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MEDICAL NOTES POWERHOUSE

Medical Notes Powerhouse

The Complete High-Yield Notes for NEET SS & INI SS-ET

Infectious Disease II
Viruses, Fungi & Parasites

04 VOLUME
of 10 · Volume IV · CH 187–242

56 CHAPTERS

5 SECTIONS

10 VOLUME SET

SECTIONS IN THIS VOLUME

- Spirochaetes & Atypicals
- Virology — DNA Viruses
- RNA Viruses & Emerging
- Fungal Infections
- Parasitology

Sources Harrison's Principles of Internal Medicine, 22nd Edition

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SECTION I

Spirochaetes & Atypical Bacteria

Syphilis, Lyme, Rickettsia, Mycoplasma and Chlamydia

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CH 187 · Syphilis — Treponema pallidum subsp. pallidum — Pri...

Chronic STI with classical 4-stage natural history (primary chancre → secondary rash → latent → tertiary gumma/CV/neuro). Penicillin G remains undefeated. Resurgence in MSM + congenital syphilis. Doxy-PEP emerging. High-yield NEET / USMLE.

Etiology & Microbiology

- ***Treponema pallidum* subsp. pallidum** = venereal syphilis.
- Other subspecies: **pertenue (yaws), endemicum (bejel)**; *T. carateum* (pinta) separate species.
- Thin spiral **spirochaete**; **endoflagella** in periplasmic space → motility.
- Trilaminar cytoplasmic membrane + thin peptidoglycan + lipid-rich outer membrane.
- **Historically uncultivable**; long-term in vitro culture now possible.
- Limited metabolism — relies on host nutrients.
- **TprK** = variable outer membrane protein; **antigenic variation** drives immune evasion + persistence.
- Generation time ~33 h; infective dose ~57 organisms.

Epidemiology

- **~8 million new cases/y** globally; 22.3 M prevalent.
- US: P&S; syphilis ↑ 10× from 2000 → 59,061 cases in 2022.
- **~45% in MSM**; ~40% co-infected with HIV.
- **Congenital syphilis**: **11× ↑** US in last decade (334 → 3755); 2022 = 282 stillbirths/deaths.
- Risk factors: late/no prenatal care, illicit opioid use, homelessness, transactional sex, incarceration.
- **Transmission**: sexual contact with chancre, mucous patch, rash, condylomata lata; in utero; blood transfusion; rare via skin/oral.
- 30–60% of unprotected exposures → infection.

♥ NEET SS HIGHLIGHTS

- ♥ **Primary: painless indurated chancre + nontender regional LAP**; heals 4–6 wk.
- ♥ **Secondary: maculopapular rash on palms + soles** + condylomata lata + mucous patches + LAP; 6–12 wk after infection.
- ♥ **Tertiary**: gumma / cardiovascular (ascending aortic aneurysm, vasa vasorum) / late neurosyphilis (tabes dorsalis, paresis).
- ♥ **Treatment of choice: Penicillin G benzathine 2.4 MU IM single dose** for primary/secondary/early latent.
- ♥ **Neurosyphilis: aqueous crystalline penicillin G 18–24 MU/d × 10–14 d.**
- ♥ **Jarisch-Herxheimer reaction**: fever, myalgia within hours of first dose — not allergic.
- ♥ **Argyll Robertson pupil**: accommodation+, light−; tabes + paresis.
- ♥ **Hutchinson teeth + mulberry molars + saddle nose + saber shins + 8th nerve deafness + interstitial keratitis** = late congenital syphilis.
- ♥ **Doxy-PEP** 200 mg within 72 h of exposure ↓ syphilis (and chlamydia, gonorrhea) in MSM.
- ♥ **Pregnancy**: penicillin only — desensitise if allergic.

Clinical Stages

Primary syphilis



Fig 187.2 — Primary syphilis: firm, nontender penile chancre with characteristic cartilaginous edge

- Incubation **2–6 wk** (median 21 d).
- **Painless single papule** → erodes to indurated, cartilaginous-edged ulcer (chancre).
- Sites: penis, vulva, cervix, vagina, anal canal, rectum, mouth (oral sex).
- Often unrecognized in women + MSM (internal sites).
- **Regional LAP within 1 wk of chancre** — firm, nonsuppurative, painless, bilateral.
- Heals 4–6 wk; LAP persists for months.
- DDx: HSV, chancroid (painful), donovanosis (beefy-red bleeding), trauma.

Secondary syphilis (6–12 wk after infection)



Fig 187.3 — Secondary syphilis (L→R): maculopapular truncal eruption, papules on palms, papules on soles

- **Generalized nontender LAP (85%)**; healing chancre still present in 15%.
- **Mucocutaneous rash**: pale red/pink macules → papules on trunk + extremities + **palms + soles**.
- **Condylomata lata**: broad moist grey-white highly infectious in intertriginous areas (10%).
- **Mucous patches** (10–15%): painless silver-grey erosions on oral/genital mucosa.

- Patchy alopecia (5%) of scalp, eyebrows, beard.
- **Lues maligna** = severe necrotic lesions in HIV+ with low CD4.
- Constitutional: sore throat (15–30%), fever, malaise, weight loss, headache, meningismus.
- Acute meningitis 1–2%; **CSF abnormal in up to 40%** early syphilis.
- **Ocular**: uveitis (5–10%), pupillary abnormalities, optic neuritis — fails topical steroids.
- **Otic**: sensorineural hearing loss, vertigo, tinnitus.
- Hepatitis (↑ LFTs in 25%), nephropathy (immune complex), GI (gastritis, proctitis, rectosigmoid mass), arthritis, periostitis.
- Resolves spontaneously in 1–6 mo.

Latent syphilis

- **Positive serology + normal CSF + asymptomatic**.
- **Early latent**: <1 year duration.
- **Late latent**: ≥1 y OR unknown duration.
- **CDC 2021**: combined as 'syphilis, unknown duration or late' for surveillance.
- May transmit to fetus + via blood transfusion in latent phase.
- Reinfection (esp. MSM): often asymptomatic; less likely to revert RPR to nonreactive.

