
Navigating the Bicillin L-A Shortage: A Conversation with PharmD Dr. Kathy Yang

Kelly A. Johnson, MD, MPH

Medical Director, CAPTC

Assistant Professor,
Infectious Diseases, UCSF

Medical Officer, CDPH

Katherine Yang, PharmD, MPH

Co-Vice Dean, Clinical Innovation &
Entrepreneurship

Professor, UCSF School of Pharmacy

ID Clinical Pharmacist, UCSF

Disclosure Statement

- No conflicts of interest to disclose

Learning Objectives

- List at least 2 factors contributing to ongoing Bicillin L-A shortages
- Describe a framework for prioritizing Bicillin L-A when supplies are limited
- Name potential alternative treatments for syphilis in non-pregnant people
- Develop a decision-making process for the treatment of syphilis when standard guidelines cannot be followed or when data is insufficient.

Audience response question

- A 23 yo MSM is diagnosed with syphilis. His RPR is 1:256. He had a non-reactive RPR 6 months ago. You have a very limited amount bicillin on hand, but supplies are running low. What do you do?
 - A) Treat with bicillin anyway – it is the first line treatment for syphilis
 - B) Treat with doxycycline 100 mg PO BID x 14 days
 - C) Treat with doxycycline 100 mg PO BID x 28 days
 - D) Something else

Background

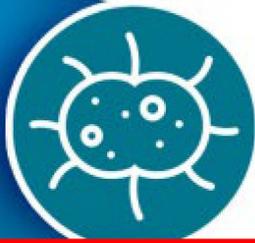
**Syphilis is on the Rise
Bicillin L-A is Tx of Choice**

THE
STATE OF STIs
IN THE
UNITED STATES,
2022

CDC's 2022 STI Surveillance Report underscores that STIs must be a public health priority



