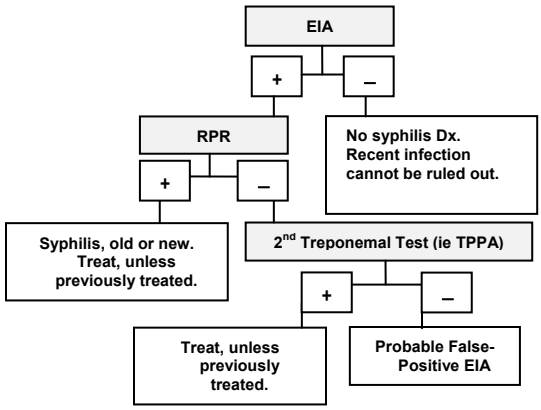
Syphilis is a complex STD with a highly variable clinical course. Cases were first described in the 1490s. The causative organism is a spirochete, *Treponema pallidum*. Evaluation for possible syphilis should include History→Past history of syphilis? Sexual contact of early case (1°/2°/Early Latent)? Typical signs/Sx in past yr? Exam→Check oral cavity, full skin, lymph nodes, genitals, perianal, pelvic - females, abdomen for liver tenderness, neurologic exam focusing on cranial nerves including II optic, III oculomotor, VI abducens, VII facial, and VIII auditory. Laboratory→Confirm + / reactive serology with a 2nd test.

INTERPRETATION OF 4 POSSIBLE SEROLOGY SCENARIOS [4,5]

Serum *Non*-treponemal Test (RPR)	Serum *Treponemal* Test (TPPA, or EIA IgG or IgG/IgM) –	Serum *Treponemal* Test (TPPA, or EIA IgG or IgG/IgM) +
–	➢ **No syphilis** ➢ **Incubating syphilis:** Incubation period 10-90 days; average 21 days. ➢ **Very early Primary Syphilis** (chancre): Repeat serology in 2-4 weeks.	➢ **Very early Primary Syphilis** (chancre): Repeat 2-4 wks. ➢ **Secondary Syphilis with 'prozone phenomenon'**: Rarely, very high antibody levels yield a spurious RPR–. Ask lab to 'R/O prozone' and they will dilute serum further. ➢ **Treated syphilis**: RPR can become negative after adequate Tx; more common if treated during earlier stage. ➢ **Late untreated syphilis with sero-reversal of RPR:** ~25% with late syphilis are RPR–, even in absence of Tx.
+	**Biologic False Positive:** Lupus, viral hepatitis, pneumonia, Lyme disease, HIV/AIDS, pregnancy, old age, IV drug use, etc. Titers usually ≤1:8.	➢ **Syphilis:** May represent old or new syphilis. ➢ **Late untreated syphilis:** Many people with untreated late syphilis will have a reactive RPR. ➢ **Old treated syphilis:** Even with adequate treatment, some have peristent low titers ('serofast'). The serofast state is more common if treatment occurred at later stage.

KEY: + = REACTIVE , – = NON-REACTIVE. R/O = Rule Out. RPR = Rapid Plasma Reagin (non-treponemal antibody test). TPPA = Treponema Pallidum Particle Agglutination, EIA=Enzyme ImmunoAssay (both TPPA and EIA are treponemal antibody tests.)

USING TREPONEMAL EIA (IgG or IgG/IgM) FOR INITIAL SYPHILIS SCREENING [4,5,6]



OVERVIEW OF SYPHILIS STAGES, TREATMENT (Tx), AND PARTNER MANAGEMENT [2,3,5,7]

