Treatment of Syphilis
Dr Craig Tipple

Overview

• Principles of therapy
• Current therapy
• Treatment protocols for early/late disease
• Treatment protocols for neurosyphilis/HIV/congenital/pregnancy
• Drug reactions & management
Principles of Therapy

• Clinical data lacking on:
  – optimal dose
  – duration of Rx
  – long-term efficacy of Rx with antimicrobials
• Treatment developed before RCTs
• Lab considerations, biological plausibility, expert opinion, case series & clinical experience

Principles of Therapy

• Fussy...
  – Micro-aerophilic
  – Cannot be cultivated for sustained periods on artificial media
  – Infectious capacity lost within 2 days of harvest
  – Doesn’t do well above 37 degrees
  – Slow doubling time (30-33 hours)

• Why so fussy?
  – Small genome (1.13Mb) (E. coli has 4.6Mb)
  – Limited metabolic capability: Glycolysis, but no TCA cycle or electron transport chain
  – No oxidase or catalase
  – No classic heat shock proteins
Principles of Therapy

• Duration of therapy at least 7 days
• Cover a no. of division times for *T. pallidum* (30-33 hrs)
• Penicillin-free/sub-treponemicidal interval no more than 24-30 hrs (no weekend breaks in Rx)
• Slower dividing treponemes in late disease, duration longer
• Treponemocidal concentration should be achieved: 0.018mg/l (WHO)
• >0.36mg/l may be desirable - more rapid elimination

Syphilis treatment

• Nothing (effective)
• Salvarsan
• PENICILLIN
• Doxycycline
• (Macrolides)
• Cephalosporins
Early Syphilis

First Line:
- Benzathine penicillin G 2.4 MU single dose IM or x2 (day 1 and 8)
  • Long t1/2
  • Good activity
  • No/poor CNS penetration

Alternative first line:
- Procaine penicillin G 600,000 units IM 10/7
  • Good activity
  • Penetrates CSF

Early Syphilis

Penicillin Allergy:
- Doxycycline 100mg BD PO14/7
- Ceftriaxone 500mg OD IM 10/7 (if no anaphylaxis)

- Erythromycin 500mg QDS PO 14/7
- Azithromycin 500mg OD PO 10/7 or 2g STAT PO

Parenteral Rx declined:
- Amoxicillin 500mg QDS +probenecid 500mg QDS 14/7
- As for penicillin allergy
Azithromycin

- 400 participants at 5 sites in USA and 3 in Madagascar (2000-2007)
- HIV negative patients with early syphilis
- 2g azithromycin vs 2.4M units benzathine
- Primary outcome: 4-fold (2 dilution) reduction in RPR at 6 months

<table>
<thead>
<tr>
<th>Population, time from treatment</th>
<th>Serological cure rate, proportion (% of participants with cure)</th>
<th>Azithromycin group</th>
<th>Penicillin group</th>
<th>Difference, %</th>
<th>One-sided 95% confidence interval lower bound, %</th>
</tr>
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<tbody>
<tr>
<td>Intent-to-treat</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>3 Months</td>
<td></td>
<td>177/238 (74.4)</td>
<td>187/247 (75.7)</td>
<td>-1.3</td>
<td>-7.8</td>
</tr>
<tr>
<td>6 Months</td>
<td></td>
<td>180/232 (77.6)</td>
<td>186/237 (78.5)</td>
<td>-0.9</td>
<td>-7.2</td>
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<tr>
<td>Per protocol</td>
<td></td>
<td></td>
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</table>

Macrolide resistance

- 2000: RCTs demonstrated azithromycin comparable to benzathine penicillin¹,²
- 2000: Link made between genotypic and phenotypic resistance
  - A→G point mutation in 23srRNA gene at position 2058³
- 2002: Clinical failures reported⁴
- 2009: Second mutation discovered: A2059G⁵

