

Syphilitic eye disease with overlapping primary syphilis: How to manage a penicillin allergic patient

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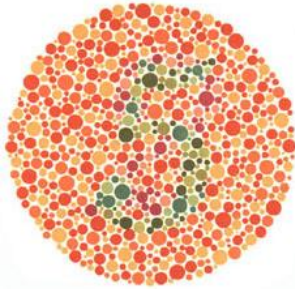
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Case



- 24 year old MSM
- 2 months of worsening visual loss (Lt >> Rt)
 - Painless, progressive
- Seen for non-urgent review in eye clinic (Sep 16)
- Diagnosis - retinitis / uveitis
- Referred for MRI orbits/head
- Referred for neurology opinion - ? demyelinating pathology
 - Others causes of uveitis considered e.g. Ank Spond, Sarcoid

Ophthalmology evaluation

- Snellen **visual acuity** (VA) 6/48 in the left eye (lower than normal) and 6/7.5 in the right
- Bilaterally **reduced color vision** (right eye 1/13, left eye 0/13)  measured using Ishihara plates
- Mild **vitritis** bilateral
- Fundus examination: **bilateral optic nerve head swelling** more pronounced on the left, multiple **active choroidal inflammatory lesions** and evidence of multiple older chorioretinal lesions (Figure 1)
- Humphrey **visual field testing** showed significant temporal visual field defects in his left eye and a few nasal field defects in the right eye, with (Figure 2)

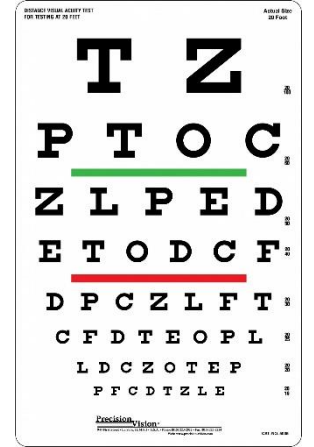




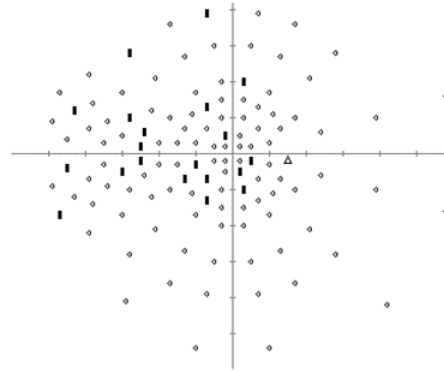
Figure 1: Retinal photograph of the left eye at presentation:

1. Optic nerve head swelling with blurring of the disc margins, disc hyperaemia and splinter haemorrhages (blue arrow).
2. Acute creamy (green arrow) and older, more defined (black arrow) choroidal lesions.

Right eye

Date: 14-09-2016 09:21:50
Age: 24
Fixation target: Central
Fixation losses: 2/16
False POS errors: 0/13
False NEG errors: 6/15 xx
Test duration: 06:06
Fovea: OFF
Stimulus: III, White on 31.5 ASB
Strategy: Threshold related

◊ Seen
■ Not Seen
△ Blindspot



Left eye

Date: 14-09-2016 09:29:47
Age: 24
Fixation target: Central
Fixation losses: 0/19
False POS errors: 0/16
False NEG errors: 6/17 xx
Test duration: 07:13
Fovea: OFF
Stimulus: III, White on 31.5 ASB
Strategy: Threshold related

◊ Seen
■ Not Seen
△ Blindspot

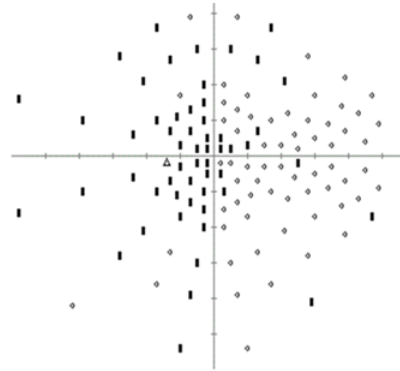


Figure 2: Humphrey visual field testing showed significant temporal visual field defects in his left eye and a few nasal field defects in the right eye.

