Improving Antimicrobial Stewardship in Sexually Transmitted Infections

Glenn Harnett MD

December 8th, 2021

Learning Objectives

1. Review STI rates and 2021 CDC STI Guidelines
2. Examine key challenges with STI testing today
3. Evaluate the implications of today's STI testing to Antibiotic Stewardship
4. Explore what is needed to combat the growing number of antibiotic resistant STIs

Dr. Harnett Biography

- BA Psychology: University of New Hampshire
- MD: Medical College of Georgia
- Residency: Emory Emergency Medicine, Chief Resident
- > 15 years Urgent Care experience
- 5 years Chief Medical Officer, American Family Care
- Fellow: College of Urgent Care Medicine
- Urgent Care Association Foundation and College of Urgent Care Medicine: Board of Trustees 2017-2019
- Former Urgent Care Advisor to the Antibiotic Resistance Action Center, Milken School of Public Health at George Washington University
- Awarded Inaugural UCA Antibiotic Stewardship Commendation: 2019
- Principal: No Resistance Consulting Group - Urgent care clinical trial site recruitment & management company

AUGUSTA UNIVERSITY
MEDICAL COLLEGE OF GEORGIA

afc
american family care
URGENT CARE

No Resistance

Disclosures

- Dr. Harnett received consulting fees in 2020 from Visby Medical for assistance in development of a clinical trial protocol and trial site recruitment (2020)
- Dr. Harnett is a principal investigator in ongoing clinical trials evaluating the performance of Visby Medical devices

Patient Case Study – Urgent Care Setting

Day 1 →

- 23 yo female presents with mild vaginal itching, odor/discharge x 1 week. No prior history of STI. She reports that she is in a monogamous relationship and takes birth control pills, but her period is late
- Provider 1 performs a pelvic exam and collects a vaginal NuSwab VG+ for send-out to LabCorp for CT, NG, TV, BV, Candida testing. Clinic is out of urine pregnancy tests, so a serum pregnancy test is sent out
- Provider 1 chooses to wait for STI lab results rather than treat presumptively. No STI counseling is performed. Patient is told that she will be notified of lab results in 2-3 days

Day 4
Lab Results Return →

- Provider 2 on duty. Test results received electronically into EHR at 4:30pm. Positive Gonorrhea (other STI results negative). Serum pregnancy test positive. Clinic also notified of positive Gonorrhea result via fax to email and lab tech prints results and places in Provider One's inbox

Day 6 →

- Provider 1 returns to work and sees the positive Gonorrhea results and places note in EMR tasking staff to ask patient to return to the clinic for CDC recommended treatment (IM Ceftriaxone injection)

Day %

Patient Case Study – Urgent Care Setting cont.

Day 7 1st & 2nd contact attempt	• Staff attempts to contact patient 2x by phone with no answer. Leaves 2 message to call clinic.
Day 8 3rd contact attempt	• Staff calls patient again. No answer, leaves 3rd message. Staff informs manager of failure to contact patient after three attempts
Day 9: Certified Letter	• Per clinic policy, a certified letter is sent to the patient's address
Day 12: Certified Letter Returned	• Certified letter returned to sender due to inability to deliver letter directly to patient

Patient Lost to Follow Up

Positive for Gonorrhea. Pregnant. Untreated.

Outcome Unknown

Day %

Poll Question 1

What types of benefits would your clinic(s) realize if a rapid, point of care test for gonorrhea and chlamydia was made available to your providers? (choose one or more)

- ❑ Clinical (less empiric treatment due to testing results available at initial visit)
- ❑ Clinical (fewer treatment delays, reduced disease progression, less complications)
- ❑ Operational (decreased time spent tracking results and notifying patients)
- ❑ Financial (patient treated without need for 2nd clinic visit)
- ❑ Fewer patients lost to follow up without treatment
- ❑ Increased patient and provider satisfaction with real-time, actionable results
- ❑ None

Learning Objective

1. STI rates and CDC Guidelines

The Changing Face of STI Care

- 1980s and 1990s: Most specialized STI care was provided in STI clinics and HIV programs
- 2008 and 2012: Funding cuts led to decreases in the availability of such services
- With decreased availability of STI clinics, patients have sought care for STIs at primary care clinics, emergency departments, and urgent care clinics
- Between 71% and 80% of STI cases reported in 2018 were in non-STI clinics
- 2019: Reported STIs in the U.S. reach all-time high for 6th consecutive year. More than 2.5 million cases of chlamydia, gonorrhea, and syphilis reported

Chlamydia: 1,808,703 reported cases in 2019

- 10% increase among females aged 15–24 years since 2015[1]
- Up to 80% of women are asymptomatic[2]

Gonorrhea: 616,392 reported cases in 2019

- Rates among women increased 5.1% during 2018–2019 and 43.6% during 2015–2019
- 50% of patients are asymptomatic

Trichomoniasis: 2,600,000 estimated cases in 2018

- 70-85% of women are asymptomatic[3]
- 1.4x greater likelihood of pre-term birth, premature rupture of membranes, and infants who are small for gestational age
- TV can also increase the risk of getting or spreading HIV

1. https://www.cdc.gov/std/statistics/2019/overview.htm 2. In: Markos AR, ed. Sexually transmitted diseases. Nova Science Publishers, Inc.; 2009:37-43.] 3. https://www.cdc.gov/std/trichomonas/stdfact-trichomoniasis.htm

CDC Treatment Guidelines: Gonorrhea

Gonococcal Infections

Risk Category	Recommended Regimen	Alternatives
Uncomplicated infections of the cervix, urethra, and rectum: adults and adolescents <150 kg[6]	ceftriaxone 500 mg IM in a single dose[17]	If cephalosporin allergy: gentamicin 240 mg IM in a single dose **PLUS** azithromycin 2 gm orally in a single dose If ceftriaxone administration is not available or not feasible: cefixime 800 mg orally in a single dose[17]
Uncomplicated infections of the pharynx: adults and adolescents <150 kg[6]	ceftriaxone 500 mg IM in a single dose[17]	
Pregnancy	ceftriaxone 500 mg IM in a single dose[17]	