Tertiary syphilis

- **Untreated 1/3 progress in pre-antibiotic era**.
- **Gumma** (late benign syphilis): solitary granulomatous lesions in skin, bone, viscera.
- **Cardiovascular** (10–40 y after infection):
- **Mechanism: endarteritis obliterans of vasa vasorum**
  - **Ascending aortic aneurysm** (saccular).
  - Aortic regurgitation.
  - Coronary ostial stenosis.
- **Late neurosyphilis**:
- **Tabes dorsalis** (25–30 y)
  - Demyelination of dorsal columns, dorsal roots, dorsal root ganglia.
  - **Lightning pain, ataxia, foot drop, paresthesia, areflexia, ↓ position + deep pain + temp.**
  - Argyll Robertson pupil, optic atrophy, bladder dysfunction.
- **General paresis** (~20 y)
  - **PARESIS**: Personality, Affect, Reflexes ↑, Eye (Argyll Robertson), Sensorium (delusions), Intellect ↓, Speech.

Neurosyphilis

- **CNS invasion early** in 40% of secondary syphilis; T. pallidum in CSF in 30% primary/secondary.
- Asymptomatic CNS in 25% late latent.
- **Symptomatic forms by time**:
- **Early**:
  - **Meningeal syphilis** (<1 y): headache, CN palsies (esp. CN VII/VIII), seizures, ↑ ICP.
  - **Meningovascular** (up to 10 y): **stroke in young adult, MCA territory**; subacute encephalitic prodrome.
- **Late parenchymal**:
  - **General paresis** (~20 y): cortical dementia, psychiatric features (PARESIS).
  - **Tabes dorsalis** (25–30 y): dorsal column + DRG demyelination.
- **Argyll Robertson pupil**: small, irregular, accommodates but no light reflex.
- **Risk factors** for clinical neurosyphilis: **HIV (esp. CD4 ≤350)**; **RPR titer ≥1:32**.
- **Ocular + otic syphilis** = treat as neurosyphilis regardless of CSF.

Congenital Syphilis

- **Transplacental infection** any time during pregnancy; ↑ during early maternal disease.
- **Early (<2 y)**:
- **Early features:**
  - **'Snuffles' (rhinitis, infectious)**
  - Mucocutaneous rash, condylomata lata, jaundice, anaemia, thrombocytopenia, leukocytosis
  - **Periostitis** on long bones (61%)
  - Hepatosplenomegaly, LAP
  - CNS invasion 22%
  - Death from pulmonary haemorrhage, sepsis, hepatitis
- **Late (>2 y)**:
- **Late stigmata:**
  - **Hutchinson teeth** (notched peg-shaped upper central incisors)
  - **Mulberry molars** (multiple poorly developed cusps on 6th-year molars)
  - **Saddle nose**
  - **Saber shins** (gummatous tibial periostitis)
  - **Interstitial keratitis** (5–25 y)
  - **8th nerve deafness**
  - **Hutchinson triad** = teeth + keratitis + 8th nerve deafness
  - Recurrent arthropathy (Clutton joints), neurosyphilis

Diagnosis

Direct organism detection

- **Dark-field microscopy** of chancre/condylomata lata: motile spirochaetes (rarely available).
- DFA-TP, IHC, in-house PCR on tissue/swab/CSF/blood.
- **Silver stains** (Warthin-Starry) — caution: artefacts mimic T. pallidum.

Serology

- **Two types: lipoidal (non-treponemal) + treponemal**.
- **Lipoidal (VDRL, RPR)**: antibody vs cardiolipin-lecithin-cholesterol; **titre tracks disease activity**; declines with treatment; **VDRL preferred for CSF**.
- **Treponemal (FTA-ABS, TPPA, EIA/CIA)**: antibodies vs T. pallidum antigens; stay positive lifelong.
- **Sensitivity primary**: treponemal 85–90% > lipoidal ~80%.
- **All reactive in secondary** (peak titre >1:32).
- **Prozone**: false-negative in <1% secondary syphilis with high titre — dilute serum.
- **Adequate response: 4-fold decline in RPR/VDRL titre** after treatment.

Table 187.1 — CDC reverse-sequence screening algorithm

Step 1 (Treponemal EIA/CIA)	Step 2 (RPR)	Step 3 (TPPA)	Interpretation
+	+	—	Active or past syphilis
+	−	+	Past or treated syphilis
+	−	−	False positive — unlikely syphilis
−	—	—	Probably no syphilis (early primary may miss)

Neurosyphilis CSF diagnosis

- **Pleocytosis (≥5 WBC/µL)**, ↑ protein, **reactive CSF VDRL** (highly specific, low sens).
- **CSF FTA-ABS** highly sensitive but low specificity; useful to exclude.
- **Indications for LP:**
- **When to LP:**
  - Neurologic, ocular, otic symptoms (LP not required for ocular/otic alone — treat as neurosyphilis)
  - Treatment failure / serofast
  - Active tertiary syphilis
  - **HIV+ with RPR ≥1:32 or CD4 ≤350**

> **CLINICAL PEARLS**
>
> - **'Painless ulcer' on the genitalia** = syphilis until proven otherwise; biopsy + PCR + serology.
> - **Rash on palms + soles** = think syphilis (or RMSF, viral exanthem, hand-foot-mouth).
> - **Ocular syphilis** often misdiagnosed as autoimmune uveitis — fails topical steroids.
> - **Test all syphilis patients for HIV**; conversely test all HIV+ for syphilis at diagnosis + q3 mo in high-risk.
> - Pregnant women with penicillin allergy → **desensitise + give penicillin**; no alternative is adequate.
> - **Argyll Robertson pupil**: 'prostitute's pupil' — accommodates but doesn't react to light.
> - **Hutchinson triad**: notched teeth + interstitial keratitis + 8th nerve deafness (late congenital).
> - **Jarisch-Herxheimer**: 1–8 h post-treatment fever/myalgia/headache from endotoxin release — NOT allergic; pretreat with antipyretics; warn pregnant pts (may cause contractions).

