Diversifying Treatment Options for Pregnant People with Syphilis

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IMPAACT

International Maternal Pediatric Adolescent AIDS Clinical Trials Network

ANNUAL MEETING

2024

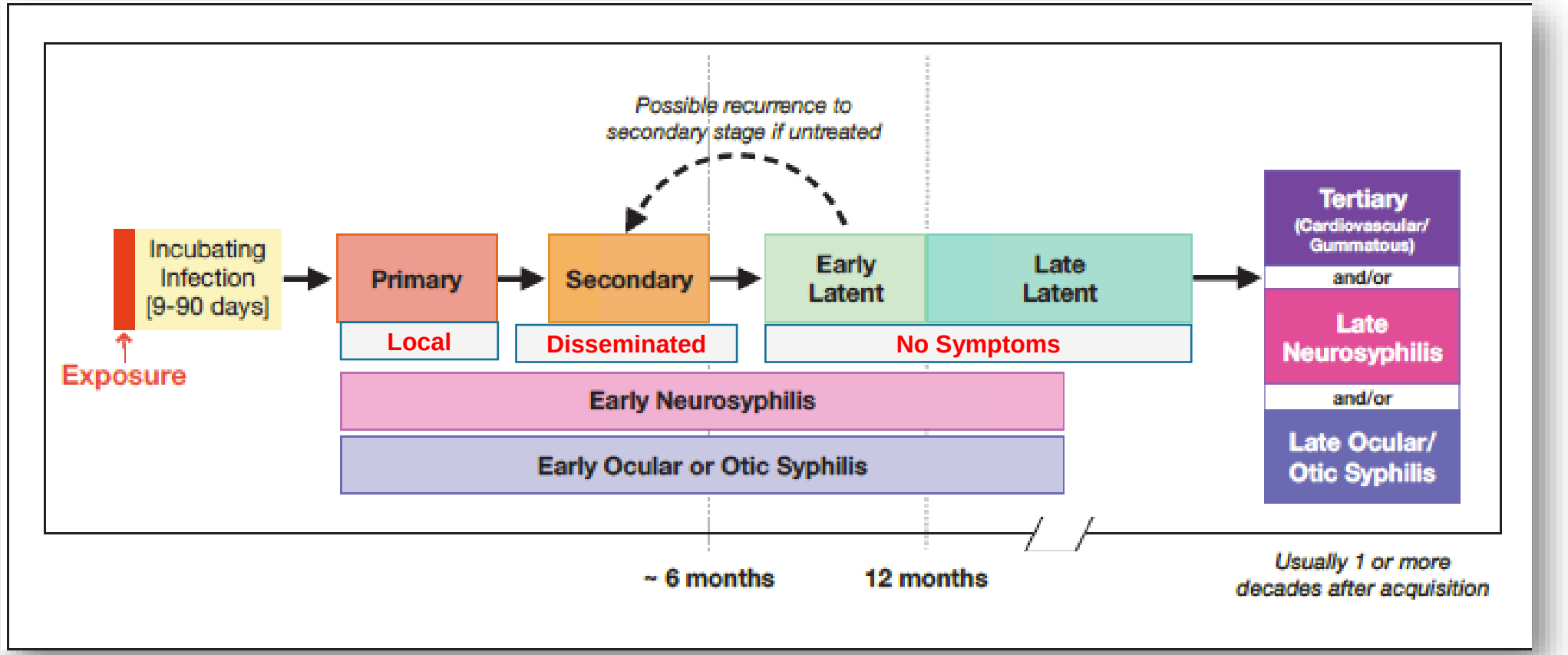
Outline

1. Introduction to syphilis in pregnancy
2. Epidemiology and impact on maternal and fetal health
3. Current standard treatments and their limitations
4. The need for diversifying treatment options
5. Alternative antibiotics and recent and ongoing research

Introduction to Syphilis

- What is Syphilis?
  - A bacterial infection caused by *Treponema pallidum*, primarily spread through sexual contact

Introduction to Syphilis – Staging and Symptoms



https://www.nycptc.org/x/Syphilis_Monograph_2019.PRESS.WEB.r4a.pdf

Introduction to Syphilis – Treatment

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***
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, Bachmann LH, Chan PA, et al. Sexually Transmitted Infections Treatment Guidelines, 2021. MMWR Recomm Rep. 2021;70(4):1-187. Published 2021 Jul 23. doi:10.15585/mmwr.rr7004a1

