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Syphilis Treatment Guidelines

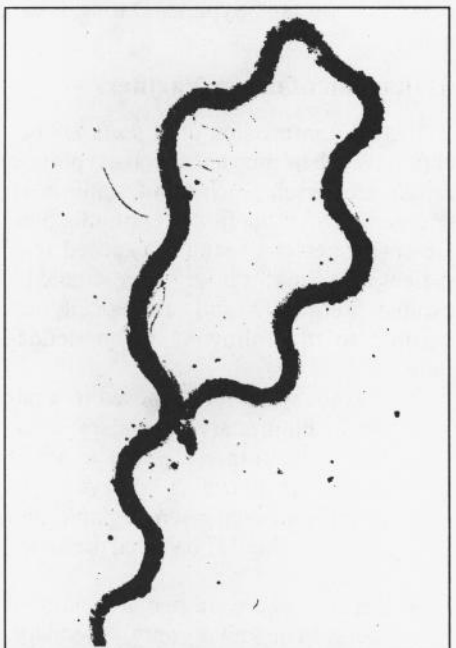
*Recommendations from the Centers for Disease Control and Prevention**

General Principles

Background

Syphilis is a systemic disease caused by *T. pallidum*. Patients with syphilis may seek treatment for signs or symptoms of primary infection (ulcer or chancre at site of infection), secondary infection (manifestations that include rash, mucocutaneous lesions, and adenopathy), or tertiary infection (cardiac, neurologic, ophthalmic, auditory, or gummatous lesions). Infections also may be detected during the latent stage by serologic testing. Patients with latent syphilis who are known to have been infected within the preceding year are considered to have early latent syphilis; others have late latent syphilis or syphilis of unknown duration. Theoretically, treatment for late latent syphilis (as well as tertiary syphilis) requires therapy of longer duration because organisms are dividing more slowly; however, the validity of this division and its timing are unproven.

In This Issue:



Electron photomicrograph of *T. pallidum* ~30,000X

Diagnostic Considerations and Use of Serologic Tests

Darkfield examinations and direct fluorescent antibody tests of lesion exudate or tissue are the definitive methods for diagnosing early syphilis. Presumptive diagnosis is possible with the use of two types of serologic tests for syphilis: a) nontreponemal (e.g., Venereal Disease Research Laboratory [VDRL] and RPR, and b) treponemal (e.g., fluorescent treponemal antibody absorbed [FTA-ABS] and microhemagglutination assay for antibody to *T. pallidum* [MHA-TP]). The use of one type of test alone is not sufficient for diagnosis. Nontreponemal test antibody titers usually correlate with disease activity, and results should be reported quantitatively. A fourfold change in titer, equivalent to a change of two dilutions (e.g., from 1:16 to 1:4, or from 1:8 to 1:32), is necessary to demonstrate a substantial difference between two nontreponemal test results that were obtained using the same serologic test. A patient who has a reactive treponemal test usually will have a reactive test for a lifetime, regardless of treatment or disease activity (15%-25% of patients treated during the primary stage may revert to being serologically nonreactive after 2-3 years). Treponemal test antibody titers correlate poorly with disease activity and should not be used to assess response to treatment.

Sequential serologic tests should be performed using the same testing method (e.g., VDRL or RPR) by the same laboratory. The VDRL and RPR are equally valid, but quantitative results from the two tests cannot be directly compared because RPR titers are often slightly higher than VDRL titers.

Abnormal results of serologic testing (unusually high, unusually low, and fluctuating titers) have been observed among HIV-infected patients. For such patients, use of other tests (e.g., biopsy and direct microscopy) should be considered. However, serologic tests appear to be accurate and reliable for the diagnosis of syphilis and for evaluation of treatment response for the vast majority of HIV-infected patients.

No single test can be used to diagnose neurosyphilis among all patients. The diagnosis of neurosyphilis can be made based on various combinations of reactive serologic test results, abnormalities of cerebro-

spinal fluid (CSF) cell count or protein, or a reactive VDRL-CSF (RPR is not performed on CSF) with or without clinical manifestations. The CSF leukocyte count is usually elevated (greater than 5 WBC/mm^3) when active neurosyphilis is present, and it is also a sensitive measure of the effectiveness of therapy. The VDRL-CSF is the standard serologic test for CSF; when reactive in the absence of substantial contamination of the CSF with blood, it is considered diagnostic of neurosyphilis. However, the VDRL-CSF may be nonreactive when neurosyphilis is present. Some experts recommend performing an FTA-ABS test on CSF. The CSF FTA-ABS is less specific (i.e., yields more false positives) for neurosyphilis than the VDRL-CSF; however, the test is believed to be highly sensitive.

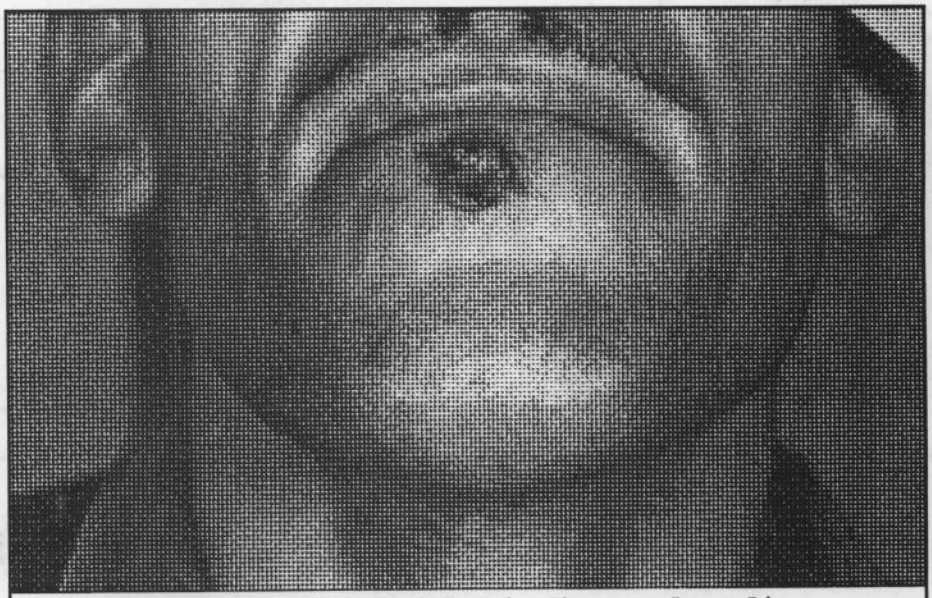
Treatment

Parenteral penicillin G is the preferred drug for treatment of all stages of syphilis. The preparation(s) used (i.e., benzathine, aqueous procaine, or aqueous crystalline), the dosage, and the length of treatment depend on the stage and clinical manifestations of disease

The effic.. penicillin for the treatment of syphilis was well established through clinical experience before the value of randomized controlled clinical trials was recognized. Therefore, nearly all the recommendations for the treatment of syphilis are based on expert opinion reinforced by case series, open clinical trials, and 50 years of clinical experience.

