SCREENING & TESTING FOR SEXUALLY TRANSMITTED INFECTIONS IN GAY, BISEXUAL & OTHER MEN WHO HAVE SEX WITH MEN

Jeanne Marrazzo, MD, MPH
Seattle STD/HIV Prevention Training Center
University of Washington
CONTINUING MEDICAL EDUCATION DISCLOSURE

- **Program Faculty**: Jeanne Marrazzo, MD, MPH
- **Current Position**: Professor in the Division of Allergy & Infectious Diseases, University of Washington, Seattle
- **Disclosure**: Financial relationships with Cepheid, GenProbe, Astra-Zeneca and Merck (Research grants and Consultant for fee). Content of presentation contains no use of unlabeled and/or investigational uses of products.

It is the policy of The National LGBT Health Education Center, Fenway Health that all CME planning committee/faculty/authors/editors/staff disclose relationships with commercial entities upon nomination/invitation of participation. Disclosure documents are reviewed for potential conflicts of interest and, if identified, they are resolved prior to confirmation of participation. Only participants who have no conflict of interest or who agree to an identified resolution process prior to their participation were involved in this CME activity.
MEDICAL DISPATCHES

SEX AND THE SUPERBUG

The rise of drug-resistant gonorrhea.

BY JEROME GROOPMAN

Gonorrhea mutates in the pharynx, making oral sex far more risky than people think.

The New Yorker, October 1, 2012
OBJECTIVES

- Summarize CDC screening guidelines for STIs and HIV in MSM
  - Rationale: epidemiology
- Review STI testing and diagnostic issues specific to MSM
- Identify barriers to effective STI screening and testing with MSM in health care settings
- Identify potential strategies for overcoming these barriers
STD SURVEILLANCE NETWORK (SSUN)—PROPORTION OF MSM* ATTENDING STD CLINICS WITH PRIMARY AND SECONDARY SYphilis, GONORRHEA OR CHLAMYDIA BY HIV STATUS, 2010

* MSM = men who have sex with men.  
† HIV negative status includes persons of unknown status for this analysis.  
‡ GC urethral and CT urethral include results from both urethral and urine specimens.

See also Ganesan 2012; Spaulding 2012: military cohort data
STD SCREENING IN MSM

- At least annually for sexually active MSM:
  - HIV serology, if HIV negative or not tested within the previous year;
  - Syphilis serology
  - Urine NAAT for N. gonorrhea and C. trachomatis if insertive intercourse during preceding year;
  - Rectal NAAT for GC/CT if receptive anal intercourse during preceding year
  - Pharyngeal NAAT for GC if receptive oral sex in preceding year
    - Testing for CT not recommended
STD SCREENING IN MSM

• Evaluation for HSV-2 infection with type-specific serologic tests also can be considered if infection status is unknown; knowledge of HSV-2 serostatus might be helpful in identifying persons with previously undiagnosed genital tract infection.

• Screening for anal cytologic abnormalities can be considered; evidence limited concerning natural history of AIN, reliability of screening, safety and response to treatments, and programmatic support needed.

• More frequent screening is indicated for MSM who have multiple or anonymous partners. In addition, MSM who have sex in conjunction with illicit drug use (particularly methamphetamine use) or whose sex partners participate in these activities should be screened more frequently.
STD SCREENING IN MSM

- HBsAg testing to detect current infection
- Hepatitis A and B vaccination if nonimmune
- Hepatitis C virus (HCV) sexual transmission (HIV+ MSM)
  - HCV serology at initial visit
  - HCV RNA with unexplained alanine aminotransferase rise
  - Routine HCV testing - high-risk sexual behavior or ulcerative STDs
  - Prevention (condoms) at sites of penetration
STD SCREENING: 2009 HIVMA PRIMARY CARE GUIDELINES

- Syphilis: At entry to care and periodically thereafter, depending on risk
- Gonorrhea: At entry to care and periodically thereafter, depending on risk
  - Rectal testing if receptive anal sex
  - Oral testing if receptive oral sex
- Chlamydia: At entry to care and periodically thereafter, depending on risk
  - Rectal testing if receptive anal sex
STD SCREENING: REQUIRES ASKING

“Whoa—way too much information.”

www.nnptc.org/online_training/asi
Proportion of infections that would NOT be identified if only urine/urethral screening is performed among gay/bisexual men

Chlamydia (n = 655):
- 46% Identified
- 54% Not Identified

Gonorrhea (n = 892):
- 56% Identified
- 44% Not Identified
NEW CHALLENGES

I ordered syphilis serology on my patient and instead of getting the usual RPR, I got a *Treponema pallidum* IgG result.

