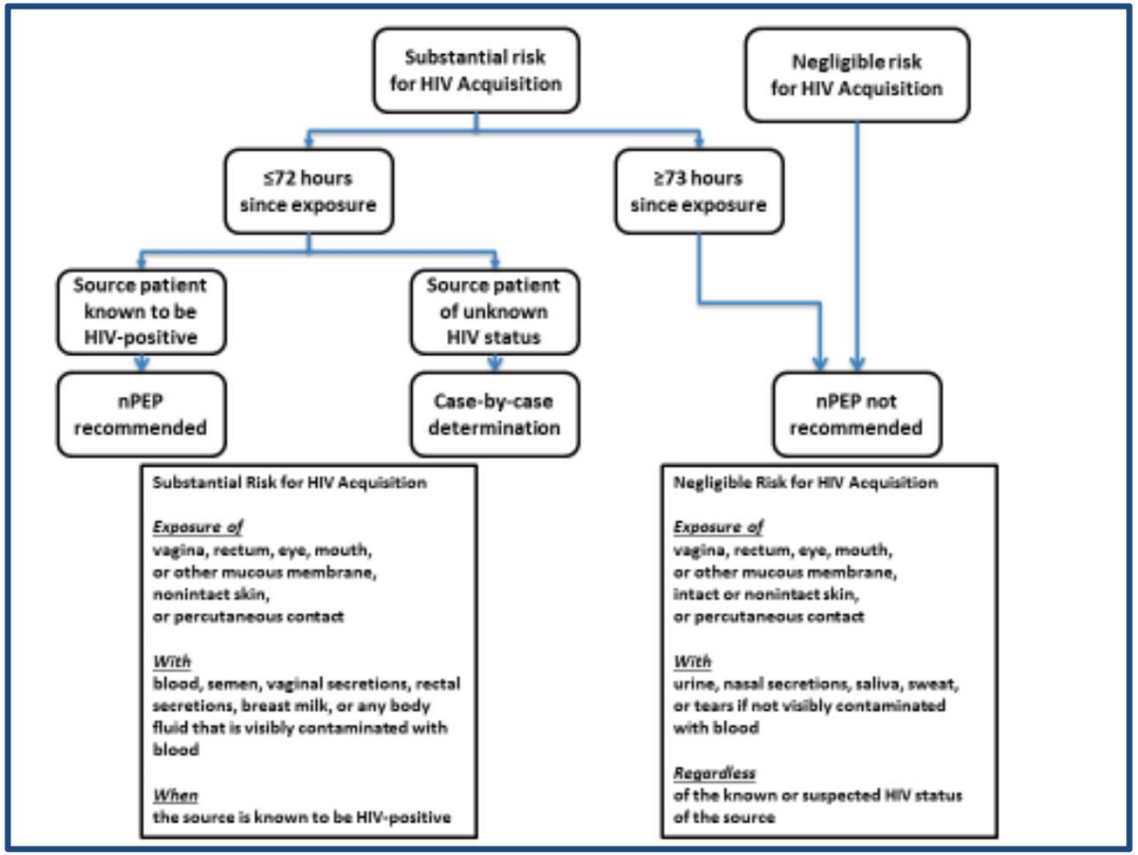
Metronidazole 500mg twice daily for 14 days

Metronidazole 500mg twice daily for 14 days

- Parenteral

CDC algorithm for NPEP for HIV

Figure 1. Algorithm for evaluation and treatment of possible nonoccupational HIV exposures



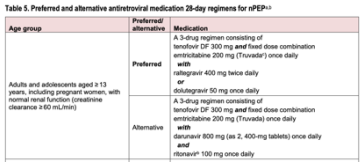


Table 5. Preferred and alternative antiretroviral medication 28-day regimens for nPEP[a,b]

Age group	Preferred/ alternative	Medication
Adults and adolescents aged ≥ 13 years, including pregnant women, with normal renal function (creatinine clearance ≥ 60 mL/min)	Preferred	A 3-drug regimen consisting of tenofovir DF 300 mg *and* fixed dose combination emtricitabine 200 mg (Truvada®) once daily *with* raltegravir 400 mg twice daily *or* dolutegravir 50 mg once daily
	Alternative	A 3-drug regimen consisting of tenofovir DF 300 mg *and* fixed dose combination emtricitabine 200 mg (Truvada) once daily *with* darunavir 800 mg (as 2, 400-mg tablets) once daily *and* ritonavir® 100 mg once daily

Consider BIC/TAF/FTC?