Treatment (CDC 2021)

Table 187.2 — Syphilis treatment

Stage	First-line	Penicillin-allergic
Primary, secondary, early latent	**Penicillin G benzathine 2.4 MU IM single dose**	Doxycycline 100 mg BD or tetracycline 500 mg QID × **14 d**
Late latent or unknown duration	**Penicillin G benzathine 2.4 MU IM weekly × 3 wk (total 7.2 MU)**	Doxy/tetra × **28 d**
Cardiovascular / benign tertiary	Penicillin G benzathine 2.4 MU IM × 3 wk	Desensitise
Neurosyphilis, ocular, otic	**Aqueous crystalline penicillin G 18–24 MU/d IV × 10–14 d** (3–4 MU q4h or CI)	Desensitise; alt: ceftriaxone 2 g/d IV × 10–14 d
Alt neurosyphilis	Procaine penicillin G 2.4 MU/d IM + probenecid 500 mg QID × 10–14 d	—
Pregnancy	**Penicillin per stage**	**Desensitise + penicillin**
Congenital (early)	Aqueous penicillin G 100–150,000 U/kg/d ÷ q4–6h × 10 d, OR procaine penicillin G 50,000 U/kg IM × 10 d	—

- **Penicillin G remains undefeated** — NO documented penicillin resistance after 75 y.
- **Benzathine penicillin does NOT achieve treponemicidal CSF levels** — never use alone for neurosyphilis.
- **Doxy-PEP**: 200 mg PO within 72 h of condomless sex — ↓ syphilis, chlamydia, gonorrhea in MSM; concerns about resistance selection.
- **Treatment monitoring**: clinical + RPR/VDRL titres at 6, 12, 24 mo (early); at 12 + 24 mo (late).
- **Inadequate response** = lack of 4-fold decline by 6–12 mo (early) or 12–24 mo (late) → re-evaluate, LP, retreat.
- **Serofast state**: persistently positive low-titre RPR after treatment — common; not necessarily treatment failure.

Special — HIV Co-infection

- **Test all newly diagnosed HIV for syphilis + vice versa.**
- Manifestations may be altered: **lues maligna** in low CD4; more rapid progression to neurosyphilis.
- **LP threshold lower**: RPR ≥1:32 OR CD4 ≤350.
- Same treatment regimens; closer follow-up.
- Re-screen q3 mo in high-risk MSM on PrEP.

✦ MNEMONIC

PARESIS *General paresis features (late neurosyphilis)*
- **P** — Personality changes
- **A** — Affect — emotional lability
- **R** — Reflexes hyperactive
- **E** — Eye — Argyll Robertson pupil
- **S** — Sensorium — illusions, delusions, hallucinations
- **I** — Intellect ↓ — memory, judgment
- **S** — Speech — dysarthria, tremor

Tabes dorsalis = posterior columns + dorsal roots → ataxia, areflexia, lightning pain, Argyll Robertson.

CONGENITAL HUTCH *Late congenital syphilis stigmata*
- **H** — Hutchinson teeth (notched incisors)
- **U** — Uveitis / interstitial keratitis
- **T** — Tibia saber shins
- **C** — Clutton joints (recurrent arthropathy)
- **H** — Hearing loss (8th nerve)
- **(M)** — Mulberry molars + Saddle nose

Early: snuffles, rash, periostitis, hepatosplenomegaly. Late: stigmata above.

✎ MCQ CORNER

Q1. 30 y/o MSM: single painless indurated penile ulcer + nontender inguinal LAP × 1 wk. Dark-field+. Best treatment?
- A. Doxycycline 100 mg BD × 14 d
- ✓ **B. Benzathine penicillin G 2.4 MU IM single dose**
- C. Aqueous penicillin G 24 MU/d IV × 14 d
- D. Ceftriaxone 1 g IM × 1

► *Primary syphilis: benzathine penicillin 2.4 MU IM single dose. Doxy alternative if allergic. Always test HIV.*

Q2. Confirmed neurosyphilis. Best regimen?
- A. Benzathine penicillin G IM weekly × 3
- ✓ **B. Aqueous crystalline penicillin G 18–24 MU/d IV × 10–14 d**
- C. Doxycycline × 28 d
- D. Single-dose ceftriaxone

► *Benzathine does NOT achieve CSF treponemicidal levels. Use IV aqueous penicillin G 18–24 MU/d × 10–14 d.*

Q3. Pregnant woman, RPR 1:64, FTA-ABS+, severe penicillin anaphylaxis. Best management?
- A. Doxycycline × 14 d
- B. Erythromycin × 14 d
- ✓ **C. Penicillin desensitisation + benzathine penicillin**
- D. Azithromycin

► *Penicillin only in pregnancy. Desensitise + treat. Doxy/tetra C/I; erythromycin doesn't cross placenta well.*

Q4. Young adult: MCA stroke + subacute encephalitic prodrome. No atherosclerosis. Best test?
- A. MRA
- ✓ **B. RPR + treponemal serology + CSF VDRL**
- C. Echocardiogram
- D. Lupus anticoagulant

► *Young stroke + encephalitic prodrome = meningovascular syphilis. Treat as neurosyphilis.*

✎ MCQ CORNER

Q1. 1-mo-old: snuffles + HSM + jaundice + periostitis. Mother had untreated RPR+. Best Rx?
- A. Single dose benzathine penicillin
- ✓ **B. Aqueous penicillin G 100–150,000 U/kg/d ÷ q4–6h × 10 d**
- C. Ceftriaxone × 10 d
- D. Doxycycline

► *Early congenital syphilis: aqueous penicillin G IV or procaine IM × 10 d. Doxy C/I in kids.*

Q2. Best test of treatment success after benzathine penicillin?
- A. Negative FTA-ABS
- ✓ **B. 4-fold ↓ RPR/VDRL titre by 6–12 mo**
- C. Negative dark-field
- D. Resolution of LAP

► *RPR/VDRL 4-fold decline = adequate response. Treponemal tests stay positive lifelong.*

Q3. Fever + headache + myalgia 4 h after first dose of penicillin for 2° syphilis. Best management?
- A. Stop penicillin — anaphylaxis
- B. Switch to doxycycline
- ✓ **C. Continue Rx + supportive (Jarisch-Herxheimer)**
- D. IV epinephrine

► *JHR = not allergic; endotoxin release. Self-limited <24 h. Pretreat with antipyretics in pregnancy.*

Q4. Doxy-PEP indication?
- A. Pregnant women with prior syphilis
- ✓ **B. MSM at high risk — 200 mg doxy within 72 h of condomless sex**
- C. All HIV+ patients
- D. Children <8 y