¹ Hook EW et al. J Infect Dis. 2010;201:1729-1735
⁴ CDC Brief Report MMWR Morb Wkly Rep 53:197-8
⁵ J Med Microbiol 2009;58:832-6
**Macrolide resistance**

![Map showing the distribution of resistance in different regions]

<table>
<thead>
<tr>
<th>Region</th>
<th>Wild-Type</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>St Mary's, London</td>
<td>66.7%</td>
<td>33.3%</td>
</tr>
<tr>
<td></td>
<td>2006-7</td>
<td>2011-12</td>
</tr>
</tbody>
</table>

Tipple C et al. Sex Transm Infect. 2011;87(6):486-8
Chisholm et al, ECCMID conference abstract, May 2013

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**Rx for Early Syphilis: Follow-Up**

- RPR at 3/12, (6/12, 12/12)
- Sustained 2 dilution (4 fold) increase suggests re-infection or treatment failure (expect 2 dilution decrease every 3-6 months)
- Provide documentation for patient to prevent re-treatment

- Serologic failure at 12m; clinical recurrence or a 4-fold rise in titre (re-infection excluded) → CSF examination
Monitoring syphilis treatment

Wasserman A et al. Deutsche medicinische Wochenschrift. 1906;32:745-6

Rx for Early Syphilis: Other considerations

- Recommend GU screen & HIV testing
- Abstain until lesions healed or for two weeks (whichever is longer).
- Patients requiring Rx for other STI & who are being investigated for ? Syphilis:
  - Chlamydia: Ofloxacin
  - Gonorrhoea: Ciprofloxacin/Ofloxacin*

  (ie. Antibiotics which are NOT active against Treponemes: Increase the likelihood of positive Treponemal identification on DG microscopy)

*If adopting this strategy then vigilance for gonorrhoea treatment failure must be high and sensitivities established.
**Rx for Early Syphilis: Contacts**

- ID$_{50}$ is 57 organisms
- Significant risk with oral sex

- Partner Notification
  - 1$^{a}$: 3 months (although probably much shorter)
  - 2$^{o}$ and Early latent: up to 2 yrs

- Epidemiological Rx:
  - Benzathine penicillin 2.4 MU x1
  - Doxycycline 100mg BD x 14/7

**Rx for Late Syphilis without neurologic involvement**

- First-line:
  - Benzathine penicillin G 2.4g IM weekly x 3 injections

- Alternative:
  - Doxycycline 100mg BD PO 28 days
  - Amoxicillin 2g TDS PO +probenecid 500mg QDS PO for 28 days

- Consider steroids in CV syphilis (30-60mg for 3/7 started 24 hours before abx)

**Follow-up**

- Serology checked every 6/12 until ‘serofast’ i.e. unchanged.
- N.B. May be negative or neat at baseline…
Late Syphilis: Contacts

• Individuals with late syphilis usually unable to transmit infection to sexual partners
• Vertical transmission unusual after > 2yrs
• Try to locate previous neg. result in index patient
• Incubation periods between initial infection & late symptomatic syphilis aids partner notification:
  – Gummata >2 years
  – CNS >15yrs
  – Cardiovascular >10 yrs
• Contacts to undergo serological screening

Number of STI diagnoses among MSM by HIV status: England, 2013

- Data from routine GUM service returns
- * First episode; ** Includes diagnoses of primary, secondary & early latent syphilis
- HIV diagnosed includes those who were diagnosed with HIV more than 6 weeks prior to their STI infection
- Data type: service data
Clinical observations/issues

• Early observations of aggressive disease

• Potential differences in presentation
  – Multiple and deeper chancres
  – Primary and secondary overlap (or no obvious primary stage)

• Degree of immunosuppression important and effects of Syphilis on CD4 and Viral Load

• Asymptomatic neurosyphilis

Impact of syphilis on CD4 count and HIV-1 viral load

- FHDH-ANRS CO4 cohort
- 1998-2006
- 1233 STS neg and 282 incident syphilis cases
Neurosyphilis

- 25-30% of patients with early syphilis have *T. pallidum* detectable in CSF by RIT\(^1\)

- 70% of patients will have abnormal CSF\(^1\)

- Less than 10% will develop late neurological complications\(^2\)

- In patients with clinical neurosyphilis (in early or late disease) – the need for investigation and treatment is clear...

