Syphilis in adults

B T Goh

Syphilis is a sexually transmitted disease with protean manifestations resulting from infection by Treponema pallidum. It is systemic early from the outset, the primary pathology being vasculitis. Acquired syphilis can be divided into primary, secondary, latent, and tertiary stages. The infection can also be transmitted vertically resulting in congenital syphilis, and occasionally by blood transfusion and non-sexual contact. Diagnosis is mainly by dark field microscopy in early syphilis and by serological tests. The management in the tropics depends on the diagnostic facilities available: in resource poor countries, primary syphilis is managed syndromically as for anogenital ulcer. The introduction of rapid “desktop” serological tests may simplify and promote widespread screening for syphilis. The mainstay of treatment is with long acting penicillin. Syphilis promotes the transmission of HIV and both infections can simulate and interact with each other. Treponemes may persist despite effective treatment and may have a role in reactivation in immunosuppressed patients. Partner notification, health education, and screening in high risk populations and pregnant women to prevent congenital syphilis are essential aspects in controlling the infection.

Genital ulcerative diseases (GUD), including syphilis, increase the risk of transmission of HIV. In addition, HIV infection may cause more severe manifestations of early syphilis or more rapid progression to late syphilis.

Epidemiology

Prevalence of syphilis in the tropics comes from studies of GUD and serological tests screening. Syphilis is usually the second or third commonest cause of genital ulcers, either chancroid or genital herpes being commoner. Using polymerase chain reaction (PCR), GUD was caused by syphilis in 14% of affected people in Dar es Salaam, Tanzania, 10% in Peru, 5% in the Dominican Republic, 4.2% in HIV positive men and 10.6% in HIV negative men in South Africa, and 10% in Pune, India. In the latter, co-infection with chancroid, herpes, or both occurs in 4%. Serological screening for syphilis in antenatal patients and different population groups showed a variable prevalence. For example, in antenatal clinics, the prevalence was 3% in both Vitoria, Brazil and Nairobi, Kenya, 6.3% in HIV positives and 3.7% in HIV negative women in Kigali, Rwanda, and 13.7% in Ethiopia. In other population groups, the prevalence in STD clinics was 2% in Hong Kong and for women attenders it was 6% in Nairobi, Kenya and 15.1% in Mumbai, India.

The prevalence in sex workers was 7.2–11.6% in Singapore and 32% in Papua New Guinea; 13.3% in long distance truck drivers in south India; 2.3% in factory workers in Harare, Zimbabwe; and in the rural community the prevalence was 11.3% in Lesotho and 2.2% for men and 9.7% for women in the Gambia.

Clinical Presentation

The primary lesion, chancre, presents as an anogenital ulcer that appears 9–90 days after exposure (fig 1). The chancre may not be apparent or not recognised by the patient. The ulcer is classically indurated and painless but may commonly be atypical (painful, soft, multiple). Painful “chancre” can also result from co-infection with chancroid or genital herpes. Extra-anogenital sites include lip, tongue, and tonsils from oral sex and kissing, nipple from kissing or wet nursing of infected babies, and finger with minor abrasion from touching infectious lesions.

Abbreviations: DFA, direct fluorescent antibody; DFM, dark field microscopy; EIA, enzyme immunoassay; GUD, genital ulcerative diseases; PCR, polymerase chain reaction; RPR, rapid plasma reagent; TPPA, Treponema pallidum particle agglutination; VDRL, Venereal Disease Research Laboratory
Regional lymphadenopathy results in moderately enlarged rubbery lymph nodes.

Secondary syphilis presents with generalised rash affecting the palms and soles (fig 2), generalised lymphadenopathy, oro-genital mucosal lesions (fig 3), including snail tract ulcers and condylomata lata (fig 4). The rash which begins as macules becoming papules is usually non-itchy but pruritus may be present, particularly in dark skinned patients. It may be polymorphic, indolent, or transient but is not vesicular or bullous. Less common presentations include patchy alopecia, anterior uveitis, retinitis, cranial nerve involvement, meningitis, laryngitis, gastritis, hepatosplenomegaly including hepatitis, glomerulonephritis, and periostitis.

Tertiary syphilis includes gummatous, cardiovascular, and neurological involvement. Gummatous syphilis (sometimes known as benign tertiary syphilis) can involve the organs or supporting structure and can result in infiltrative or destructive lesions leading to granulomatous lesions or ulcers (for example, palate, nasal septum) or organomegaly. Gumma of the tongue may be prone to leucoplakia leading to malignant change. Late neurosyphilis can cause meningovascular syphilis leading to stroke syndromes, parenchymal involvement leading to general paresis and tabes dorsalis. Cardiovascular syphilis involves the aortic arch which can lead to angina from coronary ostitis, aortic incompetence, and aortic aneurysm.

