

Stand By

You will hear silence until the presentation begins

- The HIV/STD/TB/Hepatitis Program in the Division of Disease Control conducts Lunch and Learn Webinars for health-care professionals.

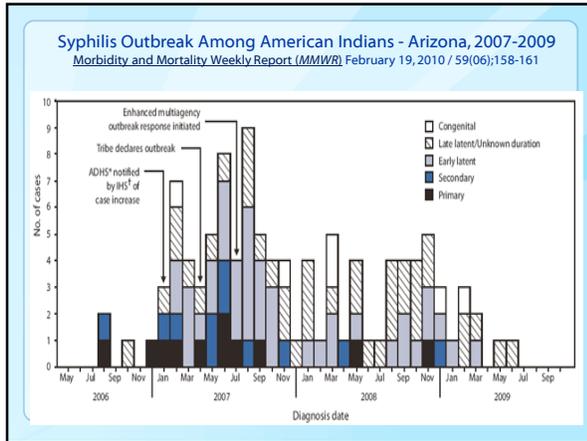
- Each month a new topic will be held from 12:00 p.m. to 1:00 p.m. CST on the fourth Wednesday of the month.

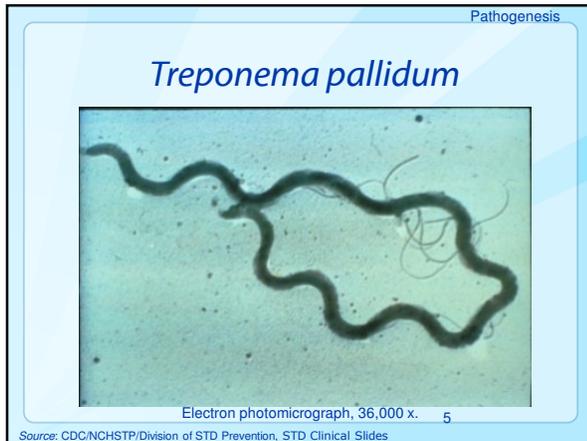
- Nursing education credits will be available for these presentations. Registration and schedule of topics are available at: <http://www.ndhealth.gov/HIV/events.htm>.

Syphilis Clinical Update

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Pathogenesis

Microbiology

- Etiologic agent: *Treponema pallidum*, subspecies *pallidum*
 - Corkscrew-shaped, motile microaerophilic bacterium
 - Cannot be cultured in vitro
 - Cannot be viewed by normal light microscopy

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Pathogenesis

Treponema pallidum on darkfield microscopy



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Source: CDC/NCHSTP/Division of STD Prevention, STD Clinical Slides

Syphilis

- Divided into stages:
 - Primary
 - Secondary
 - Latent
 - Early latent (< 1 year)
 - Late Latent (>1 year)
 - Tertiary

Pathogenesis

Pathology

- **Penetration:**
 - *T. pallidum* enters the body via skin and mucous membranes through abrasions during sexual contact
 - Transmitted transplacentally from mother to fetus during pregnancy
- **Dissemination:**
 - Travels via the lymphatic system to regional lymph nodes and then throughout the body via the blood stream
 - Invasion of the CNS can occur during any stage of syphilis

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Transmission

- Vaginal sex
- Anal sex
- Oral sex
- Digital contact with infectious lesions (rare)
- Vertical transmission from mother to infant
- Blood transfusion, needle sharing (rare)

Primary/Secondary Syphilis

- **Primary:** Characterized one or more painless chancres or ulcers at the site of infection developing 1-3 weeks after exposure
- **Secondary:** Characterized by skin rash, mucocutaneous lesions, lymphadenopathy, occurring 1-3 months after exposure

Clinical Manifestations

Primary Syphilis

- Primary lesion or "chancre" develops at the site of inoculation
- **Chancre:**
 - Progresses from macule to papule to ulcer
 - Typically painless, indurated, and has a clean base
 - Highly infectious
 - Heals spontaneously within 1 to 6 weeks
 - 25% present with multiple lesions
- Regional lymphadenopathy: classically rubbery, painless, bilateral
- **Serologic tests for syphilis may not be positive during early primary syphilis**

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Primary Syphilis Chancres



Primary Chancre on Glans



Vaginal Chancre



Labial Chancere "Kissing"



