Objectives:
1. Discuss the etiology, pathophysiology, and the signs and symptoms of syphilis and neurosyphilis
2. Identify the current recommended treatments for syphilis and neurosyphilis
3. Evaluate the evidence supporting alternative treatments and their place in therapy
**Syphilis**

**Introduction**

I. Complex systemic illness

II. “The great imitator” or “great impostor”

III. Leading cause of cardiovascular disease among middle-aged persons at the turn of the 20th century

IV. From 1911 to 1920, 20% of first admissions to New York State mental hospital were due to general paresis

V. Knowledge of disease progression comes from Tuskegee Study of Untreated Syphilis in the Negro Male

   A. 399 African American males prospectively followed without treatment

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**Figure 1.** Primary and secondary syphilis - rates by state: United States and outlying areas. Adapted from Centers for Disease Control and Prevention STD Surveillance 2008: National Profile. Available at http://www.cdc.gov/std/stats08/figures/33.htm

**Figure 2.** Primary and secondary syphilis—rates: total and by sex and male-to-female rate ratios: United States, 1989–2008. Adapted from Centers for Disease Control and Prevention STD Surveillance 2008: National Profile. Available at http://www.cdc.gov/std/stats08/figures/31.htm
Epidemiology\textsuperscript{1,4-5}

I. Acquired by
   A. Sexual contact
   B. Passage through the placenta
   C. Kissing or close contact with an active lesion
      i. Chancre, condyloma
   D. Transfusion of contaminated fresh human blood
   E. Accidental direct inoculation

II. Most infectious early in the disease

III. Majority of cases occur in 15 to 30 year-old women and 15 to 54 year-old men

Etiology\textsuperscript{6-9}

I. Infection is caused by \textit{Treponema pallidum} subsp. \textit{pallidum}

II. Moves with a drifting, rotary, corkscrew motion

III. Cannot be cultured in vitro by normal laboratory means

Pathogenesis\textsuperscript{1,10-13}

I. Within hours to days after penetration, \textit{T. pallidum} enters the lymphatic system and bloodstream

II. Almost any organ in the body can be infected

III. Organism divides every 30-33 hours

IV. >2/3 of untreated patients control their infection and do not progress to late disease

Table 1. Stages of syphilis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description of Stage</th>
<th>Onset</th>
<th>Resolution or Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>• Small, painless chancre at site of infection</td>
<td>Within 3 weeks (3-90 days)</td>
<td>Heals in 2-8 weeks without treatment</td>
</tr>
<tr>
<td></td>
<td>• Spirochetes in lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Possible regional lymphadenopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>• Treponemes in many tissues – skin, lymph nodes</td>
<td>2-12 weeks</td>
<td>May resolve spontaneously</td>
</tr>
<tr>
<td></td>
<td>• Enlargement of epitrochlear lymph nodes, rash, fever, patchy hair loss, headaches,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• weight loss, muscle aches, fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latent</td>
<td>• Based on serologic evidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• No signs or symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>• Relapse possible</td>
<td>Within 1 year</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Considered infectious</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late</td>
<td>• Relapse less likely</td>
<td>&gt; 1 years</td>
<td></td>
</tr>
<tr>
<td>Tertiary or Late</td>
<td>• Slow, progressive, destructive inflammatory disease</td>
<td>5 to 30 or more years</td>
<td>1/3 of untreated patients may progress to this stage</td>
</tr>
<tr>
<td></td>
<td>• May affect any organ</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Divided into neurosyphilis, cardiovascular syphilis, gummatous syphilis and leutic</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>osteitis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Serologic Testing - The Principle Mode of Diagnosis\textsuperscript{1,4,14-20}

I. Nontreponemal test
   A. Examples
      i. RPR – rapid plasma reagin
      ii. VDRL – venereal disease research laboratory
   B. Measures the reactivity of human IgG and IgM antibodies to \textit{T. pallidum} with synthetic cardiolipin-lecithin-cholesterol antigen
   C. Titers are followed to judge response to treatment
      i. For early stage disease, a 4-fold decrease in 6 to 12 months is expected
      ii. For late stage disease, 4-fold decline is expected by 12 to 24 months
   D. Sensitivity depends on stage of infection
      i. 70% in primary syphilis and 100% in secondary and early latent syphilis
      ii. Over time the sensitivity to detect untreated late syphilis declines
         a. In early neurosyphilis - almost always positive
         b. In late neurosyphilis - 30% of patients may have negative tests\textsuperscript{4,16}
   E. Expected to become nonreactive with time after treatment in most patients

