Syphilis Treatment Update

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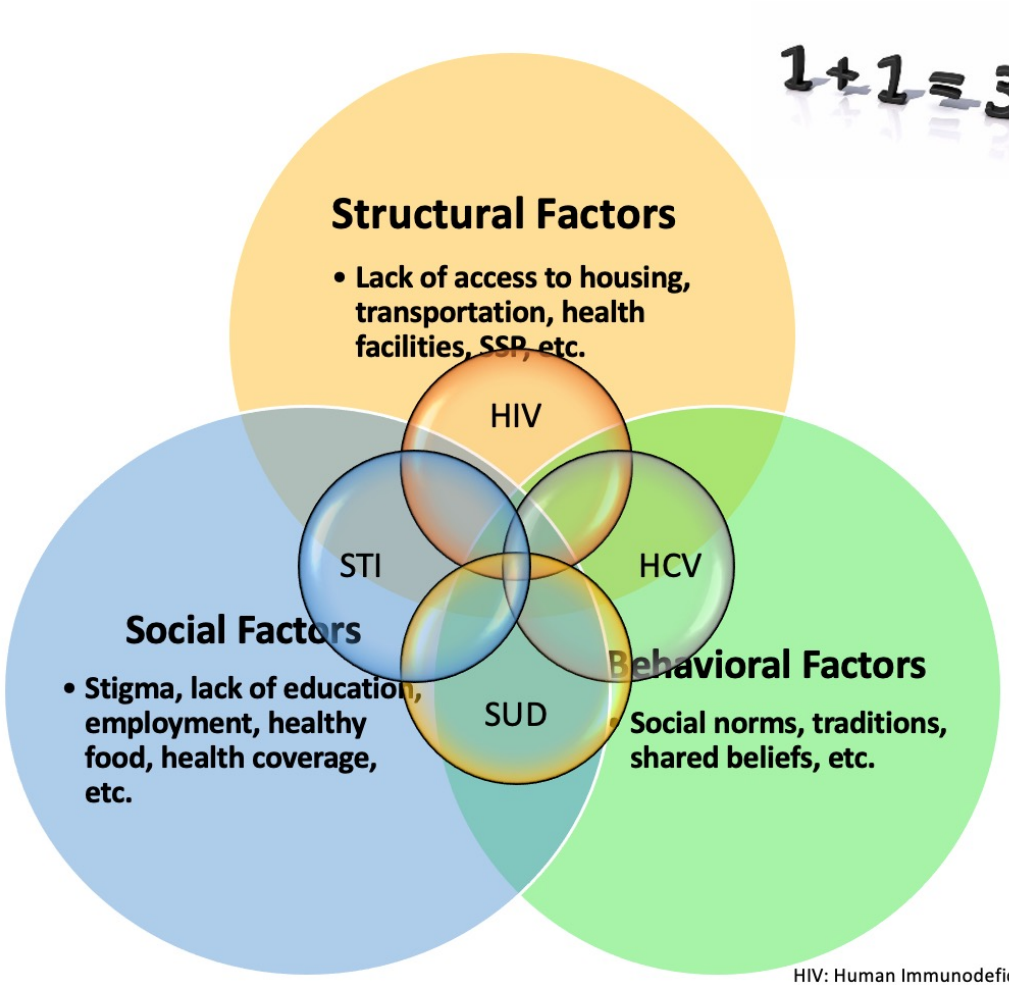
Outline

- Principles of Syphilis Treatment
- Early syphilis and late syphilis treatment
- Neurosyphilis
- Prevention

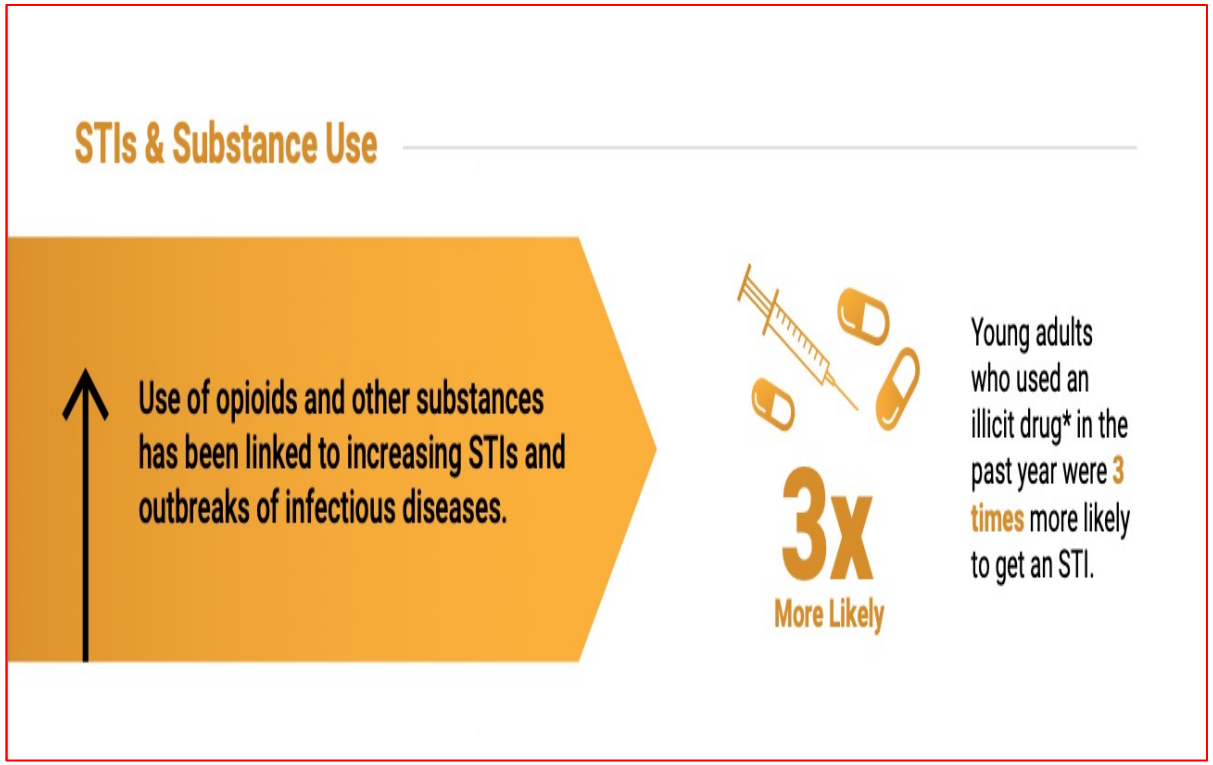
Frequently Asked Questions

Why do we need longer treatments for latent syphilis?
In late latent syphilis can we extend the interval between shots longer than 7 days? and if so, how long?
How to manage PG allergic patients
When should I repeat RPR in a pregnant female treated for syphilis?
Management of patients with RPR titers that have not decreased 4-fold at the end of the follow-up period

Syphilis Syndemic



HIV: Human Immunodeficiency Virus
HCV: Hepatitis C virus
SUD: Substance Use Disorder



Principles for Syphilis Treatment

Parenteral penicillin is the drug of choice for all stages of syphilis

- The preparation, dosage, and duration of T. depend on the stage and clinical manifestations
- *T pallidum* in the CNS and aqueous humor are poorly accessed by BPG

Treatment recommendations are based on

- A few randomized controlled clinical trials
- Observational studies
- Decades of experience

BPG: Benzathine Penicillin G

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

Principles of Syphilis Treatment

Bull World Health Organ. 1954;10(4):507-561. The Journal of Clinical Pharma, First published: 12 May 2024, DOI: (10.1002/jcph.2454)

