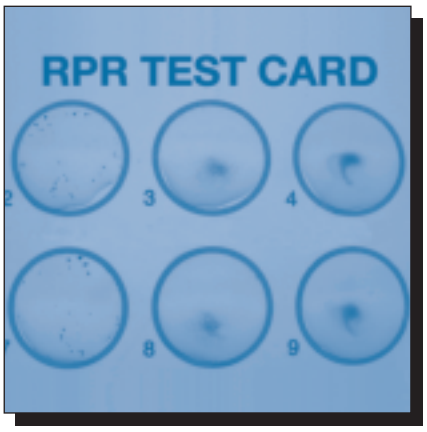
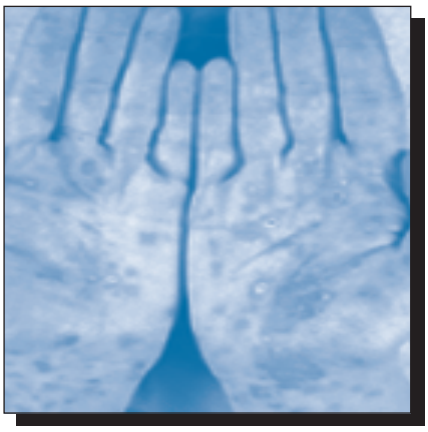
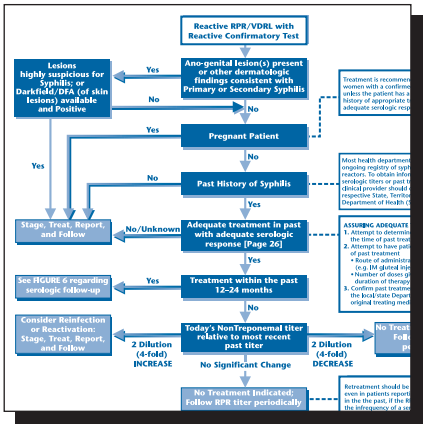
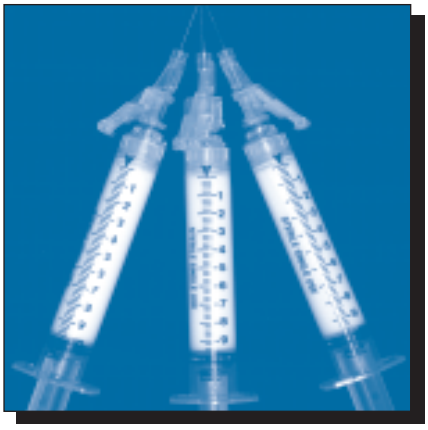
An Update and Review of the Diagnosis and Management of Syphilis









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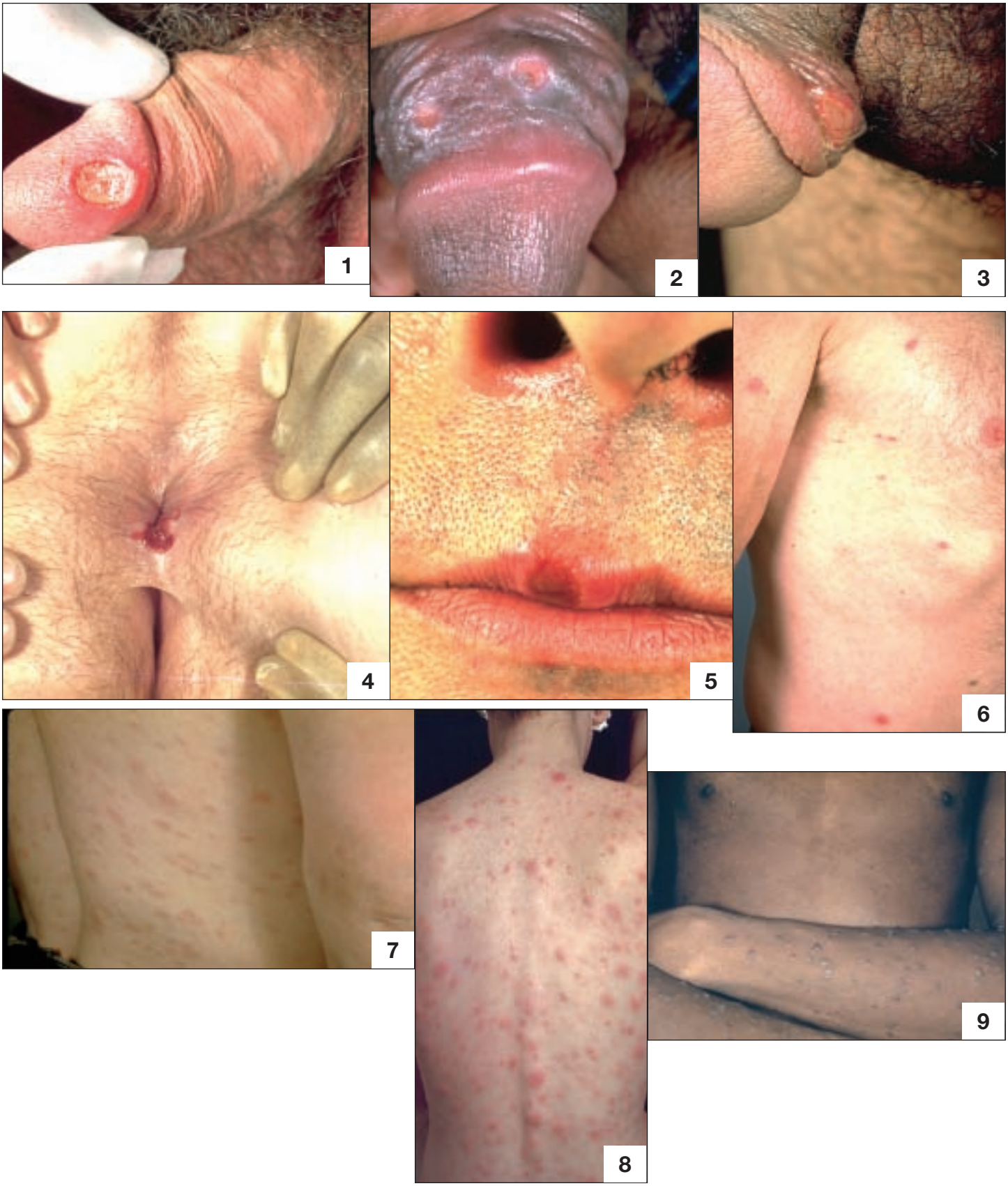

LESIONS OF PRIMARY SYPHILIS

1. Syphilitic chancre of the glans of the penis, 2. Multiple syphilitic chancres on the distal penile shaft, 3. Single syphilitic chancre on the distal penile shaft, 4. Syphilitic chancre of the anus, 5. Syphilitic chancre of the upper lip

LESIONS OF SECONDARY SYPHILIS

6. Papulosquamous lesions of trunk and upper arm, 7. Pityriasis-like papulosquamous eruption of the back,
8. Generalized urticarial lesions of the back and neck, 9. Papular eruption of arms and trunk

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Much of the content presented in this review module is based upon the recommendations made within the Centers for Disease Control and Prevention's 2002 Sexually Transmitted Diseases Treatment Guidelines, MMWR May 10, 2002; Volume 51 (RR06); **David Fleming, MD**, Editor.

Appendix C- Syphilis in Persons with HIV Infection

Taken from Prevention and Management of Sexually Transmitted Diseases in Persons Living with HIV/AIDS

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For a complete listing of acknowledgements see Appendix C.

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CONTENTS

As a source of quick reference in the clinical setting, some common scenarios are listed below with references to corresponding content:

Which of my patients should be **routinely screened** for syphilis?

- Page 8, Maximize Case Detection by Screening for Syphilis when Indicated
- Page 9, US Preventive Services Task Force Recommendations

I'm evaluating a patient with a **genital ulcer**. Which characteristics suggest the likelihood of primary syphilis?

- Page 10, Figure 1: Clinical Features of Genital Ulcers

A patient who I suspect may be infected with syphilis has a **nonreactive RPR. Could the patient still have a syphilis infection?**

- Page 13, Figure 3: Table top row - Nonreactive Nontreponemal test
- Page 14, Diagnostic Considerations in Patients with Early Primary Syphilis

I'm evaluating a patient with a reactive RPR and a nonreactive FTA-ABS (ie. confirmatory, treponeme-specific test). What could cause this **Biologic False Positive RPR?**

- Page 12, Figure 2: Causes of Biologic False Positive Reactions

How should I interpret a reactive RPR, or VDRL, in a patient with a history of syphilis treatment?

- Page 14, Diagnostic Considerations in Patients with a History of Treated Syphilis
- Page 19, Overview of Management of Reactive Syphilis Serology

How do I **determine the stage of syphilis infection** in a patient with no known history of syphilis treatment who presents with a reactive RPR and a reactive Confirmatory test (ie. FTA-ABS)?

- Page 16, Staging in Persons with a Diagnosis of Syphilis
- Page 17, Figure 4B: Syphilis Staging Algorithm

What are the **optimal treatment regimens** for each stage of syphilis infection?

- Page 20, Figure 5B: Treatment Table for Syphilis Infection in Nonpregnant Adults

A patient reports that their recent sex partner was treated for syphilis. How should this patient who is a **contact to a case of syphilis** be managed?

- Page 23-24, Partner Referral and Treatment of Any Contacts to Infectious Syphilis

I'm treating a patient for syphilis. Should I **report the case to my local department of health**, and if so, how?

- Page 25, Promptly notify your state/local health department of any newly diagnosed case of syphilis

I treated a patient for syphilis. How do I know that they are cured and that no further treatment is needed?

- Page 26, Monitor Treated Patients Serologically to Ensure Adequate Response to Therapy

What are the indications for **CSF examination** to rule out neurosyphilis?

- Page 42, Indications for CSF Examination

I. INTRODUCTION

The control and prevention of syphilis requires both clinical and public health preventive considerations. The prompt recognition of signs and symptoms of primary, secondary, and tertiary syphilis, effective screening strategies to detect asymptomatic cases, accurate staging, adequate treatment and follow-up, and risk reduction counseling all represent critical clinical activities in the management and prevention of syphilis. In addition to these, public health activities play an equally important role when faced with a communicable disease such as syphilis; such activities include the identification and empiric treatment of sexual partners of an infectious case; population-based screening efforts; maximization of the effectiveness of existing surveillance systems (including prompt reporting of all newly diagnosed infections) to track trends and distribution of disease; and the interview of every person diagnosed with early syphilis, in order to identify emerging risk factors associated with ongoing syphilis transmission.

The following material is provided as a source of clinical guidance in the diagnosis and management of syphilis. These guidelines should not be construed as inflexible rules or standards. They are primarily based upon the 2002 Centers for Disease Control Sexually Transmitted Disease Treatment Guidelines. For a complete discussion of the evaluation and management of syphilis (including neurosyphilis and congenital syphilis), as well as other sexually transmitted infections please refer to the current CDC Guidelines, a complete copy of which can be found on the Region II STD/HIV Prevention Training Center web site at *www.nyc.gov/health/std.*

The optimization of the diagnosis, management and prevention of syphilis can be broken down into 10 key steps.

KEY STEPS IN THE DETECTION AND CARE OF PATIENTS INFECTED WITH SYPHILIS

1. **Screen patients at risk to identify asymptomatic infections**
2. **Maintain a high index of clinical suspicion for syphilis in any patient with anogenital lesions or an unexplained skin eruption**
3. **Carefully interpret available serologic results**
4. **Accurately stage the disease once a syphilis infection has been diagnosed**
5. **Provide appropriate pharmacotherapy**
6. **Rule out coexisting sexually transmitted infections**
7. **Ensure referral and treatment of any at risk sexual partners**
8. **Notify local or state department of health of any newly diagnosed case**
9. **Monitor treated patients serologically to ensure adequate response to therapy**
10. **Encourage behaviors that will decrease the risk of syphilis reinfection**

II. NATURAL HISTORY OF SYPHILIS

Syphilis results from infection by the corkscrew-shaped bacterium, *Treponema pallidum*. Initial inoculation occurs via visible or microscopic abrasions of the skin or mucous membranes which can result from sexual contact. The average incubation period of syphilis (ie. time from exposure to the development of primary syphilis) is 3 weeks but can be as long as 3 months and as short as 9-10 days.

Some inoculating organisms lodge at the site of entry, proliferate and sensitize lymphocytes and macrophages, resulting in the development of a **primary syphilis** lesion or "chancre" – a dermatologic lesion which progresses from macule to papule to ulcer, typically remaining painless, demonstrating induration and a nonpurulent base. Multiple chancres are noted in up to 40% of primary syphilis cases [Chapel, 1978]. The chancre heals spontaneously, usually without scarring, within 1-6 weeks, heralding the end of the primary stage.

After hematogenous dissemination, generalized or local skin and mucous membrane eruptions can occur, often accompanied by generalized lymphadenopathy and constitutional symptoms, signaling the onset of **secondary syphilis**. Lesions of secondary syphilis generally occur 3-6 weeks after the appearance of the primary ulcer but up to one third of patients with signs of secondary syphilis have a primary lesion still present at the time of diagnosis [Chapel, 1980; Mindel, 1989]. The rash of secondary syphilis is nonspecific in appearance (ie. macular, papular, or any combination), with usually nonpruritic lesions scattered on the trunk and extremities and involves the palms and soles (discrete, scaly, oval lesions) in more than half of cases.

Other findings of secondary syphilis include mucous patches (flat, silver-grey erosions involving the mouth, pharynx, larynx, genitals, or anus), condyloma lata (moist, grey-white, wartlike growths appearing on the genitals, perianal area, and perineum, in gluteal folds, nasolabial folds, axillae, between toes, and under breasts), and patchy alopecia which often has a moth-eaten appearance. Secondary syphilis (ie. condyloma lata) should be included in the differential diagnosis of any lesion with the appearance of condyloma acuminata (ie. Human Papillomavirus infection), and a syphilis serology should be performed when treating any anogenital wart. Many cases of secondary syphilis have nontreponemal serologic titers in the range of 1:128 or higher, although in general, the height of the titer should not be used for staging purposes. Symptoms of secondary syphilis may persist weeks to months before spontaneously remitting, even without treatment. A relapse of secondary signs/symptoms can occur, usually during the first year of infection.

The host immune response suppresses infection enough to eliminate any signs or symptoms of disease, but does not eradicate the infection completely, resulting in latent stage infection. During latency, either **early latent** (duration of infection ≤ 1 year) or **late latent** (> 1 year), no clinical manifestations are evident, and infection can only be detected by serologic screening.

The natural history of late latent syphilis in the immunocompetent patient follows the rule of thirds: one third of patients will sero-revert to a nonreactive nontreponomal syphilis serology, with no recurrence of disease; one third will remain reactive by nontreponomal syphilis serology but remain free of symptoms or signs of disease; and the remaining one third will go on to develop **tertiary syphilis,** sometimes after decades of chronic, persistent, asymptomatic infection. Patients with tertiary syphilis may develop granulomatous lesions (gummas) of the skin or viscera, cardiovascular disease (including aortic aneurysm, aortic valve insufficiency, coronary stenosis, and myocarditis), or neurologic disease (acute meningitis, meningovascular disease, general paresis, tabes dorsalis, and gummatous disease of the brain and spinal cord).

Therefore, untreated syphilis can ultimately lead to devastating, irreversible sequelae which include the complications of neurosyphilis and tertiary syphilis. In addition, untreated syphilis infection in a pregnant woman can have tragic consequences for a developing fetus when transmitted in utero (ie. congenital disease) [See Appendix F – Congenital Syphilis].

It has also become well recognized that STDs such as syphilis interact synergistically with HIV. The likelihood of HIV acquisition by an HIV-negative individual is markedly increased in the presence of syphilis or other sexually transmitted infections [Quinn 1990]. Similarly, in the presence of a genital ulcer, persons infected by HIV more effectively transmit HIV to uninfected partners [Hutchinson 1991].

Although susceptibility to syphilis re-infection is decreased immediately after an episode of adequately treated infection, any acquired immunity is short-lived after which time, exposure can result in reinfection. Therefore a person can become re-infected multiple times over their sexually active lifetime and each infection may have a similar natural history, passing through the primary, secondary, and latent stages, as described above.