1.6 million
CASES OF CHLAMYDIA
6.2% decrease since 2018



648,056
CASES OF GONORRHEA
11% increase since 2018



207,255
CASES OF SYPHILIS
80% increase since 2018



3,755
CASES OF SYPHILIS AMONG NEWBORNS
183% increase since 2018

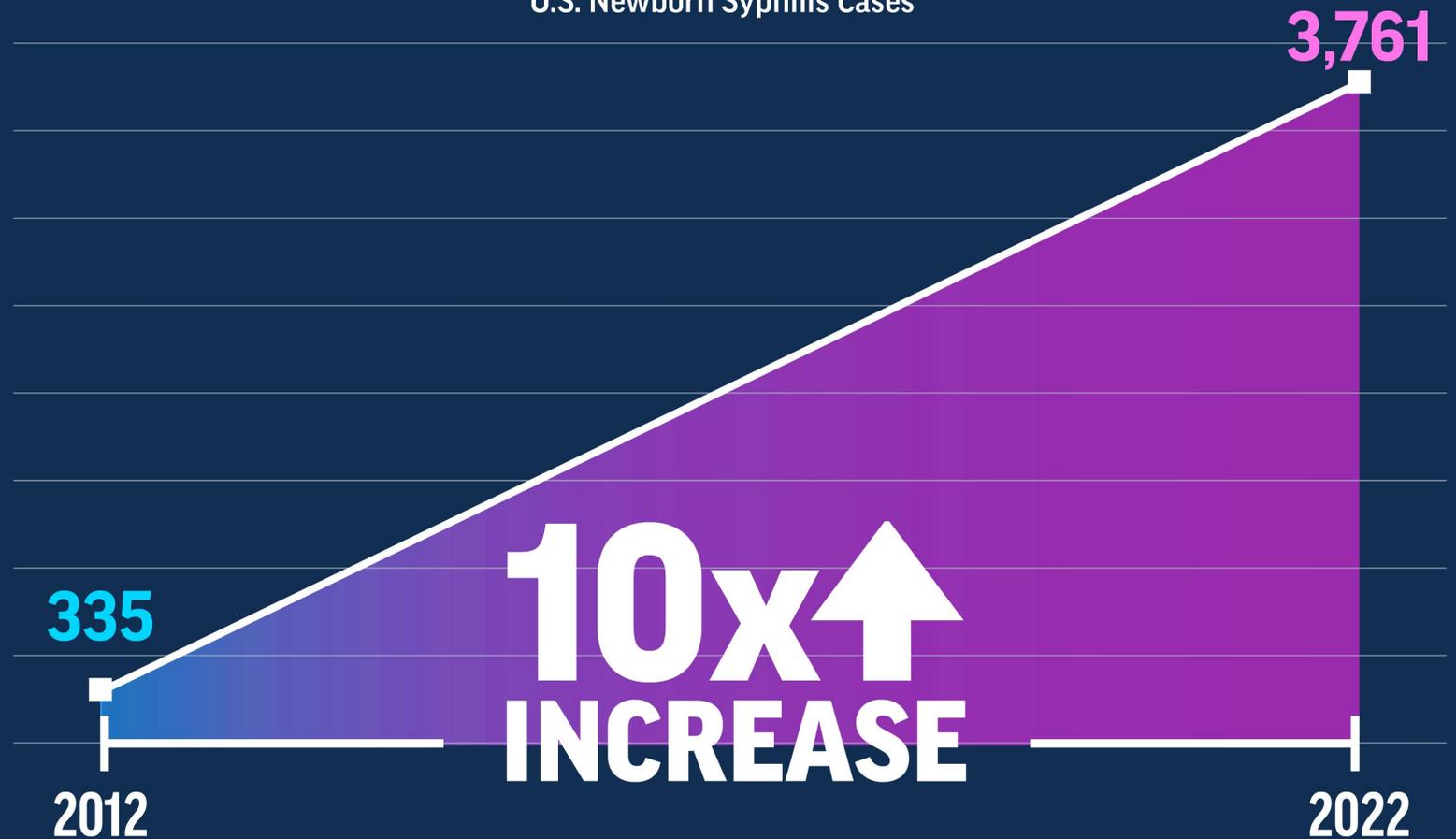
LEARN MORE AT: www.cdc.gov/std/

ANYONE WHO HAS SEX COULD GET AN STI, BUT SOME GROUPS ARE MORE AFFECTED

- YOUNG PEOPLE AGED 15-24
- GAY & BISEXUAL MEN
- PREGNANT PEOPLE
- RACIAL & ETHNIC MINORITY GROUPS

U.S. Newborn Syphilis Cases Surge Over 10 Years

U.S. Newborn Syphilis Cases



^{CDC}
Vitalsigns™

Source: November 2023 Vital Signs



CS341746

CDC: “Up to 40% of infants born to [persons] with untreated syphilis may be stillborn or die from the infection”

Key Findings: CDC Vital Signs Report

- **Almost 9 in 10 cases** of newborn syphilis in 2022 might have been prevented with timely testing and treatment during pregnancy.
 - **More than half** were among people who tested positive for syphilis during pregnancy but did not receive adequate or timely treatment.

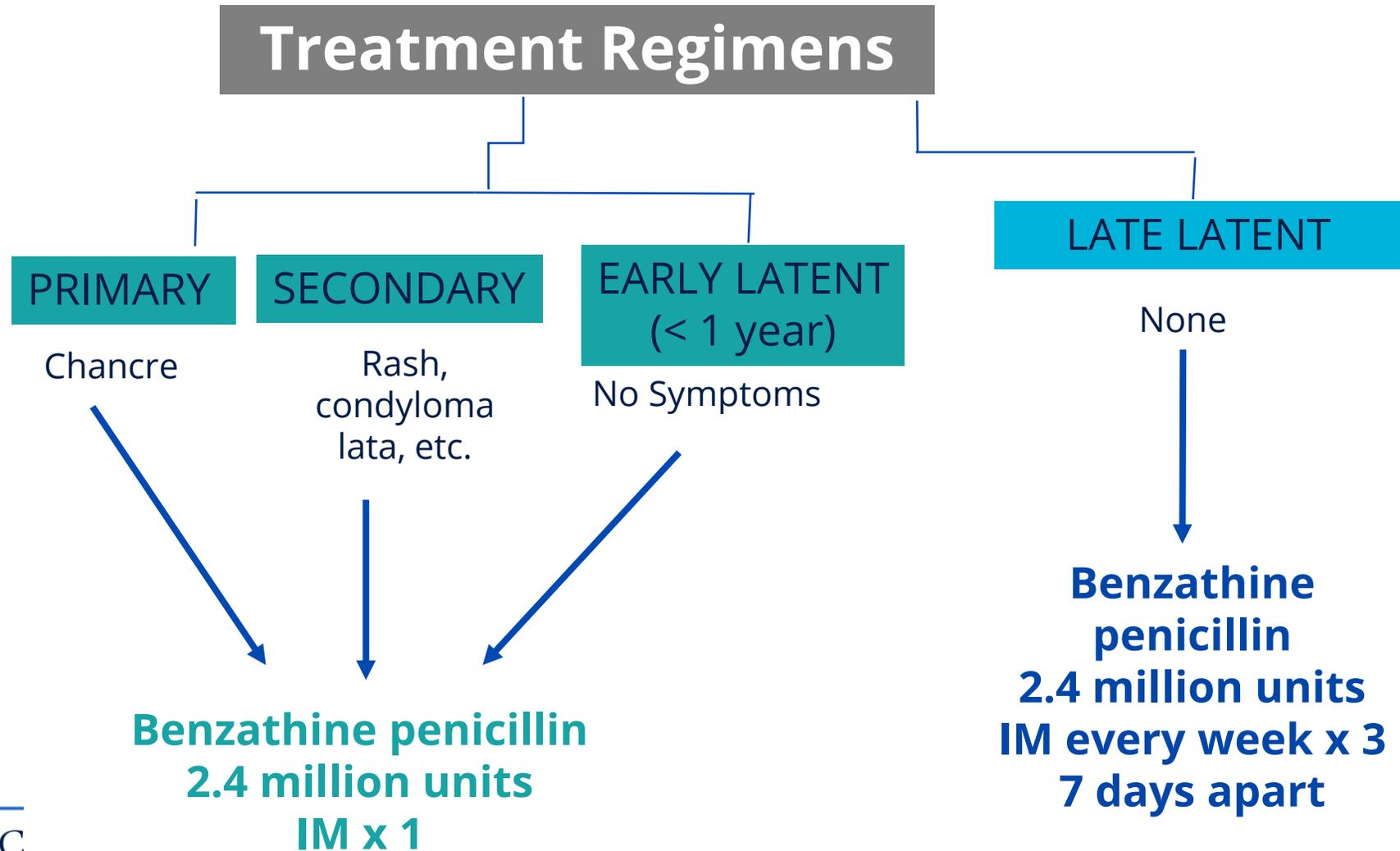
Morbidity and Mortality Weekly Report (*MMWR*)