Importance of Syphilis in Pregnancy

Risks for Pregnant Persons

- Pre-term labor and premature birth
- Miscarriage
- Stillbirth

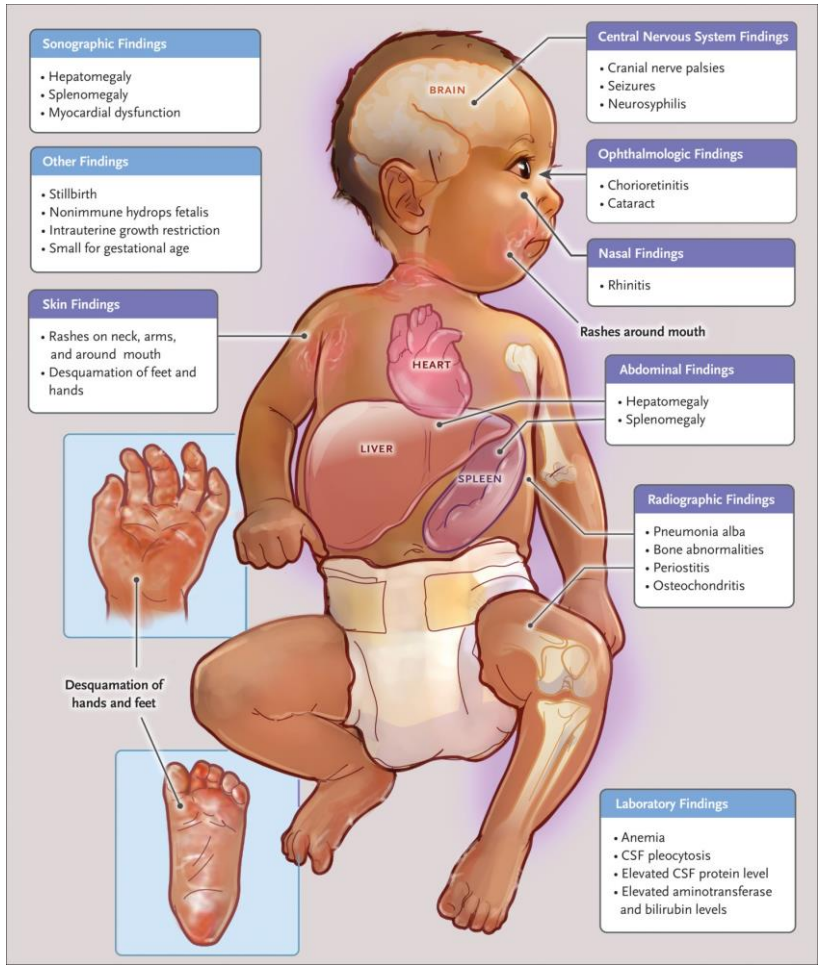
Risks for Babies

- **Congenital syphilis**

Congenital Syphilis (CS)

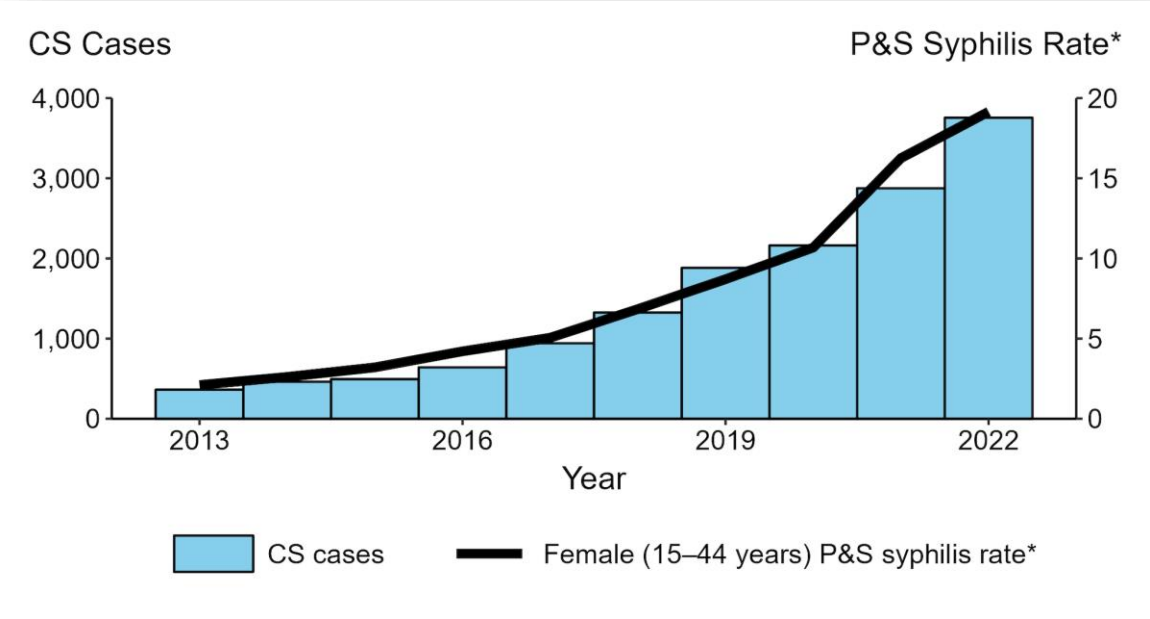
- **Congenital syphilis** occurs when infection is passed from the birthing parent during pregnancy.
  - This happens if the birthing parent has syphilis and doesn't receive proper treatment.
  - The infection can cause serious health problems for the baby, both at birth and as they grow
  - Early testing and treatment of pregnant persons can help prevent congenital syphilis and protect the baby's health