Therapeutic concentration of Penicillin G (PG)	• **To kill T. pallidum is 0.008 IU/mL - 0.03 IU/mL (0.5-18 ng/mL)** • This is > 10 - 36 times the in vitro MIC* (0.0025 IU/mL)**
To cure early syphilis	• PG concentrations > 0.03 IU/mL for 7–10 days are needed
To Cure latent and Tertiary syphilis	• T. pallidum multiplies twofold in 30–33 h*** • concentrations > 0.03 IU/mL for longer periods are needed

* The 10-fold margin is to account for free (active) penicillin due to protein binding (60%), as well as other possible individual variations in concentrations

** Required to immobilize 50% of treponemes within 16 h in vitro

*** As assessed in animal models and cell cultures

Pharmacokinetics and Safety of Intramuscular Injectable Benzathine Penicillin G in Japanese Healthy Participants

Six Male and female participants ages 20-55

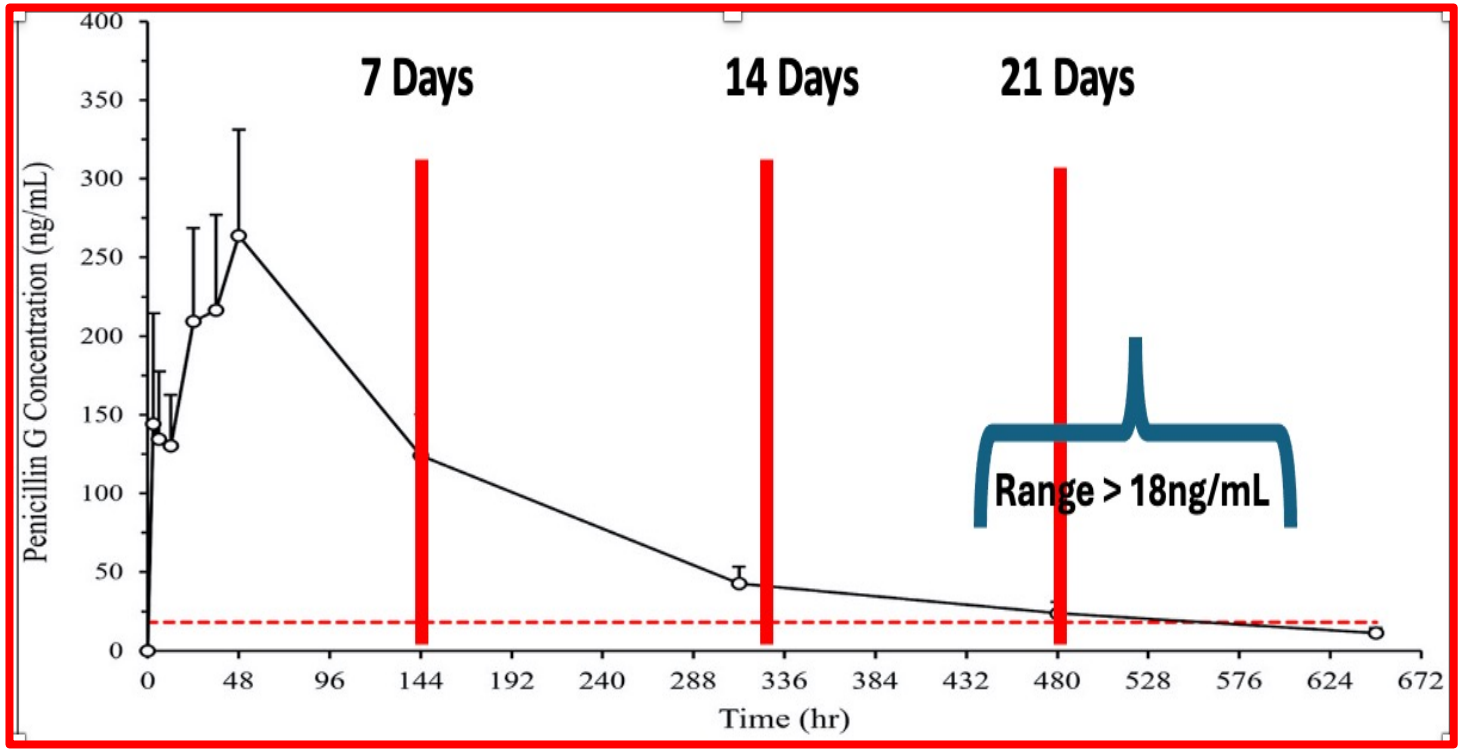
Received BPG by deep IM injection on day 1

PK samples collected were collected at:

- Pre dose (0 h), 3, 6, 12, 24, 36, and 48 h
- 144 h (day 7)
- 312 h (day 14)
- 480 h (day 21)
- 648 h (day 28) post-dosing.

Li, Y., Okayama, A., Hagi, T., Muto, C., Raber, S. and Nagashima, M. (2024), J Clin Pharm.

Plasma penicillin G concentration–time profiles following single IM administration of 2.4 million units benzathine penicillin G



- Concentration values below the lower limit of quantification (0.500 ng/mL) were set to 0.
- Red dashed lines are the therapeutic concentration of **0.03 IU/mL**

- **The median time above the target efficacious concentration (0.03 IU/mL) was 561 h with a range of 439–608 h (18–25 days).**
- **Exceeding the 7–10 days recommended to eradicate the microorganism**

Li, Y., Okayama, A., Hagi, T., Muto, C., Raber, S. and Nagashima, M. (2024), J Clin Pharm.

	Range tested (mg/L)	Primary MIC	Secondary MIC	MBC (mg/L)	Drug plasma concentrations*		
		Primary MIC (mg/L)†	Secondary MIC (mg/L)†		C_{min} (mg/L)	Dose administered for the C_{min} calculation	Unbound fraction
Natural penicillins							
Benzathine penicillin G	0·0001–0·06‡	Not tested in this study	0·003‡	0·003‡	0·012§	1·2 million units single dose, IM	0·55–0·72
Aminopenicillins							
Amoxicillin	0·0025–0·16	0·02	0·01	0·01	>0·2¶	500 mg single dose, PO	0·83
Cephalosporins							
Ceftriaxone	0·00063–1	0·0025	0·0025	0·0025	29·7	1000 mg/24 h, IM	0·50
Cephalexin	0·0625–8	0·25	0·25	0·25	0·30¶	1000 mg single dose, PO	0·85–0·90
Cefetamet	0·0039–0·25	0·0313	0·0625	0·0625	>0·3	500 mg/12 h, PO	0·78
Cefuroxime	0·0039–0·25	0·0156	0·0156	0·0156	0·20¶	250 mg single dose, PO	0·50
Cefixime	0·0039–0·25	0·0313	0·0313	0·0313	0·08	400 mg/24 h, PO	0·34
Carbapenems							
Ertapenem	0·00375–2	>2	>2	>2	0·8	1 g/24 h, IV	0·05
Tetracyclines							
Doxycycline	0·004–2·5‖	0·1‖	Not determined in this study	0·1‖	>1	100 mg/24 h, PO	0·07–0·18
Fluoroquinolones							
Moxifloxacin	0·06–2‡	Not determined in this study	2‡	>2‡	0·4–0·6	400 mg/24 h, PO	0·50
Balofloxacin	0·25–16	2	2	>2	0·23	100 mg/12 h, PO	..
Macrolides							
Azithromycin	0·0313–2	<0·0313**	0·125**	<0·0313**	0·05	250 mg/24 h, PO	0·5–0·9
Oxazolidinones							
Linezolid	0·0156–2	0·5	0·125	0·125	6·2	600 mg/12 h, PO	0·69
Tedizolid	0·0078–0·5	0·0625	0·313	0·0156–0·0313	0·41	200 mg/24 h, PO	0·10–0·30
Lipoglycopeptides							
Dalbavancin	0·0039–0·25	0·125	0·125	0·125	19·5††	1500 mg single dose, IV	0·07
Aminoglycosides							
Spectinomycin	0·02–2	0·1	0·1	0·25	15¶	2000 mg single dose, IM	..
Antimycobacterials							
Isoniazid	0·0078–0·5	>0·5	>0·5	>0·5	Undetectable	300 mg/24 h, PO	..
Pyrazinamide	1·0–64	>64	>64	>64	7	1500 mg/24 h, PO	..
Clofazimine	0·06–2‡	Not determined in this study	1‡	1‡	0·02§§	200 mg single dose, PO	..
Antiparasitics							
Ivermectin	0·125–40	MIC threshold unattained‡‡	MIC threshold unattained‡‡	MIC threshold unattained‡‡	0·01§§	12 mg single dose, PO	..
Nitroimidazoles							
Metronidazole	0·0313–2	>2	>2	>2	11·8	500 mg/8 h, PO	0·8
Spiropyrimidinetrione							
Zoliflodacin	0·250–4	2	1	2	1§§	3000 mg single dose, PO	..

