

Earthquakes in Management of Chlamydia Infection

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Objectives

- **Discuss [rectal] chlamydia**
 - MSM
 - Women
 - Transmission pathway theories
- **Consider azithromycin vs. doxycycline for chlamydia treatment**
- **Discuss partner management**
 - EPT implementation best practices



Case

- A 25-year-old woman presents for routine STI screening.
- She has no symptoms, is not pregnant, and has no known chronic medical problems.
- Laboratory test results show:
 - HIV antibody/antigen: **Negative**
 - Treponemal antibody: **Negative**
 - Vaginal gonorrhea/chlamydia NAAT: **Positive** for *Chlamydia trachomatis*, **negative** for *Neisseria gonorrhoeae*



What is the best treatment for her infection?

- A. Azithromycin 1 gram by mouth once
- B. Doxycycline 100 mg by mouth twice daily for 7 days
- C. Ceftriaxone 500 mg by intramuscular injection once
- D. Ciprofloxacin 250 mg by mouth twice daily for 3 days

**EVIDENCE THAT DOXYCYCLINE X 1 WEEK IS
SUPERIOR TO AZITHROMYCIN X 1 DOSE FOR
[RECTAL] CHLAMYDIA**



First-Pass Answer: RCT: Chlamydia Treatment Azithromycin vs. Doxycycline for **Urogenital** Chlamydia infection

Antibiotic group	Treatment failures	Efficacy
Doxycycline	0	100%
Azithromycin	5 (3.2%; 95%CI 0.4-7.4%)	97%

- Captive audience: juvenile detention facilities
- Difference in failure rates was 3.2%
- The non-inferiority of azithromycin was not established
- Both medications are effective
- **Azithro had some treatment failures, but adherence is likely to be much greater with single-dose azithromycin**

BUT WHAT ABOUT RECTAL CHLAMYDIA?