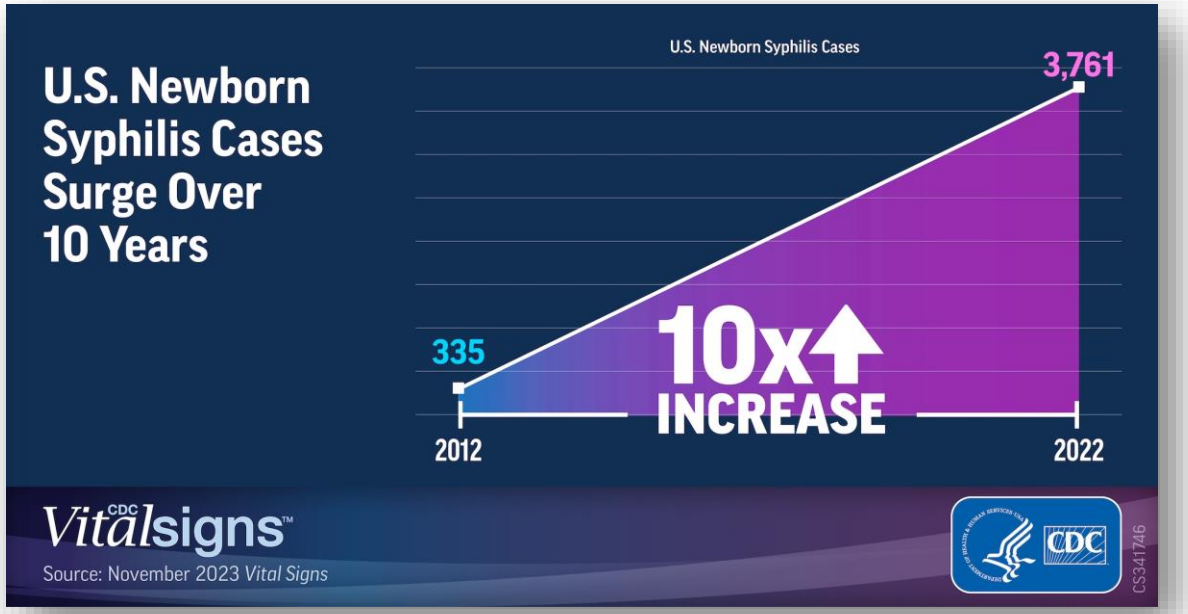
Congenital Syphilis (CS)



Stafford IA, Workowski KA, Bachmann LH. Syphilis Complicating Pregnancy and Congenital Syphilis. Reply. N Engl J Med. 2024;390(13):1251. doi:10.1056/NEJMc2401932

Epidemiology of Syphilis in Pregnancy





https://www.cdc.gov/std/statistics/2022/figures/cs-1.htm
https://www.cdc.gov/media/releases/2023/s1107-newborn-syphilis.html

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Epidemiology of Syphilis in Pregnancy

Original Research

Rising Stillbirth Rates Related to Congenital Syphilis in the United States From 2016 to 2022

Aliza Machefsky, MD, Kaitlin Hufstetler, MD, Laura Bachmann, MD, MPH, Lindley Barbee, MD, MPH, Kathryn Miele, MD, MA, and Kevin O'Callaghan, MB, BCh

"Stillbirths occurred in more than 1 in 20 pregnancies complicated by congenital syphilis….If the prevalence of congenital syphilis continues to rise, there will be a corresponding increase in the overall stillbirth rate nationally"

Machefsky A, Hufstetler K, Bachmann L, Barbee L, Miele K, O'Callaghan K. Rising Stillbirth Rates Related to Congenital Syphilis in the United States From 2016 to 2022. Obstet Gynecol. Published online August 15, 2024. doi:10.1097/AOG.0000000000005700

Preventing Congenital Syphilis

Early Detection

- Treatment of the pregnant person reduces the risk of congenital syphilis
- Current recommendations
  - Screening in the first and third trimester and at delivery

Preventing Congenital Syphilis

Early Detection

- Treatment of the pregnant person reduces the risk of CS
- Current recommendations
  - Screening at first and third visit and at delivery

Challenges in CS Prevention

- Limited access to prenatal care (screening)
- Stigma associated with STIs
- **Challenges with Treatment**

Syphilis Treatment

Penicillin

Challenges

- Penicillin allergies
- Supply chain issues
- Administration challenges

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Syphilis Treatment

Limitations

- **Penicillin allergies**
- Supply chain issues
- Administration challenges

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***
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	Procaine penicillin G 2.4 million units IM once daily *PLUS* Probenecid 500mg 4 times daily for 10–14 days
Tertiary		

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Syphilis Treatment

CDC Guidelines: Early Syphilis Treatment in Pregnancy

- Preferred
  - Benzathine penicillin G 2.4 million units x1 IM

“Pregnant persons with primary or secondary syphilis who are allergic to penicillin should be desensitized and treated with penicillin G.”

