Dr Edward Coughlan

Clinical Director

Christchurch Sexual Health

All about Syphilis - Concurrent Workshop

Saturday, 17 August 2013 Start 4:30pm Duration: 60mins Lounge 2

Christchurch Sexual Health
33 St Asaph Street

Dr Edward Coughlan
Clinical Director

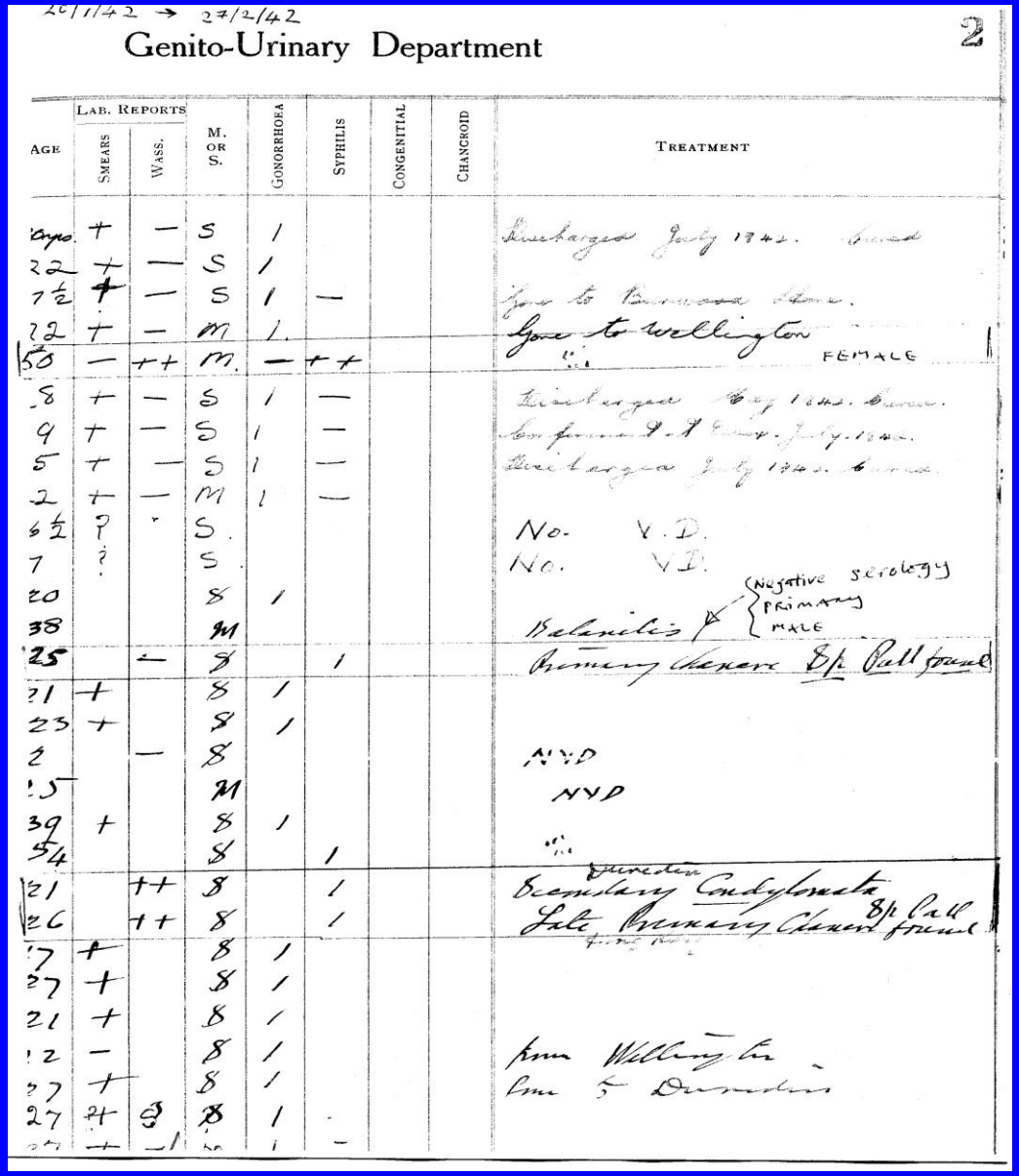
Why this Work Shop on Syphilis ?

- Because it is here
- Very easy to miss in the secondary stages
- Very easy to miss in primary stages!
- Easy to give the wrong penicillin

“Know syphilis in all its manifestations and relations, and all other things clinical will be added unto you”