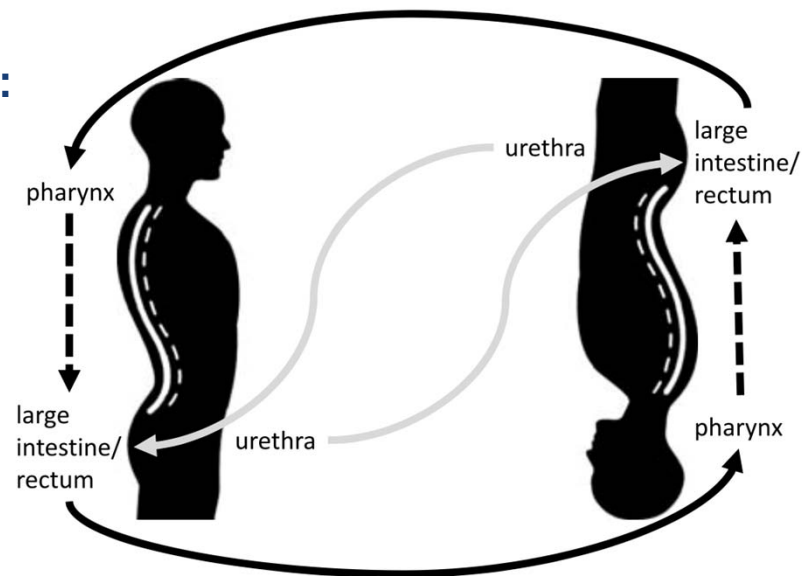


Chlamydia Transmission

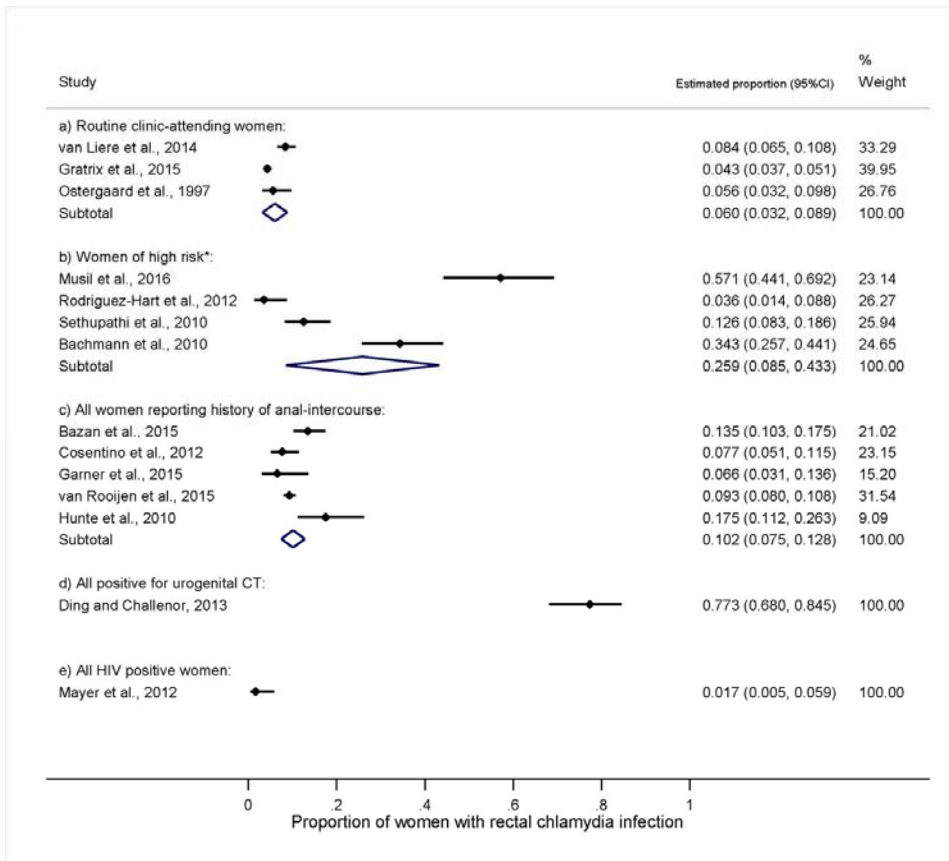
- Infectiousness / reservoir not been accurately defined
- Transmission has been attributed largely to asymptomatic carriers

Proposed transmission patterns:

- Genitoanal (grey)
- Ano-oral (black)
- Gastrointestinal transit to large intestine and rectum



Individual study and study subgroup summary estimates of rectal chlamydia positivity in women stratified by clinical subgroup/population type (n=14).



Chandra et al. *Sex Transm Infect* 2018;94:320-326

Rectal CT summary prevalence in women:

- Attending routine clinics: 6% (95% CI 3 – 9%)
- Among those positive for vaginal chlamydia: 68% (95% CI 57 – 80%)
- Using reported anal intercourse as an indicator for rectal testing leads to missed diagnoses

STI

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Azithro vs doxy for rectal chlamydia

		N (%) positive at follow-up	
		Azithro	Doxy
White 2009	UK	8/18 (44%)	0/119 (0%)
Steedman 2009	UK	7/68 (10%)	----
Elgalib 2010	UK	5/26 (19%)	1/186 (1%)
Drummond 2011	Australia	5/85 (6%)	----
Hathorn 2012	UK	9/42 (21%)	0/40 (0%)
Ding 2013	UK	2/11 (18%)	----
Khosropour 2013	US	8/49 (16%)	2/21 (10%)
Khosropour 2014	US	50/230 (22%)	2/56 (4%)

Slide courtesy of Brad Stoner



Next Answer: Rectal Chlamydia: Microbiologic Cure is Better with Doxycycline

- **Dombrowski et al., CID 2021**

- Randomized, double-blind, placebo-controlled trial in MSM in Seattle and Boston
- Microbiologic cure in rectal infxns across analysis groups
 - azithromycin 71 – 77%
 - doxycycline 91 – 100%
- Trial stopped early due to interim analysis

- **Lau et al., NEJM 2021**

- Randomized, double-blind, placebo-controlled trial in Australian men with asymptomatic rectal chlamydia
- Microbiologic cure in rectal infxns
 - azithromycin 76.4%
 - doxycycline 96.9%

- **Dukers-Muijers et al., CID 2019**

- Prospective multicenter cohort study (FemCure) in **women**
- Microbiologic cure in rectal infxns
 - azithromycin 78.5%
 - doxycycline 95.5%