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

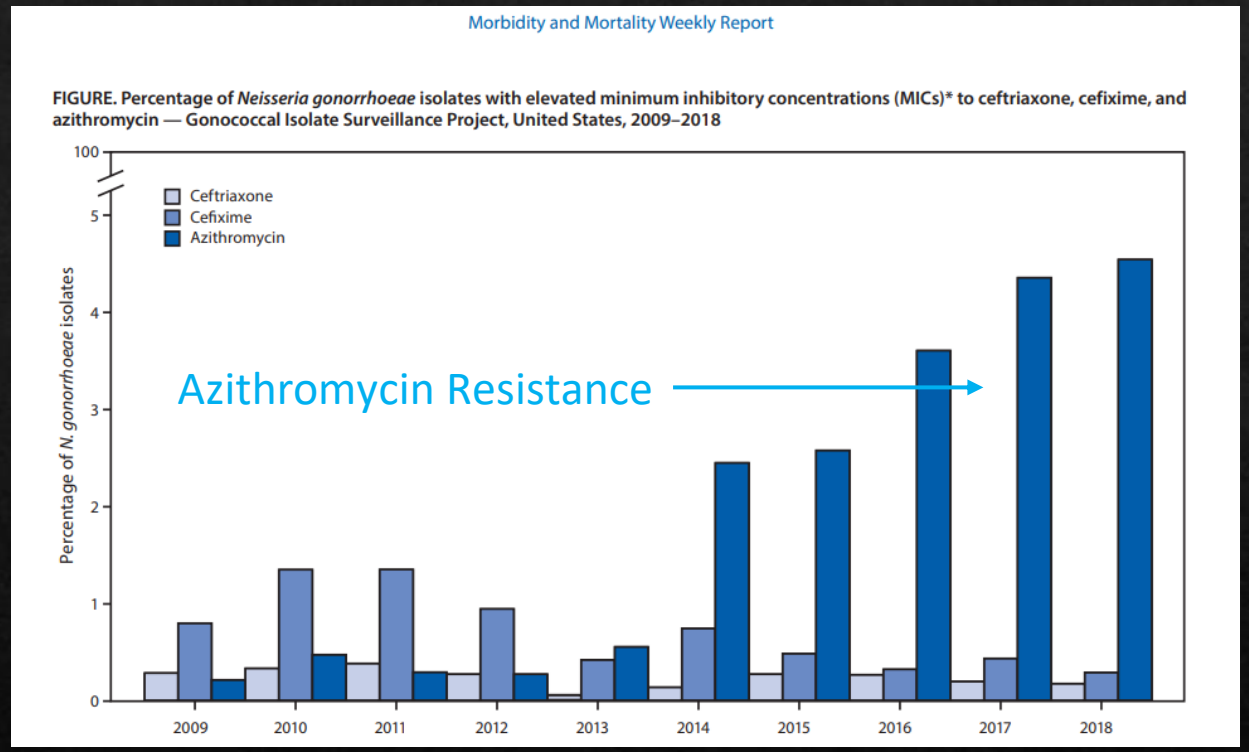
CDC Treatment Guidelines: Chlamydia

Chlamydial Infections

Risk Category	Recommended Regimen	Alternatives
Adults and adolescents	doxycycline 100 mg orally 2x/day for 7 days	azithromycin 1 gm orally in a single dose **OR** levofloxacin 500 mg orally 1x/day for 7 days
Pregnancy	azithromycin 1 gm orally in a single dose	amoxicillin 500 mg orally 3x/day for 7 days

Rationale Behind 2021 Guideline Changes

- Increased incidence of azithromycin resistance to N. gonorrhoeae (NG)
- Treatment recommendations are influenced by antimicrobial resistance - especially for NG
- Pharmacokinetic and pharmacodynamic modeling has also affected the understanding of optimal antimicrobial dosing for N. gonorrhoeae treatment (250 mg ceftriaxone has insufficient MIC to adequately treat)
- Increasing concern for antimicrobial stewardship and the potential impact of dual therapy on the microbiome and concurrent pathogens



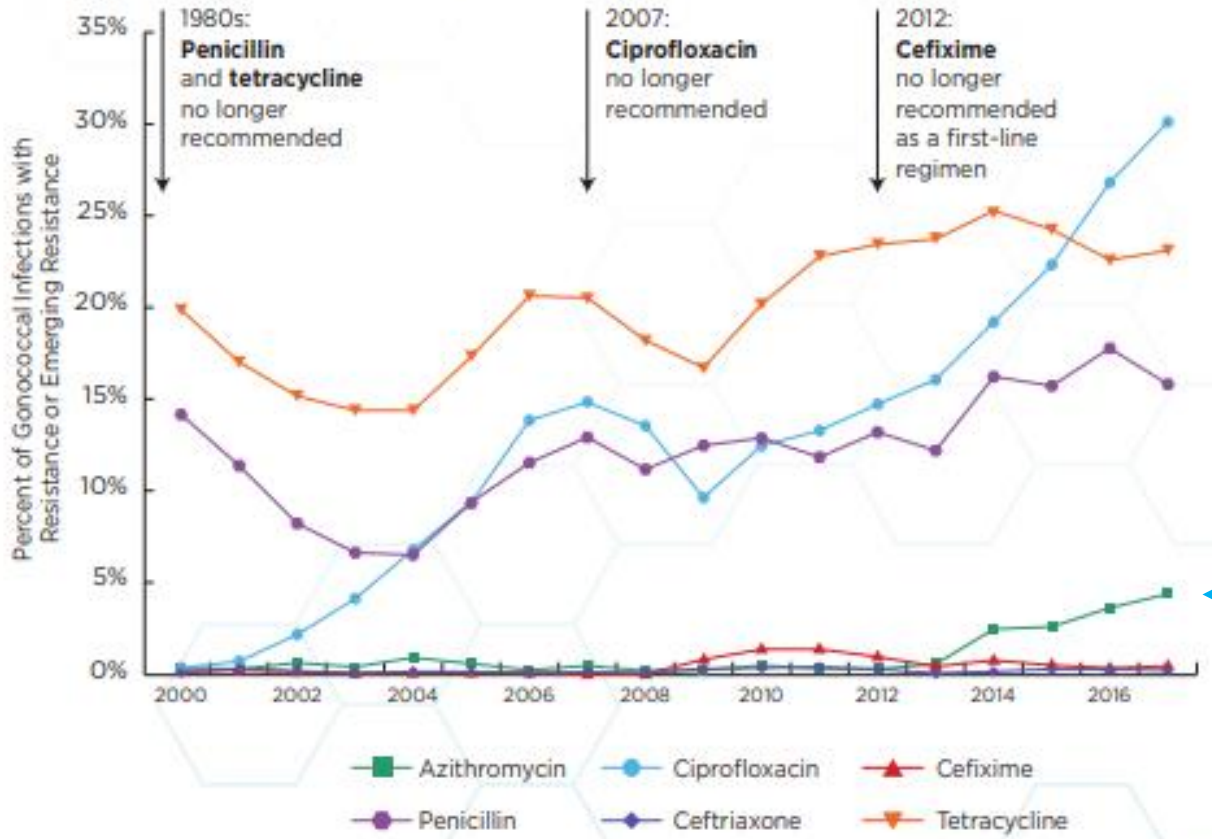
CDC. Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2019.