III. KEY STEPS IN THE DIAGNOSIS AND MANAGEMENT OF SYPHILIS

1. MAXIMIZE CASE DETECTION BY SCREENING FOR SYPHILIS WHEN INDICATED

Because the majority of patients diagnosed with syphilis deny any lesions consistent with primary or secondary syphilis, screening remains a vital source of case detection [Singh, 1999]. Risk markers for infection historically have included crack cocaine use, the exchange of sex for drugs or money, poverty, lack of health care, and having multiple sexual contacts. Specific risk factors associated with the recent increase in syphilis in NYC and other areas of the US remain unclear, although men who have sex with men and persons infected with HIV appear to be at particular risk for infection. In addition to risk assessment and history of recent symptoms, a thorough oropharyngeal, skin, and anogenital examination is important to detect physical findings associated with primary or secondary disease.

Serologic screening (using a nontreponemal test with reactive specimens confirmed by a treponeme-specific serologic test) should be performed in the following groups:

- Anyone diagnosed with a sexually transmitted infection or anyone presenting for full STD evaluation or screen for HIV
- Anyone with a possible sexual exposure to a known case of infectious syphilis (Primary, Secondary, Early latent)
- Any HIV-positive person (at time of diagnosis, at least annually, and more frequently, every 3-6 months, depending on risk history)
- Any member of a group considered to be at increased risk of infection
  - » Persons with multiple sex partners especially in geographic areas of high syphilis morbidity
  - » Sexually active men who have sex with other men
  - » Users of crack cocaine
  - » Persons engaging in the exchange of sex for money or drugs
- All women at the first prenatal visit
- All women early in the 3rd trimester, at 28 weeks gestation, and at delivery, for communities or populations in which the prevalence of syphilis is high or in patients at high risk of infection.*
- All women delivering a stillborn infant after 20 weeks gestation.**

Periodic screening should be considered, depending on frequency of exposure and other sexual risk factors.

*Laws regarding syphilis screening may vary from state to state. Please check your local and state health department websites.

**Neonatal serum is preferred because of greater likelihood of false-positive results when cord blood is used [Chhabra, 1993]. The CDC currently recommends routine screening of all mothers at the time of delivery, because serologic tests performed on infant serum can be nonreactive if the mother's titer is low or if she was infected late in pregnancy.

U.S. Preventive Services Task Force Recommendation

"Routine serologic testing for syphilis is recommended for all pregnant women and for persons at increased risk for infection, including commercial sex workers, persons who exchange sex for money or drugs, persons with other STDs (including HIV), and sexual contacts of persons with active syphilis. The local incidence of syphilis in the community and the number of sex partners reported by an individual should also be considered in identifying persons at high risk of infection. The optimal frequency for such testing has not been determined and is left to clinical discretion."

2. MAINTAIN A HIGH INDEX OF SUSPICION FOR SYPHILIS WHEN EVALUATING ANY ANOGENITAL LESIONS OR UNEXPLAINED, GENERALIZED SKIN ERUPTION AMONG SEXUALLY ACTIVE PERSONS

Anogenital Lesions

One of the more common presentations of genital disease is a genital ulceration for which sexually transmitted infections must be considered. Etiologies include: Herpes simplex virus; *Treponema pallidum* (primary syphilis); *Haemophilus ducreyi* (chancroid); *Chlamydia trachomatis* L1, L2, L3 serovars (lymphogranuloma venereum); and *Calymmatobacterium granulomatis* (Donovanosis, ie. granuloma inguinale). Although specific diagnostic tests are useful in excluding many of these etiologies, the clinical provider should attempt to make a presumptive diagnosis and consider offering treatment based on characteristics of the lesion(s) noted on examination. The following table reviews the classic presentation for each of these causes of genital ulcer disease.

FIGURE 1: CLINICAL FEATURES OF GENITAL ULCERS

	Syphilis	Herpes	Chancroid	LGV	Donovanosis
Incubation Period	9-90 days	2-7 days	1-14 days	3 days-6 weeks	1-4 weeks (up to 6 months)
Primary Lesion(s)	Papule	Vesicle (erosion)	Papule/Pustule	Papule, pustule,or vesicle	Papule
Number of Lesions	Usually one	Multiple , may coalesce	Multiple , may coalesce	Usually one	Variable
Edges	Sharp, Well demarcated, Round or Oval	Erythematous, Cratered	Ragged, Undermined, Irregular	Elevated, round, or oval	Elevated, irregular
Depth	Deep or Superficial	Superficial	Excavated	Superficial or deep	Superficial or deep
Base	Smooth, Nonpurulent, Relatively nonvascular	Serous, Erythematous, Nonvascular	Purulent, Vascular, Friable	Variable, nonvascular	Red and velvety, bleeds readily
Induration	Indurated	None	Soft	Occasionally firm	Firm
Pain	Rare	Often Tender	Very Tender	Variable	Uncommon
LYMPHADENOPATHY					
Fluctuance	Firm	None	May suppurate	May suppurate	None; pseudobuboes
Tenderness	None	Tender	Tender	Tender	
Distribution	Bilateral	Bilateral with primary infection	Usually Unilateral	Usually Unilateral	

(Used with permission from "Genital Ulcer Adenopathy Syndrome" by Ronald C. Ballard, Page 888 in Sexually Transmitted Diseases, 3rd Ed., 1998. Editors: K. Holmes, PF. Sparling, P. Mardh, S. Lemon, W. Stamm, P. Piot, and J. Wasserheit. McGraw-Hill publisher)

The classic syphilis chancre is a singular, indurated, painless, clean-based ulceration. The most specific of these exam findings for the lesion of primary syphilis appears to be induration [DiCarlo, 1997].

Even in the case of a genital or anal ulceration not attributed to a syphilis diagnosis (such as recurrent anogenital herpes) a screening RPR should always be performed if the patient reports sexual contact within the previous 3 months. The presence of one

STD at the site of a genital lesion does not exclude a coexisting infection in the same lesion. In case series, two or more pathogens have been detected in up to 20% of genital ulcer. The two most common in the United States are herpes simplex virus and *Treponema pallidum* [Dillon, 1997].

Any patient with anogenital condyloma or maculopapular lesions should be serologically screened for syphilis to rule out the possibility of secondary stage infection.

Unexplained dermatologic eruptions

Secondary syphilis can present as a macular, papular, or rarely, pustular eruption and may therefore be difficult to distinguish from other, more common, dermatologic conditions such pityriasis rosea, drug eruption, viral exanthema and, in the case of annular syphilitic lesions in darker-skinned patients, erythema annulare centrifugum, granuloma annulare, or sarcoidosis. Syphilis should be ruled out in any sexually active patient with a rash (generalized or localized) of unknown origin or unexplained hair loss, especially when associated with systemic complaints. An RPR or VDRL is a relatively inexpensive, easily performed, and readily available means of excluding secondary syphilis in patients at risk with the exception of prozone phenomenon. Please refer to page 13.

Clinical photos reviewing the dermatologic presentations of syphilis are presented on the front and back covers.

3. CAREFULLY INTERPRET AVAILABLE SEROLOGIC RESULTS

Serologic tests for syphilis include a variety of assays which fall into two general categories: Nontreponemal; and Treponeme-specific.

Nontreponemal Assays

Nontreponemal assays, such as the RPR and VDRL, are useful to screen for syphilis infection (past or present), to evaluate the effectiveness of therapy for a syphilis infection, and, in patients with a history of previous treatment for syphilis, to determine the likelihood of re-infection. The quantitative result of nontreponemal tests (ie. the titer) typically will rise in early infection, peak during the secondary stage, and decline over time, even in the absence of treatment.

The RPR and VDRL are, for clinical purposes, equivalent tests, although when assessing an individual's titer over time the same test type, ideally performed by the same laboratory, should be used to avoid quantitative variations between tests, ie. RPR titers often are slightly higher than VDRL titers for the same specimen.

Treponeme-specific Assays

Treponeme-specific assays are most often used to confirm a syphilis diagnosis in a patient with a reactive RPR or VDRL, and in so doing, rule out a biologic false-positive nontreponemal result (See Figure 2, Below). Treponeme-specific assays should only be used as a qualitative test (ie. Reactive vs. Nonreactive). Although quantitative results are often reported by the laboratory these do not correlate well with disease activity and should not be used to guide clinical management. Treponeme-specific assays include: FTA-ABS; TP-PA (which has replaced the MHA-TP); IgG EIA. Treponeme-specific tests most often remain reactive for life in patients infected with syphilis, even following adequate therapy.

Any reactive nontreponemal test (RPR/VDRL) should be confirmed with a treponeme-specific assay [FTA, TP-PA (MHA-TP), IgG EIA] in order to rule out a biologic false-positive result. Causes of a biologic false-positive test for syphilis are listed in Figure 2. Patients with a biologic false positive serology should have a repeat RPR/VDRL performed after 6 months. If persistently reactive, the possibility of an underlying chronic infection or autoimmune disorder should be considered, especially if the patient exhibits other unexplained signs or symptoms.

FIGURE 2: CAUSES OF BIOLOGIC FALSE POSITIVE REACTIONS

(REACTIVE NONTREPONEMAL TEST WITH A NON-REACTIVE TREPONEME-SPECIFIC TEST)

[Adapted from Nandwani, 1995; Hook, 1992; Larsen, 1995]

ACUTE (lasting < 6 months)	
Physiologic	Pregnancy
Spirochete Infections	Lyme disease Leptospirosis Relapsing fever Rat-bite fever
Acute Infections	Herpes simplex Viral hepatitis HIV seroconversion illness Chickenpox & Varicella-zoster Infectious mononucleosis Bacterial endocarditis Chancroid Rickettsial disease Toxoplasmosis Cytomegalovirus Measles Mumps Pneumococcal and viral pneumonia Mycoplasma Pneumonia Malaria Other acute viral or bacterial sepsis
Immunizations	Smallpox Typhoid Yellow fever

CHRONIC (lasting > 6 months)	
Physiologic	Older age
Chronic Infection	HIV/AIDS Tuberculosis Lymphogranuloma venereum Lepromatous leprosy Malaria Kala-azar Trypanosomiasis Tropical spastic paraparesis (HTLV-1)
Autoimmune Disorders	Systemic Lupus Erythematosus Polyarteritis nodosa Rheumatoid arthritis Sjogren's syndrome Mixed connective tissue disease Autoimmune thyroiditis (Hashimoto's) Autoimmune hemolytic anemia Primary biliary cirrhosis Idiopathic thrombocytopenic purpura Multiple myeloma
Other Conditions	Malnutrition Malignancy Hepatic cirrhosis Intravenous drug use Lymphoproliferative disorders Dysproteinemias

Traditionally in the United States, the nontreponemal tests have been used for initial screening. Using the RPR as the initial screening test has offered two advantages: 1) Cost- In the United States, the RPR is much less expensive, compared with the FTA-ABS or TP-PA; 2) Seroreversion- In contrast to the FTA-ABS or TP-PA, the RPR in a person previously treated for syphilis has a higher likelihood of becoming nonreactive. [Schroeter 1972; Fiumara, 1980] Therefore, patients with previously treated syphilis and seroreversion (ie. nonreactive RPR/VDRL) would not be detected by a screening RPR and potentially confused with an active case, thus minimizing the risk of unnecessary treatment.

For a discussion of the use and interpretation of IgG EIA testing in syphilis screening see Appendix B.

The diagnosis of syphilis must take into consideration the results of both a nontreponemal test as well as a treponeme-specific one. Figure 3 (below) summarizes the interpretation of each of the four possible serologic scenarios:

	NONTREPONEMAL	TREPONEMAL
1.	NONREACTIVE	NONREACTIVE
2.	NONREACTIVE	REACTIVE
3.	REACTIVE	NONREACTIVE
4.	REACTIVE	REACTIVE

FIGURE 3:

nontreponemal [RPR/VDRL]	TREPONEME-SPECIFIC [FTA-ABS/TP-PA (MHA-TP)/IgG EIA] NON-Reactive	TREPONEME-SPECIFIC [FTA-ABS/TP-PA (MHA-TP)/IgG EIA] Reactive
NON-Reactive	**1** No Syphilis Diagnosis Incubating syphilis infection Very Early Primary Syphilis[1]	**2** Very Early Primary Syphilis[1] Secondary Syphilis with Prozone Phenomenon[2] Late untreated syphilis with seroreversal of RPR[3] Treated Syphilis[4] False-negative Nontreponemal test[5] False-positive Treponemal Test[6] (rare)
Reactive	**3** Biologic False Positive[7] False-negative Treponemal Test (rare)[5]	**4** Positive Syphilis Diagnosis[8] Lyme disease Endemic nonsexually transmitted treponemal disease[9]

[1] Patients with early primary syphilis may be nonreactive by all serologic tests at the time of presentation, with seroconversion taking as long as 10-14 days after the appearance of a primary lesion [Larsen, 1999]. Therefore patients with a lesion suspicious for primary syphilis should have a repeat RPR performed 2 weeks following an initial nonreactive result. If possible, dark field microscopy, or Direct Fluorescent Antibody testing (DFA) should be performed on any skin lesions suspicious for a primary ulcer or condyloma lata. Darkfield microscopy is available to patients free of charge at many governmentally funded STD clinics. [See Appendix G].

[2] Prozone Phenomenon occurs in 1-2% (up to 10%) of patients with secondary syphilis as a result of the presence of excessive amounts of antibody [Berkowitz, 1990; Jurado, 1993]. Prozone occurs more commonly in HIV-infected persons [Schofer, 1996]. If prozone is suspected, testing on a diluted specimen or testing with a treponeme specific test should be requested to "rule out prozone."

[3] Seroreversal of nontreponemal tests (ie. reversion of a serology from a reactive to nonreactive result) occurs in a significant proportion of later stage syphilis even without treatment; nontreponemal tests [eg. RPR] may be nonreactive in up to 30% of patients with untreated late syphilis [Larsen, 1999], although the treponemal test [eg. FTA] usually remains reactive.

[4] Seroreversal of nontreponemal tests can be seen after adequate treatment especially if treated in the early stages of infection. A patient may have received adequate treatment in the past, although fail to recall any such diagnosis or therapy or may have been inadvertently cured when treated for a nonsyphilis infection.

[5] Case reports have described atypical serologic responses to syphilis in HIV-positive persons [Hicks, 1987; Radolf, 1988; Hutchinson, 1991; Tikjob, 1991].

[6] False-positive treponemal test occurs in fewer than 1% of healthy individuals [Goldman, 1971], although are more common during pregnancy, in the elderly, and in patients with connective tissue/autoimmune diseases, type-1 diabetes mellitus, lyme disease, certain viral infections (including genital HSV), infectious mononucleosis, or leprosy [Buchanan, 1970; Carlsson, 1991; Wright, 1975; Hughes, 1970; Kraus, 1970; McKenna, 1973].

[7] The rate of a biologic false-positive reaction in the general population is 0.3-1%, although can be seen more commonly in the presence of certain acute and chronic conditions [Nandwani, 1995] See Figure 2, page 12.

[8] May represent acquired infection, whether treated or untreated. It is important to document any history of past treatment, and the adequacy of post-treatment serologic response.

[9] Endemic treponematoses (eg. yaws, pinta, bejel) are found most commonly in certain parts of Africa, Southeast Asia, Central and South America, the Middle East, and the Pacific Islands. A history of endemic treponemal disease in the past does not eliminate the possibility of a syphilis infection in the present and should not be used, per se, to rule out syphilis in a patient with a confirmed reactive serology.

DIAGNOSTIC CONSIDERATIONS IN PATIENTS WITH A HISTORY OF TREATED SYPHILIS

Although nontreponemal tests serorevert (ie. from reactive to nonreactive) in many patients treated for early syphilis, the RPR/VDRL may remain reactive lifelong (a serofast serology). The likelihood of seroreversion depends upon the stage at the time of treatment, the degree of reactivity (ie. the height of the titer at the time of treatment), and whether the current infection represents an initial or repeat infection. Patients treated at an earlier stage, at the time of a lower titer,or who have never been infected in the past are more likely to serorevert to nonreactive. Long lasting immunity does not occur following syphilis infection. In a patient with a history of syphilis in the past, repeat infection should be suspected if a nonreactive nontreponemal test converts to reactive, or there is a 2 dilution (four-fold) rise in titer, compared with the most recent past titer (eg. a rise in titer from 1:4 to 1:16). The VDRL and RPR, both nontreponemal serologic tests, are equally valid in the diagnosis of syphilis. Nevertheless quantitative results should not be directly compared between RPR and VDRL, since RPR titers often are slightly higher than VDRL titers.

