Syphilis and Hansen’s Disease

Christine Olson, MD, MPH
Medical Assessment and Policy Team
Immigrant, Refugee, and Migrant Health Branch
Division of Global Migration and Quarantine (DGMQ)
cdcqap@cdc.gov
Learning Objectives

After this session, you should be able to understand:

- New requirements for classification and treatment of syphilis
- Clinical manifestations of and treatment of syphilis
- New requirements for classification and treatment of Hansen’s disease
Overview of Presentation

- **Syphilis**
  - Newly revised Technical Instructions on syphilis
  - Disease background, classification, and treatment

- **Hansen’s disease (Leprosy)**
  - Newly revised Technical Instructions for Hansen’s disease
  - Disease background, classification, and treatment
Syphilis
Syphilis Background

Syphilis is a systemic disease caused by *Treponema pallidum*

Updated Syphilis Technical Instructions

- January 1, 2013
- Key updates
  - Testing
  - Treatment
  - Classification
  - Validity period
Updated Syphilis Technical Instructions Testing

- At panel site laboratory
- At time of visa medical examination
Updated Syphilis Technical Instructions - Treatment

- Follow CDC’s Sexually Transmitted Diseases Treatment Guidelines (2010)

Updated Syphilis Technical Instructions Classification

- **Class A** at time of diagnosis (inadmissible)
- **Class B** after complete treatment at time of visa medical examination, regardless of residual neurologic deficit status
  - Applicants who report history of prior treatment and have normal laboratory results at time of visa medical examination should **not** be classified as Class B
Matches the validity period for the applicant’s tuberculosis classification
Required Physical Examination

- Extensive syphilis is a systemic disease and requires evaluation of
  - External genitalia
  - Oral mucosa
  - Integument
  - Lymph nodes
  - Neurologic system
  - Ophthalmologic system
Syphilis Background: Disease Stages

**Primary Infection**
- Ulcer or chancre at the infection site

**Secondary Infection**
- Manifestations include, but are not limited to, skin rash, mucocutaneous lesions, and lymphadenopathy

**Latent Infection**
- Stage lacks clinical manifestations
- Detected only by serologic testing

**Tertiary Infection**
- Gumma or cardiac lesions
Syphilis Testing

Testing Process (use same sample for initial and confirmatory tests):

≥15 Years of age

Screening tests: VDRL or RPR

Positive

Confirmatory tests: TPPA, MHA-TP, EIA or CIA*

If confirmatory test is positive:

- Class A condition (inadmissible)
- Treatment required before U.S. admission

Negative

No further testing required

Tests must be performed at panel site lab and at the time of the physical examination

* T. pallidum passive particle agglutination (TP-PA) assay, T. pallidum microhaemagglutination assay (MHA-TP), enzyme immunoassays (EIAs) or chemiluminescence immunoassays (CIAs)
Primary and Secondary Syphilis

- Goals of treatment:
  - Heal lesions
  - Prevent transmission
  - Prevent late sequelae

- Benzathine penicillin G 2.4 million units IM in a single dose *UNLESS* neurological findings are present

- CAUTION: Administer:
  - Standard benzathine penicillin product (Bicillin L-A)
  - NOT combination benzathine-procaine penicillin (Bicillin C-R)
Primary and Secondary Syphilis (cont.)

- Signs or symptoms suggesting neurologic syphilis
  - Meningitis and hearing loss, or ophthalmic disease (uveitis, iritis, neuroretinitis, and optic neuritis)
  - Cerebrospinal fluid (CSF) analysis, ocular slit-lamp ophthalmologic and otologic exam required
  - Guide treatment by evaluation results

- In absence of neurologic findings, CSF evaluation not indicated
Latent Syphilis

- Latent = seroreactivity without other evidence of disease

- Patients diagnosed with latent syphilis who demonstrate any of the following criteria should have a prompt CSF examination:
  - Neurologic (e.g., auditory disease, cranial nerve dysfunction, acute or chronic meningitis, stroke, acute or chronic altered mental status, and loss of vibration sense) or ophthalmic signs or symptoms
  - Evidence of active tertiary syphilis (e.g., aortitis, gumma)
  - Serologic treatment failure
Early Latent Syphilis

- Latent syphilis acquired in preceding year
- Must review titer, symptoms, and history to confirm early latent syphilis
- To evaluate for internal mucosal lesions and exclude primary syphilis, examine
  - Oral cavity, perianal area, perineum
  - Underneath the foreskin in uncircumcised men
- Goal of treatment is to prevent complications
- Benzathine penicillin G 2.4 million units IM, single dose
Late Latent Syphilis or Latent Syphilis of Unknown Duration

- Asymptomatic individuals with seroreactivity and no other evidence of disease
- Acquired more than one year ago (or unknown)
- Treat with Benzathine penicillin G 7.2 million units total
  - 3 doses of 2.4 million units IM each
  - 1-week intervals
Tertiary Syphilis

- Gumma or cardiovascular syphilis but not all neurosyphilis

- Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals

- If symptomatic late syphilis, CSF examination required before therapy initiated to evaluate for neurosyphilis
  - Some providers treat all individuals who have cardiovascular syphilis with a neurosyphilis regimen
  - Manage with an infectious disease specialist
Neurosyphilis