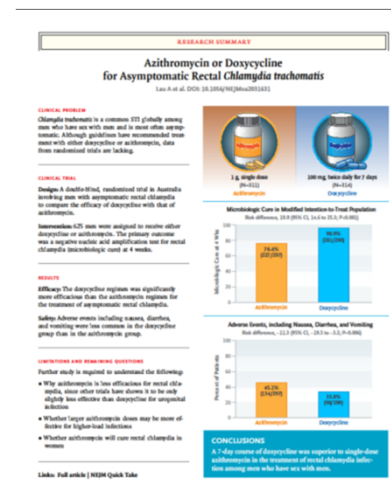
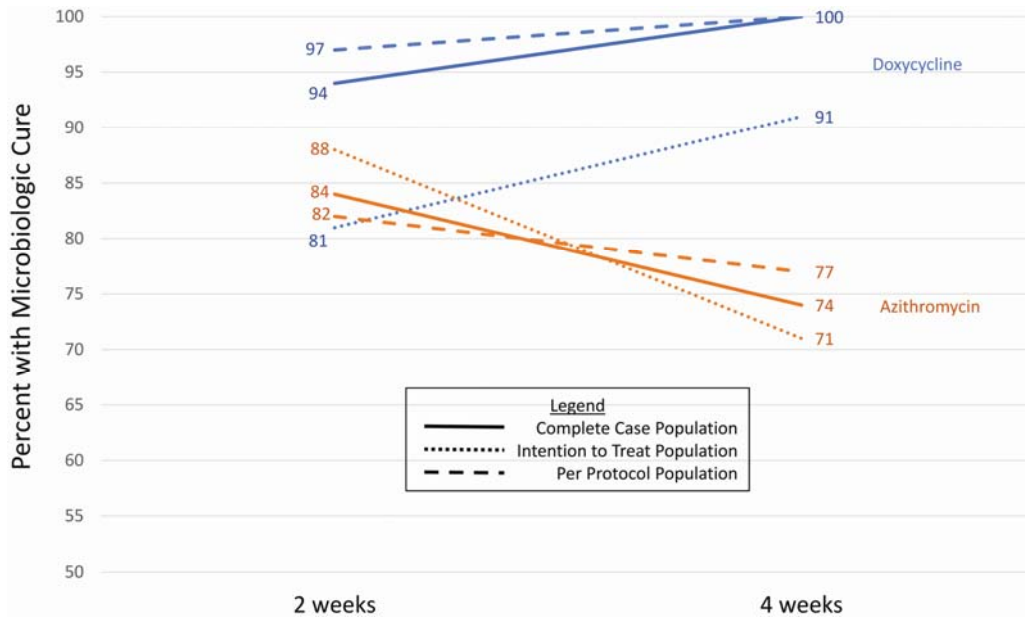


Figure 2. Comparison of 2-week and 4-week cure percentage by treatment group and analysis population.



“Azithromycin performed so poorly that even in the context of expected imperfect adherence in real-world use, doxycycline should be the recommended treatment for rectal CT in MSM.”

Dombrowski et al., *Clin Infect Dis*, 2021

<https://doi.org/10.1093/cid/ciab153>

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Dombrowski et al., *CID* 2021

RESEARCH SUMMARY

Azithromycin or Doxycycline for Asymptomatic Rectal *Chlamydia trachomatis*

Lau A et al. DOI: 10.1056/NEJMoa2031631

CLINICAL PROBLEM

Chlamydia trachomatis is a common STI globally among men who have sex with men and is most often asymptomatic. Although guidelines have recommended treatment with either doxycycline or azithromycin, data from randomized trials are lacking.

CLINICAL TRIAL

Design: A double-blind, randomized trial in Australia involving men with asymptomatic rectal chlamydia to compare the efficacy of doxycycline with that of azithromycin.

Intervention: 625 men were assigned to receive either doxycycline or azithromycin. The primary outcome was a negative nucleic acid amplification test for rectal chlamydia (microbiologic cure) at 4 weeks.

RESULTS

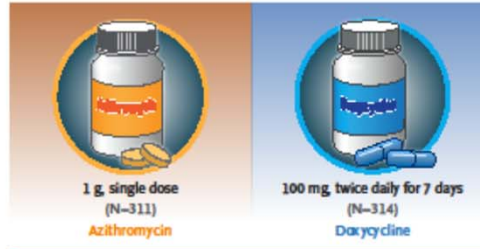
Efficacy: The doxycycline regimen was significantly more efficacious than the azithromycin regimen for the treatment of asymptomatic rectal chlamydia.

Safety: Adverse events including nausea, diarrhea, and vomiting were less common in the doxycycline group than in the azithromycin group.

LIMITATIONS AND REMAINING QUESTIONS

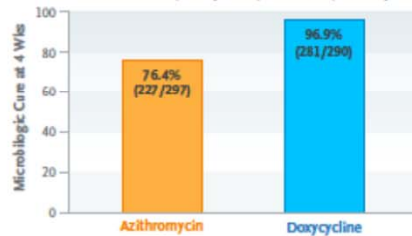
Further study is required to understand the following:

- Why azithromycin is less efficacious for rectal chlamydia, since other trials have shown it to be only slightly less effective than doxycycline for urogenital infection
- Whether larger azithromycin doses may be more effective for higher-load infections
- Whether azithromycin will cure rectal chlamydia in women



Microbiologic Cure in Modified Intention-to-Treat Population

Risk difference, 19.9 [95% CI, 14.6 to 25.3; P<0.001]



Adverse Events, including Nausea, Diarrhea, and Vomiting

Risk difference, -11.3 [95% CI, -19.5 to -3.2; P=0.006]



CONCLUSIONS

A 7-day course of doxycycline was superior to single-dose azithromycin in the treatment of rectal chlamydia infection among men who have sex with men.

