



Syphilis: A Clinical Case Presentation - Solutions and Learnings

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Chief Complaint

- Diffuse, whole body rash and blisters
- 




HPI

- 43 year-old female with a history of depression who presented to the ER with a diffuse erythematous rash for 2-3 months.
- Rash first started as “itchy bumps” on her back and has progressively spread to her chest, abdomen, upper extremities, face and genitals.
- Complains of intense pruritus and notes oozing and bleeding from some lesions when she scratches
- She was seen at an urgent care when the rash first started and was prescribed hydrocortisone cream and an antihistamine, but the rash became worse




Review of Systems

- Positive: 21 lb weight loss over 2 months
- Negative:
 - Fevers
 - Chills
 - Joint pains
 - Animal exposures
 - New detergent/soaps/products
 - Known bug bites



Past Medical/Surgical History

- Past Medical History
 - Depression
- Past Surgical History
 - Partial hysterectomy



Social History

- From Bronx, NY - USA
- Smokes cigarettes, 7 pack-year
- Does not drink alcohol
- Uses marijuana every 1-2 weeks, no IV DU
- Sexually active with 1 male partner with last sexual encounter 4 months prior to presentation. No longer in this relationship.
- Contraception: does not use any forms of protection
- Currently living alone



Family History

- No history of Lupus or cancers
- 



Medications/Allergies

- Medications:

- Antihistamine as needed
- Mineral oil-hydrophilic petrolatum ointment as needed

- Allergies:

- Penicillin: develops a rash



Physical Examination



- Vitals: Temp 98.2 F, HR 72 bpm, BP 136/85, SpO2 100% on RA
- General: no acute distress
- HEENT: No oral mucosal lesions; Face with multiple erythematous/violaceous papules and nodules diffusely throughout face; nodules with resultant dysmorphia of right nose and lip
- Skin:
 - erythematous/violaceous patches, papules and nodules diffusely with excoriation and scale
 - palm with hyperpigmented patch
 - soles of feet spared
- Genitals: erythematous patches/plaques present

Skin:



Laboratory results

Chemistry

- Na 138
- K 3.9
- Cl 105
- CO₂ 23
- BUN 6
- Cr 0.66
- Gluc 97

CBC:

- WBC 6.3 (Neut 55%, Lymph 26%, Eos 9%)
- Hb 11.8
- Hct 37.0
- Plt 391

Liver function

- Alk Phos 115
- AST < 20
- ALT < 10
- Total Bili 0.2
- Direct Bili <0.2
- Tot Prot 8.0



Other studies?

- Consider differential diagnoses:
 - Coxsackie (hand-foot-mouth)
 - HSV (erythema multiforme)
 - Rickettsia (Rocky Mountain Spotted Fever)
 - Syphilis
 - Drug eruption
 - HIV
 - Viral exanthum



Other studies

- HSV1 and 2 PCR negative
- VZV PCR not detected
- HIV negative
- Syphilis
 - IgG/IgM Ab positive
 - TP-PA positive
 - RPR non-reactive



Poll 1

- ▶ How would you interpret the Syphilis test in this patient?
 - ▶ A. History of syphilis (previously treated)
 - ▶ B. Long-standing untreated syphilis
 - ▶ C. Further testing needed