INTERPRETING CHANGES IN NONTREPONEMAL SEROLOGIC TITERS	
NONTREPONEMAL **SEROLOGIC TITERS** 1:512 1:256 1:128 1:64 1:32 1:16 1:8 1:4 1:2 1:1 (“Minimally reactive”) Nonreactive	Each increase (or decrease) in dilution level represents a 2-fold titer change, therefore a “4-fold change” corresponds to a 2 dilution change (eg. decreasing from 1:32 to 1:8). A 2 dilution (ie. 4-fold) change in titer is considered necessary to demonstrate a clinically significant difference between 2 sequential nontreponemal test results. In a patient with a seqential history of adequately treated syphilis, a one dilution (ie. 2-fold) increase (eg. from 1:2 to 1:4) can result from testing variation without clinical significance and can be followed expectantly, whereas as a 2 dilution change (ie. 1:2 to 1:8) should raise the suspicion of reinfection or reactivation and prompt the need for reevaluation and treatment.

DIAGNOSTIC CONSIDERATIONS IN PATIENTS WITH EARLY PRIMARY SYPHILIS

As discussed above, all available serologic tests for syphilis have limited sensitivity during the first 10-14 days following the onset of a primary lesion. Therefore, a patient with a lesion consistent with primary syphilis which has been present for less than 10 days and in whom serologic results are initially nonreactive, may benefit from serologic retesting 2 weeks later to rule out serologic conversion.

During very early primary syphilis, lesion based testing is the most sensitive way to make the diagnosis. Lesion based testing can be performed on any anogenital ulcer or other moist anogenital lesions (eg. condyloma lata), and may be available through local or state health departments (See Appendix H).

4. ACCURATELY STAGE THE DISEASE IN PATIENTS WITH A CONFIRMED REACTIVE SEROLOGY [SEE STAGING TABLE]

Once it is determined that a patient is infected with syphilis (ie. serologic results consistent with infection +/- signs or symptoms), the stage of disease must be determined. Accurate staging of syphilis is vitally important in order to:

i) Select the appropriate treatment regimen,
ii) Evaluate the expected serologic response to treatment,
iii) Identify at-risk partners and guide partner management,
iv) Determine the risk for late complications or congenital syphilis,
v) Ensure accurate assessment of disease trends within the community (via local public health surveillance systems).

A diagnosis of primary, secondary or tertiary syphilis is prompted by serologic results consistent with syphilis infection *and* the presence of symptoms and exam findings of primary, secondary, or tertiary syphilis, respectively. Latent disease is, by definition, asymptomatic with the serologic results representing the only evidence of infection. Latent disease is divided into "early latent" and "late latent" based on the length of time the infection is thought to have been present. Patients who appear to have acquired their infection within the preceding 12 months are considered to have "early latent syphilis." Those who appear to have acquired their infection greater than 12 months prior to diagnosis are considered to have "late latent syphilis." The importance of differentiating early latent from late latent syphilis lies in the fact that persons with late latent infection requires a longer duration of therapy, and persons with early latent are considered potentially infectious to their sexual contacts.

Note: All patients thought to have latent (ie. asymptomatic) syphilis should undergo a physical exam which includes the following: examination of oral, vaginal, anal and mucosal surfaces to rule out the presence of primary or secondary lesions or evidence of tertiary disease. Any history of lesions consistent with syphilis may also help determine the stage of infection.

A proportion of asymptomatic patients with serologic evidence of infection deny any past history of signs, symptoms or known exposure and represent persons with "latent syphilis of unknown duration." Patients with "latent syphilis of unknown duration" are treated with the longer duration regimen (ie. as a case of late latent syphilis), although they may have acquired the infection within the past year and thus could still be infectious. Therefore, all partners within the past 12 months of persons diagnosed with "latent syphilis of unknown duration" should be considered at possible risk for infection and managed accordingly, especially if the case patient's nontreponemal titer ≥ 1:32.

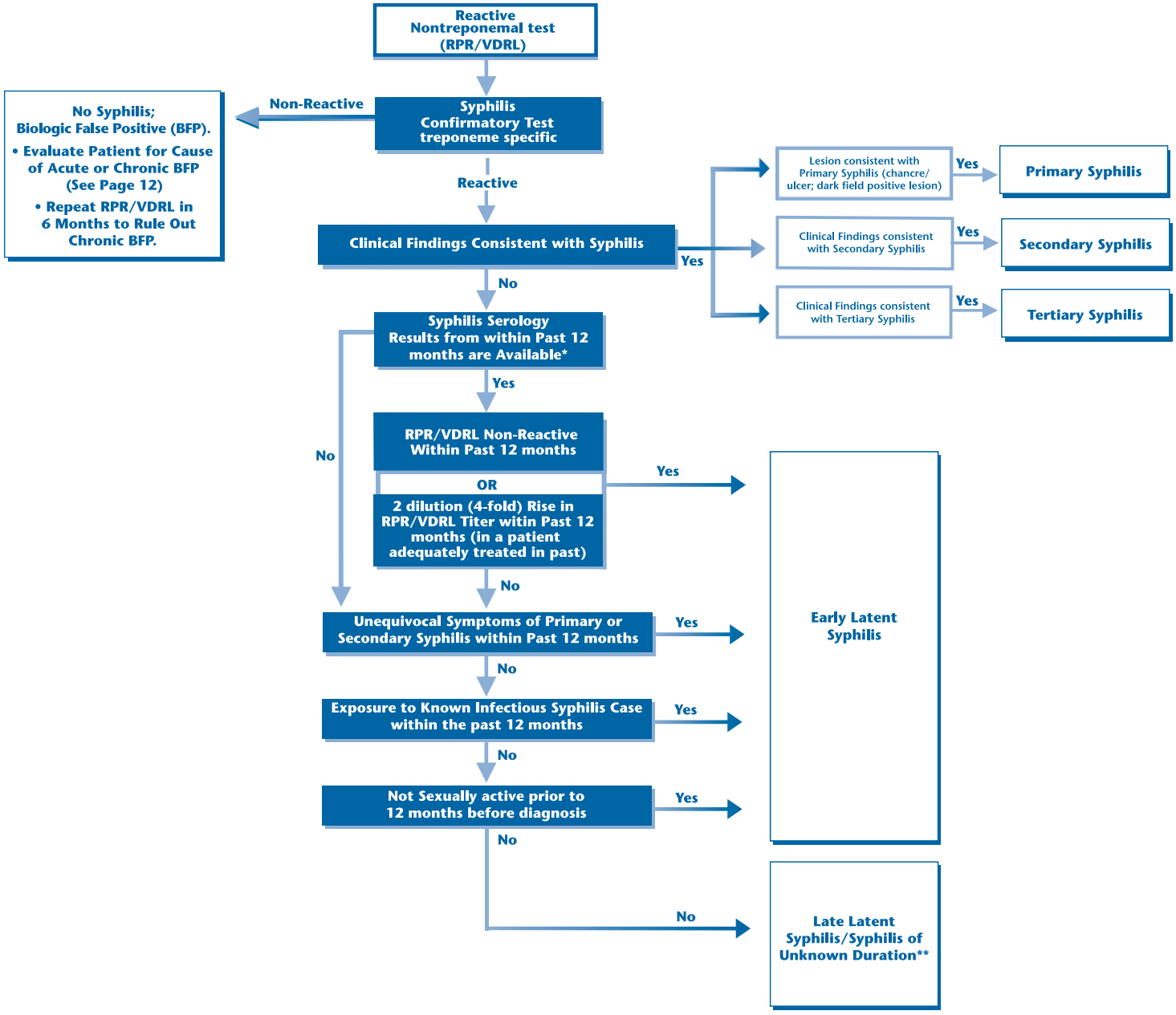
Figure 4A summarizes the key characteristics of each stage of syphilis and Figure 4B provides a decision tree which outlines a general approach to syphilis case staging.

FIGURE 4A: STAGING IN PERSONS WITH A DIAGNOSIS OF SYPHILIS (ie. A CONFIRMED REACTIVE SEROLOGY)

STAGE	DIAGNOSTIC CRITERIA	PROBABLE EXPOSURE DATE
Primary	**Consistent Exam Findings** Usually a single, painless, rubbery ulcer (genital or non-genital) which is found to be positive by dark field/DFA/PCR or which is highly suspicious for a syphilitic chancre on clinical grounds.	**Within the past 3 months**
Secondary	**Consistent Exam Findings** (+/- dark field positive lesion) • Cutaneous eruption (generalized or localized) without explanation • Palmar or plantar rash • Mucous patches (membranous lesions of tongue, buccal mucosa, lips) • Condyloma Lata (moist, flat, whitish-gray plaques) • Patchy alopecia	**Within the past 6 months**
Early Latent	**Negative exam (ie. no findings consistent with primary or secondary syphilis) PLUS** **Any of the Following WITHIN THE PAST 12 MONTHS** 1. History of unequivocal symptoms of primary or secondary syphilis OR 2. Serologic conversion OR 3. A 2 dilution (4-fold) rise in nontreponemal titer in a person who has previously received adequate treatment for a syphilis infection OR 4. Exposure to an infectious case of syphilis‡ OR 5. Only possible exposure has been within the past 12 months	**Within the past year**
Late Latent	**Negative exam (ie. no findings consistent with primary or secondary syphilis) PLUS** **Any of the Following GREATER THAN 12 MONTHS IN THE PAST** 1. History of unequivocal symptoms of primary or secondary syphilis OR 2. Serologic conversion OR 3. A 2 dilution (4-fold) rise in nontreponemal titer in a person who has previously received adequate treatment for a syphilis infection OR 4. Exposure to an infectious case of syphilis‡ OR 5. No possible exposure within the past 12 months	**Greater than 1 year ago**
Latent Syphilis of Unknown Duration	No signs or symptoms of primary or secondary syphilis and insufficient information to determine the duration of infection or the most likely time of exposure.	**Uncertain.** If the nontreponemal titer is ≥1:32, there is a greater likelihood of recent infection (ie. within the previous 12 months).

‡ An infectious case includes primary, secondary, or early latent syphilis.

FIGURE 4B: SYPHILIS STAGING ALGORITHM FOR A REACTIVE SEROLOGY IN A PATIENT WITH NO PAST HISTORY OF SYPHILIS TREATMENT



**Most local Departments of Health maintain an ongoing registry of syphilis cases and serologic reactors. See Appendix H for contact information.*

***Patients who deny any history of signs/symptoms of syphilis or history of known exposure to a case of infectious syphilis, and for whom it is unclear when the exposure occurred, are often managed medically as a case of LATE LATENT SYPHILIS, although more accurately it represents "LATENT SYPHILIS OF UNKNOWN DURATION."*

5. PROVIDE THE APPROPRIATE PHARMACOTHERAPY

[SEE FIGURE 5A: MANAGEMENT OF REACTIVE SYPHILIS SEROLOGY]

Often, the decision to treat or not to treat in response to a reactive syphilis serology is particularly challenging for the health care provider, especially when a patient has had a history of previously treated syphilis. Figure 5A outlines a general approach to a patient found to have a confirmed reactive serology. Decision-making in specific clinical situations must take into consideration the details of an individual patient's history and examination to ensure proper case management. Optimal case management may require clinicians to confer with their local infectious disease or STD specialists for guidance.

Note: All patients with a diagnosis of latent syphilis should be evaluated clinically for any signs or symptoms of tertiary disease (eg. aortitis, gumma, iritis)

Management of all cases of untreated syphilis should be based on the stage of infection **at the time of treatment.** Aqueous benzathine penicillin G long-acting is the treatment of choice for all stages of syphilis. Oral therapy with multiple daily doses of doxycycline is an accepted alternative in penicillin allergic patients. Although the administration of injectable penicillin as a treatment for syphilis is at times avoided by clinicians concerned with possible patient discomfort and concerns about anaphylactic reactions, ensuring compliance with 2 to 4 weeks of twice daily or four-times-a-day oral therapy may be nearly impossible. Strict compliance with multi-dose, multi-day oral therapies in the treatment of STDs has been shown to occur in only a small proportion of patients even when medication is provided free of charge at the time of diagnosis [Augenbraun 1998]. Therefore, unless contraindicated, injectable directly-observed therapy with long-acting benzathine penicillin is the treatment of choice for all stages of syphilis. Neither a combination of benzathine penicillin and procaine (ie. short-acting) penicillin, nor oral penicillin are appropriate for the treatment of syphilis. Neither injectable bicillin CR nor oral penicillin is appropriate for the treatment of syphilis. Intramuscular Benzathine penicillin remains the only regimen currently recommended for treatment during pregnancy and for the prevention of congenital syphilis [CDC STD Treatment Guidelines, 2002].

Jarisch-Herxheimer Reaction

Patients treated for syphilis should be warned about the possibility of a Jarisch-Herxheimer reaction which may occur within the first 24 hours (usually 2-8 hours) after initiation of treatment [Holmes K et al (Editors). Sexually Transmitted Diseases, 1998; Third Edition]. Symptoms include local and systemic exacerbation of existing, or unrecognized, manifestations of primary or secondary syphilis in the face of malaise, myalgias, headache, nausea/vomiting, tender adenopathy, pharyngitis or fever. The reaction is believed to be a result of the rapid killing of spirochetes and is seen most commonly among patients treated for primary or secondary syphilis (1/3 to 2/3 of cases). Treatment is supportive utilizing antipyretics and analgesics and symptoms usually resolve within 24 hours. During pregnancy, the Jarisch-Herxheimer reaction has been associated with fetal distress and preterm labor (the greatest risk occurring during the first 48 hours after treatment) [Klein, 1990]. Nevertheless, this potential complication should not prevent or delay treatment. Women treated for syphilis during pregnancy should be informed about the possibility of a Jarisch-Herxheimer Reaction and should seek immediate obstetric attention if they notice any contractions or decreased fetal movements.