“Adverse events including nausea, diarrhea, and vomiting were less common in the doxycycline group than in the azithromycin group.”

Lau et al., *NEJM* 2021

Links: Full article | NEJM Quick Take



What about chlamydia in pregnancy?

First-line therapy is still single-dose azithromycin.

Original Research

High rates of persistent and recurrent chlamydia in pregnant women after treatment with azithromycin



Jodie Dionne-Odom, MD, MSPH; Akila Subramaniam, MD, MPH; Kristal J. Aaron, DrPH, MPH; William M. Geisler, MD, MPH; Alan T. N. Tita, MD, PhD; Jeanne Marrazzo, MD, MPH

BACKGROUND: *Chlamydia trachomatis* is a common bacterial sexually transmitted infection that can persist or recur after antibiotic treatment. Universal screening for chlamydia in pregnancy is recommended to prevent adverse birth outcomes. Single-dose oral azithromycin has been the first-line therapy for chlamydia in pregnancy since 2006.

OBJECTIVE: In the setting of limited data and rising sexually transmitted infection rates in the United States, our goal was to document rates and risk factors for persistent or recurrent chlamydia after azithromycin treatment in pregnancy.

STUDY DESIGN: This retrospective cohort study included pregnancies with urogenital chlamydia and follow-up testing in women who delivered at an Alabama facility between November 2012 and December 2017. Pregnancies with prescribed azithromycin therapy and repeat chlamydia testing ≥ 21 days later were included. *Chlamydia trachomatis* nucleic acid amplification testing was performed on genital swab or urine samples. Descriptive characteristics and birth outcomes were compared for categories stratified by repeat test results: persistence (+ +), recurrence

(+ - +), or clearance (+ -). Logistic regression models were used to identify demographic and clinical risk factors for persistent or recurrent chlamydia in pregnancy.

RESULTS: Among 810 women with 840 pregnancies with repeat chlamydia testing after azithromycin treatment, 114 (14%) had persistence and an additional 72 (9%) had recurrence later in pregnancy. The median time to repeat testing was 30 days (interquartile range, 24–49 days). Concomitant gonorrhea or syphilis in pregnancy was independently associated with persistent or recurrent chlamydia (adjusted odds ratio, 1.6; 95% confidence interval, 1.1–2.4).

CONCLUSION: Persistent or recurrent chlamydia after azithromycin treatment was detected in nearly 1 in 4 pregnancies with repeat testing in our urban center, highlighting the importance of performing a test of cure and ensuring partner therapy to reduce recurrent chlamydia risk.

Key words: azithromycin, *Chlamydia trachomatis*, infection in pregnancy, recurrent chlamydia

Introduction

Chlamydia trachomatis is an intracellular bacterium that causes cervical infection. More than 1.1 million cases of chlamydia in women were reported to the US Centers for Disease Control and Prevention (CDC) in 2018.¹ Women between the ages of 15 and 24 years and women who reside in the southeastern United States, where the case rate is 744 cases per 100,000 persons, are disproportionately affected by chlamydia.^{1–4} Untreated chlamydia in pregnancy has been associated with preterm delivery and low birthweight (LBW) infants.^{5–9} Infection in women is usually asymptomatic, and timely screening and treatment in pregnancy can prevent adverse outcomes.¹⁰ Despite rising

chlamydia rates in the US, few studies focus on chlamydia treatment outcomes after azithromycin therapy in pregnant women.^{1,11}

The American College of Obstetricians and Gynecologists (ACOG) has recommended universal screening for chlamydia in pregnancy since 2007.¹² CDC recommends performing a test of cure for pregnant women with chlamydia at least 21 days after treatment and repeat testing 12 weeks later to screen for reinfection.^{13,14} In an observational study from a commercial laboratory database in the United States (2005–2008), 59% of pregnant women had chlamydia testing and 3.5% had a positive result. Among women with chlamydia who underwent repeated testing, 6% had repeat positivity during pregnancy but treatment data were not available.¹² Recurrent chlamydia in nonpregnant women is well documented: a systematic review suggested a 14% recurrence rate during follow-up periods ranging from 2 months to 13 years.¹⁵ Younger age (<26 years) and bacterial sexually transmitted infection (STI) coinfection have been associated

with recurrent chlamydia in nonpregnant women.^{16–19}

Chlamydia infection that recurs after antibiotic treatment and clearance (defined by a negative test) usually represents reinfection from a sexual partner. The mechanism for repeatedly positive chlamydia testing is more varied. It may represent recurrent infection (after undocumented clearance), false-positive polymerase chain reaction test result owing to residual DNA/RNA, or treatment failure.¹⁶ Unlike gonococcal infection, antimicrobial resistant chlamydial infection is rare.^{20–22} Single-dose oral azithromycin (1 g) is the CDC-recommended treatment for chlamydia in pregnancy.²³ Azithromycin has a favorable safety profile in pregnancy, and it is one of the most commonly prescribed antibiotic agents worldwide.²⁴ Recent reports suggest that clinical treatment failure can occur with azithromycin treatment for rectal chlamydia and nonresponse to azithromycin for urogenital chlamydia in pregnancy has been reported.^{21,25–27}

Cite this article as: Dionne-Odom J, Subramaniam A, Aaron KJ, et al. High rates of persistent and recurrent chlamydia in pregnant women after treatment with azithromycin. *Am J Obstet Gynecol* MFM 2020;2:100216.