Parenteral penicillin G is the only therapy with documented efficacy for neurosyphilis or for syphilis during pregnancy. Patients with neurosyphilis and pregnant women with syphilis in any stage who report penicillin allergy should almost always be treated with penicillin, after desensitization, if necessary. Skin testing for penicillin allergy may be useful for some patients and in some settings (see Management of the Patient With a History of Penicillin Allergy). However, minor determinants needed for penicillin skin testing are not available commercially.

The Jarisch-Herxheimer reaction is an acute febrile reaction — accompanied by headache, myalgia, and other symptoms — that may occur within the first 24 hours after any therapy for syphilis; patients should be advised of this possible adverse reaction. The Jarisch-Herxheimer reaction is common among patients with early syphilis. Antipyretics may be recommended, but there are no proven methods for preventing this reaction. The Jarisch-Herxheimer reaction may induce early labor or cause fetal distress among pregnant women. This concern should not prevent or delay therapy (see Syphilis During Pregnancy).



Primary Syphilis: Typical Hunterian Chancre on Lower Lip

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 sexually exposed to a patient with syphilis in any stage should be evaluated clinically and serologically according to the following recommendations:

- Persons who were exposed to a patient with primary, secondary, or latent (duration <1 year) syphilis within the preceding 90 days might be infected even if seronegative, and therefore should be treated presumptively.
- Persons who were sexually exposed to a patient with primary, secondary, or latent (duration <1 year) syphilis greater than 90 days before examination 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 who have syphilis of unknown duration and who have high nontreponemal serologic test titers (≥1:32) may be considered to be infected with early syphilis.
- Long-term sex partners of patients with late syphilis should be evaluated clinically and serologically for syphilis.

The time periods before treatment used for identifying at-risk sex partners are 3 months plus duration of symptoms for primary syphilis, 6 months plus duration of symptoms for secondary syphilis, and 1 year for early latent syphilis.

Primary and Secondary Syphilis

Treatment

Four decades of experience indicate that parenteral penicillin G is effective in achieving local cure (healing of lesions and prevention of sexual transmission) and in preventing late sequelae. However, no adequately conducted comparative trials have been performed to guide the selection of an optimal penicillin regimen (i.e., dose, duration, and preparation). Substantially fewer data on nonpenicillin regimens are available.

Recommended Regimen for Adults

Nonallergic patients with primary or secondary syphilis should be treated with the following regimen:

☞ Benzathine penicillin G, 2.4 million units IM in a single dose.

NOTE: Recommendations for treating pregnant women and HIV-infected persons for syphilis are discussed in separate sections.

Recommended Regimen for Children

After the newborn period, children diagnosed with syphilis should have a CSF examination to exclude a diagnosis of neurosyphilis, and birth and maternal medical records should be reviewed to assess whether the child has congenital or acquired syphilis (see Congenital Syphilis). Children with acquired primary or secondary syphilis should be evaluated (including consultation with child-protection

services) and treated using the following pediatric regimen (see Sexual Assault or Abuse of Children).

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

Other Management Considerations

All patients with syphilis should be tested for HIV. In areas with high HIV prevalence, patients with primary syphilis should be retested for HIV after 3 months.

Patients who have syphilis and who also have symptoms or signs suggesting neurologic disease (e.g., meningitis) or ophthalmic disease (e.g., uveitis) should be fully evaluated for neurosyphilis and syphilitic eye disease (including CSF analysis and ocular slit-lamp examination). Such patients should be treated appropriately according to the results of this evaluation.

Invasion of CSF by *T. pallidum* with accompanying CSF abnormalities is common among adults who have primary or secondary syphilis. However, few patients develop neurosyphilis after treatment with the regimens described in this report. Therefore, unless clinical signs or symptoms of neurologic involvement are present (e.g., auditory, cranial nerve, meningeal, or ophthalmic manifestations), lumbar puncture is not recommended for routine evaluation of patients with primary or secondary syphilis.

Follow-Up

Treatment failures can occur with any regimen. However, assessing response to treatment is often difficult, and no definitive criteria for cure or failure exist. Serologic test titers may decline more slowly among patients with a prior syphilis infection. Patients should be re-examined clinically and serologically at 3 months and again at 6 months.

Patients with signs or symptoms that persist or recur or who have a sustained fourfold increase in nontreponemal test titer compared with either the baseline titer or to a subsequent result, can be considered to have failed treatment or to be reinfected. These patients should be re-treated after evaluation for HIV infection. Unless reinfection is likely, lumbar puncture also should be performed.

Failure of nontreponemal test titers to decline fourfold by 3 months after therapy for primary or secondary syphilis identifies persons at risk for treatment failure. Those persons should be evaluated for HIV infection. Optimal management of such patients is unclear if they are HIV negative. At a minimum, these patients should have additional clinical and serologic follow-up. If further follow-up cannot be assured, retreatment is recommended. Some experts recommend CSF examination in such situations.

When patients are re-treated, most experts recommend re-treatment with three weekly injections of benzathine penicillin G 2.4 million units IM, unless CSF examination indicates that neurosyphilis is present.

Management of Sex Partners

Refer to General Principles, Management of Sex Partners.

Special Considerations

Penicillin Allergy

Nonpregnant penicillin-allergic patients who have primary or secondary syphilis should be treated with the following regimen.

- ☞ Doxycycline 100 mg orally 2 times a day for 2 weeks

or

- ☞ Tetracycline 500 mg orally 4 times a day for 2 weeks.

There is less clinical experience with doxycycline than with tetracycline, but compliance is likely to be better with doxycycline. Therapy for a patient who cannot tolerate either doxycycline or tetracycline should be based upon whether the patient's compliance with the therapy regimen and with follow-up examinations can be assured.