2. Oslo Study, Gjestland Acta Derm Ven Suppl 1965;35:3-368

Neurosyphilis in the context of HIV-1 infection

- HIV-1 may increase the risk of developing neurological complications during early syphilis (eye and ear symptoms and meningitis)\(^1\)
  - 1.7% risk of symptomatic neurosyphilis among HIV positive MSM diagnosed with early syphilis in 4 US cities\(^2\)

- Risk of neurosyphilis is associated with RPR titres ≥ 1:32\(^3,4\) and CD4 counts ≤ 350\(^3\)
  - (18.6x more likely to have neurosyphilis when both present)

- Could it be a failure to clear, rather than increased invasion?
  - Seems related to CD4 count (≤ 200 3.7x less likely to normalise CSF)\(^3\)

Selecting patients for LP - guidelines

Which patients should have a lumbar puncture?

- General consensus with current UK, IUSTI and CDC guidelines\(^1,2,3\):
  
  - Relevant symptoms and signs
  - Serological treatment failure
  - Eye disease
  - PLWH: CD4 <350 or RPR 1:32

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3. CDC STD Treatment Guidelines 2010);729-40

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CSF Testing: More recent findings

- Recent evidence that VDRL should not be replaced with RPR\(^1\):
  - 149 patients with syphilis investigated for neurological disease
  - 45 were VDRL positive in CSF. Of these only 64.4% were also RPR positive.
  - VDRL 15% more sensitive than RPR when compared directly

- CSF WCC >20/\(\mu\)L may be a better predictor of neurosyphilis in HIV-1 infected patients (compared with >5 in HIV-1 uninfected patients)\(^1\)

- An association has been made with type 14d/f and neurosyphilis\(^2\)
  - 21/42 patients with 14d/f had neurosyphilis
  - 10/42 patients with another type had neurosyphilis

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Benzathine penicillin- Poor/No CSF penetration

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Proportion with Treponemicidal Level in CSF (&gt;0.018mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzathine Penicillin: 2.4 MU x 1-3</td>
<td>0/25</td>
</tr>
<tr>
<td>Benzathine penicillin: 3.6 MU x 4 +</td>
<td>1/13</td>
</tr>
<tr>
<td>Probenecid^2</td>
<td></td>
</tr>
<tr>
<td>Benzathine penicillin: 2.4-4.8 MU</td>
<td>2/6</td>
</tr>
<tr>
<td>+ Probenecid^3</td>
<td></td>
</tr>
</tbody>
</table>

Persistence of CSF *T. Pallidum* after Rx with Benzathine Penicillin in PLWH with 2^0 syphilis

- Benzathine penicillin 2.4 MU:
  - Failure in 3/4
  - Retreated with procaine pen 2.4MU + probenecid x 10/7
  - Neg TP isolation in CSF by RIT

- Pre-HAART era

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Treatment of neurosyphilis with high-dose IV Penicillin in HIV-1 infection

- 11 patients with neurosyphilis
- 5 previously Rx for early syphilis:
  - Benzathine penicillin: 1 - 3 doses
  - Median interval to neurosyphilis 8/12
- All 11 Rx with Pen G 18-24 MU x 10/7
  - 11/11 neg TP isolation in CSF by RIT
  - 1 meningovascular relapse
  - 2 no change in serum/CSF markers
- Early HAART era

Enhanced treatment in HIV and/or neurosyphilis?