It was “reactive” – Help!

www.syphilisrising.org
SYphilis EIA/CIA

- Treponemal tests FDA cleared for clinical use
- IgG, IgM* tests available
  - IgM in early syphilis diagnosis (Knaute CID 2012)
- Automated, occupational advantages (no pipette), no prozone, less costly to lab
- “Reverse sequence syphilis screening” is result (treponemal test used *first*)

Limitations:
- Can’t distinguish between active and old disease (treated / not)
- Can’t use to monitor therapy (no titers)
- False positive results in low prevalence
- Confirm positives with standard nontreponemal test titer (RPR/VDRL) to guide management
- If this is negative, perform a different treponemal test (TPPA)
- Patients with discrepant serology (e.g., positive EIA/CLIA and negative RPR)
- Early untreated, false-positive EIA, OR previously treated syphilis
• Relentless upward trends in men (MSM, HIV)
• Anecdotal increase in neuro presentations (uveitis, otitis)
• Increasing use of new serologic tests (EIA)
• Don’t use azithromycin for treatment
I’m really confused about when to get an LP in patients with syphilis.

www.syphilisrising.org
CASE: TO LP OR NOT?

- 31 y.o. man presents for initiation of ART
- No prior history of syphilis; has genital herpes and prior history of gonorrhea (most recent one year ago)
- Normal history and physical exam
- CD4 11 (1%); plasma viral load 230,000 copies/ml
  - Treponemal CIA + (IgM/IgG), RPR + 1:128
WOULD YOU PERFORM LP TO RULE OUT NEUROINVASIVE SYPHILIS?

a) No
b) Yes
c) I need more information
EVALUATION OF CNS IN SYPHILIS, HIV+, 2010

- CNS invasion occurs in early syphilis regardless of HIV or neurologic symptoms (protein, pleocytosis)
  - Clinical significance unknown (HIV+/-)
  - Clinical and CSF consistent with neurosyphilis associated with RPR ≥ 1:32 and/or CD4 ≤350
    - Criteria likely sensitive, but non-specific (many negative LPs)
    - Unless neurologic symptoms present, CSF exam has not been associated with improved clinical outcomes
    - Guidelines are non-directive and leave LP decision up to providers’ discretion

2010 CDC STD Treatment Guidelines: www.cdc.gov/std

MANAGEMENT OF SYphilis & HIV: GENERAL THEMES

- Use standard treatment appropriate to stage
- Serologic follow-up more frequent
  - 3, 6, 9, 12, 18 and 24 month follow up serology with quantitative test (RPR or VDRL; use same one consistently)
- For neurosyphilis, clearance problem in HIV+
  - Poorer neurosyphilis treatment response with low CD4, no ARV
- Three approaches:
  - LP for all HIV+ patients with syphilis, regardless of stage
  - LP using algorithm based on CD4 and syphilis titer
    - Treat for neurosyphilis if CSF WBC elevated or CSF-VDRL reactive
  - LP only if symptoms/signs indicate CNS involvement
NEUROSYPHILIS:  
CAN OCCUR AT ANY STAGE OF SYPHILIS

- CNS invasion occurs early in infection ~30-40%
  - Majority asymptomatic

- Neurosyphilis
  - Early symptomatic forms (months to a few years)
    - Acute syphilitic meningitis (CN VI, VII, VIII), hearing loss, meningovascular (stuttering stroke), altered mental status
  - Late symptomatic forms (> 2 years)
    - General paresis and Tabes dorsalis

- Ocular syphilis
  - Posterior chamber uveitis
  - Retinitis and retinal detachment
HIV INFECTED? LP OR NOT...

- Studies document clinical and CSF abnormalities consistent with neurosyphilis in HIV + with low CD4 (≤350) or RPR ≥ 1:32
  - No change in clinical outcomes if asymptomatic
- Unless neurologic symptoms, no evidence that CSF exam is associated with improved outcomes, so not recommended
  - Assess for neurologic/opthalamic/otologic symptoms
  - LP all HIV + with syphilis and neurologic symptoms

NEUROSYPHILIS DIAGNOSIS

- CSF VDRL has limitations
  - Very specific but not very sensitive
  - Only test approved for CSF specimen
  - CSF VDRL negative patients consider neurosyphilis treatment if no other etiology identified and
    - CSF WBCs >5 in HIV negative patients
    - CSF WBCs >20 in HIV infected patients*

- CSF FTA-abs is not specific but a negative test result may help rule out neurosyphilis (but may not if clinical suspicion is high**)
SYPHILIS SCREENING PARADIGM