WHO Guidelines: Early Syphilis Treatment in Pregnancy

- Preferred
  - Benzathine penicillin G 2.4 million units x1 IM
- Alternative
  - Ceftriaxone 1g IM ***daily*** x 10-14d

Syphilis Treatment

Limitations

- Penicillin allergies
- **Supply chain issues**
- Administration challenges

Recurrent Shortages

NEW YORK CITY DEPARTMENT OF HEALTH AND MENTAL HYGIENE
Ashwin Vasan, MD, PhD
Commissioner

Presentation last saved: 8m ago

Long-Acting Penicillin G Benzathine Injectable Suspension Products (Bicillin L-A®) Shortage

- Long-acting penicillin G benzathine injectable suspension products (Bicillin L-A®), the first-line treatment for syphilis and the only recommended treatment for pregnant people and infants with syphilis, continues to be in short supply, with supply shortages likely to continue until mid-2024.
- With rising rates of syphilis and congenital syphilis in New York City (NYC), the NYC Department of Health and Mental Hygiene (NYC Health Department) strongly encourages providers to review their existing Bicillin L-A inventory and reserve Bicillin L-A for pregnant people with syphilis or exposure to syphilis, infants with syphilis, and for people with syphilis who are unable to take doxycycline if their inventory is running low.
- Doxycycline is the acceptable alternative recommendation for people who are not pregnant; providers should closely follow patients to encourage treatment completion.
- Other intramuscular formulations of penicillin, such as Bicillin C-R, are not acceptable alternatives for the treatment of syphilis.

Syphilis Treatment

Limitations

- Penicillin allergies
- Supply chain issues
- **Administration challenges**
- Intravenous vs Intramuscular vs Oral
- Frequency of dosing

Characteristics of Alternative

- Safety for the pregnant person and their fetus
- Active against syphilis
  - Resistance patterns of syphilis
- Easily administered oral or via intramuscular injection
  - Long-half life
  - Understandable pharmokinetics in pregnancy
- Efficacy
  - Crosses the placenta

Alternative Agents

1. Azithromycin
2. Doxycycline
3. Linezolid
4. Amoxicillin
5. Cefixime
6. Ceftriaxone

Alternative Agents

1. **Azithromycin**
2. Doxycycline
3. Linezolid
4. Amoxicillin
5. Cefixime
6. Ceftriaxone

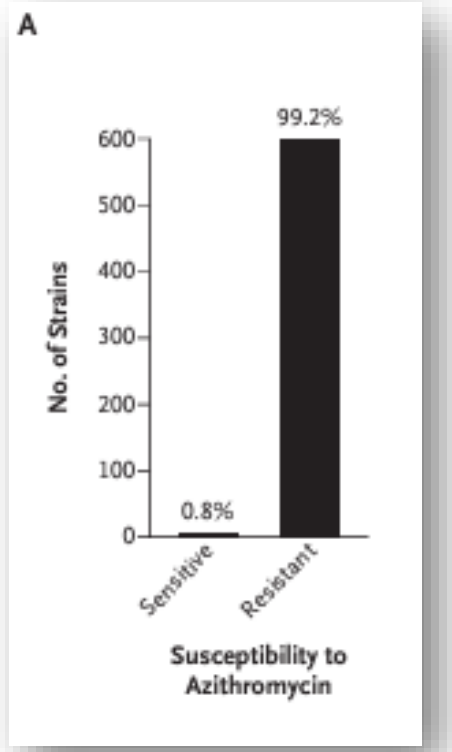
- Azithromycin is a macrolide antibiotic
- Generally considered **safe in pregnancy** (category B)
- Positive: **Oral administration** with a long half-life (convenient dosing)
- Limitation: Increasing **resistance** of *Treponema Pallidum*

Alternative Agents

1. **Azithromycin**
2. Doxycycline
3. Linezolid
4. Amoxicillin
5. Cefixime
6. Ceftriaxone

Near-Universal Resistance to Macrolides of *Treponema pallidum* in North America

TO THE EDITOR: In 2024, the Centers for Disease Control and Prevention (CDC) estimated that syphilis cases had risen by 79% between 2018 and 2022.[1] CDC and Canadian guidelines for syphilis treatment recommend penicillin G, administered parenterally, for all stages of syphilis.[2] A single 2-g oral dose of azithromycin was listed as an alternative regimen for those with penicillin allergy starting in 2002, until mutations conferring macrolide resistance were found also see the Supplementary Methods). The median age of the patients was 33 years (range, 0 to 76). A total of 466 of 588 patients (79.3%) were male. Among male patients with sex-partner information available, 73 of 88 (83%) were men who have sex with men. The syphilis stage was documented for 115 patients, with secondary syphilis being the most prevalent (56 of 115 [48.7%]). Among strains with a near-complete genome obtained, 23 of 54 (43%) belonged to the Nichols-like lineage and 31