DRUG-RESISTANT
NEISSERIA GONORRHOEAE

THREAT LEVEL **URGENT**

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Gonorrhea rapidly develops resistance to antibiotics—ceftriaxone is the last recommended treatment.



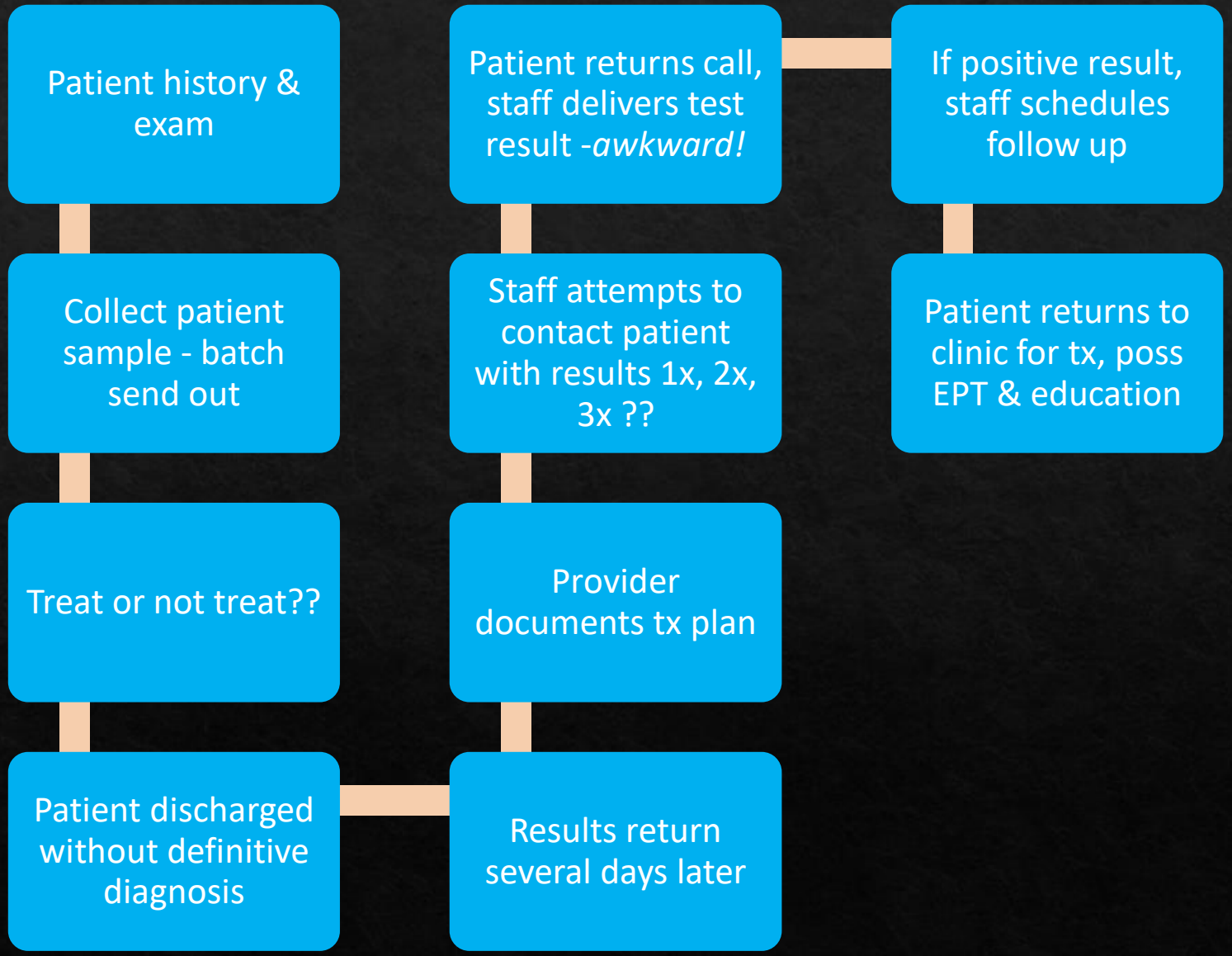
Gonorrhea has quickly developed resistance to all but one class of antibiotics (Cephalosporins)