Sir William Osler 1897

Historical evidence



26/1/42 → 27/2/42

Genito-Urinary Department

2

Age	Lab. Reports: Smears	Lab. Reports: Wass.	M. or S.	Gonorrhoea	Syphilis	Congenital	Chancroid	Treatment
[illegible]	+	—	S	/				Discharged July 1942.
22	+	—	S	/				
7½	+	—	S	/	—			Gone to [illegible]
22	+	—	M	/				Gone to Wellington
50	—	++	M.	—	++			" FEMALE
8	+	—	S	/	—			Discharged July 1942. Cured.
9	+	—	S	/	—			Sent from [illegible] July 1942.
5	+	—	S	/	—			Discharged July 1942. Cured
2	+	—	M	/	—			
6½	?		S.					No. V.D.
7	?		S.					No. V.D.
20			S	/				(Negative serology) PRIMARY MALE
38			M					Balanitis
25		—	S		/			Primary Chancre S/L Call found
21	+		S	/				
23	+		S	/				
2		—	S					N.V.D
15			M					N.V.D
39	+		S	/				
54			S		/			"
21		++	S		/			Secondary Condylomata Discretion
26		++	S		/			Late Primary Chancre S/L Call Found
17	+		S	/				
27	+		S	/				
21	+		S	/				
12	—		S	/				from Wellington
27	+		S	/				Cure 5 Discretion
27	+	S	S	/				
[illegible]	+	—	[illegible]	/	—			

What is happening - ESR

- Enhanced Surveillance of Infectious Syphilis at NZ Sexual Health Clinics started in Jan 2011
- Co-ordinated through AIDS Epidemiology Group and now ESR
  - Rebecca Psutka
  - Nigel Dickson

- The epidemiology of syphilis in New Zealand has undergone a series of evolutions in the last half century, and the rise in numbers seen in Christchurch in 2012 was associated with worrying new trends.

- In the 1990's, places around the world were seeing an increase in the number of syphilis cases and were largely attributing the rise in numbers to crack cocaine use and those exchanging in drugs or money for sex, the outbreak in San Francisco at the time being no exception (1)

- In the last decade, outbreaks of syphilis around the world in Canada, the US, Europe and Australia have disproportionately occurred amongst MSM, and those with HIV are more at risk. [2]

- In the New Zealand data from 2002-2004 MSM comprised 45% of those infected - where infection was usually acquired in New Zealand.[3]

During 2007-2008 Auckland experienced a similar outbreak with the incidence rate reaching 7.0 per 100,000, and in Wellington there was also a rise on a slightly smaller scale with a rate of 5.9 per 100,000 of reported cases.

During these outbreaks there was a notable rise in the numbers of MSM who are being diagnosed with the disease, but it was felt at the time that cases were being underreported and the true extent of the problem wasn't known.

Azariah, S Sexual Health, 2008. 5: p. 303-304

There have been several studies published in recent years about the epidemiology of syphilis in New Zealand.

A report from Auckland SHC found that in the period from January 2002 to September 2004 the number of people presenting there with infectious syphilis more than doubled.

Most of these people were men who have sex with men (MSM) and heterosexuals who had recently had sex overseas

Azariah S. Is syphilis resurgent in New Zealand in the 21st century? A case series of infectious syphilis presenting to Auckland Sexual Health Service. New Zealand Medical Journal 2005;118;1211

- A retrospective audit from Wellington published in 2007 found that between 2004 and 2006 (the end of the study period) the city experienced an outbreak, again principally amongst MSM

  Cunningham R et al. An outbreak of infectious syphilis in Wellington,New Zealand NZMJ Vol 120 No 1260 24 August 2007

- A prospective study over a 12 month period from July 2006 to July 2007 found, that based on Auckland laboratory data, there were 92 cases of infectious syphilis there, of which about half were among MSM.(3)

Azariah S, Perkins N, Austin P, Morris AJ. Increase in incidence of infectious syphilis in Auckland, New Zealand: results from an enhanced surveillance survey. Sexual Health, 2008, 5, 303-3044

Christchurch Cases

- In 2011: 8 cases of early syphilis - average age 46
- In 2012: 26 cases - average age 26 and mostly MSM
- In 2013:10 cases

Case study 1

A 61 year old man referred by GP – rash on trunk, legs and arms

- Presumptive diagnosis of guttate psoriasis (but did syphilis serology)

Result:

- RPR +ve 1:128
- TPPA Reactive
- Syphilis EIA Reactive
- Also HIV positive

Case Study 2

- R is a 37 year old man
  - Presented with a penile rash for 2 weeks
- On Examination
  - Ulceration on roof of the mouth
  - Ulceration on his tongue
  - Scrotal and penile rash

Case Study 3

A 57 year old man had presented to his GP with peri-anal lesions which were ?genital warts. Treated with Imiquimod and lesions became inflamed.

Syphilis serology done:

- RPR : (T = 32)
- Syphilis EIA reactive
- TPPA- reactive
- HIV negative

On further questioning - “a lot of spots on chest” “very blotchy” – almost resolved now- had 3 weeks ago

Contact history

(1)

- Male contact 3 to 4 weeks previously
- a local sex on site venue
- Anal receptive sex without a condom
- No oral sex

(2)

- 3-4 months previously, same place, anonymous contact, anal receptive sex with a condom

- From perianal lesions:
  - Dark ground – negative
  - DFA-Treponemes – negative
  - HSV - negative

- Initially denied any MSM contact

But then stated:

- One contact at sex on site venue
- Other “regular casual “ partner for 3 months.