Lieberman NAP, Reid TB, Cannon CA, et al. Near-Universal Resistance to Macrolides of Treponema pallidum in North America. N Engl J Med. 2024;390(22):2127-2128. doi:10.1056/NEJMc2314441

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Alternative Agents

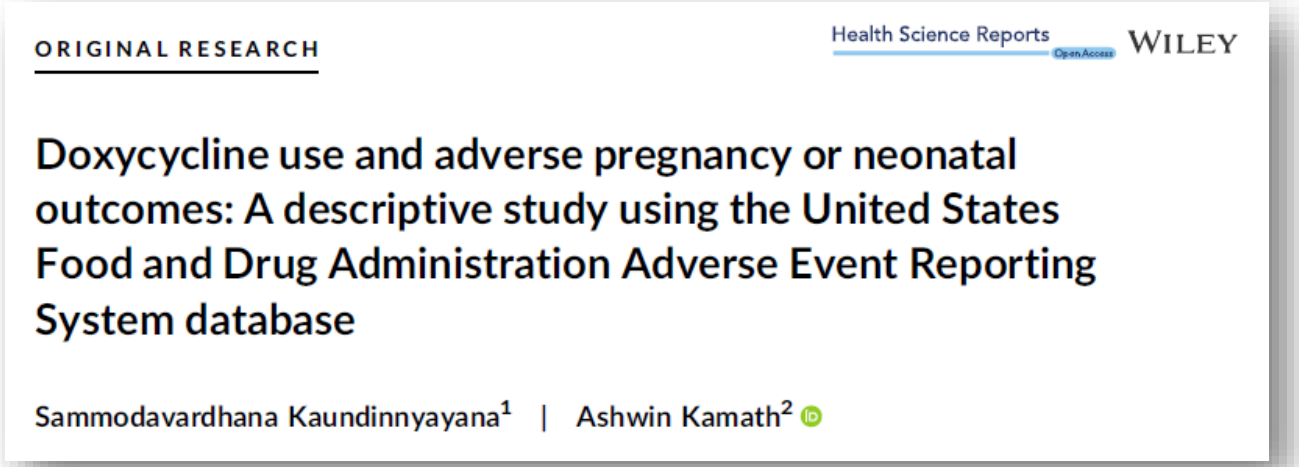
1. Azithromycin
2. **Doxycycline**
3. Linezolid
4. Amoxicillin
5. Cefixime
6. Ceftriaxone

- Doxycycline is a tetracycline antibiotic
- Generally considered **contraindicated in pregnancy**
- Positive: **High efficacy** in non-pregnant adults with syphilis
- Limitation: **Unsafe in pregnancy**

Alternative Agents

1. Azithromycin
2. **Doxycycline**
3. Linezolid
4. Amoxicillin
5. Cefixime
6. Ceftriaxone

- **Is Doxycycline Unsafe in Pregnancy?**



ORIGINAL RESEARCH

Health Science Reports Open Access WILEY

Doxycycline use and adverse pregnancy or neonatal outcomes: A descriptive study using the United States Food and Drug Administration Adverse Event Reporting System database

Sammodavardhana Kaundinnyayana[1] | Ashwin Kamath[2]

Kaundinnyayana S, Kamath A. Doxycycline use and adverse pregnancy or neonatal outcomes: A descriptive study using the United States Food and Drug Administration Adverse Event Reporting System database. Health Sci Rep. 2022;5(6):e931. Published 2022 Nov 14. doi:10.1002/hsr2.931

Alternative Agents

1. Azithromycin
2. Doxycycline
3. **Linezolid**
4. Amoxicillin
5. Cefixime
6. Ceftriaxone

- Linezolid is a oxazolidinone antibiotic
- Limited data in pregnancy; use **only if benefits outweigh risks** (category C)
- Positive: **Oral administration**
- Limitation:
  - **Insufficient data on efficacy for congenital syphilis**
  - **Insufficient data on safety in pregnancy**

Alternative Agents

1. Azithromycin
2. Doxycycline
3. **Linezolid**
4. Amoxicillin
5. Cefixime
6. Ceftriaxone

Oral linezolid compared with benzathine penicillin G for treatment of early syphilis in adults (Trep-AB Study) in Spain: a prospective, open-label, non-inferiority, randomised controlled trial

Maria Ubals, Patricia Nadal-Baron*, Maider Arando*, Ángel Rivero, Adrià Mendoza, Vicent Descalzo Jorro, Dan Ouchi, Clara Pérez-Mañá, Marlene Álvarez, Andrea Alemany, Yannick Hoyos-Mallecot, Ethan Nunley, Nicole A P Lieberman, Alexander L Greninger, Cristina Galván-Casas, Clara Suñer, Camila G-Beiras, Roger Paredes, Alicia Rodríguez-Gascón, Andrés Canut, Vicente García-Patos, Magí Farré, Michael Marks, Lorenzo Giacani, Martí Vall-Mayans†, Oriol Mitjà†