Vital Signs: Missed Opportunities for Preventing Congenital Syphilis — United States, 2022

Weekly / November 17, 2023 / 72(46);1269–1274

[Print](#)

Bicillin L-A = First-Line for All Stages of Syphilis



Syphilis in Pregnancy

Penicillin is the only tx for syphilis in pregnancy

- Treat with the penicillin regimen appropriate for stage of infection
- **Pregnant people with history of penicillin allergy should be desensitized and still treated with penicillin**

Primary, Secondary, and Early Latent Syphilis

Benzathine penicillin G* 2.4 million units IM in a single dose

*** Bicillin L-A is the trade name. DO NOT use bicillin C-R!**

Alternatives (non-pregnant penicillin-allergic adults):

- **Doxycycline 100 mg po bid x 2 weeks (14 days)**
- Tetracycline 500 mg po qid x 2 weeks
- Ceftriaxone 1 g IV or IM qd x 10-14 d

Syphilis of Late Latent or Unknown Duration

Benzathine penicillin G 2.4 million units IM weekly* x 3

*** Bicillin L-A is the trade name. DO NOT use bicillin C-R!**

Alternatives (non-pregnant penicillin-allergic adults):

- **Doxycycline 100 mg po bid x 4 weeks (28 days)**
- Tetracycline 500 mg po qid x 4 weeks

The Problem

Bicillin L-A Shortages

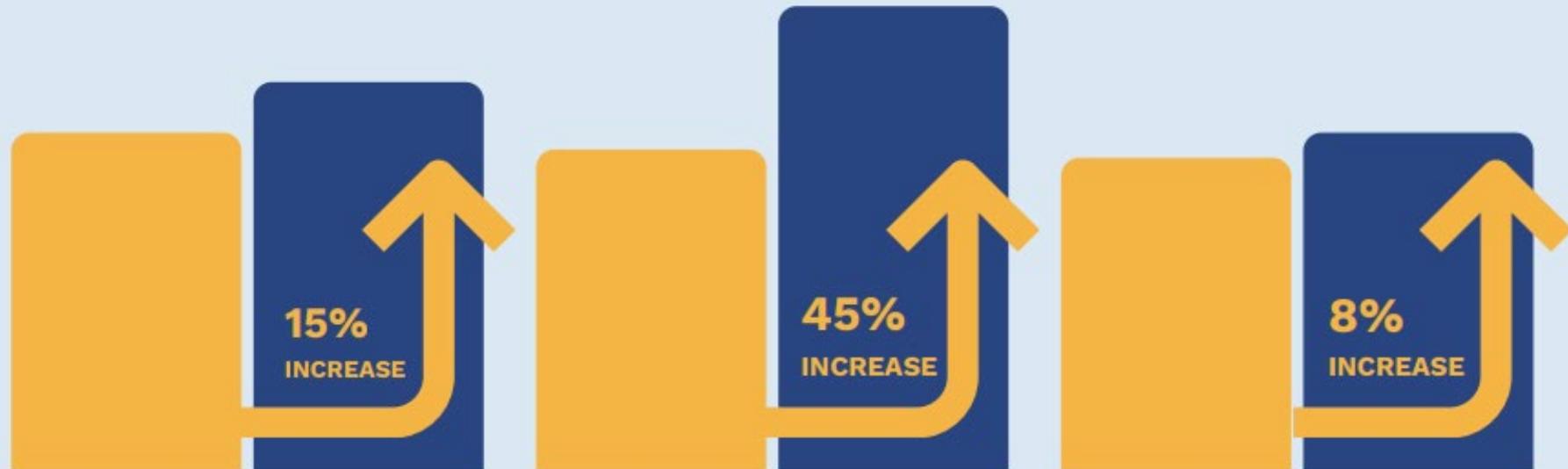
April 2023: FDA Announces Bicillin L-A Shortage