Primary Chancre





Primary Chancre of the Buttocks



Primary Chancre of the Lip



Primary Chancre of the Eyelid

Anal Chancere



Clinical Manifestations

Secondary Syphilis

- Secondary lesions occur 3 to 6 weeks after the primary chancre appears; may persist for weeks to months
- Primary and secondary stages may overlap
- Mucocutaneous lesions most common
- Manifestations:
 - Rash (75%-100%)
 - Lymphadenopathy (50%-86%)
 - Malaise
 - Mucous patches (6%-30%)
 - Condylomata lata (10%-20%)
 - Alopecia (5%)
- Serologic tests are usually highest in titer during this stage

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Secondary Skin Lesions



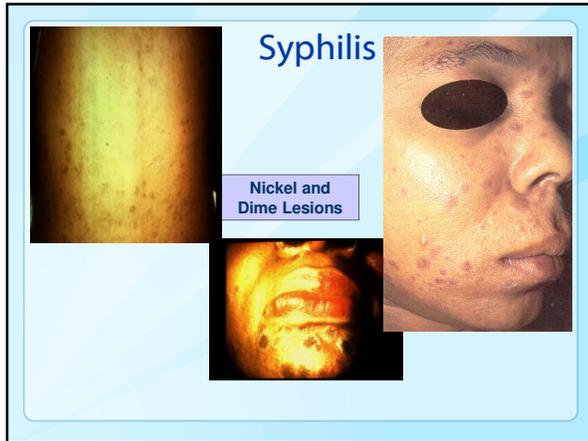
Disseminated Syphilitic Rash

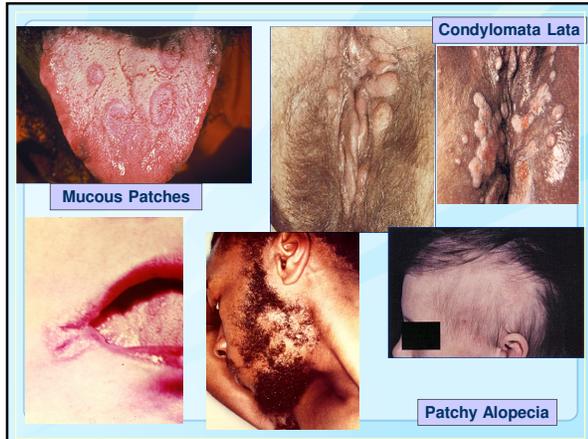


Condyloma Lata









Diagnosis

Physical Examination

- Oral cavity
- Lymph nodes
- Skin of torso
- Palms and soles
- Genitalia and perianal area
- Neurologic examination

Clinical Manifestations

Latent Syphilis

- Host suppresses infection-no lesions are clinically apparent
- Only evidence is positive serologic test
- May occur between primary and secondary stages, between secondary relapses, and after secondary stage
- Categories:
 - **Early latent:** <1 year duration
 - **Late latent:** ≥1 year duration

Latent Syphilis

- Asymptomatic
- **Early latent** if infection was acquired within the preceding year.
- Late latent (or “unknown latency”) if infection acquired more than one year ago or at an unknown time.

Tertiary Syphilis

- Cardiac abnormalities
- Ophthalmic abnormalities
- Gummatous lesions
- Auditory abnormalities

Non-treponemal Tests (Screen)

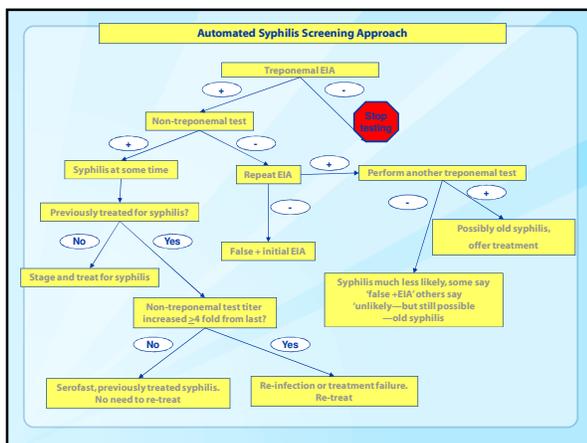
RPR and VDRL

- Fourfold change in titer (ie 1:4 to 1:16) indicates a clinical difference or treatment response
- Cannot compare RPR and VDRL
- Can remain positive after treatment
- False positives occur due to other clinical conditions
- False negative due to prozone in early infection

Treponemal Testing

FTA-ABS and TP-PA

- Required confirmatory test
- Generally remain positive for life (15-25% revert to seronegative)
- Cannot be used to gauge clinical response



Diagnosis

Sensitivity of Serological Tests in Untreated Syphilis

Stage of Disease (Percent Positive [Range])

Test	Primary	Secondary	Latent	Tertiary
VDRL	78 (74-87)	100	95 (88-100)	71 (37-94)
RPR	86 (77-99)	100	98 (95-100)	73
FTA-ABS*	84 (70-100)	100	100	96
Treponemal Agglutination*	76 (69-90)	100	97 (97-100)	94
EIA	93	100	100	

*FTA-ABS and TP-PA are generally considered equally sensitive in the primary stage of disease.