Randomised, placebo controlled trial of standard vs enhanced treatment for early syphilis

1. PLWH more likely to fail?
2. Does enhanced treatment increase CSF level of penicillin and improve outcome?
3. Is central nervous system involvement in early syphilis clinically important?

541 patients (19% HIV-1 infected) with untreated early syphilis.
>18 years old
No treponemocidal antibiotics in last 2/52
randomised 1:1

Single dose (2.4mU) benzathine penicillin IM + placebo

Single dose (2.4mU) benzathine penicillin IM + 2 g amoxicillin and 500 mg of probenecid, both TDS PO for 10/7
**Key Study Findings**

Clinical outcomes did not differ according to treatment or HIV status

Enhanced treatment with amoxicillin and probenecid did not improve the outcomes

- 18% serologic failure at 6/12 (standard treatment) vs 17% (enhanced treatment)

*T. pallidum* was found at enrolment in the CSF of 32/131 patients (24%) and after therapy in 7/35 (20%) patients tested.

- None had clinically evident neurosyphilis
- Rate of detection of *T. pallidum* did not differ according to HIV status.

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**Recommended First Line Treatment**

<table>
<thead>
<tr>
<th></th>
<th><strong>UK (2015)</strong></th>
<th><strong>Alternative Treatment</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Procaine penicillin 1.8 MU-2.4 MU IM OD plus probenecid 500 mg PO QDS for 14 days OR Benzylpenicillin 10.8–14.4g daily, given as 1.8–2.4 g IV every 4 h for 14 days:</td>
<td>UK</td>
</tr>
<tr>
<td></td>
<td><strong>DOXYCYCLINE</strong> 200 mg PO b.d. for 28 days OR Amoxicillin 2 g PO t.d.s. PLUS probenecid 500 mg PO QDS for 28 days OR Ceftriaxone 2 g IM or IV for 10–14 days</td>
<td><strong>IUSTI</strong></td>
</tr>
<tr>
<td><strong>IUSTI (2014)</strong></td>
<td>Benzyl penicillin 18–24 million units IV daily, as 3–4 million units every 4 h during 10–14 days</td>
<td>Second line therapy option if hospitalization and IV benzyl penicillin is impossible</td>
</tr>
<tr>
<td></td>
<td>Ceftriaxone 1-2 g IV daily during 10–14 days [III; B] OR Procaine penicillin 1.2–2.4 million units IM daily AND probenecid 500 mg four times daily, both during 10–14 days [IIb; B]</td>
<td>Penicillin allergy. Desensitization to penicillin followed by the first line regimen [III; B]</td>
</tr>
<tr>
<td><strong>CDC (2015)</strong></td>
<td>Aqueous crystalline penicillin G 18–24 million units per day for 10–14 days</td>
<td>Procaine penicillin 2.4 million units IM once daily PLUS Probenecid 500 mg orally four times a day, both for 10–14 days OR Ceftriaxone 2 g daily either IM or IV for 10–14 days</td>
</tr>
</tbody>
</table>

*Some experts recommend desensitization in preference to doxycycline

No differences between HIV-1 infected and uninfected patients
Treatment response

Standard serological follow-up should be under-taken, with close observation for treatment failure

Repeat lumbar puncture?

- CDC recommends 6-monthly until WCC normalizes (if pleocytosis initially)
- IUSTI recommend repeat at 6 weeks – 6 months following treatment
- Serum RPR normalisation may predict CSF normalisation, but less so in PLWH\(^1\)

Long-term NCI following syphilis?