Presentation	Availability and Estimated Shortage Duration
Bicillin L-a, Injection, 2400000 [iU]/4 mL (NDC 60793-702-10)	Limited Supply. Next delivery: September 2023; Estimated recovery: Q2 2024

NCSD
Survey:
Increasing
Severity of
Bicillin L-A
Shortage

DIFFICULTY ORDERING BICILLIN L-A

■ August ■ November



46% of clinics have attempted to order Bicillin L-A, but the **drug was not available.**

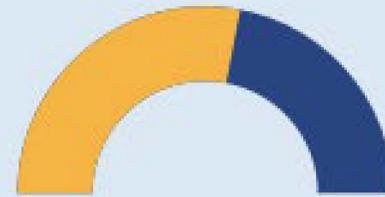
55% of clinics that had **orders completely unfilled** had more than half of their orders unfilled.

40% of clinics have had their **Bicillin L-A orders delayed** in the past three months.

IMPACT ON PREGNANT PEOPLE

In the past three months, health department respondents from 13 different states and one Indian Health Service agency say they've received **reports of a pregnant person in their jurisdiction who was unable to access Bicillin L-A.**

Most respondents were able to confirm that pregnant patients who could not immediately get Bicillin L-A were eventually able to receive treatment.



only 56% could say that treatment was provided **within one week**



31% said it took **between 8 and 28 days to receive treatment**

Potential Solutions

Bicillin L-A Prioritization Schema

Ex: California Dept of Public Health, June 2023

- 1. Prioritize Bicillin® L-A for pregnant people with syphilis infection (or exposure) as well as for infants exposed to syphilis in utero.**
- 2. Prioritize Bicillin® L-A for patients with contraindications to doxycycline (e.g., anaphylaxis, hemolytic anemia, Stevens Johnson syndrome).**
- 3. Conserve Bicillin® L-A by using alternative drugs** for the treatment of infectious diseases (e.g., streptococcal pharyngitis) where oral medications or other effective antimicrobials are available.



TOMÁS J. ARAGÓN, M.D., Dr.P.H.
State Public Health Officer & Director

State of California—Health and Human Services Agency
California Department of Public Health



GAVIN NEWSOM
Governor

Health Advisory

To: Healthcare Providers

Subject: Bicillin® L-A (Benzathine Penicillin G) Shortage

6/1/2023

<https://www.cdph.ca.gov/Programs/OPA/Pages/CAHAN/Health-Advisory-Bicillin-L-A-Benzathine-Penicillin-G-Shortage.aspx#:~:text=Given%20the%20current%20Bicillin%C2%AE%20L-A%20drug%20shortage%2C%20the,as%20for%20infants%20exposed%E2%80%8B%E2%80%8B%20to%20syphilis%20in%20utero.>

CDC Clinical Reminders During Bicillin Shortage

Take inventory:

- Monitor local supply of Bicillin L-A® and [determine the local pattern of use to forecast need](#).
- Contact distributors to procure Bicillin L-A® as appropriate. Contact Pfizer (see [“Dear Patient Letter”](#) posted on the FDA website) if there is less than a 2-week supply, the distributor has no supply, and there is a risk that patients may not be treated.

Appropriately stage syphilis cases to ensure appropriate use of antimicrobials. Early syphilis (primary, secondary and early latent) only requires 2.4 million units of Bicillin L-A®.

Prioritize using Bicillin L-A® to treat pregnant people with syphilis and babies with congenital syphilis.

- **Choose doxycycline for non-pregnant people to help preserve Bicillin L-A® supplies.**
- Consider involving antimicrobial stewardship leaders to help institute systems-level approaches to limit the use of Bicillin L-A® and encourage the use of alternative effective antimicrobials for treatment of other infectious diseases.