► *Doxy-PEP 200 mg within 72 h ↓ syphilis + chlamydia + gonorrhea in MSM.*

◷ LAST MINUTE REVISION

► ***T. pallidum* subsp. pallidum**: spirochaete, uncultivable historically.
► **TprK antigenic variation** → immune evasion.
► Sexual + transplacental + transfusion transmission.
► Resurgence in MSM + congenital cases (11× US in last decade).
► **Primary**: painless indurated chancre + nontender LAP; 2–6 wk incubation; heals 4–6 wk.
► **Secondary**: 6–12 wk; **palms + soles rash**; condylomata lata; mucous patches; alopecia; LAP 85%.
► Ocular (uveitis) + otic (SNHL) in secondary — fails topical steroids.
► Hepatic + renal + GI + arthritic involvement possible.
► **Latent**: early <1 y; late ≥1 y or unknown.
► **Tertiary**: gumma, CV (aortitis, ascending aortic aneurysm, AR), neurosyphilis.
► **Cardiovascular**: endarteritis obliterans of vasa vasorum, 10–40 y after infection.
► **Tabes dorsalis** (25–30 y): ataxia, areflexia, Argyll Robertson, lightning pain.
► **General paresis** (20 y): PARESIS mnemonic.
► **Meningovascular**: stroke + encephalitic prodrome in young adult.
► **Argyll Robertson pupil**: accommodates+, light−.

LAST MINUTE REVISION

► **Congenital early**: snuffles, rash, condylomata, periostitis, HSM, jaundice, anaemia.
► **Congenital late stigmata: Hutchinson teeth, mulberry molars, saddle nose, saber shins, interstitial keratitis, 8th nerve deafness.**
► **Hutchinson triad**: teeth + keratitis + deafness.
► Clutton joints, neurosyphilis in late congenital.
► **Dx: dark-field** of chancre/condylomata; PCR; **serology.**
► **Lipoidal (RPR, VDRL)**: titre tracks activity; declines with Rx.
► **Treponemal (FTA-ABS, TPPA, EIA/CIA)**: stay positive lifelong.
► **Reverse-sequence algorithm**: EIA/CIA → RPR → TPPA (if discordant).
► **Prozone**: high-titre antibody → false-neg → dilute serum.
► **CSF**: VDRL specific, FTA sensitive; pleocytosis + ↑ protein.
► **LP** if: neuro/ocular/otic symptoms, RPR ≥1:32, HIV+ + CD4 ≤350, treatment failure, tertiary.
► **Rx: Penicillin G benzathine 2.4 MU IM** single dose (primary/secondary/early latent); ×3 wk for late latent.
► **Neurosyphilis: aqueous crystalline penicillin G 18–24 MU/d IV × 10–14 d.**
► **Penicillin allergy**: doxy/tetra × 14 d (early) or 28 d (late); pregnancy = **desensitise + penicillin.**
► **Adequate response**: 4-fold ↓ RPR/VDRL.
► **Jarisch-Herxheimer** = transient febrile reaction post-1st dose; NOT allergic.
► **Doxy-PEP** 200 mg PO within 72 h = MSM STI prophylaxis.
► Always test HIV; rescreen q3 mo in high-risk MSM.

UPDATES

◉ **CDC 2021 STI guidelines**: standard regimens unchanged; revised case definitions (early non-primary non-secondary; unknown duration or late).
◉ **2023 US benzathine penicillin shortage** — major treatment challenge.
◉ **Doxy-PEP**: 200 mg PO within 72 h of exposure ↓ STIs in MSM (DoxyPEP, ZEPHYR trials); concerns about resistance.
◉ Long-term *in vitro* culture of *T. pallidum* achieved — opens drug-susceptibility testing.
◉ **Macrolide resistance** documented in some *T. pallidum* strains — avoid azithromycin for syphilis.
◉ **Congenital syphilis ↑ 11×** US in 2012–22 — major public health crisis.

CH 188 · Endemic Treponematoses — Yaws, Bejel, Pinta

Non-venereal treponematoses — yaws, bejel, pinta. Spirochetes 99.8% identical to T. pallidum. WHO MDA azithromycin eradication. NEET SS high yield: organisms, geography, primary lesion, late stigmata (gangosa, crab yaws).

Overview

- **Endemic treponematoses** = chronic spirochetal diseases, transmitted by **direct (non-sexual) contact**, usually in **childhood**.
- Cause severe late manifestations years after infection — like syphilis.
- Three diseases: **Yaws · Bejel (endemic syphilis) · Pinta**.
- Organisms **99.8% identical** to *T. pallidum* subsp. *pallidum* at genome level → morphologically indistinguishable, no antigenic differences.
- Distinguished from venereal syphilis by: transmission mode, age, geography, clinical features (overlap exists).
- WHO actively pursues **yaws eradication** via mass drug administration (MDA).

Agents — At a Glance

Table 188.1 — Treponematoses: organism, transmission, age

Disease	Organism	Transmission	Age	Geography
Syphilis	*T. pallidum* subsp. *pallidum*	Sexual, transplacental, skin	Sexual maturity / in utero	Worldwide
Yaws	*T. pallidum* subsp. *pertenue*	Skin-to-skin	Childhood	Moist tropics (Africa, Asia-Pacific, Americas)
Bejel	*T. pallidum* subsp. *endemicum*	Mouth-to-mouth, shared utensils, skin, **sexual** (new)	Early childhood / adult	Arid W. Africa, Middle East
Pinta	*T. carateum*	Skin-to-skin	Late childhood	Central / S. America

- **Pinta** = ONLY non-T. pallidum spp; remains a separate species — no isolates available for genetic studies.
- Yaws-like genital lesions + treponemal seroreactivity found in **wild non-human primates** in sub-Saharan Africa → animal reservoir suspected (NHP genomes virtually identical to human pertenue).

Epidemiology

- **1952–1969 WHO mass eradication**: >160 million examined, >50 million treated. Yaws prevalence dropped **>20% → <1%** in many areas.
- Resurgence after 1970s due to lack of surveillance.
- 2022: **168,239 suspected yaws cases** reported — mostly Papua New Guinea, Côte d'Ivoire, Ghana, Solomon Islands.
- Other active yaws foci: Cameroon, Togo, Benin, CAR, Nigeria, Congo, Liberia, DRC, Timor Leste, Vanuatu, Philippines, Indonesia.
- **India declared yaws-free (2016).**
- **Bejel** prevalence >10% in some areas of N. Ghana, Mali, Niger, Burkina Faso, Senegal.
- Recent molecular reports: *T. p.* subsp. *endemicum* in **genital lesions** (Cuba, Japan, Pakistan) → sexual transmission emerging.
- **Pinta**: limited to remote Central / N. South America. Recent cases — Panama (1980s), Brazil/Colombia/Peru (1987–93), Cuban tourist Austria (1999), S. Brazil (2021).