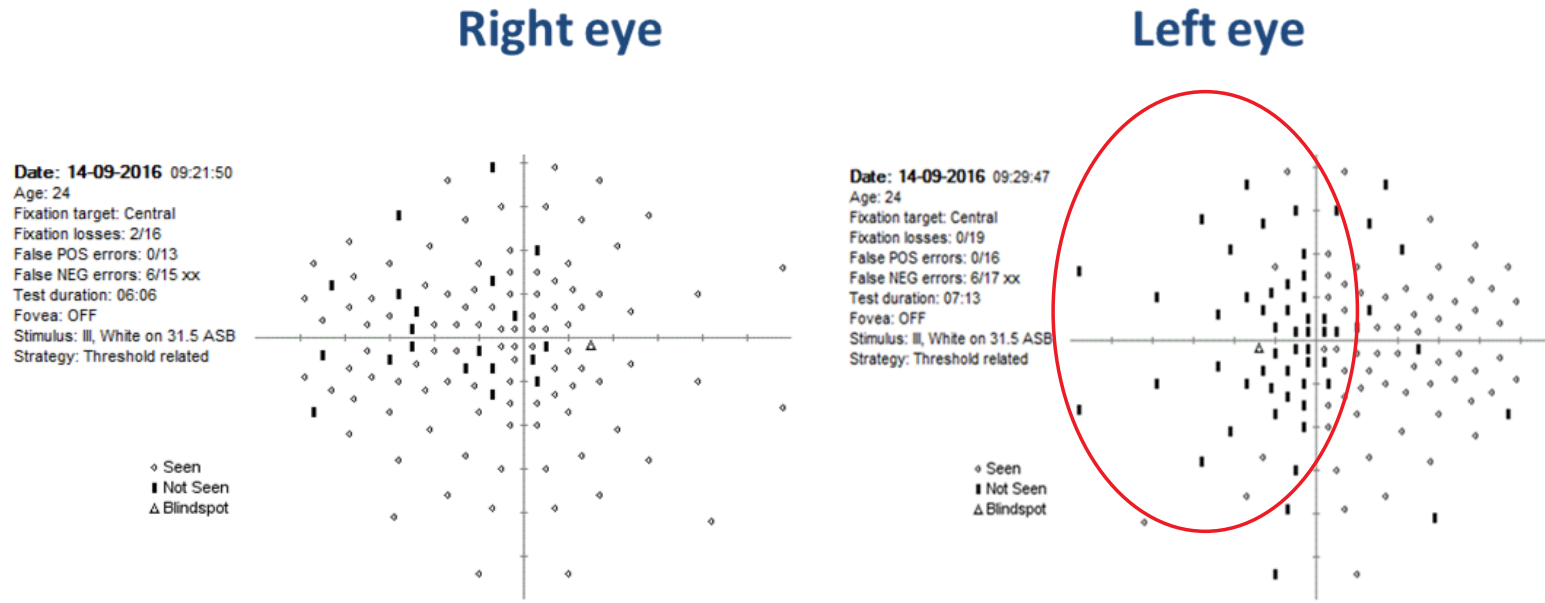


Figure 2 (Right eye, Left eye):

Humphrey visual field testing showed significant temporal visual field defects in his left eye and a few nasal field defects in the right eye.

Case - i

- Attends ophthalmology clinic again within a month
 - MRI – reported normal
 - Wait for neurology - weeks - months
- Seen by a ophthalmology fellow/registrar
- Noted to have retinitis, decreased visual fields
- Concern for PHI (limited to case reports) or established HIV
 - Fellow/registrar established patient had recently taken PEP
 - Hirschel T, et al. Blinded by Zika? A missed HIV diagnosis that resulted in optic neuropathy and blindness: a case report. **BMC Res Notes.** 2017 Dec 1;10(1):664. doi: 10.1186/s13104-017-2970-5
 - Graber P, et al. Multiple sclerosis-like illness in early HIV infection. **AIDS.** 2000 Oct 20;14(15):2411-3.
 - Brack MJ, et al. Anterior ischaemic optic neuropathy in the acquired immune deficiency syndrome. **BMJ** 1987;295:696.