FIGURE 5A: OVERVIEW OF THE MANAGEMENT OF REACTIVE SYPHILIS SEROLOGY

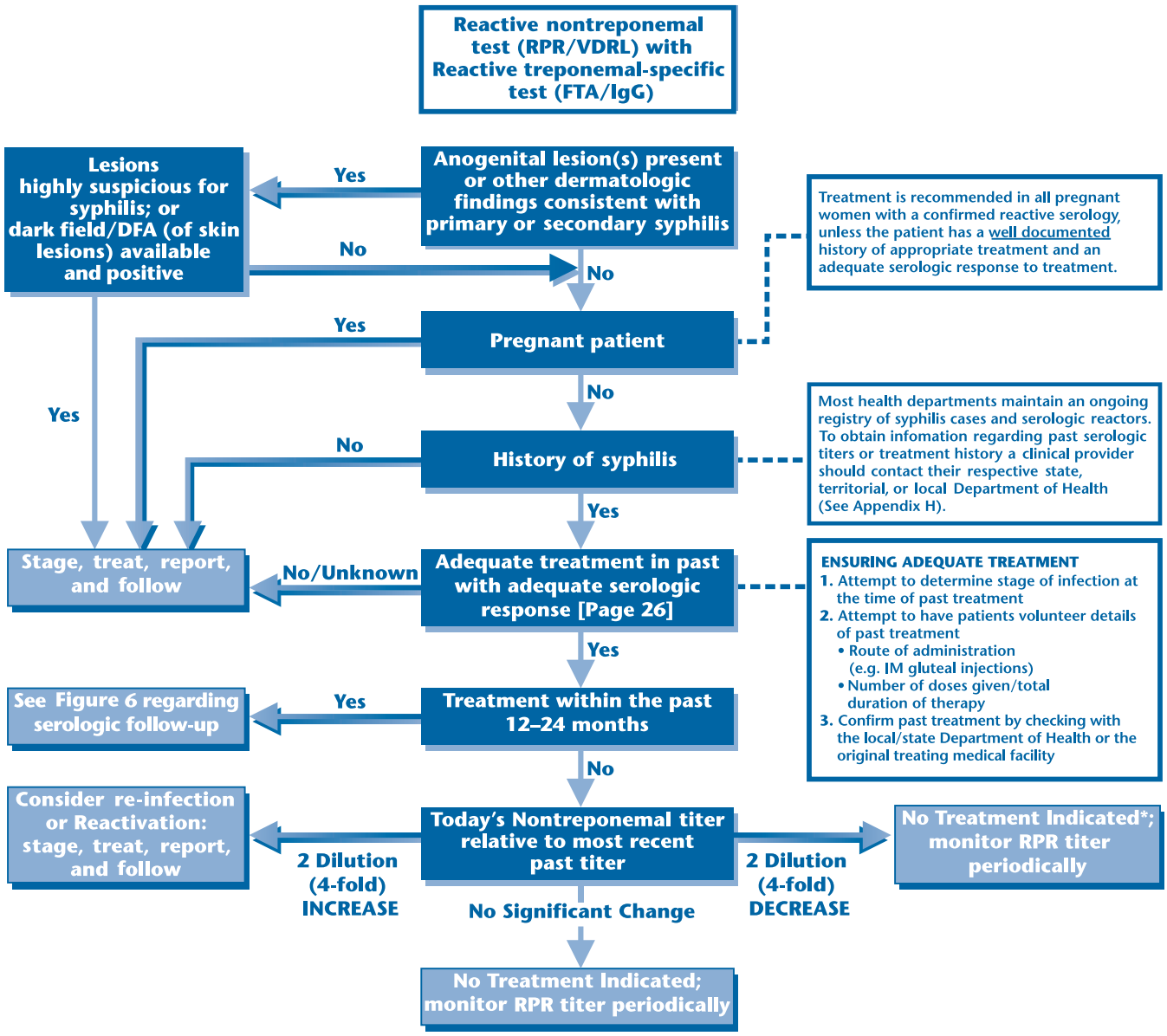


FIGURE 5B: Treatment Table for Syphilis Infection in Non-Pregnant Adults

Stage [Onset post-exposure]	Considered Infectious	HIV Status	Treatment[1]	At Risk Partner(s)
Primary [3-90 days, average 21 days]	YES		IM benzathine penicillin G 2.4 million units- single injection[1] Some experts recommend additional doses in HIV- positive patients (eg. Intramuscular benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units each at 1 week intervals, although the formal CDC recomendation is for a single injection of 2.4 mU. CDC recommended alternatives for Non-pregnant patients with a documented penicillin allergy[1,4] Oral doxycycline 100mg twice each day x 2 weeks[1,4] **OR** Oral tetracycline 500mg four times a day x 2 weeks[1,4] **OR** ceftriaxone IM or IV 1g daily x 8-10 days[1,4]	Partners exposed up to **3 months** prior to first symptom.[2]
Secondary [1.5 - 6 months]	YES		SEE Treatment of Primary Syphilis[1]	Partners exposed up to **6 months** prior to first symptom[2]
Early Latent [≤ 1 year]	YES[3]		SEE Treatment of Primary Syphilis[1]	Partners exposed up to **12 months** prior to diagnosis[2]
Late Latent [> 1 year]	NO[8]	HIV Negative	IM benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units each at 1 week intervals[5] CDC recommended alternatives for nonpregnant patients with a documented penicillin allergy[1] Oral doxycycline 100mg twice each day x 4 weeks[1] **OR** Oral tetracycline 500mg four times a day x 4 weeks[1]	Evaluate spouses and long-term partners clinically and serologically. Children born outside of the U.S. should be evaluated to rule out congenital infection.
		HIV Positive	IM benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units each at 1 week intervals[4,5,6]	
Latent Syphilis Of Unknown Duration [??]	Possibly		Since the duration of infection is uncertain, therapy of maximal duration is recommended (SEE Late Latent Syphilis, above)	For purposes of partner notification and management of exposed sexual partners, patients with Latent Syphilis of Unknown Duration who have high nontreponemal serologic titers (ie. ≥1:32) may be considered as having early latent syphilis.
Tertiary [months- yrs]	NO[7]		SEE Late Latent Syphilis (above)	See Late Latent (above)
Neurosyphilis			SEE Appendix D	

For information regarding the treatment of syphilis in HIV-infected persons, syphilis during pregnancy, congenital syphilis, and syphilis in children refer to Appendices C, E, F, and G.

For Footnotes – see page 21.

Footnotes for Figure 5B:, previous page

[1] Benzathine Penicillin is the treatment of choice for all stages of syphilis (except neurosyphilis); other regimens should be used only when penicillin is contraindicated. Penicillin is the only acceptable treatment regimen during pregnancy; penicillin-allergic pregnant women should be hospitalized, desensitized, and treated with penicillin. If a patient is penicillin allergic and a doxycycline/tetracycline regimen is used, they should be followed closely to encourage full compliance with the 2-4 weeks of therapy; compliance is likely to be better with doxycycline than tetracycline because of less frequent dosing and fewer gastrointestinal side effects. Penicillin desensitization should be considered for patients with a known penicillin allergy but a high likelihood of non- compliance with oral medications. Limited preliminary data suggest that ceftriaxone should be an effective alternative for the treatment of early stage syphilis; the optimal dose and duration of therapy remain unclear however some experts recommend Ceftriaxone IM or IV 1g daily for 8-10 days. Since the response rate to this therapy is not well documented, close follow-up is essential. [MMWR; March12, 2004]

[2] Partner Management:

The maximum incubation period for syphilis is 3 months, therefore a non-reactive serology in a sexual partner whose last potential exposure was < 90 days ago could represent a false-negative result (falling within the "window period" for syphilis serologic testing). Therefore partners whose last contact with an infectious case was ≤ 90 days ago should be treated empirically, regardless of serologic tests results. Serologic testing is still important to establish a final diagnosis (ie. incubating syphilis vs. early infection). If a partner is found to be already infected (to have a confirmed reactive serology), his/her partners require evaluation and management. Partners whose last contact with an infectious case was >90 days ago who are found to be non-reactive serologically can be considered uninfected. If a STAT RPR is reactive (in a patient without past syphilis treatment), OR if serologic results are not available immediately and follow-up is uncertain, presumptive treatment should be strongly recommended at the initial visit.

[3] Because of the significant risk of relapse to secondary syphilis during the first year of infection, early latent cases are considered to be infectious and partners managed accordingly.

[4] The efficacy of non-penicillin regimens (eg. doxycycline or tetracycline for 28 days) in HIV-infected persons has not been well studied, and thus must be considered with caution.

[5] The optimal management of patients being treated for late latent syphilis who miss scheduled doses of penicillin therapy remains uncertain. Based upon the pharmacology of benzathine penicillin, an interval of 10-14 days between doses is likely to be acceptable before having to restart the injection series. This flexibility in dosing should not be considered acceptable in the treatment of syphilis during pregnancy.

[6] Rule out neurosyphilis by CSF examination before initiating therapy (although some experts would recommend doing both simultaneously).

[7] Except potentially for maternal-fetal transmission.

6. RULE OUT ANY OTHER CO-EXISTING SEXUAL INFECTIONS

Because many sexual risk behaviors are common to a variety of sexually transmitted infections, patients diagnosed with syphilis should also be screened for other potentially asymptomatic STDs such as chlamydia, gonorrhea, trichomonas, and HIV.

All patients diagnosed with syphilis should be tested for HIV infection. In geographic areas in which the prevalence of HIV is high, patients who have primary syphilis should be retested for HIV after 3 months if the first HIV test result was negative.

For a discussion of available tests used in the diagnosis of gonorrhea, chlamydia and other STDs visit:

http://www.cdc.gov/STD/LabGuidelines/default.htm

http://www.depts.washington.edu/nnptc

7. ENSURE PARTNER REFERRAL AND TREATMENT OF ANY CONTACTS TO INFECTIOUS SYPHILIS (IE. PARTNERS EXPOSED DURING THE CASE'S INFECTIOUS PERIOD)

[SEE FIGURE 5B: TREATMENT TABLE]

It is important for many clinical providers to recognize the importance of their participation in facilitating partner management. Prompt partner management can stem ongoing transmission in the community. The relatively long incubation period of primary syphilis (an average of 3 weeks, compared with the usual 2-7 days seen with gonorrhea [Chin, 2000]) furnishes the opportunity to provide effective post-exposure prophylaxis. Once inoculated, most persons become infectious themselves in just over 3 weeks. If post-exposure prophylaxis can be provided promptly enough to persons exposed to an infectious case of syphilis, incubating infection can be aborted and the risk of ongoing transmission eliminated.

One of the case patient's partners represents the source of infection and other partners could represent spread of infection (ie. partners who were exposed and now may be infected or incubating infection). Partner management attempts to address both the source and spread of a diagnosed infection. Determining which previous partners require evaluation and/or treatment relies upon the stage of infection in the case patient (See Figure 5B). In general, all patients with a syphilis infection of 12 months duration are considered to be infectious (ie. primary, secondary, and early latent syphilis).

Persons potentially exposed within 90 days before presentation may be incubating syphilis and all serologic screening tests will be negative. For this reason, the CDC recommends presumptive treatment (even in the absence of clinical or laboratory findings) of partners exposed to an infectious case of syphilis within the past 90 days.

Serologic screening for syphilis is also indicated for partners being presumptively treated (as a contact to an infectious case of syphilis) to determine whether they themselves are infected. In persons with incubating infections, serology will be negative.

Presumptive therapy is also recommended for persons exposed > 90 days before index case presentation if follow-up for serologic results and treatment cannot be ensured.

Partner Management Summary:

The maximum incubation period for syphilis is 90 days, therefore, a nonreactive serology in a sexual partner whose last potential exposure was ≤ 90 days ago could represent a false- negative result (falling within the "window period" for syphilis serologic testing).

Partners whose last contact with an infectious case was 90 days should be treated empirically at the time of initial evaluation, regardless of ultimate serologic tests results. Serologic testing is still important to help establish a diagnosis. If a partner is found to be already infected (to have a confirmed reactive serology), his/her partners require evaluation and management.

Partners whose last contact with an infectious case was 90 days who are found to be nonreactive serologically can be considered uninfected. If a STAT RPR is reactive (in a patient without past syphilis treatment), or if serologic results are not available immediately and follow-up is uncertain, presumptive treatment should be strongly recommended for these contacts at the initial visit.

Public Health Resources For Assistance in Partner Management

Local health departments routinely provide assistance in ensuring that all persons potentially exposed to infectious syphilis are offered clinical management. In most areas, all persons with primary, secondary and early latent syphilis are offered follow-up by specially-trained health department staff who document that adequate treatment was received and who attempt to identify at-risk partners. Department of Health Disease Intervention Specialists (DIS) attempt to contact patients and partners for whom adequate therapy cannot be confirmed, in order to encourage medical follow-up. Partner notification services provided by the health department occur without revealing any information about the original case patient, thereby protecting the patient's confidentiality.

8. PROMPTLY NOTIFY STATE OR LOCAL HEALTH DEPARTMENT OF ANY NEWLY DIAGNOSED CASES OF SYPHILIS.

Public Health Codes mandate that all diagnosing/treating providers (or their designees), in addition to all laboratories, promptly report all cases of the following sexually transmitted diseases:

	Contact Information	Providers are Mandated to Report:	Laboratories are Mandated to Report:
New York City	STDs: 1-866-NYC-DOH1 Hepatits: 212-788-9830 HIV/AIDS: 212-442-3388	• Syphilis (any stage, including congenital) • *Chlamydia trachomatis* • *Neisseria gonorrhoeae* • Chancroid *(Haemophilus ducreyi)* • Donovanosis/ Granuloma inguinale *(Calymmatobacterium granulomatis)* • Lymphogranuloma venereum (LGV) • Nongonococcal urethritis/ nonspecific urethritis • Hepatitis A, B, and C • HIV/AIDS	• Syphilis (any stage, including congenital) • *Chlamydia trachomatis* • *Neisseria gonorrhoeae* • Chancroid *(Haemophilus ducreyi)* • Donovanosis/ Granuloma inguinale *(Calymmatobacterium granulomatis)* • Lymphogranuloma venereum (LGV) • Hepatitis A B and C • HIV/AIDS
New York State	Disease reporting within New York State should be made directly to the local/county health department. For a listing of contact numbers visit: www.health.state.ny.us/nysdoh/lhu/map.htm	• Syphilis • *Chlamydia trachomatis* • *Neisseria gonorrhea* • Chancroid *(Haemophilus ducreyi)* • Donovanosis/Granuloma inguinale *(Calymmatobacterium granulomatis)* • Hepatitis A, B, and C • Lymphogranuloma venereum (LGV)	• Syphilis • *Chlamydia trachomatis* • *Neisseria gonorrhea* • Chancroid *(Haemophilus ducreyi)* • Donovanosis/Granuloma inguinale *(Calymmatobacterium granulomatis)* • Hepatitis A, B, and C • Lymphogranuloma venereum (LGV)
New Jersey	STDs: Phone: 609-588-7480 Fax: 609-588-7462 Hepatitis: Phone: 609-588-7500	• Syphilis (primary and secondary in outpatient settings, congenital in hospitals) • *Chlamydia trachomatis* (outpatient settings) • *Neisseria gonorrhoeae* (outpatient settings) • Hepatitis A (institutional settings) • Hepatitis B surface antigen test positive in a pregnant woman (outpatients settings) • Hepatitis C (outpatient & hospital settings)	• Syphilis • *Chlamydia trachomatis* • *Neisseria gonorrhoeae* • Chancroid *(Haemophilus ducreyi)* • Hepatitis A, B, and C

In cases of early primary, secondary, early latent syphilis, prompt reporting of cases allows for timely partner services which are critical in the interruption of ongoing disease transmission. On average, persons who have been exposed to infectious syphilis will themselves become infectious in approximately 3 weeks; if empiric therapy (ie. post-exposure prophylaxis) can be provided during this time, ongoing transmission can be prevented. Therefore, prompt reporting of cases can contribute significantly to disease prevention. For details on the reporting of syphilis and other sexually transmitted diseases, refer to the above contact numbers.

For Information regarding reporting and partner services in other states refer to the contact listing in Appendix H.

9. MONITOR TREATED PATIENTS SEROLOGICALLY TO ENSURE ADEQUATE RESPONSE TO THERAPY

[SEE FIGURE 6: FOLLOW-UP TABLE]

Currently, there is no readily available test-of-cure for syphilis, and "cure" is based upon the resolution of clinical signs and symptoms if present, and a 2 dilution (ie. four-fold) decrease in nontreponemal serologic titer within an appropriate time period. "Appropriate time period" is determined by the stage of disease at the time of treatment – *See Figure 6: Follow-up Table.* Note: nontreponemal titers may decline more slowly in patients with a history of treated syphilis.

FIGURE 6: FOLLOW UP OF TREATED SYPHILIS CASES

Stage	HIV Negative	HIV Positive	Inadequate Response to Therapy
	Follow up Serologies		
Primary or Secondary		3 months	Persistence or recurrence of signs/symptoms
	6 months	6 months	OR Failure of nontreponemal titer to decrease 2 dilutions (4 fold) within 6 months
		9 months	OR A 2 dilution (4 fold) or greater rise in nontreponemal titer since initiation of treatment (as compared with initial
	12 months	12 months	baseline or subsequent result)
		24 months[†]	
Latent (Early or Late)	6 months	6 months	In patients with an initial titer ≥1:32, failure of the non treponemal titer to decrease 2 dilutions (4-fold)
	12 months	12 months	within 12-24 months of the initiation therapy
		18 months	OR A 2 dilution (4-fold) or greater rise in nontreponemal since initiation of treatment
	24 months	24 months[†]	OR The development of signs/symptoms attributable to syphilis

NOTE: All patients treated for syphilis during pregnancy who are at high risk for re-infection or are in a geographic area in which the prevalence of syphilis is high should receive serologic follow-up monthly until the time of delivery, so as to detect and treat reinfection as early as possible.

[†] HIV-positive patients treated for syphilis should be followed yearly to ensure continued stable serofast or nonreactive nontreponemal titer.

Intervention in the face of an Inadequate Serologic Response to Therapy

1. Consider reinfection
   - Document interim sexual history and consider reinfection and need for retreatment if risk of re-exposure exists
   - Re-treat if patient follow-up of serial titers is uncertain
2. Consider Treatment Failure
   - Re-screen for HIV
   - If oral therapy was used, consider suboptimal compliance
3. Perform CSF Exam to identify unrecognized CNS infection
4. If risk of re-exposure is low and the presence of neurosyphilis has been ruled out by lumbar puncture most specialists would re-treat for late latent syphilis (eg. benzathine penicillin G 2.4 mU each week for three weeks for a total of 7.2 mU). In rare instances, patients with normal CSF findings who are given a repeated course of therapy may experience no further decline in nontreponemal titers. The need for additional therapy or CSF exams is unclear in these circumstances.