Emerging... non-treponemal tests (e.g., RPR, VDRL)
• non-specific antibody to lipoidal antigens
• quantitative
• reactivity declines with time

Treponemal tests (e.g., EIA, CIA, MBIA)
• specific to TP
• qualitative
• reactivity persists over lifetime
• reactivity declines with time

Reflex to non-treponemal tests (e.g., RPR, VDRL)

NATIONAL LGBT HEALTH EDUCATION CENTER
A PROGRAM OF THE FENWAY INSTITUTE
REVERSE SEQUENCE SCREENING ALGORITHM

EIA or CIA

- Negative: Not Syphilis
- Positive: Non-trep test (RPR)

Non-trep test (RPR)

- Negative: 2nd Trep Test
- Positive: Syphilis (past or present)

2nd Trep Test

- Negative: 1) Unconfirmed EIA
  - Unlikely syphilis; if pt at risk retest in 1 month
- Positive: 1) Past Syphilis
  - 2) Early Syphilis

APHL-CDC Consultation Report, 1/2009 MMWR 2011/Vol 60 (5)
INTERPRETING COMMONLY USED SEROLOGIES

- HerpeSelect (Focus) ELISA is commonly used
- Although package insert states that an index value >1.1 should be interpreted as positive, several experts use a cutoff of 3.5
  - PPV as low as 38% in college students with very low HSV2 seroprevalence (3.4%) [Mark 2007]
  - Leads to higher negative predictive value [Golden 2005; Philip 2008]
    - Correctly reports uninfected people as uninfected
    - Fewer false positives
- For patients who REALLY want to know, consider Western blot
  - Call #206-598-6066 to request HSV Type-Specific Serology information packet
  - http://depts.washington.edu/herpes/
Gonorrhea causes blindness, arthritis, invalidism and misery. It can be prevented and cured.

For examination and free pamphlets, go to your doctor or Dept. of Health Clinic.

St. George — 61 Stuyvesant Place
Staten Island Case Finding Project

NATIONAL LGBT HEALTH EDUCATION CENTER
A PROGRAM OF THE FENWAY INSTITUTE
The Emerging Threat of Untreatable Gonococcal Infection

Gail A. Bolan, M.D., P. Frederick Sparling, M.D., and Judith N. Wasserheit, M.D., M.P.H.

It is time to sound the alarm. During the past 3 years, the wily gonococcus has become less susceptible to our last line of antimicrobial defense, threatening our ability to cure gonorrhea and prevent severe sequelae.

Gonorrhea is the second most commonly reported communicable disease in the United States, with an estimated incidence of more than 600,000 cases annually. It disproportionately affects vulnerable populations such as minorities who are marginalized because of race, ethnic group, or sexual orientation. Unfortunately, Neisseria gonorrhoeae has always Control and Prevention (CDC) are now limited to third-generation cephalosporins.²

But susceptibility to cephalosporins has been decreasing rapidly.³ The proportion of GISP isolates for which the minimum inhibitory concentration (MIC) of cefixime is elevated (≥0.25 μg per milliliter) has increased by a factor of 17 — from 0.1% in 2006 to (0.04% of those in the GISP) had a MIC of ceftriaxone of 0.25 μg per milliliter in the first half of 2011, the proportion of GISP isolates with an elevated ceftriaxone MIC (≥0.125 μg per milliliter) has increased by a factor of 10 since 2006 (from 0.05% to 0.50%). Again, increases were greatest in the west (from 0.04% to 1.90%) and among men who have sex with men (from 0.0% to 1.0%). These geographic and demographic patterns are worrisome because they mirror those observed during the emergence of fluoroquinolone-resistant N. gonorrhoeae.
INTERNATIONAL EMERGENCE OF N. GONORRHOEA WITH DECREASED SUSCEPTIBILITY TO CEPHALOSPORINS

- Increasing proportion of isolates with laboratory evidence of decreased susceptibility (GISP)
  - Elevated MICs
- Case reports of oral cephalosporin treatment failures
  - East Asia and Western Pacific, 2000-present
  - Europe, 2010-present
  - N. America, 2010-2011: Cefixime treatment failure in 25% with MIC >0.12 (Allen 2013)
- Extended Spectrum Cephalosporin Resistance
  - H014: Japanese sex worker with pharyngeal isolate with ceftriaxone MIC 2-4 (Ohnishi 2011)
  - F89: French MSM urethral isolate with cefixime MIC 4, ceftriaxone 1-2 (Unemo 2012)
THE GONOCOCAL ISOLATE SURVEILLANCE PROJECT (GISP)

- CDC-supported US sentinel surveillance since 1987
- Monitors trends in N. gonorrhoeae antibiotic susceptibility in men attending STD clinics