**DIAGNOSIS**

The diagnosis is by identification of treponemes using dark field microscopy (DFM) or direct fluorescent antibody stain (DFA), staining of treponemes in histology specimen, and by serological tests. In DFM, the treponemes are identified by the morphology and characteristic movements. PCR singly or as part of multiplex testing for *T pallidum* in genital ulcer is available mainly as a research tool. Serological tests are treponemal antigen based such as treponemal enzyme immunoassay (EIA), *T pallidum* particle agglutination (TPPA) or haemagglutination (TPHA) and fluorescent antibody absorption (FTA-abs) tests or “non-treponemal” cardiolipin based tests such as the Venereal Disease Research Laboratory (VDRL) or rapid plasma reagin (RPR) tests.$^4^3$

In primary syphilis, the diagnosis is by DFM or DFA stain of serum from the ulcer or lymph node aspirates. DFM and DFA staining have sensitivities of 74–86% and 73–100% and specificities of 85–100% and 89–100%, respectively. The serological tests may initially be negative and the first tests to be positive are the EIA IgM or FTA-195 IgM tests, with a sensitivity of 86.5–93% and 90%, respectively, while the sensitivity of EIA is 48–77%, VDRL 44–76%, TPHA 50–83%, and FTA-abs is 75–92% for primary syphilis.$^4^4^–^5^2$

The diagnosis of secondary syphilis can be made by DFM of condylomata lata, genital mucosal lesions, skin papules and lymph node aspirate, and/or by serological tests, which are invariably positive, except for prozone phenomenon in the cardiolipin tests$^5^3$ and occasional delayed seroreactivity or false negative in HIV co-infection.

Latent syphilis is diagnosed by the presence of positive serological tests in the absence of clinical evidence of syphilis, and if acquired within the first 2 years is classified as early latent and after 2 years as late. In late latent syphilis the...
false positives for cardiolipin tests (VDRL, RPR) and prozone phenomenon can also occur in HIV infection.54–59

TREATMENT

Treatment guidelines for syphilis from the World Health Organization (WHO),60 Europe,61 United States,62 and United Kingdom63 have been published. Intramuscular benzathine penicillin 2.4 megaunits either as a single dose or weekly in two to three doses is the mainstay of treatment in developing countries. In patients allergic to penicillin, oral doxycycline 100 mg twice daily for 2 weeks is given or tetracycline 500 mg four times daily for 2 weeks or azithromycin 500 mg daily for 1 week. A recent study suggest that azithromycin 2 g as a single dose or as two doses 1 week apart may be as good as benzathine penicillin for the treatment of early syphilis.64 However, the emergence of azithromycin/macrolide resistant T pallidum is cause for concern.46

There are controversies surrounding treatments of pregnant women with a single dose of benzathine penicillin as failures has been reported.46–48 Although a single dose may be effective,69 70 some prefer to treat pregnant women with two to three doses of benzathine penicillin at weekly intervals.64 In one study treatment of pregnant women using a single dose benzathine penicillin improved pregnancy outcome but the risk of adverse outcome remained high when compared with uninfected mothers,65 but these result were not found in another study.66

In HIV positive patients, single dose benzathine penicillin for early syphilis is effective with up to 1 year follow up.66 However, in that study, the dropout rate was high with a serological relapse of 17% and the follow up is not sufficiently long enough to decide whether neurosyphilis could be prevented. A study using benzathine penicillin 2.4 megaunits weekly for three injections among HIV positive and HIV negative women showed similar serological response to conventional therapy for syphilis.71 As treponemal persist despite clinical cure together with the numerous report of progression to neurosyphilis following treatment of single dose of benzathine penicillin, it might be preferable to treat with three doses of benzathine penicillin 2.4 megaunits at weekly intervals. Should neurological signs appear in HIV positive patients, neurosyphilis should be considered in the differential diagnoses. Neurosyphilis should be treated with intravenous benzyl penicillin G 12–24 megaunits daily (2–4 megaunits 4 hourly) for 14 days, intramuscular procaine penicillin G 1.8 megaunits daily together with oral probenecid 500 mg 6 hourly for 17 days, or doxycycline 200 mg twice daily for 4 weeks.