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Diagnosis

Causes of False-Positive Reactions in Serologic Tests for Syphilis

Disease	RPR/VDRL	FTA-ABS	TP-PA
Age		Yes	
Autoimmune Diseases	Yes	Yes	
Cardiovascular Disease		Yes	Yes
Dermatologic Diseases	Yes	Yes	--
Drug Abuse	Yes	Yes	
Febrile Illness	Yes		
Glucosamine/chondroitin sulfate		Possibly	
Leprosy	Yes	No	--
Lyme disease		Yes	
Malaria	Yes	No	
Pinta, Yaws	Yes	Yes	Yes
Pregnancy	Yes*		
Recent Immunizations	Yes	--	--
STD other than Syphilis		Yes	

*May cause increase in titer in women previously successfully treated for syphilis

Source: Syphilis Reference Guide, CDC/National Center for Infectious Diseases, 2002

Treatment of Primary, Secondary and Early Latent

**Benzathine penicillin G:
2.4 million units IM x 1 dose**

- Alternatives:
- Doxycycline 100mg PO BID x 2 weeks OR
- Tetracycline 500 mg PO QID x 2 weeks OR
- Ceftriaxone 1 gm IM/IV QD x 8-10 days

(2010 CDC Treatment Guidelines)

Treatment of Late Latent and Unknown Duration

Benzathine Penicillin G:

- 2.4 million units IM x 3 doses spaced one week apart (Total 7.2 million units)
- Alternatives:
- Doxycycline 100mg PO BID x 4 weeks OR (2006 CDC Treatment Guidelines)

Jarish Herxheimer Reaction

- Acute febrile reaction occurring after treatment with PCN
- May occur at any stage
 - Most common during early syphilis
- May cause exacerbation of primary & secondary symptoms

Penicillin Allergy

- Important in relation to treatment of pregnant women or HIV infection
- True penicillin allergy is not common
- Allergy skin testing/desensitization is required

***Desensitization is not permanent

Case : Jeff



- Malaise, truncal and palmar rash for two weeks
- On exam, maculopapular rash on abdomen chest, palms and soles of feet.
- What diagnostic tests should be performed?
- What treatment should he receive?

Case : Male with rash



Test Results



- ❑ RPR positive 1:512
- ❑ TP-PA Positive
- ❑ HIV negative
- ❑ Treatment with Benzathine PCN provided on the day of testing.
- ❑ His case is reported to the public health department to initiate partner elicitation and referral
- ❑ What additional followup is needed?
 - Repeat RPR 6, 12 months to assess treatment response

Management

Follow-Up

- **Primary or secondary syphilis**
 - Re-examine at 6 and 12 months
 - Follow-up titers should be compared to the maximum or baseline nontreponemal titer obtained on day of treatment.
- **Latent syphilis**
 - Re-examine at 6, 12, 18, and 24 months
- **HIV-infected patients**
 - 3, 6, 9, and 12 months for primary or secondary syphilis
 - 6, 12, 18, and 24 months for latent syphilis
- **Neurosyphilis**
 - Serologic testing as above
 - Repeat CSF examination at 6-month intervals until normal

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Management

Treatment Failure

- Indications of probable treatment failure or possible reinfection include:
 - Persistent or recurring clinical signs or symptoms
 - Sustained 4-fold increase in titer
 - Titer fails to show a 4-fold decrease within 6-12 months
- Retreat and re-evaluate for HIV infection
- Some specialists recommend CSF examination

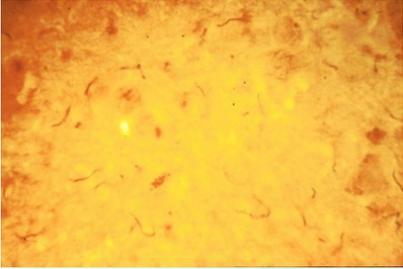
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Neurosyphilis

- **Can occur at any stage**
- Meningitis type symptoms common with cranial nerve palsies
- Positive CSF VDRL is diagnostic if non-bloody tap
- CSF leukocyte count is elevated >5 WBCs/mm
- Consider FTA-ABS on CSF (high sensitivity)