> **CLINICAL PEARLS**
>
> - Reported "yaws" cases are **often unconfirmed** — based on clinical ulcer appearance only.
> - Molecular studies of PNG lesions: **only ~30% contain *T. pallidum* DNA**.
> - **~50%** have *Haemophilus ducreyi* DNA (overlap with chancroid possible).
> - *Streptococcus pyogenes* = most common organism in lesions with no treponeme or ducreyi.

Clinical Features — General

- All treponemal infections = chronic, staged: **primary → secondary → latency → late**.
- Primary + secondary often **overlap** in yaws + bejel (unlike syphilis).
- Pinta = late manifestations are **mild** (dyschromic only, NOT destructive).
- Modern terminology: divide into **"early" vs "late"** stages.
- Traditional dogma: **no congenital, no CNS** involvement in non-venereal forms — *not firmly established*. Some evidence supports CNS, cardiovascular, congenital involvement in yaws + bejel.

Yaws (pian, framboesia, bouba)

- Causes destructive late lesions of skin, bone, joints in **~10% untreated**.
- **Incubation 3–4 weeks** → first papule on extremity → ulcerated or papillomatous ("raspberry-like" → *framboesia*).
- **"Mother yaw"** = primary lesion. Heals in 6 months. Regional LAD develops.
- Dissemination during early weeks → generalized secondary eruption (macular / papular / papillomatous) + generalized LAD.
- **Crab yaws** = painful papillomatous lesions on soles → crab-like gait.
- **Periostitis** → nocturnal bone pain + polydactylitis.
- Cutaneous relapses common in **first 5 years**.

Late yaws (10%)

- **Gummas** of skin + long bones — extensive, destructive.
- **Hyperkeratoses** of palms + soles.
- Osteitis, periostitis, hydrarthrosis.
- **Gangosa** = destruction of nose, maxilla, palate, pharynx (mimics leprosy, leishmaniasis).

Bejel (endemic syphilis, siti, dichuchwa, njovera, skerljevo)



Fig 188.2 — Early yaws: primary ulcer, papillomata, periostitis, polydactylitis

- Transmission: direct contact, kissing, premastication of food, shared drinking/eating utensils. **Sexual transmission** newly recognized.
- Initial lesion = **intraoral papule** (often unrecognized).
- Secondary: **mucous patches** on oral mucosa + mucocutaneous lesions resembling **condylomata lata**.
- May persist for months–years; treponemes readily demonstrated in early lesions.
- Periostitis + regional LAD common.
- Late: **osseous + cutaneous gummas**; destructive gummas, osteitis, gangosa MORE common than in yaws.

Pinta

- ONLY treponematosis confined to **skin** (no bone, organ, CNS).
- **Primary**: nonulcerating papule with satellites, pruritic — face / extremities.
- **Secondary (pintides)**: **pigmented, pruritic** macules.
- **Late**: **dyschromic / achromic** (depigmented) macules — nondestructive.
- No infectious relapses described.

Diagnosis

- **Darkfield microscopy** of lesion exudate — see spirochetes.
- **Serology**: non-treponemal (VDRL/RPR) + treponemal (TPHA, FTA-ABS) — cross-react with syphilis, **cannot differentiate**.
- Reactive serology may reflect past/latent infection — interpretation cautious.
- **PCR / molecular**: emerging, can subspecies-type.

Treatment & Eradication

- **Single-dose azithromycin** 30 mg/kg PO (max 2 g) — first-line for MDA; macrolide resistance reported in some strains.
- **Benzathine penicillin G** 1.2 MU IM (adults), 600,000 U (children <10 yr) — alternative.
- WHO **Morges strategy**: community-wide single-dose azithromycin MDA to eradicate yaws.
- Re-treatment / contact tracing essential.

♥ NEET SS HIGHLIGHTS

♥ **Yaws** = *T. p.* subsp. *pertenue* · moist tropics · papilloma ("framboesia").
♥ **Bejel** = subsp. *endemicum* · arid · oral primary lesion.
♥ **Pinta** = *T. carateum* · skin only · pintides → achromic macules.
♥ **Mother yaw** = primary lesion of yaws.
♥ **Crab yaws** = sole papillomas → crab gait.
♥ **Gangosa** = destruction of nose/palate (late yaws + bejel; NOT pinta).
♥ **Azithromycin 30 mg/kg single dose** = WHO MDA drug.
♥ All treponematoses are **serologically indistinguishable** from syphilis.

✦ MNEMONIC

YBP *Endemic treponematoses*
Y — Yaws — pertenue · papilloma · tropics · crab yaws · gangosa
B — Bejel — endemicum · oral · arid · gangosa more than yaws
P — Pinta — carateum · pintides · achromic · skin only
All treated with azithromycin 30 mg/kg single dose.

GANGOSA *Destructive late lesion features*
G — Gumma
A — Anterior nasal destruction
N — Nose collapse
G — Gnawed maxilla
O — Oral palate destruction
S — Septum eroded
A — Always in yaws + bejel, NEVER pinta

✎ MCQ CORNER

Q1. A 12-y/o boy from Papua New Guinea presents with a papillomatous "raspberry-like" ulcer on his leg. Single-dose treatment of choice per WHO?

A. Doxycycline 100 mg BD × 14d
B. Benzathine penicillin G 2.4 MU IM
✓ **C. Azithromycin 30 mg/kg PO single dose**
D. Ceftriaxone 1 g IM × 10 days

► *WHO Morges strategy = single-dose azithromycin 30 mg/kg (max 2 g) PO. Used for both index case and MDA in endemic regions. Bz-pen 1.2 MU is alternative.*

Q2. Which endemic treponematosis is characterized solely by skin lesions (achromic macules late) and does NOT cause bone/CNS destruction?

