F076-AIDS and STDs: Hot Topics

Syphilis Update
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Disclosures

• None
Objectives

• At the end of this presentation, participants should be able to:
  ▪ Describe the changing epidemiology of syphilis in the United States
  ▪ Recognize the clinical manifestations of syphilis- including some of the less common ones
  ▪ Describe the serological approach to diagnosis and follow-up
  ▪ Recognize indications for CSF examination
  ▪ Describe the optimal treatment approach
  ▪ Recognize emerging interventions to mitigate increasing rates

Epidemiology

Part 1
Where we were in 1999...

https://www.cdc.gov/stopsyphilis/plan.htm

Where we are now...

There are 2 distinct epidemics that are ongoing in the United States at this time

CDC. Sexually Transmitted Disease Surveillance 2017. Atlanta: U.S. Department of Health and Human Services; 2018
Syphilis: The MSM epidemic

• Increasing rates since early 2000s
  ▪ >70% increase since 2013
  ▪ Nearly 50% are HIV-infected
  ▪ Nearly 30% are re-infected 3-6 months after treatment

CDC. Sexually Transmitted Disease Surveillance 2017. Atlanta: U.S. Department of Health and Human Services; 2018

Syphilis: The heterosexual epidemic

• During 2013–2017, the P&S syphilis rate among women increased by 155.6%
• During 2013–2017, the number of cases of congenital syphilis doubled (~1000 cases/year)

CDC. Sexually Transmitted Disease Surveillance 2017. Atlanta: U.S. Department of Health and Human Services; 2018
The intersection of epidemics:
Drug use and heterosexual syphilis transmission

CDC. Sexually Transmitted Disease Surveillance 2017. Atlanta: U.S. Department of Health and Human Services; 2018

Congenital syphilis: A failure of public health

https://www.cdc.gov/std/stats17/figures/49.htm
CDC. Sexually Transmitted Disease Surveillance 2017. Atlanta: U.S. Department of Health and Human Services; 2018
The Solution

1. Case finding through serological screening
2. Prompt effective therapy
3. Identification of exposed partners
4. Mandatory serological evaluation of people who may transmit infection to others
5. Public education

So why are we failing?

- Screening rates, even in high-risk populations, are low
- Partner notification has become more challenging
  - The number of patient interviews needed to identify one untreated partner increased from 2 in the 1950s, to 4 to 5 in the 1990s, and 10 in 2003. In some areas, the number of patient interviews needed to identify a new case has been as high as 25

Peterman 2018 Sex Transm Dis; 45(05):565
De Voux 2018 STD Prevention Conference, Washington DC; Pos:272
So why are we failing?

- Lack of resources:
  - Over the last 15 years, STD prevention funding at the CDC has seen a $21 million reduction

Epidemiology: Implications

- Identify people who are at high risk for infection and screen them
  - MSM
  - Men and women who use drugs
- Frequent screening of high-risk persons is critical
  - In some cases, quarterly screening is appropriate
- Women who are pregnant and who have clinical evidence of syphilis should be treated immediately
Management

Part 2
Patient 1

- 46 year old gay man with sudden onset of fluctuating bilateral hearing loss and tinnitus
  - Sensorineural with poor word discrimination
- Diffuse maculopapular rash on trunk sparing palms and soles and patchy alopecia
- Serum CIA reactive; RPR 1:2048
- IV aqueous crystalline penicillin G 4,000,000 units IV q 4 hours + steroids X 10 days
- JH reaction after 1st dose of penicillin
- Complete resolution of symptoms 1 month after therapy

Otosyphilis

- **Diagnostic criteria**: cochleovestibular dysfunction and syphilis infection without an alternate diagnosis; ~50% bilateral
  - Diagnosis is presumptive; CSF examination is normal in 90% of cases
- **Therapy**: IV penicillin (+ corticosteroids)
- **Prognosis**: 23% experience improvement in hearing; up to 80% experience improvement in tinnitus and vertigo
  - Absence of hearing fluctuations, longer duration of symptoms, and age >60 years are poor prognostic indicators

Patient 2

- 58 y/o man R eye pain and redness X 4 days
  - No medical care X 20 years
  - No sex in the past 4 years
  - Right eye: Panuveitis
  - Serum CIA reactive; RPR 1:128
  - CSF examination:
    - VDRL 1:4
    - Lymphocytic pleocytosis

Ocular Syphilis

- **Any part of the eye** can be involved during **any stage** of the infection
- The vast majority of eye problems associated with syphilis are also associated with many other infectious and non-infectious diseases
- **30-40% of persons with ocular syphilis will have a normal CSF examination**
- Reasons for CSF examination:
  - If the CSF VDRL is positive in someone who has eye symptoms, you can make a more definitive diagnosis of ocular syphilis
  - If CSF abnormalities are detected, follow-up CSF examinations may provide objective evidence of response to therapy
  - ? Some have suggested that a CSF examination may help to identify alternate diagnoses
- Treatment: Use the same regimen as neurosyphilis **EVEN IF THE LUMBAR PUNCTURE IS NORMAL.** The use of steroids is controversial
Patient 3