Stage‡	Possible Signs (Sx) and Symptoms	Probable Exposure Date	Considered Infectious Sexually ∞	In Utero Transfer Possible	Patient (pt) Tx (See p.3 for alternate treatment regimens.)	At-Risk Sex Partners and Recommended Partner Treatment (See p.3 for alternate treatment regimens.)
Primary / 1°	1° Sx occur after 10-90 day incubation period (avg. 21 days): Usually a single chancre (painless ulcer with firm edges) on genitals, anus, cervix, or lips/oral area. Non-tender, firm regional lymphadenopathy.	Within past 3 mos	Yes.	Yes	Bicillin ® L-A (Long-Acting) / Benzathine PCN G: 2.4 million units IM x1	At risk: Partners in past 3 mos. **Treat all partners in past 3 mo with Bicillin® L-A x1.†**
Secondary / 2°	2° Sx occur ~1.5 - 4.5 mos after infection: Rash in ~90%: diffuse or focal, palms/soles in >50%, non-itchy, papular-macular-squamous, faint to coppery. Flu-like Sx. Patchy alopecia. Anogenital or oral *mucous patches* (eroded mucous membranes) or *condyloma lata* (moist, wart-like growths).	Within past 6 mos	Yes.	Yes	Bicillin ® L-A / Benzathine PCN G: 2.4 million units IM x1	At risk: Partners in past 6 mos. **Treat all partners in past 3 mo with Bicillin® L-A x1†**; others if serology results not available right away and F/U uncertain.
Early Latent	Asymptomatic. *(However, if untreated, can relapse to 2° stage during the 1st year of infection.)*	Within past 12 mos	Possibly. *(Considered infectious if relapses to 2° stage).*	Yes	Bicillin ® L-A / Benzathine PCN G: 2.4 million units IM x1	At risk: Partners in past 12 mos. **Treat all partners in past 3 mo with Bicillin® L-A x1†**; others if serology results not available right away and F/U uncertain.
Late Latent	Asymptomatic.	>12 mos ago	No.	Yes	Bicillin ® L-A / Benzathine PCN G: 2.4 million units IM x3 (1 dose/wk x3 wks)	At risk: Evaluate long-term partners; consider also children born in past few yrs to R/O congenital infection. Treat: Based on clinical and serology findings; if indicated, recommended treatment would be Bicillin® L-A x3.
Latent / Unknown Duration	Asymptomatic.	Uncertain. *(If titer ≥1:32, recent infection is more likely, ie within the past 12 mos.)*	Possibly. *(If pt was infected within the past 12 mos, can relapse to 2° stage if untreated).*	Yes	Bicillin® L-A / Benzathine PCN G: 2.4 million units IM x3 (1 dose/wk x3 wks)	**If Pt Titer ≥1:32: ⊒** At risk: Partners in past 12 mos. **Treat all partners in past 3 mo with Bicillin® L-A x1†**; others if serology results not available right away and F/U uncertain. **If Pt Titer ≤1:16:** At risk: Evaluate long-term partners; consider also children born in past few yrs to R/O congenital. Treat: Based on clinical & serology findings; if indicated, treatment would be Bicillin® L-A x3.

‡Tertiary Syphilis is much less common with widespread antibiotic use; for more info, see References. Neurosyphilis can occur at any stage; risk is greater if HIV co-infected.
∞Syphilis also facilitates HIV transmission and acquisition. An HIV+ pt with syphilis is 2-9x more likely to *transmit* the HIV. An HIV– pt with syphilis is 2-4x more likely to *acquire* HIV.
†Presumptively treat **all** partners within past 3 mos of pts with 1°,2°,Early Latent, or Latent-Unknown Duration & RPR ≥1:32. *Partners may be incubating syphilis & test seronegative.*
⊒ Patients with Latent/Unknown Duration should receive Bicillin L-A x 3 regardless of titer; if patient titer is high, ie ≥1:32, their *partners* can be presumptively treated with x1 dose.