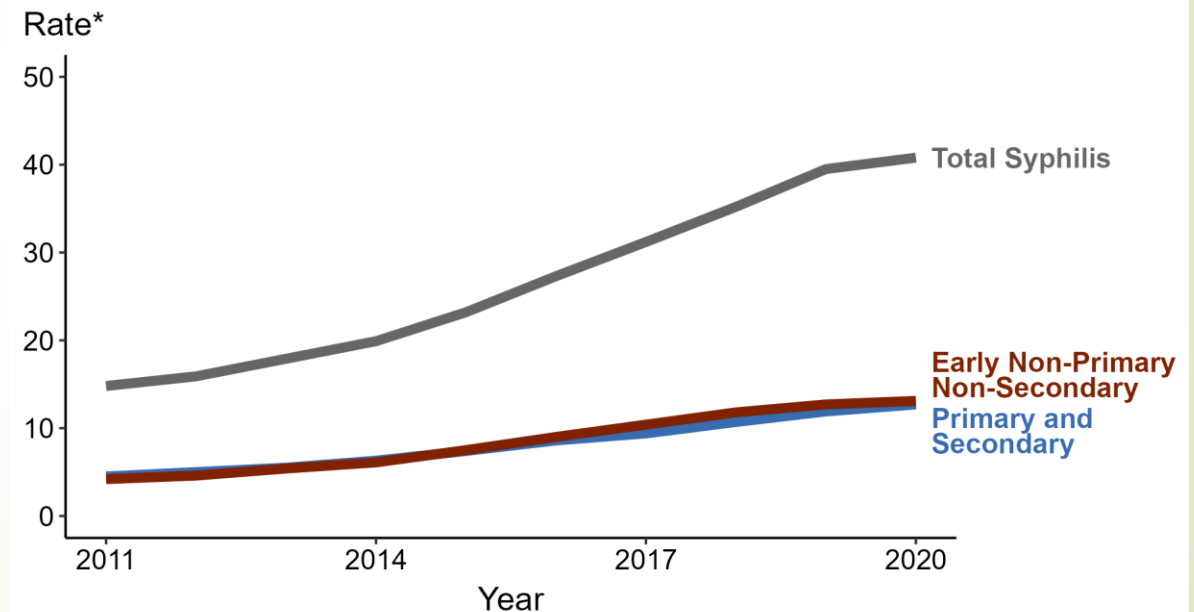
Poll 2

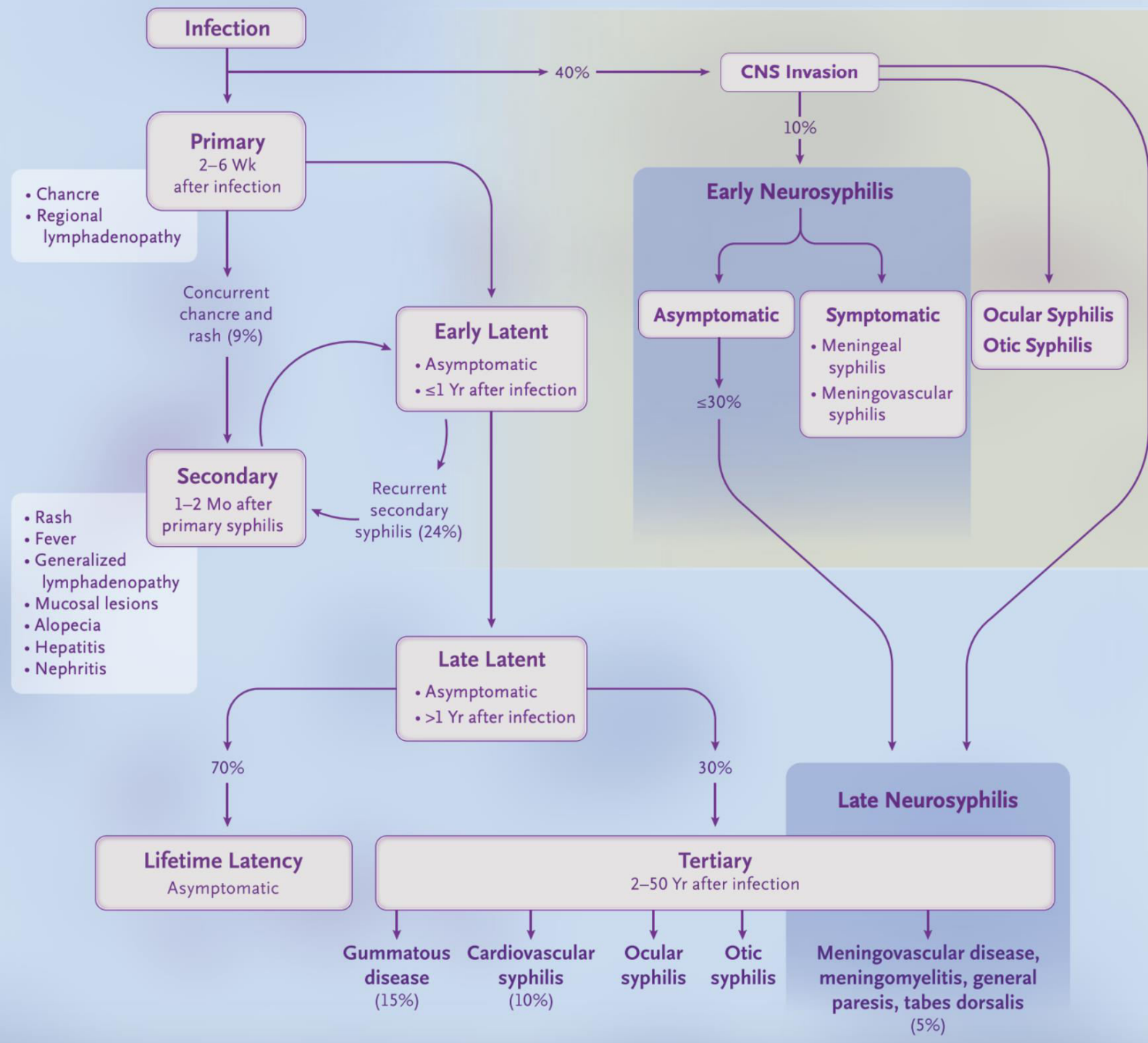
- ▶ If this is active syphilis, what stage of illness is this considered to be?
 - ▶ A. Primary
 - ▶ B. Secondary
 - ▶ C. Tertiary