Azithromycin Resistance Rising

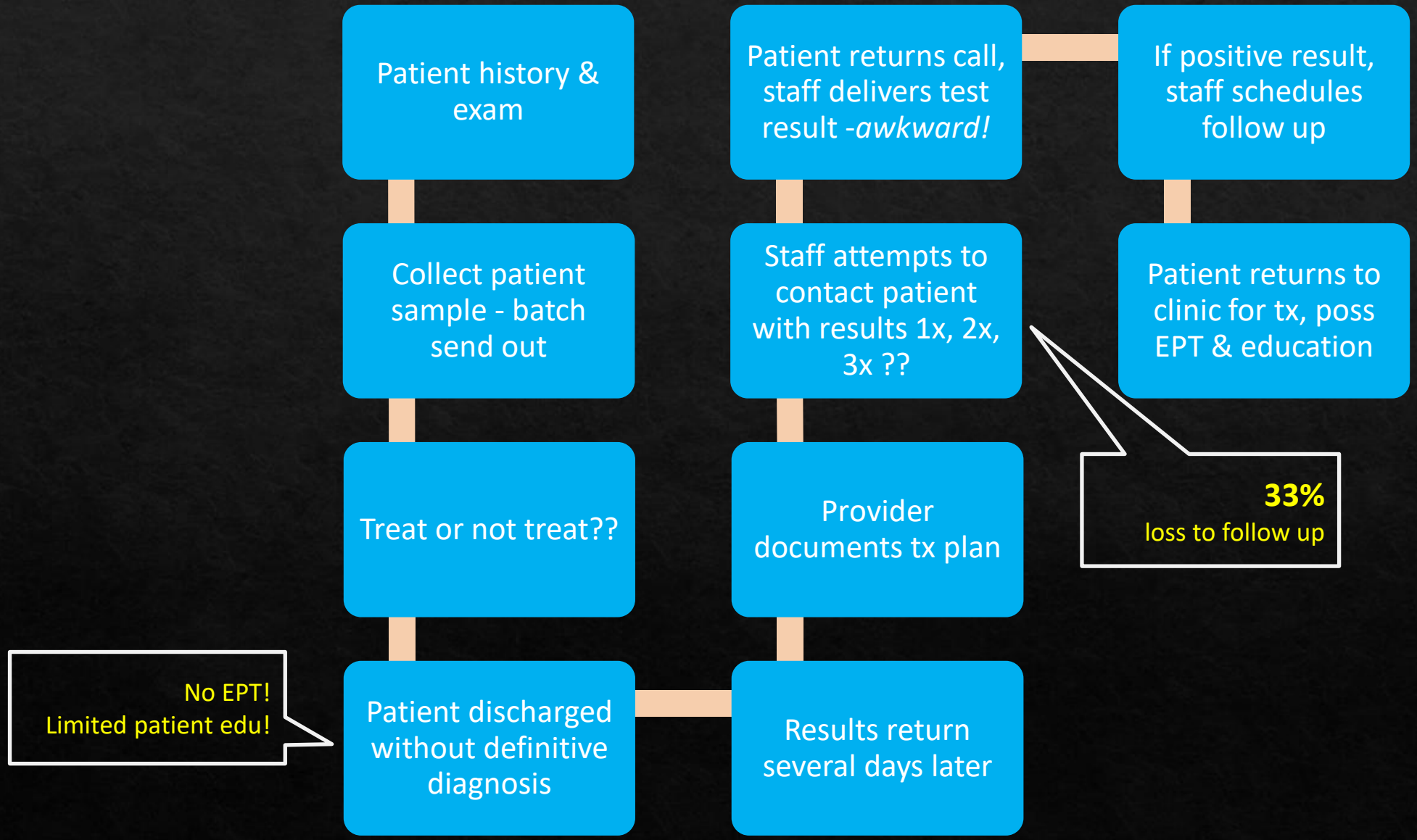
Learning Objective

2. Today’s challenges in STI testing

Traditional STI Testing



Traditional STI Testing



Traditional STI Testing

Patient/Provider challenges

- Until recently there have been no FDA approved rapid POC tests for STIs, forcing Providers to make treatment decisions without benefit of test results
- Missed opportunity for patient education without definitive diagnosis
- Poor follow-up rates – as high as 33% in some studies (unable to contact, no access to portal, socioeconomic factors, etc)
- Provider continuity - Provider on duty in the clinic/ER on the day the results return likely not the same provider who originally saw the patient and ordered the test. New provider then must review the patient's medical record before making a treatment decision
- Relaying positive STI testing results over the phone is not ideal
- Patients not treated presumptively will need to return to the clinic for CDC recommended first line treatment (IM Ceftriaxone)
- TV testing often via wet mount -- 40% of positive patients were missed when comparing PCR to wet mount

Traditional STI testing

Operational challenges

- Potential for notification errors with delayed results
- Delayed results can go missing…
- Due to delayed testing results (48hrs+), staff must notify patients when results return
- Time burden of results notification (multiple calls, certified letters, etc)
- Time burden of scheduling follow-up appointments for Tx if/when patient is contacted (Don’t forget - ceftriaxone is IM – can’t call in an Rx)
- Multiple providers may become involved in follow up and treatment decisions
- Time spent on documentation

Traditional STI testing

Public Health Challenges

- Delay in treatment for eventual lab positive patients while awaiting test results who are not treated presumptively can lead to disease progression and complications
- Transmission may continue while waiting for test results
- Missed opportunity for expedited partner(s) treatment (EPT)
- Patients treated presumptively with antibiotics are placed at risk for antibiotic complications unnecessarily
- Unnecessary antibiotics may contribute to antibiotic resistance

“Presumptive” and “Empiric" Treatment of STIs

Long delays in test results for samples sent to central labs, as well as poor follow-up, often lead clinicians to treat before a lab result is obtained

- **Empiric Treatment** → Treatment for patients who have a proven or suspected infection, but the responsible organism(s) has or have not yet been identified
- **Presumptive Treatment** → Treatment begun on the basis of an educated guess and in the absence of laboratory confirmation of disease
- **Syndromic Treatment** → Treatment occurs before confirmation of a definitive diagnosis

Problem: NG and CT infections in women are often asymptomatic. Relying on signs and symptom to treat NG and CT often leads to under-treatment in women

By contrast: result- or data-driven treatment is treatment guided by, or informed by, a test result

Over- vs Under- Treatment

OVER-treatment

A patient who was treated presumptively but had negative laboratory results.

UNDER-treatment

A patient who had a positive laboratory result but was not initially treated.

A Real Conundrum…

SETTING	LOCATION	% OVER-treated	% UNDER-treated
Emergency Dept 	Chicago, IL[1]	**21.6%**	**43.4%**
	Inner city [2]	**86%**	**4%**
	Urban academic [3]	**46.7%**	**43.8%**
	St. Louis, MO (pregnant women) [4]	**15.6%**	**80%**
	St. Louis, MO (women) [5]	**67.5%**	**87.5%**
Urgent Care	Baton Rouge, LA [6]	**87%**	**12%**

33%

undertreated patients lost to follow up

54%

UT patients contacted did NOT return for treatment

Catch-22

To treat or not to treat???

Consequences of Under-Treatment (UT) of an STI

- **Public health concern**, creating a pool of untreated patients at risk of spreading the infection
- **Delayed treatment may result in complications** of an untreated progressive infection (details on next slide)
- **Delayed expedited partner treatment**
- Reduced opportunity for result-enabled, face-to-face clinician—patient dialogue

Dangers of Untreated STIs

Gonorrhea

- Untreated gonorrhea can result in pelvic inflammatory disease (PID). Complications include:
  - Ectopic pregnancy
  - Infertility
  - Chronic abdominal pain
  - Increased risk of HIV transmission

Chlamydia

- Untreated chlamydia can spread to and damage uterus or fallopian tubes and cause PID
- Symptomatic PID occurs in 10-15% of women with untreated chlamydia
- Damage can lead to chronic pelvic pain, tubal factor infertility, and ectopic pregnancy

Consequences of Over-Treatment of an STI

- Unnecessary exposure of the patient to a medication leading to possible adverse effects
- Selection of antibiotic-resistant microorganisms thus contributing to the further emergence of antibiotic-resistant infections
- Ineffective or misleading clinician-patient dialogue because discussion will be biased by an incorrect diagnosis
- Inefficient clinic workflow: staff needs to contact patient by phone (often problematic) and schedule return appointment for the correct treatment
- Reduced patient-satisfaction
- Reduced clinician-satisfaction

Poll Question 2

Do your clinicians routinely treat patients who present with gonorrhea / chlamydia symptoms (or suspected exposure) with presumptive antibiotics?