Methods

- Urethral isolates obtained from the first 25 men per site each month
- Susceptibility testing conducted by 5 regional laboratories
  - Minimum inhibitory concentrations (MICs) by agar dilution
- Confirmatory testing by CDC
- Limited demographic & clinical data from participating men

http://www.cdc.gov/std/gisp/
PERCENTAGE OF NEISSERIA GONORRHOEAE ISOLATES WITH ELEVATED CEFIXIME MINIMUM INHIBITORY CONCENTRATIONS (MICS) (≥ 0.25 G/ML)

Gonococcal Isolate Surveillance Project (GISP), 2005-2012
PERCENTAGE OF NEISSERIA GONORRHOEAE ISOLATES WITH ELEVATED CEFTRIAXONE MINIMUM INHIBITORY CONCENTRATIONS (MICS) (≥ 0.125 µG/ML)

Figure 24. Percentage of Neisseria gonorrhoeae Isolates with Elevated Ceftriaxone Minimum Inhibitory Concentrations (MICs) (≥0.125 µg/ml), Gonococcal Isolate Surveillance Project (GISP), 2005 – 2012
**PERCENTAGE OF ISOLATES WITH ELEVATED MICS OR RESISTANCE BY SEX OF SEX PARTNER, 2005 - 2010**

---


Robert D. Kirkcaldy, MD, MPH; Akbar Zaidi, PhD; Edward W. Hook III, MD; King H. Holmes, MD, PhD; Olusegun Soge, PhD; Carlos del Rio, MD; Geraldine Hall, PhD; John Papp, PhD; Gail Bolan, MD; and Hillard S. Weinstock, MD, MPH

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MSM n=8,117</th>
<th>MSW n=26,483</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone*</td>
<td>0.4</td>
<td>0.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cefixime**</td>
<td>1.7</td>
<td>0.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Azithromycin†</td>
<td>0.9</td>
<td>0.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Tetracycline†</td>
<td>37.5</td>
<td>13.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ciprofloxacin‡</td>
<td>29.9</td>
<td>6.9</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

* ≥ 0.125 µg/mL
** ≥ 0.25 µg/mL
† ≥ 2.0 µg/mL
‡ ≥ 1.0 µg/mL

SO WHAT DO WE DO?

- Change treatment recommendations
- Study old drugs in new doses, combinations
- Study new drugs
- Know how to manage suspected cephalosporin treatment failures now
Update to CDC’s Sexually Transmitted Diseases Treatment Guidelines, 2010:
Oral Cephalosporins No Longer a Recommended Treatment for Gonococcal Infections

Gonorrhea is a major cause of serious reproductive complications in women and can facilitate human immunodeficiency virus (HIV) transmission (1). Effective treatment is a cornerstone of U.S. gonorrhea control efforts, but treatment of gonorrhea has been complicated by the ability of Neisseria gonorrhoeae to develop antimicrobial resistance. This report, using data from CDC’s Gonococcal Isolate Surveillance Project

From 2006 to 2010, the minimum concentrations of cefixime needed to inhibit the growth in vitro of N. gonorrhoeae strains circulating in the United States and many other countries increased, suggesting that the effectiveness of cefixime might be waning (4). Reports from Europe recently have described patients with uncomplicated gonorrhea infection not cured by treatment with cefixime 400 mg orally (5–8).
CURRENT CDC STD TREATMENT GUIDELINES

- Uncomplicated Gonococcal Infections of Cervix, Urethra & Rectum

- Ceftriaxone 250 mg as a single intramuscular dose
- (Or if not an option, Cefixime 400 mg orally in a single dose)

- PLUS
- Azithromycin 1 g orally or
- Doxycycline 100 mg twice daily for 7 days
A 21-year-old woman presented for testing. Her male partner had recently been treated for urethritis (NAAT GC+). She was treated with ceftriaxone 250 mg & Azithromycin 1 g. Testing was positive for GC by NAAT and Cx. The MIC to Azithromycin was >256 (Hawaii State Lab) and ≥ 1,024 (Univ of WA). Tet MIC = 2; Cefixime MIC = 0.125; Ceftriaxone MIC = 0.03; Cefpodoxime MIC = 0.25.