- 48 year old man with a history of Hepatitis C infection and alcohol abuse presents to ED with a pustular rash, decreased PO intake, and nausea
  - Pustular rash on arms, back, and abdomen; no stigmata of chronic liver disease
  - AST 52 U/L; ALT 58 U/L; AP 1260 U/L; t-bilirubin 1.2 mg/dl
  - Serum CIA reactive; RPR 1:128
  - Sent to ultrasound for HCC screening and discharged after PCN therapy
    - 12 cm mass in liver consistent with HCC
    - Follow-up appointment with IR scheduled 1 week later for CT-guided biopsy
    - At follow-up with IR, mass had disappeared

Syphilitic Hepatitis

- Involvement of the liver in late stages of the disease as fibrosis, gumma, and hepar lobatum well documented in the pre-antibiotic era
- Early stage asymptomatic involvement usually as a disproportionately elevated alkaline phosphatase in the setting of secondary syphilis is a more recent observation- but is not universal
  - Clinical: Association with rash and anorectal lesions
  - Histology: pericholangiolar inflammation; mild (proliferation of sinus endothelial cells and Kupffer cells, eosinophils, and lymphocytes) to severe (diffuse necrosis especially in periportal region and central vein)
  - In half of the cases spirochetes were found in the necrotic foci, walls of sinusoids, and in the endothelial cells
- Incidence of LFT abnormalities in both immunocompetent and HIV-infected persons in secondary syphilis noted in up to 38% -but majority are asymptomatic
- Rare occurrence of abscesses in liver

References:
- Int J STD AIDS. 2012;23(8):e4-6
- West J Med. 1978;128(1):64-7
- Int J STD AIDS. 2009;20(4):278-84
Clinical Pearls

- CSF examination should **always** be done if there are neurological and/or ocular signs/symptoms
  - Ask all patients with clinical/serological evidence of syphilis about:
    - Headaches, weakness, gait disturbances
    - Changes in memory or personality
    - Visual changes, flashing lights, floaters, eye pain/redness
    - Decreased hearing, tinnitus (isolated otic symptoms do not require a CSF examination)

- Current CDC recommendations for a CSF examination also include:
  - Patients without neurological signs/symptoms who have tertiary syphilis
  - Patients without neurological signs/symptoms who do not demonstrate a four-fold decline in non-treponemal serological titers following stage-appropriate therapy (and were not re-infected)

The following is NOT a recommendation but a **STATEMENT** that appears in the Guidelines:

- [HIV+ patients with a CD4 count ≤350 cells/ml or RPR titer ≥1:32 are more likely to have CSF abnormalities consistent with neurosyphilis]

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Treatment Recommendations

- **Early syphilis:** Primary, secondary, early latent
  - Benzathine penicillin G 2.4 million units IM in a single dose
  - Alternate: Doxycycline 100mg orally X 14d

- **Late latent/unknown duration**
  - Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals
  - Alternate: Doxycycline 100mg orally X 28d

- **Neurosyphilis, ocular syphilis, or otic syphilis**
  - Aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units IV every 4 hours or continuous infusion, for 10–14 days
  - Alternate: Procaine penicillin G 2.4 million units IM once daily + Probenecid 500 mg orally four times a day, both for 10–14 days
**Treatment Pearls**

- HIV infection status does **not** impact treatment recommendations irrespective of degree of immunosuppression
- If you treat an HIV-infected person with an alternate regimen for syphilis, careful follow-up is necessary
- Only penicillin should be used in pregnant women. No alternates are acceptable. Desensitize if penicillin-allergic
  - If using a 3 dose BPG regimen, no need to re-desensitize as long as the patient follows-up on time for their subsequent doses
- If a person is late for a BPG dose, clinical experience suggests that an interval of 10–14 days between doses of benzathine penicillin for latent syphilis might be acceptable before restarting the sequence of injections (i.e., if dose 1 is given on day 0, dose 2 is administered between days 10 and 14). Pharmacologic considerations suggest that an interval of 7–9 days between doses, if feasible, might be more optimal
  - Delayed doses are not acceptable for pregnant women receiving therapy for latent syphilis. Pregnant women who miss any dose of therapy must repeat the full course of therapy.

