Question 99 – Infectious diseases
A patient presents with the rash shown in the photograph below and is found to have a rapid plasma reagin (RPR) test titre of 1:256 and a positive fluorescent treponemal antibody associated absorbed (FTA-ABS) test.

The most appropriate treatment is:
A) Doxycycline 100mg twice daily for 14 days (oral)
B) Benzylpenicillin 1.8g sixth hourly for 10 days (intravenous)
C) Benzathine penicillin 1g daily as a single dose (intramuscular)
D) Procaine penicillin 1g daily for 10 days (intramuscular)
E) Ceftriaxone 250mg daily for 5 days (intramuscular)

Answer:
Learning issues:
- Ddx of erythematous macular rash and rash affecting hands/feet
- Syphilis (and more broadly STDs, I suspect there’ll be one STD question per year, excluding HIV) and laboratory testing
- Penicillins

Ddx erythematous macular rash
1) Drug eruption
2) Psoriasis (though characteristic sites eg extensor surfaces, often scaly)
3) Pityriasis rosea
4) Lichen planus (characteristic sites eg dorsum of hands, often hexagonal and purplish)
5) Acute viral exanthem (eg measles, varicella zoster, acute HIV seroconversion illness)

Ddx rash involving hands/feet
1) Infection
   - Secondary syphilis
   - Coxsackie virus (Hand, foot and mouth disease)
   - Scabies
2) Immune mediated
   - Kawasaki’s disease (usually peeling of hands and feet, rather than rash)

Syphilis
   - *Treponema pallidum*
   - Horizontal spread (sexual contact) or vertical transmission (transplacental infection of foetus)
   - Does not survive well outside body; inactivated by drying, heat and disinfectants
   - Grows very slowly - > endarteritis

Syphilis laboratory features

1) Microscopy
   - T.pallidum cannot be cultured
   - Exudate from primary chancre examined by dark-ground microscopy / UV microscopy (stained)/ biopsy material (silver stain)
   - Not seen in gram stain
   - Tightly wound, slender coils, sluggish but motile

2) Serology

<table>
<thead>
<tr>
<th>Indirect (non-treponemal)</th>
<th>Testing for Ag that are not treponemal in origin</th>
<th>Good screening test</th>
</tr>
</thead>
<tbody>
<tr>
<td>- VDRL</td>
<td>- Detecting Ig M and Ig G formed in response to lipoidal material released from damaged cells + from lipid on surface of treponema</td>
<td>False positives:</td>
</tr>
<tr>
<td>- RPR</td>
<td></td>
<td>- Viral infections</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Direct (treponemal)</th>
<th>Use treponemal Ag extracted from T.pallidum</th>
<th>Good to confirm syphilis when indirect test is positive</th>
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<tbody>
<tr>
<td>- FTA-ABS</td>
<td></td>
<td>False positives:</td>
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<tr>
<td>- TPHA (T.pallidum haemagglutination assay)</td>
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<td>- Disease associated with increased or abnormal globulins</td>
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- Recent increase incidence especially among MSM (men who have sex with men)
- HIV infection changes natural history/ treatment and outcome of syphilis
  - Diagnosis more difficult (> false negatives or atypical responses)
  - Neurosyphilis tends to manifest earlier and progress more rapidly
  - Uveitis and meningitis also more common

T.pallidum is highly sensitive to penicillin and should be the 1st drug of choice. If hypersensitive, consider desensitisation.

If not possible, 2nd line agent (in non-pregnant)
- Doxycycline 100mg oral BD (14 days)
Some limited studies suggest that ceftriaxone or azithromycin may also be effective (but optimum dose and duration unknown).

**Other treatment considerations**
- Avoid sexual contact till lesions healed and completed treatment
- All sexual contacts in last 3 months should be treated despite negative serology
- HIV +ve patients need close surveillance due to increase neuro-risk (clinical exam and serology at 6, 12, 18, 24 months post therapy. If neuro symptoms or 4 fold increase in serology, should have LP
- Pregnancy and syphilis
- Typically 3 stages (but not everyone goes through all)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical Features</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Primary</td>
<td>Painless ulcerating nodule at infection site (chancre)</td>
<td>Benzathine penicillin 1.8g IM (single dose)</td>
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<td></td>
<td>If HIV, chancre may be absent, atypical or multiple</td>
<td>or</td>
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<td></td>
<td>Lymphadenopathy (usually resolves)</td>
<td>Procaine penicillin 1g IM (10 days)</td>
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<tr>
<td>Secondary</td>
<td>Flu like illness</td>
<td>As above</td>
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<tr>
<td>(2-8 weeks post</td>
<td>Mucocutaneous rash (spontaneously resolves)</td>
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<tr>
<td>exposure)</td>
<td>Condylomata lata (grey/pink raised lesion where skin joins mucous membrane)</td>
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<td></td>
<td>Aseptic meningitis</td>
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<tr>
<td>Latent</td>
<td>Asymptomatic (some may relapse with features of secondary syphilis)</td>
<td>Early latent (&lt; 2 years): As above</td>
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<tr>
<td>(3-30 years)</td>
<td>Note that HIV +ve patients should have LP prior treatment</td>
<td>Late latent (&gt; 2 weeks or uncertain duration): Benzathine penicillin 1.8g IM weekly (3 weeks)</td>
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<td></td>
<td>- If negative: treat as per protocol</td>
<td>Or</td>
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<td></td>
<td>- If positive: treat as neurosyphilis</td>
<td>Procaine penicillin 1g IM (15 days)</td>
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<tr>
<td>Tertiary/ late</td>
<td>Neurosyphilis</td>
<td>Benzylpenicillin 1.8g IV 4/24 (15 days)</td>
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<td></td>
<td>Cardiovascular syphilis</td>
<td>+ prednisolone to prevent Jarisch-Herxheimer reaction</td>
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<td></td>
<td>Gummatous syphilis</td>
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<tr>
<td>Congenital</td>
<td>Risk of congenital syphilis low for:</td>
<td>Benzylpenicillin 50mg/kg IV or IM BD (10 days)</td>
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<td>Any mother with positive serology/ active syphilis who was adequately treated before 28 weeks and not re-infected (Placenta should still be examined)</td>
<td>or</td>
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<td></td>
<td>Untreated maternal infection</td>
<td>Procaine penicillin 50mg/kg IM daily (10 days)</td>
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<td></td>
<td>- Foetal loss 40%</td>
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<td></td>
<td>- High risk stillborn</td>
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<tr>
<td></td>
<td>- At birth: fulminant infection and</td>
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Penicillins
- Beta lactams: bacteriocidal by interfering with peptidoglycan cell wall synthesis
- Bind to and inhibits PBP (penicillin binding proteins) which are responsible for final cross-linking of new subunits onto the growing chain
- Not active against species lacking a cell wall (eg Mycoplasma), impenetrable cell walls (eg mycobacterium) or intracellular pathogens (eg Chlamydia)
- Some bacteria produce beta-lactamases which catabolise the beta lactam ring, rendering it useless – this can be surmounted by the addition of beta-lactamase inhibitor eg clavulanic acid