❑ YES

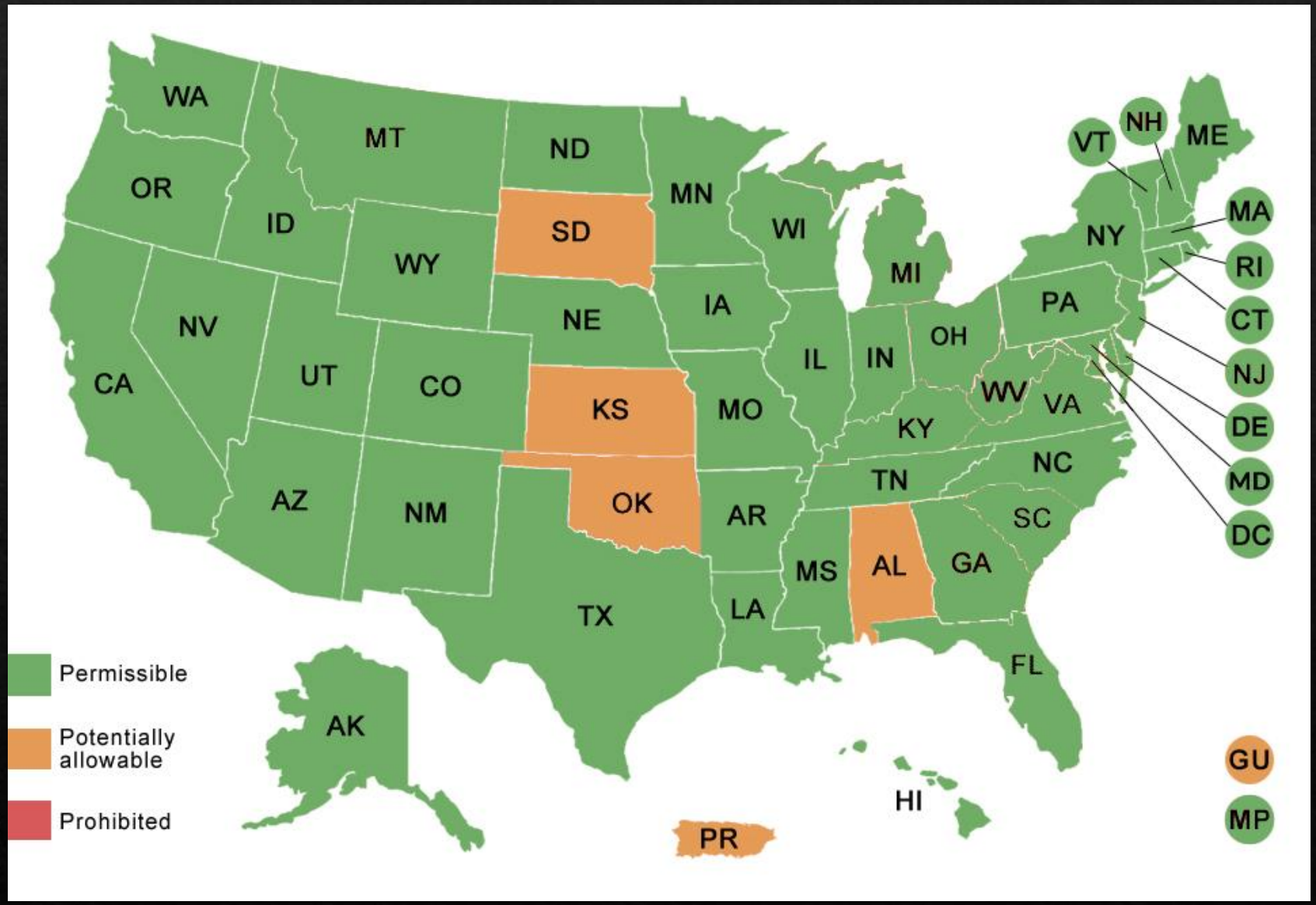
❑ NO

❑ Unsure

CDC Expedited Partner Treatment

- Expedited Partner Therapy (EPT) is the clinical practice of treating the sex partners of patients diagnosed with chlamydia or gonorrhea by providing prescriptions or medications to the patient to take to his/her partner without the health care provider first examining the partner
- Prevent reinfection and curtail further transmission
- Since CDC no longer recommends exclusively oral treatment for gonorrhea, how does CDC recommend EPT be practiced for gonorrhea?
  - Partner may be treated with a single 800 mg oral dose of cefixime, if a chlamydia infection in the patient has been excluded. If a chlamydia test result has not been documented, the partner may be treated with a single dose of oral cefixime 800 mg plus oral doxycycline 100 mg 2 times/day for 7 days
  - Medication or prescriptions provided as part of EPT should be accompanied by treatment instructions, appropriate warnings about taking medications (if the partner is pregnant or has an allergy to the medication), general gonorrhea health education and counseling, and a statement advising that partners seek personal medical evaluation, particularly women with symptoms of PID

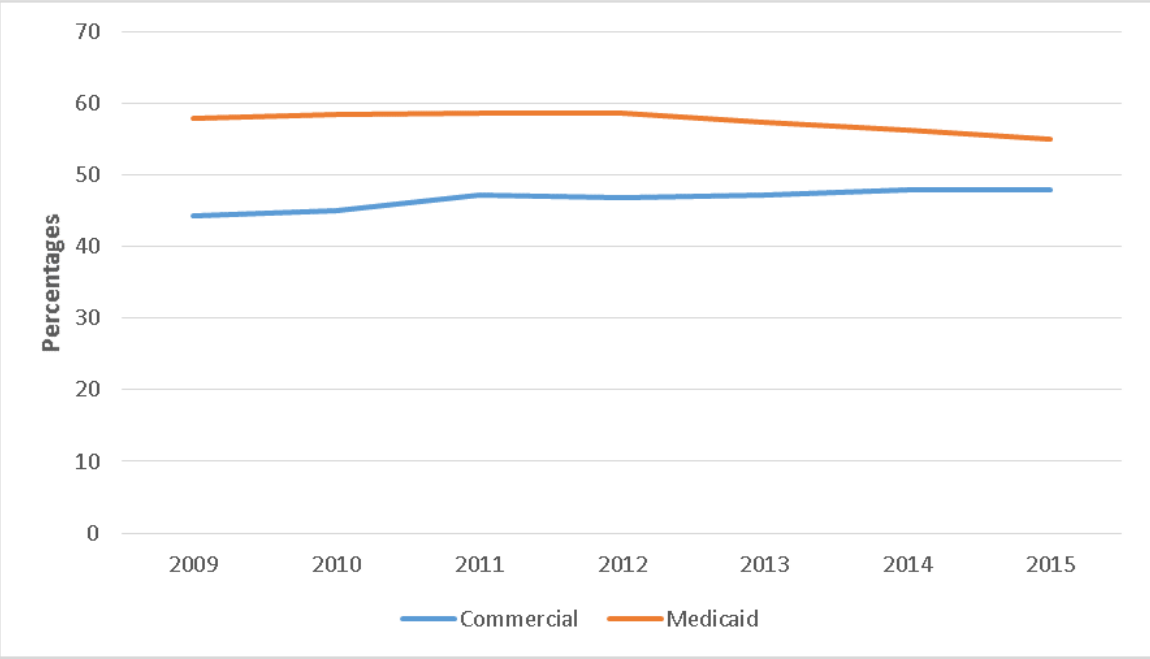
Legal Status of Expedited Partner Therapy



Chlamydia screening rates are stagnant

Percentage of sexually active female enrollees aged 16-24 years who were screened for Chlamydia trachomatis infection - Healthcare Effectiveness Data and Information Set (HEDIS), United States, 2015

State	2009	2010	2011	2012	2013	2014	2015
USA	47.0	48.1	49.6	49.2	49.3	49.9	49.8



- Screening tests are the only method for identifying asymptomatic infections
- Medicaid screening > Commercial screening
- Lack of awareness among some health care providers
- Poor reimbursement for screening
- Newer generations do not have a PCP

How Can We Improve Screening Rates?