Clinical Manifestations

Neurosyphilis - Spirochetes in Neural Tissue



Silver stain, 950x

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Source: CDC/ NCHSTP/ Division of STD Prevention, STD Clinical Slides

Indications for Lumbar Puncture

- Any patient with reactive syphilis serology and neurologic symptoms (including visual)
- Late latent (>1 year duration) or syphilis of unknown duration in a patient with HIV
- Treatment failure in non-neurologic syphilis
- Active tertiary syphilis

Treatment of Neurosyphilis

- 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
- (2010 CDC Treatment Guidelines)

Diagnosis

Effect of HIV Infection on Syphilis

- Syphilis and HIV infections commonly coexist.
- Clinical course is similar to non-HIV-infected patients.
- Serological tests are usually equivalent in sensitivity in HIV-infected and non-infected persons.
- Conventional therapy is usually effective.
- HIV-infected patients may be more likely to present with symptomatic neurosyphilis.

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Risks for HIV Transmission

- Persons with a genital ulcer disease are at 2-5 times greater risk for HIV acquisition
- HIV-infected persons are more likely to transmit HIV if co-infected with a genital ulcer disease
- Integrated testing is recommended

Prevention

Management of Sex Partners

- For sex partners of patients with syphilis in any stage:
 - Draw syphilis serology
 - Perform physical exam
- For sex partners of patients with primary, secondary, or early latent syphilis
 - Treat presumptively as for early syphilis at the time of examination, unless:
 - The nontreponemal test result is known and negative AND
 - The last sexual contact with the patient is > 90 days prior to examination.

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Prevention

Reporting

- Laws and regulations in all states require that persons diagnosed with syphilis are reported to public health authorities . Reporting can be provider or laboratory based.
- The follow-up of patients with early syphilis is a public health priority.

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Every baby is a



Help your patients protect theirs.
Remember to test all expectant mothers for syphilis.

Syphilis in Pregnancy

- **Transmission rate by stage of maternal infection:**
 - Primary: 70-100%
 - Secondary: 90%-100%
 - Latent: 10-30%
- **Outcome in untreated early syphilis:**
 - 25% intrauterine death
 - 25% perinatal death
 - 50% congenital syphilis (50% asymptomatic)

Congenital Syphilis

- Infection can be transmitted to the fetus through placenta or by contact with infectious lesion at delivery
- *T. pallidum* is able to invade the fetal compartment at any time during gestation
- Risk of prematurity, perinatal death and congenital infection directly related to maternal stage of syphilis during pregnancy

Congenital Syphilis Case Definition

- Syphilitic stillbirth
 - (≥ 20 wks or ≥ 500 grams)
- Confirmed cases
 - Tissue/lab confirmed
- Presumptive cases

Delivery Outcomes

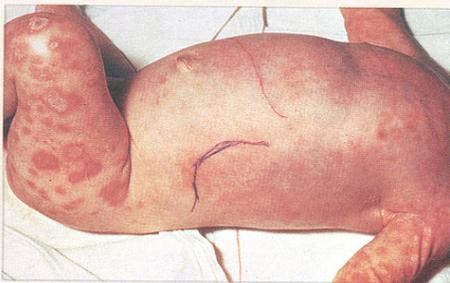
- Asymptomatic
- Stillborn
- Low birth weight (IUGR)
- Premature delivery
- Birth defects
- Non-immune hydrops fetalis
- Spontaneous abortion

Early Congenital Syphilis Signs and Symptoms

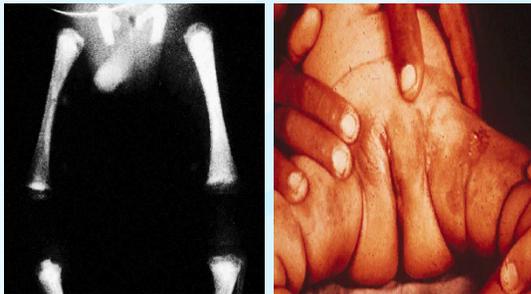
- Skin lesions
- Mucous membrane lesions
- Long bone abnormalities
- Anemia
- Hepatosplenomegaly
- Central nervous system
- Rhinitis (rare)

Congenital Syphilis

(Hepatosplenomegaly & skin lesions)



Congenital Syphilis



Infant evaluation should include the following:

- CSF VDRL, cell count and protein
- CBC
- Long bone x-ray

Case 1: 19 year old female

- Was called by the health department and told to report to your clinic for testing and treatment
- Partner of high-risk MSM case
- Single painless vaginal lesion on exam
- Urine pregnancy test positive
- Penicillin allergic

Case 1: Management Considerations

- 70%-100% likelihood of transmission to infant during maternal primary stage.
- Presumptive treatment with 2.4 MU of benzathine penicillin is needed.
- She reports her allergy to PCN as hives and difficulty breathing.
- What is the next management step?