Narrow-spectrum penicillins
Narrow-spectrum penicillins are mainly active against Gram-positive organisms, but are inactivated by beta-lactamases.

- **Benzylpenicillin** (penicillin G) is administered parenterally and remains the treatment of choice for susceptible infections.
- **Procaine penicillin** is an IM preparation designed to extend the half-life of benzylpenicillin. It provides blood levels for up to 24 hours, but these are adequate only against highly susceptible organisms.
- **Benzathine penicillin** is given IM and provides low levels of benzylpenicillin for up to 4 weeks.
- **Phenoxymethylpenicillin** (penicillin V) is acid-stable and thus may be given orally, although food impairs absorption. It is intrinsically less active than benzylpenicillin.

Narrow-spectrum penicillins with antistaphylococcal activity
**Dicloxacillin**, **flucloxacillin** and **methicillin** are stable to beta-lactamase produced by staphylococci. Flucloxacillin and dicloxacillin are reliably absorbed by the oral route. Food reduces absorption and they are best taken half to one hour before food. Methicillin, the parent drug, is not used in clinical practice. Laboratories test with either oxacillin or cefoxitin rather than methicillin to determine susceptibility to antistaphylococcal drugs.

Flucloxacillin is generally well tolerated, but is occasionally associated with cholestatic jaundice, particularly in older patients on prolonged therapy. This may occur after oral or IV administration and up to 6 weeks after treatment. It may last for months, can be irreversible and, rarely, may be fatal. Dicloxacillin appears to cause less irreversible hepatotoxicity but results in more infusion phlebitis (see Intravenous administration of antimicrobials) and interstitial nephritis. Dicloxacillin may be preferable to flucloxacillin for oral therapy or in patients requiring prolonged therapy. In these guidelines, di/flucloxacillin refers to dicloxacillin or flucloxacillin.

MRSA should be regarded as clinically resistant to all beta lactams.

Moderate-spectrum penicillins
The aminopenicillins, **amoxicillin** and **ampicillin**, have greater activity than benzylpenicillin against some Gram-negative organisms (eg Escherichia coli, Haemophilus influenzae), but are destroyed by beta-lactamase–producing strains. They are drugs of choice for enterococcal infections. Amoxicillin is better absorbed orally than ampicillin, is not affected significantly by food and requires fewer oral doses per day, but when administered parenterally they are equivalent. In these guidelines, amoxy/ampicillin refers to amoxicillin or ampicillin.
**Broad-spectrum penicillins (beta-lactamase inhibitor combinations)**

The beta-lactamase inhibitors clavulanate, sulbactam and tazobactam inhibit the enzymes produced by *Staphylococcus aureus* and *Bacteroides fragilis* and also the beta-lactamase enzymes found in *Escherichia coli*, *Klebsiella* species, *Neisseria gonorrhoeae* and *Haemophilus influenzae*. These 3 drugs possess little inherent antibacterial activity, but significantly extend the spectra of activity. Reserve these combinations for the treatment of infections due to organisms in which resistance to the beta lactam is due to enzymes that the beta-lactamase inhibitors are able to inhibit. The combinations are often more expensive.

Amoxycillin-clavulanate can cause diarrhoea and hepatotoxicity, which occur more frequently than with amoxycillin.

**Broad-spectrum penicillins with antipseudomonal activity**

**Piperacillin** and **ticarcillin** are the only penicillins that have activity against *Pseudomonas aeruginosa*, but high doses are required. The addition of clavulanate to ticarcillin and tazobactam to piperacillin extends their spectra of activity, with piperacillin-tazobactam having greater *in vitro* activity against enterococci and *Klebsiella* species. Piperacillin-tazobactam is more expensive than ticarcillin-clavulanate, and both are more expensive than most other penicillins.