SYPHILIS TREATMENT [2,3]

	NON-PREGNANT		PREGNANT
	HIV-	HIV+ ▼	
Primary Stage, Secondary Stage, or Early Latent Stage	Recommended: Bicillin® L-A x1 IM	Recommended: Bicillin® L-A x1 IM	Recommended: Bicillin® L-A x1 IM
	Alternatives: Doxycycline 100 mg po bid x 14 d Tetracycline 500 mg po qid x 14 d Ceftriaxone 1g IM / IV x 8-10 d	Alternatives: Doxycycline 100 mg po bid x 14 d Tetracycline 500 mg po qid x 14 d Ceftriaxone 1g IM / IV x 8-10 d	Alternatives: **None.**
Late Latent Stage or Unknown Duration Stage	Recommended: Bicillin® L-A x3 IM (1 dose/wk x3 wks)	Recommended: Bicillin® L-A x3 IM (1 dose/wk x3 wks)	Recommended: Bicillin® L-A x3 IM (1 dose/wk x3 wks)
	Alternatives: Doxycycline 100 mg po bid x **28** d Tetracycline 500 mg po qid x **28** d	Alternatives: Doxycycline 100 mg po bid x **28** d Tetracycline 500 mg po qid x **28** d	Alternatives: **None.**
Neurosyphilis (can occur at any stage)	Recommended: AqPCN IV x 10-14 d	Recommended: AqPCN IV x 10-14 d	Recommended: AqPCN IV x 10-14 d
	Alternative: ProPCN IM + Prob po x 10-14 d	Alternative: ProPCN IM + Prob po x 10-14 d	Alternative: ProPCN IM + Prob po x 10-14 d

KEY: AqPCN = Aqueous crystalline penicillin G, 18-24 million units daily, administered as 3-4 million units IV q 4 hours x 10-14 d.
Bicillin® L-A = Bicillin® Long-Acting (trade) / Benzathine penicillin G (generic) 2.4 million units IM per dose. (Do **NOT** use Bicillin® **C-R**.)
ProPCN + Prob = Procaine penicillin G 2.4 million units IM qd x 10-14 d plus Probenecid 500 mg po qid x 10-14 d.

Jarisch-Herxheimer Reaction (JHR): Advise patients of this possible acute febrile reaction with chills, headache, myalgias, nausea, etc. that can occur within hours of treatment initiation and usually resolves within 24 hrs. It is thought to be an endotoxin reaction to spirochete destruction, and is more common in early stages. Antipyretics may be used, but are not considered preventative. *In the 2nd half of pregnancy, the JHR might induce early labor or cause fetal distress, but this should not prevent or delay therapy.*

▼ CDC's 2006 Guidelines recommend a Cerebral Spinal Fluid (CSF) exam for HIV+ patients before treatment for either Late Latent or Latent-Unknown Duration, even in the absence of clinical findings of neurosyphilis. However, CDC's 2010 Guidelines (update in progress) will likely downgrade this to "CSF exam may be considered" in these patients.

FOLLOW-UP OF TREATED SYPHILIS CASES [3,5]

	F/U RPR Titers		Inadequate Response to Treatment (Tx)
Primary Stage or Secondary Stage	**HIV-**	**HIV+**	➢ Signs/Sx persist or recur. ➢ Titers shows a sustained 4-fold rise since initiation of Tx, compared with 'baseline' titer drawn Tx day #1 (or titer obtained closest and prior to start of Tx). Examples of 4-fold rise: 1:8→1:32, 1:16→1:64, 1:32→128, etc. ➢ Titers that don't decline 4-fold (ie 1:64→1:16) within 6-12 mos of Tx for 1°/2° may indicate Tx failure.ŧ
	6 mos	3 mos	
		6 mos	
	12 mos	9 mos	
		12 mos	
		24 mos	
Latent Stages (Early Latent, Late Latent, or Unknown Duration)	**HIV-**	**HIV+**	➢ Signs/Sx attributable to syphilis develop. ➢ Titers show a sustained 4-fold rise since initiation of Tx, compared with 'baseline' drawn on Tx day #1 (or titer obtained closest and prior to start of Tx). ➢ An initially high titer (≥1:32) that doesn't decline 4-fold (ie 1:32→1:8) within 12-24 mos of Tx for a Latent Stage.ŧ
	6 mos	6 mos	
	12 mos	12 mos	
		18 mos	
	24 mos	24 mos	
Pregnancy, Any Stage	At 28 (-32) wks EGA		➢ Inadequate maternal Tx is likely if: ▹ Delivery occurs within 4 weeks of Tx, ▹ Mother has clinical signs/Sx that are present at delivery, or ▹ Maternal titer rises 4-fold compare to the pre-Tx titer. *Most women will deliver before the treatment response can be assessed definitively.* ➢ Syphilis diagnosed during the 2nd half of pregnancy: ultrasound findings that indicate greater risk for fetal treatment failure include placental thickening, hepato-splenomegaly, polyhydramnios, ascites, etc. Specialty consultation needed.
	At delivery		
	(Consider checking titers monthly in women at high-risk for re-infection, per CDC 2006 MMWR, p. 30.)		