II. Treponemal tests
   A. Examples
      i. Automated enzyme immunoassays (EIA)
      ii. \textit{T. pallidum} agglutination tests (TPPA, TPHA, MHA-TP, PaGIA)
      iii. Fluorescent treponemal antibody absorbed (FTA-ABS)
   B. Become positive in the primary stage of infection
   C. Remain positive for life
      i. Exception: 15 to 25% of patients treated during the primary stage revert to being nonreactive at 2 to 3 years\textsuperscript{4}

III. Serologic testing order for syphilis

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{serologic_testing_order.png}
\caption{Serologic Testing Order\textsuperscript{14,18,20}}
\end{figure}
**Syphilis Treatment**

I. Historical treatments
   A. Arsphenamine or salvarsan (arsenic derivatives)
   B. Mercury and bismuth preparations
   C. Fever-inducing therapy
      i. Heat box
      ii. Hot baths
      iii. Malaria
         a. 1927 Dr Julius Wagner von Jauregg won the Nobel Prize in Medicine for using malaria injections with subsequent fevers to treat “paralytica dementia” (neurosyphilis)

II. Primary, secondary and early latent syphilis → benzathine penicillin 2.4 million units IM as a single dose
   A. Note: Bicillin CR (penicillin G benzathine and penicillin G procaine) and oral penicillin may result in subtherapeutic levels for treatment
   B. Only Bicillin LA (penicillin G benzathine) should be used for syphilis treatment
   C. Alternatives for early syphilis: doxycycline, tetracycline, ceftriaxone, azithromycin
      i. Increasing azithromycin resistance

III. Retreatment, late latent, unknown duration, or tertiary syphilis → 2.4 million units IM weekly x 3 weeks
   A. Alternatives: doxycycline or tetracycline for 28 days only if close follow-up may be pursued

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**Human Immunodeficiency Virus (HIV) and Syphilis**

I. Common coinfection
   A. Obtaining either syphilis or HIV predisposes a patient to the other
   B. Estimated syphilis increases HIV transmission 2- to 9-fold and HIV acquisition 2- to 4-fold

II. Neurosyphilis may occur earlier in HIV-infected patients
   A. Estimated risk of symptomatic, early neurosyphilis in HIV-infected men who contract syphilis from other men is 1.5%

III. HIV-infected patients may be at increased risk of neurologic complications and potential treatment failures with syphilis
   A. Exact clinical correlation is unknown

IV. Rolfs, et al study suggested serologic differences between HIV-infected patients and those without HIV may exist but clinical responses to treatment were no different

V. No evidence at the current time to suggest additional treatment beyond standard therapy
   A. Note: cellular immunity plays a critical role in clearing syphilis so it is theorized that those deficient in cellular immunity (ie HIV-infected patients) may require more vigorous treatment
   B. Some experts treat HIV-infected patients as if they have late latent or neurosyphilis

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**Neurosyphilis**

**Introduction**

I. The central nervous system (CNS) becomes involved in up to 40% of patients
   A. Invaded during the early stages of the disease
   B. Neurosyphilis may manifest at any time
II. Spirochetes have been isolated from the Cerebrospinal Fluid (CSF) in patients without CSF abnormalities.

III. Unless scarring of the brain has occurred during the infection, dramatic improvement may be seen with treatment.

Types of Neurosyphilis

I. Asymptomatic neurosyphilis
   A. Most common
   B. Peak incidence ~ 12 to 18 months after the infection
   C. Incidence ranges 8 to 40%
   D. 4-10% may progress to symptomatic late neurosyphilis

II. Early symptomatic neurosyphilis
   A. Acute syphilitic meningitis
   B. Headache, photophobia, nausea, cranial nerve palsy, or seizures
   C. Ehrlich - “neurorecurrence” - after the majority of acute meningitis cases occurred after treatment
   D. Rare occurrence pre-HIV
      i. Suggesting immune system + drug was enough to control early CNS invasion but now in the HIV-era cases reported with and without penicillin treatment