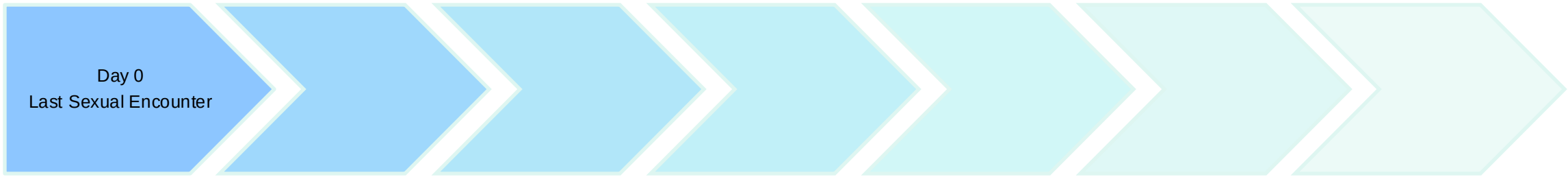
- Efficacy
  - Animal studies demonstrated up to 91% protection with early initiation.
  - Animal studies suggest improved efficacy with late initation
  - No HIV seroconversions reported in multiple human studies.
- Tolerability
  - Significantly fewer side effects (e.g., diarrhea, fatigue) compared to older PEP regimens.
  - Well-tolerated in both real-world and clinical trial settings.
- Completion Rates:
  - Over 90% regimen completion in multiple studies.
  - Single-tablet regimen enhances adherence.
- Accessibility
  - On most formularies
  - Single manufacturer for patient assistance programs
- Recommended in the NYS AIDS Institute Guidelines and **gaining traction in other jurisdictions**
- Consistent findings across animal, observational, and randomized studies highlight its safety and effectiveness.

Jana

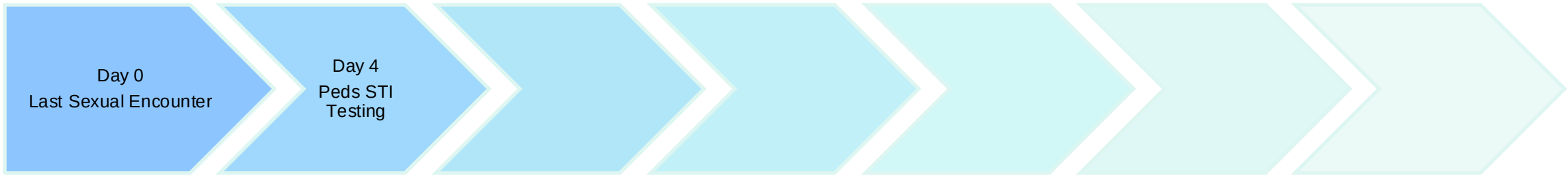
- 22-year-old female with presented to her GYN with vaginal discharge, vulvar tenderness, and labial edema

- Sexually active with one male partner
  - Last sexual intercourse 4 days prior
  - No prior STI history but did take treatment for chlamydia exposure last year
  - On an injectable form of birth control