Case - ii

- Referred to STI clinic – Friday afternoon
 - Patient frantic
- Recent discovery of RMP's infidelity
- Had had a high risk sexual exposure several months ago therefore PEP
 - Since then: Negative STI screen (outside clinic) +/- 6 months prior

Case - iii

- History review
 - Penicillin **anaphylaxis**
 - (STD clinic records not linked to other health records)
- No features of PHI/immunosuppression in history
- No features of secondary syphilis
 - No reports fevers/weight loss/headache/constitutional symptoms
 - No other symptoms except visual loss
- Patient insisted never had **any** genital/oral lesions

Case - iv



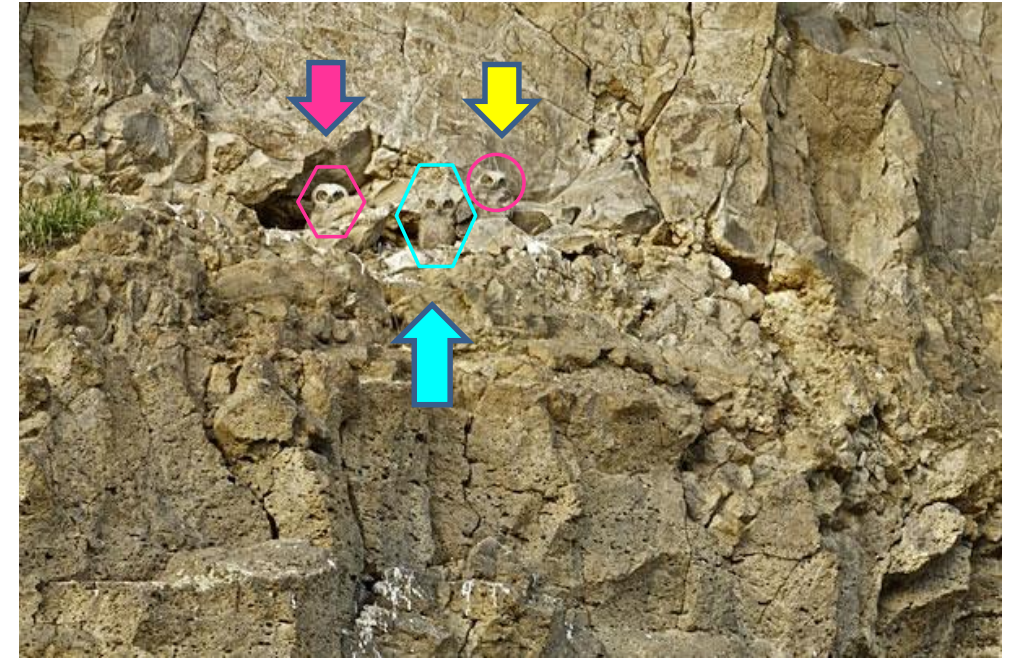
o/e

- Well, Thin, Anxious++
- Top to toe examination
- Hair/mouth/skin (including palms/soles)/LN/chest/abdo/neuro
 - normal (including pupils and eye movements)
 - Optic disc swelling bilaterally, fields grossly intact
 - Perianal – normal
 - HoweverTiny, <2mm healed/healing ulcer on prepuce