III. Meningovascular syphilis
   A. Endarteritis of vessels anywhere in the CNS may result in thrombosis and infarction

IV. Parenchymatous syphilis
   A. Paretic neurosyphilis
   B. General paralysis of the insane

V. Tabetic neurosyphilis
   A. Progressive locomotor ataxy

VI. Gummas of the CNS
   A. Manifestations of typical space-occupying lesion

Figure 4. Progression of neurosyphilis. Adapted from Ghanem KG. Neurosyphilis: A Historical Perspective and Review. CNS Neurosci Ther 2010 Jul 8 [Epub ahead of print].
Diagnosis of Neurosyphilis

I. Made by indirect methods because the organism cannot be cultured by normal laboratory methods
II. No gold standard diagnostic test
III. CSF changes without neurologic changes in the clinical setting are considered active neurosyphilis
IV. Symptomatic neurosyphilis may be present in as many as 4% of patients with normal CSF findings
V. Indications for CSF exam
   A. Neurologic, otologic, ophthalmic signs and symptoms
   B. Symptomatic late syphilis
   C. Treatment failure
   D. HIV-infected patients with late latent or latent syphilis of unknown duration
   E. Some experts consider RPR >1:32 in any patient and CD4 of < 350 cells/mm³ in HIV-infected patients indications for lumbar puncture (LP)

VI. CSF evaluations
   A. Pleocytosis
      i. Cut off in HIV-negative patients is ≥ 5 cells/mL
      ii. HIV patients - less specificity due to nonspecific abnormalities in HIV-positive populations → the cut off has been suggested to be moved to ≥ 10 cells/mL if on ART and ≥ 20 cells/mL if not on ART but no official consensus has been reached
   B. Protein abnormalities
   C. CSF VDRL
      i. Highly specific but rather insensitive - interpret with clinical picture and other tests
   D. CSF fluorescent treponemal antibody
      i. Negative FTA may be used to help rule out neurosyphilis
      ii. May be positive with high serum titers
      iii. Not recommended by CDC due to positive results may not reflect neurosyphilis

VII. Centers for Disease Control and Prevention (CDC) definitions for diagnosis of neurosyphilis

   A. Confirmed neurosyphilis
      i. Any stage of syphilis
      ii. Reactive CSF VDRL
   B. Presumptive neurosyphilis
      i. Any stage of syphilis
      ii. Nonreactive CSF VDRL
      iii. CSF pleocytosis or elevated protein
      iv. Clinical signs or symptoms consistent with syphilis without and alternative diagnosis

Treatment of Neurosyphilis

I. Penicillin - the standard of care
   A. Ideal dose is unknown as no randomized comparative studies were done
II. Current recommended neurosyphilis treatment
   A. Aqueous penicillin G 3 to 4 million units IV q4h or continuously x 10-14 days
   B. Alternative: procaine penicillin G 2.4 million units IM daily plus probenecid 500 mg 4 x day po x 14 days
   C. Some experts continue 2.4 million units of benzathine penicillin weekly x 3 weeks after the above therapy
III. Penicillin allergy
   A. Desensitize the patient
   B. Some experts consider ceftriaxone

IV. Pregnancy
   A. ONLY penicillin
   B. If allergy exists, MUST desensitize the patient to penicillin

V. Follow-up for neurosyphilis
   A. No clear definition of cure
   B. If initial pleocytosis was present, LP every 6 months until normal
   C. If the cell count does not decrease after 6 months or normalize by 24 months, retreatment should be considered
   D. HIV-infected patients may have persistent CSF abnormalities
   E. May perform LP to follow-up VDRL or protein but these changes are slower than cell counts and persistent abnormalities may be less important

VI. Other authors use a goal of CNS abnormality resolution by 12 to 24 months\textsuperscript{1,5,11}

**Penicillin Failure Rate in Neurosyphilis**

I. Penicillin failure rate in neurosyphilis is unknown
II. Studies from 1940s to 1960s suggested 10\% failure rate in neurosyphilis\textsuperscript{37}
III. A 39\% failure rate in general paresis with penicillin treatment was suggested in 1968\textsuperscript{38}
   A. Early neurosyphilis may be easier to treat with improved outcomes over later neurosyphilis that has progressed into the parenchyma
IV. Early studies of penicillin used different formulations than what is available today\textsuperscript{22,40-44}
   A. Formulations were in beeswax and peanut oil with calcium penicillin
   B. Benzathine penicillin was used to treat neurosyphilis
   C. 600,000 units or 24 megaunits of procaine penicillin total over 14 days were used

V. Syphilis rate per 100,000\textsuperscript{45}
   A. 368 cases in 1944 → 83 cases in 1954 → 37 cases in 1975

VI. Difficult to refute penicillin’s efficacy when looking at the drastic decline in mortality rates due to syphilis (figures 5 & 6)

![Figure 5](image-url) **Figure 5.** Death rates from general paralysis of the insane. Adapted from Martin JP. Conquest of general paralysis. Br Med J 1972;3(5819):159-160.