Jana's Course

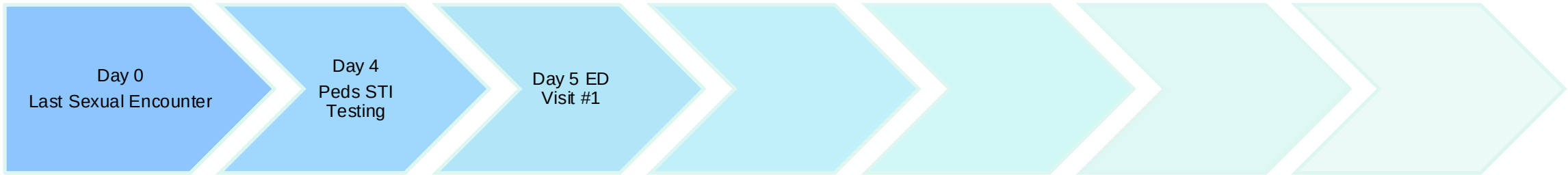


Jana's Course



- GU GC/CT – negative
- GU trichomonas - negative
- HIV Ab/Ag – negative
- RPR – negative

Jana's Course



Worsening dysuria, white vaginal discharge, labial pain and swelling

- Declined pelvic examination
- Prescribed oral fluconazole
- Prescribed cephalexin
  - After urine culture returned with >100k GPCs

Jana's Course

Additional history obtained

- Boyfriend tested negative for "all" STIs
- He had two "bug bites" on his penis that resolved quickly with a cream

Additional work-up:

- BV – negative
- HSV swab – negative
- Outpatient Ob/Gyn follow-up scheduled

Jana's Course

- "Whole vagina and lips are swollen"
- Multiple sitz baths without improvement
- Provider concerned for a possible Bartholin cyst and **referred to ED**

Jana's Course

OB/Gyn:

- Bilateral labial edema
- Thin blood-tinged white discharge
- Midline perineal defect with ulcer like base
- Desquamation of the vaginal mucosa
- Admit for exam under anesthesia

Jana's Course

OB/Gyn:

- Bilateral labial edema
- Thin blood-tinged white discharge
- Midline perineal defect with ulcer like base
- Desquamation of the vaginal mucosa
- Admit for exam under anesthesia

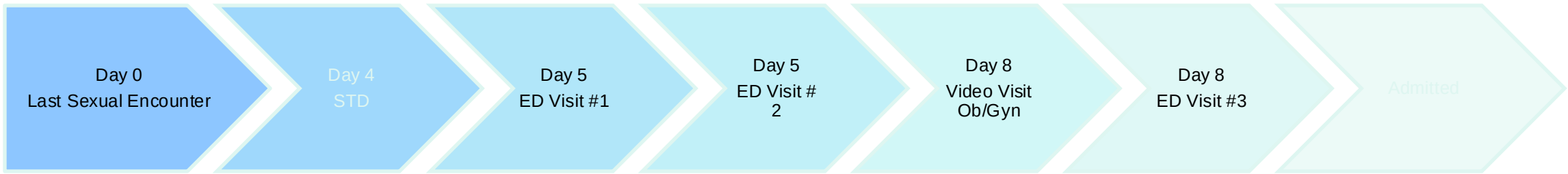
Dermatology:

- Superficial erosions on bilateral inner thigh, buttocks and labia majora
- Significant bilateral edema of labial majora

Poll: What testing would you like to do for this patient?