For nonpregnant patients whose compliance with therapy and follow-up can be assured, an alternative regimen is erythromycin 500 mg orally 4 times a day for 2 weeks. Various ceftriaxone regimens also may be considered.

Patients whose compliance with therapy or follow-up cannot be assured should be desensitized, if necessary, and treated with penicillin. Skin testing for penicillin allergy may be useful in some situations (see Management of the Patient With a History of Penicillin Allergy).

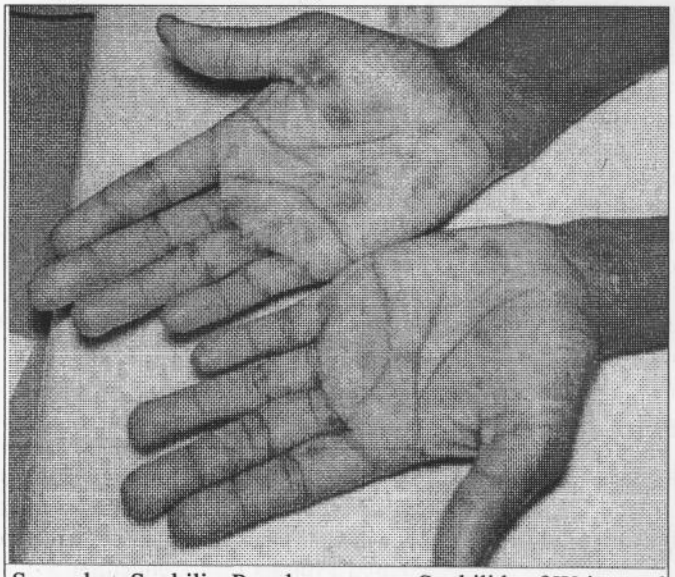
Erythromycin is less effective than other recommended regimens. Data on ceftriaxone are limited, and experience has been too brief to permit identification of late failures. Optimal dose and duration have not been established for ceftriaxone, but regimens that provide 8-10 days of treponemicidal levels in the blood should be used. *Single dose ceftriaxone therapy is not effective for treating syphilis.*

Pregnancy

Pregnant patients who are allergic to penicillin should be treated with penicillin, after desensitization, if necessary (see Management of the Patient With a History of Penicillin Allergy and Syphilis During Pregnancy).

HIV Infection

Refer to Syphilis Among HIV-Infected Patients.



Secondary Syphilis: Papulosquamous Syphilids of Wrists and Palms

Latent Syphilis

Latent syphilis is defined as those periods after infection with *T. pallidum* when patients are seroreactive, but show no other evidence of disease. Patients who have latent syphilis and who have acquired syphilis within the preceding year are classified as having early latent syphilis. Patients can be demonstrated to have acquired syphilis within the preceding year on the basis of documented seroconversion, a fourfold or greater increase in titer of a nontreponemal serologic test, history of symptoms of primary or secondary syphilis, or if they had a sex partner with primary, secondary, or latent syphilis (documented independently as duration <1 year). Nearly all others have latent syphilis of unknown duration and should be managed as if they had late latent syphilis.

Treatment

Treatment of latent syphilis is intended to prevent occurrence or progression of late complications. Although clinical experience supports belief in the effectiveness of penicillin in achieving those goals, limited evidence is available for guidance in choosing specific regimens. There is very

little evidence to support the use of non-penicillin regimens.

Recommended Regimens for Adults

These regimens are for nonallergic patients with normal CSF examination (if performed).

Early Latent Syphilis

☞ Benzathine penicillin G, 2.4 million units IM in a single dose.

Late Latent Syphilis or Latent Syphilis of Unknown Duration

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

Recommended Regimens for Children

After the newborn period, children diagnosed with syphilis should have a CSF examination to exclude neurosyphilis, and birth and maternal medical records should be reviewed to assess whether the child has congenital or acquired syphilis (see Congenital Syphilis). Older children with acquired latent syphilis should be evaluated as described for adults and treated using the following pediatric regimens (see Sexual Assault or Abuse of Children). These regimens are for nonallergic children who have acquired syphilis and who have had a normal CSF examination.

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

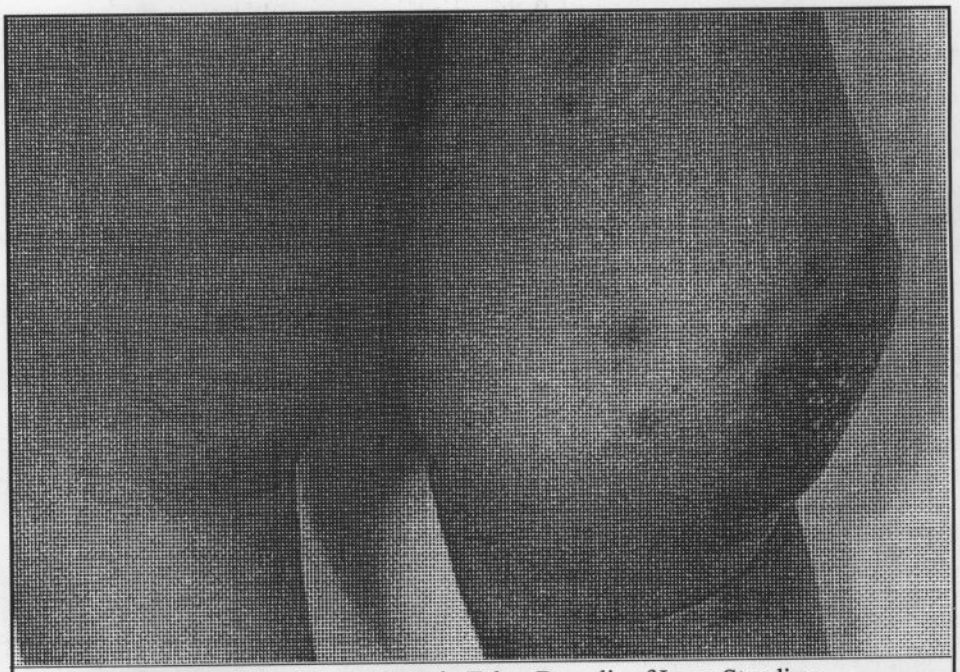
☞ Benzathine penicillin G, 50,000 units/kg IM, up to the adult dose of 2.4 million units, for three total doses (total 150,000 units/kg up to adult total dose of 7.2 million units).