- RPR reactive (T= 64)
- TPHA reactive
- Syphilis EIA reactive
- HIV negative

He was treated with i.m. penicillin

When seen 1 week later all his lesions were improving

Case Study 5

- A 22 year old man
- Referred from Dermatology for treatment and contact tracing etc
- 3 months previously – “swabs on his penis”
- “Then hands peeling ,mouth ulcers and rash on his trunk”

- “Penile scabs”- not particularly painful
- Had swabs for HSV done and serology which was positive for types 1 and 2
- These resolved but then developed rash on his hands (starting to resolve)
- And chest rash
- And mouth ulcers

- Had STI screen: HIV, gonorrhoea, chlamydia etc.

- Past History: Chlamydia 1 year ago

- Sexual History

  1) Semi casual, most recently 2 weeks ago, female, over the last 2 months, condoms – ve

  2) multiple casual contacts ???

  3) Regular partner, with her 1.5 years. LSI Jan 09

Treponema Species

- Treponema pallidum subspecies pallidum
  - Venereal Syphilis
- Treponema pallidum subspecies pertenue
  - Yaws
- Treponema pallidum subspecies endemicum
  - endemic syphilis, bejel
- Treponema pallidum subspecies carateum
  - Pinta

- Non pathogenic treponemes in the mouth
- Organisms are slender, tightly coiled, helical cells
- Particular coil motion > see on darkground
- Outer membrane contains few surface exposed proteins > “stealth “hypothesis”
- Genome conserved (with some exception) > extremely sensitive to penicillin

Features include

- Discrete stages
- Early lesions which resolve
- Persistent infection
- Dissemination to most organs
- Can reappear decades later
- Re-infection can occur

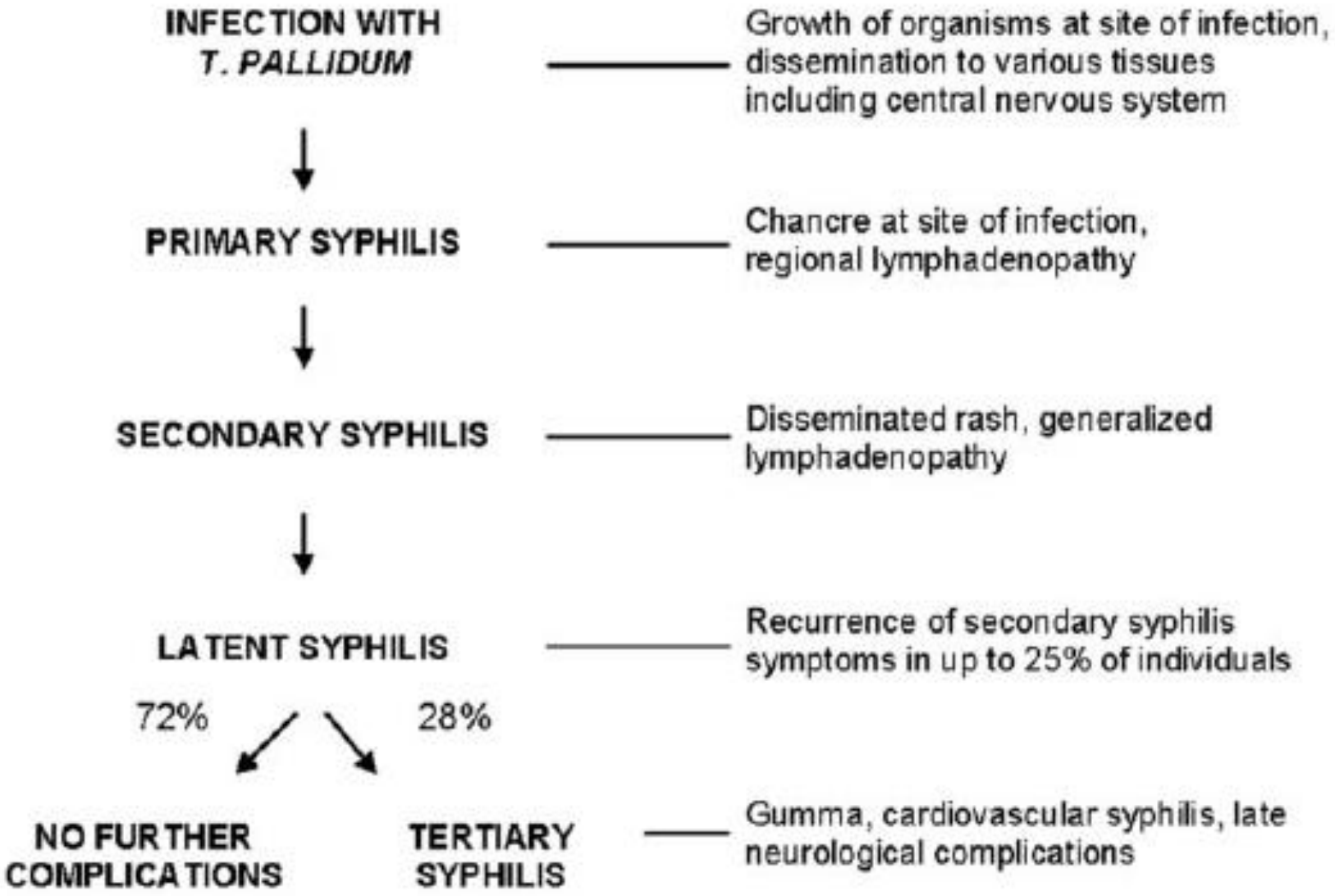


FIG. 1. Natural history of untreated syphilis, according to Gjestland (112).