*MMWR Recomm Rep. 2015;64(RR-03):1-137*

**Serological tests for syphilis**

- **Nontreponemal tests**
  - VDRL and RPR
    - Should not be used interchangeably
    - Become nonreactive over time even without treatment
- **Treponemal tests**
  - MHA-TP, FTA-ABS, TPPA; CIA, EIA, MFI, ICS
  - Once reactive, always reactive

*Peeling RW, Ye H: Bull WHO 2004;82:439–446*
False-Positive Serological Tests

• Nontreponemal
  ▪ Age
  ▪ Pregnancy (?) [controversial]
  ▪ Other infections (particularly viral)
    • HIV
  ▪ Autoimmune diseases

• Treponemal
  ▪ Other pathogenic treponematoses (yaws, pinta)
  ▪ Non-pathogenic treponemes associated with necrotizing gingivitis and chronic periodontitis*
    ▪ Lyme disease
    ▪ Autoimmune diseases (rare)

*Riviere NEJM 1991: 325:539-43

Serological Testing: The Reverse Sequence Algorithm

Slide courtesy of Dr. Barbara Detrick
Monitoring nontreponemal titers

• 4-fold (i.e. 2 dilution) decline = cure
• 4-fold (i.e. 2 dilution) increase = reinfection or treatment failure
• When a nontreponemal titer does not decline after treatment (“serofast”):
  ▪ Make sure it is not reinfection
  ▪ Make sure the patient does not have signs/symptoms of active disease
  ▪ Repeat the serological titer before you decide to retreat
  ▪ Give it more time (wait a full year after treatment for early syphilis and two years after treatment for late latent infection)
    • Low pre-treatment titers (i.e. <= 1:4) may not decline after treatment- leave them be
    • THEN decide whether retreatment is warranted
  ▪ Have a low threshold to re-treat women who are pregnant

Point-of-Care Diagnostics

• Treponemal tests
  ▪ Trinity Syphilis Health Check is FDA cleared and CLIA waived
• Combined nontreponemal and treponemal tests
• Combined treponemal /HIV tests*

* Not FDA cleared
Novel biomedical interventions

Part 3

Vaccines

Syphilis Vaccine Development: Requirements, Challenges, and Opportunities
Caroline E. Cameron, PhD

ARTICLE

A defined syphilis vaccine candidate inhibits dissemination of Treponema pallidum subspecies pallidum
Karen V. Lithgow1, Rebecca Hopp1, Charmaine Mather1, Drew Phillips1, Simon Houston1
& Caroline E. Cameron1

Sexually Transmitted Infections (STI)
Cooperative Research Centers (CRC): Vaccine Development
RFA-AI-18-005

Johns Hopkins School of Medicine
## Syphilis PrEP & PEP: Doxycycline

### PrEP
- 30 MSM who had syphilis twice or more since their HIV diagnosis randomized to daily DOXY 100 mg or placebo
- F/U at weeks 12, 24, 36, and 48
- Outcomes: CT, NG, TP
  - OR 0.28 (95%CI: 0.09-0.83)

Molina 2018 Lancet Infect Dis; 18: 308–17

Bolan 2015 Sex Transm Dis; 42(2):98-103

### PEP
- 232 MSM in IPERGAY TDF/FTC PrEP Study
- Randomized 1:1: Two 100 mg tablets of DOXY to be taken within 72 hours of condomless sex (on-demand)
- 8.7 months F/U; median 7 pills/month
- HR for any STD: HR 0.53 (95% CI: 0.33-0.85)
  - HR for syphilis: 0.27 (0.07-0.98)
  - HR for CT: 0.30 (0.13-0.70)
  - No benefit for GC

## Syphilis PrEP & PEP with Doxycycline: Pros & Cons

### Pros
- It seems to work
- Relatively safe drug
  - Chronic use in acne vulgaris
- Easy to administer
- Lack of other effective options for prevention
- >80% interest among MSM

Dombrowski et al, personal communication

### Cons
- Limited data
- Costs
- Side effects of doxycycline
  - Esophagitis/ulceration
  - Sunburn
  - Intracranial HTN
- Antibiotic resistance*
- Microbiome effects*
- Risk compensation

*Antibiotic resistance and Microbiome effects are potential concerns related to long-term use of doxycycline, which can alter the normal bacterial balance in the body.

*Risk compensation: This term refers to the possibility that individuals may engage in riskier sexual behaviors due to the perception of being protected, potentially increasing the risk of other sexually transmitted infections (STIs), including syphilis.

JH SOM logo
Summary

- Syphilis rates are increasing—particularly among MSM but now among heterosexuals—with a strong link to drug use
- Limited $ for control
- Serological screening is a **critical** component of our approach to syphilis control: Can we not do better?
- The vaccine is years (decades?) away
- Doxycycline is here, it’s exciting, but it’s immediate implementation is problematic: *Primum non nocere*

“The charm of history and its enigmatic lesson consist in the fact that, from age to age, nothing changes and yet everything is completely different.”

*Aldous Huxley*
Thank you!

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