In some treated patients, nontreponemal titers can persist for an indefinite period of time (sometimes lifelong); these patients are said to be "serofast."

Even after an adequate serologic response to treatment has been documented, all treated patients should continue to be followed serologically, using a nontreponemal test such as RPR, either until seroreversal is achieved or a serofast serologic titer is well documented. The posttreatment serofast titer will serve as the baseline against which all future syphilis serologic results are compared. Therefore, assuring that the titer is as low as possible is critical to future patient management. Patients at continued risk of reinfection should be re-screened periodically every 6-12 months, depending on interval sexual history.

The CDC currently recommends that patients treated for neurosyphilis who have increased CSF WBCs at the time of diagnosis should have repeat CSF examinations every 6 months. If the cell count has not decreased after 6 months, or if the CSF is not entirely normal after 2 years, retreatment should be considered (2002 CDC Treatment Guidelines, 23).

HIV screening should be encouraged at the time of initial diagnosis and repeated in 3-6 months if initially negative.

10. ENCOURAGE BEHAVIORS WHICH PREVENT RE-INFECTION

Patients at risk for sexually transmitted infections, especially those recently diagnosed with such infection, should be engaged by the clinician in risk reduction counseling. Such counseling should attempt to address gaps in risk perception, identify specific risk behaviors which could be modified, assess barriers to behavior change, and assist in the development of a plan of action providing necessary referral if indicated.

For a more detailed discussion of behavioral counseling for STD/HIV risk reduction visit http://depts.washington.edu/nnptc/core_training/clinical/PDF/BEHAVIORAL%20COUNSELING.pdf

Key messages/behaviors that should be stressed include:

- Abstinence, monogamy, or reduction in number of sexual contacts can lower sexual risk.
- Barriers such as condoms do not protect against all exposures to body secretions and skin lesions. Nevertheless, when employed as part of a safer sex strategy, condom use can significantly reduce the risk of acquiring a sexually transmitted infection including HIV.
- If there is a question of exposure to a known infected partner, prompt evaluation and possible post-exposure prophylaxis should be sought.
- Periodic screening should be performed depending on risk history and local disease prevalence.

IV. APPENDICES

APPENDIX A: A COMPARISON OF SCREENING AND DIAGNOSTIC TESTS FOR SYPHILIS

Taken from Syphilis Reference Guide May 2002
Vickie Pope, PhD
Syphilis Serology Reference Laboratory
Sexually Transmitted Infections Branch
Division of AIDS, STD, and TB Laboratory Research
National Center for HIV, DTD, and TB Prevention
Centers for Disease Control and Prevention

Test	Advantages	Disadvantages
Dark field Microscopy	Definitive immediate diagnosis, in primary and secondary disease Inexpensive Rapid	Requires specialized microscope condenser and lenses or lens adapter. Requires experienced microscopist. Possible confusion with nonpathogenic spirochetes. Generally not recommended on oral lesions because of specificity problem with nonpathogenic spirochetes in the oral cavity. Must be read immediately; motility important to identify. False negatives increase with use of topical substances (eg. soap & water). Sensitivity decreases as the lesion heals
Direct Fluorescent Antibody (DFA-TP)	CDC Syphilis Lab generally recommends the use of monoclonal antibody since it is more specific – polyclonal antibody can cross react with other treponemes that are normal flora of the oral cavity and the GI tract. Commercially available, but not widely utilized. Compares favorably with darkfield microscopy.	Turnaround time 1-2 days, so requires patient to return for treatment. Usually a referral lab test requiring 1-1.5 hours to perform. Requires a fluorescence microscope in good working condition. Monoclonal antibody may be available from the CDC, although polyclonal is available commercially.
Nontreponemal Serologic Tests (RPR, VDRL, TRUST, USR)*	Rapid (RPR) and inexpensive. Easy to perform and can be done in clinic/office (RPR/TRUST) Yields both qualitative and quantitative. Used to follow response to therapy. Can be used to evaluate possible reinfection.	May be insensitive in certain stages (particularly primary and late latent). Prone to biological false positive reactions (See Page 12) Rarely, a phenomenon called "the prozone effect" may cause a false negative reaction. The prozone effect occurs when the test reaction is overwhelmed by antibody excess and may occur in late primary or in secondary syphilis. If clinical suspicion of secondary syphilis is high, the lab should dilute the serum to at least a 1/16 dilution to rule out the prozone effect. Affected by changes in temperature (eg. < 23˚ C, false negatives, > 28˚ C, false positives).
Treponemal Serologic Tests (TP-PA, FTA-ABS)	More specific than nontreponemal tests. More sensitive in Late Syphilis, when nontreponemal tests may have sero-revert to nonreactive.	More expensive than nontreponemal tests. Cannot be performed in a clinic or office for STAT evaluations. Remains reactive (positive) for life in 75-85% of all individuals with syphilis, regardless of whether the person was adequately treated
IgG EIA	IgM-specific test may be available through the CDC (samples submitted through the State Health Department)	Not quantitative, therefore a positive result needs to be followed by a nontreponemal test.

*All nontreponemal serologic tests are of relatively equal sensitivity and specificity, Although all nontreponemal serologic tests for syphilis are of relatively equal sensitivity and specificity, the titer of any given specimen may differ if subject to different nontreponemal tests. Therefore, when possible, longitudinal titers for a given patient shuld be determined using the same nontreponemal assay.

APPENDIX B:

INTERPRETATION AND MANAGEMENT OF *TREPONEMA PALLIDUM* IgG RESULTS

In November of 2000, the FDA approved the Captia Syphilis-G IgG EIA assay for commercial use as a screening test for the qualitative detection of IgG to Treponema pallidum in serum specimens.

This recently approved use of a treponemal test allows for automation and offers laboratory cost savings when screening a large number of specimens, compared with the RPR, which to date remains manual. Consequently, several local laboratories which perform a high volume of syphilis testing, have chosen to switch from using the RPR/VDRL as the initial screening test to a strategy which utilizes IgG EIA (with RPRs performed only on IgG-positive specimens). Laboratories performing IgG EIAs as a screening test may employ either a second IgG or alternative treponemal test to retest IgG EIA positive specimens.

Although not as extensively studied as the RPR or FTA-ABS, the IgG EIA appears to have similar performance characteristics in general populations in which the prevalence of syphilis is low.[B6,B7,B8,B9] However, some studies have raised the concern that the IgG EIA may have a limited sensitivity for detecting very early primary syphilis, a fact which is also true of the RPR/VDRL, and both tests should be interpreted with caution when attempting to rule out primary syphilis.[B10]

INTERPRETATION OF *T. Pallidum* IgG EIA RESULTS

The following can be used as guidelines for the interpretation of IgG EIA results.

Note: Specific recommendations regarding individual patients need to factor in the details of the patient history and examination, and clinicians should confer with their local infectious disease specialists for guidance in specific case management.

- For the purposes of general screening, **a negative IgG EIA** result most likely represents a patient without current or past syphilis infection. A negative IgG result cannot exclude a diagnosis of incubating syphilis (or possibly very early primary syphilis). There is some evidence which suggests that the FTA-ABS is one of the most sensitive tests during primary syphilis and is routinely ordered for all NYC Department of Health and Mental Hygiene STD clinic patients with an ulcerative lesion consistent with primary syphilis.
- A result of **a positive IgG EIA** and **reactive RPR** should be interpreted as current active syphilis or old treated syphilis.

  As is the case with a confirmed reactive RPR, patients with *no history* of treatment in the past should be treated based upon stage of disease.

  Patients with a history of past treatment for syphilis should be managed according to current CDC STD Treatment Guidelines (ie. based upon serologic response to past treatment, any significant changes in RPR titer, compared with previous titers, recent exposure history, current/recent symptoms and exam findings).
- Serologic results of a **positive IgG EIA** but a **nonreactive RPR** could represent one of the following clinical scenarios:

1. **False positive treponemal test**
   This phenomenon is not unique to IgG testing and has been documented with other treponeme specific tests. False positive result for trepenome-specific tests, such as the FTA-ABS is seen in less than 1% of healthy individuals, although more commonly in the elderly[B6] especially in patients with connective tissue disorders, autoimmune disease, type-1 diabetes, Lyme disease, and certain viral infections including Herpes Simplex Virus, and infectious mononucleosis.[B1, B7]

2. **Laboratory Error**
   Laboratory error may play an important role in the false-positive rate of treponemal tests such as the FTA or IgG EIA.[B8,B9] Technical error may be ruled out by repeat testing, unless systematic laboratory problems exist.

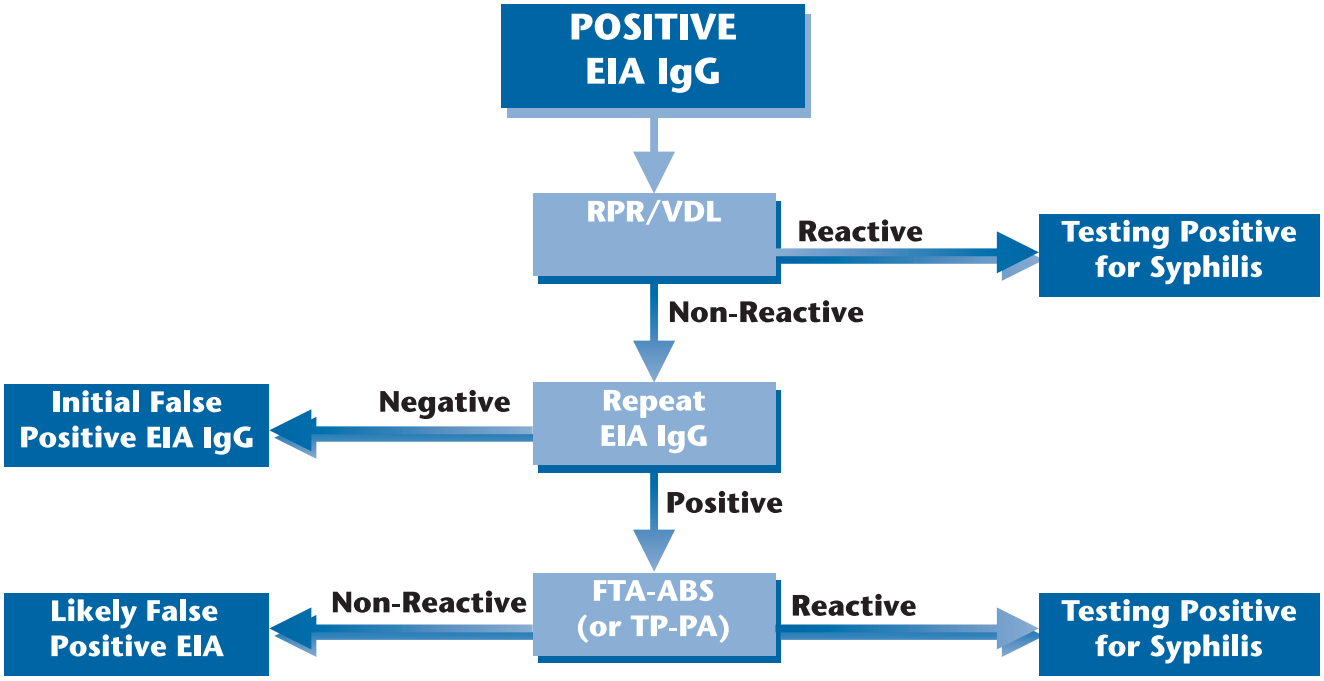
3. **Very early primary syphilis**
   The interval from the appearance of a primary lesion to initial sero-conversion depends upon the serologic assay used. Treponemal tests (FTA, IgG) may be the first test to become reactive in early syphilis infection. The RPR takes, on average, 10 days after the onset of a primary lesion to become reactive and therefore may be nonreactive at the onset of a chancre.[B1,]

4. **Secondary syphilis with prozone phenomenon**
   A prozone phenomenon can cause a false-negative RPR in response to excessively high antibody titers and is seen in 1-2% of cases of secondary syphilis.[B2] A prozone phenomenon can be ruled out by having the lab repeat RPR testing on the same specimen after the specimen dilution.

5. **Late untreated syphilis with seroreversion**
   A total of 25% to 30% of patients diagnosed with *late syphilis* will have nonreactive nontreponemal values for VDRL/RPR despite the absence of treatment.[B1,B3,B4] This scenario may be ruled out by repeat treponemal testing using a different treponeme specific assay, such as TP-PA or FTA-ABS.

6. **History of old, treated syphilis**
   Whereas the RPR may serorevert to nonreactive after adequate treatment, the treponemal test generally remains reactive for life (85%).[B5] A patient with a positive treponemal serology result may have been treated in the past but failed to recall such treatment, or the infection may have been cured inadvertently at the time of treatment for a nonsyphilis infection.

RECOMMENDED LABORATORY TESTING ALGORITHM AND INTERPRETATION OF EIA IgG RESULTS IN THE DIAGNOSIS OF SYPHILIS



MANAGEMENT GUIDELINES FOR PATIENTS WITH *POSITIVE IgG EIA* AND *NONREACTIVE RPR*

Based upon discussions with the Centers for Disease Control and Prevention (CDC), local laboratories and infectious disease specialists, and published literature (Pope 2004), the following outlines an approach to the interpretation of a **positive IgG EIA** in the face of a **nonreactive RPR** in a patient with no history of recent exposure to an infectious case and no exam findings consistent with a syphilis diagnosis.

- First, the specimen should be retested by IgG EIA to rule out a false-positive IgG due to laboratory error.[1]
- If the repeat IgG EIA is also positive, a second treponemal test (TP-PA or FTA-ABS) should be performed for confirmatory purposes.[1]

  If the second treponemal test is negative the patient can be considered currently uninfected.

  If the second treponemal test is positive, the patient should be considered infected or adequately treated for syphilis in the past, and managed according to exposure history, current/recent symptoms and exam findings, serologic response to past treatment, and any significant changes in RPR titer, compared with previous titers.

[1] It is important to check with the referral laboratory performing syphilis IgG EIA testing for your facility as some labs will do additional confirmatory testing (including a repeat IgG or alternative treponemal test) before reporting a positive IgG.

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APPENDIX C: SYPHILIS IN HIV-INFECTED PERSONS

Taken from:

Prevention and Management of Sexually Transmitted Diseases in Persons Living with HIV/AIDS

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APPENDIX C: SYPHILIS IN HIV-INFECTED PERSONS

I. GENERAL OVERVIEW

- Syphilis is a systemic disease caused by T. pallidum.
- Cases of rapid progression from early syphilis to neurosyphilis in HIV-infected patients, some having received appropriate therapy for early syphilis have been reported (Gordon, 1994).
- There are some associations between accelerated ulcerating syphilis and advancing HIV disease.
- One study found no association between HIV stage and syphilis progression or treatment failure (Rolfs, 1997).

II. CLINICAL PRESENTATION

- Stages often present similarly to stages in non-HIV-infected individuals (Musher, 1998). Differences are highlighted in the following text.

PRIMARY SYPHILIS

- **Chancre:** begins as a macule/papule which progressively erodes into a clean based, painless, indurated ulcer with smooth firm borders. **Although usually singular, multiple chancres can occur in at least 25% of cases, and are more common in HIV-infected persons (up to 70% of cases in one study) (Rolfs, 1997; Rompalo, 2001).**
- **Lymphadenopathy** is classically painless, rubbery, and bilateral. No difference in clinical presentation has been documented between HIV infected and non-infected persons.

SECONDARY SYPHILIS

- Symptoms usually occur 3-6 weeks after primary stage.
- Symptoms may include constitutional symptoms (malaise, fever, headache, etc.), a maculopapular rash which often involves palms and soles, generalized lymphadenopathy, mucous patches in the mouth, and condyloma lata.

LATENT SYPHILIS

- Is defined as the presence of a positive serology in the absence of evidence of clinical disease and is divided for contact tracing and treatment purposes into two sub-categories:

  Early latent < 1 year duration

  Late latent > 1 year duration

- The latent stage can last 2 to 50 years

TERTIARY SYPHILIS

Late benign syphilis or gummatous syphilis

- The "gumma" is felt to be a marked inflammatory response to a small number of organisms. Pathologically, it is a granuloma with coagulative necrosis. There can be involvement of any organ system, and lesions may occur in the skeletal, spinal, and mucosal areas, as well as in the eye, viscera and the brain.
- Among all individuals with syphilis, the average onset is 4 to 10 years. However, **rapid progression from the primary chancre to gummatous lesions has been observed to occur over a period of months in some HIV-infected patients (Friedman-Kien, 1996)**.