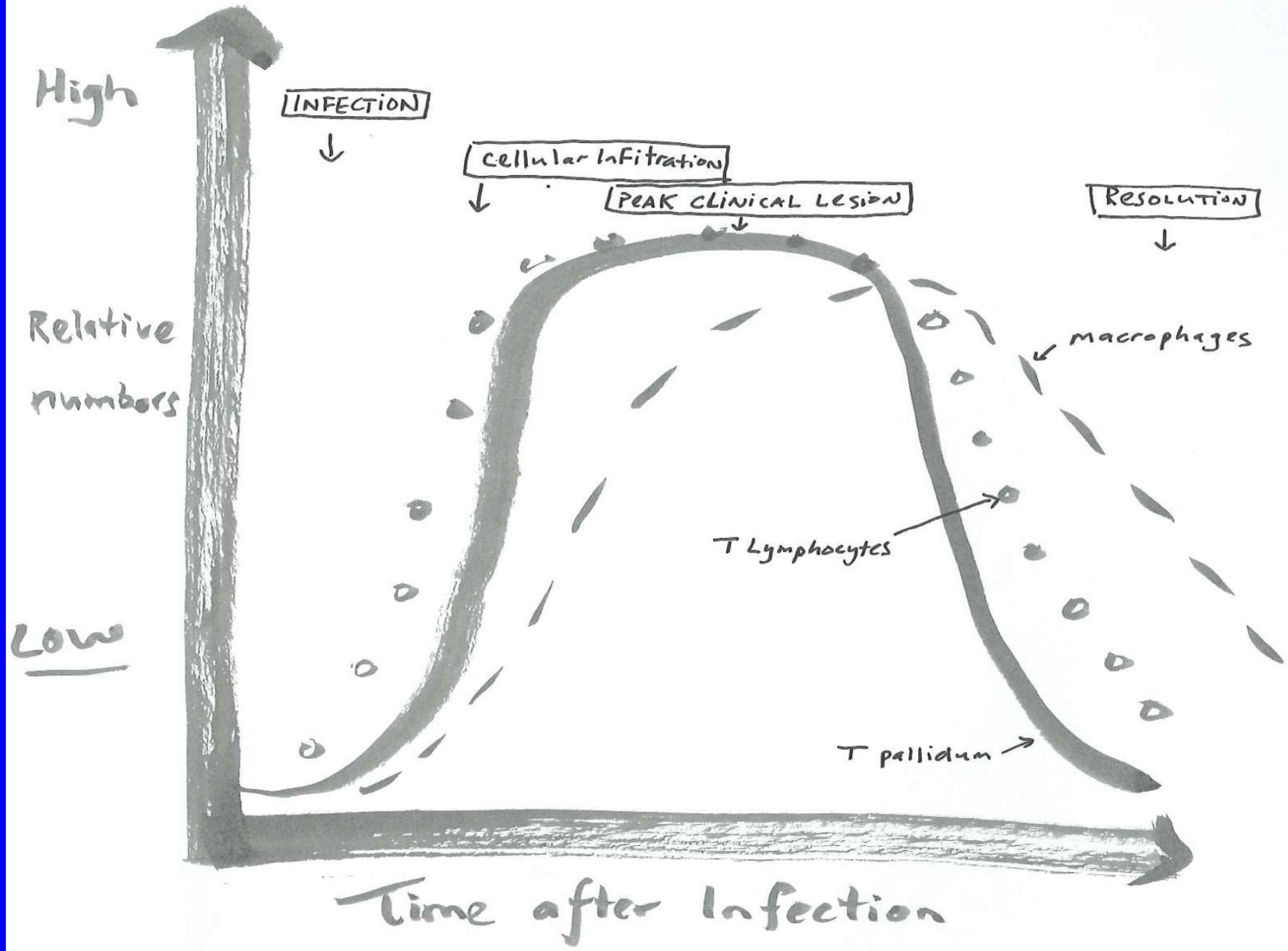
Primary Syphilis

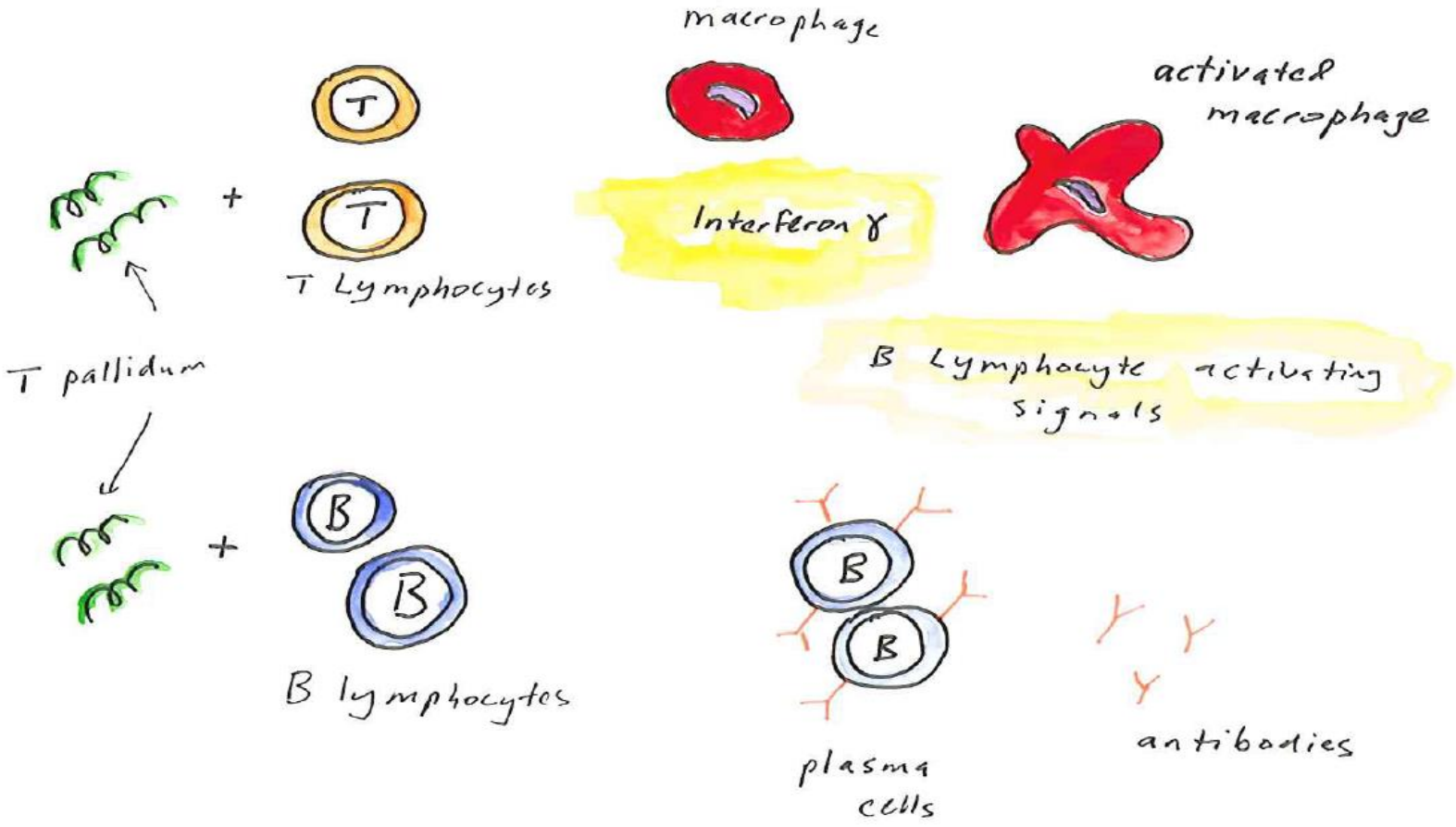
- The primary lesion usually appears 9-90 days dependant on inoculum
- Usually only a single, firm, non-tender ulcerated lesion is present
- Organisms can be observed in exudate from the lesion by dark-ground microscopy

In primary syphilis, serological tests for syphilis are positive in only 25% of patients at the time of the initial appearance of the chancre.

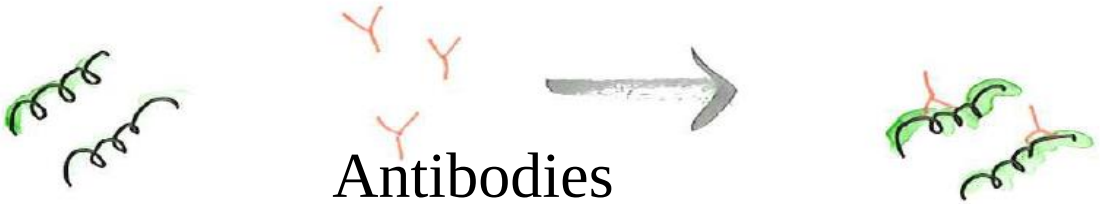
PRIMARY SYPHILIS

- Incubation period 10-90 days > average 3 weeks
- Chancre develops > Note: 30% have no chancre
- Usually single but may be multiple
- Usually painless > Note: perianal may be painful
- Most have regional lymphadenopathy within 1 week of chancre
- Heals in a few weeks