Antimicrobial susceptibility of *Treponema pallidum* subspecies *pallidum*: an in-vitro study

www.thelancet.com/microbe **Published online October 9, 2023**
https://doi.org/10.1016/S2666-5247(23)00219-7

Amoxicillin, ceftriaxone, several oral cephalosporins, tedizolid, and dalbavancin exhibited anti-treponemal activity at concentrations achievable in human plasma following regular dosing regimens

"Cephalosporins and oxazolidinones are potential candidates for expanding the current therapeutic repertoire for syphilis. Our findings warrant testing efficacy in animal models and, if successful, clinical assessment of efficacy."

Cmin =minimum blood plasma concentration. IM=injection into a muscle. IV=injection into a vein. MBC=minimum bactericidal concentration. MIC=minimum inhibitory concentration. PO=oral administration. *The appendix (p 7) provides the literature sources used as a reference for pharmacokinetic information. †The primary MIC was defined as the lowest antibiotic dilution at which the tp0574 qPCR values were not significantly higher than the inoculum wells (day 0 control group), as previously defined by Edmondson and colleagues.13 A secondary MIC was defined as the lowest antibiotic dilution at which the tp0574 qPCR values were significantly lower than the positive control wells (day 7 control group), which more closely follows the broth dilution procedure. ‡Haynes and colleagues.12 §22 days after single dose administration. ¶8 h after administration. ||Edmondson and colleagues.13 **Only for susceptible strains. ††168 h after administration. ‡‡Because of ivermectin toxicity to Sf1Ep cells. §§24 h after administration. Table : MIC and literature plasma concentration valuesA

Primary and Secondary Syphilis
Recommended Regimens

Adults

- **Benzathine penicillin G (BPG)** 2.4 million units IM in a single dose
- Additional doses of, amoxicillin, or other antibiotics do not enhance efficacy of this regimen, regardless of HIV status

Infants and children

- **BPG** 50,000 units/kg IM, up 2.4 million units, in a single dose
- Assess infants aged ≥1 month for congenital vs acquired syphilis.
- Management of Infants aged ≥1 month should be done in consultation with pediatric ID specialist and evaluated for sexual abuse

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

Primary and Secondary Syphilis
Follow-up

Clinical and serologic evaluation at 6 and 12 months after treatment

- RPR might decrease slower for persons previously treated for syphilis or in those with HIV

When to suspect treatment failure or reinfection:

- Persistent or recurrent signs or symptoms
- 4-fold increase in RPR titer persisting for >2 weeks
- Failure of RPR to decrease fourfold within 12 months*

How to manage patients with treatment failure

- Rule out HIV and neurosyphilis
- Weekly IM injections of BPG, G 2.4 million units X 3 weeks unless neurosyphilis is present

*Clinical trial data have demonstrated that 10%–20% of persons treated with the recommended therapy will not achieve the 4-fold decrease in RPR titer within 12 months after treatment.

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

Primary and Secondary Syphilis
Alternative Treatments

Pregnant women or patients with neuro/ocular/otic syphilis

- Penicillin is the only options, patients will need to be desensitized

For the rest of the patients

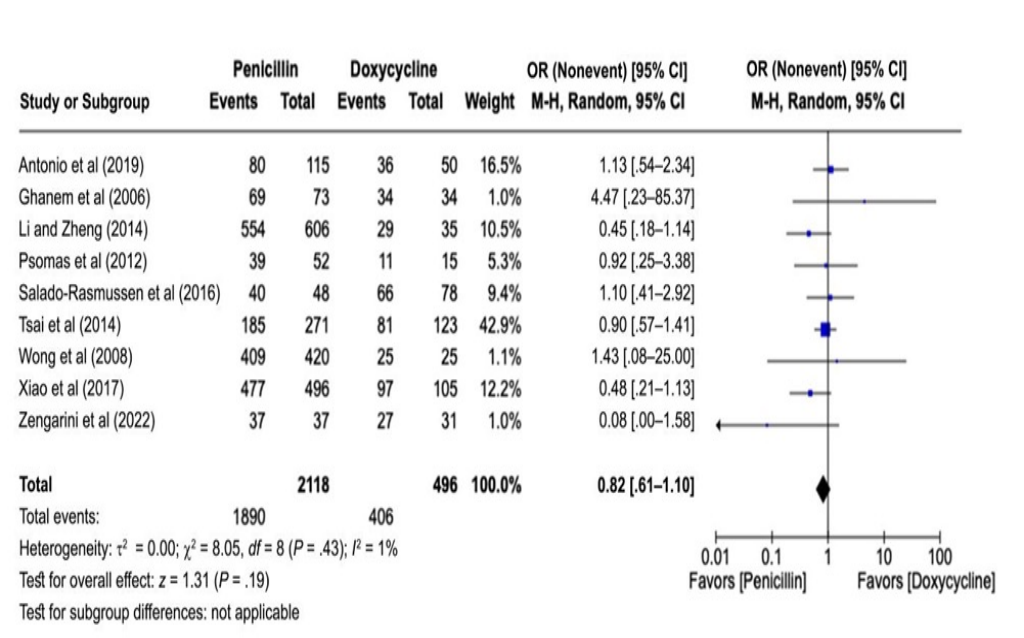
- Doxycycline (100 mg orally 2 times/day for 14 days)
- Tetracycline (500 mg orally 4 times/day for 14 days)
- Ceftriaxone (1 g daily either IM or IV for 10 days)
  - Optimal dose and duration of ceftriaxone therapy have not been defined
- Azithromycin should not be used as treatment for syphilis