Case - iv

o/e

- Well, Thin, Anxious++
- Top to toe examination
- Hair/mouth/skin (including palms/soles)/LN/chest/abdo/neuro
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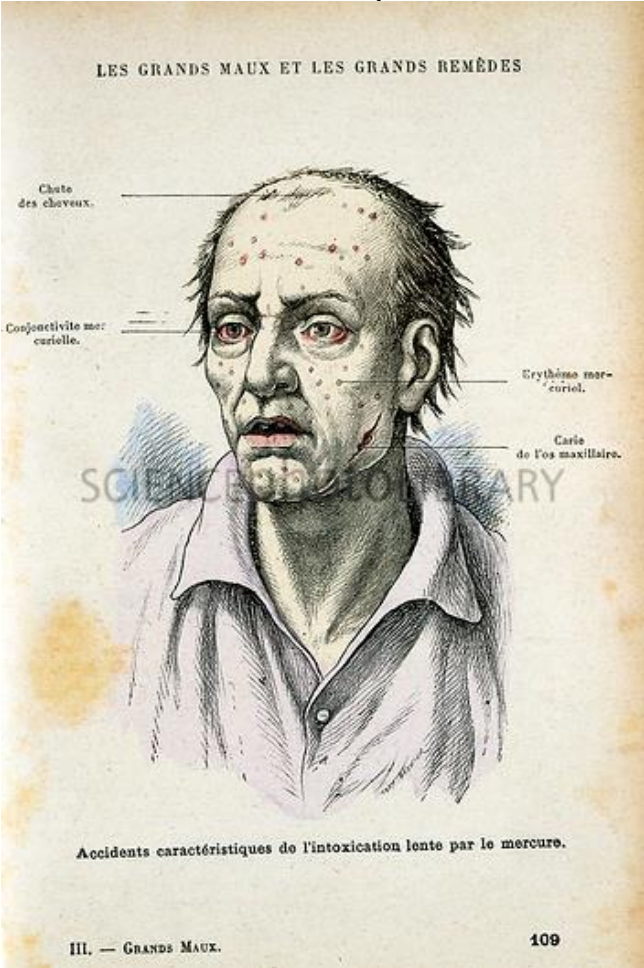
Case - v

Ix

- No DFM
- Rapid HIV (POCT) & 4th gen Ab/Ag negative
- Hepatitis B/C, triple NAATS – negative
- HSV 1 & 2 – negative
- Ulcer multiplex PCR – HSV/H. Ducreyi – negative
 - **T Pal – positive** (PHE lab: 68bp fragment of the 47Kd lipoprotein of T. pallidum. Positives confirmed on a different PCR targeting DNA polymerase A gene (polA))
- EIA/TPPA – positive
 - RPR – positive 1:128

Table 1 Summary of laboratory analysis, treatment and follow up.

Date of investigation	Serum RPR	Treatment	CSF result	GUD PCR
Baseline: 10/10/16	1:128	Prednisolone 40mg OD 3/7		Positive
11/10/16		Doxycycline 200mg BD 28/7		
4/11/16			TPPA: Positive, titre 1:320 RPR: Positive, Neat ent to perform ive RPR)	
			0.69 g	



Progress

Date	Investigation / finding			
Sep 2016	Initial presentation/abnormal eye exam			
	Serum RPR	Treatment	CSF result	GUD PCR
Oct 10, 2016	1:128	Prednisolone 40mg daily for 3 days [#]		Positive
Oct 11, 2016		Doxycycline 200mg twice daily for 28 days [#]		
Nov 4, 2016			TPPA: Positive, titre 1:320 RPR: Positive, (insufficient to perform quantitative RPR) 3 WBC (lymphocytes) Protein 0.69 g/L (<0.60)	
Dec 7, 2016	1:32			
Feb 1, 2017	1:8		TPPA: Positive, titre 1:80 RPR: Negative 1 WBC (lymphocytes) Protein 0.72 g/L (<0.60) Glucose CSF/plasma: normal	
Jun 2, 2017	1:8			
Nov 4, 2017	1:8			