Other Management Considerations

All patients with latent syphilis should be evaluated clinically for evidence of tertiary disease (e.g., aortitis, neurosyphilis, gumma, and iritis). Recommended therapy for patients with latent syphilis may not be optimal therapy for the persons with asmptomatic neurosyphilis. However, the yield from CSF examination, in terms of newly diagnosed cases of neurosyphilis, is low.

Patients with any one of the criteria listed below should have a CSF examination before treatment:

- Neurologic or ophthalmic signs or symptoms;
- Other evidence of active syphilis (e.g., aortitis, gumma, iritis);



Late Syphilis: Charcot knee in Tabes Dorsalis of Long Standing.

- Treatment failure;
- HIV infection;
- Serum nontreponemal titer ≥1:32, unless duration of infection is known to be <1 year; or
- Nonpenicillin therapy planned, unless duration of infection is known to be <1 year.

If dictated by circumstances and patient preferences, CSF examination may be performed for persons who do not meet the criteria listed above. If a CSF examination is performed and the results show abnormalities consistent with CNS syphilis, the patient should be treated for neurosyphilis (see Neurosyphilis).

All syphilis patients should be tested for HIV.

Follow-Up

Quantitative nontreponemal serologic tests should be repeated at 6 months and again at 12 months. Limited data are available to guide evaluation of the response to therapy for a patient with latent syphilis. If titers increase fourfold, or if an initially high titer (≥1:32) fails to decline at least fourfold (two dilutions) within 12-24 months, or if the patient develops signs or symptoms attributable to syphilis, the patient should be evaluated for neurosyphilis and re-treated appropriately.

Management of Sex Partners

Refer to General Principles, Management of Sex Partners.

Special Considerations

Penicillin Allergy

For patients who have latent syphilis and who are allergic to penicillin, non-penicillin therapy should be used only after CSF examination has excluded neurosyphilis. Nonpregnant, penicillin-allergic patients should be treated with the following regimens.

☞ Doxycycline 100 mg orally 2 times a day

or

☞ Tetracycline 500 mg orally 4 times a day.

Both drugs are administered for 2 weeks if duration of infection is known to have been <1 year; otherwise, for 4 weeks.

Pregnancy

Pregnant patients who are allergic to penicillin should be treated with penicillin, after desensitization, if necessary (see Management of the Patient With a History of Penicillin Allergy and Syphilis During Pregnancy).

HIV Infection

Refer to Syphilis Among HIV-Infected Patients.

Late Syphilis

Late (tertiary) syphilis refers to patients with gumma and patients with cardiovascular syphilis, but not to neurosyphilis. Nonallergic patients without evidence of neurosyphilis should be treated with the following regimen.

Recommended Regimen

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

Other Management Considerations

Patients with symptomatic late syphilis should undergo CSF examination before therapy. Some experts treat all patients who have cardiovascular syphilis with a neurosyphilis regimen. The complete management of patients with cardiovascular or gummatous syphilis is beyond the scope of these guidelines. These patients should be managed in consultation with experts.

Follow-Up

There is minimal evidence regarding follow-up of patients infected with late syphilis. Clinical response depends partly on the nature of the lesions.

Management of Sex Partners

Refer to General Principles, Management of Sex Partners.

Special Considerations

Penicillin Allergy

Patients allergic to penicillin should be treated according to treatment regimens recommended for late latent syphilis.

Pregnancy

Pregnant patients who are allergic to penicillin should be treated with penicillin, after desensitization, if necessary (see Management of the Patient With a History of Penicillin Allergy and Syphilis During Pregnancy).

HIV Infection

Refer to Syphilis Among HIV-Infected Patients.

Neurosyphilis

Treatment

Central nervous system disease can occur during any stage of syphilis. A patient with clinical evidence of neurologic involvement (e.g., ophthalmic or auditory symptoms, cranial nerve palsies) with syphilis warrants a CSF examination. Although four decades of experience have confirmed the effectiveness of penicillin, the evidence to guide the choice of the best regimen is limited.

Syphilitic eye disease is frequently associated with neurosyphilis, and patients with this disease should be treated according to neurosyphilis treatment recommendations. CSF examination should be performed on all such patients to identify those patients with CSF abnormalities who should have follow-up CSF examinations to assess response to treatment.

Patients who have neurosyphilis or syphilitic eye disease (e.g., uveitis, neuroretinitis, or optic neuritis) and who are not allergic to penicillin should be treated with the following regimen.

Recommended Regimen

☞ 12-24 million units aqueous crystalline penicillin G daily, administered as 2-4 million units IV every 4 hours, for 10-14 days.

If compliance with therapy can be assured, patients may be treated with the following alternative regimen.

Alternative Regimen

☞ 2.4 million units procaine penicillin IM daily, plus probenecid 500 mg orally 4 times a day, both for 10-14 days.

The durations of these regimens are shorter than that of 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.

Other Management Considerations

Other considerations in the management of the patient with neurosyphilis are the following:

- All patients with syphilis should be tested for HIV.
- Many experts recommend treating patients with evidence of auditory disease caused by syphilis in the same manner as for neurosyphilis, regardless of the findings on CSF examination.

Follow-Up

If CSF pleocytosis was present initially, CSF examination should be repeated every 6 months until the cell count is normal. Follow-up CSF examinations also may be used to evaluate changes in the VDRL-CSF or CSF protein in response to therapy, though changes in these two parameters are slower and persistent abnormalities are of less certain importance. If the cell count has not decreased at 6 months, or if the CSF is not entirely normal by 2 years, re-treatment should be considered.

Management of Sex Partners

Refer to General Principles, Management of Sex Partners.

Special Considerations

Penicillin Allergy

No data have been collected systematically for evaluation of therapeutic alternatives to penicillin for treatment of neurosyphilis. Therefore, patients who report being allergic to penicillin should be treated with penicillin, after desensitization if necessary, or should be managed in consultation with an expert. In some situations, skin testing to confirm penicillin allergy may be useful (see Management of the Patient With a History of Penicillin Allergy).

Pregnancy

Pregnant patients who are allergic to penicillin should be treated with penicillin, after desensitization if necessary (see Syphilis During Pregnancy).

HIV Infection

Refer to Syphilis Among HIV-Infected Patients.