Q+A with Dr. Kathy Yang, PharmD

Doxycycline Basics, including Pk/Pd

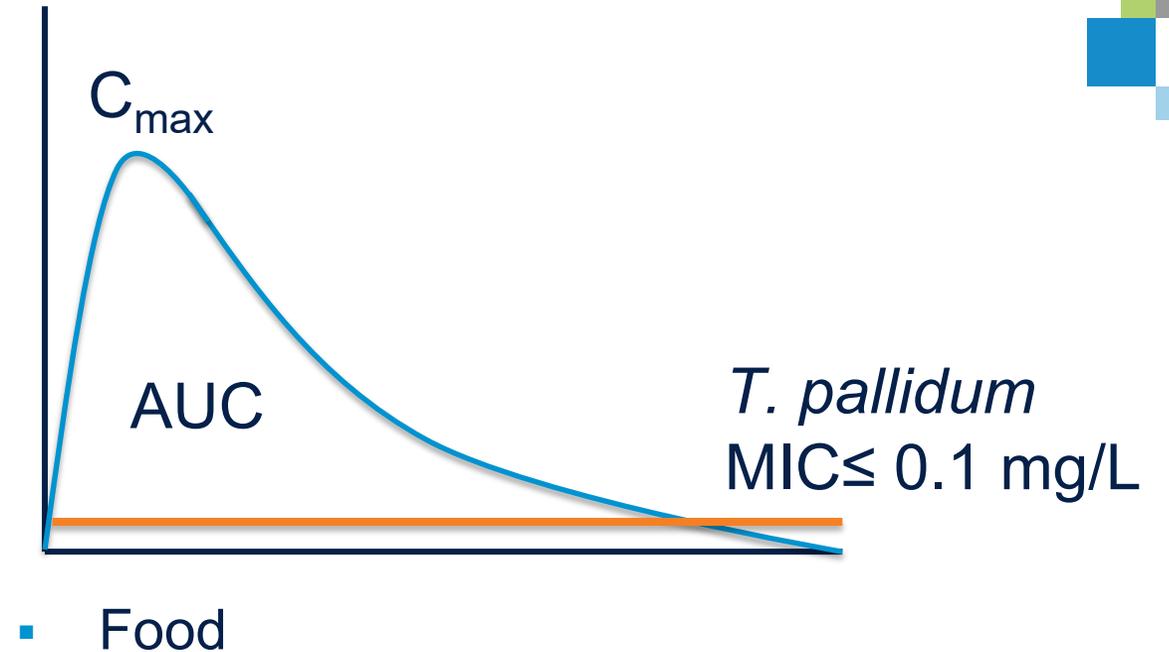


- Pharmacokinetics:
 - Oral absorption >90% from GI tract
 - Distribution:
 - Widely distributed including sputum, pleural, synovial, prostatic, seminal fluid saliva, and aqueous humor
 - Poor distribution into CSF
 - 40% of dose gets into breast milk
 - Elimination is mixed renal and fecal
 - With renal impairment, there is

Doxycycline Pharmacokinetics



PK (with a single 100 mg dose)	
C_{max}	1.5-2 (\pm 1) mg/L
Time to C_{max}	2-3 h (IR and DR)
Half-life	18-22 h
AUC	31 μ g*hr/ml



Any tips for supporting doxycycline adherence?

What are common doxycycline adverse reactions?

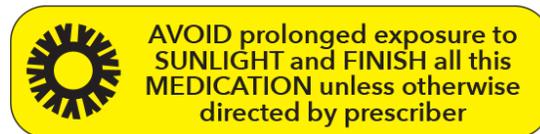
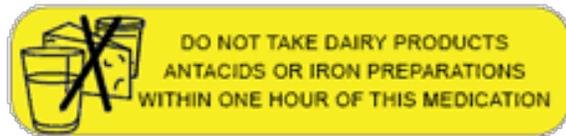
How can we minimize intolerances?

Patient Education



Adverse Effects

- GI upset/esophageal irritation
- Photosensitivity-wear sunscreen



Patient Counseling

- OK to take with food if GI upset
- Separate with antacids, iron products
- Wear sunscreen

What about breast/chest feeding?

Current labeling includes warning against use in pregnancy, lactation, children < 8 yo due to teeth discoloration, depression of skeletal growth

- “class effect” warning originated with tetracycline (1970)
- Doxycycline GI absorption inhibited by calcium in milk
- Exposure in milk is low:
 - Peak levels 5-7 h after dose
 - Levels typically <1 mg/L
- No reports of bone/teeth adverse events in breast/chest fed babies with doxycycline
- Monitor for diarrhea

How do you think about
missed doses?

Audience response question

- *“Our clinic is treating a non-pregnant 28 year old cis-gender female with doxycycline x 28 days for syphilis of late latent or unknown duration. She has missed two doses. Do I need to start the treatment course over?”*
 - Yes
 - No
 - I don't know
 - It depends

What if my patient forgets to take their doxycycline?