Syphilis

- Caused by the spirochete *Treponema pallidum*
- Globally
 - 7.1 million new cases in 2020
 - 1 million pregnant women with active syphilis in 2016,
 - > 350,000 adverse birth outcomes
 - 200,000 stillbirth or neonatal death.
- In 2020, the US had 133,945 new cases (all stages) with 41,655 being either primary or secondary syphilis
 - 6.8% increase since 2019
 - 53% in males

Syphilis — Rates of Reported Cases by Stage of Infection, United States, 2011–2020



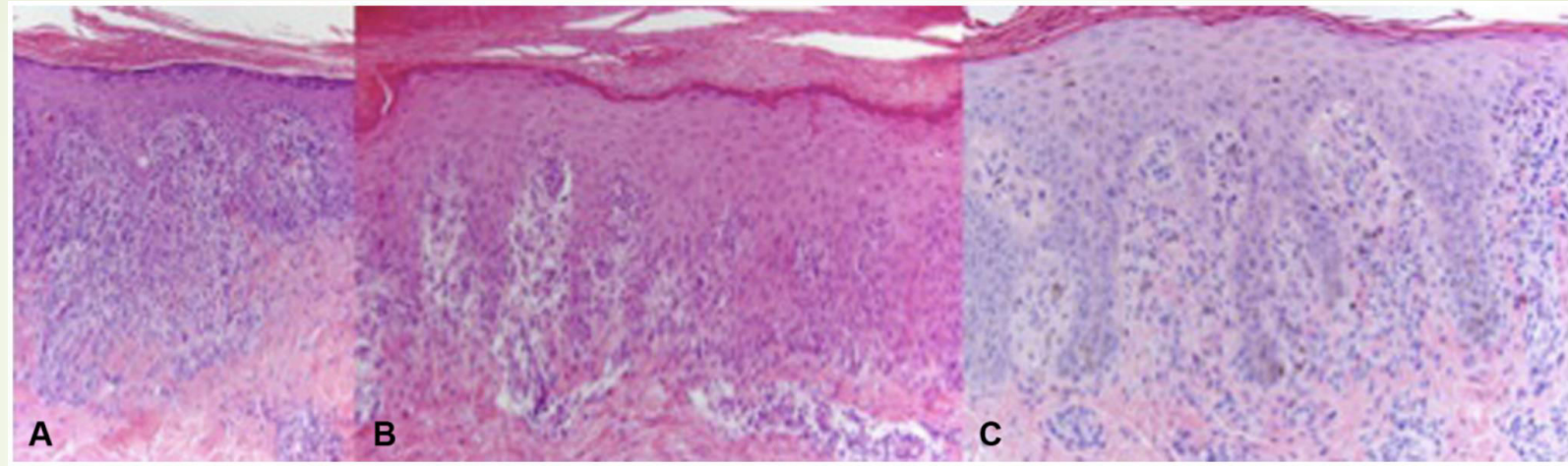




Pathophysiology of Secondary Syphilis

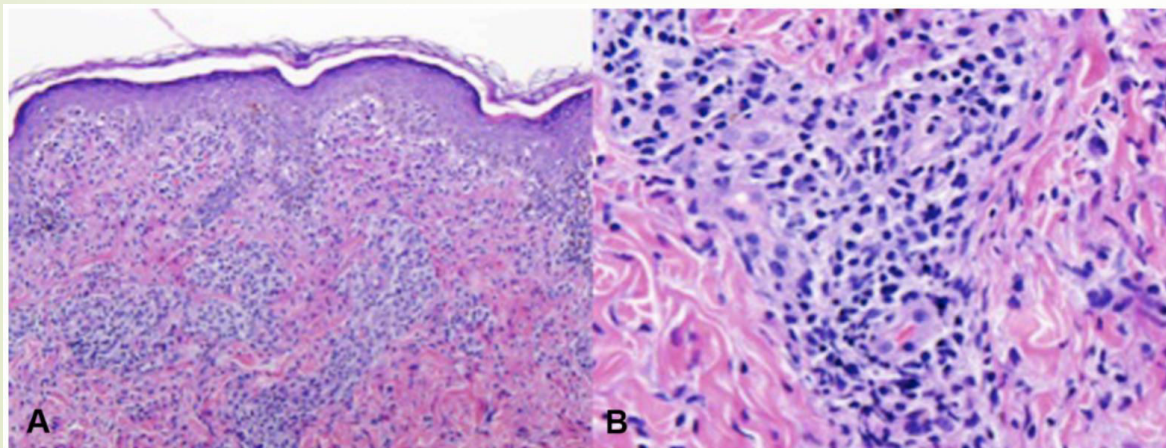
- Due to hematogenous dissemination of the infection
- Immune response:
 - Humoral response
 - Cell-mediated response: CD4+ and CD8+ T cells, activated monocytes, macrophages, and dendritic cells