- 29 patients with past syphilis. 100% treated (89% with benzathine). Poorer scores in learning and memory domains\(^2\)
- 82/1574 pts in CHARTER had positive RPRs. Matched to RPR negative controls. Increase in impaired NP domains\(^3\)

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\(R_x\) of Syphilis in Pregnancy

- Treatment appropriate to stage of disease with Procaine or Benzathine penicillin
  - Consider de-sensitising allergic patients
  - If treated in third trimester – give a second dose on day 8
- 2nd line: Procaine, amoxicillin, ceftriaxone
  - N.B. NOT Doxycycline
- 3rd line: erythromycin/azithromycin: poor placental penetration.
  - Neonate requires treatment at delivery with penicillin
- Future pregnancies: re-treatment not required if documented Rx in past but exclude re-infection
- F/U essential and consider third trimester screening.
- Close liaison with obstetric, midwifery and paediatric colleagues.
- UseBirth plan available from BASHH (on website)
Rx of Congenital Syphilis

Rx infant if mother:
- Untreated, re-infected or inadequately treated
- treated with any 2nd line treatment
- treated < 1/12 before delivery
- Baby has signs of syphilis

Treatment:
- **First line**: Benzyl penicillin sodium 60–90 mg/kg daily IV (in divided doses given as 30 mg/kg 12 hourly in the first 7 days of life and 8 hourly thereafter for 10 days)
- **Alternative**: Procaine penicillin 50,000 u/kg daily IM 10 days

Follow-up:
- RPR titre and EIA IgM (if available) at birth and then 3-monthly until negative
  - RPR should be negative by 6 months
  - EIA should be negative at 18 months
  - If stable or increasing → investigate for congenital syphilis

Drug Reactions & Management
Penicillin Allergy

- 3-5% allergic
- Anaphylactic shock
  - Secure airway & restore BP
  - Adrenaline 1:1000 IM 0.5 ml
  - Oxygen
  - Antihistamine IV/IM e.g 10mg chlorphenamine
  - IV hydrocortisone 100mg
- Delayed reaction: urticaria, arthralgia, angioedema & fever

Penicillin Desensitisation

- Penicillin allergy skin testing first
- Induced with increasing doses of antigen
- Oral Pen V safer than IV

- Wendel et al:
  - 100 i.u. benzylpenicillin increasing by doubling oral dose every 15 mins x 14 doses.
  - Close supervision for 24 hrs
  - Mild cutaneous reactions allowed to resolve spontaneously or treated with diphenhydramine 25 mg IV.
  - Patients then able to tolerate Penicillin IM in doses appropriate to stage of disease
Procaine Reaction

- Inadvertent IV injection
- Minimise by aspiration technique
- Immediate & resolves within 20-30 mins.
- Fear of impending death, hallucinations, confusion and rarely fits
- More common in CVS insufficiency, chronic respiratory disease, previous psychiatric disease
- Management: exclude allergy, calm & reassurance
- May require restraint, rectal diazepam if fits

Jarisch-Herxheimer Reaction

- Acute febrile reaction with exacerbations of skin and mucosal lesions, lasts 24 hours
- 4-12 hrs after 1st injection resolving within 24hrs
- Usually not important unless neuro/opthalmic/pregnancy or involve strategic sites e.g. larynx
- Steroids in symptomatic late syphilis (neuro/CVS) or early neurosyphilis: 1/7 prior to Rx 30-60mg tds for 3/7 total.
Thank you

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Some more references


Penicillin treatment for early syphilis in the presence of HIV-1 infection: the long or the short of it? Int J STD AIDS 19(9): 648


J. F. Mahoney, MD; R. C. Arnold, MD; Burton L. Sterner, MD; et al Penicillin Treatment of Early Syphilis JAMA. 1944;126(2):63-67.

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**Publication Date:** November 2009

2. **Jarisch-Herxheimer reaction after penicillin therapy among patients with syphilis in the era of the hiv infection epidemic: incidence and risk factors.**

**Author(s):** Yang CJ, Lee NY, Lin YH, Lee HC, Ko WC, Liao CH, Wu CH, Hsieh CY, Wu PY, Liu WC, Chang YC, Hung CC

**Citation:** Clinical Infectious Diseases, October 2010, vol./is. 51/8(976-9), 1058-4838;1537-6591 (2010 Oct 15)

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