- EMR clinical decision tools
- Standing orders for the registration/triage staff
- Express visits
- Specimen panels
- Reflex testing
- Designate a clinical champion!
- Carve out payments for CDC recommended screenings
- Because of a high likelihood of reinfection, the CDC also recommends re-testing all patients diagnosed with chlamydial or gonococcal infection **3 months after** treatment, regardless of whether they believe their partners have been treated

3. Implication of today’s STI testing to Antibiotic Stewardship

Antibiotic Stewardship Implications

- Presumptive/Empiric treatment: may lead to increased antibiotic resistance
- Unnecessary antibiotics promote the transmission of genes for antibiotic resistance between gut bacteria
- Antibiotics directly induce the expression of key genes that affect the stress response
- Antibiotics can also eliminate antibiotic-susceptible organisms, allowing resistant organisms to proliferate
- Repeated use of broader-spectrum antibiotics in children <24 months of age increases the risk of developing childhood obesity

What is needed to combat growing number of Abx resistant STI? POC testing

Antibiotics are NOT Benign

TABLE 1

Known and potential harms of antibiotic overprescribing[1-6]

Known harms	Potential harms
Antibiotic-associated diarrhea	Increased asthma
Clostridium difficile colitis	Increased obesity
Tendon rupture (quinolones)	Impaired immune system
Long QT syndrome (macrolides and others)	Mental health effects
Renal compromise	
Allergic reactions	

Fiore, D., et al, Antibiotic Overprescribing: Still a Major Concern. Fam Pract. 2017 December;66(12):730-736

Antibiotics are NOT Benign!

Antibiotic Class	Antibiotic Names	Known potential adverse drug reactions/side effects
Penicillin	Penicillin, Amoxicillin, Ampicillin, Dicloxacillin, Oxacillin Sodium, Piperacillin, Ampicillin/Sulbactam, Nafcillin	Allergic reaction* If given in high doses: Coma, seizure, hyperreflexia, myoclonus, electrolyte disturbance, neutropenia, acute interstitial nephritis Pseudomembranous colitis
Cephalosporins	Cefazolin, Cefuroxime, Cefoxitin, Cefotetan, Cefotaxime, Ceftriaxone, Ceftazidime, Cefepime, Ceftaroline	Allergic reaction* Abdominal cramps, seizure, hepatitis, blood disorders, increase serum creatinine, fever
Miscellaneous	Nitrofurantoin (Brands: Macrobid, Furadantin, Macrodantin)	Allergic reaction* Gastrointestinal distress, peripheral neuropathy, rash, acute pulmonary reaction, hepatotoxicity, hemolytic reaction, ECG changes
Sulfonamide derivative	Trimethoprim- Sulfamethoxazole (Brand: Bactrim, Sulfatrim)	Allergic reaction* Nausea, diarrhea, vomiting, fever, thrombocytopenia, leukopenia, megaloblastic anemia – G6PD deficiency, crystalluria, acute interstitial nephritis, acute tubular necrosis, false elevation of serum creatinine in patients with decreased renal function, hyperkalemia, acute psychosis
Fluoroquinolones	Ciprofloxacin, Levofloxacin, Ofloxacin	Allergic reaction* Nausea, abdominal discomfort, vomiting, diarrhea, rash, pruritus, hypo/hyperglycemia, liver failure, nephritis, nephropathy, crystalluria, prolongation of the QTC interval, confusion, headache, dizziness, agitation, anxiety, restlessness, hallucinations, depression, sleep disturbances, seizures, tendonitis, tendon rupture, peripheral neuropathy
Lincosamide	Clindamycin (Brand: Cleocin)	Allergic reaction* Colitis, abdominal pain, *Clostridium difficile* associated diarrhea, esophageal ulcer, esophagitis, abnormal hepatic function tests, hypotension, metallic taste, azotemia
Macrolides	Azithromycin (Brand: Zithromax), Clarithromycin, Erythromycin	Common: Vomiting, diarrhea Less common: Dizziness, drowsiness, fatigue, headaches, skin rash, dermatitis, increased serum potassium, decreased serum glucose, dyspepsia, gastritis, vaginitis, blood disorders, hepatitis, increased serum creatinine, bronchospasm, rash
Tetracycline derivatives	Doxycyline (Brand: Doryx, Oracea, Monodox), Minocycline, Tetracycline	Allergic reaction* Gastrointestinal distress, esophagitis/esophageal ulceration Bluish gray nail, skin and sclera pigment With Minocycline – CNS effects including vertigo, light-headedness, loss of balance, dizziness, and tinnitus; autoimmune disorders: lupus, hepatitis, serum sickness, vasculitis, pneumonitis

Statements about the potential harm of antibiotics to the individual have a greater impact than statements about resistance or societal impact of antibiotics