- Can occur during any stage of syphilis

- A CSF examination should be performed if clinical evidence of neurologic involvement is observed
  - Cognitive dysfunction
  - Motor or sensory deficits
  - Ophthalmic or auditory symptoms
  - Cranial nerve palsies
  - Symptoms or signs of meningitis

- Treatment
  - Aqueous crystalline penicillin G IV for 10-14 days OR
  - Consider 2-drug IM and PO treatment if adherence can be assured
# Treatment of Different Stages of Syphilis

<table>
<thead>
<tr>
<th>Stage of syphilis</th>
<th>Recommended treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary or secondary</td>
<td>Benzathine penicillin G 2.4 million units IM in a single dose</td>
</tr>
<tr>
<td>Early latent</td>
<td>Benzathine penicillin G 2.4 million units IM, single dose</td>
</tr>
<tr>
<td>Late latent</td>
<td>Benzathine penicillin G 7.2 million units total 3 doses of 2.4 million units IM each At 1-week intervals</td>
</tr>
<tr>
<td>Tertiary</td>
<td>Benzathine penicillin G 7.2 million units total 3 doses of 2.4 million units IM each At 1-week intervals</td>
</tr>
<tr>
<td>Neurosyphilis</td>
<td>Aqueous crystalline penicillin G IV for 10-14 days</td>
</tr>
</tbody>
</table>
Syphilis: Special Considerations
Syphilitic Eye Disease

- Uveitis, neuroretinitis, and optic neuritis
- A CSF examination should be performed to evaluate for pre-treatment abnormalities
- Requires neurosyphilis treatment regimen
- Requires follow-up CSF examinations to assess treatment response
- Manage in collaboration with an ophthalmologist
Syphilis Treatment for Special Groups

- Refer to CDC Sexually Transmitted Diseases Guidelines at: http://www.cdc.gov/std/treatment/

- Guidelines provides details on:
  - Alternative drug regimens
  - Treatment of:
    - HIV-infected persons
    - Pregnant women
    - Infants and children (work-up and treatment)
    - Persons with medication allergies
    - Complicated infections
Alternative Drug Regimens for Penicillin-Allergic Individuals

- Primary or secondary syphilis
  - Doxycycline 100 mg orally 2x/day for 14 days or
  - Tetracycline 500 mg 4x/day for 14 days

- Late latent or latent syphilis of unknown duration
  - Doxycycline 100 mg orally 2x/day for 28 days or
  - Tetracycline 500 mg orally 4x/day for 28 days

- Close follow-up of individuals receiving alternative therapies is essential

- Alternative regimens should only to be used for patients with a medical contraindication to penicillin
Penicillin Allergy Management

- No proven alternatives to penicillin for:
  - Neurosyphilis
  - Congenital syphilis
  - Syphilis in pregnant women

- Penicillin recommended for HIV-infected individuals

- Management of penicillin allergy
  - Alternative regimens inappropriate for above groups and for individuals whose compliance with therapy or follow-up cannot be ensured
  - Penicillin skin test if available
  - If positive skin test, desensitize in hospital setting (usually 4-12 hours)
Applicant Follow-Up Post-Treatment

- After treatment, applicants should be advised to follow up with a healthcare provider for clinical and serologic re-evaluation in 6 months
  - 2-3 months for infants
  - During third trimester for pregnant applicants
  - 3 months for HIV-infected persons with 1º or 2º syphilis
  - After initial treatment, need for follow-up does NOT prevent medical clearance by panel physician

- If titers do not decline appropriately, consider HIV infection
Jarisch-Herxheimer Reaction – Adverse Reaction to Treatment

- An acute febrile reaction frequently accompanied by
  - Headache, myalgia, and fever
  - Usually occurs within the first 24 hours after initiation of any syphilis therapy

- Occurs most frequently in early syphilis, presumably because of higher bacterial burdens

- Patients, especially pregnant patients, should be informed about this possible adverse reaction
No treatment → Class A (Inadmissible)

Treatment → Class B (WITH OR WITHOUT residual disability: note change with new TI)
Hansen’s Disease

Prepared with contributions by Barbara M. Stryjewska, MD and David Scollard, MD of the National Hansen’s Disease Center, and images from A. Colin McDougall’s A New Atlas Of Leprosy
Updated Hansen’s Disease (HD) Technical Instructions

- January 1, 2013
- Key updates
  - Treatment
  - Classification
  - Validity period
Updated HD Technical Instructions
Treatment

- Length of treatment required for reclassification from Class A to Class B has **changed** from 6 months to 1 week.
- Must follow WHO treatment guidelines
  - Except: applicants with a single skin lesion should be treated with full 6 months of paucibacillary regimen.
- Provide 60-day supply of medication for use during relocation.
- Provide affected applicant with printed patient information about U.S. National Hansen’s Disease Program services.
Updated HD Technical Instructions

Classification

- Both multibacillary and paucibacillary HD are Class A
Updated HD Technical Instructions
Validity Period