The Problem with Current Treatment Options (ie Penicillin)

I. Penicillin allergies
   A. Desensitization requires extensive resources - ICU bed, personnel, time intensive

II. Hospitalization or home health needed for IV antibiotics
   A. Continuous infusion or multiple daily doses due to short half-life of penicillin
   B. IV access required or IM injection
   C. Compliance
      i. Asymptomatic patients may not be willing to commit to 10 to 14 days of a continuous infusion

III. Seizures with high dose penicillin

IV. Renal adjustments

Alternative Treatments for Neurosyphilis

I. Procaine penicillin G 2.4 million units IM daily plus probenecid 500 mg 4 x day po x 14 days
   A. World Health Organization (WHO) penicillin minimum inhibitory concentration (MIC) for T. pallidum is 0.018\(^\text{41}\)
   B. Dunlop, et al\(^\text{46,47}\) – regimen listed above given to 38 patients
      i. CSF penicillin levels 2 to 10 hours after the dose on days 2 to 9 ranged 0.07 to 1.5 \(\mu\text{g/mL}\)
      ii. No outcome data provided
   C. van der Valk, et al\(^\text{48}\) – study using the same dosing regimen did not consistently produce treponemicidal concentrations
      i. CSF levels drawn on second day <0.018 \(\mu\text{g/mL}\) in 17/40 patients
         a. Levels at 6 hours – 4/10 did not reach 0.018 \(\mu\text{g/mL}\)
         b. Levels at 18 hours – 6/18 did not reach 0.018 \(\mu\text{g/mL}\)
         c. Levels at 24 hours – 7/10 did not reach 0.018 \(\mu\text{g/mL}\)
   D. Penicillin procaine without probenecid does not reach treponemicidal concentrations\(^\text{42,43}\)
II. Amoxicillin
   A. Morrison, et al\textsuperscript{49}
      i. Rabbits were used in a laboratory setting to determine that amoxicillin concentrations of 0.11 µg/mL were needed to be curative
      ii. 17 patients with latent syphilis with normal CSF exams were given amoxicillin 2 grams po TID + probenecid 500 mg po BID
         a. CSF levels were obtained before the 3\textsuperscript{rd} or 4\textsuperscript{th} dose
         b. All patients achieved treponemicidal CSF concentrations
            i. Lowest concentration was 0.32 µg/mL
   b. Faber, et al\textsuperscript{50}
      i. Animal controls gave an amoxicillin MIC of 0.42 µg/mL
      ii. 7 patients in various stages of syphilis (early latent, secondary, symptomatic neurosyphilis, asymptomatic neurosyphilis)
      iii. Given amoxicillin 1 gram po 6 x day and probenecid 500 mg po 4 x days
         iv. Amoxicillin CSF trough levels were 0.5 µg/mL to >10 µg/mL (= treponemicidal)
            a. \textbf{Note}: in their previous poster presentation using the same dose of amoxicillin without probenecid, CSF levels of 0.02 to 1 µg/mL were obtained
               i. Only 3/12 achieved the minimal 0.42 µg/mL