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<https://doi.org/10.1016/j.ajogmf.2020.100216>

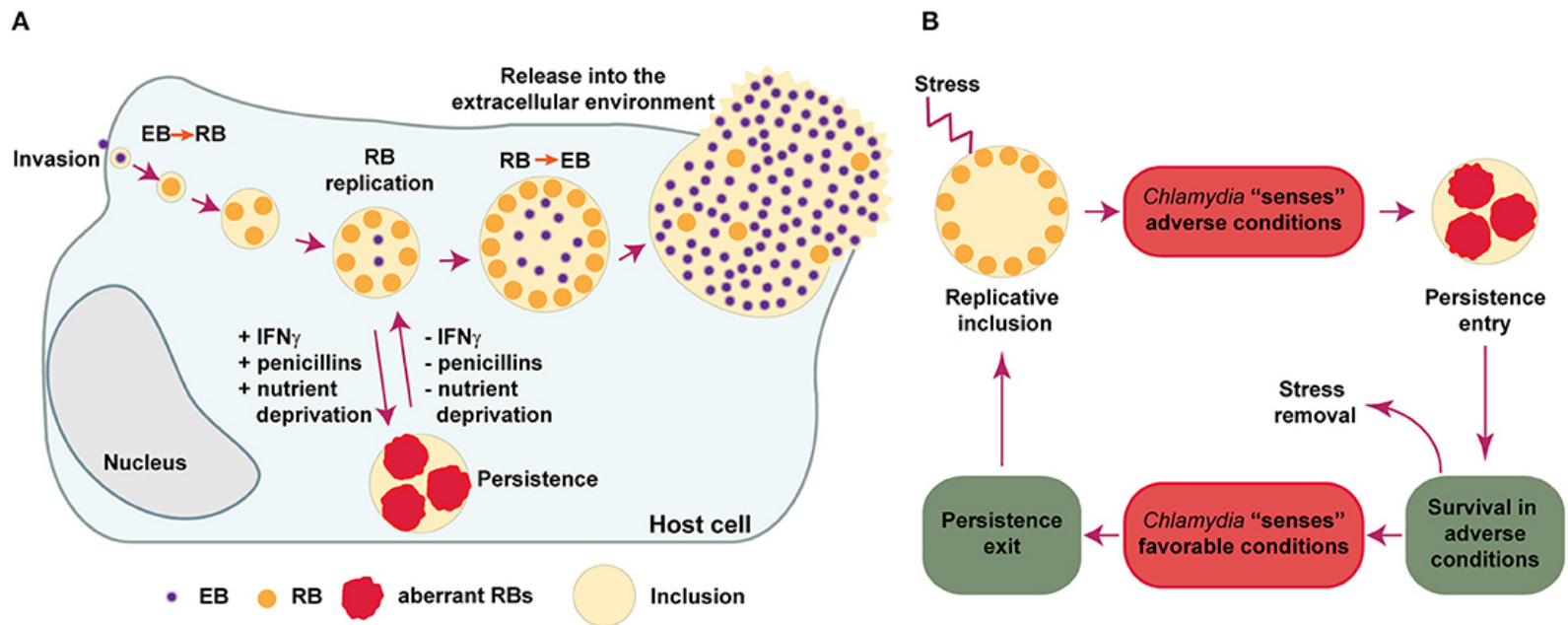
“In this retrospective cohort study of 810 pregnant women with urogenital chlamydia treated with first-line azithromycin, nearly 1 in 4 pregnancies with repeat chlamydia testing had persistence or recurrence. STI coinfection with gonorrhea or syphilis during pregnancy was the only significant risk factor for persistent or recurrent chlamydia in a model that adjusted for age, race, and insurance status.”

