INFECTIOUS DISEASE REFERENCE

Syphilis: Clinical Breakdown

Etiology, Transmission, Clinical Staging, Diagnostic Testing, and Management

1. Etiology and Pathophysiology

Syphilis is a systemic, chronic sexually transmitted infection (STI) caused by the spirochete bacterium *Treponema pallidum* subspecies *pallidum*. Because the organism is extremely thin and fragile, it cannot be cultured on standard laboratory media and requires darkfield microscopy or serological assays for identification.

Upon inoculation through intact mucous membranes or micro-abrasions in the skin, *T. pallidum* rapidly disseminates via the bloodstream and lymphatic system. Its outer membrane contains very few exposed proteins, allowing the bacteria to evade host immune clearance and persist for decades if untreated, causing progressive vascular and neurological damage (obliterative endarteritis).

2. Modes of Transmission

- **Direct Sexual Contact:** The primary route of transmission occurs through direct contact with a syphilitic sore (chancre) or mucocutaneous lesion during vaginal, anal, or oral sex.
- **Vertical (Mother-to-Child) Transmission:** *T. pallidum* can cross the placenta at any stage of pregnancy or during delivery, leading to congenital syphilis, miscarriage, stillbirth, or severe neonatal morbidity.
- **Bloodborne Contact:** Rare transmission via blood transfusions or shared needles, mitigated today by routine blood donor screening and refrigeration of blood products (which kills spirochetes).

3. Clinical Stages of Syphilis

Untreated syphilis progresses through four distinct overlapping stages. Patients are most contagious during the primary and secondary stages, when active mucocutaneous lesions are present.

Stage	Typical Onset	Key Clinical Manifestations	Infectiousness & Course
Primary	10–90 days post-exposure (avg. 21 days)	Single (occasionally multiple) firm, round, **painless chancre** at the inoculation site (genitals, anus, rectum, lips, or mouth), accompanied by painless regional lymphadenopathy.	**Highly contagious.** Chancre heals spontaneously in 3–6 weeks even without treatment, though infection persists.
Secondary	2–10 weeks after chancre appears	Diffuse, non-pruritic maculopapular rash involving the **palms and soles**; condylomata lata (moist wart-like genital lesions); mucous patches; fever, malaise, sore throat, patchy alopecia, and generalized lymphadenopathy.	**Highly contagious.** Symptoms resolve within weeks to months, transitioning into latency.

Stage	Typical Onset	Key Clinical Manifestations	Infectiousness & Course
Latent	After secondary symptoms subside	Complete absence of clinical signs or symptoms; infection is detectable only via positive serological blood tests. Divided into **Early Latent** (<1 year) and **Late Latent** (≥1 year or unknown duration).	Early latent carries risk of mucocutaneous relapse; late latent is generally non-infectious sexually (vertical transmission still possible).
Tertiary (Late)	10–30+ years after initial infection	Occurs in ~15–30% of untreated cases. Presents as **gummatous syphilis** (destructive granulomatous lesions of skin, bone, or liver) or **cardiovascular syphilis** (aortitis, ascending aortic aneurysm, aortic regurgitation).	**Not sexually contagious.** Causes irreversible organ damage and can be fatal.

> **Neurosyphilis, Ocular, and Otic Syphilis:** Central nervous system, ocular, or auditory involvement can occur at *any* stage of infection—not just tertiary syphilis. Early manifestations include meningitis, cranial nerve palsies, uveitis, and sensorineural hearing loss; late manifestations include general paresis (dementia) and tabes dorsalis (dorsal column degeneration).

4. Congenital Syphilis

When an untreated pregnant person transmits *T. pallidum* to the fetus, outcomes depend on maternal stage and gestational timing. Early congenital syphilis (presenting before age 2) features hepatosplenomegaly, snuffles (hemorrhagic nasal discharge), desquamating rash on palms/soles, and osteochondritis. Late congenital syphilis (after age 2) causes permanent developmental stigmata, including Hutchinson's triad (notched incisors, interstitial keratitis, eighth-nerve deafness), saddle nose, and saber shins.

5. Diagnostic Evaluation

Presumptive diagnosis relies on combining two types of serological blood tests, as neither test alone is sufficient to confirm active infection:

- **Nontreponemal Tests (RPR, VDRL):** Detect antibodies against lipoidal material released from damaged host cells and bacteria. Results are reported quantitatively as titers (e.g., 1:32). Because titers decline following successful therapy, these tests are essential for monitoring treatment response and detecting reinfection. False positives can occur in pregnancy, autoimmune disease, or acute viral infections.
- **Treponemal Tests (FTA-ABS, TP-PA, EIA/CIA):** Detect antibodies specifically directed against *T. pallidum* antigens. These tests generally remain positive for life regardless of treatment, making them useful for confirming a reactive nontreponemal screen (traditional algorithm) or serving as the initial screen (reverse sequence algorithm).

- **Direct Detection & CSF Analysis:** Darkfield microscopy or PCR swabs of lesion exudate confirm early primary/secondary disease. Lumbar puncture for cerebrospinal fluid (CSF) VDRL, cell count, and protein is indicated when neurological, ocular, or otic symptoms are present.

6. Treatment and Follow-Up

Parenteral **Penicillin G** is the preferred treatment for all stages of syphilis. Dosing and duration depend on the clinical stage and whether central nervous system involvement is present:

Clinical Stage	First-Line Regimen	Penicillin-Allergic Alternative
Primary, Secondary, or Early Latent	Benzathine penicillin G 2.4 million units IM in a single dose	Doxycycline 100 mg PO twice daily for 14 days
Late Latent or Unknown Duration	Benzathine penicillin G 2.4 million units IM once weekly for 3 weeks (7.2 million units total)	Doxycycline 100 mg PO twice daily for 28 days
Neurosyphilis, Ocular, or Otic Syphilis	Aqueous crystalline penicillin G 18–24 million units/day IV (3–4 million units every 4 hours) for 10–14 days	Desensitization to penicillin is strongly recommended (ceftriaxone 2 g IV/IM daily for 10–14 days is an alternative)
Syphilis in Pregnancy	Stage-appropriate Benzathine penicillin G regimen (only proven therapy to prevent fetal transmission)	No acceptable alternative; patients must undergo penicillin desensitization and treatment

Clinical Monitoring & Jarisch-Herxheimer Reaction

Patients should be counseled about the **Jarisch-Herxheimer reaction**—an acute, self-limiting febrile reaction accompanied by headache and myalgias occurring within 24 hours of initiating therapy due to rapid spirochete lysis. Following treatment, quantitative nontreponemal titers (RPR or VDRL) must be rechecked at 6 and 12 months (or 6, 12, and 24 months for late latent disease); a fourfold decline in titer (e.g., from 1:32 to 1:8) indicates an adequate therapeutic response. Sexual partners exposed within 90 days of a primary, secondary, or early latent diagnosis should be treated presumptively even if seronegative.