Syphilis Among HIV-Infected Patients

Diagnostic Considerations

Unusual serologic responses have been observed among HIV-infected persons who also have syphilis. Most reports involved serologic titers that were higher than expected, but false-negative serologic test results or delayed appearance of seroreactivity have also been reported. *Nevertheless, both treponemal and nontreponemal serologic tests for syphilis are accurate for the majority of patients with syphilis and HIV coinfection.*

When clinical findings suggest that syphilis is present, but serologic tests are nonreactive or confusing, it may be helpful to perform such alternative tests as biopsy of a lesion, darkfield examination, or direct fluorescent antibody staining of lesion material.

Neurosyphilis should be considered in the differential diagnosis of neurologic disease among HIV-infected persons.

Treatment

Although adequate research-based evidence is not available, published case reports and expert opinion suggest that HIV-infected patients with early syphilis are at increased risk for neurologic complications and have higher rates of treatment failure with currently recommended regimens. The magnitude of these risks, although not precisely defined, is probably small. No treatment regimens have been demonstrated to be more effective in preventing development of neurosyphilis than those recommended for patients without HIV infection. *Careful follow-up after therapy is essential.*

Primary and Secondary Syphilis Among HIV-Infected Patients

Treatment

Treatment with benzathine penicillin G 2.4 million units IM, as for patients without HIV infection, is recommended. Some experts recommend additional treatments, such as multiple doses of benzathine penicillin G as suggested for late syphilis, or

other supplemental antibiotics *in addition* to benzathine penicillin G 2.4 million units IM.

Other Management Considerations

CSF abnormalities are common among HIV-infected patients who have primary or secondary syphilis, but these abnormalities are of unknown prognostic significance. Most HIV-infected patients respond appropriately to currently recommended penicillin therapy; however, some experts recommend CSF examination before therapy and modification of treatment accordingly.

Follow-Up

Patients should be evaluated clinically and serologically for treatment failure at 1 month and at 2, 3, 6, 9, and 12 months after therapy. Although of unproven benefit, some experts recommend performing CSF examination after therapy (i.e., at 6 months).

HIV-infected patients who meet the criteria for treatment failure should undergo CSF examination and be retreated just as for patients without HIV infection. CSF examination and re-treatment also should be strongly considered for patients in whom the suggested fourfold decrease in nontreponemal test titer does not occur within 3 months for primary or secondary syphilis. Most experts would re-treat patients with benzathine penicillin G 7.2 million units (as 3 weekly doses of 2.4 million units each) if the CSF examination is normal.

Penicillin Allergy

Penicillin regimens should be used to treat HIV-infected patients in all stages of syphilis. Skin testing to confirm penicillin allergy may be used (see Management of the Patient With a History of Penicillin Allergy), but data on the utility of that approach among immunocompromised patients are inadequate. Patients may be desensitized, then treated with penicillin.

Latent Syphilis Among HIV-Infected Patients

Diagnostic Considerations

Patients who have both latent syphilis (regardless of apparent duration) and HIV infection should undergo CSF examination before treatment.

Treatment

A patient with latent syphilis, HIV infection, and a normal CSF examination can be treated with benzathine penicillin G 7.2 million units (as 3 weekly doses of 2.4 million units each).

Penicillin Allergy

Penicillin regimens should be used to treat all stages of syphilis among HIV-infected patients. Skin testing to confirm penicillin allergy may be used (see Management of the Patient With a History of Penicillin Allergy), but data on the utility of that approach in immunocompromised patients are inadequate. Patients may be desensitized, then treated with penicillin.

Syphilis During Pregnancy

All women should be screened serologically for syphilis during the early stages of pregnancy. In populations in which utilization of prenatal care is not optimal, RPR-card test screening and treatment, if that test is reactive, should be performed at the time a pregnancy is diagnosed. In communities and populations with high syphilis prevalence or for patients at high risk, serologic testing should be repeated during the third trimester and again at delivery. (Some states mandate screening at delivery for all women.) Any woman who delivers a stillborn infant after 20 weeks gestation should be tested for syphilis. No infant should leave the hospital without the serologic status of the infant's mother having been determined at least once during pregnancy.

Diagnostic Considerations

Seropositive pregnant women should be considered infected unless treatment history is clearly documented in a medical or health department record and sequential serologic antibody titers have appropriately declined.

Treatment

Penicillin is effective for preventing transmission to fetuses and for treating established infection among fetuses. Evidence is insufficient, however, to determine whether the specific, recommended penicillin regimens are optimal.

Recommended Regimens

Treatment during pregnancy should be the penicillin regimen appropriate for the woman's stage of syphilis. Some experts recommend additional therapy (e.g., a second dose of benzathine penicillin 2.4 million units IM) 1 week after the initial dose, particularly for those women in the third trimester of pregnancy and for women who have secondary syphilis during pregnancy.

Other Management Considerations

Women who are treated for syphilis during the second half of pregnancy are at risk for premature labor or fetal distress, or both, if their treatment precipitates the Jarisch-Herxheimer reaction. These women should be advised to seek medical attention following treatment if they notice any change in fetal movements or if they have contractions. Stillbirth is a rare complication of treatment; however, since therapy is necessary to prevent further fetal damage, that concern should not delay treatment. All patients with syphilis should be tested for HIV.

Follow-Up

Serologic titers should be checked monthly until adequacy of treatment has been assured. The antibody response should be appropriate for the stage of disease.

Management of Sex Partners

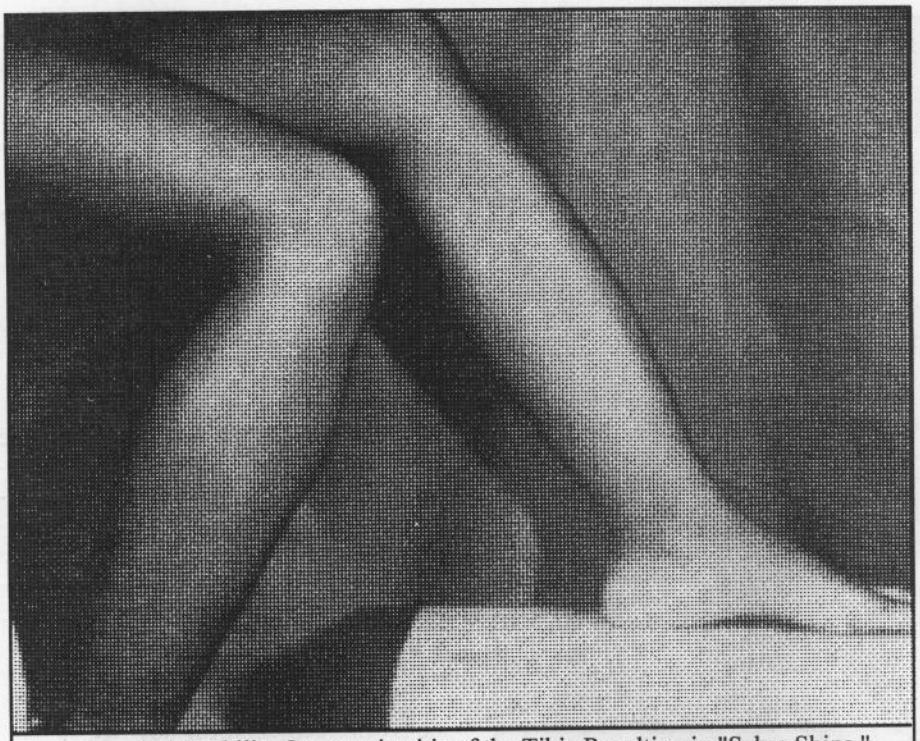
Refer to General Principles, Management of Sex Partners.

