U025-Sex, Sores, Science, and Surveillance: Syphilis in the 21st Century

Difficult Clinical and Patient Management Issues

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Disclosures

• None
Objectives

• At the end of this presentation, participants should be able to:
  ▪ Recognize some of the less common clinical manifestations of syphilis
  ▪ Assess the impact of HIV co-infection on syphilis management
  ▪ Describe the algorithms for serological testing, limitations of serological tests, and the clinical significance of the serofast state
  ▪ Recognize the limitations of data supporting the recommendations for performing lumbar punctures in persons with syphilis
  ▪ Describe novel syphilis prevention strategies

RJ

• **HPI:** 38 year old HIV+ gay man (CD4 190 cells/mm³; HIV RNA undetectable on ART) with low-grade fevers and a rash for 3 days. He noticed a painless ulcer that appeared on his penis a week earlier and severe rectal pain associated with defecation.

• **PMHx:** (1) PCP
  
  (2) Gonorrhea X3 (pharyngeal X1)

• **Social:** No tobacco; drugs; 3 sex partners in the last 3 months (all HIV+); inconsistent condom use

• **PE:** Diffuse rash and penile ulcer (see next slide); exquisite tenderness on DRE; no lesions noted around the anus or any other mucosal site
Laboratory Results

- Treponemal CIA: **Reactive**
- Serum RPR: **Reactive 1:512**
- Rectal/pharyngeal gonorrhea and chlamydia NAATs negative
- Rectal HSV PCR negative
- LFTs: AST 62 U/L; ALT 78 U/L; **AP 1260 U/L**; total bilirubin 1.2 mg/dl
What is the clinical diagnosis?

- Overlap of primary and secondary stages of syphilis
- Syphilitic hepatitis
- Syphilitic proctitis
Clinical Manifestations of Syphilis

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
Management: Antimicrobial therapy

• What is the optimal treatment regimen for early syphilis?
  ▪ The CDC recommends 2.4 MU of long-acting BPG given intramuscularly X 1
• BUT the patient is HIV-infected with advanced immunosuppression. Does enhanced antimicrobial therapy (i.e. additional doses of BPG) improve outcomes?
  ▪ The available data suggest that enhanced therapy for HIV-infected persons with syphilis does not improve outcomes. As such, the treatment recommendations for syphilis are identical in HIV-infected and uninfected persons
• If this patient were penicillin allergic, what are the options?
  ▪ Doxycycline is an acceptable alternative to treat early (x2w) and late latent (X4w) syphilis; although penicillin is preferred- especially in HIV-infected persons, the available data suggest that doxycycline is an acceptable alternative
  ▪ Azithromycin 2g orally should NOT be used due to high prevalence of macrolide resistance

Management: Need for CSF examination

• Does he need a CSF examination?
  ▪ Controversial question
• Current CDC recommendations for a CSF examination:
  ▪ Patients with neurological signs/symptoms
  ▪ 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]
CSF Examination in Neurologically Asymptomatic HIV+ Persons with Syphilis?

Yes
- HIV+ persons appear to be more susceptible to neurological complications
- In the pre-antibiotic era, asymptomatic neurosyphilis (whether early or late) was a strong predictor of future neurological complications

No
- HIV+ persons are more likely to have non-specific pleocytosis in their CSF
- In the antibiotic era, lack of data to suggest improved outcomes with CSF examination

RJ
- RJ is treated with intramuscular Bicillin 2.4 MU X1. A CSF examination is not performed
  - Signs and symptoms resolve within 14 days
- Follow up serologies:
  - 3m: 1:1024
  - 6m: 1:516
  - 12m: 1:516
  - At the 12m follow-up examination, he is asymptomatic and denies any high-risk exposures (monogamous with boyfriend for past 9 months). Physical examination is normal. CD4 is 448 cells/mm³ and HIV RNA is undetectable on ART
Serologies in Managing Syphilis: The Dilemma

- What do nontreponemal titers really mean in the antibiotic era?
  - 4-fold decline: Cure
  - 4-fold increase: Reinfection/relapse
  - Lack of a four-fold decline in titers following therapy (“serofast state” or “seroresistance”)
  - “High serofast” state

Assumption: changes in nontreponemal antibody titers reflect underlying disease activity

Nontreponemal titers decline more slowly in HIV-infected persons


Seroresistance in the Antibiotic Era

- 82 HIV-negative early syphilis participants in a RCT who were serofast at 6 months were retreated using benzathine penicillin 2.4MU
  - Only 27% exhibited serological response 6m after retreatment
  - None of the participants available for follow-up exhibited symptoms suggestive of neurosyphilis during the study period (i.e. 12m).
- In another study, 74.3% (26/35) of the cases with latent syphilis who failed to achieve serological cure at 12 months after initial therapy were randomized to additional therapy or observation
  - ~80% achieved serological cure in both groups
Management: Need for CSF examination

• Does he need a CSF examination?
  ▪ Based on the CDC recommendations, now he does!