Neisseria gonorrhoeae With High-Level Resistance to Azithromycin: Case Report of the First Isolate Identified in the United States

Alan R. Katz,1,2 Alan Y. Komeya,2 Olusegun O. Soge,3 Mandy I. Kiaha,2 Maria Veneranda C. Lee,2 Glenn M. Wasserman,2 Eloisa V. Maningas,4 A. Christian Whelen,1,4 Robert D. Kirkcaldy,5 Steven J. Shapiro,5 Gail A. Bolan,5 and King K. Holmes3
CEPHALOSPORIN TREATMENT FAILURES

- Recommendations
  - Infectious disease consultation
  - Culture and susceptibility
  - Ceftriaxone 250 mg IM + 2 gm azithromycin
  - Ensure partner treatment
  - Test of cure one week after treatment
  - Report to CDC via state or local public health
ALTERNATIVE UROGENITAL GC REGIMEN

- NIH-sponsored multicenter randomized open-label non-comparative trial
- Men/women with urogenital gonorrhea (culture-positive)
- Treatment with either
  - Gentamicin 240 mg IM + azithromycin 2 g PO, OR
  - Gemifloxacin 320 mg PO + azithromycin 2 g PO
- Rationale
  - Additive effect between gentamicin and azithromycin (in vitro)
  - Gemifloxacin more active against GC with known cipro resistance or mutations in the GyrA and ParC regions (in vitro); possibly due to stronger inhibitory activity of gemifloxacin for GyrA and ParC
- Test-of-cure (culture) in 10–17 days

Kirkaldy, ISSTD 2013
TEST OF CURE

7 days post-treatment; culture or NAAT

- Challenges
- Local guidelines may differ
- Resources
- Few data inform likelihood of negative test in adequately treated infection at 7 days (Bachmann 2002; Hjelmevoll SO 2012)
PATIENT DELIVERED PARTNER THERAPY

- Appropriate for heterosexual patients with GC whose partners’ treatment cannot be ensured or is unlikely
- NOT considered ideal for MSM
- Partners should be highly encouraged to present for ceftriaxone 250mg IM + azithromycin 1g PO
- If will not or cannot: cefixime 400mg PO x 1 AND azithromycin 1g PO x 1
HEPATITIS C VIRUS INFECTION IN MSM

- Increasing incidence of HCV among MSM
- Risks:
  - Unprotected receptive anal intercourse; h/o syphilis
  - Rougher or poorly lubricated unprotected anal penetration, including fisting
- CDC guidelines: screen if HIV+, IDU, and/or born 1945-65
- Acute infection may be HCV antibody negative
  - Check HCV RNA in patients with new, unexplained transaminase elevation

Vandeler, Clin Infect Dis 2012
ANAL DYSPLASIA AND CANCER

- HIVMA / IDSA primary care guidelines: anal Papanicolaou (Pap) test if history of receptive anal intercourse, abnormal cervical Pap, genital warts: weak recommendation, moderate quality evidence
  - Patients with abnormal results should be evaluated with high-resolution anoscopy
- Human papillomavirus (HPV) DNA screening not recommended; role not defined
- Vaccinate against HPV: safe and immunogenic in HIV+
  - Prevents anal cancer, AIN 2-3
REDUCTION IN HUMAN PAPILLOMAVIRUS (HPV) PREVALENCE AMONG YOUNG WOMEN FOLLOWING HPV VACCINE INTRODUCTION IN THE UNITED STATES, NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEYS, 2003-2010

Markowitz L. J Infect Dis. 2013:308
Genital warts in young Australians five years into national human papillomavirus vaccination programme: national surveillance data

Fig 1 Proportion of Australian born women diagnosed as having genital warts at first visit, by age group, 2004-11

Fig 2 Proportion of Australian born women aged under 21 years diagnosed as having genital warts at first visit to Sydney and Melbourne Sexual Health Centres, by vaccination status, 2009-11. Numbers are number diagnosed as having genital warts/number seen
TAKE-HOME MESSAGES

- Screen, appropriately!
- Rescreen for chlamydial and gonococcal infections 3 to 6 months after initial +
- Be aware of antibiotic-resistant GC
- Syphilis: it’s not going away.Know what the EIA is and recognize neuroinvasive disease
- Sexual health
  - Vaccinate for HPV (but continue Pap test screening)
  - Prevention messages
DOWNLOAD THE CDC STD TREATMENT GUIDELINES APP …

http://www.cdc.gov/std/std-tx-app.htm
STD RESOURCES

- Seattle STD/HIV Prevention Training Center
  - www.seattlestdhivtraining.org
- National Network of STD/HIV Prevention Training Centers
  - www.stdhivpreventiontraining.org
- CDC Treatment Guidelines
  - www.cdc.gov/std/treatment
- American Social Health Association (ASHA) booklets, books, handouts, the Helper www.ashastd.org
  - (800) 230-6039
- ASHA patient herpes hotline (919) 361-8488
THANK YOU!!