ŧ Decline in titers may be slower in some, ie those who are HIV+ and those who were treated previously for syphilis.

Clinical Considerations Regarding Inadequate Tx Response

➢ **Re-infection:** Does sexual history shows risk of re-exposure? If so, re-treat Using appropriate regimen.
➢ **Tx failure**: If po meds given, was pt compliant?; if not, recommend Bicillin® L-A (desensitize if allergic). HIV seroconversion?; re-screen pts whose previous HIV was –. Unrecognized CNS infection, especially if HIV+? Consider CSF exam.

INTERPRETING CHANGES IN RPR TITERS [5]

Negative / Non-reactive	One increase or decrease in dilution represents a 2-fold change in titer, so 2 dilutions would yield a '4-fold' change (ie rise of 1:4→1:16). A 2 dilution or 4-fold change is regarded as clinically significant between 2 sequential test results. With adequately treated syphilis, a 1 dilution increase (ie 1:4→1:8) can result from testing variation without clinical significance and can be followed expectantly; a 2 dilution or 4-fold rise should be evaluated for possible re-infection or treatment failure.
1:1	
1:2	
1:4	
1:8	
1:16	
1:32	
1:64	
1:128	
1:256	
1:512	

CONGENITAL SYPHILIS: See next page.

References, pp. 2-4:
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2. Calif. Dept. of Public Health (CDPH) STD Branch. STD Treatment Guidelines Table for California, Nov 2007 http://www.sjcphs.org/healthcare_providers/providers.htm
3. CDC. STD treatment guidelines, 2006. *MMWR* 2006;55 (No. RR-11) See latest guidance at http://www.cdc.gov/std/treatment/
4. CDC. Syphilis Testing Algorithms Using Treponemal Tests for Initial Screening — 4 Labs. *MMWR* 2008;57:872-875 http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5732a2.htm
5. Cherneskie, T. An Update & Review of the Dx & Mgt of Syphilis. Region II STD/HIV PTC; NYC DHMH: 2006. http://www.nyc.gov/html/doh/downloads/pdf/std/syphilis-report.pdf
6. Katz, K. Newer lab testing algorithms for syphilis begin with EIA. *Medical Laboratory Observer*. Jan 2010 http://www.mlo-online.com/features/2010_january/0110_clinical_issues.pdf
7. T. Narula, T. et al. HIV and Syphilis: The Great Imitator. *HIV Clinician.* Spring 2010. http://www.deltaaetc.org/hcissues/hcspring2010.pdf

Other Resources:
- California STD/HIV Prevention Training Center. *In-person and online training* http://www.stdhivtraining.org/ | *Syphilis Clinical Algorithms – Primary Syphilis Algorithm:* http://www.stdhivtraining.org/resource.php?id=38&ret=clinical_resources | *Secondary Syphilis Algorithm:* http://www.stdhivtraining.org/resource.php?id=42&ret=clinical_resources
- CDC. Self-Study STD Module for Clinicians - Syphilis http://www2a.cdc.gov/stdtraining/self-study/syphilis.asp
- Hardin Library, U. of Iowa. Link to CDC's syphilis pictures http://www.lib.uiowa.edu/hardin/md/cdc/syphilis.html