Dionne-Odom et al., *AJOG MFM* 2021

Unanswered Questions

- **What about alternative regimens – azithromycin daily or weekly?**
- **Mechanism of azithromycin failure unknown**
 - **Not likely:**
 - Mechanism of action (doxycycline and azithromycin both target bacterial protein synthesis and are considered bacteriostatic)
 - Antibiotic resistance (never (!) conclusively demonstrated *in vivo*)
 - Inadequate tissue penetration of drug in rectal environment (Fong et al. *PLoS One* 2017: azithromycin concentration above MIC for chlamydia for at least 14 days)
 - Prevalence of LGV biovars (uncommon in Dombrowski et al. study)
 - **Temporary suppression with single-dose azithromycin? (chlamydia persistence)**
 - **Different host-microbe interactions in rectal environment vs. genital tract?**

Chlamydia trachomatis is atypical ...



BACK TO THE CASE ...





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Training Centers

NEW Testing

Chlamydia Repeat Testing

- Abstain from sex until partners have completed treatment or 7 days after single dose therapy
- Routine repeat testing at 3 months for re-infection
 - High prevalence of chlamydia infection seen following prior infection + treatment
- Test of cure at 4 weeks if pregnant
- Consider repeat testing at 4 weeks for rectal CT treated with azithromycin due to lower efficacy

From your individual device, please go to www.menti.com and enter code 58300009

HOW DO YOU TREAT SEX PARTNERS OF PATIENTS WITH CHLAMYDIA INFECTION?



How do you treat sex partners of patients with chlamydia infection?

give doxy

doxy

azithromycin

doxycycline

doxy 100 mg



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Training Centers

Case, continued

- She's had sex with one man in the past 60 days.
- You'd like to provide expedited partner therapy for chlamydia, and she agrees to deliver it.



Slide courtesy of K Ard

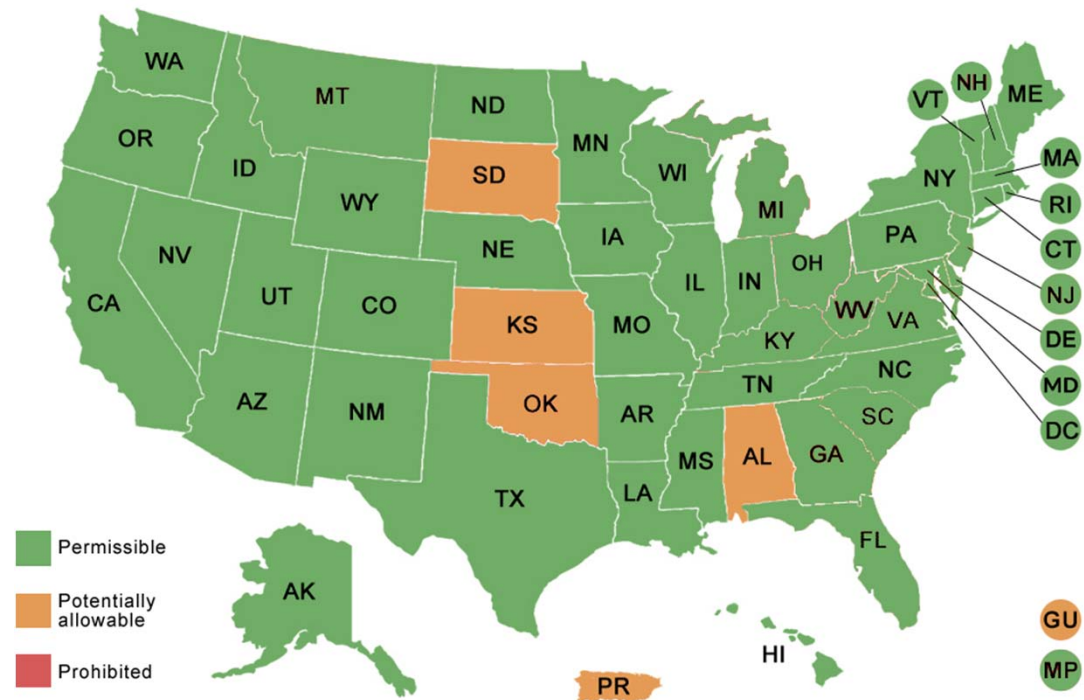


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Management of Sex Partners

NEW States

Expedited
Partner
Therapy
(EPT)



<https://www.cdc.gov/std/ept/legal/default.htm>



What's the best drug for EPT for chlamydia?

- A. Azithromycin 1 gram by mouth once
- B. Doxycycline 100 mg by mouth twice daily for 7 days
- C. It depends ...