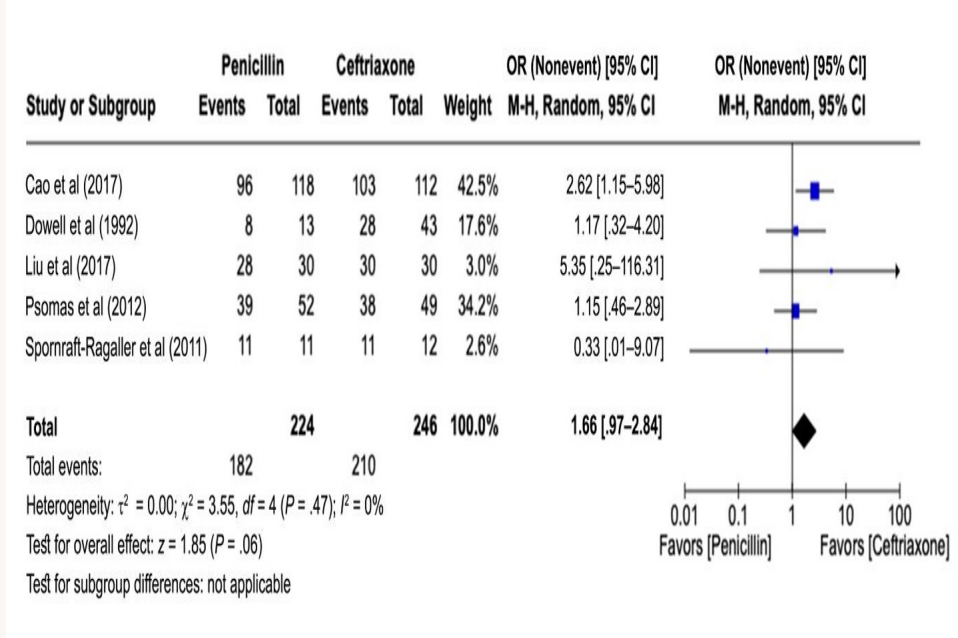
Thorough clinical and serologic follow-up is needed for all

Clinical trial data have demonstrated that 10%–20% of persons with primary and secondary syphilis treated with the recommended therapy will not achieve the fourfold decrease in nontreponemal titer within 12 months after treatment.
NTT: Non-Treponema Test Titers

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

Syphilis Treatment: Systematic Review and Meta-Analysis Investigating Nonpenicillin Therapeutic Strategies





"Alternative treatment strategies have serological cure rates equivalent to penicillin, potentially reducing global dependence on this antibiotic"

Yano Callado G, Gutfreund MC, Pardo I, et al., *Open Forum Infectious Diseases*, Volume 11, Issue 4, April 2024, ofae142, https://doi.org/10.1093/ofid/ofae142

Latent Syphilis

Treatment for Adults

Early Latent Syphilis:	• BPG 2.4 million units IM in a single dose
Late Latent Syphilis:	• BPG, 3 doses of 2.4 million units IM each at 1week intervals

Confirm the Diagnosis of Latent Syphilis!!!

Physical exam that includes oral cavity, perianal area, perineum, rectum, and genitals

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

BPG: Benzathine Penicillin G

Late Latent Syphilis: Delayed BPG Dosing
CDC Recommendations

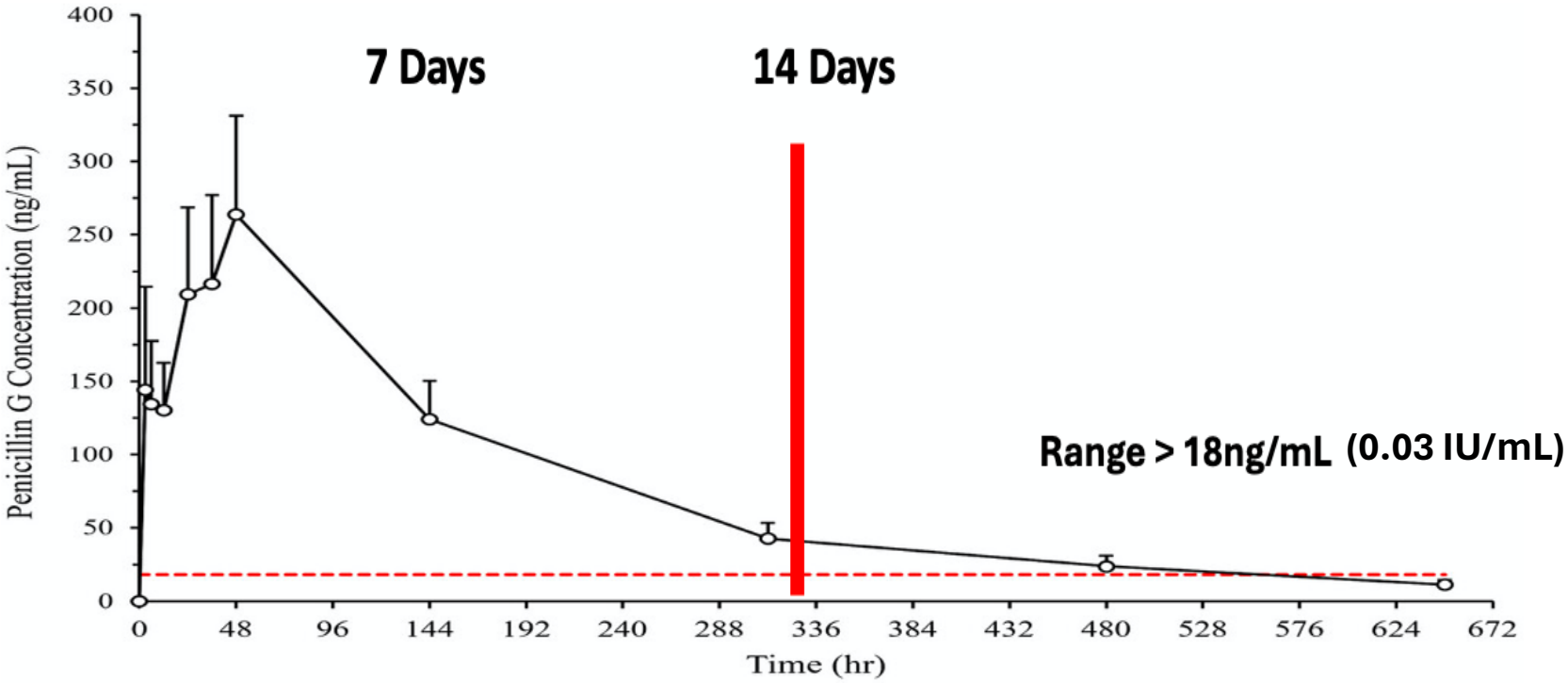
Up to 14 days between doses might be acceptable for non pregnant patients

For pregnant women, the interval between doses should not be greater than 9 days

BPG: Benzathine Penicillin G

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

Plasma penicillin G concentration–time profiles following single IM administration of 2.4 million units benzathine penicillin G



- The median time above the target efficacious concentration 0.03 IU/mL (18ng) was 561 h with a range of 439–608 h (18–25 days).
- Exceeding the 7–10 days recommended to eradicate the microorganism

Li, Y., Okayama, A., Hagi, T., Muto, G., Raber, S. and Nagashima, M. (2024), J Clin Pharm

Comparing 7 vs 6-8 Day Penicillin Treatment Intervals Among Pregnant People with Syphilis of Late or Unknown Duration: No Difference Found in Incidence of Congenital Syphilis

Johnson et al., 2023 | *Open Forum Infectious Diseases*

IDSA
Infectious Diseases Society of America

Guidelines recommend that pregnant patients with syphilis of late/unknown duration be treated with benzathine penicillin G, dosed as 3 weekly intramuscular injections (BPGx3) given ideally at strict 7-day intervals. It is unknown whether more flexible BPG treatment intervals might be effective in preventing congenital syphilis (CS).

METHODS

A. Used California surveillance data to identify birthing parent/infant dyads wherein the pregnant parent had syphilis of late/unknown duration (01/01/2016 – 06/30/2019).

B. Divided the dyads into 3 groups based on prenatal treatment: (1) BPGx3 at strict 7-day intervals, (2) BPGx3 at 6-8 day intervals, and (3) no/inadequate treatment.