1. CT with LGV specific NAAT
2. HSV 1/2 NAAT
3. HSV 1/2 IgG/IgM
4. RPR
5. Syphilis PCR
6. Mpox PCR

Jana's Course



Day 8 - Admitted for pain control

Day 10 – Mpox testing returned positive

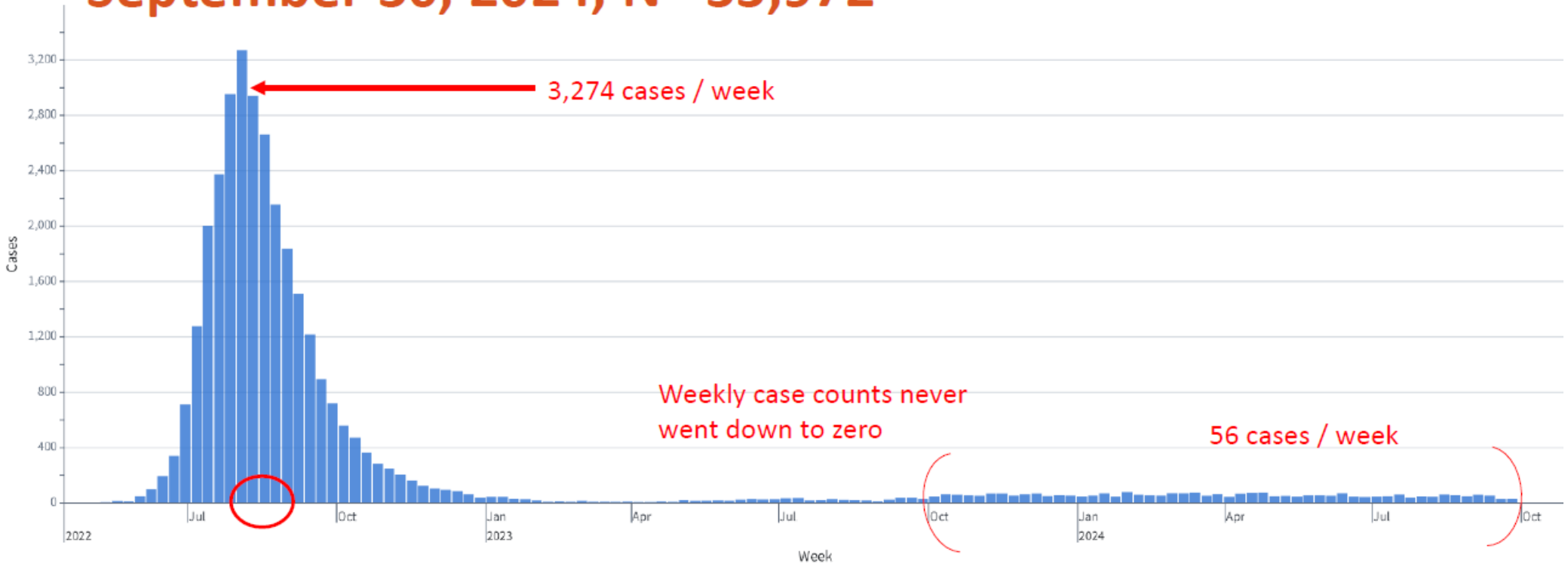
Day 11 – Treatment

- Lidocaine gels
- Pain medication (incl. Opioids)
- Tecovirimat via clinical trial