A. Yaws
B. Bejel
✓ **C. Pinta**
D. Venereal syphilis

► *Pinta is unique — only skin involvement, characterized by pintides (pigmented) → achromic (depigmented) macules. No destructive lesions.*

Q3. "Gangosa" refers to:

A. Painful sole papilloma in yaws
✓ **B. Destructive lesion of nose/palate in late yaws or bejel**
C. Primary papule of pinta
D. CNS gumma in tertiary syphilis

► *Gangosa = mutilating destruction of nose, maxilla, palate, pharynx in late yaws + bejel. Differential: leprosy, leishmaniasis. NEVER pinta.*

Q4. Which organism is NOT classified as a subspecies of *T. pallidum*?

A. *T. pallidum* subsp. *pertenue*
B. *T. pallidum* subsp. *endemicum*
✓ **C. *T. carateum***
D. *T. pallidum* subsp. *pallidum*

► *T. carateum (pinta) remains a separate species — no isolates available for genetic studies. The other three are subspecies of T. pallidum.*

Q5. A child in Sahelian West Africa has oral mucous patches and condyloma-lata-like skin lesions. Most likely diagnosis?

A. Yaws
✓ **B. Bejel**
C. Pinta
D. Congenital syphilis

► *Bejel (endemic syphilis) — arid W. Africa / Middle East. Primary intraoral papule → mucous patches + condyloma-lata-like lesions. Now also recognized as sexually transmissible.*

◷ LAST MINUTE REVISION

► Three endemic treponematoses: **yaws, bejel, pinta.**
► Yaws = *T.p. pertenue*; Bejel = *T.p. endemicum*; Pinta = *T. carateum*.
► Yaws → moist tropics · skin-to-skin · papilloma framboesia.
► Bejel → arid (W Africa, Middle East) · oral/utensil · now also sexual.
► Pinta → Latin America · skin only · pintides → achromic.
► **99.8% genomic identity** with *T. pallidum*.
► Primary yaws = **mother yaw** on extremity, 3–4 wk incubation.
► **Crab yaws** = sole papillomas.
► Periostitis → polydactylitis + nocturnal bone pain.
► **Gangosa** = nose/palate destruction in late yaws + bejel.
► Hyperkeratoses palms/soles in late yaws.
► Bejel late = osseous + cutaneous gummas, more destructive than yaws.
► Pinta = ONLY skin, NO bone/CNS, NO infectious relapse.
► **Serology cannot differentiate** from syphilis (cross-react).
► Rx: **azithromycin 30 mg/kg PO × 1** (WHO Morges); alt Bz-pen 1.2 MU IM.
► Macrolide resistance reported.
► **India declared yaws-free 2016.**
► Wild non-human primates = potential reservoir for yaws.

◉ UPDATES

◉ **WHO yaws eradication** ongoing — target 2030 via azithromycin MDA.
◉ **Doxy-PEP** (Luetkemeyer 2023 NEJM) — doxycycline post-exposure cuts bacterial STIs incl. syphilis incidence.
◉ **Tri-antigen syphilis vaccine** (Lukehart 2022) — attenuates chancre in animal models.
◉ Sexual transmission of **bejel** newly described (Cuba, Japan, Pakistan).

CH 189 · Leptospirosis — Weil's Syndrome & Spectrum

Zoonotic spirochetosis · rats + freshwater · ~1M severe cases/yr · CFR ~10% · biphasic illness · Weil's triad (jaundice + AKI + hemorrhage) · pulmonary hemorrhage. Conjunctival suffusion + calf pain + retroorbital headache = NEET SS classic.

Overview

- Globally important **zoonosis** · pathogenic *Leptospira* spp.
- Spectrum: asymptomatic → fulminant fatal disease.
- Mild = nonspecific fever + headache + myalgia.
- Severe = **Weil's syndrome** = jaundice + renal dysfunction + hemorrhagic diathesis.
- **Severe pulmonary hemorrhage** (with/without jaundice) = increasingly recognized.
- **~1 million** severe cases/yr globally · case-fatality **~10%**.

Etiologic Agent



Fig 189.1 — Leptospira: phylogenetic classification

- Family Leptospiraceae, order Spirochaetales.
- Traditional: *L. interrogans* (pathogenic) + *L. biflexa* (free-living).
- Modern phylogeny: **64 species** = 17 pathogenic · 21 intermediate · 26 saprophytic.
- **>260 pathogenic serovars in 26 serogroups**.
- Coiled, thin, motile · **hooked ends** · 2 periplasmic flagella.
- Size: 6–20 µm × 0.1 µm.
- Stain poorly → **dark-field** or **silver impregnation**.
- Culture requires special media · **weeks-to-months** to become positive.

Reservoirs & Transmission

Table 189.1 — Serovar–host associations (classic)

Serovar	Reservoir
Icterohaemorrhagiae · Copenhageni	Rats (most severe disease in humans)
Grippotyphosa	Voles
Hardjo	Cattle
Canicola	Dogs
Pomona	Pigs

- **Rodents = primary reservoir**; symbiotic colonization of urogenital tract for years.
- Excreted in urine; survive in **humid environment for months**.
- Human entry through **cuts, abraded skin, conjunctival / oral mucosa**.
- **Water = main vehicle**; soil also.
- Recent challenges to dogma: **household clustering**, asymptomatic renal colonization, prolonged human excretion → human-human possible.

Epidemiology & Risk Factors

- Worldwide; peaks **tropics + rainy season**, summer-fall in temperate.
- Most cases in **men**.
- **Occupational**: veterinarians, agricultural / sewage / slaughterhouse / fishing workers.
- **Recreational**: canoeing, windsurfing, swimming, waterskiing.
- Outbreaks: 1998 Springfield IL triathlon (lake water swallows); 2000 Eco-Challenge-Sabah (Borneo Segama River — **42% attack rate**); modern mud-runs.
- **Traveler's disease**: SE Asia (esp Thailand) — 52% of GeoSentinel cases.
- Floods + agricultural runoff increase risk (but no 1:1 link).
- Also: car accidents → contaminated water immersion; animal bites.

