A Case Study:
Serologic dilemmas and Syphilis

Susan Tuddenham, MD, MPH

studden1@jhmi.edu

JOHNS HOPKINS
SCHOOL of MEDICINE

Disclosures

- None

Clinical Case

30 year old married woman, HIV+ (CD4 840, VL UD, on Triumeq) diagnosed with latent syphilis of unknown duration in 2012, TPPA positive, RPR titer 1:64; treated with 3 doses of BPG. She has been treated with at least one dose of BPG every year since. She has always been asymptomatic. Husband RPR and TPPA negative every year.

The latest 4 titers:

- Jan 2015: 1:128 BPG X3
- February 2016: 1:128 BPG X3; CSF exam negative
- December 2016: 1:16
- Jan 2018: 1:128 BPG X3
- May 2018: 1:512, physical exam WNL, still monogamous

…What now? …Repeat titer 2 weeks later is 1:512 again.

Definitions

- **SEROLOGICAL CURE: reverting nontreponemal tests to negative**
- **SEROFAST: failure of non-treponemal test to decline four fold in the appropriate time frame.**

Questions raised

- What is the expected decline in titers after treatment (and in what time frame)?
- In the antibiotic era, does a lack of serologic cure or at least a 4-fold decline in non treponemal test titers predict poor syphilis outcomes?
  - Need for a CSF exam in asymptomatic patients?
    - Does identifying and treating asymptomatic neurosyphilis (ANS) in serofast asymptomatic patients improve outcomes?
      - In those with rising titers?
    - Does this differ in HIV+ vs. HIV- patients?
- What is the impact of additional doses of penicillin in serofast patients?

What is the expected decline in titers after treatment (and in what time frame)?

- Four fold decline (e.g 1:32→1:8)
  - 12 mos for primary, secondary, early latent
  - 24 mos for late latent
  - Titers less likely to decline/decline more slowly with:
    - Later stages of syphilis
    - Lower initial titers
    - HIV infection
      - Primary and secondary: 12-24 mos (Follow at 3,6,9,12,24 mos)
      - Latent: 12-24 mos

- CDC guidelines: CSF for ANS (in the absence of reinfection)
  - Primary and secondary: if 4 fold increase, consider if titer fails to decline 4-fold in 12 mos.
  - Latent syphilis: 4-fold increase in titer,

  >=1:32 fails to decline 4 fold in 12-24 mos.

CDC STD treatment guidelines, 2015

Pre-penicillin: Failure of serologic cure

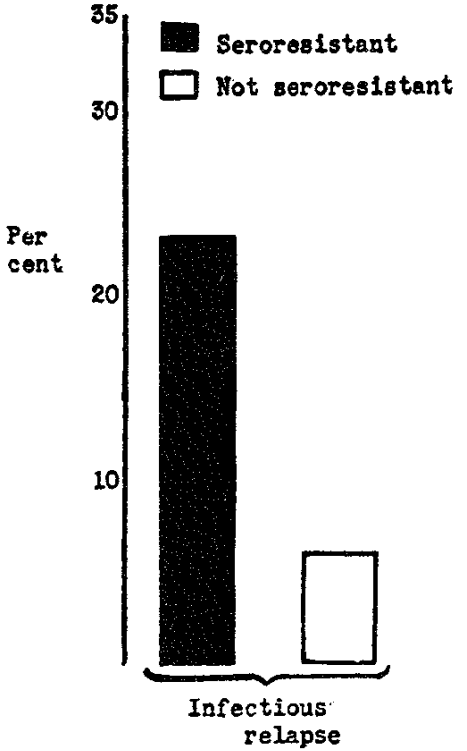


FIG. 93.—Relationship between seroresistance and infectious relapse in early syphilis (Moore and Padget).