- Matches the validity period for the applicant’s tuberculosis classification
Hansen’s Disease

- Bacterial infection with *Mycobacterium leprae*
  - Multiplies very slowly
  - Organism has never been grown in bacteriologic media or cell culture
  - Has been grown in mouse foot pads

- Mainly affects
  - Skin
  - Peripheral nerves
  - Eyes
  - Mucosa of the upper respiratory tract

- Early diagnosis and treatment prevents nerve involvement, without which Hansen’s disease is a minor skin disease

- Clinical manifestations of Hansen’s disease depend on host resistance
Hansen’s Disease

- Epidemiology (2011, WHO)
  - 192,246 new cases detected worldwide
  - Pockets of high endemicity remain in Angola, Brazil, Central African Republic, D. R. Congo, India, Madagascar, Mozambique, Nepal, and Tanzania

- United States
  - Average 130 cases per year
  - 75% in foreign-born persons from endemic areas
  - 25% in U.S.-born persons
    - Texas, Louisiana, Hawaii
Hansen’s Disease

Transmission

- Low communicability
- Mode of transmission unknown, likely respiratory in many cases
- Not easily transmitted to another person
- Nearly 95% of world’s population naturally immune
- Isolation procedures not necessary
- Clinical manifestations of Hansen’s disease depend on host resistance
Hansen’s Disease: Diagnosis

- Suggestive clinical presentation
  - Skin lesions that do not resolve with treatment
    - Flat, raised, or nodular
    - Pale to dark red color
    - Cooler parts of body (legs, arms, ears, and nose)
  - Loss of/diminished sensation in lesion
    - Use cotton wool and pin prick
  - Decreased sweating in lesion
  - Eye findings
  - Patient from endemic area

- Lab: no definitive laboratory markers; punch biopsy or skin smears may be helpful, but are not required
Disease Categories

- **Multibacillary (skin smears show bacilli)**
  - 6 or more lesions
  - Lepromatous
  - Borderline lepromatous
  - Midborderline

- **Paucibacillary (no bacilli in skin smears)**
  - 1-5 lesions
  - Borderline tuberculoid
  - Tuberculoid
  - Indeterminate
Approach to Differential Diagnosis

- History---length of time lesion present
- Lesion characteristics
  - Sensation
  - Ability to sweat
- Presence or absence of other symptoms, (e.g. itching)
- Response to treatment
- Presence of other signs to suggest Hansen’s
  - Palpable enlarged peripheral nerves
Hansen’s Disease
Cardinal Signs and Symptoms

- Hypoesthetic skin lesions
- Enlarged, palpable nerves
  - Greater auricular, median, radial cutaneous, ulnar, peroneal, posterior tibial
- Loss of eyebrows and eyelashes
- Painless wounds or burns
- Inflammatory eye changes

Source: A New Atlas of Leprosy
Multibacillary (Lepromatous)
Nature of Skin Lesions

- Many (6 or more)
- Small symmetrical
- Vague edge (inverted saucer)
- Smooth surface
- Sensation variable
- Tend to coalesce

Annular, “punched-out” lesions

Multiple, small, coalescing lesions

Source: A New Atlas of Leprosy
Paucibacillary (Tuberculoid) Nature of Skin Lesions

- Less than 6 lesions
- Asymmetrical
- Larger
- Definite edge
- Rough and scaly
- Usually anesthetic

Source: A New Atlas of Leprosy
## Hansen’s Disease Treatment

- Multi-drug treatment (MDT) critical (single-drug treatment results in resistance)
- MDT free of charge since 1995 through WHO

<table>
<thead>
<tr>
<th>Multibacillary</th>
<th>Paucibacillary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medications:</strong></td>
<td><strong>Medications:</strong></td>
</tr>
<tr>
<td>Rifampin, Clofazimine, Dapsone*</td>
<td>Rifampin, Dapsone*</td>
</tr>
<tr>
<td><strong>After 3-drug treatment for 7 days:</strong></td>
<td><strong>After 2-drug treatment for 7 days:</strong></td>
</tr>
<tr>
<td>- Change to Class B</td>
<td>- Change to Class B</td>
</tr>
<tr>
<td>- Eligible to travel to U.S.</td>
<td>- Eligible to travel to U.S.</td>
</tr>
</tbody>
</table>

*Minocycline may be substituted for dapsone-intolerance. Consult in-country Hansen’s disease treatment specialist or U.S. National Hansen’s Disease Program for alternative anti-microbial regimens if necessary or for pediatric cases.
References

- **2013 Technical Instructions**

- **World Health Organization**
  - www.who.int/lep/en/

- **National Hansen’s Disease Program**
  - http://www.hrsa.gov/hansensdisease/

- **Infolep Leprosy Information Services**
  - A.C. McDougall: A New Atlas of Leprosy
  - http://infolep.scoolaid.net/bin/home
Thank You Questions?

For more information please contact Centers for Disease Control and Prevention
1600 Clifton Road NE, Atlanta, GA 30333
Telephone, 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
E-mail: cdcinfo@cdc.gov  Web: www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

National Center for Emerging and Zoonotic Infectious Diseases
Division of Global Migration and Quarantine