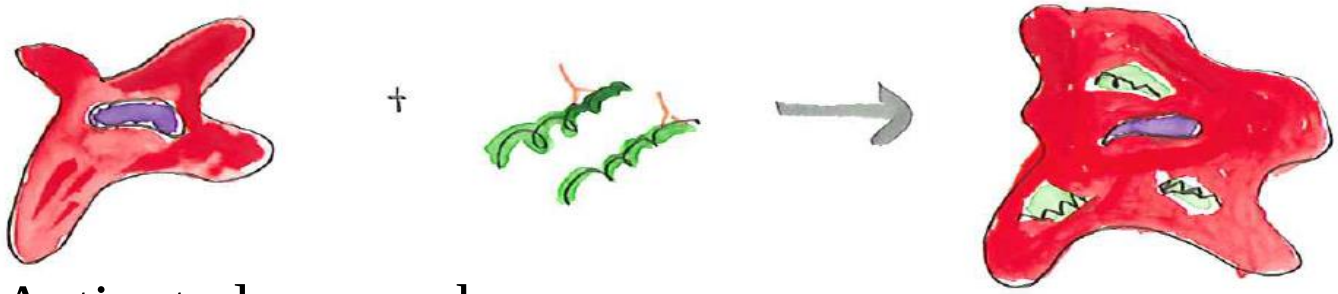

High
Relative numbers
Low
INFECTION
Cellular Infiltration
PEAK CLINICAL LESION
RESOLUTION
macrophages
T Lymphocytes
T pallidum
Time after Infection



Local immune response



T pallidum



Clearance of T pallidum from Early Lesions

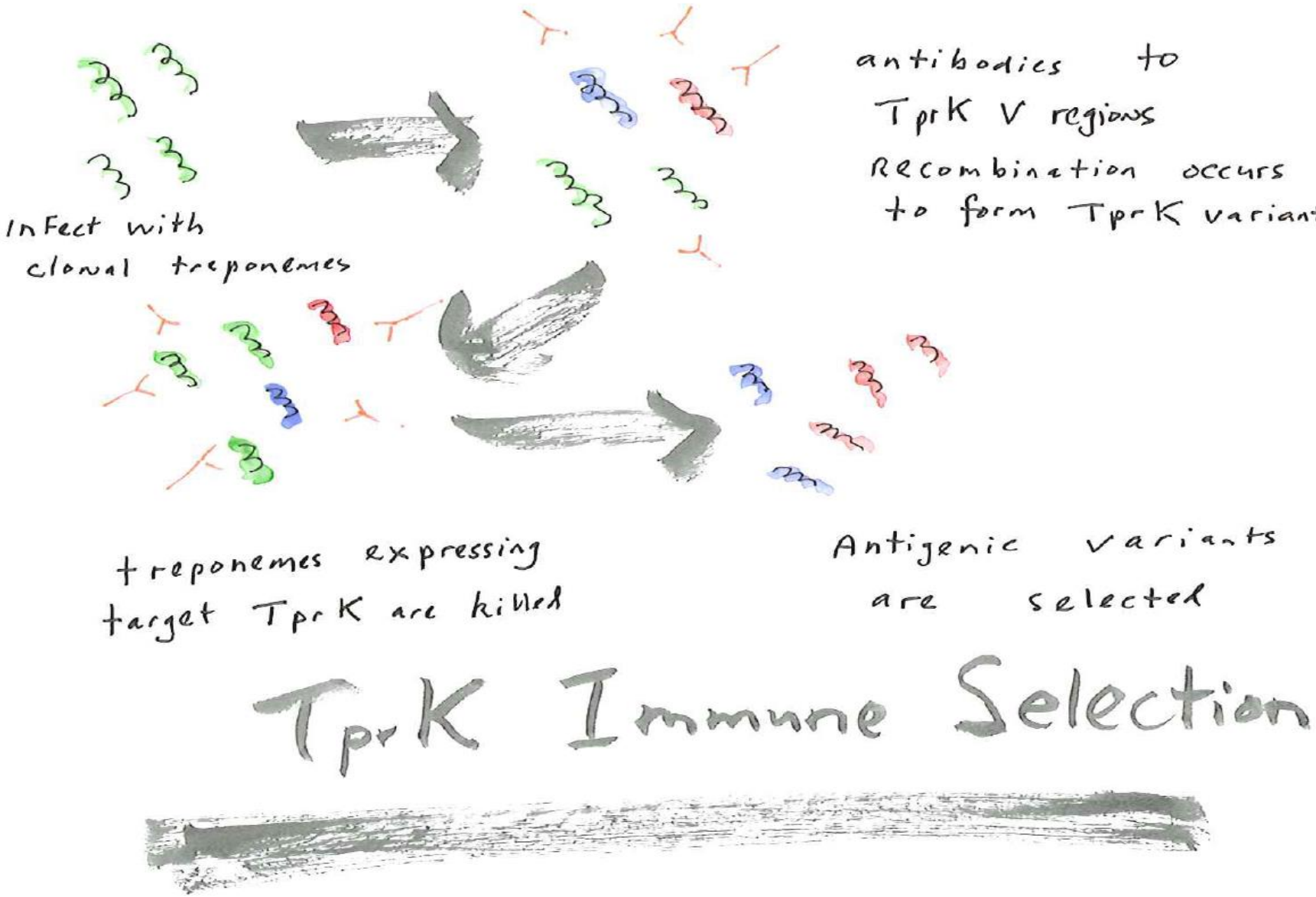
- Primary lesion heals with local host response
- BUT secondary syphilis follows with chronic infection
- Evasion of the immune response