- Histopathology:
 - Interstitial inflammation, endothelial swelling, irregular acanthosis, elongated rete ridges, a vacuolar pattern with lymphocytic infiltration
- Microbiology:
 - Silver staining can detect spirochetes but have high rate of false negatives

Lesion biopsy

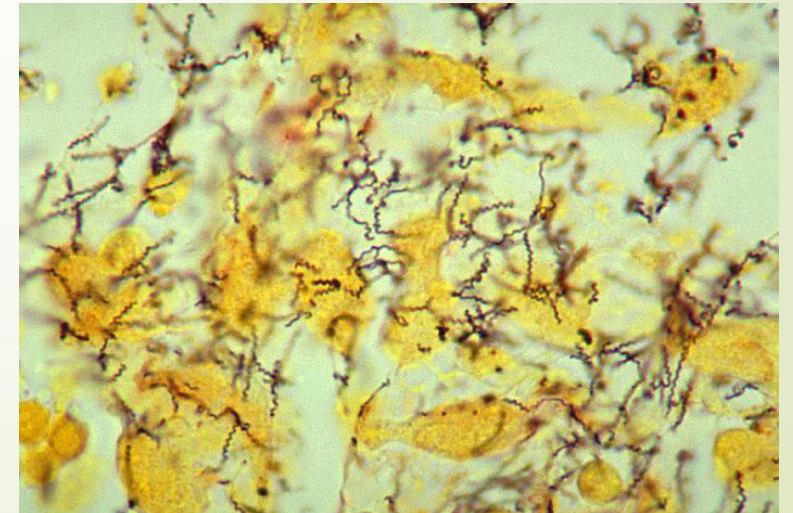


A
Irregular acanthosis

B
Elongated rete ridges



A
Endothelial swelling, inflammatory pattern



Silver staining showing *T pallidum*



Diagnostics

➤ Serology:

➤ Treponemal tests

- Fluorescent treponemal antibody absorption (FTA-ABS)
- *T. pallidum* particle agglutination assay (TPPA)
- *T. pallidum* enzyme immunoassay (TP-EIA)

➤ Non-treponemal tests

- Rapid plasma regain (RPR)
- Venereal Disease Research Laboratory (VDRL)

➤ Direct method:

- Darkfield microscopy

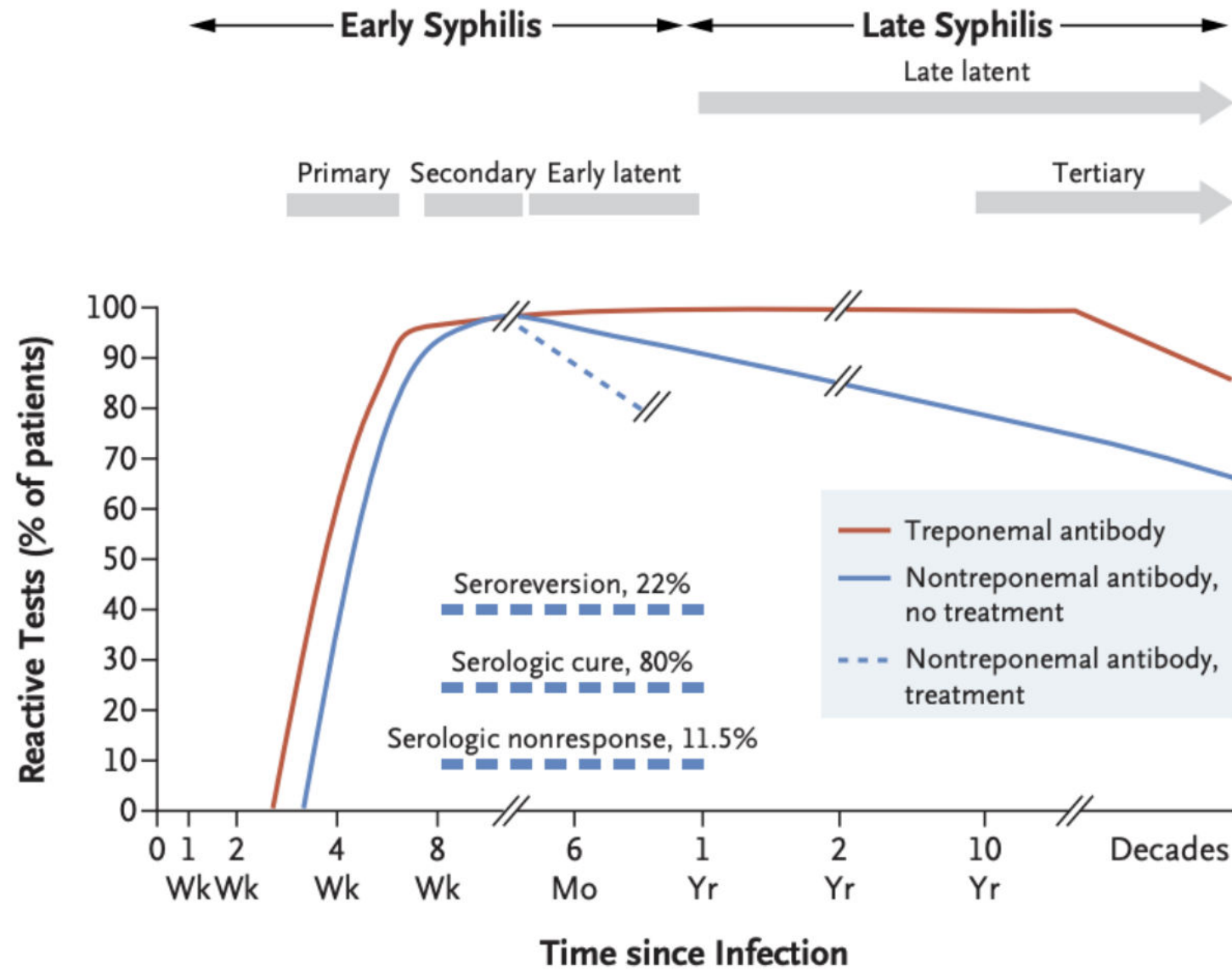


Figure 3. Serologic Responses (in Serum) throughout the Natural History of Treated and Untreated Syphilis.

Ghanem KG, Ram S, Rice PA. The Modern Epidemic of Syphilis. *NEJM*. 2020;382(9):845-854.