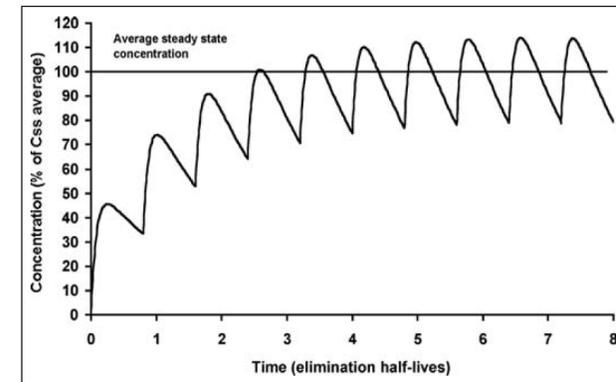
There is no hard and fast rule on what to do

If single dose:

- Take as soon as remember (don't skip it)
- Don't worry about food/cation interactions at this point
- Don't double up
- Take next dose on time
- Add missed dose at the end

If multiple doses or days:

- How many days of treatment have they had so far?



Considerations:

Takes about 3-4 half-lives to reach steady state

MIC for *T. pallidum* is low

Doubling time for *T. pallidum* is about 36 h

Don't know how much doxycycline we really need

What if we run out of
bicillin in the middle of a
treatment course?



Audience Response Question

- You are treating a 22 yo trans woman for syphilis of late latent/unknown duration. She received her 1st Bicillin L-A injection 7 days ago, but now your clinic has run out of Bicillin. What do you do?
 - A) Give her doxycycline x 7 days
 - B) Give her doxycycline x 14 days
 - C) Give her doxycycline x 28 days

• CDPH DCL – Sept 2023

• No data for mix & match approach

• Safest course = Restart doxy x 28 d

[https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/Dear Colleague Letter_Special Considerations for Treatment of Syphilis Alt Therapies_9 12 23.pdf](https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/Dear%20Colleague%20Letter_Special%20Considerations%20for%20Treatment%20of%20Syphilis%20Alt%20Therapies_9%2023.pdf)



TOMÁS J. ARAGÓN, MD, DrPH
Director and State Public Health Officer

State of California—Health and Human Services Agency
California Department of Public Health



GAVIN NEWSOM
Governor

September 12, 2023

**Special Considerations for the Treatment of Syphilis
using Alternative Therapies in Non-pregnant Persons**

Dear Colleague,

In early June, the California Department of Public Health (CDPH) released a [Health Advisory](#) informing providers of **long-acting penicillin G benzathine injectable suspension product (Bicillin® L-A) shortages**, along with acceptable alternatives (e.g., doxycycline), recommendations for Bicillin® L-A prioritization (e.g., pregnant people & infants), and conservation guidance (e.g., non-Bicillin® L-A based antimicrobials for non-syphilis infectious diseases). Regrettably, [updated estimates from the U.S. Food & Drug Administration](#) indicate inadequate Bicillin® L-A supplies at least until the 2nd quarter of 2024 due to increased demand and limited manufacturing capacity.

In the setting of Bicillin® L-A supply shortages, CDPH would like to provide further guidance regarding the use of alternative syphilis treatment regimens for non-pregnant persons in unique situational and clinical case scenarios:

Combining the Use of Bicillin® L-A and Doxycycline:

Late latent syphilis or syphilis of unknown duration

Providers may be compelled to switch non-pregnant patients to doxycycline after receiving their first or second weekly injection (Bicillin® L-A 2.4 mu IM). Currently, there are no data supporting effective combination therapy. **Therefore, when using doxycycline following only one or two injections of Bicillin® L-A in the treatment of late or unknown duration syphilis, the safest and most conservative approach would be:**

- **Prescribe full 28 days of doxycycline 100mg BID following one or two injections of Bicillin® L-A**

CDPH is aware some providers may use less than 28 days of doxycycline after one or two doses of Bicillin® L-A, however currently there are no available data to support the following:

- Prescribing three weeks of doxycycline 100mg BID one week after a single injection of Bicillin® L-A
- Prescribing two weeks of doxycycline 100mg BID one week after two weekly injections of Bicillin® L-A

***If the above regimens are used, CDPH recommends getting more frequent serologies (RPR/VDRL titer) in follow up (i.e., every 3 months).**



What about Extencilline?

Poll Question

(answer in the zoom poll)

- Prior to administering Bicillin-LA, do you ask about peanut or soy allergies?
- Answer: Yes or No?