Special Considerations

Penicillin Allergy

There are no proven alternatives to penicillin. A pregnant woman with a history of penicillin allergy should be treated with penicillin, after desensitization, if necessary. Skin testing may be helpful for some patients and in some settings (see Management of the Patient With a History of Penicillin Allergy).

Tetracycline and doxycycline are contraindicated during pregnancy. Erythromycin should not be used because it cannot be relied upon to cure an infected fetus.



Congenital Syphilis: Osteoperiostitis of the Tibia Resulting in "Sabre Shins."

Congenital Syphilis

Diagnostic Considerations

Who Should Be Evaluated

Infants should be evaluated for congenital syphilis if they were born to seropositive (nontreponemal test confirmed by treponemal test) women who meet the following criteria:

- Have untreated syphilis;† or
- Were treated for syphilis during pregnancy with erythromycin; or
- Were treated for syphilis <1 month before delivery; or
- Were treated for syphilis during pregnancy with the appropriate penicillin regimen, but nontreponemal antibody titers did not decrease sufficiently after therapy to indicate an adequate response (≥ fourfold decrease); or
- Do not have a well-documented history of treatment for syphilis; or
- Were treated appropriately before pregnancy but had insufficient serologic follow-up to assure that they had responded appropriately to treatment and are not currently infected (≥ fourfold decrease for patients treated for early syphilis; stable or declining titers ≤1:4 for other patients).

No infant should leave the hospital without the serologic status of the infant's mother having been documented at least once during pregnancy. Serologic testing also should be performed at delivery in communities and populations at risk for congenital syphilis. Serologic tests can be nonreactive among infants infected late during their mother's pregnancy.

Evaluation of the Infant

The clinical and laboratory evaluation of infants born to women described above should include the following:

- A thorough physical examination for evidence of congenital syphilis;
- A quantitative nontreponemal serologic test for syphilis performed on the infant's sera (not on cord blood);
- CSF analysis for cells, protein, and VDRL;
- Long bone x-rays;
- Other tests as clinically indicated (e.g., chest x-ray, complete blood count, differential and platelet count, liver function tests);
- For infants who have no evidence of congenital syphilis on the above evaluation, determination of presence of specific antitreponemal IgM antibody by a testing method recognized by CDC as having either provisional or standard status;
- Pathologic examination of the placenta or amniotic cord using specific fluorescent antitreponemal antibody staining.

Treatment

Therapy Decisions

Infants should be treated for presumed congenital syphilis if they were born to mothers who, at delivery, had untreated syphilis or who had evidence of relapse or reinfection after treatment (see Congenital Syphilis, Diagnostic Considerations). Additional criteria for presumptively treating infants with congenital syphilis are as follows:

- Physical evidence of active disease;
- X-ray evidence of active disease;
- A reactive VDRL-CSF or, for infants born to seroreactive mothers, an abnormal CSF white blood cell count or protein, regardless of CSF serology;‡
- A serum quantitative nontreponemal serologic titer that is at least fourfold greater than the mother's titer;§
- Specific antitreponemal IgM antibody detected by a testing method that has been given provisional or standard status by CDC;
- If they meet the previously cited criteria for "Who Should Be Evaluated," but have not been fully evaluated (see Congenital Syphilis, Diagnostic Considerations).

NOTE: Infants with clinically evident congenital syphilis should have an ophthalmologic examination.

Recommended Regimens

☞ Aqueous crystalline penicillin G, 100,000-150,000 units/kg/day (administered as 50,000 units/kg IV every 12 hours during the first 7 days of life and every 8 hours thereafter) for 10-14 days,

or

☞ Procaine penicillin G, 50,000 units/kg IM daily in a single dose for 10-14 days.

If more than 1 day of therapy is missed, the entire course should be restarted. An infant whose complete evaluation was normal and whose mother was a) treated for syphilis during pregnancy with erythromycin, or b) treated for syphilis <1 month before delivery, or c) treated with an appropriate regimen before or during pregnancy but did not yet have an adequate serologic response should be treated with benzathine penicillin G, 50,000 units/kg IM in a single dose. In some cases, infants with a normal complete evaluation for whom follow-up can be assured can be followed closely without treatment.

Treatment of Older Infants and Children with Congenital Syphilis

After the newborn period, children diagnosed with syphilis should have a CSF examination to exclude neurosyphilis and records should be reviewed to assess whether the child has congenital or acquired syphilis (see Primary and Secondary Syphilis and Latent Syphilis). Any child who is thought to have congenital

Table 1. Oral Desensitization Protocol for Patients With a Positive Skin Test*

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

Observation period: 30 minutes before parenteral administration of penicillin.
*Reprinted with permission from the *New England Journal of Medicine*: Oral desensitization protocol for patients with a positive skin test (Table). N Engl J Med 1985;312:1229-32.
†Interval between doses, 15 minutes; elapsed time, 3 hours and 45 minutes; cumulative dose, 1.3 million units.
§The specific amount of drug was diluted in approximately 30 mL of water and then administered orally.

syphilis (or who has neurologic involvement) should be treated with aqueous crystalline penicillin G, 200,000-300,000 units/kg/day IV or IM (administered as 50,000 units/kg every 4-6 hours) for 10-14 days.