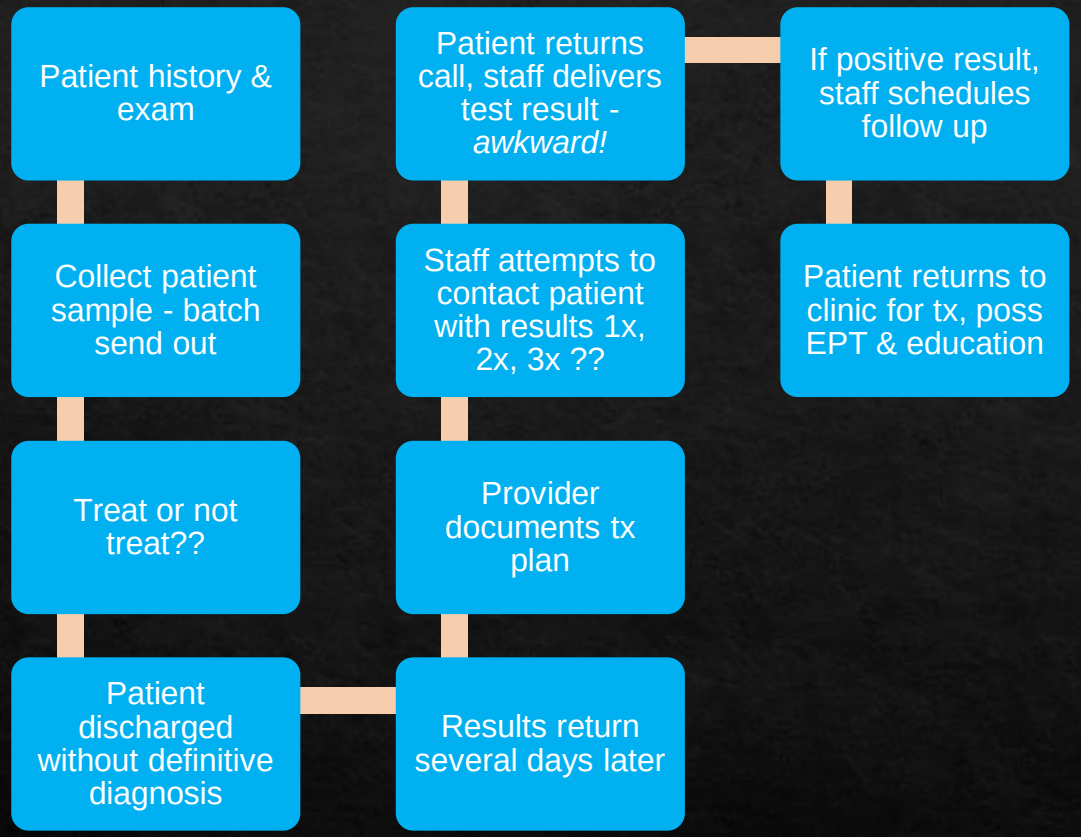
Accessed 11.23.2021: https://qioprogram.org/exploring-antibiotics-and-their-role-fighting-bacterial-infections

4. Can POC testing help us combat antibiotic resistant STIs?

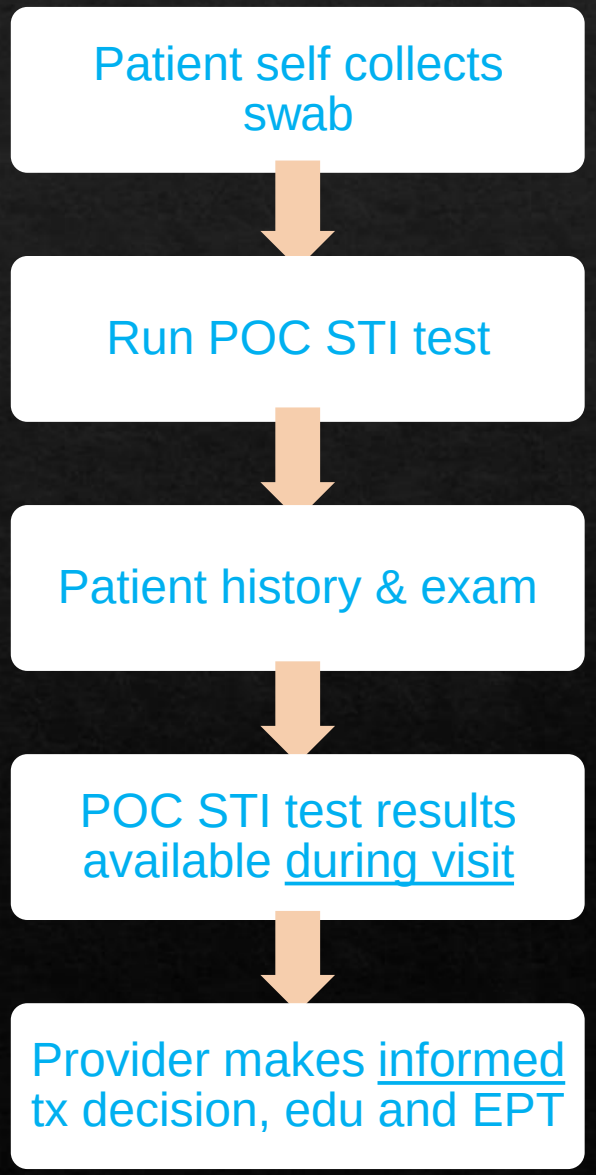
Criteria for STI point-of-care test

01	FAST	• Under 30 mins TAT - during patient visit • To eliminate presumptive treatment
02	ACCURATE	• Ideally PCR • Highly sensitive detection of CT, NG, TV
03	EASY	• Less than 1 min operator time • Does not require extensive training/edu • Simple to deploy
04	SAMPLE TYPE	• Urogenital - vaginal, penile, urine • Extra-genital - pharyngeal, rectal
05	SCALABLE	• Capacity to handle multiple patient samples
06	NO INSTRUMENT	• No capital equipment needed • No maintenance