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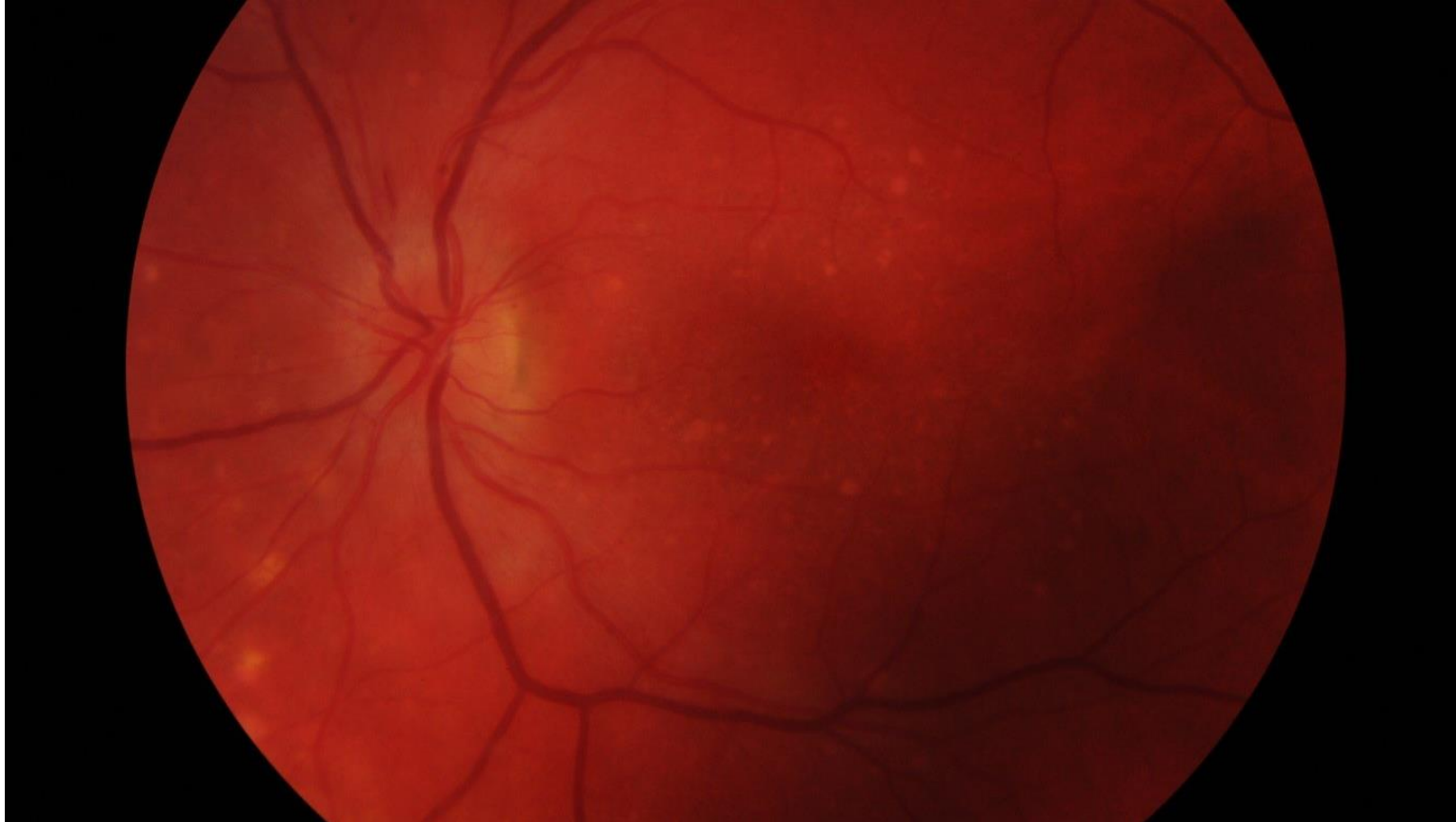


Figure 3: Retinal photograph of left eye after 9 months:

The disc margins are more defined and the chorioretinal lesions are paler and punched out.