Follow-Up

A seroreactive infant (or an infant whose mother was seroreactive at delivery) who is not treated for congenital syphilis during the perinatal period should receive careful follow-up examinations at 1 month and at 2, 3, 6, and 12 months after therapy. Nontreponemal antibody titers should decline by 3 months of age and should be nonreactive by 6 months of age if the infant was not infected and the titers were the result of passive transfer of antibody from the mother. If these titers are found to be stable or increasing, the child should be re-evaluated, including CSF examination, and fully treated. Passively transferred treponemal antibodies may be present for as long as 1 year. If they are present >1 year, the infant should be re-evaluated and treated for congenital syphilis.

Treated infants also should be followed every 2-3 months to assure that nontreponemal antibody titers decline; these infants should have become nonreactive by 6 months of age (response may be slower for infants treated after the neonatal period). Treponemal tests should not be used to evaluate response to treatment because test results can remain positive despite effective therapy if the child was infected. Infants with CSF pleocytosis should undergo CSF examination every 6 months, or until the cell count is normal. If the cell count is still abnormal after 2 years, or if a downward trend is not present at each examination, the child should be re-treated. The VDRL-CSF also should be checked at 6 months; if still reactive, the infant should be re-treated.

Follow-up of children treated for congenital syphilis after the newborn period should be the same as that prescribed for congenital syphilis among neonates.

Special Considerations

Penicillin Allergy

Children who require treatment for syphilis after the newborn period, but who have a history of penicillin allergy, should be treated with penicillin after desensitization, if necessary. Skin testing may be helpful in some patients and settings (see Management of the Patient With a History of Penicillin Allergy).

HIV Infection

Mothers of infants with congenital syphilis should be tested for HIV. Infants born to mothers who have HIV infection should be referred for evaluation and appropriate follow-up.

No data exist to suggest that infants with congenital syphilis whose mothers are coinfected with HIV require different evaluation, therapy, or follow-up for syphilis than is recommended for all infants.

Management of the Patient With a History of Penicillin Allergy

No proven alternatives to penicillin are available for treating neurosyphilis, congenital syphilis, or syphilis among pregnant women. Penicillin also is recommended for use, whenever possible, with HIV-infected patients. Unfortunately, 3%-10% of the adult population in the United States have experienced urticaria, angioedema, or anaphylaxis (upper airway obstruction, bronchospasm, or hypotension) with penicillin therapy. Re-administration of penicillin can cause severe immediate reactions among these patients. Because anaphylactic reactions to penicillin can be fatal, every effort should be made to avoid administering penicillin to penicillin-allergic patients, unless the anaphylactic sensitivity has been removed by acute desensitization.

However, only approximately 10% of persons who report a history of severe allergic reactions to penicillin are still allergic. With the passage of time after an allergic reaction to penicillin, most persons who have experienced a severe reaction stop expressing penicillin-specific IgE. These persons can be treated safely with penicillin. Many studies have found that skin testing with the major and minor determinants can reliably identify persons at high risk for penicillin reactions. Although these reagents are easily generated and have been available in academic centers for >30 years, currently only penicilloyl-poly-L-lysine (Pre-Pen, the major determinant) and penicillin G are available commercially. Experts estimate that testing with only the major determinant and penicillin G detects 90%-97% of the currently allergic patients. However, because skin testing without the minor determinants would still miss 3%-10% of allergic patients, and serious or fatal reactions can occur among these minor determinant positive patients, experts suggest caution when the full battery of skin test reagents listed in the table is not available.

Recommendations

If the full battery of skin-test reagents is available, including the major and minor determinants (see Penicillin Allergy Skin

Testing), patients who report a history of penicillin reaction and are skin-test negative can receive conventional penicillin therapy. Skin-test positive patients should be desensitized. If the full battery of skin-test reagents, including the minor determinants, is not available, the patient should be skin tested using penicilloyl (the major determinant, Pre-Pen) and penicillin G. Those with positive tests should be desensitized. Some experts believe that persons with negative tests, in that situation, should be regarded as probably allergic and should be desensitized. Others suggest that those with negative skin tests can be test-dosed gradually with oral penicillin in a monitored setting in which treatment for anaphylactic reaction is possible.

Penicillin Allergy Skin Testing

Patients at high risk for anaphylaxis (i.e., a history of penicillin-related anaphylaxis, asthma or other diseases that would make anaphylaxis more dangerous, or therapy with beta-adrenergic blocking agents) should be tested with 100-fold dilutions of the full-strength skin-test reagents before testing with full-strength reagents. In these situations, patients should be tested in a monitored setting in which treatment for an anaphylactic reaction is possible. If possible, the patient should not have taken antihistamines (e.g., chlorpheniramine maleate or terfenadine during the past 24 hours, diphenhydramine HCl or hydroxyzine during the past 4 days, or astemizole during the past 3 weeks).

Reagents (Adapted from Beall)¶

Major Determinant

- Benzylpenicilloyl poly-L-lysine (Pre-Pen [Taylor Pharmacal Company, Decatur, Illinois]) (6 x 10^{-5}M).

Minor Determinant Precursors**

- Benzylpenicillin G (10^{-2}M, 3.3 mg/mL, 6000 U/mL),
- Benzylpenicilloate (10^{-2}M, 3.3 mg/mL),
- Benzylpenilloate (or penicilloyl propylamine)(10^{-2}M, 3.3 mg/mL).

Positive Control

- Commercial histamine for epicutaneous skin testing (1 mg/mL).

Negative Control

- Diluent used to dissolve other reagents, usually phenol saline.

Procedures

Dilute the antigens 100-fold for preliminary testing if the patient has had a life-threatening reaction, or 10-fold if the patient has had another type of immediate, generalized reaction within the past year.

Epicutaneous (prick) tests: duplicate drops of skin-test reagent are placed on the volar surface of the forearm. The underlying epidermis is pierced with a 26-gauge needle without drawing blood.

An epicutaneous test is positive if the average wheal diameter after 15 minutes is 4 mm larger than that of negative controls; otherwise, the test is negative. The histamine controls should be positive to assure that results are not falsely negative because of the effect of antihistaminic drugs.

Intradermal test: if epicutaneous tests are negative, duplicate 0.02 mL intradermal injections of negative control and antigen solutions are made into the volar surface of the forearm using a 26- or 27-gauge needle on a syringe. The crossed diameters of the wheals induced by the injections should be recorded.

An intradermal test is positive if the average wheal diameter 15 minutes after injection is 2 mm or larger than the initial wheal size and also is at least 2 mm larger than the negative controls. Otherwise, the tests are negative.