CARDIOVASCULAR SYPHILIS

- Predilection for the vasa vasorum of the proximal aorta, with development of endarteritis.
- Cases of **rapidly developing aortitis have been reported in HIV-positive persons.**

NEUROSYPHILIS

- Neurosyphilis should always be considered in the differential diagnosis of neurologic disease in HIV-infected persons.
- Despite appropriate treatment, **patients with HIV have been reported to progress to neurosyphilis in the first two years after the diagnosis of syphilis** (Malone, 1995).
- There are various case reports of HIV-infected patients who experienced rapid progression from early syphilis to neurosyphilis. These patients presented with meningitis or cranial nerve deficits such as optic neuritis and deafness (Johns, 1987; Musher, 1990; Flood, 1998).
- According to a multicenter randomized trial, the detection of *T. pallidum* in the CSF in early syphilis is not more common in HIV infected persons, is not predictive of symptomatic neurosyphilis and is not linked to higher rates of serologically defined treatment failures. These findings suggest that **aggressive evaluation of the CSF in HIV-infected persons presenting with early syphilis may not be useful to guide therapy** (Rolfs, 1997).

III. SUMMARY OF UNIQUE FEATURES ASSOCIATED WITH HIV INFECTION:

1. Primary stage of syphilis consisting of **multiple or very extensive chancres.**
2. Neurosyphilis - Reports suggest that HIV-positive patients **have early neurological involvement and a higher risk of developing neurosyphilis than HIV negative patients,** despite previous therapy for syphilis. Case reports also suggest a more rapid progression of disease, with symptomatic neurosyphilis likely to occur sooner after infection in the HIV- positive patient compared with the HIV-negative patient. **Syphilitic meningitis** occurs more commonly in HIV-positive patients. However, **HIV-positive patients with or without neurosyphilis, are more likely to be younger, have higher CSF WBC counts and higher CSF protein levels.**

3. **Published case reports describe gummatous lesions** with possible involvement of skin, groin, penis, calf, thigh, oral cavity, and cerebrum.
4. Rapidly developing cases of **syphilitic aortitis.**
5. Presentation of syphilis as encephalitis and arteritis.
6. **Condyloma latum,** seen in patients with secondary syphilis, have been reported as more common in HIV-infected patients. Conflicting data exist.
7. Other unusual cutaneous manifestations include **lues maligna (syphilis with vasculitis), sclerodermiform lesions, keratodermas, extensive oral ulcers, deep cutaneous nodules, rubelliform eruptions, and hepatitis.**

IV. DIAGNOSIS

SEROLOGIC TESTS FOR SYPHILIS AND HIV INFECTION

- **The vast majority of HIV-positive patients will have nontreponemal and treponemal tests results that are consistent with their HIV-negative counterparts, and so appear to be accurate and reliable for diagnosis and following response to treatment.** However, HIV-infected patients may present with atypical serologic results (higher than expected, false negatives, delayed appearance of seroreactivity or fluctuating titers).
- Recent data suggests that **HIV-positive patients respond less well serologically and titers decline more slowly than do patients without HIV infection when treated for early syphilis,** but clinically defined failure is uncommon in both groups. Rates of serologically defined treatment failures appear unrelated to CD4 cell counts in HIV-infected persons.
- **Negative syphilis serologies have been reported in HIV-positive patients with clinical evidence of syphilis.** This infrequent finding is limited to patients with CD4 < 200. **Dark field examination of ulcerative lesions, as well as biopsy of skin rashes and lesions with subsequent direct fluorescent antibody (DFA) staining, should be considered in these cases.**
- Treponemal tests may return to negative in HIV-positive patients over time. A study by Haas et al. suggests that the reactivity to treponemal tests may decrease when the CD4 count < 200 (Haas, 1990).
- **HIV can cause a false-positive syphilis nontreponemal test. (eg. RPR, VDRL).**

INDICATIONS FOR CSF EVALUATION

- Any time clinical signs and symptoms of CNS and/or ophthalmic involvement are present (these can occur in early syphilis in HIV infected persons).
- Treatment failure (See Section 9).
- **In syphilis of > 1 year duration or unknown duration if HIV infection.**
- Evidence of active tertiary syphilis (gummas, aortitis, iritis).

- **CSF abnormalities such as mononuclear pleocytosis and elevated protein are common in early syphilis and in HIV infection. As a result, the clinical prognostic significance of CSF abnormalities in HIV-infected persons with primary or secondary infection is uncertain.** Most HIV-infected persons respond appropriately to standard penicillin therapy. However, some experts recommend CSF examination before treatment of early syphilis and intensified therapy if CSF abnormalities are present.

- **Neurosyphilis should be considered in the differential diagnosis of neurological disease in HIV infected persons.**

V. TREATMENT

RECOMMENDED TREATMENT REGIMEN FOR EACH STAGE OF SYPHILIS REMAINS THE SAME FOR HIV INFECTED AND NON-INFECTED PERSONS.

- Penicillin is the drug of choice in HIV-infected patients. If the patient is allergic, he/she should be managed according to the recommendations for penicillin-allergic HIV-negative patients. The use of alternatives to penicillin have not been well studied in HIV-infected patients.

- **Treatment failures with currently recommended regimens for syphilis have been reported in HIV-infected patients.** In addition, other reports suggest that HIV-infected patients with early syphilis are at increased risk of neurologic complications. However, a recent randomized clinical trial suggests that the magnitude of these risks is probably small, and no treatment regimen other than the ones recommended have been proven to be more effective in preventing neurosyphilis. Therefore, close follow-up is warranted for all HIV-infected persons treated for syphilis, regardless of treatment regimen.

- **The Jarisch-Herxheimer reaction** is a febrile reaction with chills, fever, arthralgias, headache, and a transiently increased prominence of lesions. It is due to the release of treponemal constituents, probably in an endotoxin-like reaction (Musher, 1998). This reaction is **reported more frequently in HIV-infected persons than noninfected persons, following treatment for early syphilis (26% vs. 12%, respectively).**

RECOMMENDED TREATMENT FOR PRIMARY, SECONDARY AND EARLY LATENT SYPHILIS (< 1 YEAR'S DURATION)

Benzathine penicillin G 2.4 million units IM one dose.

- Some experts recommend **additional treatment, such as three weekly doses of benzathine penicillin or additional antibiotics.**

- Penicillin allergy: Data are limited; however, doxycycline 100 mg orally twice daily for 14 days and tetracycline 500 mg four times daily for 14 days are regimens that have been used. Some specialists recommend ceftriaxone 1 gram IM or IV daily for 8-10 days. **The use of any of these therapies in HIV infected persons has not been studied and must be undertaken with caution.**

- **Pregnant HIV-infected patients who are penicillin allergic must be desensitized and treated with penicillin.**

RECOMMENDED TREATMENT FOR LATE LATENT SYPHILIS (> 1 YEAR'S DURATION) OR OF UNKNOWN DURATION

Benzathine penicillin G 2.4 million units IM weekly x 3 consecutive weeks

- Rule out tertiary disease in all patients with latent syphilis (neurosyphilis, aortitis, gummas, iritis) by clinical examination.
- Perform lumbar puncture before treatment if patient has HIV infection (in both late latent syphilis or latent syphilis of unknown duration).
- Penicillin-allergy: Doxycycline 100 mg orally twice daily for 28 days or tetracycline 500 mg four times daily for 28 days. If follow-up cannot be ensured or if the HIV infected patient is pregnant, desensitize and treat with penicillin. The efficacy of alternative nonpenicillin regimens in HIV-infected person have not been well studied.

RECOMMENDED TREATMENT FOR NEUROSYPHILIS & OCULAR INFECTION

Aqueous crystalline penicillin G 18-24 million units IV daily, administered as 3-4 million units every 4 hours, or by continuous infusion, for 10-14 days

(OR)

Procaine penicillin 2.4 million units IM daily, for 10-14 days

PLUS

Probenecid 500mg PO four times a day for 10-14 days

- The durations of the recommended regimens for neurosyphilis are shorter than that for the regimen used for late syphilis in the absence of neurosyphilis. Therefore, some experts administer benzathine penicillin, 2.4 million units IM after completion of these neurosyphilis treatment regimens to provide a comparable total duration of therapy. Some experts administer three doses one week apart.
- Despite the use of this treatment regimen, patients with ocular infection should have a lumbar puncture (LP) performed to rule out neurosyphilis, as those patients with positive LP results would require follow-up LPs to assess adequacy of treatment.

VI. SYPHILIS FOLLOW-UP AFTER TREATMENT

PRIMARY, SECONDARY AND EARLY LATENT SYPHILIS

- Re-examine serologically and clinically at 3, 6, 9, 12, and 24 months after treatment.
- Some experts recommend CSF exam 6 months after therapy (unproven benefit).
- CSF exam if treatment failure suspected (persistent signs and symptoms, fourfold increase in titers) or failure of titers to decrease fourfold after 6 to 12 months; retreat with 2.4 million units IM of benzathine penicillin if no neurosyphilis per CSF exam.

LATE LATENT SYPHILIS

- Re-examine serologically and clinically at 6, 12, 18 and 24 months after therapy.
- If titers fail to decrease fourfold between 12 and 24 months, clinical symptoms develop, or titers rise fourfold, repeat LP and treat according to CSF results.

NEUROSYPHILIS

- If initial pleocytosis was present, CSF examination every 6 months until cell count is normal.
- If CSF cell count has not decreased after 6 months, or if CSF is not entirely normal after 2 years (negative VDRL and normal protein level), consider retreatment.

VII. MANAGEMENT OF SEX PARTNERS

Sexual transmission of T. pallidum occurs only when mucocutaneous syphilitic lesions are present; such manifestations are uncommon after the first year of infection. However, persons exposed sexually to a patient who has syphilis in any stage should be evaluated clinically and serologically according to the following recommendations:

- Persons who were exposed within the 90 days preceding the diagnosis of primary, secondary, or early latent syphilis in a sex partner might be infected even if seronegative. Therefore such persons should be treated presumptively.
- Persons who were exposed >90 days before the diagnosis of primary, secondary, or early latent syphilis in a sex partner should be treated presumptively if serologic test results are not available immediately and the opportunity for follow-up is uncertain.
- For purposes of partner notification and presumptive treatment of exposed sex partners, patients with syphilis of unknown duration who have high nontreponemal serologic test titers (>1:32) can be assumed to have early syphilis. However, serologic titers should not be used to differentiate early from late latent syphilis for the purpose of determining treatment (see Latent Syphilis Treatment).
- Long term sex partners of patients who have latent syphilis should be evaluated clinically and serologically for syphilis and treated on the basis of the evaluation findings.

For identification of at-risk partners, the time periods before treatment are as follows:

Primary Syphilis: 3 months plus duration of symptoms,

Secondary Syphilis: 6 months plus duration of symptoms, and

Early Latent Syphilis: 1 year

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APPENDIX D: DIAGNOSIS AND MANAGEMENT OF NEUROSYPHILIS

Central nervous system invasion occurs early in syphilis infection in 30-40% of patients, but most patients eventually clear this site of infection with appropriate early syphilis therapy.

Asymptomatic neurosyphilis can occur at any stage. Early forms of symptomatic neurosyphilis usually occur a few months to a few years after infection. Clinical manifestations include acute syphilitic meningitis, a basilar meningitis (typically involving cranial nerves VI, VII and VIII) or meningovascular syphilis (an endarteritis that presents as a stuttering, stroke-like syndrome with seizures).

Late forms of neurosyphilis usually occur decades after infection and are rarely seen in the U.S. Clinical manifestations of parenchymatous involvement include general paresis and tabes dorsalis.

Ocular involvement can also be seen in early or late neurosyphilis, in which uveitis may be the most common early presentation.

INDICATIONS FOR CSF EXAMINATION [CDC STD TREATMENT GUIDELINES, 2002]

- Signs or symptoms of neurosyphilis (including ophthalmologic). A slit lamp examination is also recommended.
    - » Headache, vertigo, neck stiffness without fever, seizures, focal symptoms
    - » Cognitive dysfunction, mental status or personality changes, dementia, psychosis
    - » Cranial nerve dysfunction (especially facial and auditory)
    - » Ophthalmologic manifestations (optic neuritis, iritis, pupillary dysfunction)
    - » Peripheral neuropathies (lightning pain, sensory, motor, or reflex deficiencies, gait disturbance)
- Evidence of active tertiary syphilis (aortitis, gumma, or iritis)
- Treatment failure (including inadequate serologic response to therapy) *[See Follow-up Table, Figure 6, page 26]*
- HIV-infected persons with late latent syphilis or latent syphilis of unknown duration
- Some experts recommend CSF examination in patients (regardless of HIV status) with latent syphilis with an RPR OR VDRL ≥1:32.

Note: Performing and obtaining a CSF exam for neurosyphilis should ideally occur before starting treatment. However, some experts choose to begin treatment while awaiting the results of neurosyphilis workup.

ABNORMAL CSF FINDINGS

> 5 WBC/mm^3
> 40-50 mg/dL of protein
Reactive CSF-VDRL**

** The CSF-VDRL is a very specific test and, when reactive in the absence of substantial contamination of CSF with blood, is considered diagnostic of neurosyphilis. Nevertheless this test is not very sensitive; therefore a diagnosis of neurosyphilis should be considered in a patient with a nonreactive CSF-VDRL if CSF WBCs >5 (>10-20 WBCs in HIV-infected patients) and no other etiology has been identified. Although some specialists believe that a negative CSF FTA-ABS test can exclude neurosyphilis, there are no data to support the use of FTA-ABS for this purpose.

TREATMENT

- Aqueous crystalline penicillin G 18-24 million units per day, administered as 3-4 million units intravenous every 4 hours or by continuous infusion, for 10-14 days.

  (OR)

- Procaine penicillin 2.4 million units intramuscular daily *plus* probenecid 500 mg orally 4 times daily, both for 10-14 days. [This regimen should be used as an outpatient regimen only if compliance can be ensured].

When treating neurosyphilis during late latent syphilis or latent syphilis of unknown duration, some experts recommend adding benzathine penicillin G 2.4 million units intramuscular once per week for up to 3 weeks after the completion of one of the above neurosyphilis treatment regimens to provide a total duration of therapy comparable to that used for late latent syphilis.

Penicillin allergy: Patients who are skin-test-reactive for an allergy to penicillin should be hospitalized, desensitized, and treated with penicillin. Ceftriaxone can be used as an alternative treatment for patients with neurosyphilis who are allergic to penicillin although the possibility of cross-reactivity between this agent and penicillin exists. There are little data to support the use of any specific dose. Some experts recommend ceftriaxone 2 grams daily intramuscular/intravenous for 10-14 days (CDC 2002 Treatment Guidelines).

Neurosyphilis in pregnancy: Pregnant women with a known history of penicillin allergy should be desensitized and treated with penicillin.

Auditory disease attributed to syphilis infection: Many specialists recommend treating patients with syphilis-related auditory disease with a neurosyphilis regimen regardless of CSF results.

Note: All patients treated for syphilis should be screened for HIV.

FOLLOW-UP

If the initial CSF examination showed pleocytosis, the CDC recommends repeat CSF exams every 6 months following treatment until the cell the count is normal. If the cell count has not decreased after 6 months or if the CSF is not completely normal after 2 years, retreatment should be considered. [2002 CDC Treatment Guidelines].

APPENDIX E: SYPHILIS IN PREGNANCY

Pregnant women who are found to be seropositive for syphilis should be considered infected unless an adequate treatment history can be well documented and sequential serologic titers have declined appropriately following past therapy.

In the second half of pregnancy, management and counseling may be facilitated by a sonographic fetal evaluation for congenital syphilis, but this should not delay therapy. Sonographic signs of fetal infection (hepatomegaly, ascites, and hydrops) indicate a greater risk of fetal treatment failure; such cases should be managed in consultation with an obstetrics specialist [2002 STD Treatment Guidelines].

Penicillin is the only CDC recommended regimen for the treatment of syphilis during pregnancy and the prevention of congenital syphilis in the newborn. Tetracyclines (including doxycycline) are contraindicated during pregnancy because of their potential negative effect on tooth coloration and long-bone growth [Elder, 1971]. The effectiveness of erythromycin in preventing congenital syphilis is questionable given the expected suboptimal adherence due to associated gastrointestinal side effects, unpredictable maternal serum drug levels, and erratic transplacental drug transfer [Fenton, 1976; Philipson, 1973]. These concerns are borne out by reports of clinical evidence of congenital syphilis among children born to mothers treated with erythromycin during gestation [Wendel, 1998; Sanchez, 1997; Hook, 1992; Mascola, 1984]. Currently, there is insufficient evidence to support azithromycin or ceftriaxone as effective in preventing congenital disease.