C. Compared CS incidence among infants in each group.

1 n = 607 (55.6%) in the 7-day intervals treatment group

2 n = 70 (6.4%) in the 6-8 day intervals treatment group

3 n = 415 (38.0%) in the no/inadequate treatment group

Incidence proportion of infants meeting CS criteria in each group was, respectively, 5.6%, 5.7%, and 36.9% in the 7-day, 6-8 day, and no/inadequate treatment groups

Compared with BPGx3 at 7-day intervals, the odds of CS were 1.0 [95% CI 0.4-3.0] in the 6-8 day intervals group and 9.8 [95% CI 6.6-14.7] in the no/inadequate treatment group.

Prenatal BPGx3 at 6-8 day intervals was no more likely to lead to CS in infants than 7-days. These findings hint that 6-8-day intervals might be adequate to prevent CS among pregnant people with syphilis of late/unknown duration.

Open Forum Infectious Diseases

https://doi.org/10.1093/ofid/ofad300

Latent Syphilis

Alternative Treatments for Persons with a Penicillin Allergy

- **Pregnant women and persons with neuro/ocular/otic syphilis**
  - Should be treated with penicillin only
  - Will need to be desensitized
- The rest of the patients with **early latent syphilis**
  - Same as alternatives to penicillin for treating primary and secondary syphilis
- The rest of the patients with **late latent syphilis**
  - Doxycycline (100 mg orally 2 times/day for 28 days)
  - Tetracycline (500 mg orally 4 times/day for 28 days)

https://www.cdc.gov/std/treatment-guidelines/STI-Guidelines-2021.pdf

Latent Syphilis: Follow-up

- **Clinical and serologic evaluation at 6 , 12 and 24 months after treatment**
  - Definite criteria for cure or failure by serologic criteria have not been well established.
- **When to suspect treatment failure or reinfection:**
  - Persistent or recurrent signs or symptoms
  - 4-fold increase in RPR titer persisting for >2 weeks
  - Failure of RPR to decrease fourfold within 24 months*

*Despite a repeated course of treatment and a negative CSF, serologic titers might not decrease especially if the initial nontreponemal titer is low (<1:8); in these circumstances, the need for additional therapy or repeated CSF examinations is unclear but is usually not recommended.

https://www.cdc.gov/std/treatment-guidelines/STI-Guidelines-2021.pdf

Latent Syphilis:

Management when < 4-fold decrease in titers at 24 months

- **If initial titer was <1:8.**
  - Rule out HIV and neurosyphilis
  - If negative clinical and serologic follow-up is an option

- **If initial titer was >1:32**
  - Rule out HIV and neurosyphilis if negative:
    - Retreat with weekly BPG 2.4 million units IM X 3 weeks* **OR**
    - Continue to monitor annually for any sustained increases in nontreponemal titer.

*Despite a repeated course of treatment and a negative CSF, serologic titers might not decrease especially if the initial nontreponemal titer is low (<1:8); in these circumstances, the need for additional therapy or repeated CSF examinations is unclear but is usually not recommended.

https://www.cdc.gov/std/treatment-guidelines/STI-Guidelines-2021.pdf

Syphilis in Pregnancy Follow-up

If syphilis is diagnosed and treated at or before 24 weeks' gestation

- RPR titers should not be repeated before 8 weeks after treatment (32 weeks gestation)
- RPR titers should be obtained at delivery in mother and neonate
- RPR titers should be repeated sooner if reinfection or treatment failure is suspected

For syphilis diagnosed and treated after 24 weeks' gestation

- RPR titers should be obtained at delivery in mother and neonate

Syphilis in Pregnancy
Follow-up

RPR titer expectations

- The majority will not achieve a 4-fold decrease in RPR titers before delivery,
- A 4-fold increase in titer after treatment that is sustained for >2 weeks is concerning for reinfection or treatment failure.
- RPR titers can increase immediately after treatment, presumably related to the treatment response

Congenital syphilis is a concern if:

- Delivery occurs within 30 days of therapy
- Clinical signs of infection are present at delivery
- Maternal RPR titer at delivery are 4-fold higher than the pretreatment titer
- Neonate RPR titer is 4-fold higher than maternal titer

Regardless of Syphilis Stage

Other Management Considerations

- **Obtain RPR titer the day treatment starts**
- **persons with syphilis should be:**
  - Evaluated for neurologic, ocular and otic signs or symptoms
  - Screened for other STIs including HIV
  - Offered HIV PrEP/PEP if HIV is negative
  - Offered Doxy PEP regardless of HIV status
- **Persons with symptoms or signs of ocular syphilis should have a:**
  - Thorough cranial nerve (CN) exam and ophthalmologic examinations.
  - In the absence of neurologic signs or symptoms, CSF examination is not needed.
- **Persons with symptoms or signs of otic syphilis should have**
  - An otologic examination
  - In the absence of neurologic signs or symptoms, CSF examination is not needed.

https://www.cdc.gov/std/treatment-guidelines/STI-Guidelines-2021.pdf

Penicillin Reactions

Immediate, immunoglobulin E (IgE)-mediated reactions

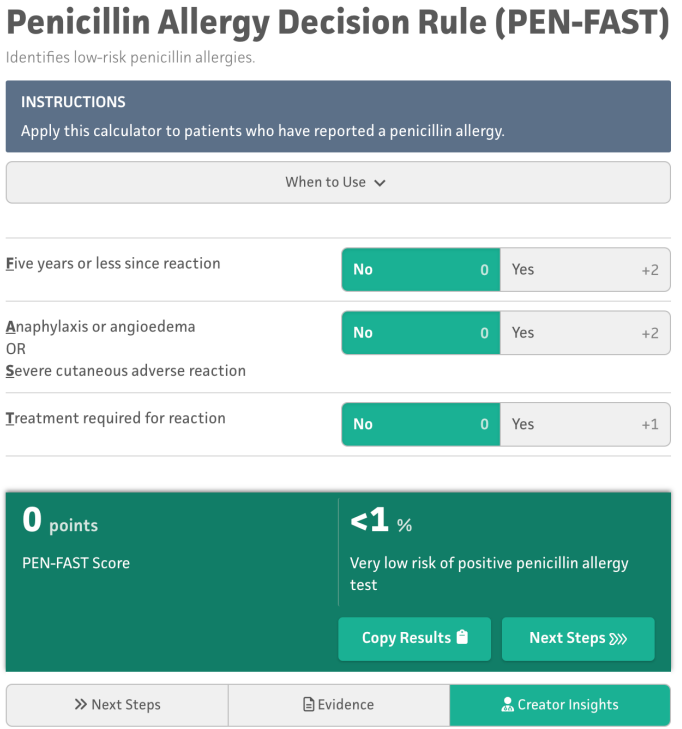
Serious forms of non-immediate (delayed) reactions

- Toxic epidermal necrolysis (TEN), Lyells Syndrome
- Drug-induced organ damage or cytopenia.
- Drug Rash eosinophilia systemic syndrome (DRESS)
- Drug induced hemolytic anemia
- Serum sickness
- Steven Johnson Syndrome
- Interstitial Nephritis

IgE Mediated Penicillin Allergy

Patients often are Incorrectly Labeled

- **Evaluate symptoms**
  - 10 % of US patients report a Penicillin allergy
  - Only 1.5% to 6.1% will be found to be truly allergic (type I IgE mediated reaction)
  - ~ 80% of patients with a true IgE-mediated reaction will lose sensitivity after 10 years
- **Consider allergy testing or oral challenge**
- **Always desensitize**
  - Pregnant women
  - Persons with neuro/ocular/otic syphilis
  - Those whose follow-up can not be assured



1-2 Point : 5 % risk of positive penicillin allergy test
3 Points : 20 % risk of positive penicillin allergy test
4-5 Points : 50 % risk of positive penicillin allergy test

https://www.cdc.gov/std/treatment-guidelines/STI-Guidelines-2021.pdf

https://www.mdcalc.com/calc/10422/penicillin-allergy-decision-rule-pen-fast

The Jarisch–Herxheimer reaction

It is an acute febrile reaction

- Frequently accompanied by headache, myalgia, and fever
- Can occur within the first 24 hours after the initiation of any syphilis therapy

It is a reaction to the treatment

- Not an allergic reaction to penicillin

It occurs most frequently among persons who have early syphilis

- Presumably because bacterial loads are higher during these stages.