Desensitization

Patients who have a positive skin test to one of the penicillin determinants can be desensitized. This is a straightforward, relatively safe procedure that can be done orally or IV. Although the two approaches have not been compared, oral desensitization is thought to be safer, simpler, and easier. Patients should be desensitized in a hospital setting because serious IgE-mediated allergic reactions, although unlikely, can occur. Desensitization can usually be completed in about 4 hours, after which the first dose of penicillin is given (Table 1). STD programs should have a referral center where patients with positive skin tests can be desensitized. After desensitization, patients must be maintained on penicillin continuously for the duration of the course of therapy.

**Reprinted from: Centers for Disease Control and Prevention. 1993 Sexually transmitted diseases treatment guidelines. MMWR 1993;42 (No. RR-14):27-46. Photomicrographs and photographs reprinted from: Bureau of Disease Prevention and Environmental Control, National Communicable Disease Center. Syphilis, a synopsis. Public Health Service Publication no. 1660, U.S. Department of Health, Education, and Welfare, Public Health Service, Atlanta, Georgia, 1968.*

†A woman treated with a regimen other than those recommended for treatment of syphilis (for pregnant women or otherwise) in these guidelines should be considered untreated.

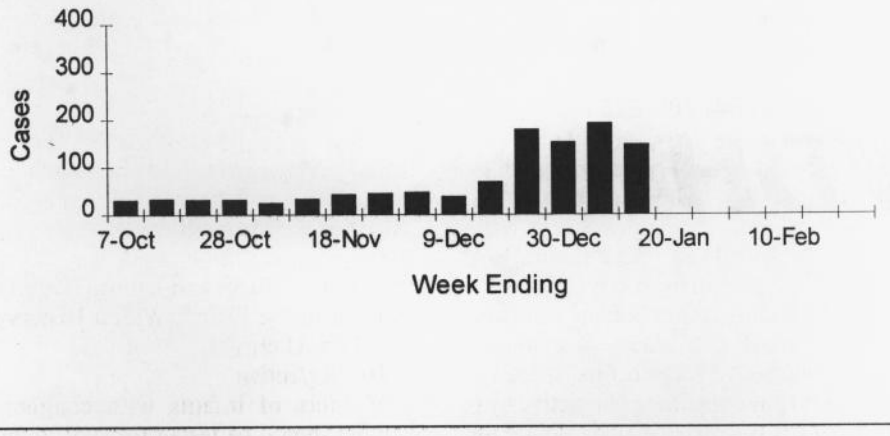
‡In the immediate newborn period, interpretation of CSF test results may be difficult; normal values vary with gestational age and are higher in preterm infants. Other causes of elevated values also should be considered when an infant is being evaluated for congenital syphilis. Though values as high as 25 white blood cells(WBC)/mm^3 and 150 mg protein/dL occur among normal neonates, some experts recommend that lower values (5 WBC/mm^3 and 40 mg/dL) be considered the upper limits of normal. The infant should be treated if test results cannot exclude infection.

§The absence of a fourfold greater titer for an infant cannot be used as evidence against congenital syphilis.

¶Reprinted with permission from: Beall GN. Penicillins. In: Saxon A, moderator. Immediate hypersensitivity reactions to beta lactam antibiotics. Ann Intern Med 1987;107:204-15.

***Aged penicillin is not an adequate source of minor determinants. Penicillin G should be freshly prepared or should come from a fresh-frozen source.*

Reports through January 13, 1994 of flu-like illness from sentinel physicians in Virginia (33 offices reporting). The predominant isolate to date has been the type A/Beijing/32/92(H3N2)-like strain. Activity is characterized as "widespread."



Cases of Selected Notifiable Diseases, Virginia, December 1 through December 31, 1993.*

Disease	Total Cases Reported This Month						Total Cases Reported to Date in Virginia		
		Regions							
	State	NW	N	SW	C	E	This Yr	Last Yr	5 Yr Avg
AIDS	118	7	44	6	21	40	1638	748	577
Campylobacteriosis	72	16	19	7	16	14	706	656	663
Gonorrhea†	1406	-	-	-	-	-	12144	16605	16577
Hepatitis A	21	2	7	1	4	7	157	164	271
Hepatitis B	27	1	2	7	5	12	157	193	271
Hepatitis NANB	9	0	0	1	6	2	54	48	56
Influenza	144	1	1	136	0	6	1223	148	1422
Kawasaki Syndrome	1	0	0	0	0	1	24	27	22
Legionellosis	1	0	0	0	0	1	10	29	17
Lyme Disease	13	0	1	9	1	2	86	123	97
Measles	0	0	0	0	0	0	4	16	79
Meningitis, Aseptic	43	2	8	5	3	25	343	310	357
Meningitis, Bacterial‡	15	2	3	2	2	6	106	124	156
Meningococcal Infections	7	2	3	0	0	2	51	61	58
Mumps	4	0	0	0	0	4	40	58	100
Pertussis	14	6	3	3	1	1	73	18	27
Rabies in Animals	22	7	2	5	8	0	387	362	289
Reye Syndrome	0	0	0	0	0	0	3	0	1
Rocky Mountain Spotted Fever	1	1	0	0	0	0	13	26	21
Rubella	0	0	0	0	0	0	0	0	2
Salmonellosis	94	14	19	17	24	20	1058	957	1389
Shigellosis	124	7	8	2	90	17	780	253	340
Syphilis (1° & 2°)†	57	1	7	1	8	40	663	728	725
Tuberculosis	85	5	21	8	26	25	484	379	404

Localities Reporting Animal Rabies: Amelia 1 raccoon; Augusta 1 cat; Bedford 1 raccoon; Campbell 2 skunks; Carroll 1 dog; Chesterfield 1 raccoon; Cumberland 1 raccoon, 1 skunk; Fairfax 1 raccoon; Hanover 1 raccoon; Loudoun 1 raccoon; Louisa 1 raccoon; Nottoway 1 skunk; Page 1 cat, 1 skunk; Powhatan 1 raccoon; Prince Edward 1 raccoon; Pulaski 1 skunk; Rockingham 1 fox; Spotsylvania 1 raccoon; Warren 1 fox.
Occupational Illnesses: Asbestosis 28; Carpal Tunnel Syndrome 66; Coal Workers' Pneumoconiosis 8; Loss of Hearing 9.

*Data for 1993 are provisional. †Total now includes military cases to make the data consistent with reports of the other diseases. ‡Other than meningococcal.

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