Traditional STI testing

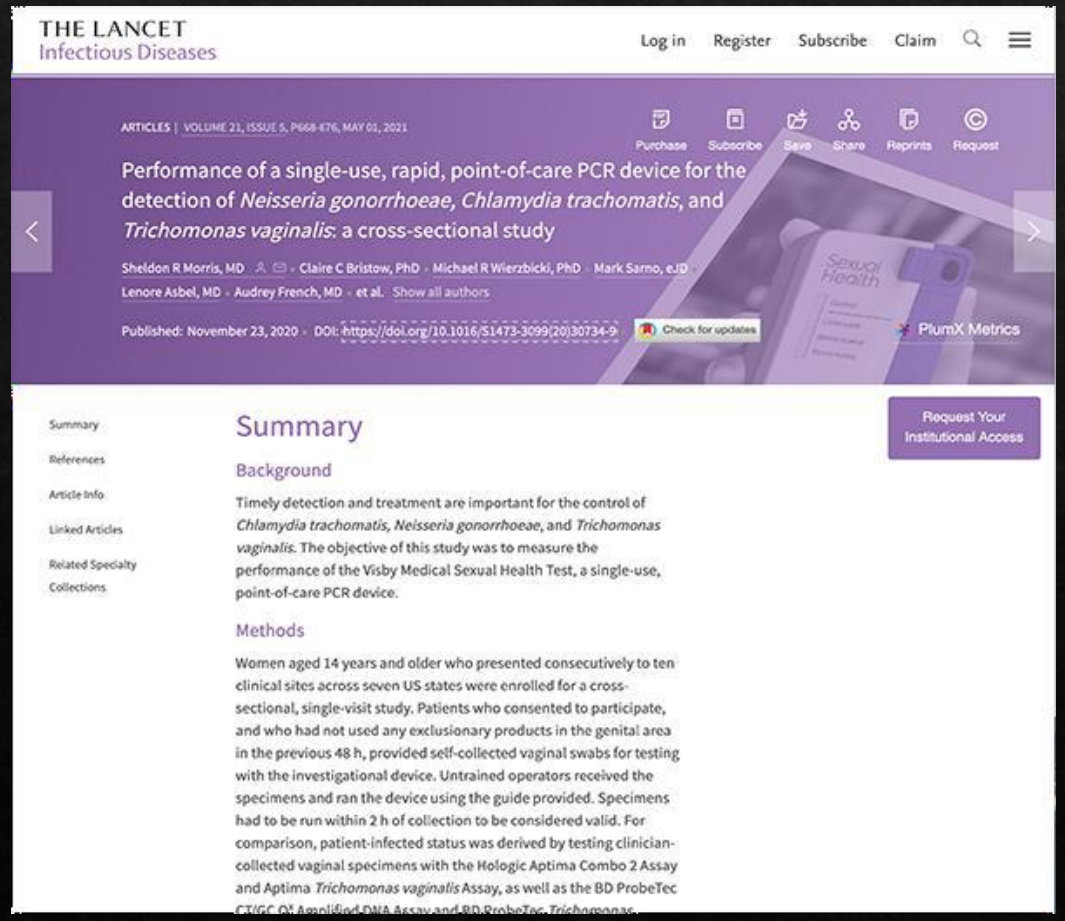


Rapid STI POC testing



A New FDA Cleared, CLIA-Waived, POC Device for CT/NG/TV Detection

THE LANCET
Infectious Diseases



https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30734-9/fulltext

Performance of a single-use, rapid, point-of-care PCR device for the detection of *Neisseria gonorrhoeae, Chlamydia trachomatis*, and *Trichomonas vaginalis*: a cross-sectional study Published November 23, 2020

Summary Background

- Timely detection and treatment are important for the control of *Chlamydia trachomatis, Neisseria gonorrhoeae*, and *Trichomonas vaginalis*. The objective of this study was to measure the performance of the Visby Medical Sexual Health Test, a single-use, point-of-care PCR device

- **Impact** on community spread
- **Impact** on clinician & patient
- **Simplicity of patient self-collected vaginal swab (+ benefit of patient involvement)**

Advantages of STI point-of-care tests

CLINICAL advantages

- Enables result-driven, effective treatment within the span of a single clinic visit
- Reduces probability of untreated STI infection progression
- Reduces probability of onward transmission
- Facilitates patient education by providing an accurate diagnosis before the patient leaves the clinic
- Enables the prompt treatment of the diagnosed person's sexual partner(s) via the CDC-sanctioned EPT program (Expedited Partner Treatment)

OPERATIONAL advantages

- By expediting the test and treat paradigm, it improves clinic workflow, increases the efficiency of clinic staff and likely positively impacts that clinic's cost effectiveness
- Increases patient and physician satisfaction by providing a clinician with an accurate diagnosis (which is essential for being able to provide effective treatment) during the initial visit

FINANCIAL advantages

- Time = Money
- Patient treated immediately without need for 2nd clinic visit - free up schedule to see other patients
- Will a second visit for the same diagnosis be reimbursed?
- Sexual partner(s) may be referred to clinic for testing/treatment
- No more follow up calls

Poll Question 3

If offered, what percentage of your providers would likely utilize a rapid, point of care test for STI detection?

- 75-100%
- 50-75%
- 25-50%
- Less than 25%
- Unsure

Patient Case Study

Urgent Care Setting with rapid POC STI testing

Day 1: →

- 23 yo female presents with mild vaginal itching, odor/discharge x 1 week. No prior history of STI. She reports that she is in a monogamous relationship and takes birth control pills
- Provider One orders a rapid POC GC/CT/TV test and patient self collects a vaginal swab
- 30 minutes later the test reports a positive gonorrhea result
- Provider notes results and informs patient. Education is provided and questions are answered. Ceftriaxone 500mg IM is ordered and administered
- EPT is considered and initiated if appropriate
- Patient discharged and instructed to return in 90 days for re-test

Day 2: →

- **There is no Day 2!**

Key takeways

- The CDC released new STI treatment recommendations in 2021 in response to rising antibiotic resistance rates to STIs
- Current treatment and testing regimens for STIs can result in both over AND under treatment of STIs
- Antibiotics are not benign!
- Almost 50% of women in the US are not adequately screened for Chlamydia and Gonorrhea as recommended by the CDC
- A Rapid, POC test for STIs may reduce over and under treatment of STIs and become a new tool for antibiotic stewardship

Appendix

References

Authors	Title	Patients in Study N=	% OVER treated	% UNDER treated	Setting
1.Anaene et al, International Journal of Infectious Diseases, 53 (2016) 34-38	"Factors associated with the over-treatment and under-treatment of gonorrhea and chlamydia in adolescents presenting to a public hospital emergency department"	797	(136/233) 58%	(74/564) 13%	Emergency department in large safety-net public hospital in Chicago, IL
2. Holley, et al, Am J Emerg Med, 2015 Sep 33(9):1265-8	"Overtreatment of gonorrhea and chlamydial infections in 2 inner-city emergency departments"	522	(87/101) 86%	(17/412) 4%	2 inner city emergency departments
3. Gaydos et al, Ann Emerg Med, 2019 Jul: 74(1):36-44	"Use of a Rapid Diagnostic for Chlamydia trachomatis and Neisseria gonorrhoeae for Women in the Emergency Department Can Improve Clinical Management: Report of a Randomized Clinical Trial"	127 (Std of Care)	(53/114 CT) (56/120 NG) 47%	(7/16) 44%	Urban academic Emergency Department
4. Bergquist et al, International Journal of STD and AIDS, 2020 Vol 31(2) 166-173	"Undertreatment of chlamydia and gonorrhea among pregnant women in the emergency department"	(NA)	15.6%	80%	Emergency Department, St. Louis, MO
5. Dretler et al, Am J Emerg Med 38 (2020) 566–570	"The influence of race and sex in gonorrhea and chlamydia treatment in the emergency department"	4007	(1369/3364) 41.5%	(258/643) 40%	Emergency department, St. Louis, MO
6. Dawkins et al, Manuscript submitted for review (Sept 2021)	"Clinical Integration of a Highly Accurate PCR Point-of-care Test Can Inform Immediate Treatment Decisions for Chlamydia, Gonorrhea and Trichomonas"		87%	12%	Urgent care center in Baton Rouge, LA