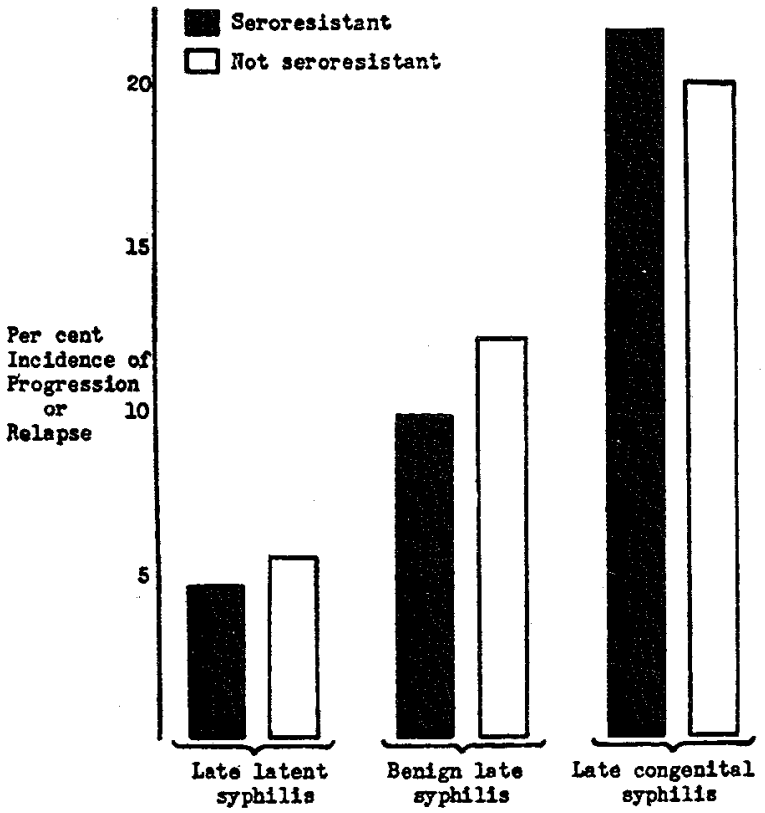
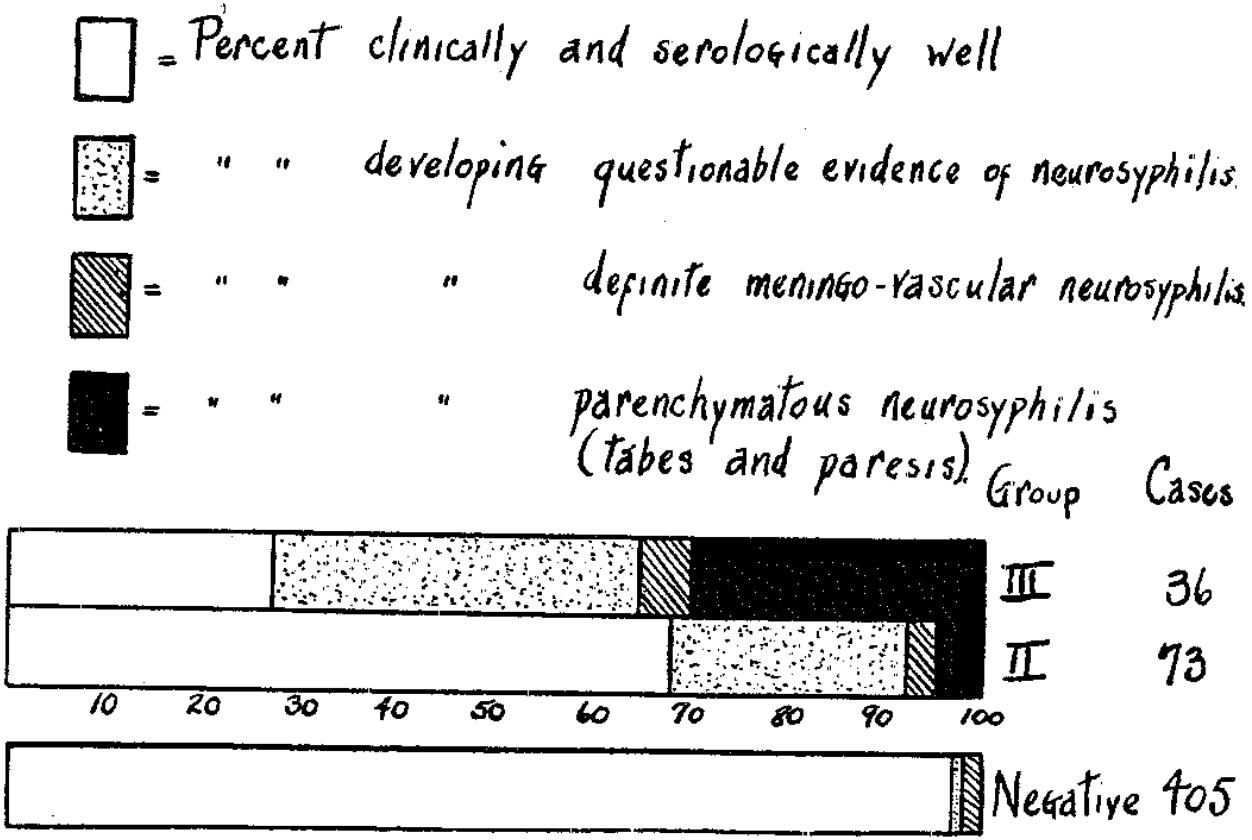


FIG. 94.—Lack of relationship between seroresistance and the incidence of progression or relapse in patients with various forms of late syphilis. (From data of the C.C.G., Diseker, Wasserman and Goodman, and Smith.)