Day 15 – Discharged home

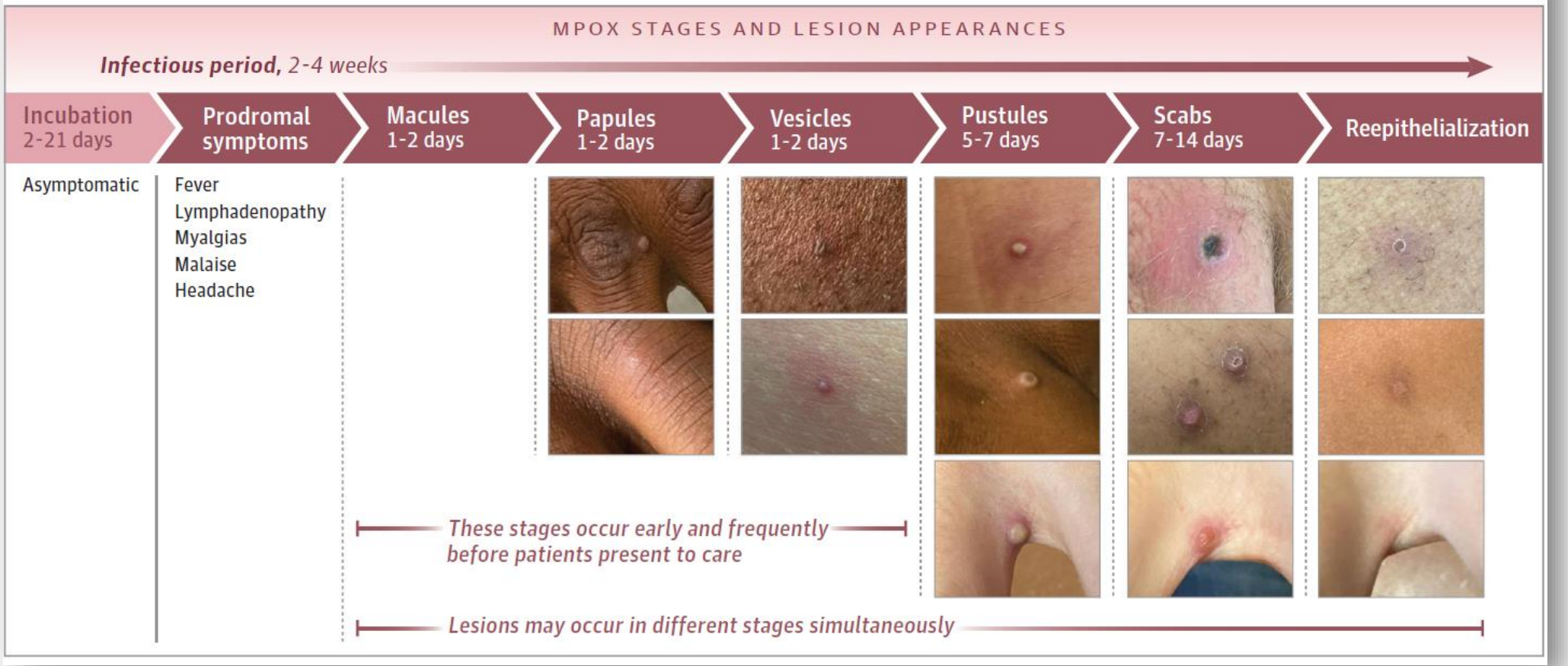
2022 United States Mpox Clade II Outbreak

Mpox clade II epi-curve—United States, May 1, 2022-September 30, 2024, N= 33,972



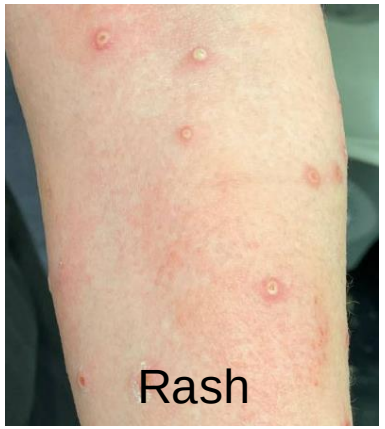
Classic Presentation

Figure. Stages of Mpox and Lesion Examples



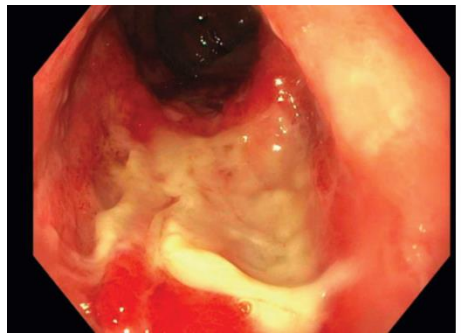
- Titanji BK, et al, JAMA. Published online October 14, 2024. doi:10.1001/jama.2024.21091