- " The efficacy of linezolid at a daily dose of 600 mg for 5 days **did not meet the non-inferiority criteria** compared with BPG and, as a result, this treatment regimen should not be used to treat patients with early syphilis. "

Ubals M, Nadal-Baron P, Arando M, et al. Oral linezolid compared with benzathine penicillin G for treatment of early syphilis in adults (Trep-AB Study) in Spain: a prospective, open-label, non-inferiority, randomised controlled trial. Lancet Infect Dis. 2024;24(4):404-416. doi:10.1016/S1473-3099(23)00683-7

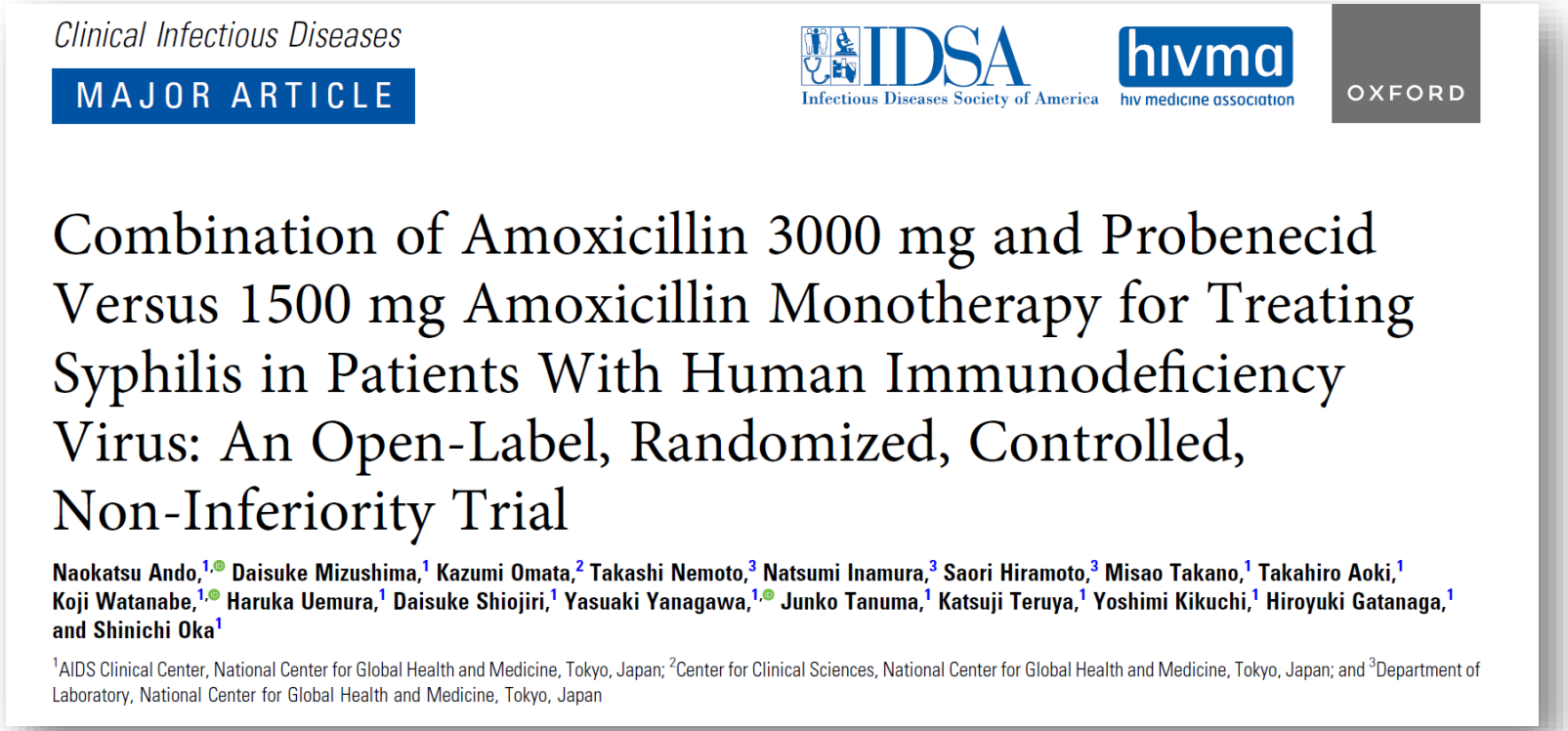
Alternative Agents

1. Azithromycin
2. Doxycycline
3. Linezolid
4. **Amoxicillin**
5. Cefixime
6. Ceftriaxone

- Amoxicillin is a beta-lactam (similar to penicillin) and probenecid enhances antibiotic levels by decreasing renal excretion
- Safety: Amoxicillin is generally considered safe in pregnancy (category B). There is limited data on probenecid
- Positive: **Oral administration**
- Limitation:
  - **Insufficient evidence** on efficacy in pregnancy
  - Limited access to probenecid worldwide