Although the formal CDC recommendations to treat primary, secondary, and early latent syphilis in a pregnant woman with a single dose of benzathine penicillin G (2.4 mU IM), some experts recommend a second 2.4mU dose 1 week after the first dose for women with primary, secondary or early latent syphilis. Pregnant women with a known penicillin allergy should be hospitalized, desensitized, and treated with penicillin as described in Section 5.

Women treated for syphilis during the second half of pregnancy are at risk for premature labor and/or fetal distress if a Jarisch-Herxheimer reaction occurs (See Page 18). Women receiving treatment during the 2nd half of gestation should be advised to seek obstetric attention after treatment if they notice any contractions or decreased fetal movements.

Women treated for syphilis during pregnancy should be monitored closely using serologic titers, eg. monthly in women at high risk for reinfection or in geographic areas with high prevalence of syphilis.

In addition, special attention should be paid to the management of sex partners of a woman treated for syphilis during pregnancy to prevent re-infection.

APPENDIX F: PREVENTION, DIAGNOSIS AND MANAGEMENT OF CONGENITAL SYPHILIS

Transmission

Syphilis can be transmitted from mother to fetus at any stage of maternal infection although risk of fetal infection is greatest among mothers with more recently acquired syphilis (ie. primary and secondary > early latent > late latent). Transmission can also occur at any point during the pregnancy but the risk of fetal infection is greatest during late pregnancy.

Prevention

The prevention of congenital syphilis relies on timely screening during pregnancy and at delivery. Screening for syphilis is recommended for the following individuals:

- All women at their first prenatal visit and at delivery
- All women early in the 3rd trimester of pregnancy and at delivery if they are at high risk for infection, are living in areas of high morbidity, or have not had prenatal testing.
- All newborns > 22 weeks gestation at the time of delivery*
- All women delivering a stillborn infant

* Routine screening of the mother's serum is preferred over testing of either the infant's umbilical cord blood or serum for the following reasons respectively: 1) Cord blood can become contaminated with maternal blood and could cause a false-positive result; 2) Serologic tests on infant serum can be nonreactive if the mother's serologic titer is low or the mother was infected late in pregnancy.

All infants born to mothers with a reactive nontreponemal and treponemal serologic result should have a quantitative nontreponemal test performed on infant serum.

No newborn should be discharged from the hospital before a review of maternal and newborn serologies obtained at the time of delivery.

Presentation

The following reviews the wide range of clinical findings in children < 2 years of age who have become infected with syphilis in utero:

Early Congenital Syphilis (< 2 years old)

- Rhinitis
- Dermatologic Abnormalities
  - « Pink-to-coppery macular eruption with a fine silvery scale which spares the anterior trunk
  - « Pemphigus syphiliticus (bullous and desquamatory eruption)
  - « Paronychia
  - « Alopecia
  - « Mucous patches on nares, lips and anus which can evolve into hemorrhagic fissures
  - « Condyloma lata
- Hepatosplenomegaly
- Adenopathy
- Epiphysitis (usually of the radius, femur, humerus, and fibula)

- Osteochondritis and periostitis
- Autoimmune hemolysis
- Central Nervous System Abnormalities
    - « Leptomeningitis and hydrocephalus
    - « Strokes
    - « Chronic meningovascular disease
    - « Hypopituitarism
    - « Ophthalmic abnormalities
        - « Chorioretinitis
        - « Glaucoma
        - « Uveitis

Management of a reactive nontreponemal syphilis serology during pregnancy
To ensure optimal diagnosis and management of children born to mothers with a reactive syphilis serology during pregnancy the following should be performed:

- A complete physical examination of both mother and child
- Laboratory evaluation via dark field or direct fluorescent antibody testing of any skin lesions or abnormal newborn fluids such as nasal discharge
- Consideration of the timing and adequacy of any treatment received by the mother (before becoming pregnant, during pregnancy, > 4 weeks before delivery, or within the final 4 weeks of the pregnancy)
- Consideration of type of maternal treatment (long-acting benzathine penicillin vs. nonpenicillin regimen)
- Consideration of maternal serologic response to therapy (Rule out "treatment failure" in the mother)
- A quantitative nontreponemal serologic test (RPR or VDRL) performed on both the infant's and mother's serum at delivery

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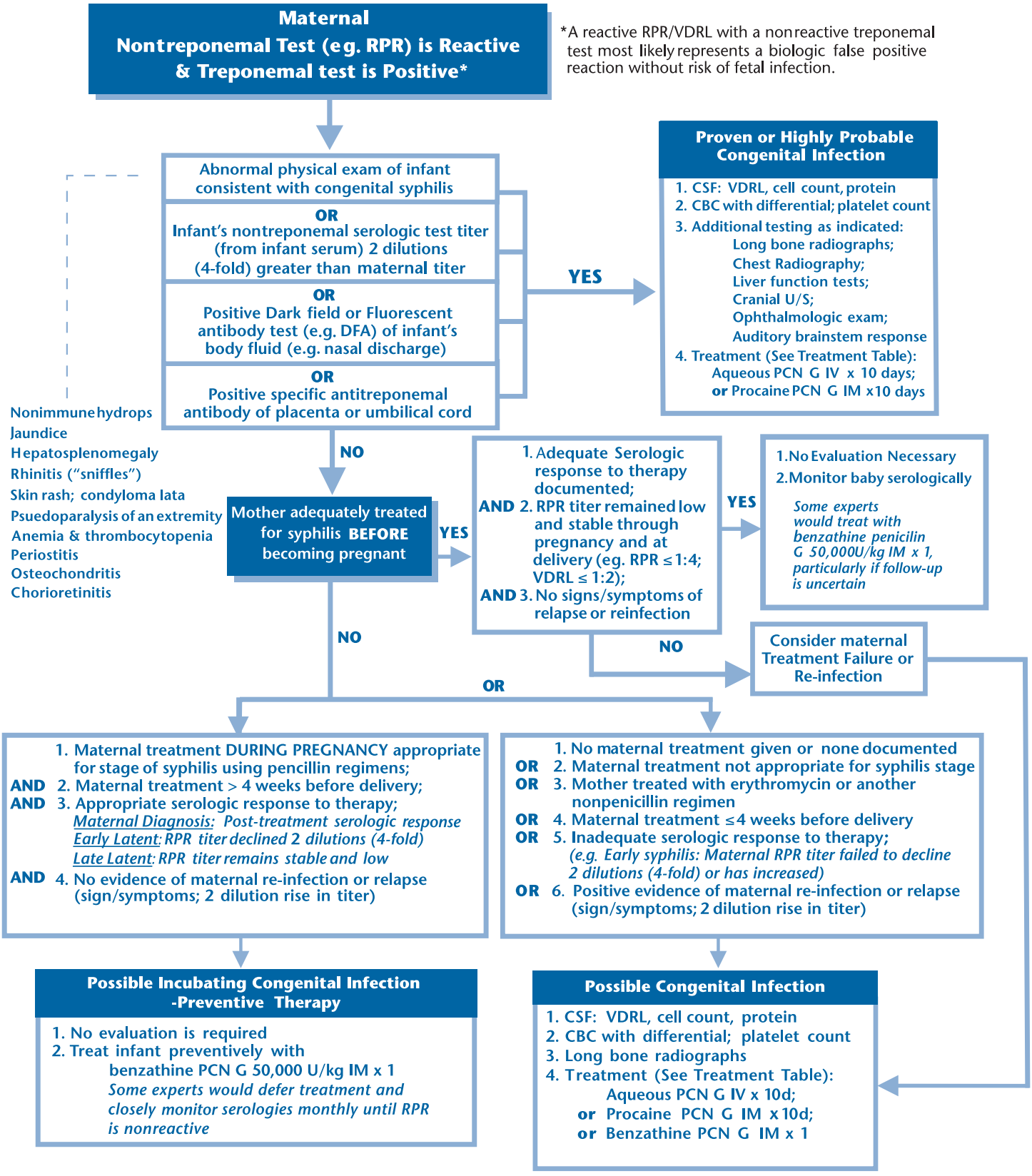
The algorithm on the next page outlines an approach to evaluation and management based on 2002 CDC guidelines.

CHART F1- EVALUATION AND MANAGEMENT OF THE INFANT IN THE FIRST MONTH OF LIFE



Adapted from the 2002 CDC STD Treatment Guidelines

TREATMENT OF SYPHILIS IN THE INFANT		
Indications for Treatment*	**Recommended Treatment Regimens**	**Comments**
Proven or Highly Probable Congenital Infection	• Aqueous crystalline penicillin G 100,000-150,000 units/kg/day, administered as 50,000 units/kg/dose IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days **OR** • Procaine penicillin G 50,000 units/kg/dose IM in a single daily dose for 10 days	• Data are insufficient regarding the use of other antibiotic regimens including ampicillin. • If more than 1 day of therapy is missed, the entire course should be re-administered.
Possible Congenital Infection	• Aqueous crystalline penicillin G 100,000-150,000 units/kg/day, administered as 50,000 units/kg/dose IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days **OR** • Procaine penicillin G 50,000 units/kg/dose IM in a single daily dose for 10 days	• Aqueous crystalline penicillin or procaine penicillin is preferred by some specialists if the mother has untreated early syphilis at delivery • A complete evaluation of the infant is not necessary when these regimens are used, although a lumbar puncture documenting CSF abnormalities would be useful to prompt close follow-up • If more than 1 day of therapy is missed, the entire course should be re-administered.
	OR • Benzathine penicillin G 50,000 units/kg IM in a single dose	• Infant must be fully evaluated (CSF exam, long bone radiographs, and CBC with platelet count) and the evaluation must be normal • Follow-up must be certain
Possible Incubating Congenital Infection, or Need for Preventive Therapy	• Benzathine penicillin G 50,000 units/kg IM in a single dose	• Some specialists would provide close serologic follow-up rather than provide treatment

*See Management Flow Chart for details on treatment indications and types of infection

Note: Infants experiencing an allergic reaction to penicillin should be desensitized and then treated with penicillin.

POST-TREATMENT FOLLOW-UP

All seroreactive infants or infants born to seroreactive mothers who were seroreactive at delivery should receive follow-up examination and nontreponemal serologic testing every 2-3 months, until their nontreponemal serologic titer has decreased 2 dilutions (4-fold) or has become nonreactive.

Infants with an initially abnormal CSF exam should undergo repeat CSF testing approximately every 6 months until the results are normal. A reactive CSF VDRL or abnormal CSF indices not attributable to other ongoing illness require re-treatment for possible neurosyphilis.

In uninfected children born to infected mothers (or to mothers with a history of old, treated syphilis), the RPR should become nonreactive by 6 months.

If infected, a child's RPR may take until 12 months of life to become nonreactive; the FTA usually remains reactive after treatment (even after 15 months of age).

Infant's Infection Status	Expected Serologic Changes†
Infant not infected Reactive serologic test results caused by passive transfer of maternal antibodies	By 3 months- Decline in nontreponemal titer By 6 months- Nontreponemal test becomes nonreactive After 15-18 months- Treponemal serologic test nonreactive
Infant infected but adequately treated	By 3 months- Decline in nontreponemal titer By 6 months- Nontreponemal test becomes nonreactive After 15-18 months- Treponemal serologic test **remains reactive**
Persistent congenital infection Need for re-evaluation and, possible retreatment with 10 day course of parenteral penicillin G.	After 6-12 months- No decline (or a rise) in nontreponemal titer **OR** **At 18 months - nontreponemal tests remains reactive**

†Serologic response after therapy may be slower for infants treated after the neonatal period.

APPENDIX G: EVALUATION AND MANAGEMENT OF SYPHILIS IN CHILDREN (TAKEN FROM THE 2002 CDC STD TREATMENT GUIDELINES, MMWR 2002; 51 (RR06): 20, 22, 28)

Primary and Secondary Syphilis

After the newborn period, children with syphilis should have a CSF examination to detect asymptomatic neurosyphilis, and birth and maternal medical records should be reviewed to assess whether such children have congenital or acquired syphilis. Children with acquired primary or secondary syphilis should be evaluated (eg. through consultation with child-protection services) and treated by using the following pediatric regimen.

Benzathine penicillin G 50,000 units/kg IM, up to the adult dose of 2.4 million units in a single dose.

Latent Syphilis

After the newborn period, children with syphilis should have a CSF examination to exclude neurosyphilis. In addition, birth and maternal medical records should be reviewed to assess whether children have congenital or acquired syphilis. Older children with acquired latent syphilis should be evaluated as described for adults and treated using the following pediatric regimens. These regimens are for nonallergic children who have acquired syphilis and who have normal CSF examination results.

Early Latent Syphilis: **Benzathine penicillin G** 50,000 units/kg IM, up to the adult dose of 2.4 million units in a single dose.

Late Latent Syphilis or Latent Syphilis of Unknown Duration: **Benzathine penicillin G** 50,000 units/kg IM, up to the adult dose of 2.4 million units, administered as three doses at 1-week intervals (total 150,000 units/kg, up to the adult total dose of 7.2 million units).

Evaluation and Treatment for Congenital Syphilis in Older Infants and Children

Children who are identified as having reactive serologic tests for syphilis after the neonatal period (ie. at >1 month of age) should have maternal serology and records reviewed to assess whether the child has congenital or acquired syphilis. Any child at risk for congenital syphilis should receive a full evaluation and testing for HIV infection.

Recommended Evaluation

* CSF analysis for VDRL, cell count, and protein.
* Complete blood count (CBC), differential, and platelet count.
* Other tests as clinically indicated (eg. long-bone radiographs, chest radiograph, liver function tests, abdominal ultrasound, ophthalmologic examination, and auditory brain stem response).

Recommended Treatment Regimen: Aqueous crystalline penicillin G

200,000-300,000 units/kg/day IV, administered as 50,000 units/kg every 4-6 hours for 10 days.

Any child who is suspected of having congenital syphilis or who has neurologic involvement should be treated with aqueous penicillin G. Some specialists also suggest giving these patients a single dose of benzathine penicillin G, 50,000 units/kg IM following the 10-day course of IV aqueous penicillin.

Follow-up of children treated for congenital syphilis after the newborn period should be conducted as is recommended for neonates.

APPENDIX H: CONTACT INFORMATION AND ADDITIONAL RESOURCES

IN NEW YORK CITY

Providers can call (212) 788-4443 or 788-4444 Monday-Friday, 8:00 A.M. to 5 P.M. to access:

- New York City's Syphilis and Serologic Reactor Registry for your patients' serologic and treatment histories.
- To report a case of primary, secondary, and early latent syphilis promptly to the New York City Department of Health and Mental Hygiene (DOHMH).
- Free "stat" dark-field microscopy, available at DOHMH STD clinics.
- Expert medical consultation on any aspect of the diagnosis, treatment, management, or prevention of any sexually transmitted disease.
- Partner notification assistance.

Others can call 311 or the STD HOTLINE (212) 427-5120 Monday-Friday, 9 A.M. to 4 P.M.

- For answers to questions about syphilis and other sexually transmitted diseases.
- For hours and locations of free, public STD clinics in all boroughs of New York City.

IN NEW YORK STATE

For information regarding STD reporting and other services available in the county in which you practice, visit the New York State website at: www.health.state.ny.us/nysdoh/lhu/map.htm

See "New York State County Health Departments"

IN NEW JERSEY

Providers may contact the Sexually Transmitted Disease (STD) Program 609-588-7526 Monday-Friday, 8:00 A.M. to 5:00 P.M.:

- To report a sexually transmitted disease promptly to the New Jersey Department of Health and Senior Services (NJDHSS) STD Program.
- To receive expert consultation on any aspect of the diagnosis, treatment, management, prevention, or reporting of any STD.
- To receive partner notification assistance.
- To report HIV/AIDS, please call 609-984-5980.

Patients may contact the STD Program at 609-588-7526 Monday-Friday 8:00 A.M.-5:00 P.M.

- For answers to questions about STDs.
- For hours and locations of public health STD clinics throughout New Jersey.
- For questions on HIV/AIDS, please call the NJ HIV/AIDS/STD Hotline 800-764-7661.