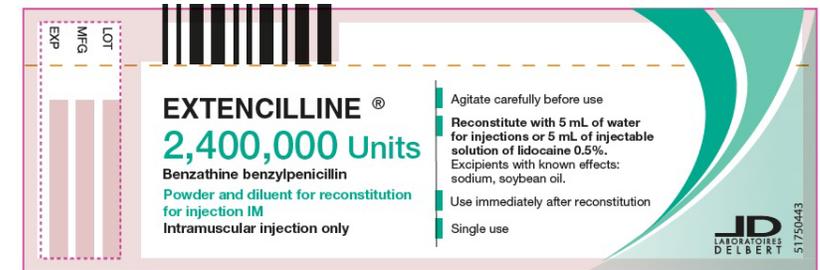


Dear Healthcare Provider Letter (Nov 21, 2023)

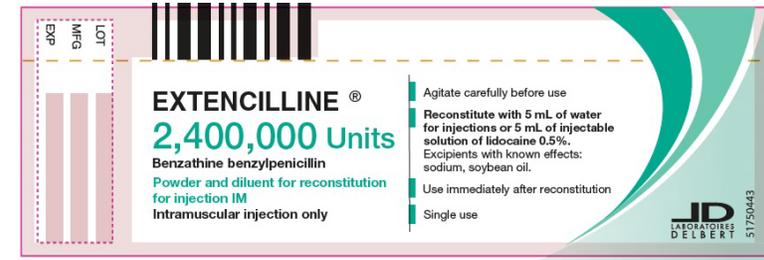
Subject:

Temporary Importation of Extencilline, (benzathine benzylpenicillin) Powder and diluent for reconstitution for injection, 1,200,000 units and 2,400,000 units with Foreign, non-U.S. Labeling to Address Supply Shortage

- Available to order as of Jan 22, 2023 from Direct Success
- WAC pricing:
 - 1.2 MU vial (NDC 81284-0521-01): \$250.00/vial
 - 2.4 MU vial (NDC 81284-0522-01): \$500.00/vial
- Minimum order: 5 vials
- No 340B pricing



Major differences



	Bicillin-LA	Extencilline
Formulation	pre-filled syringe	powder packaged with SWFI (can be made with 0.5-1% lidocaine)
Final volume	4 ml	7 ml (will need to be split)
Storage	Refrigerated	Room temp
Excipients	0.53% lecithin	lecithin
Contraindications (in label)	h/o hypersensitivity to penicillins	h/o hypersensitivity to penicillins and soy

CAUTION: there are LESS warnings with Extencilline, follow all warnings with Bicillin-LA

Poll Question

(answer in the zoom poll)

- Would you administer Extencilline in a patient with a soy allergy?
- Answer: Yes or No?



What about the soy warning?

Lecithin is a phospholipid derived from soybean oil



- FDA regulations for food and drug labeling are not the same
 - FALCPA and FASTER require food to be labeled with allergy information if they contain the following 9 allergens:
 - Milk, eggs, fish, Crustacean shellfish, tree nuts, peanuts, wheat, soybeans, sesame
 - No requirement for excipients (inactive ingredient)
- FDA and EMA (European Medicines Agency) rules for labeling are not the same

FALCPA; Food Allergen Labeling and Consumer Protection Act of 2004

FASTER; Food Allergy Safety, Treatment, Education, and Research ACT (2021)

<https://www.fda.gov/food/buy-store-serve-safe-food/food-allergies-what-you-need-know> (Accessed Jan 27, 2024)

<https://www.ema.europa.eu/en/product-information-requirements/excipients-labelling> (Accessed Jan 27, 2024)

What is the risk of hypersensitivity?



- Soy allergy: 0.4% of population; true anaphylaxis very rare
- No “safe” level has been established in people with soy allergy
- Reaction is due to the soy proteins
- Case reports of excipient-associated hypersensitivity reactions to soy have been reported in the literature
 - omeprazole, propofol, inhalers
 - 1 case of papular rash at site of injection of benzathine PCN in an 11 yo allergic to soy in Italy

What about peanut allergy?

- Some soy allergens share high sequence homology to peanut allergens
- Cross-sensitization to soy is common
 - 30-50% of peanut-allergic patient had positive skin prick test to soy
- Clinical cross-reactivity is rare (<5%)

Practice parameter

Food allergy: A practice parameter update—2014

Patients with peanut allergy. Because patients with peanut allergy generally tolerate other legumes, including soy, a recommendation to empirically avoid all legumes is generally unnecessary.^{50,51} Possible legume allergy should be evaluated on a case-by-case basis in patients with peanut allergy.

[Immunol Allergy Clin North Am. 2012 Feb; 32\(1\): 11–33.](#)

[Journal of Allergy and Clinical Immunology. 2014 Nov; 135\(5\):1016-25.](#)

[Journal of Allergy and Clinical Immunology: In Practice. 2019 Feb; 7\(2\):381-6](#)

How many FDA approved products contain lecithin?