Pathogenesis

- Entry → hematogenous dissemination → **leptospiremic phase** (blood culture +).
- Evades complement-mediated killing + phagocytosis.
- **Immune phase**: antibodies appear, organism disappears from blood, persists in liver, lung, kidney, heart, brain.
- **Renal**: acute tubular damage → interstitial edema → ATN. Deranged tubular transporters → **hypokalemia, polyuria, Mg wasting**.
- **Hepatic**: focal necrosis (not widespread), hepatocyte apoptosis, bile canalicular plugging → **cholestatic jaundice without massive necrosis**.
- **Hemorrhage**: petechiae in heart, lung, kidney, adrenals, pancreas, GI, muscles, prostate, testes, brain (subarachnoid).
- Mechanism: **thrombocytopenia + endothelial activation + DIC**; ↑ E-selectin, vWF, TAT, D-dimer; ↓ antithrombin, protein C.
- LPS = unusual structure, **low endotoxic potency**; humoral immunity = serovar-specific LPS Ab.

Clinical — Biphasic Course

- **Incubation 1–2 wk** (range 2–30 days).
- **Acute leptospiremic phase** (3–10 days): fever; blood + CSF culture / PCR positive.
- **Immune phase**: symptoms resolve, antibodies appear, **urine culture positive**.
- Mild cases may not show second phase; severe may be monophasic fulminant.
- Serovar–syndrome link **refuted** (some serovars tend to cause severe disease).

Mild leptospirosis

- Flulike sudden onset: fever, chills, headache, N/V, abdominal pain.
- **Conjunctival suffusion** (redness without exudate) — characteristic.
- **Intense myalgia — calves, back, abdomen**.
- **Frontal / retroorbital headache** (mimics dengue) ± photophobia.

- **Aseptic meningitis** — esp. children.
- Possible: rash (transient, macular / hemorrhagic), hepatosplenomegaly, LAD, crackles.
- Spontaneous resolution in 7–10 days; mortality low.

Severe leptospirosis (Weil's syndrome)

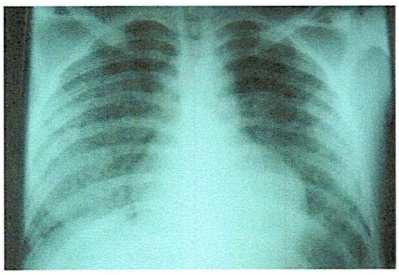



Fig 189.2 — Severe pulmonary hemorrhage in leptospirosis

- **Triad**: hemorrhage + jaundice + AKI.
- Case-fatality **1–50%.**
- **Mortality predictors**: age >40, altered mental status, ARF, respiratory failure, hypotension, arrhythmias.
- **Bleeding**: pulmonary hemorrhage (cough, chest pain, hemoptysis, ARDS), GI (melena, hematemesis), GU (hematuria), skin (petechiae, ecchymosis, venipuncture site bleeding).
- **Jaundice**: 5–10% of all cases; orange skin cast; **no fulminant hepatic necrosis**; tender hepatomegaly.
- **AKI**: nonoliguric or oliguric; **hypokalemia, hyponatremia, ↓ Mg (unique)**; HD lifesaving; usually full renal recovery.
- Meningitis in severe = mortality **13% untreated vs 2% treated.**
- Other: necrotizing pancreatitis, cholecystitis, rhabdomyolysis (↑ CK), myocarditis, ECG ST-T changes / arrhythmias (poor prognosis), TTP, HUS.
- **Chronic uveitis** = autoimmune sequela.
- Long-term: fatigue, myalgia, headache for years.

Diagnosis

Lab clues

- Leukocytosis with left shift; ↑ CRP, procalcitonin, ESR.
- **Thrombocytopenia ≤ 100 × 10⁹/L** common — associated with bleeding + AKI.
- Severe: DIC pattern.
- Urinalysis: WBC, RBC, hyaline/granular casts, mild proteinuria.
- **Nonoliguric hypokalemic renal insufficiency** = characteristic of early disease.
- Bilirubin high (predom. direct); AST/ALT/ALP **moderate.**
- **Amylase elevated** (clinical pancreatitis uncommon).
- CSF: pleocytosis (few → >1000/µL); early PMN → late lymph predominance; protein mildly ↑, glucose normal.
- **CXR**: patchy bilateral alveolar pattern (lower lobes), pleura-based densities, ground-glass = ARDS.

Definitive tests

- **Culture**: blood + CSF (first week), urine (after week 2).
- **PCR** — test of choice in first 5 days; blood / serum / urine.
- **MAT (microscopic agglutination test)** = serologic gold standard.
- Single titer ≥ **1:200–1:800** (depending on endemicity) + clinical picture, OR **4-fold rise** acute-vs-convalescent.
- Antibodies appear **week 2**; early treatment delays / blunts response.
- **ELISA** — broad antigen; lateral-flow rapid tests available.
- MAT identifies presumptive serogroup but cross-reactions common.

CLINICAL PEARLS

- Triad on exam: **conjunctival suffusion + calf tenderness + retroorbital headache.**
- Hyperbilirubinemia **out of proportion** to mildly elevated AST/ALT = clue.
- **Mg wasting** in urine unique to leptospiral nephropathy.
- Pulmonary hemorrhage may have NORMAL CXR initially — index high.
- Serology negative in first week — don't rule out leptospirosis on early titer.

Differential Diagnosis

- **Fever + myalgia + headache**: influenza, SARS-CoV-2, dengue, chikungunya.
- **Jaundice + AKI + fever**: malaria (esp. *P. falciparum*), viral hepatitis, scrub typhus, acute HIV.
- **Hemorrhagic fever**: dengue hemorrhagic, hantavirus (HFRS / HCPS), yellow fever, Rift Valley, filovirus, Lassa.
- **Rickettsioses** share epidemiology + clinical features — order serology in parallel.
- Dual infections reported.

Treatment

- **Susceptible**: β-lactams, cephalosporins, aminoglycosides, macrolides, doxycycline.
- **NOT susceptible**: vancomycin, rifampicin, metronidazole, chloramphenicol.
- Treat early — empirical based on clinical suspicion + exposure.