• Current CDC recommendations for a CSF examination:
  ▪ Patients with neurological signs/symptoms
  ▪ 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)

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

RJ

• A CSF examination is normal
• He is given the first dose (day 0) of a planned 3 doses of intramuscular Bicillin regimen. Due to an unforeseen conflict, RJ returns on day 13 (instead of day 7) for his second dose of Bicillin
Would you restart treatment over again?

- If a person misses a dose of penicillin in a course of weekly therapy for latent syphilis, the appropriate course of action is unclear. Clinical experience suggests that an interval of 10–14 days (i.e. if dose 1 is given on day 0, dose 2 is given between days 10 and 14) between doses of benzathine penicillin for late latent syphilis or syphilis of unknown duration might be acceptable before restarting the sequence of injections. Pharmacologic considerations suggest that an interval of 7 to 9 days between doses, if feasible, may be more optimal. Missed doses are not acceptable for pregnant women receiving therapy for late latent syphilis. Pregnant women who miss any dose of therapy must repeat the full course of therapy.

RJ

- Six months after completing the three dose regimen of BPG, RJ returns complaining of increased tearing and decreased vision in his right eye and a rash. He and his boyfriend broke up and he reports several new sexual partners with inconsistent condom use.
- On examination, the rash is very similar to his previous rash. An urgent ophthalmology consult is requested.
Physical Examination

Visual acuity was intact in both eyes and visual field testing revealed no abnormalities.

Constricted pupil which was irregularly shaped.

Hypopyon

Ophthalmological Diagnosis

• Anterior Uveitis
  ▪ inflammation of the middle layer of the eye: iris and the adjacent ciliary body
Laboratory Studies

- Lyme serology: NR
- Urine GC/CT: Negative
- T-Spot: NR
- Syphilis CIA: Reactive
- RPR: 1:2048

CSF Examination
- 22 mononuclear cells/mm³
- VDRL: Reactive 1:2
- Protein 78 mg/dl

RJ

- RJ was treated for early ocular syphilis with 14 days of intravenous penicillin and the concomitant use of topical steroid eye drops
Ocular Syphilis

• Diff Dx of anterior uveitis: **Idiopathic**; **Infectious**: HSV; VZV; TB; **Syphilis**; Lyme
  Malignancy: Lymphoma; Leukemia; Autoimmune: HLA-B27-related (ankylosing spondylitis; Reiter’s; IBD; psoriatic); JRA

• **Every** 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

FYI- 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 bad prognostic indicators
RJ

• Now that RJ is no longer monogamous, should we use doxycycline PEP/PrEP to decrease his risk of incident syphilis infection?
  • Probably not (not yet!)

Neurosyphilis: Questions to Ask

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<thead>
<tr>
<th>SYMPTOMS OF NEUROSYPHILIS</th>
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<td>5) Have you recently been having headaches?</td>
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<tr>
<td>6) Have you had new-onset weakness in any part of your body (including your arms, legs, or face)?</td>
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<td>7) Have you had problems walking?</td>
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<td>8) Have you had problems with memory or confusion?</td>
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<td>9) Do you feel (or have you been told) that your personality has changed?</td>
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Providers should consider evaluation and treatment for neurosyphilis in patients with new-onset of headaches (or headaches that are different from their usual headaches); new and persistent change in personality, memory or judgment; new numbness or weakness in the face, arms or legs; and/or new gait incoordination.
Ocular syphilis: Questions to Ask

<table>
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<tr>
<th>SYMPTOMS OF OCULAR SYPHILIS</th>
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<td>1) Have you recently had a change or blurring in your vision?</td>
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<td>2) Do you see flashing lights?</td>
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<td>3) Do you see spots that move or float by in your field of vision?</td>
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<tr>
<td>4) Have you recently had pain or redness in the eyes?</td>
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Providers should consider evaluation and treatment for ocular syphilis in patients with new changes in vision, including loss of vision, blurring, seeing spots or flashing lights and pain and/or redness in one or both eyes.

Syphilis Control: 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

**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

Bolan et al. Sex Transm Dis. 2015;42(2):98-103
Lancet Infect Dis 2018; 18: 308-17
Syphilis PrEP & PEP: 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

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

Syphilis: Take-Home Messages

• As rates continue to rise, be aware of the less common clinical manifestations of syphilis
• Ask about and assess for neurological/ocular/otic signs and symptoms in every patient with syphilis (no matter the stage of infection)
• Treatment of syphilis is not impacted by HIV status
  ▪ HIV infection may increase the risk for neurological/ocular complications
  ▪ Serological titers may decline more slowly in HIV-infected persons
  ▪ It is unclear whether neurologically asymptomatic persons co-infected with syphilis and HIV benefit from a CSF examination
• The use of doxycycline as PrEP/PEP is not yet recommended
Thank you!

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