Patients should be warned of the Jarisch-Herxheimer reaction that causes a flu-like illness within 24 hours of starting treatment. This can be serious in patients with neuro/ocular/cardiovascular syphils and may be ameliorated by prenisolone 10–20 mg three times a day for 3 days starting 24 hours before giving antitreponemal treatment.

SYNDROMIC MANAGEMENT

GUD can have multifactorial causes. In regions where there are no diagnostic facilities or where the costs of diagnostic tests are prohibitive, syndromic management of GUD to cover common causes such as chancroid and syphilis is recommended. If there is a history of genital blisters suggestive of genital herpes or in a region endemic for lymphogranuloma venereum or donovanosis, treatment should also cover for these organisms. This usually consists of a single dose of benzathine penicillin for syphilis, and a single dose of ciprofloxacin for chancroid. Syndromic algorithms for GUD were most effective in identifying syphilis and chancroid.72 Adding a RPR test to the algorithm for better detection of syphilis may disadvantage chancroid management. A positive
The RPR test may lead to treatment of syphilis only, and treatment for chancre is missed in patients with dual infection. It is recommended that patients with a positive RPR should also be treated for chancre.28 Syndromic management for GUD, besides covering all causes, may also need to cover other STDs, as shown by a recent study,29 where urethritis commonly coexists with GUD. Of 186 mine workers with GUD in South Africa, 53% had urethritis, of whom 45% had gonorrhoea and 20% had chlamydial or mycoplasma infection; 64.5% were HIV positive. These illustrate the principle that the presence of one STD indicates the presence of others. There is a need for simple and effective oral treatment and adverse interactions between the two infections. There is a need for partner notification and provision of epidemiological treatment to sexual partners, otherwise public health control will fail.

CONCLUSIONS

Syphilis continues to be a major problem in the tropics causing anogenital ulcers and systemic manifestations. Primary syphilis is best treated using syndromic management algorithms tailored to suit the individual country. There is a need for simple reliable on-site test for syphilis so that results are available immediately for treatment to commence and partner notification to take place. The control of syphilis is important for the control of HIV as well as for avoiding adverse interactions between the two infections. There is a need also for simple and effective oral treatment and azithromycin should be evaluated further. The genotype of T pallidum has been sequenced with the potential of research into pathogenesis, novel tests, and a vaccine.27

REFERENCES

Postal screening for chlamydia is unsatisfactory

Evidence from a postal screening study has indicated that the best way of systematic chlamydial screening in the United Kingdom is still to be found. Postal screening, though feasible, gave limited coverage and risked missing those potentially at most risk.

The study within the CLaSS project invited nearly 20 000 people aged 16–39 randomly selected from general practitioner registers in west midlands and Avon to undergo postal screening for genital chlamydia. This entailed those contacted posting back to the practice samples they had taken themselves and a completed questionnaire on risk factors for infection.

Coverage achieved was 73%, and uptake was modest, just 22% to the initial invitation in the 16–24 age group, rising by about 5% with a postal reminder and a further 3% after a house visit or flagging medical records. Women responded better than men—25% versus 19% initially. Coverage was lower in communities with more ethnic minority groups and uptake was less in deprived areas.

Prevalence of infection was 5–6% in men and women aged under 25 but highest among those women who needed most reminders. Under 1% of men over 24 and women over 29 were positive. Having new sexual partners in the past year was a risk factor.

Systematic chlamydia screening could drastically reduce pelvic inflammatory disease. Opportunistic screening will start in England for women under 25, without good evidence of effectiveness. Randomised trials of postal screening in Denmark looked promising, but more are needed to find the right approach in England, it seems.

ECHO

Please visit the Sexually Transmitted Infections website [www.stijournal.com] for a link to the full text of this article.

www.stijournal.com
Syphilis in adults

B T Goh

Sex Transm Infect 2005 81: 448-452
doi: 10.1136/sti.2005.015875

Updated information and services can be found at:
http://sti.bmj.com/content/81/6/448

These include:

References
This article cites 69 articles, 9 of which you can access for free at:
http://sti.bmj.com/content/81/6/448#ref-list-1

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

- Syphilis (793)
- Screening (epidemiology) (991)
- Screening (public health) (984)
- Clinical diagnostic tests (279)
- Confidentiality (230)
- Drugs: infectious diseases (3182)
- Health education (960)
- HIV / AIDS (2514)
- HIV infections (2514)
- HIV/AIDS (2514)
- Pregnancy (472)
- Reproductive medicine (1356)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/