Current Presentations

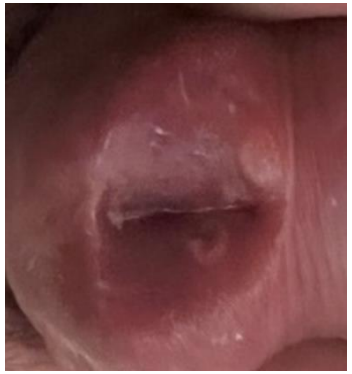


Rash

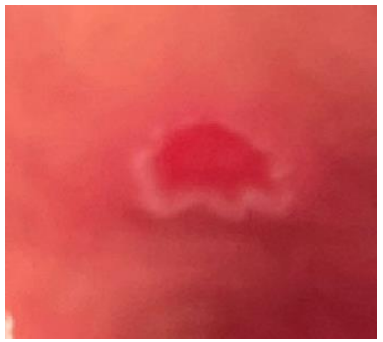
Genital/Anal Lesions



Proctitis

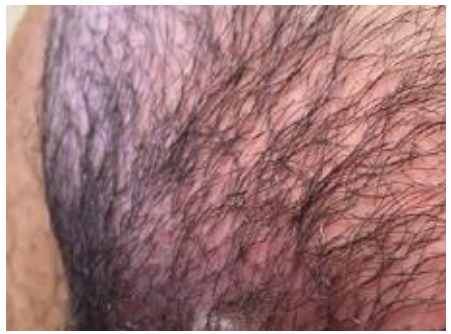


Urethritis

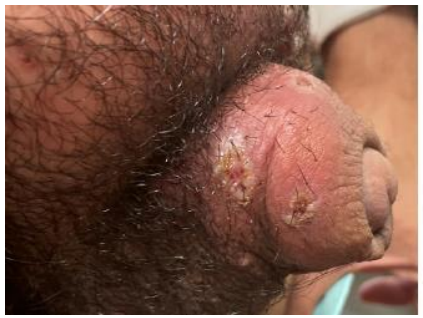


Pharyngitis

Ocular Disease



Lymphadenopathy



Bacterial superinfection

Differential Diagnosis for Mpox

Diffuse Rash

- **Syphilis**
- Varicella
- **Herpes simplex virus**
- Molluscum contagiosum
- Other pox viruses
- Disseminated fungal infections
- **Disseminated gonococcal infection**
- **Enterovirus infection (Hand, Foot, and Mouth Disease (HFMD))**

Genital Ulcer Disease

- **Herpes simplex virus**
- **Syphilis**
- **Chancroid**
- **Lymphogranuloma venereum (LGV)**

Proctitis

- **Gonorrhea**
- **Chlamydia (including LGV)**
- **Herpes simplex virus**
- **Syphilis**

How Can I Treat Mpox?

- Supportive care
  - Most patients fully recover
  - Symptomatic treatment
- Antibody therapy
  - Vaccinia Immunoglobulin (VIGIV)
- Antiviral medications
  - Tecovirimat
  - Cidofovir
  - Brincidofovir
  - Trifluridine (eye disease)

Supportive Care

- **Supportive care**
  - Most patients fully recover
  - **Symptomatic treatment**
- Antibody therapy
  - VIGIV
- Antiviral medications
  - Tecovirimat
  - Cidofovir
  - Brincidofovir
  - Trifluridine (eye disease)

Table 2. Supportive Care Recommendations for Mpox

	Skin (including genital) lesions	Proctitis	Pharyngitis
Supportive care recommendations	Lidocaine gel Nonsteroidal anti-inflammatory medications Opioids (if indicated) Keep lesions clean and dry If infected: Debridement with wet-to-dry dressings Antibiotics	Lidocaine gel Nonsteroidal anti-inflammatory medications Opioids (if indicated) Stool softeners Sitz baths Gabapentin	Viscous lidocaine Nonsteroidal anti-inflammatory medications Opioids (if indicated) Saltwater gargles Oral antiseptics

- https://www.cdc.gov/poxvirus/mpox/clinicians/pain-management.html
- Titanji Bket al, JAMA. Published online October 14, 2024. doi:10.1001/jama.2024.21091

Medical Countermeasures (MCM) Against Mpox

- Supportive care
  - Most patients fully recover
  - Symptomatic treatment
- **Antibody therapy**
  - Vaccinia Immunoglobulin (VIGIV)
- **Antiviral medications**
  - Tecovirimat
  - Cidofovir
  - Brincidofovir
  - Trifluridine (eye disease)

Medical Countermeasures (MCM)

- Severe disease
- At risk of severe disease
  - Immunocompromised
  - Serious underlying skin conditions
  - Pregnant persons
  - Pediatric persons (Age <8 or <1)
- Participation in clinical trials


Interim Clinical Treatment Considerations for Severe Manifestations of Mpox — United States, February 2023

Agam K. Rao, MD[1]; Caroline A. Schrodt, MD[1]; Faisal S. Minhaj, PharmD[1,2]; Michelle A. Waltenburg, DVM[3]; Shama Cash-Goldwasser, MD[2]; Yon Yu, PharmD[4]; Brett W. Petersen, MD[1]; Christina Hutson, PhD[1]; Inger K. Damon, MD, PhD[3]

Rao et al, MMWR, PMID:36862595

Vaccination to Prevent Mpox?