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16 x decline in RPR titer

Syphilis & eye

Davis JL. Ocular syphilis. *Curr Opin Ophthalmol*. 2014;25(6):513-518.
Marx GE, Dhanireddy S, Marrazzo JM, et al. Variations in Clinical Presentation of Ocular Syphilis: Case Series Reported From a Growing Epidemic in the United States. *Sex Transm Dis*. 2016;43(8):519-523.
Oliver SE, Cope AB, Rinsky JL, et al. Increases in Ocular Syphilis-North Carolina, 2014-2015. *Clin Infect Dis*. 2017.
Wells J, Wood C, Sukthankar A, Jones NP. Ocular syphilis: the re-establishment of an old disease. *Eye (Lond)*. 2017.
Mathew RG, Goh BT, Westcott MC. British Ocular Syphilis Study (BOSS): 2-year national surveillance study of intraocular inflammation secondary to ocular syphilis. *Invest Ophthalmol Vis Sci*. 2014;55(8):5394-5400.

- Any part of the eye
 - **Wender, JD et al. How to Recognize Ocular Syphilis. Review of Ophthalmology. 2008**
- Any stage of disease, but early also
 - Seminal work by Lukehart et al: CNS involvement occurs early (**Lukehart SA Ann Inter Med 1988**)
- 58 untreated underwent LP. T Pal isolated in CSF in:
 - 30% of 1° and 2° syphilis
 - 67% of EL
 - 20% of LL



Syphilis & eye & doxycycline



- Part of UK and Irish guidelines as alternative
 - Option of urgent allergy opinion, testing & desensitization, not feasible
 - Pt reluctance to undergo re-treatment when excellent response
- **CDC/IUSTI** – penicillin only, no role doxycycline
- Data for doxycycline for neurosyphilis are **very** limited
 - Yim CW, et al. Penetration of oral doxycycline into the cerebrospinal fluid of patients with latent or neurosyphilis. **Antimicrob Agents Chemother.** **1985;28(2):347-348**
 - 5 cases
 - Mean CSF penetration 26%
 - Treated for 21 days (compared to 28 days in BASHH guidelines)
 - See also:
 - Chotmongkol V, et al. Doxycycline treatment of otosyphilis with hearing loss. **Sex Transm Infect** **2012;** **88:177–8.**
 - Zenilman JM, et al. Asymptomatic neurosyphilis after doxycycline therapy for early latent syphilis. **Sex Transm Dis.** **1993;20(6):346-347.**

Syphilis & eye & doxycycline

Neurosyphilis including neurological/ophthalmic involvement in early syphilis



1. Procaine penicillin 1.8 MU–2.4 MU IM OD plus probenecid 500mg PO QDS for 14 days^{3,99}: 1C.
2. Benzylpenicillin 10.8–14.4 g daily, given as 1.8–2.4 g IV every 4 h for 14 days: 1C.

Alternative regimens

1. Doxycycline 200 mg PO BD for 28 days¹²⁸: 2D.

2. Amoxycillin 2 g PO TDS plus probenecid 500 mg PO QDS for 28 days¹²⁹: 2D.
3. Ceftriaxone 2g IM or IV for 10–14 days^{3,84–86,90,130,131}: 2D.
 - Steroids should be given with all anti-treponemal antibiotics for neurosyphilis; 40–60 mg prednisolone OD for three days starting 24h before the antibiotics.

Yim CW, Flynn NM and Fitzgerald FT. Penetration of oral doxycycline into the cerebrospinal fluid of patients with latent or neurosyphilis. *Antimicrob Agents Chemother* 1985; 28: 347–348.

Harshan V and Jayakumar W. Doxycycline in early syphilis: a long term follow up. *Indian J Dermatol* 1982; 27: 119–124.

Corticosteroids

larynx and nervous system). There is no evidence that the use of steroids prevents these serious consequences; however, there is evidence in early syphilis that steroids prevent the fever associated with the Jarisch-Herxheimer reaction.¹³⁴ This suggests a biological plausibility that steroids may also prevent the wider complications of the reaction. Furthermore, severe clinical deterioration in early syphilis with optic neuritis and uveitis has been reported following treatment and, as steroids are also used in the management of these conditions unrelated to syphilis, biological plausibility would suggest that they may help.



Gudjónsson H and Skog E. The effect of prednisolone on the Jarisch-Herxheimer reaction. *Acta Derm Venereol* 1968; 48: 15–18.