Table 1. Traditional and Reverse-Sequence Algorithms for Serologic Testing.*


Algorithm	NTT	TT	Confirmatory TT†	Interpretation‡
Traditional	Nonreactive			No serologic evidence of syphilis (most likely) Early primary syphilis (extremely recent infection cannot be ruled out) Treated or long-standing untreated syphilis
Traditional	Reactive	Nonreactive		Biologic false positive NTT§
Traditional and reverse-sequence	Reactive	Reactive		Untreated syphilis (likely) Treated syphilis (likely) Endemic treponematoses
Reverse-sequence	Nonreactive	Reactive	Nonreactive	Biologic false positive TT¶
Reverse-sequence	Nonreactive	Reactive	Reactive	Treated syphilis (most likely) Long-standing untreated syphilis Early primary syphilis (before NTT has turned positive) Prozone reaction (more common with VDRL test than with RPR test)
Reverse-sequence		Nonreactive		No serologic evidence of syphilis (most likely) Early primary syphilis (extremely recent infection cannot be ruled out) Long-standing treated syphilis if TT shows seroreversion

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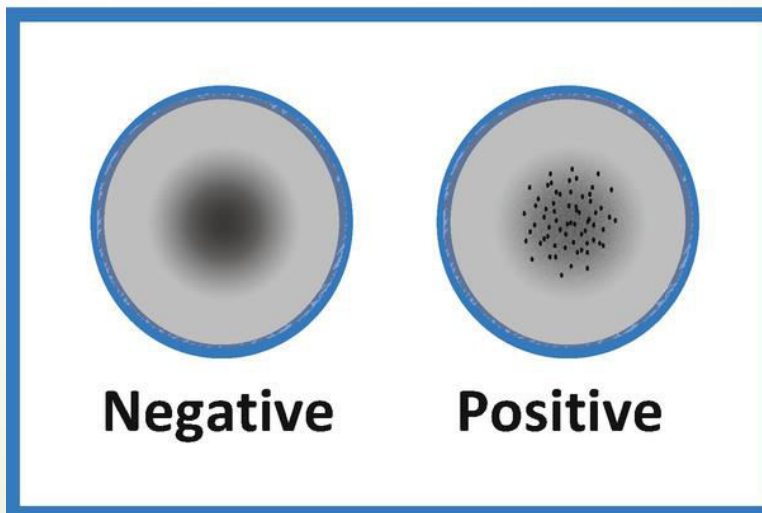
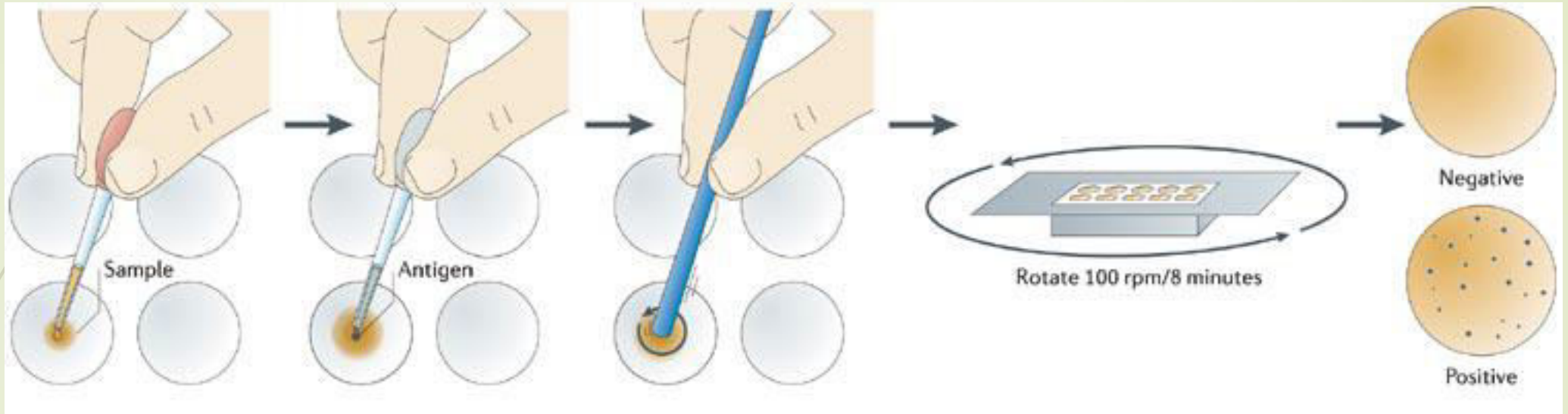
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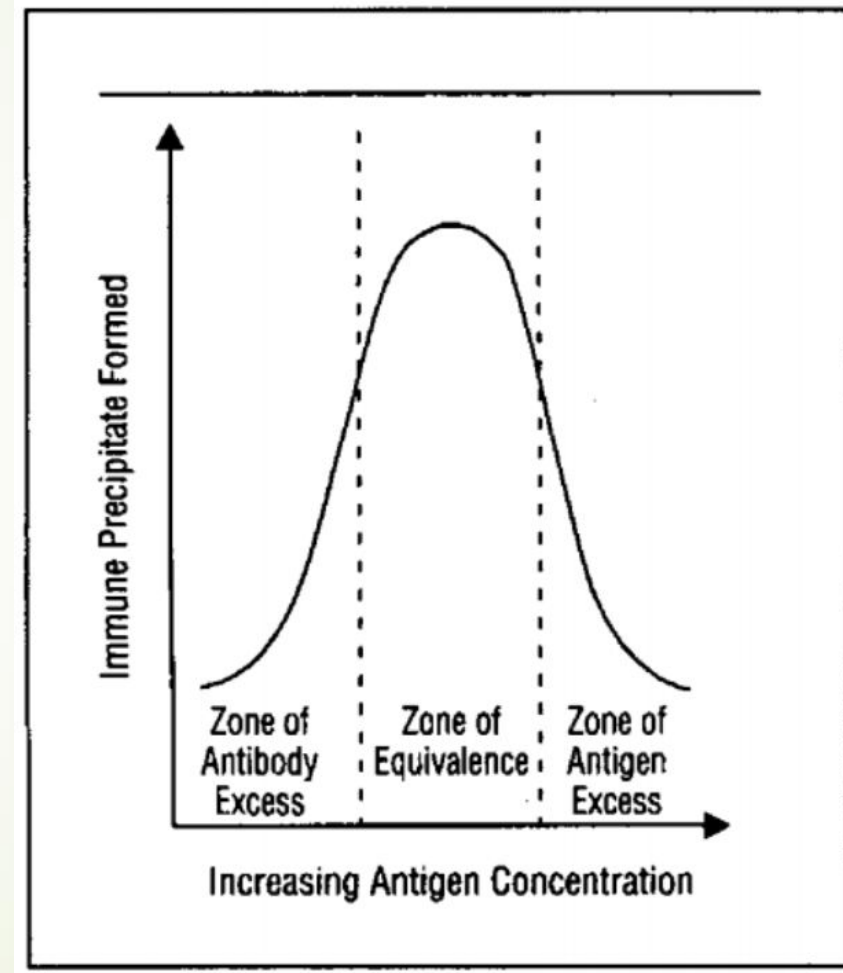
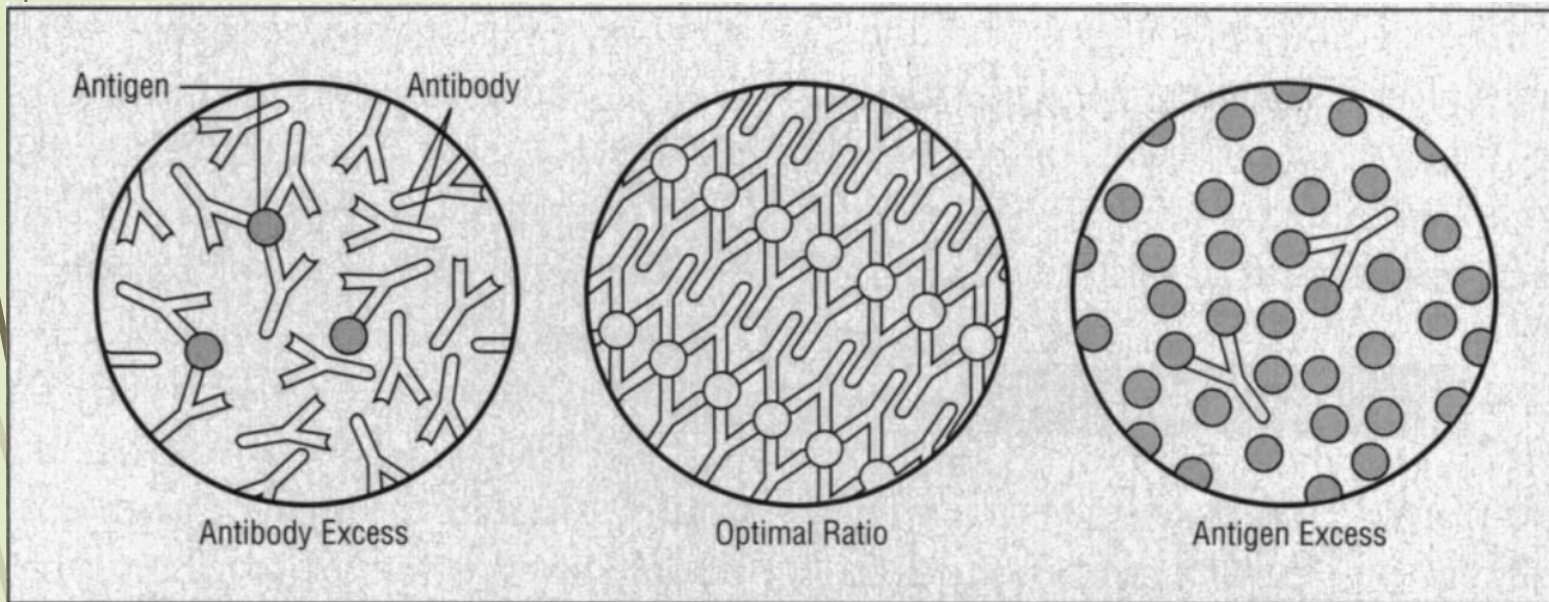
Prozone phenomenon