Moore JE. Modern Treatment of Syphilis 1943:540-1

Pre-penicillin: Asymptomatic Neurosyphilis



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The Antibiotic Era

- Does a lack of serologic cure predict poor syphilis outcomes in asymptomatic patients? A lack of four fold decline?
  - Unclear
  - Association of serofast state with HIV status is inconsistent (Sena et al. BMC ID 2015, Meta-Analysis)
- What is the incidence of ANS in serofast patients?
  - Cai, Sci Rep 2017
    - N=402 HIV-, serofast (definitions unclear but seemed to include all patients who failed to serorevert after treatment-timeframe unclear) patients.
      - 74/197 or 37% of those with a decline of <4 fold serum RPR after initial treatment had CSF abnormalities c/w ANS, 43/142 or 30% of those with a decline of >=4 fold serum RPR after initial treatment c ANS (Defined as at least one CSF abnormality). (No statistically significant difference)
  - Ghanem, CID 2009
    - 4/13 (31%) HIV+ patients who had an LP done because of a rising titer (>=30 days after tx) or lack of 4 fold decline had CSF abnormalities c/w ANS.

The Antibiotic Era

- Does treatment of asymptomatic neurosyphilis improve outcomes?
  - Little data.

What is the impact of additional doses of penicillin in serofast patients?

Study	*Design*	*Population/Definitions*	*Outcome*
Ren, Int J STD AIDS 2016	Retro-spective case-control	**Serofast treated cases**: 21/697 late latent, 14/971 latent syphilis unknown duration, retreated with 3 doses of BPG. **Matched controls:** 35	**No difference** between groups at 24 mos. (p=0.57)
Sena, CID 2013	Treatment trial	N=82 patients with treated early syphilis, HIV negative, who were serofast: either no change in RPR titer or a 2 fold decrease or increase in titer (none with sx NS) Retreated with 1 dose of BPG	87% remained serofast at 12 mos, **likely incremental, if any benefit.** No comparison group
Wang, J Antimicrob chemo 2018	Treatment	N=70 serofast (no decline in RPR or a 2 fold increased or decrease after treatment) at 6 months got 3 doses of BPG.	51% remained serofast. No comparison group

Take homes

- Consider repeating the titer
  - There is significant subjectivity in the RPR.
  - Guidelines call for a sustained (>2 week) change
- In the pre-penicillin era, having a positive non-treponemal test after treatment of early (but not late latent) syphilis was associated with poor outcomes, as was asymptomatic neurosyphilis.
- In the post-antibiotic era, the relationship between four fold-decline and long term outcomes is unclear regardless of syphilis stage.
  - No data on whether treating asymptomatic NS improves outcomes, even in HIV+ patients.
  - The benefit of LP in asymptomatic serofast patients is unclear.
- Based on relatively little evidence, retreatment does not appear to impact non treponemal serologies in serofast patients.

Clinical Case

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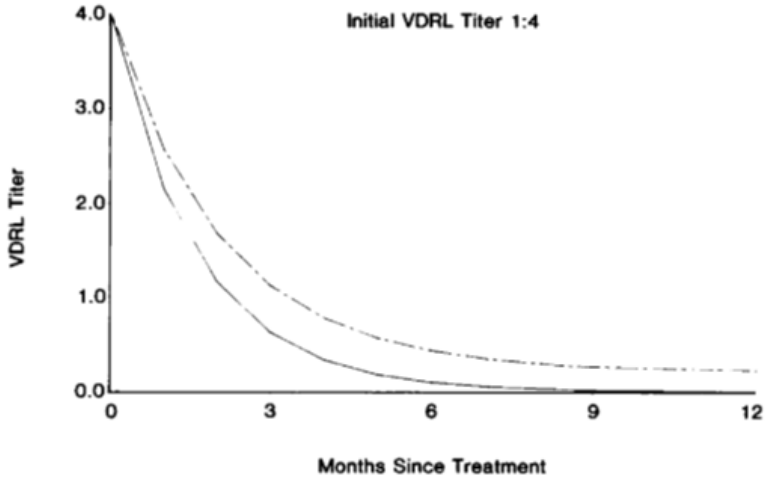
THANK YOU!