Alternative Agents

1. Azithromycin
2. Doxycycline
3. Linezolid
4. **Amoxicillin**
5. Cefixime
6. Ceftriaxone



Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

Combination of Amoxicillin 3000 mg and Probenecid Versus 1500 mg Amoxicillin Monotherapy for Treating Syphilis in Patients With Human Immunodeficiency Virus: An Open-Label, Randomized, Controlled, Non-Inferiority Trial

Naokatsu Ando,[1] Daisuke Mizushima,[1] Kazumi Omata,[2] Takashi Nemoto,[3] Natsumi Inamura,[3] Saori Hiramoto,[3] Misao Takano,[1] Takahiro Aoki,[1] Koji Watanabe,[1] Haruka Uemura,[1] Daisuke Shiojiri,[1] Yasuaki Yanagawa,[1] Junko Tanuma,[1] Katsuji Teruya,[1] Yoshimi Kikuchi,[1] Hiroyuki Gatanaga,[1] and Shinichi Oka[1]

[1]AIDS Clinical Center, National Center for Global Health and Medicine, Tokyo, Japan; [2]Center for Clinical Sciences, National Center for Global Health and Medicine, Tokyo, Japan; and [3]Department of Laboratory, National Center for Global Health and Medicine, Tokyo, Japan

Ubals M, Nadal-Baron P, Arando M, et al. Oral linezolid compared with benzathine penicillin G for treatment of early syphilis in adults (Trep-AB Study) in Spain: a prospective, open-label, non-inferiority, randomised controlled trial. Lancet Infect Dis. 2024;24(4):404-416. doi:10.1016/S1473-3099(23)00683-7

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Alternative Agents

1. Azithromycin
2. Doxycycline
3. Linezolid
4. Amoxicillin
5. **Cefixime**
6. Ceftriaxone

- Cefixime is a third-generation cephalosporin
- Generally considered **safe in pregnancy** (category B)
- Positive: **Oral administration**
- Limitation: **Insufficient data on efficacy for syphilis**

Alternative Agents

1. Azithromycin
2. Doxycycline
3. Linezolid
4. Amoxicillin
5. **Cefixime**
6. Ceftriaxone

Clinical Infectious Diseases

BRIEF REPORT

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

Clinical Efficacy of Cefixime for the Treatment of Early Syphilis

Chrysovalantis Stafylis,[1] Kori Keith,[2] Shivani Mehta,[2] David Tellalian,[3] Pamela Burian,[3] Carl Millner,[3] and Jeffrey D. Klausner[1]

[1]Department of Preventive Medicine, University of Southern California Keck School of Medicine, Los Angeles, California, USA; [2]Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California, USA; and [3]Department of Medicine, AIDS Healthcare Foundation, Los Angeles, California, USA

Safe and efficacious alternative treatment options for syphilis are necessary. This randomized, 2-arm, noncomparative pilot study evaluated the efficacy of oral cefixime 400 mg in achieving a ≥4-fold rapid plasma reagin titer decrease by 3 or 6 months after treatment. The proportion of cefixime arm participants treated successfully was 87% (95% confidence

treatment with ceftriaxone requires multiple daily intramuscular injections or intravenous administration, making treatment adherence potentially challenging. There is a need to identify safe, effective, and convenient antibiotics to treat early syphilis.

Cephalosporins could be good candidates for evaluation; they are β-lactams that inhibit bacterial cell wall synthesis. A study by Norris et al [7] has shown that the minimum inhibitory concentrations of various third-generation cephalosporins for *T. pallidum* are low (ceftriaxone: 0.0007 mg/L, ceftazidime: 0.007 mg/L, cefetamet: 0.04 mg/L). Considering that ceftriaxone, a parenterally administered third-generation cephalosporin, has demonstrated effectiveness for syphilis, we hypothesized that other third-generation cephalosporins could

Ando N, Mizushima D, Omata K, et al. Combination of Amoxicillin 3000 mg and Probenecid Versus 1500 mg Amoxicillin Monotherapy for Treating Syphilis in Patients With Human Immunodeficiency Virus: An Open-Label, Randomized, Controlled, Non-Inferiority Trial. Clin Infect Dis. 2023;77(5):779-787. doi:10.1093/cid/ciad278

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Alternative Agents

1. Azithromycin
2. Doxycycline
3. Linezolid
4. Amoxicillin
5. Cefixime
6. **Ceftriaxone**

- Antibiotic: Ceftriaxone is a third-generation cephalosporin
- Safety: Generally considered **safe in pregnancy** (category B)
- Positive:
  - **Effective against Treponema pallidum**
  - **Crosses the placenta**
- Limitation: **Daily injections**