Antipyretics can be used to manage symptoms

- They have not been proven to prevent this reaction.

May induce early labor or cause fetal distress in pregnant women

Neuro/Oto/Ocular Syphilis Treatment

PCN G 18-24 mU IV/day for 10-14 days with optional 1-3 doses of weekly Benzathine PCN

Procaine Penicillin 2.4 mU IM/day plus Probenecid 500 mg po QID for 10-14 days (No longer available)

Ceftriaxone 2 gm daily is an alternate treatment validated for persons with HIV

Repeat Lumbar Puncture is no longer required if the RPR titer is falling over the next 2 years and there is no progression of disease

Recommendations based on:

- Case series
- Retrospective studies
- Pharmacokinetic/dynamic data
- Clinical experience

Neurosyphilis review • **CID 2024:78 (15 May)** • e57

Basic Principles for the Treatment of Neurosyphilis

The optimal duration of therapy has not been studied in a clinical trial

- Clinical experience suggests 10–14 days of IV Penicillin G
- No studies have directly compared 10 vs 14 days
- Courses as short as 8 days have been reported

Role of steroids is unclear

- Not recommend by CDC
- They are often used in ocular/otic syphilis without RCT to prove benefit

No regimen other than IV penicillin G should be used to treat neurosyphilis

- Unless an absolute contraindication exists

Cerebrospinal Fluid Penicillin Levels During Therapy for Latent Syphilis

Mean Serum Penicillin Concentrations and Adequate CSF Penicillin Levels

Group (No. of Patients)	Therapy	Mean Serum Penicillin Concentration, Units/mL (Range)			No. of Patients With CSF Concentration >0.03 Units/mL
		Serum Sample 1*	Serum Sample 2	Serum Sample 3	
1 (10)	Penicillin G benzathine, 2.4 million units intramuscularly	0.19 (0.04-0.48)	0.25 (0.06-0.48)	0.32 (0.17-0.52)	0
2 (8)	Penicillin G benzathine, 2.4 million units intramuscularly, plus probenecid†	0.33 (0.06-0.68)	0.41 (0.19-0.76)	0.41 (0.21-0.70)	0
3 (9)	Penicillin G benzathine, 4.8 million units intramuscularly	0.31 (0.19-0.50)	0.59 (0.31-1.20)	0.75 (0.38-1.50)	0
4 (6)	Penicillin G benzathine, 4.8 million units intramuscularly, plus probenecid†	0.50 (0.21-0.95)	0.73 (0.30-1.42)	1.00 (0.47-1.85)	2

*Serum sample 1 obtained seven days after first weekly injection of penicillin G benzathine; sample 2, seven days after second injection; and sample 3, seven days after third injection.

†Probenicid, 500 mg orally four times daily for three weeks.

Only Two of six patients in the last group had CSF penicillin concentrations greater than 0.03 units/mL.

JAMA1981;246:2583-2584

Penetration of Oral Doxycycline into the Cerebrospinal Fluid of Patients with Latent or Neurosyphilis

- **Bioavailability is ~ 95%**
- **After a 200 mg oral dose**
  - Mean plasma concentrations is 2.6 mg/L at 2 h and 1.45 mg/L at 24 h.
  - At 4 hours reaches a CSF concentration of **0.6 mg/mL**
- **After the 7th dose**
  - The mean level in the CSF of **1.3 mg/L**
- **MICs reported for *T. pallidum* (0.2 mg/L).**

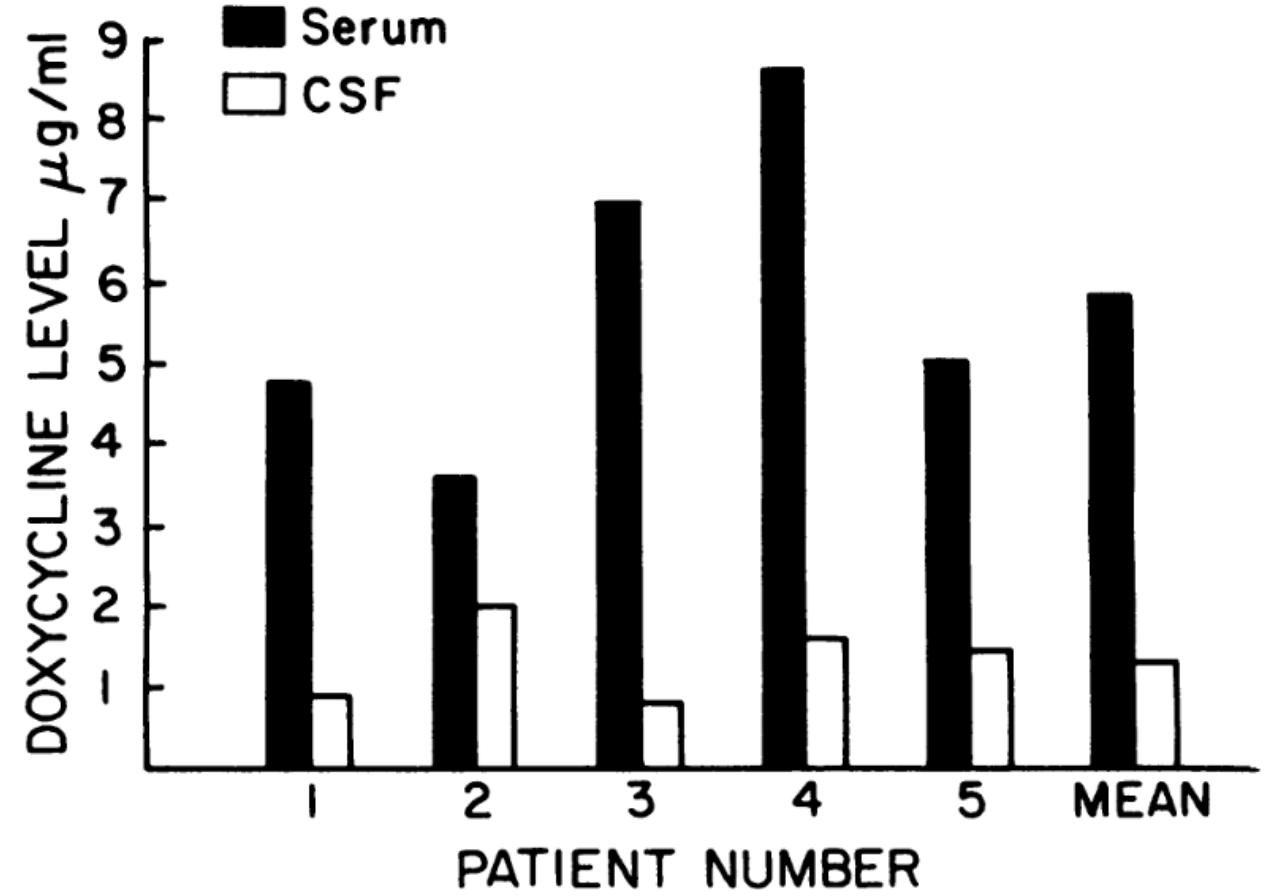


FIG. 1. Doxycycline levels in serum and CSF 4 to 6 h after the seventh dose of 200 mg twice a day.