SJC PHS Website:
This *Summary Guidance* and the *Syphilis Alert* are posted at http://www.sjcphs.org/healthcare_providers/providers.htm

CONGENITAL SYPHILIS (CS): Maternal-fetal transmission can occur via the transplacental route during any stage, but is much more likely with recent infection (1°/2°>Early Latent>Late Latent). **Untreated 1°/2° maternal syphilis can result in ~40% fetal loss.** Congenital Syphilis can be prevented by early detection of maternal infection & treatment with PCN more than 4 wks before delivery. *No infant or mother should leave the hospital unless maternal serostatus has been documented at least once during pregnancy (& at delivery for women at higher risk for STDs[§]).* Any woman delivering a stillborn >20 weeks EGA should also be tested for syphilis.

Only severe cases of Congenital Syphilis are clinically apparent at birth. Infected infants may return in weeks to months with "snuffles" (syphilitic rhinitis), rash (some have peeling of palms/soles), anemia, jaundice, etc.

All infants of mothers with reactive serology should have a serum RPR (& titer if reactive); **do not use** cord blood, which can be contaminated with maternal blood. Treponemal testing of infants is not necessary. Interpretation of a reactive RPR in infants is complicated by passive transfer of maternal non-treponemal antibodies (treponemal also transfer). In newborns with RPR titers ≥4x the maternal titer, diagnosis is straightforward. In practice, diagnosis is often based on maternal serology & whether or not the mother had adequate Tx during pregnancy.

Infants should be treated for presumed CS if they have any evidence of active disease, RPR titer ≥4x maternal titer, or were born to mothers who at delivery: 1) had untreated syphilis, 2) were treated with a *non-PCN* regimen during pregnancy, 3) were treated ≤4 weeks before delivery, or 4) had evidence of relapse or re-infection after treatment.

Infants with a reactive RPR should be re-tested q 2-3 mos until it becomes non-reactive or titer decreases 4-fold (titers should decrease by 3 mos & become non-reactive by 6 mos if infant was adequately treated, or was uninfected & initially reactive due to passive maternal transfer).

Mothers who screen EIA+: Some labs are now screening with the newer treponemal EIA test instead of the RPR. Reactive EIAs are reflexed to an RPR for confirmation; if the RPR is non-reactive, a 2nd treponemal test is used to confirm. The clinical significance of detecting asymptomatic patients who are EIA+/RPR-/TPPA+ is currently unknown. These test results may reflect old treated syphilis, old untreated syphilis, very early syphilis, or false positive treponemal tests (very rare). Asymptomatic pregnant women who test EIA+/RPR-/TPPA+ & have no documentation of previous Tx should be treated for Late Latent/Unknown Duration with Bicillin® L-A x3 (desensitize if allergic). Per the State STD Branch, these women should be re-evaluated in 1 wk to repeat the RPR & also to assess if they had a Jarisch-Herxheimer Reaction, which would be some evidence of early infection. If no change in results, testing should be repeated at 28 wks & at delivery. Infants of mothers who are EIA+/RPR+ or EIA+/RPR-/TPPA+ need a serum RPR at birth; follow the algorithm below based on the results.

These cases can be complicated. If there are questions please call (209) 468-3845 / 3820. After hours, weekends, & holidays, medical providers may reach Public Health Services via the San Joaquin General Hospital operator at 468-6000.

[§]*History of any STD, new partner or multiple sexual partners, illicit drug use, etc. Regarding geographic risk, the highest rates of female 1°/2° syphilis in the US are currently found in the south, including Alabama, Arkansas, Louisiana, Mississippi, Tennessee, & Texas*