Syphilis & corticosteroids

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Centers for Disease Control and Prevention

MMWR

Morbidity and Mortality Weekly Report

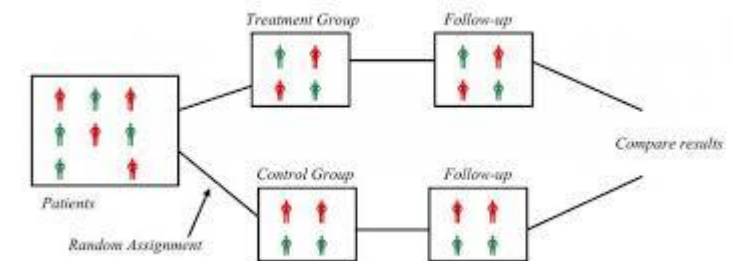
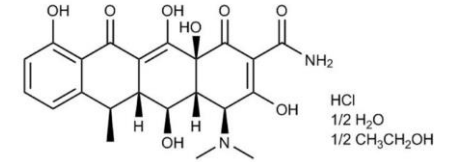
Recommendations and Reports / Vol. 64 / No. 3

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Although systemic steroids are used frequently as adjunctive therapy for otologic syphilis, such drugs have not been proven to be beneficial.

Discussion points

- Doxycycline for neuro/ocular/oto-syphilis?
- Corticosteroids for JHR?
- Desensitization and retreat vs. monitor?
- Need for RCT – doxycycline, corticosteroids?



Some key publications

Epidemiology

- Oliver SE, Aubin M, Atwell L, et al. Ocular Syphilis - Eight Jurisdictions, United States, 2014-2015. **MMWR Morb Mortal Wkly Rep.** **2016;65(43):1185-1188.**
- Tuddenham S, Ghanem KG. Ocular syphilis: opportunities to address important unanswered questions. **Sex Transm Infect.** **2016;92(8):563-565.**
- Oliver S, Sahi SK, Tantaló LC, et al. Molecular Typing of Treponema pallidum in Ocular Syphilis. **Sex Transm Dis.** **2016;43(8):524-527.**
- Mathew RG, Goh BT, Westcott MC. British Ocular Syphilis Study (BOSS): 2-year national surveillance study of intraocular inflammation secondary to ocular syphilis. **Invest Ophthalmol Vis Sci.** **2014;55(8):5394-5400.**
- Davis JL. Ocular syphilis. **Curr Opin Ophthalmol.** **2014;25(6):513-518.**
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- Oliver SE, Cope AB, Rinsky JL, et al. Increases in Ocular Syphilis-North Carolina, 2014-2015. **Clin Infect Dis.** **2017.**

JHR

- Gudjónsson H, Skog E. The effect of prednisolone on the Jarisch-Herxheimer reaction. **Acta Derm Venereol.** **1968;48(1):15-18.**
- Fathilah J, Choo MM. The Jarisch-Herxheimer reaction in ocular syphilis. **Med J Malaysia.** **2003;58(3):437-439.**

Doxycycline

- Ghanem KG. Management of Adult Syphilis: Key Questions to Inform the 2015 Centers for Disease Control and Prevention Sexually Transmitted Diseases Treatment Guidelines. **Clin Infect Dis.** **2015 Dec 15;61 Suppl 8:S818-36.**
- Chotmongkol V, Sawanyawisuth K, Yimtae K, Chantarojanasiri T, Chotmongkol R. Doxycycline treatment of otosyphilis with hearing loss. **Sex Transm Infect** **2012; 88:177-8.**
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- Zenilman JM, Rand S, Barditch P, Rompalo AM. Asymptomatic neurosyphilis after doxycycline therapy for early latent syphilis. **Sex Transm Dis.** **1993;20(6):346-347.**

RPR/VDRL

- Marra CM, Tantaló LC, Maxwell CL, Ho EL, Sahi SK, Jones T. The rapid plasma reagin test cannot replace the venereal disease research laboratory test for neurosyphilis diagnosis. **Sex Transm Dis.** **2012;39(6):453-457.**

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