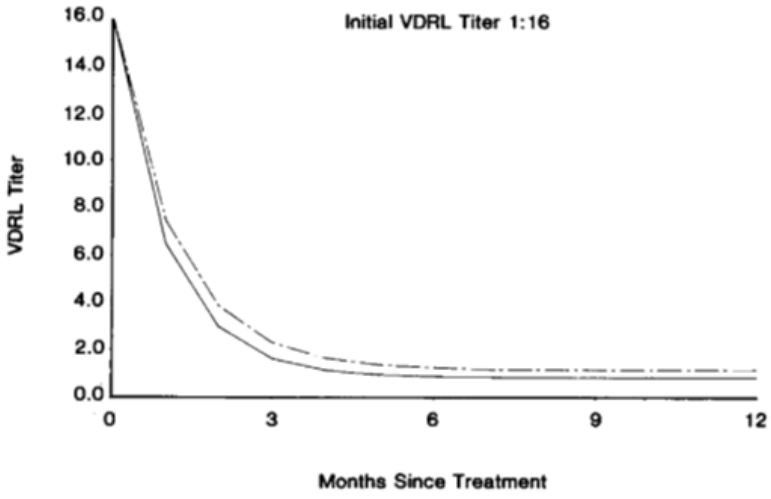
The Antibiotic Era

- Does treatment of asymptomatic neurosyphilis improve outcomes?
  - Little data.
  - CSF abnormalities are not uncommon in early syphilis (30% from those with primary and secondary) Lukehart Ann Int Med 1988.
    - Ghanem, CID 2009. 10/48: 20.8% of asymptomatic HIV+ patients who got an LP had ANS. 8/37 (22%) of those with LL/UD had ANS. 23% of those with a CD4<=350 and RPR >=1:32 had ANS. 4/13 (31%) of those who had an LP done because of a rising titer or lack of 4 fold decline had ANS.
    - Yet, after the introduction of BPG, few (if any) treatment failures with 1 dose of BPG for early syphilis.
    - With the advent of HIV, more concerns re: neurosyphilis even after appropriate BPG treatment, however several studies (Ganesan et al, Andrade et al) did not find that multiple doses were better than 1 dose, even in HIV+. In Ganesan et al, no clinical treatment failures with development of NS reported.
      - Until 1980's, three doses of IM BPG were used to treat neurosyphilis with good efficacy.

What is the meaning of a 4-fold decline (or increase) in titers?

- 1993-US treatment guidelines: 4-fold decline or seroreversion=appropriate response
  - 4 fold had been used prior to this. (e.g. WHO guidelines)
  - Based on study by Brown et al., JAMA 1985 which described approximately a 4-fold decline in VDRL at 3 months and an 8-fold decline at 6 months.
    - Only 7% of patients cured with penicillin or tetracycline had values outside of the 95% bound for these curves
    - 46% of those cured but with a history of primary syphilis
    - 89% of those who were not cured
- Serologic non-response 20.5% at 6 mos, 11.2% at >=12 mos for all stages of syphilis (Sena et al, BMC ID 2015.)





Summary: Pre-Penicillin era

- In the pre-penicillin era, being serofast, at least in early syphilis, was predictive of late complications (tertiary syphilis, including neurosyphilis).
- LP was advocated in all patients (including asymptomatic), because CSF abnormalities (Asymptomatic NS) were predictive of treatment failure, unless treatment was intensified.
  - Those with early syphilis and a negative CSF at 6 months were highly unlikely to develop clinical relapse. Those with late syphilis (>4 yrs) and negative CSF were also highly unlikely to develop clinical relapse.

The Antibiotic Era

- Does treatment of asymptomatic neurosyphilis improve outcomes?
  - Little data.
    - CSF abnormalities are not uncommon in early syphilis (30% from those with primary and secondary) Lukehart Ann Int Med 1988.
    - Until 1980's, three doses of IM BPG were used to treat neurosyphilis with good efficacy.
    - With the advent of HIV, more concerns re: neurosyphilis even after appropriate BPG treatment, and concerns re: more treatment failures.

The Pre-Penicillin Era: Failure of serologic cure in primary and secondary syphilis

Neoarsphenamine & bismuth

9 mos PS seronegative
15 mos PS seropositive
21 mos SS

Repeat anticardiolipin Ab serology negative in >95%

~3% developed late tertiary disease

Repeat anticardiolipin Ab serology positive in ~5%

~25% developed late tertiary disease

Moore JE. Modern Treatment of Syphilis 1943:540-1