- First described by Lewis Thomas for meningococcus in rabbits in 1941
 - False negative response secondary to high antibody titer which interferes with formation of antigen-antibody lattice formation that is necessary for visualizing a positive flocculation test.
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RPR test



Prozone phenomenon



Prozone phenomenon

- Incidence: 0.2-2% of syphilis cases
- Associated factors:
 - Pregnancy
 - HIV co-infection
 - Phase of syphilis: primary, secondary, neurosyphilis
- Detecting the phenomenon:
 - Dilute antibody sample to 1:16 to obtain optimal concentration

Back to our patient

RPR non-reactive

Dilution



RPR 1:128



Treatment

- Early syphilis (primary, secondary, and early latent)
 - Penicillin G benzathine 2.4 million units IM once
- Late syphilis (tertiary, late latent)
 - Penicillin G benzathine 2.4 million units IM once weekly for three weeks
- Neurosyphilis
 - Aqueous penicillin G 3 to 4 million units IV every four hours (or 18 to 24 million units continuous IV infusion) for 10 to 14 days
 - OR Penicillin G procaine 2.4 million units IM daily **plus** probenecid 500 mg orally four times daily, both for 10 to 14 days

Treatment in patients with PCN allergy

- Recommended: Penicillin-desensitization
 - Especially in neurosyphilis, congenital syphilis, and syphilis in pregnant women
 - Procedure: skin test, graded-challenge
- Other options
 - Doxycycline 100mg bid x 14 days (1°, 2°, early latent) or 28 days (3° or late latent)
 - Tetracycline 500mg qid x 14 days (1°, 2°, early latent)
 - Ceftriaxone 1-2g daily IV/IM x 10-14 days
 - Azithromycin 2g PO x 1 (issues with resistance and treatment failures)



Follow-up/Monitoring

- Clinically
 - Early stages: resolution of illness
 - Late stage: significant change in symptoms is unlikely
- Jarisch-Herxheimer reaction
 - Within first 24hrs of treatment
 - Symptoms: fever and systemic symptoms (headache, myalgias, rigors, diaphoresis, hypotension, and worsening of rash)
 - Symptomatic treatment: NSAIDS or antipyretics
- Follow up serology: should see decline in RPR and VDRL titers



Our patient

- Underwent successful graded challenge with amoxicillin
- Treated with penicillin G benzathine 2.4 million units x 1 for secondary syphilis
- Repeat RPR 1 month later 1:32, improving lesions

References

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Questions?