Post-Exposure Prophylaxis

- Should be given ASAP after exposure:
  - Within 4 days to prevent disease
  - 4 to 14 days to reduce symptoms

Pre-Exposure Prophylaxis

- Clinical and research lab workers
- Public health response team members
- Epidemiological Risk Groups

Table 4. Observational Vaccine Efficacy Studies

Source	Vaccine	% (95% CI)[a] 1-Dose efficacy	2-Dose efficacy	Evaluation period
Fine et al,[86] 1988	Dryvax	85		1980 to 1984
Rimoin et al,[87] 2010	Dryvax	80.7 (68.2 to 88.4)		Nov 2005 to Nov 2007
Titanji et al,[88] 2023	Dryvax	72 (32 to 87)		Jul 1, 2022, to Oct 31, 2022
	ACAM2000	75 (68 to 85)		
Back et al,[89] 2024	MVA-BN	70 (44 to 84)	89 (12 to 99)	Aug 1, 2022, to Sep 30, 2022
Bertran et al,[90] 2023	MVA-BN	78 (54 to 89)		Jul 4, 2022, to Oct 9, 2022
Brousseau et al,[91] 2024	MVA-BN	35 (−2 to 59) 65 (1 to 87)[b]		Jun 19, 2022, to Jun 2, 2022
Charles et al,[92] 2024	MVA-BN		80	Jan 1, 2023, to Dec 31, 2023
Dalton et al,[93] 2023	MVA-BN	75 (61.2 to 84.2)	86 (73.8 to 92.4)	Aug 19, 2022, to Mar 31, 2023
Deputy et al,[94] 2023	MVA-BN	35.8 (22.1 to 47.1)	66 (47.4 to 78.1)	Aug 15, 2022, to Nov 19, 2022
Fontán-Vela et al[95] 2024	MVA-BN	79 (33.3 to 100)		Jul 12, 2022, to Dec 12, 2022
Navarro et al,[96] 2024	MVA-BN	58 (31 to 75)		Jun 2022 to Nov 2022
Ramchandani et al,[97] 2023	MVA-BN	81 (64 to 90)	83 (28 to 96)	Jan 1, 2020, to Dec 31, 2022
Rosenberg et al,[98] 2023	MVA-BN	68.1 (24.9 to 86.5)	75.7 (48.5 to 88.5)	Jul 24, 2022, to Oct 31, 2022
Wolff Sagy et al,[99] 2023	MVA-BN	86 (59 to 95)		Jul 31, 2022, to Dec 25, 2022
Yeganeh et al,[100] 2024	MVA-BN	69 (59 to 77)	85 (80 to 87)	May 19, 2022, to Jan 1, 2023

Abbreviation: MVA-BN, Modified Vaccinia Ankara Vaccine-Bavarian Nordic.

[a] All results are adjusted results for disease acquisition at ≥14 days after vaccination unless otherwise specified.

[b] Includes adjustment for self-reported risk.

https://www.cdc.gov/vaccines/acip/recommendations.html

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ACIP Recommendations

ACIP recommends vaccination with the 2-dose MVA vaccine series for persons aged 18 years and older at risk for mpox as defined by:

- Gay, bisexual, and other men who have sex with men, transgender or nonbinary people who in the past 6 months have had one of the following:
  - A new diagnosis of ≥1 sexually transmitted disease
  - More than one sex partner
  - Sex at a commercial sex venue
  - Sex in association with a large public event in a geographic area where mpox transmission is occurring
- Sexual partners of persons with the risks described above
- Persons who anticipate experiencing any of the above