- “Stealth “ pathogen – low concentrations of integral membrane proteins

- Antigenic variation changing the antigens exposed to immune response
  - Phase variation : ON - OFF
  - On but changed in variation

TprK

- Translocated Promoter Region
- This gene is highly expressed and located in outer membrane
- Induces robust early immune response
- Sequences variable in 7 discrete regions
- => Immune evasion & re-infection


Infect with clonal treponemes
antibodies to TprK V regions
Recombination occurs to form TprK variant
treponemes expressing target TprK are killed
Antigenic variants are selected
TprK Immune Selection

Secondary Syphilis

- 90% of relapses in the 1st year, 94% within 2 years
- Dissemination occurs early on and wherever organisms lodge they multiply (40% CNS)
- About 3-6 weeks (average) after appearance of chancre .Note: some don't have clinical secondary syphilis
- Delay between primary and secondary thought to be due to development of humoral and cell mediated immunity

Secondary Syphilis

- Any organ can be affected but ~90% have skin involvement : rash, condylomata lata, mucosal lesions
- Also systemic Sx such as fever, malaise, headache, adenopathy (50-86%)
- Specific organs may be affected : nephrotic syndrome (due to immune complex deposition), hepatitis, alopecia, meningitis, ocular manifestations, arthritis
- Lasts 2-12 weeks and resolves spontaneously

- Relapses of secondary disease may occur up to 4 years post chancre but very rare after 2

- “Jarisch-Herxheimer” reaction - after antibiotic Rx, acute toxic reaction, results from death of treponemes and exposure of immunogenic subsurface lipoproteins: Fever, headache, nausea, tachycardia, myalgia.

  Treatment with steroids, or supportive treatment only. Onset a few hours after first dose and subsides within 24hrs.

LATENCY

- EARLY
  - UK - </= 2 years since infection.

  USA - </= 1 year since infection.
  - considered potentially infectious as relapses still possible

- LATE - after the above. Not considered infectious.

- Late (tertiary) syphilis includes:
  - late latent syphilis
  - benign tertiary syphilis
  - Late syphilitic involvement of the viscera, cardiovascular and central nervous systems

- Cutaneous gumma (chronic granulomatous lesion): ‘punched out’ ulcer, often without secondary infection, usually occurring on the lower leg. Other sites: face, buttock, sternum, scalp – may penetrate to bone and cause necrosis, also mucocutaneaus
- Late syphilis of the bones: osteoperiostitis of long bones – painful
- Testicular enlargement: diffuse gummatous infiltration and dense fibrosis produce a smooth, painless enlargement of the testis

NeuroSyphilis

- Different Types
  - Acute
  - Meningovascular
  - Parenchymatous
  - Tabes Dorsalis

- "Blind, deaf, mad, staggering and incontinent"
- cranial nerve abnormalities
- Pupillary abnormalities
- Personality changes
- Posterior column dysfunction

Cardiovascular

- Aortic aneuryms
  - ascending region of the thoracic aorta
- Aortic regurgitation
- coronary artery disease

STI Summary of Guidelines 2013 Syphilis Management

TEST IF:

- MSM (at least annually).
- HIV positive (at least annually).
- Routine antenatal screen.
- Routine immigration screen.
- A sexual contact of a person with syphilis.
- Routine sexual health check.

Signs or symptoms of infectious syphilis:

- Genital ulcers (refer to Genital Ulcer Disease Summary).
- MSM with any genital symptoms or rash.
- Any rash affecting the palms of the hands or soles of the feet, or that is persistent or unexplained.
- Pyrexia of unknown origin, unexplained persistent lymphadenopathy, unexplained liver function disturbance, alopecia.

Tests

- Dark ground
- DFA-TP (direct fluorescent antibody test for treponema pallidum)
- PCR
- Serology
  - RPR
  - TPHA
  - EIA
  - Immunoblot (Westmead, Sydney)

Non-Treponemal

- RPR,VDRL
- can get false positives
- 25% will turn negative without treatment
- Most will turn negative with treatment but if syphilis is long standing may become serofast
- with secondary syphilis get rising titres

Treponemal Tests

- eg TPHA

- Once positive tend to remain positive even with treatment

Treatment

Penicillin remains treatment of choice

- Late latent : Injections of im penicillin – long acting (benzathine) BICILLIN LA 2.4 megaunits weekly for 3 weeks
- Early : Stat dose injection of im penicillin- BICILLIN LA 2.4 megaunits

A treponemicidal level of antimicrobial should be achieved in serum, and in the case of neurosyphilis, in the CSF. A penicillin level of >0.018 mg/L is considered treponemicidal,[59] but a higher concentration might be preferable for more rapid elimination of treponemes. The maximal elimination effect is attained at a level of 0.36 mg/L.[60] Duration of treponemicidal levels of antimicrobial should be at least seven days to cover a number of division times (30–33 hours) of treponemes in early syphilis with a subtreponemicidal interval of not more than 24–30 hours.[59] Longer duration of treatment is given in late syphilis on the basis of more slowly dividing treponemes in late syphilis. Treponemes may persist despite apparently successful treatment indicating that some treponemes may be 'resting' or dividing very slowly.[61–66] Clinical data are lacking on the optimal dose and duration of treatment and the long term efficacy of antimicrobials other than penicillin. The rec-

BICILLIN® L-A 2.3 mL
(Benzathine Benzylpenicillin Injection
for deep **IM** injection only

Intramuscular benzathine benzylpenicillin is absorbed very slowly into the bloodstream from the intramuscular site and converted by hydrolysis to benzylpenicillin. This combination of hydrolysis and slow absorption results in blood serum levels much lower but much more prolonged than other parenteral penicillins.