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NEW Populations

Management of Sex Partners

1. Evaluate all sex partners
2. Empirically treat all partners <60 days
 - Most recent partner if last contact >60 days
3. Expedited Partner Therapy
 - Heterosexuals
 - **Men Who Have Sex With Men – Shared Decision Making**



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Expedited Partner Therapy

NEW Treatment

Gonorrhea

Cefixime 800 mg PO x 1

Chlamydia

For chlamydia or if **chlamydia has not** been excluded, treat for chlamydia with:

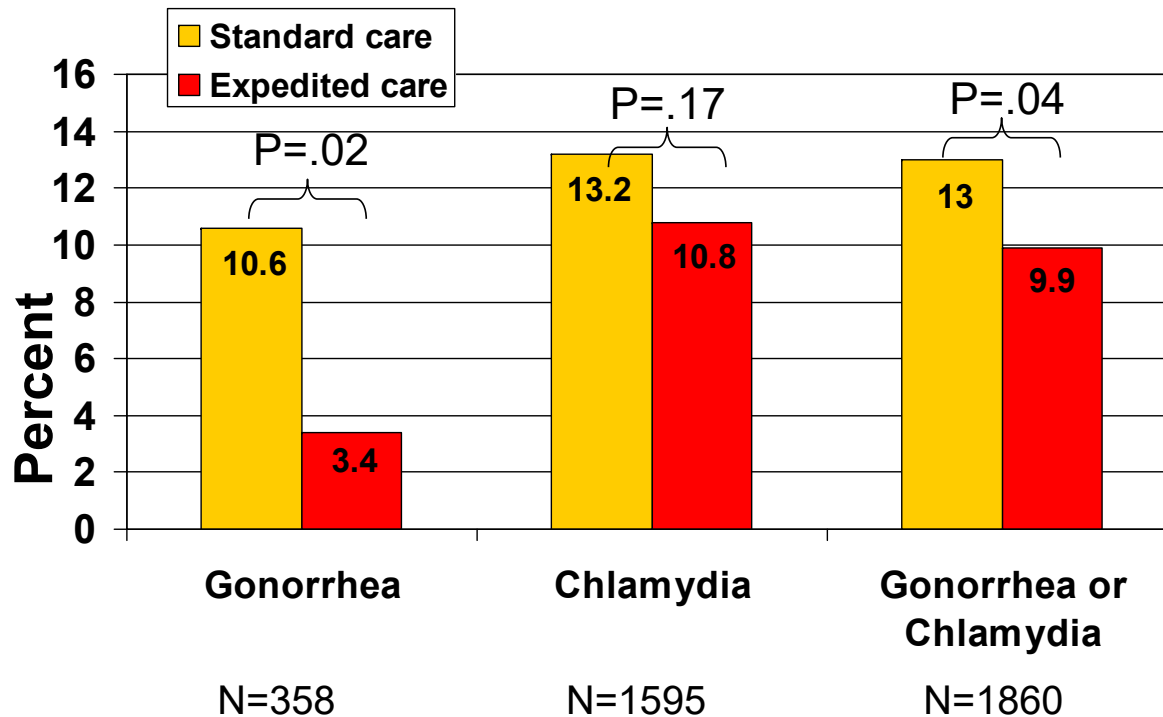
Doxycycline 100 mg PO
BID x 7 days

OR

Azithromycin 1g
orally once*

*For pregnancy

Infection During Follow-up Among Patients Completing The EPT Trial



From your individual device, please go to www.menti.com and enter code 58300009

IF YOU USE EPT, HOW DO YOU DO IT?



If you use EPT, how do you do it?

write rx

prescription

write a rx

Partner/Patient Information

A Message for Partners about Chlamydia Expedited Partner Therapy (EPT)

January 2022

- Information sheet provided by the Massachusetts DPH (or comparable to that provided by the DPH) will be given out whenever possible with each dose of EPT and be available online
- Question/Answer format – easy-to-read, will be translated into many languages
- Encouragement to follow-up with clinical provider

<https://www.mass.gov/lists/expedited-partner-therapy-ept>

Do Prescriptions for Expedited Partner Therapy for Chlamydia Get Filled? Findings From a Multi-Jurisdictional Evaluation, United States, 2017–2019

Jennifer Sanderson Slutsker, MPH,*
Lai-yi Bella Tsang, RPh, MS, MBA,† and Julia A. Schillinger, MD, MSc*‡

Background: Expedited partner therapy (EPT) is commonly provided by prescription, however, the efficacy of this modality is unknown. We examined whether EPT prescriptions are filled when the cost barrier is removed.

Methods: To track EPT prescription fill rates, we used single-use pharmacy vouchers that covered the cost of azithromycin, 1 g (chlamydia treatment). We recruited clinical sites to distribute vouchers to patients with chlamydia who would receive an EPT prescription under clinic policies. When distributing vouchers, sites recorded and retained voucher unique identifier, sex and age of index patient, distribution date, and whether partner name was written on the EPT prescription. Pharmacists receiving vouchers entered the identifier, sex and age of presenting person, and redemption date into a standard pharmacy claim transmission system. Data for redeemed vouchers were retrieved from an industry portal and linked with data retained at clinical sites.