Table 189.2 — Antibiotic regimens

Severity	First-line	Alternatives	Duration
Severe	IV penicillin G 1.5 MU q6h	Ceftriaxone 1 g/d IV · Cefotaxime 1 g q6h · Doxycycline IV	7 days
Mild	**Doxycycline** 100 mg PO BD	Azithromycin 500 mg-1g/d · Amoxicillin 500 mg q6h	7 days
Prophylaxis	Doxycycline 200 mg PO weekly	Azithromycin 250 mg weekly	Duration of exposure

- **Jarisch–Herxheimer reaction** may follow antibiotic initiation.
- Supportive: **fluid resuscitation, vasopressors, hemodialysis** in severe AKI.
- Ventilation + transfusion for pulmonary hemorrhage / ARDS.
- Prophylaxis: doxycycline 200 mg/wk during high-risk exposure (soldiers, adventure athletes).

♥ NEET SS HIGHLIGHTS

- ♥ **Weil's syndrome** = jaundice + AKI + hemorrhage.
- ♥ **Conjunctival suffusion** = classic sign (NEET pet).
- ♥ **Calf tenderness** + frontal/retroorbital headache.
- ♥ **Icterohaemorrhagiae/Copenhageni** = rat serovars → severe.
- ♥ **Hypokalemic nonoliguric AKI** with Mg wasting.
- ♥ Hyperbilirubinemia OUT of proportion to AST/ALT.
- ♥ **PCR best in first 5 days**; MAT later.
- ♥ Severe Rx = **IV penicillin G**; mild Rx = doxycycline 100 mg BD.
- ♥ NOT susceptible: vanco, rifampicin, metronidazole, chloramphenicol.
- ♥ Prophylaxis: doxycycline **200 mg weekly**.

✦ MNEMONIC

LEPTO *Severe leptospirosis features*

- **L** — Liver — jaundice (orange skin, no necrosis)
- **E** — Eyes — conjunctival suffusion, late uveitis
- **P** — Pulmonary hemorrhage — leading killer
- **T** — Thrombocytopenia, DIC
- **O** — Oliguric AKI with hypokalemia + Mg wasting

WEIL *Weil's triad*

- **W** — Watery hemorrhage (multi-site)
- **E** — Elevated bilirubin (jaundice)
- **I** — Injured kidney (AKI)
- **L** — Leptospira icterohaemorrhagiae most common

✎ MCQ CORNER

Q1. A 28-year-old man returns from a Borneo adventure race with fever, severe calf pain, conjunctival suffusion, mild jaundice, and Cr 3.5 mg/dL. K+ is 2.8. Best initial diagnostic test?

A. Blood culture for bacteria
✓ **B. PCR for *Leptospira* on serum**
C. MAT serology now
D. Liver biopsy

► *PCR is the test of choice in the first 5 days of illness. MAT antibodies are not reliably positive until week 2. Conjunctival suffusion + calf pain + AKI with hypokalemia + jaundice + recent freshwater = leptospirosis.*

Q2. Most appropriate antibiotic for severe leptospirosis with pulmonary hemorrhage?

A. IV vancomycin
✓ **B. IV penicillin G 1.5 MU q6h**
C. Oral metronidazole
D. Oral rifampicin

► *IV penicillin G is first-line for severe leptospirosis. Ceftriaxone is an equivalent alternative. Leptospira is NOT susceptible to vanco, rifampicin, metronidazole, or chloramphenicol.*

Q3. Which electrolyte abnormality is uniquely characteristic of leptospiral nephropathy?

A. Hyperkalemia
B. Hypocalcemia
✓ **C. Renal magnesium wasting**
D. Hypernatremia

► *Magnesium wasting in the urine is uniquely associated with leptospirosis renal injury. Other classic findings: nonoliguric AKI with hypokalemia + hyponatremia.*

Q4. A reservoir serovar producing the most severe human disease (Weil's) is:

A. Hardjo (cattle)
B. Canicola (dogs)
✓ **C. Icterohaemorrhagiae (rats)**
D. Pomona (pigs)

► *Rat-associated serovars (Icterohaemorrhagiae, Copenhageni) cause the most severe human disease.*

Q5. Recommended doxycycline regimen for short-term leptospirosis chemoprophylaxis (e.g., adventure travelers, soldiers)?

A. 100 mg BD daily
✓ **B. 200 mg PO once weekly**
C. 100 mg single dose
D. Doxy not used; only azithromycin

► *Doxycycline 200 mg PO once weekly during the exposure period.*

Q6. Most characteristic peripheral blood finding in severe leptospirosis is:

A. Eosinophilia
B. Atypical lymphocytes
✓ **C. Thrombocytopenia**
D. Schistocytes only

► *Thrombocytopenia ≤100 × 10^9/L is common and correlates with bleeding + AKI. Leukocytosis with left shift is typical.*

LAST MINUTE REVISION

► Spirochete · hooked ends · 2 periplasmic flagella.
► **17 pathogenic species, 260+ serovars, 26 serogroups.**
► **Rats = main reservoir**; Icterohaemorrhagiae/Copenhageni = severe disease.
► Transmission: cuts / mucosa contact with urine-contaminated **water/soil**.
► Triathletes, mud runners, jungle trekkers, sewage workers = risk.
► Incubation 1–2 wk (range 2–30 d).
► **Biphasic**: leptospiremia (blood / CSF +) → immune (urine +).
► **Weil's = jaundice + AKI + hemorrhage.**
► **Conjunctival suffusion + calf pain + retroorbital headache.**
► Pulmonary hemorrhage = increasingly fatal presentation.
► Hyperbilirubinemia >> AST/ALT rise.
► **Nonoliguric hypokalemic AKI + Mg wasting.**
► **Thrombocytopenia** + DIC.
► Aseptic meningitis (esp kids); CSF lymphocytic, glucose normal.
► **PCR best ≤5 d**; MAT after week 2; titer ≥1:200 or 4× rise.
► Severe Rx: **IV pen G** 1.5 MU q6h × 7d (alt ceftriaxone, cefotaxime).
► Mild Rx: **doxycycline 100 mg BD** (alt azithro, amox).
► Prophylaxis: **doxy 200 mg weekly**.
► **NOT susceptible**: vanco, rifampicin, metronidazole, chloramphenicol.
► Jarisch–Herxheimer may occur.
► Late uveitis = autoimmune sequela.

UPDATES

◉ 2022 trial: 3 rounds yaws MDA (similar approach being trialed for leptospirosis control in floods).
◉ PCR + multiplex assays expanding for early dx.
◉ OMP subunit vaccines in development — no licensed human vaccine yet.