III. Doxycycline
   A. The tetracycline MIC for \textit{T. pallidum} is 0.2 µg/mL\textsuperscript{9}
      i. The MICs for tetracycline and doxycycline with regards to treponemes are similar\textsuperscript{51}
   B. 5 patients with latent syphilis or neurosyphilis were treated with oral doxycycline 200 mg po BID x 21 days\textsuperscript{52}
      i. 4 to 5 hours after the 7\textsuperscript{th} dose, mean CSF levels were 1.3 µg/mL (range 0.8 to 2 µg/mL)
   C. Case report of failed doxycycline po therapy for neurosyphilis\textsuperscript{53}
      i. Previous failed benzathine penicillin
      ii. After the doxycycline treatment, patient failed procaine penicillin and aqueous penicillin G treatment
   D. 2 successful case reports of HIV-positive patients with asymptomatic neurosyphilis treated with doxycycline\textsuperscript{28}
      i. 45 year old male who refused penicillin - given doxycycline 200 mg po BID x 28 days
         a. VDRL of 1:128 $\rightarrow$ 1:64 (4 weeks)
         b. CSF VDRL 1:16 $\rightarrow$ 1:4 (2 months)
         c. CSF WBC 96 cells/mm$^3$ $\rightarrow$ 5 cells/mm$^3$
         d. CSF protein 89 mg/dL $\rightarrow$ 60 mg/dL
         e. Patient remained asymptomatic
      ii. 37 year old male refusing hospitalization - given doxycycline 200 mg po BID x 28 days
         a. VDRL was 1:64 $\rightarrow$ 1:2 (3 months)
         b. CSF VDRL negative $\rightarrow$ remained negative
         c. CSF WBC was 29 cells/mm$^3$ $\rightarrow$ 1 cell/mm$^3$
         d. At 2 years subsequent screening tests were nonreactive
IV. Ceftriaxone

A. MIC estimated to be 0.01 µg/mL for ceftriaxone

B. Ceftriaxone effectively crosses the blood brain barrier

i. CSF peak concentrations estimated to be 2 to 2.6 after 2 grams in adults with uninfammed meninges

ii. Pediatric patients given 80 mg/kg q12h had 24-hour troughs ranging 1 to 18.9 on days 4 to 6 of treatment

C. Case reports for ceftriaxone in neurosyphilis

Table 2. Ceftriaxone case reports for neurosyphilis

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of Neurosyphilis</th>
<th>Dose</th>
<th>Duration</th>
<th>HIV status</th>
<th>Clinical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hook</td>
<td>Asymptomatic</td>
<td>1 gram/day</td>
<td>14 days</td>
<td>Negative</td>
<td>Response</td>
</tr>
<tr>
<td>Gentile</td>
<td>Symptomatic</td>
<td>1 gram BID</td>
<td>14 days</td>
<td>Negative</td>
<td>Response</td>
</tr>
<tr>
<td>Sabbatani</td>
<td>Symptomatic</td>
<td>3 grams/day plus initial tetracycline (unknown duration of tetracycline) Followed by weekly benzathine penicillin x 3 weeks</td>
<td>24 days</td>
<td>No comment</td>
<td>Response</td>
</tr>
<tr>
<td>Cnossen</td>
<td>Symptomatic</td>
<td>1 gram/day</td>
<td>14 days</td>
<td>No comment</td>
<td>Response</td>
</tr>
<tr>
<td>Cnossen</td>
<td>Symptomatic</td>
<td>1 gram/day</td>
<td>14 days</td>
<td>No comment</td>
<td>Response</td>
</tr>
<tr>
<td>Shann</td>
<td>Symptomatic</td>
<td>1 gram/day</td>
<td>14 days</td>
<td>Negative</td>
<td>Response</td>
</tr>
</tbody>
</table>

D. Marra, et al – randomized, open-label pilot study of ceftriaxone versus aqueous penicillin G

i. HIV-infected patients with neurosyphilis

Table 3. Inclusion and exclusion study criteria

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPR &gt; 1:16</td>
<td>Syphilis treatment within 1 year</td>
</tr>
<tr>
<td>Confirmed MHA-TP or FTA-ABS</td>
<td>Antibiotic therapy with <em>T. pallidum</em> activity within 45 days</td>
</tr>
<tr>
<td>CSF abnormalities</td>
<td>Another CNS infection that could cause CSF abnormalities</td>
</tr>
</tbody>
</table>

ii. Randomized to either ceftriaxone 2 grams IV daily or aqueous penicillin G 4 million units IV q4h