Results: Thirty-two clinical sites distributed 931 vouchers during September 2017 to January 2019; 382 (41%) were redeemed. Vouchers distributed to patients 18 years or younger (49 [30%] of 163) were less likely to be redeemed compared with those distributed to patients older than 18 years (322 [44%] of 736; $P = 0.001$). Just over half of vouchers were redeemed the same day (194 [56%] of 352) and 1 mile or less from the clinical site (188 [54%] of 349). After excluding an outlier site, vouchers accompanied by EPT prescriptions including a partner name (15 [56%] of 27) were

more likely to be redeemed than those lacking a name (83 [34%] of 244; $P = 0.03$).

Conclusions: Less than half of EPT prescriptions were filled, even when medication was free. Whenever possible, EPT should be provided as drug-in-hand.

More than 1.7 million cases of *Chlamydia trachomatis* (chlamydia) were reported in the United States (US) in 2018, the largest number of reports for any notifiable condition.¹ Repeated chlamydia infection is common,² and sometimes results from re-summing sex with an untreated partner.³ Repeat infection increases risk for adverse outcomes, such as ectopic pregnancy and infertility.⁴ Expedited partner therapy (EPT), a strategy for treating the sex partners of an index patient with a sexually transmitted infection (STI), involves a clinician providing or prescribing additional treatment for sex partners without an intervening medical evaluation.⁵ The practice of EPT is legal in most states.⁶

Three randomized controlled trials established the evidence base for EPT preventing repeat chlamydia in the index patient.^{7–9} Two trials used medication-EPT (index patients provided with drug-in-hand to deliver to sex partners),¹⁰ and in the third trial, medication was distributed through a chain of pharmacies, an STI clinic, or direct mailing.⁸ However, the efficacy of prescription-EPT (whereby index patients are given prescription(s) to deliver to sex partners) has never been studied.

Information on EPT practices at the population-level are limited; however, evaluations in 2 states suggest that approximately half of EPT is provided in the form of prescription.^{10,11} There are several reasons prescription-EPT might not be as effective as medication-EPT. First, prescription-EPT requires more steps than medication-EPT,¹² including the need to travel to a pharmacy and render payment for the medication. Paying for medication is a documented barrier to filling EPT prescriptions,¹⁰ and the out-of-pocket cost of EPT treatment for chlamydia (generic azithromycin, 1 gram) has been reported to be as high as US \$120.^{13,14}

Second, neighborhoods with high STI rates may also have a paucity of pharmacies, making it especially difficult for people to fill prescriptions.¹³ Third, many pharmacists lack knowledge about the specifics of EPT laws¹⁵ and may refuse to fill EPT prescriptions.¹⁶ In 1 study, pharmacists refused to fill 58% of EPT prescriptions with no patient name in a state where “nameless” EPT prescriptions are legal.¹⁶

The objective of this evaluation was to measure the proportion of EPT prescriptions that get filled, because obtaining medication from a pharmacy might be a rate-limiting step in prescription-EPT. To examine prescription fill rates in a best-case scenario, we utilized a pharmacy voucher to eliminate any barriers posed by the cost of medication and simultaneously monitored the fulfillment of EPT prescriptions.

From the *Bureau of Sexually Transmitted Infections, †Division of Disease Control, New York City Department of Health and Mental Hygiene, Long Island City, NY; and ‡Division of STD Prevention, National Center for HIV, Hepatitis, STD, and TB Prevention, U.S. Centers for Disease Control and Prevention, Atlanta, GA.

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Conflict of interest: none declared.

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Figure 1. Pharmacy voucher for free EPT treatment,* with detachable “tear-off tab” to record information on the index patient.† The bottom section shows the pharmacy voucher that fully covered costs for azithromycin, 1 g, tablet form when presented at the pharmacy.* The top section shows the detachable “tear-off tab” that health care providers completed when distributing the card to an index patient with chlamydia. Providers removed this tear-off tab before distribution and placed it in a ballot box for subsequent collection by the investigators.†

“Less than half of EPT prescriptions were filled, even when medication was free. Whenever possible, EPT should be provided as drug-in-hand.”

SUMMARY

- Rectal chlamydia infection common in MSM and women
- Doxycycline x 1 week recommended over azithromycin x 1 dose for chlamydia (except in pregnant women), particularly for rectal chlamydia (or suspicion of rectal infection) in 2021 CDC STI Guidelines
 - Dombrowski et al. *CID* 2021 worth reading
 - Azithromycin x 1 dose is probably still fine for purely urogenital chlamydia infection – but this is a limited subset of patients!
- Repeat infection following initial chlamydia infection is common
 - Recall for test of re-infection for those with prior STI
 - Treating partners crucial
 - EPT should be done with meds-in-hand or with a partnering pharmacy