Alternative Agents

1. Azithromycin
2. Doxycycline
3. Linezolid
4. Amoxicillin
5. Cefixime
6. **Ceftriaxone**

Original research article

INTERNATIONAL JOURNAL OF STD & AIDS

Use of ceftriaxone as an alternative treatment method in pregnant women diagnosed with syphilis – a single centre experience

Ilona Hartmane[1,2], Iveta Ivdra[1,2], Ingmars Mikazans[1,2], Aleksejs Princevs[1], Irena Teterina[3], Vanda Bondare-Ansberga[1,2] and Lelde Reinberga[1,2]

International Journal of STD & AIDS
2024, Vol. 35(2) 130–135

DOI: 10.1177/09564624231206845
journals.sagepub.com/home/std
Sage

Hartmane I, Ivdra I, Mikazans I, et al. Use of ceftriaxone as an alternative treatment method in pregnant women diagnosed with syphilis - a single centre experience. Int J STD AIDS. 2024;35(2):130-135. doi:10.1177/09564624231206845

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Alternative Agents

1. Azithromycin
2. Doxycycline
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5. Cefixime
6. **Ceftriaxone**

- Long-acting IM Ceftriaxone would be the ideal agent
- There is interest from the Preclinical Microbicide and Prevention Research Branch (PMPRB) in the Prevention Sciences Program Within the Division of AIDS (DAIDS) at the National Institute of Allergy and Infectious Diseases (NIAID)
- IMPAACT 2044 will assist with that effort

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IMPAACT 2044

Title	Phase IV Study of the Pharmacokinetics and Safety of Ceftriaxone and Benzathine Penicillin G (BPG) During Pregnancy
Design	Opportunistic Phase IV PK study of pharmacokinetic parameters of Ceftriaxone (arm 1) and Benzathine Penicillin (arm 2) in pregnancy
Study Population	Pregnant persons receiving any dose of either ceftriaxone or benzathine penicillin for standard of care treatment for any indication
Agent	Arm 1: Ceftriaxone or Arm 2: Benzathine Penicillin
Sample Size	Arm 1a IV Ceftriaxone: 6-8 pregnant persons in each trimester Arm 1b IM Ceftriaxone: 4-6 pregnant persons in each trimester Arm 2 IM Benzathine Penicillin G:6-8 pregnant persons in each trimester
1^0 Outcomes	To describe the PK parameters of Ceftriaxone during pregnancy up to 24 hours post-treatment. To describe the PK parameters of Benzathine Penicillin G during pregnancy up to 28 days post-treatment.

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Ceftriaxone Has Limited PK Data In Pregnancy

Ceftriaxone General PK Properties

- Absorption
  - F following IM administration ~100%
  - Tmax 1-2 hr
- Distribution
  - **Vd** is small: 6 to 14 L
  - **Plasma protein binding** 95% - but saturable
- Elimination
  - Not metabolized
  - **Significant biliary excretion**
  - **Urine elimination** 33-67%.
- Clearance
  - CL_{Total} 0.6-1.45 L/h
  - CL_{Renal}: 0.32-0.73 L/hr

Subject Group	Elimination Half-Life (hr)	Plasma Clearance (L/hr)	Volume of Distribution (L)
Healthy Subjects	5.8 to 8.7	0.58 to 1.45	5.8 to 13.5
Elderly Subjects (mean age, 70.5 yr)	8.9	0.83	10.7
Patients With Renal Impairment			
Hemodialysis Patients (0 to 5 mL/min)*	14.7	0.65	13.7
Severe (5 to 15 mL/min)	15.7	0.56	12.5
Moderate (16 to 30 mL/min)	11.4	0.72	11.8
Mild (31 to 60 mL/min	12.4	0.70	13.3
Patients With Liver Disease	8.8	1.1	13.6

*Creatinine clearance.

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BPG Has Limited PK Data In Pregnancy

- We know that it works…
- Detailed pharmacokinetics in pregnancy are limited
- **A complete understanding of the PK/PD of Benzathine Penicillin in pregnancy is necessary to design potential alternatives**

Summary

- **Syphilis in pregnancy is a significant health concern** with serious risks for both birthing parent and child
- **Congenital syphilis** is increasing rapidly
- **Penicillin is the gold standard treatment** but has limitations such as allergies and supply shortages
- **Diversifying treatment options is essential** to address these limitations and improve health outcomes
- **Alternative options show promise** but require further research to ensure effectiveness and to overcome implementation challenges
- **IMPAACT 2044** will allow us to model the needed pharmokinetics of a theoretical Long-Acting (LA) formulation of ceftriaxone that can be given IM and maintain appropriate trough concentrations

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- Edmund Capparelli
- Sharon Nachman
- Rest of the IMPAACT 2044 Team

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THANKS!

Any questions?

You can find me at

- @jason10033
- jz2700@cumc.columbia.edu

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