Pregnant Woman with Primary Syphilis and Penicillin Allergy

- What is the next step in management?
 - A. Penicillin desensitization, followed by immediate treatment with 2.4 MU BZN PCN
 - B. Same day treatment with 2.4 MU BZN PCN IM in clinic
 - C. Hospitalization and PCN challenge with IV aqueous PCN
 - D. Referral to immunologist for allergy testing and documentation of true PCN allergy

Treatment of Pregnant Women with Syphilis

- Penicillin is the only recommended treatment
 - No other proven alternative
- Desensitization is standard of care for those that are penicillin allergic
- Treatment is the same as for non-pregnant
 - Some experts recommend giving two shots of benzathine penicillin to women with early syphilis
- Jarisch-Herxheimer reaction may cause premature labor or fetal distress

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

Penicillin Desensitization

Oral Desensitization Protocol for Patients with a Positive Skin Test*

Observation period: 30 minutes before parenteral administration of penicillin Interval between doses: 15 minutes Cumulative dose: 1.3 million units

Penicillin V Suspension Dose*	Amount [†] (units/mL)	mL	Units	Cumulative Dose (units)
1	1,000	0.1	100	100
2	1,000	0.2	200	300
3	1,000	0.4	400	700
4	1,000	0.8	800	1,500
5	1,000	1.6	1,600	3,100
6	1,000	3.2	3,200	6,300
7	1,000	6.4	6,400	12,700
8	10,000	1.2	12,000	24,700
9	10,000	2.4	24,000	48,700
10	10,000	4.8	48,000	96,700
11	80,000	1.0	80,000	176,700
12	80,000	2.0	160,000	336,700
13	80,000	4.0	320,000	656,700
14	80,000	8.0	640,000	1,296,700

* Exposed time is 2 hours and 45 minutes.
[†] The specific amount of drug administered is approximately 30 mL of water and then administered orally.

* Reprinted with permission from the New England Journal of Medicine.
 SOURCE: Hwang GJ, et al. Skin Test Assays for Penicillin Allergy and Desensitization in Serious Infections During Pregnancy. *New England Journal of Medicine* 1982; 312: 1228-324

Case 1: Management Considerations

- Following desensitization, she receives 2.4 MU benzathine penicillin
 - Initial RPR 1:256
 - She returns for follow-up 3 months later; now 22 weeks gestation
 - RPR titer is 1:256
 - Reports two new sexual partners
- What are the management considerations?

Case 2: Management Considerations

- Inadequate titer response
- Possible re-exposure, re-infection or treatment failure
- Does she need repeat treatment with benzathine penicillin?
- Does she need repeat desensitization?

Case 1: Delivery

- Re-treatment (2.4 MU PCN) at 23 weeks
- Delivers a live-born infant at 26 weeks
- The infant's RPR is 1:32
- Long bones are normal
- Infant's CSF VDRL is positive with a titer of 1:8
- What is the recommended management?

Infant with CSF VDRL titer of 1:8

- What should be included in the management of this infant?
 - A. Benzathine penicillin 50,000 units/kg IM in a single dose
 - B. Benzathine penicillin 2.4 MU IM single dose
 - C. Aqueous crystalline penicillin G 100,000-150,000 units/kg/day for 10 days.
 - D. Retest mother, if RPR equal or less than infants RPR titer of 1:32, no treatment needed

Prevention Recommendations

- Test mother for syphilis
 - First prenatal visit
 - During third trimester
 - At delivery (cord blood)
- Treatment history of sex partners
- HIV testing

Infants Requiring Treatment

- **Infants born to mothers who:**
 - Had untreated syphilis at delivery
 - Had serologic evidence of relapse or re-infection
 - Were treated with erythromycin or other non-penicillin regimen during pregnancy
 - Treated \leq 4 weeks before delivery
 - Poor or no documentation of treatment history
 - Adequately treated during pregnancy, but titer did not decrease at least 2 dilutions (4-fold)
 - Adequately treated, but insufficient follow-up with repeat testing

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For more information please contact Centers for Disease Control and Prevention

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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 HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Division of STD Prevention 

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