Intramuscular administration of 225 mg of benzathine benzylpenicillin in adults results in blood levels of 22.5 to 37.5 nanogram per mL, which are maintained for 4 to 5 days. Similar blood levels may persist for 10 days following administration of 450 mg and for 14 days following administration of 900 mg. Blood concentrations of 2.25 nanogram per mL may still be detectable 4 weeks following administration of 900 mg.

Penicillin G Sodium injection

Benzylpenicillin Sodium Ph Eur, powder for injection, 1 million IU, 5 million IU and 10 million IU

Presentation

Penicillin G Sodium injection is a white to whitish crystalline, water soluble powder aseptically filled into glass vials. Reconstitution yields a clear solution of Benzylpenicillin Injection BP.

The three presentations of Penicillin G Sodium injection are: a 5 ml vial containing 1 million IU (equivalent to approximately 0.6 g benzylpenicillin sodium or Penicillin G Sodium); a 15 ml vial containing 5 million IU (equivalent to approximately 3 g benzylpenicillin sodium or Penicillin G Sodium); a 30 ml vial containing 10 million IU (equivalent to approximately 6 g benzylpenicillin sodium or Penicillin G Sodium).

Penicillin G Sodium injection

Benzylpenicillin Sodium Ph Eur, powder for injection, 1 million IU, 5 million IU and 10 million IU

Elimination

In adults with normal kidney function plasma half-life is approximately 30 minutes. Most of the administered dose (50 to 80%) is eliminated along renal pathways in an unchanged form (85 to 95%). Tubular excretion is inhibited by probenecid which is sometimes given to increase plasma-penicillin concentrations. Biliary elimination of the active medicine accounts for only a minor fraction (about 5% of the dose).

An Analysis of a Medication Error

- Why?
- What happened?
- What we did
- An analysis of how it happened using different models


PRESCRIPTION MEDICINE
Cefotaxime
500 mg Injection
1 Vial
Each vial contains:
500 mg of cefotaxime as cefotaxime sodium.
Powder for intravenous and intramuscular use.
AFT pharmaceuticals
PRESCRIPTION MEDICINE
Ceftriaxone
500 mg Injection
1 Vial
Each vial contains:
500 mg of ceftriaxone as ceftriaxone sodium.
Powder for intravenous and intramuscular use.
AFT pharmaceuticals

MANAGEMENT

- Advise to refrain from any sexual activity until assessed or discussed with a specialist service.
- Do not use/prescribe any topical agents or oral antibiotics for genital ulcers.
- It is imperative that any intramuscular penicillin formulation used should be long-acting Bicillin LA (benzathine penicillin G) 1.8g, as short-acting formulations provide insufficient treatment duration.

PARTNER NOTIFICATION

- **Referral or discussion with a sexual health specialist or service is strongly recommended.**
- Be clear about language: 'partner' implies relationship.
- All sexual contacts within the intervals below should be clinically and serologically evaluated.

Infectious syphilis

- **Primary syphilis:** 90 days plus empirical treatment for syphilis is recommended, as serology may be negative.
- **Secondary syphilis:** 6 months.
- **Early latent syphilis and syphilis of unknown duration where RPR ≥ 1:32:** 12 months.

Late latent syphilis, syphilis of unknown duration with low RPR and tertiary syphilis

- Serologic evaluation of current or last sexual partner and/or serologic evaluation of children if index case is female.

FOLLOW-UP

Infectious syphilis

- Repeat serology at 3, 6 and 12 months.
- Serological cure is defined by consistent four-fold (2 dilutions) drop in RPR titre.
- Failure of RPR titre to decrease fourfold (2 dilutions) within 12 months indicates treatment failure – re-evaluation is necessary.
- A subsequent four-fold (2 dilution) rise in RPR titre is an indication of re-infection – re-evaluation is necessary.

Late latent syphilis and tertiary syphilis (excluding neurosyphilis)

- Repeat serology at 6 and 12 months to ensure remains serofast.
- Fourfold (2 dilutions) increase in titre indicates either treatment failure or re-infection – re-evaluation is necessary.

Summary

- Think of who to test: i.e. MSM, odd symptoms, rash on palm of hands and soles of feet and MSM
- Serial serology may be necessary
- Long acting penicillin

Acknowledgements

- AIDS Epidemiology Group:
  - Rebecca Psutka
  - A/Professor Nigel Dickson
- Dr Ramon Pink
- Staff at Sexual Health including Maureen Coshall who arranged the network diagram
- NZAF
- Patients providing permission for photos