Journal of Antimicrobial Chemotherapy, Volume 73, Issue 3, March 2018, Pages 553–563, https://doi.org/10.1093/jac/dkx420

Antimicrob Agents Chemother. 1985 Aug;28(2):347-8. doi: 10.1128/AAC.28.2.347. PMID: 3834836

Neurosyphilis

Managing Expectations and Shared Decision Making

Uncertainties

- The type and duration of therapy
- Use of long-acting BPG at the end of short-acting penicillin therapy

Repeat CSF examination

- Is not routinely required with appropriate clinical and serological responses
- Unless the patient has HIV and is not on antiretroviral therapy

Oral doxycycline may be an option

- Only in patients that absolutely refuse CDC-endorsed treatment regimens

CDC recommendations for use of doxycycline as postexposure prophylaxis (PEP) for bacterial sexually transmitted infections prevention

https://www.cdc.gov/mmwr/volumes/73/rr/rr7302a1.htm#B1_up

	Design	Participants	Intervention	Primary Endpoint	Findings	Limitations	Quality of Evidence
DOXYVAC France CROI 2023(3)	RCT	N=502 MSM on HIV PrEP (HIV-)	Doxycycline monohydrate 200mg orally within 24-72 hours after sex versus no PEP versus 4CMenB vaccine versus no vaccine	Impact of doxycycline as PEP on time to first episode of syphilis or chlamydia and impact of 4CMenB vaccine on first episode of gonorrhea	Doxycycline as PEP reduced gonorrhea, chlamydia and syphilis infections (aHR of 0.49 (95% CI 0.32-0.76), 0.11 (95% CI 0.04-0.30) and 0.21 (95% CI 0.09-0.47), respectively). Receipt of 4CMenB was associated with a reduction in gonococcal infection (incidence 9.8/100 person years vs 19.7/100 person years in the study arm that did not receive vaccine; aHR 0.49 (95% CI 0.27-0.88)	Open-label Short follow-up	High
dPEP Kenya CROI 2023 (4)	RCT	N= 449 Cisgender women	Doxycycline hyclate 200mg orally within 72 hours after sex versus no doxycycline PEP	Any incident C. trachomatis, N. gonorrhoeae or T. pallidum	All bacterial STIs (RR 0.88; 95%CI 0.60-1.29), C. trachomatis (RR 0.73; 95% CI 0.47-1.13); N. gonorrhoeae (RR 1.64; 95% CI 0.78-3.47). There were only two syphilis infections during the study.	Open label, short follow-up	High

	Design	Participants	Intervention	Primary Endpoint	Findings	Limitations	Quality of Evidence
iPrEx Trial France 2018(1)	RCT	N=232 MSM and TGW on TDF/FTC as PrEP (HIV-)	Doxycycline hyclate 200mg orally once within 24-72 hours after having condomless anal or oral sex versus no prophylaxis	First STI infection (gonorrhea, chlamydia or syphilis) during a 10-month follow-up period	Reduced risk of acquiring chlamydia and syphilis by 70% (HR 0.30 (95% CI 0.13-0.70) and 73% (HR 0.27 (95% CI 0.07-0.98), respectively. No significant difference in gonorrhea	Open-label Short follow-up	High
DoxyPeP USA 2023(2)	RCT	N=554 MSM and TGW (N=360 on PrEP; N=194 HIV+)	Doxycycline hyclate 200mg orally once within 72 hours after having condomless sex versus no prophylaxis	Relative risk of an STI infection per quarter.	PrEP: 65 STI endpoints (29.5%) occurred in controls and 47 (9.6%) in doxyPEP participants (RR 0.33; 95%CI 0.23-0.47; p<0.0001). HIV: 30 STI endpoints (27.8%) in controls and 31 (11.7%) in doxyPEP participants (RR 0.42; 95% CI 0.25-0.75; p=0.0014).	Open-label Short follow-up	High

DoxyPEP (Post-Exposure Prophylaxis)

- Take one dose of Doxycycline 200mg **within 72 hours** of having condomless sex
- Repeat as needed but no more than one dose within 24 hours
- Decreases Syphilis and Chlamydia infections **~ 70%**

DoxyPEP Implementation

https://www.cdc.gov/mmwr/volumes/73/rr/rr7302a1.htm#B1_down

Who should receive DoxyPEP?

- MSM/TGW on HIV PrEP or living with HIV
- MSM/TGW with:
  - History of STIs within the past 12 months
  - Engages in sex work
  - Has sex under the influence of drugs (chemsex),

3-month schedule:

- Provide enough meds and replenish after HIV/STI screening

If patient is having signs and symptoms of an STI:

- Should get immediate testing and treatment; abstain until 1-week post-treatment

"No recommendation can be given at this time on the use of doxy PEP for cisgender women, cisgender heterosexual men, transgender men, and other queer and nonbinary persons"

DoxyPrEP (Pre-Exposure Prophylaxis)

In a pilot study of 52 men who have sex with men living with HIV, doxyPrEP was feasible, and yielded significant reductions in chlamydia, syphilis and gonorrhea compared to those on placebo, over one year of follow-up.

Conclusions

- In a study of 52 GBM living with HIV, the use of daily doxyPrEP was feasible, as measured through adherence and tolerability.
- DoxyPrEP led to significant reductions in bacterial STIs: 79% reduction in syphilis incidence, 92% reduction in chlamydia incidence, and 68% reduction in gonorrhea incidence.
- These pilot findings support the ongoing evaluation of doxyPrEP compared to doxyPEP in our ongoing disco trial.

AIDS 2024 July 20-26 Munich Troy Grennan, BC Centre for Disease Control, Vancouver, Canada, et al.

References

- CDC STD 2021 Treatment Guideline: https://www.cdc.gov/std/treatment-guidelines/default.htm
- STD Prevention Training Centers: https://www.cdc.gov/std/projects/nnptc.htm
- STD online self-study: https://www.std.uw.edu/
- CDC self-study: http://www.cdc.gov/std/training/std101/home.htm
- USPS Task Force: https://www.uspreventiveservicestaskforce.org/uspstf/

Resources

- National Clinician Consultation Center http://nccc.ucsf.edu/
  - HIV Management
  - Perinatal HIV
  - HIV PrEP
  - HIV PEP line
  - HCV Management
  - Substance Use Management
- Present on ECHO
- https://hsc.unm.edu/scaetc/programs-services/echo.html

- AETC National HIV Curriculum https://aidsetc.org/nhc
- AETC National Coordinating Resource Center https://targethiv.org/library/aetc-national-coordinating-resource-center-0
- HIVMA Resource Directory https://www.hivma.org/globalassets/ektron-import/hivma/hivma-resource-directory.pdf
- Additional trainings scaetcecho@salud.unm.edu
- www.scaetc.org

IHS/Tribal Resources

- Sexually Transmitted Infections (STI) Initiative: STI Toolkit.https://www.ihs.gov/sites/nptc/themes/responsive2017/display_objects/documents/sti/Express-STI-Guide.pdf

- https://www.indiancountryecho.org/resource-hubs/syphilis-resources/ The STOP SYPHILIS campaign offers free materials, including print materials, social media posts, and short educational videos.