For additional state, regional, and key local health department contacts, refer to the following pages or visit: *http://www.cdc.gov/nchstp/dstd/Public_Health_dept.htm*

IN PUERTO RICO AND THE US VIRGIN ISLANDS

In the US Virgin Islands, providers may contact the USVI Health department at 340-774-9000.

In Puerto Rico, providers may contact the Puerto Rico Health Department at 787-274-5510.

STATE, REGIONAL, AND KEY LOCAL HEALTH DEPARTMENT CONTACTS

Info on state and local department of health can also be found on the CDC'S Website at: *www.cdc.gov/nchstp/dstd*

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APPENDIX I: SAMPLE PATIENT EDUCATION HANDOUT

See the following pages for a sample patient education handout on syphilis.

PROTECT Yourself & Others

Syphilis

What is syphilis?

Syphilis is a bacterial infection that both men and women can get. In New York and other cities, the number of syphilis cases has increased recently among men, especially men who have sex with men, many of whom are HIV-infected. For this reason, it is recommended that men who have sex with men and men who are HIV-infected be tested for syphilis and other sexually transmitted diseases (STDs) regularly. Women engaging in high-risk sexual behavior should also be screened for syphilis.

How is syphilis spread?

Syphilis is spread through direct, skin-to-skin contact with a syphilis sore, lesion, or moist rash. Usually, the contact occurs during vaginal, anal, or oral sex. Other intimate contact, such as kissing, can spread syphilis if syphilis sores are present in the mouth or on the lips. Syphilis can also be passed from a woman to her unborn baby.

What are the symptoms of syphilis?

Most people with syphilis have no recognizable symptoms. If symptoms ARE experienced, they can include rashes (especially on the palms of the hands and soles of the feet). Painless, open sores called chancres (pronounced "shankers") can appear on the penis, the anus, inside or outside the vagina, on the mouth or lips, or on any skin exposed during sex. Other symptoms include patchy hair loss, fever, swollen lymph glands, muscle aches, and fatigue.

Symptoms (when they are noticed) usually last several weeks and disappear, even without treatment. Although the symptoms go away, syphilis infection remains in the body. If left untreated, over the years, syphilis can permanently and seriously damage the heart, brain, and nervous system.

How will I know if I have syphilis?

Since most people with syphilis don't have symptoms, the best way to find out is to get a blood test. *(Giving your doctor a chance to find infections that don't have symptoms is one important reason to get regular check-ups, even when you're not feeling sick!)* If you have a sore or a rash, your doctor or other health-care provider may also collect a sample of fluid from the skin or sore with a small swab during an exam and have it tested at a laboratory.

How is syphilis treated?

Antibiotics can cure syphilis, often in a single dose. To be cured, however, syphilis must be treated early, before permanent damage occurs. Long-term damage caused by syphilis (years after exposure) cannot be cured. A person can become re-infected after treatment if exposed to syphilis again.

What happens if syphilis is left untreated?

Even though the outward symptoms of syphilis disappear without treatment, the infection itself remains in the body. Left untreated, syphilis can cause very serious and permanent damage to the heart, brain, and nervous system. The results of this damage may not show up for many years. The final result may be death.

Like other STDs, if left untreated, syphilis can increase a person's chance of getting or spreading HIV. If you have symptoms or think you've been exposed to syphilis, get examined and treated immediately to avoid any complications.

Do sex partners have to be treated?

Yes, if you're diagnosed with syphilis, it's important to tell everyone you've had sex with over the past year, so they can be examined and treated, too... Take *all* your medication as directed, even if you feel better before the medicine is finished. Don't have sex until you and the people you've had sex with have been completely treated and all of your symptoms have disappeared, or you could infect each other again.

What if I'm pregnant?

Untreated syphilis during pregnancy can cause severe problems for the newborn, including mental retardation, blindness, deformities, or death.

All pregnant women should be tested for syphilis and other sexually transmitted diseases (STDs), including HIV, as early as possible in pregnancy. Women who are infected should be treated immediately and treated again throughout the pregnancy, especially if they have any new partners, or if they have more than one partner. If left untreated, syphilis and other STDs can be devastating for your baby. To protect yourself and your baby against STDs, use a latex condom during sex, especially when you're pregnant.

How can I avoid syphilis?

Latex condoms may be helpful in preventing the spread of syphilis, but only when the infectious area is covered or protected by the condom. Anytime a person has sink-to-skin contact with a syphilis sore or rash on the penis, in the rectum, in the vagina, in the mouth or elsewhere on the body, it is possible to get syphilis.

Sexually transmitted infections can be avoided by not having sex. If you are sexually active, you can reduce your risk of getting syphilis and most other sexually transmitted diseases (STDs), including HIV, by having sex only in a mutually monogamous relationship with a partner you are sure is not infected. If you are having sex outside of such a relationship, you can reduce your risk of STDs by:

1) Always using a latex condom (or other type of latex barrier) whenever you have sex–vaginal, anal, or oral. Condoms made of "natural" materials, such as lambskin, protect against pregnancy, but not against STDs. If you are allergic to latex, you can use condoms made of polyurethane or other synthetic materials.

2) Limiting the number of people you have sex with. The more partners you have, the higher your risk.

3) Avoiding alcohol and drugs when you have sex. Drinking or getting high makes it much harder to remember to use condoms to protect yourself and others. For free, confidential help with a substance abuse problem, call 1-800-LIFENET (1-800-543-3638) or just call 311 in the City of New York.

More Information

Free, confidential STD exams and treatment, and confidential or anonymous HIV counseling and testing, are available at health department clinics in all 5 boroughs of New York City. Health insurance, proof of citizenship, and parental consent are NOT required. For a list of clinics and hours, visit www.nyc.gov/html/doh/html/std/std2.shtml, or call 311.

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ADDENDUM

In August of 2006, the Centers for Disease Control and Prevention (CDC) released an updated version of the 2002 Sexually Transmitted Disease Treatment Guidelines. The publication of these revised guidelines occurred following the printing of this module.

Use of correct formulation of penicillin for treatment of syphilis

It is important for medical providers to ensure that the correct formulation of injectible penicillin is used. When treating patients for primary, secondary, latent, or tertiary syphilis, long-acting (benzathine) penicillin G, Bicillin L-A ®, rather than combination benzathine-procaine penicillin, Bicillin C-R ®, should always be used.

Treatment issues for penicillin-allergic patients

Persons who have a known allergy to penicillin and who receive any alternative non-penicillin therapy for syphilis (e.g. doxycycline, tetracycline, or ceftriaxone) should have close serologic and clinical follow-up to verify compliance with multi-dose oral regimens and monitor response to treatment. HIV-infected patients allergic to penicillin whose compliance with treatment or follow-up is uncertain should be advised to be desensitized and treated with penicillin. Caution is advised when treating HIV infected patients with syphilis in any stage with non-penicillin regimens since the efficacy of alternative non-penicillin regimens in HIV-infected persons has not been studied.

Management of primary and secondary syphilis among HIV-Infected Persons

Although the majority of HIV-infected persons respond appropriately to standard benzathine penicillin therapy, some specialists recommend intensified therapy when central nervous system (CNS) syphilis is suspected in these persons. Therefore, some specialists recommend lumbar puncture and cerebrospinal fluid (CSF) examination before treatment of HIV-infected persons with early syphilis (i.e. primary, secondary or early latent infections), with follow-up CSF examination conducted after treatment in persons with initial abnormalities. If a CSF exam is performed on an HIV infected person with early syphilis, CSF may be abnormal secondary to HIV and not syphilis and treatment based on these changes may be of unclear benefit.

Work-up to rule out neurosyphilis

Indications for CSF examination in patients being treated for syphilis are listed on page 42 of the module. Although not a formal recommendation, the 2006 guidelines point out that some specialists suggest performing a CSF examination on patients with latent syphilis if the patient's nontreponemal serologic titer is ≥1:32 or for patients who are HIV-infected with a serum CD4 count ≤350 with any stage of syphilis. Although of unproven benefit, some specialists recommend a CSF examination 6 months after therapy for neurosyphilis in HIV-infected patients.

Treatment of neurosyphilis in penicillin-allergic patients

Ceftriaxone is a possible alternative treatment for patients with neurosyphilis who are allergic to penicillin, although the possibility of cross-reactivity between this agent and penicillin exists. If concern exists regarding the safety of ceftriaxone for a penicillin-allergic patient with neurosyphilis, the patient should obtain skin testing to confirm penicillin allergy and, if necessary, be desensitized and managed in consultation with a specialist.

Follow-up of HIV-infected patients treated for neurosyphilis

Recent data on HIV-infected persons with neurosyphilis suggest that CSF abnormalities might persist for extended periods in these persons, and close clinical follow-up is warranted.

Screening for syphilis using treponemal EIA (IgG) tests

Persons with positive treponemal screening tests should have standard nontreponemal tests with titers to guide patient management decisions. If the nontreponemal test is negative, then a different treponemal test should be performed to confirm the results of the initial test. Although the chart on p.31 suggests first repeating the treponemal IgG in this scenario, the 2006 CDC STD treatment guidelines do not suggest repeating the IgG and going directly to another treponemal test such as the FTA or TPPA. Please see pages 29 -30 of the module for clinical scenarios which would be consistent with serologic results showing a positive EIA and a non–reactive RPR.

NOTES

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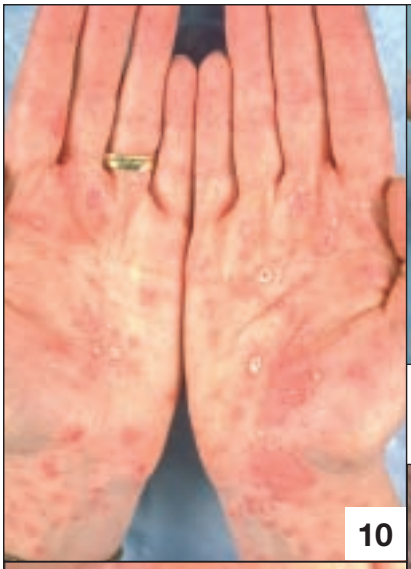

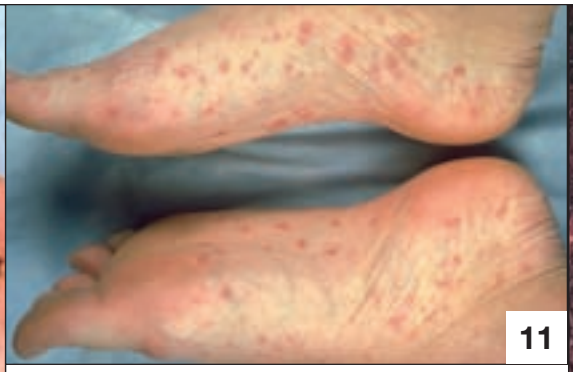

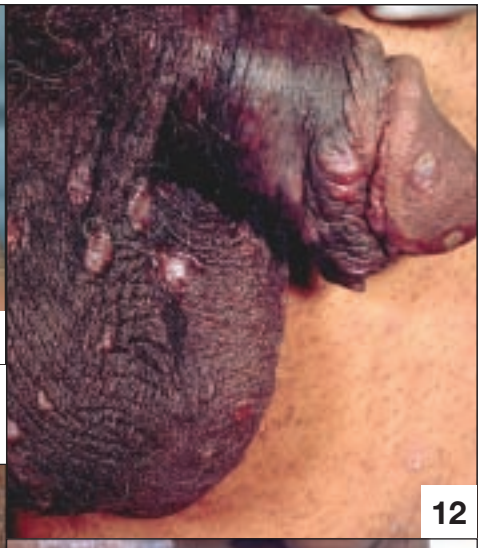

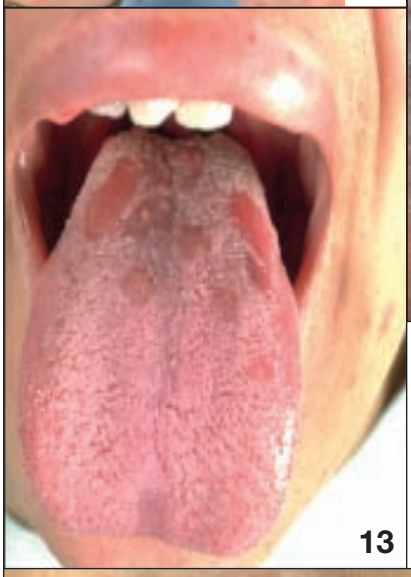

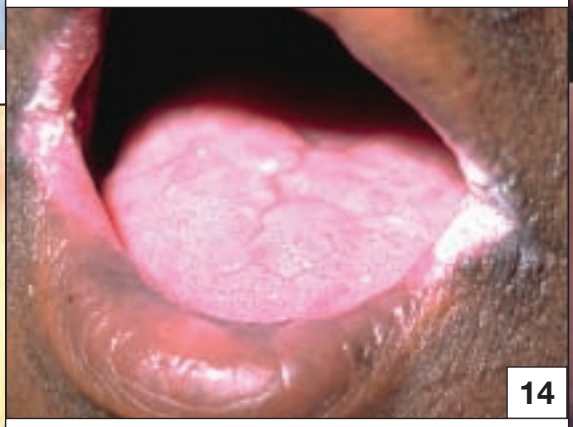

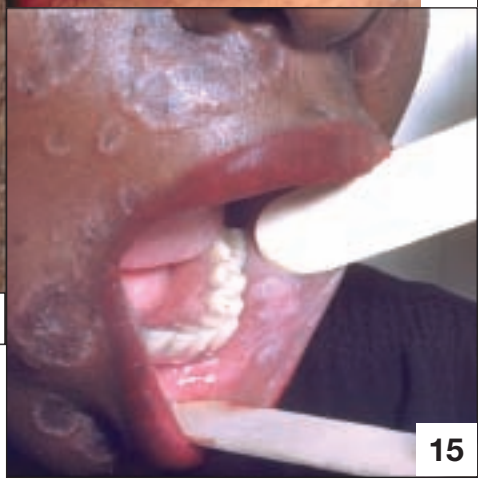

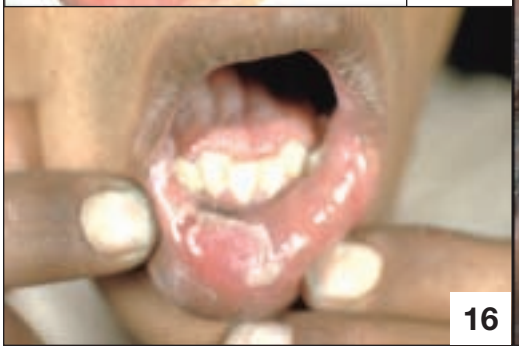

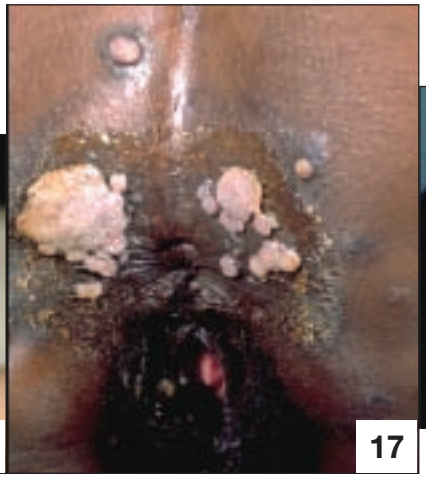

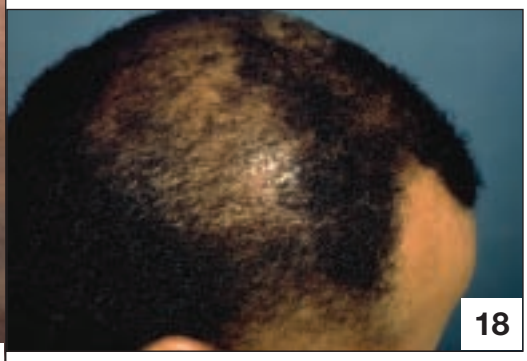

LESIONS OF SECONDARY SYPHILIS (CONTINUOUS PAGE)

10. Desquamating palmar eruption, 11. Plantar lesions on the soles of the feet, 12. Papular eruption of the penis and scrotum, 13. Mucous patches of the posterior tongue, 14. Split papules at the angles of the mouth, 15. Annular patches of face with mucosal lesions, 16. Condyloma lata of the inner lower lip, 17. Condyloma lata around the anus and buttocks, 18. Moth-eaten alopecia of scalp

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