iii. Improvement was defined as ≥ 4-fold decline in VDRL or RPR, or 10% decline in WBC or protein
iv. 14 ceftriaxone patients and 16 penicillin patients
   a. At baseline
      i. More penicillin patients had a history of neurosyphilis
      ii. More ceftriaxone patients had a rash and higher RPRs
   b. Potentially indicating early therapy with ceftriaxone group due to secondary syphilis with concomitant neurosyphilis
      i. Potential for better outcomes with earlier disease
      ii. Serum titers tend to decrease faster in those with earlier disease and higher titers
v. Similar improvements in CSF VDRL, CSF WBC, and CSF protein
vi. Improvement in serum RPR was significantly more common in ceftriaxone patients than penicillin patients (8/10 (80%) vs 2/15 (13%); p=0.03)
   a. This held true even when data analyzed for initial titer values, rash prevalence and prior neurosyphilis
vii. Due to short follow-up (26 weeks), some effects may not have been seen
viii. Due to differences between groups in this study a firm conclusion may not be drawn
E. Dowel, et al\textsuperscript{63} – latent syphilis or asymptomatic neurosyphilis study
   i. 43 HIV-infected patients with latent syphilis or asymptomatic neurosyphilis at two clinics for 16 months
   ii. Inclusion
      a. Diagnosis of latent syphilis or asymptomatic neurosyphilis
      b. Outpatient treatment with ceftriaxone or benzathine penicillin
      c. Received every dose prescribed
      d. Serologic testing and clinical follow-up at 6 months or longer
      e. No other antimicrobial agent with efficacy against \textit{T. pallidum} was given
   iii. CSF was regarded as abnormal if \( > 6 \) cells/mm\(^3\) WBC, \( > 46 \) mg/dL protein, \( < 45 \) mg/dL glucose, or positive VDRL
   iv. Treatment was chosen by individual physicians who staffed the clinics
      a. Regularly staffing physicians were more likely to prescribe ceftriaxone 1 gram IM daily x 10 to 14 days or 1 gram IM on weekdays x 10 to 14 doses
      b. Physicians who did not attend clinic regularly were more likely to prescribe 2.4 million units of benzathine penicillin weekly x 3
   v. Responses were graded into categories
      a. Response - \( > 4 \)-fold decline in RPR
      b. Serofast - no change in RPR and no signs of progressive infection
      c. Relapse - initial \( > 4 \)-fold decline in RPR followed by \( > 4 \)-fold increase
      d. Failure - increase in RPR \( > 4 \)-fold, persistent RPR \( > 1:64 \), and/or clinical disease progression
Table 4. Overall treatment responses to ceftriaxone vs penicillin for latent syphilis

<table>
<thead>
<tr>
<th>Overall response</th>
<th>Ceftriaxone (n=43)</th>
<th>Benzathine penicillin (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>28(65%)</td>
<td>8(62%)</td>
</tr>
<tr>
<td>Serofast</td>
<td>5(12%)</td>
<td>1(8%)</td>
</tr>
<tr>
<td>Serologic relapse</td>
<td>9(21%)</td>
<td>2(15%)</td>
</tr>
<tr>
<td>Failure</td>
<td>1(2%)</td>
<td>2(15%)</td>
</tr>
</tbody>
</table>

vi. Most patients declined LPs except 13 ceftriaxone patients
   a. 7 had documented CSF abnormalities
      i. 5 treated with 1 gram daily ceftriaxone x 14 doses
      ii. 2 treated with 2 grams daily ceftriaxone x 14 doses

Table 5. Neurosyphilis responses to ceftriaxone treatment

<table>
<thead>
<tr>
<th>Neurosyphilis response</th>
<th>Ceftriaxone treatment (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>5</td>
</tr>
<tr>
<td>Serofast</td>
<td>1</td>
</tr>
<tr>
<td>Serologic relapse</td>
<td>0</td>
</tr>
<tr>
<td>Failure</td>
<td>1</td>
</tr>
</tbody>
</table>

vii. No patients who received benzathine penicillin underwent initial LP
   a. 2 patients relapsed → LP suggested neurosyphilis → treated with 2 grams ceftriaxone daily x 14 doses → appeared to have responded

viii. For those who initially refused LPs and were treated, 9 patients relapsed
   a. 7 patients relapsed after ceftriaxone 1 gram daily
      i. 3 had CSF abnormalities
   b. 8 of these 9 were re-treated with ceftriaxone 2 grams daily x 14 days
      i. Follow-up at time of article publishing was < 6 months
      ii. Did not separate out responses for the 3 patients with neurosyphilis