The screenshot shows the DailyMed website's advanced search interface. At the top, there is a navigation bar with the NIH logo and 'NATIONAL LIBRARY OF MEDICINE' text, along with links for 'REPORT ADVERSE EVENTS' and 'RECALLS'. Below this is the 'DAILYMED' logo and a navigation menu with links for 'HOME', '+ NEWS', 'FDA RESOURCES', '+ NLM SPL RESOURCES', '+ APPLICATION DEVELOPMENT SUPPORT', and 'HELP'. The main content area is titled 'ADVANCED SEARCH' and features a search bar with the text 'LECITHIN' and a dropdown menu set to 'Inactive Ingredient'. There are 'REFINE SEARCH' and 'CRITERIA' options, and an 'ADD' button. Below the search bar, there are 'RESET' and 'SEARCH' buttons, and a 'Need help?' link. The footer contains the NIH NLM logo and various links including 'About DailyMed', 'Customer Support', 'Copyright', 'Privacy', 'Web Accessibility', and 'HHS Vulnerability Disclosure'.

- Search returned 3124 products
- Includes
 - Cosmetics
 - Topicals
 - IV and PO
 - OTC meds
 - Rx meds

Considerations for managing the soy warning

Take a good medication history

- ❑ Do you have a soy allergy?
- ❑ Describe the reaction? Atopic dermatitis/GI vs difficulty breathing/anaphylaxis
- ❑ Have you ever taken any medications that contain soy that you know of?
- ❑ Check medications on DailyMed



DailyMed search results

Acetaminophen AND lecithin

The screenshot shows the DailyMed homepage with the search bar and navigation menu. The search bar contains the text "Acetaminophen AND lecithin". The search criteria are listed as "ACETAMINOPHEN" in ACTIVE INGREDIENT and "lecithin" in INACTIVE INGREDIENT. The search results are not yet displayed.

The screenshot shows the search results page for the query "INGREDIENT:(ACETAMINOPHEN) AND INACTIVE_INGREDIENT:(LECITHIN)". The results are sorted by relevance and show 117 results. The first five results are listed below:

Product Name	Formulation	NDC Code(s)	Package
MULTI-SYMPTOM NITETIME (ACETAMINOPHEN, DEXTROMETHORPHAN HYDROBROMIDE, AND DOXYLAMINE SUCCINATE) CAPSULE, LIQUID FILLED	LIQUID FILLED	68210-5005-1, 68210-5005-2, 68210-5005-4	SPIRIT PHARMACEUTICALS LLC
MUCINEX COLD AND FLU (ACETAMINOPHEN, GUAIFENESIN) CAPSULE, LIQUID FILLED	LIQUID FILLED	72854-136-16	RB HEALTH (US) LLC
NIGHTTIME COLD AND FLU RELIEF (ACETAMINOPHEN, DEXTROMETHORPHAN HYDROBROMIDE, DOXYLAMINE SUCCINATE) CAPSULE, LIQUID FILLED	LIQUID FILLED	55319-968-08, 55319-968-16, 55319-968-24	FAMILY DOLLAR (FAMILY WELLNESS)
THERAFLU SEVERE COLD RELIEF DAYTIME WITH HONEY GINGER FLAVOR (ACETAMINOPHEN, DEXTROMETHORPHAN HBR, PHENYLEPHRINE HCL) POWDER, FOR SOLUTION	POWDER, FOR SOLUTION	0067-8211-01	GLAXOSMITHKLINE CONSUMER HEALTHCARE HOLDINGS (US) LLC
MUCINEX FAST-MAX SEVERE COLD (ACETAMINOPHEN, DEXTROMETHORPHAN HYDROBROMIDE, GUAIFENESIN, PHENYLEPHRINE HYDROCHLORIDE) CAPSULE, LIQUID FILL	LIQUID FILL	51013-409-14	PURACAP PHARMACEUTICAL LLC

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- Dr. K. Jacobson – California Department of Public Health (CDPH)
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- Dr. S. Adler – CAPTC

NCSD's Forecaster Tool



Q Search | Contact

STI INFORMATION & RESOURCES

LEARNING CENTER

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RESOURCES

EVENTS

NEWS & ANNOUNCEMENTS



Home > Resources > Bicillin Forecasting and Inventory

STD RESOURCE

BICILLIN FORECASTING AND INVENTORY

Recently, our field has faced occasional shortages in the supply and availability of Bicillin® L-A for the treatment of syphilis. NCSD is here to help.



Questions?

Thank you!!

kjohnson@ucsf.edu; katherine.yang2@ucsf.edu