- Go to www.stopsyphilis.org For questions about field testing and treatment policies and procedures, contact Tina Tah, Public Health Nursing Consultant, by e-mail at tina.tah@ihs.gov

Additional Slides

Syphilis Treatment: Systematic Review and Meta-Analysis Investigating Non-Penicillin Therapeutic Strategies

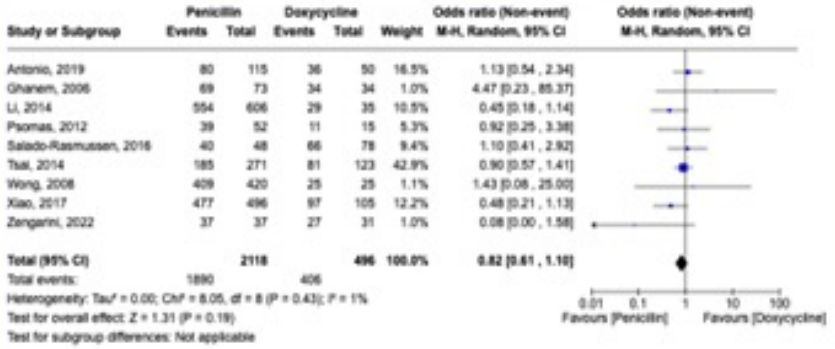
Open Forum Infectious Diseases
IDSA

Systematic literature review and meta-analysis

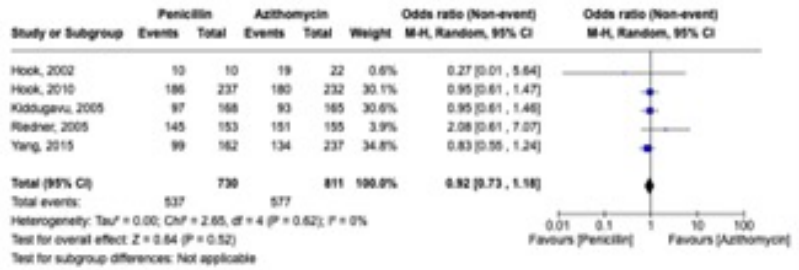
27 studies evaluating alternative drug strategies for non-neurological syphilis instead of penicillin

Alternative drug approaches, including **ceftriaxone**, **azithromycin**, and **doxycycline** monotherapies, demonstrate **equivalent serological cure rates** to benzathine penicillin G (BPG) in **non-neurological** syphilis, even among HIV-positive patients

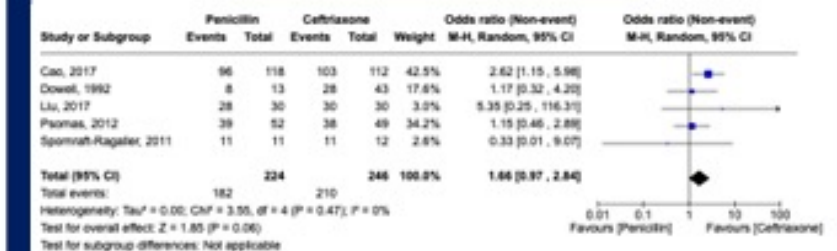
BPG vs. Doxycycline:



BPG vs. Azithromycin:



BPG vs. Ceftriaxone:



Callado, Gutfreund, Pardo, Hsieh, Lin, Sampson, Nava, Marins, Deliberato, Martino, Holubar, Salinas, Marra. *OFID*. Feb 2024

@OFIDJournal

Scenario	1: Confirmed, proven or highly probable congenital syphilis	2: Possible congenital syphilis	3: Congenital syphilis less likely	4: Congenital syphilis unlikely
Clinical Information	**Neonate with:** • A physical exam consistent with CS: Hepatomegaly, Jaundice, Nasal discharge ("snuffles"), Rash, Generalized lymphadenopathy, Skeletal abnormalities • A serum quantitative nontreponemal serology 4-fold greater than mother's or • A positive darkfield or PCR test of placenta, body fluids or positive silver stain of placenta or cord	**Neonate with** a normal physical exam and a serum quantitative nontreponemal serologic titer equal to or < 4-fold of the maternal titer at delivery and **one** of the following: • The mother was not treated, was inadequately treated, or has no documentation of treatment. • The mother was treated with erythromycin, or a regimen not recommended in these guidelines • The mother received recommended regimen, but treatment was initiated <30 days before delivery.	**Neonate with** a normal physical examination and a serum quantitative nontreponemal serologic titer equal or <4-fold of the maternal titer at delivery and **both** of the following are true: • The mother was treated during pregnancy, treatment was appropriate for the infection stage, and the treatment regimen was initiated ≥30 days before delivery. • The mother has no evidence of reinfection or relapse	**Neonate with:** • a normal physical exam • serum quantitative nontreponemal serology equal to or less than 4-fold mother at delivery and • **Mother's treatment was adequate before pregnancy** • Mother's nontreponemal titer remained low and stable before and during pregnancy and at delivery
Evaluation	**Evaluation:** CSF with VDRL, cell ct, protein, CBC/diff, long bone radiographs, neurologic eval (eye, auditory, imaging)	CSF analysis for VDRL, cell count, and protein** CBC, differential, long-bone radiographs	No evaluation is recommended	No evaluation is recommended
Treatment	**Aqueous crystalline penicillin G** 100,000–150,000 units/kg/body wt./day, administered as 50,000 units/kg body wt./dose IV q 12 hours during the first 7 days of life and q 8 hours thereafter for a total of 10 days OR **Procaine penicillin G** 50,000 units/kg body weight/dose IM in a single daily dose for 10 days	**Aqueous crystalline penicillin G** 100,000–150,000 units/kg/body wt./day, administered as 50,000 units/kg body wt./dose IV q 12 hours during the first 7 days of life and q 8 hours thereafter for a total of 10 days OR **Procaine penicillin G** 50,000 units/kg body weight/dose IM in a single daily dose for 10 days OR **Benzathine penicillin** 50,000 units/kg body wt. single IM injection	**Treatment: Benzathine penicillin G 50,000** units/kg body weight/dose IM in a single dose * Another approach involves not treating the newborn if follow-up is certain but providing close serologic follow-up every 2–3 months for 6 months for infants whose mothers' nontreponemal titers decreased at least fourfold after therapy for early syphilis or remained stable for low titer, latent syphilis (VDRL <1:2 or RPR <1:4).	**No treatment recommended** • Benzathine penicillin 50,000 units/kg body weight as a single IM injection might be considered, if follow-up is uncertain and the neonate has a reactive nontreponemal test. • Neonates should be followed serologically to ensure the nontreponemal test returns to negative

Facts about Penicillin Allergy

Characteristics of an IgE-mediated (Type 1) reaction:

- Reactions that occur immediately or usually within one hour.
- Hives: Multiple pink or red raised areas of skin that are intensely itchy.
- Angioedema: Localized edema without hives affecting the abdomen, face, extremities, genitalia, oropharynx or larynx.
- Wheezing and shortness of breath.
- Anaphylaxis.

Anaphylaxis: Must have signs or symptoms in at least two of the following systems:

- Skin: Hives, flushing, itching, and/or angioedema.
- Respiratory: Cough, nasal congestion, shortness of breath, chest tightness, wheeze, sensation of throat closure or choking, and/or change in voice-quality (laryngeal edema).
- Cardiovascular: Hypotension, faintness, tachycardia or less commonly bradycardia, tunnel vision, chest pain, sense of impending doom and/or loss of consciousness.
- Gastrointestinal: Nausea, vomiting, abdominal cramping, and diarrhea

https://www.cdc.gov/antibiotic-use/hcp/clinical-signs/index.html

Questions