Table 6. Latent syphilis retreatment responses to ceftriaxone

<table>
<thead>
<tr>
<th>Latent syphilis retreatment responses</th>
<th>Ceftriaxone treatment (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>7</td>
</tr>
<tr>
<td>Serofast</td>
<td>0</td>
</tr>
<tr>
<td>Serologic relapse</td>
<td>0</td>
</tr>
<tr>
<td>Failure</td>
<td>1</td>
</tr>
</tbody>
</table>

F. Smith, et al\textsuperscript{64} – ceftriaxone pilot study
   i. HIV-infected patients with asymptomatic syphilis (RPR ≥1:4)
   ii. Ceftriaxone 1 gram IM daily
   iii. 4/14 ceftriaxone patients had a positive CSF VDRL test, pleocytosis and increased CSF protein
      a. 2 responded
      b. 1 relapsed
      c. 1 failed
iv. 3/14 had only increased CSF protein
   a. All responded to ceftriaxone

G. Overall published responses to ceftriaxone for neurosyphilis

Table 7. Overall responses to ceftriaxone treatment for neurosyphilis

<table>
<thead>
<tr>
<th>Source</th>
<th>Positive responses</th>
<th>Total patients treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case Reports</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Marra, et al</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Dowell, et al</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Smith, et al</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>22</strong></td>
<td><strong>27</strong></td>
</tr>
</tbody>
</table>

*Unable to separate out responses for 4 patients which are not included in this table

Discussion

I. Aqueous penicillin G
   A. First-line treatment
   B. Place in therapy
      i. Use as first-line treatment option for neurosyphilis in as many patients as possible
      ii. Use in pregnant patients
   C. Most clinical experience
   D. Problems:
      i. Allergies
         a. Desensitization requires extensive time, resources and personnel
      ii. Multiple daily infusions or continuous infusion x 10 to 14 days
         a. IV access required
      iii. Renal dosing required
      iv. Potential seizure risk
      v. Sometimes hard to convince asymptomatic patient to consent to this, especially if there is history of allergy to penicillin

II. Procaine penicillin and probenecid
   A. Second-line option
   B. Place in therapy
      i. Use when continuous infusion penicillin G is not an option AND compliance may be assured
         a. If compliance is a concern, use ceftriaxone
         b. Patient refusing to have lines or deal with continuous infusion
         c. If concerned about drug interactions with probenecid, use ceftriaxone
   C. Compliance may be problematic
   D. Evidence is inconsistent
   E. Drug interactions with probenecid
      i. Major concern in patients on antiretroviral treatment
III. Ceftriaxone 2 grams IV/IM daily x 14 days
   A. Second-line option
   B. Place in therapy
      i. Use when aqueous penicillin G is not an option
         a. Mild penicillin allergy
         b. Patient refusing continuous infusion
         c. Patient refusing lines (may be given IM daily)
   C. Injection (IV/IM)
   D. Can be given IM or push once a day instead of continuous infusion like penicillin
   E. Some small studies and case reports support its use

IV. Doxycycline 200 mg po BID with assured compliance – **IF** no other option is available
   A. Third-line option
   B. Place in therapy
      i. Use when parenteral treatment is not an option
         a. Patient refuses IV/IM therapy
         b. Anaphylaxis to penicillin and refusing desensitization
   C. Oral – convenient
   D. Reaches adequate CNS concentrations
   E. Compliance is a concern
   F. Limited to case reports for neurosyphilis
   G. More evidence in non-neurosyphilis

V. Amoxicillin 2 grams po TID with probenecid 500 mg QID
   A. Last-line option
   B. Place in therapy
      i. Use when parenteral treatment and doxycycline are not options
         a. Patient is refusing IV/IM treatment AND patient has a tetracycline allergy AND
            is about to leave without any treatment
   C. Oral – convenient
   D. Compliance is a major concern
      i. High pill burden – inconvenient
   E. With compliance, adequate CNS concentrations may be achieved

**Conclusion**

I. Penicillin G is the first-line treatment for neurosyphilis
   A. All pregnant patients should only be treated with penicillin
II. When penicillin G is not an option, some evidence is available to support alternatives such as procaine penicillin, ceftriaxone, doxycycline, and amoxicillin
References


46. Dunlop EMC, Al-Egaily SS, Houang ET. Penicillin levels in blood and CSF achieved by treatment for syphilis. *JAMA* 1979;241;2538-2540.