An audit of patients treated for syphilis at Auckland Sexual Health Service

Sunita Azariah

Abstract

Aim As there is no New Zealand data, an audit of patients treated for syphilis at Auckland Sexual Health Service (ASHS) was undertaken to see if management conformed to guidelines and was achieving acceptable outcomes.

Methods Cases were initially identified from laboratory data and were categorised as being either infectious or non-infectious according to clinical and laboratory criteria. Management was compared to recommendations from ASHS treatment guidelines and treatment outcome was assessed by serological response.

Results 109 cases of syphilis were identified including 9 with HIV infection (8%). Men who had sex with men were much more likely to be diagnosed with infectious syphilis than heterosexuals (p<0.0001). Fifty-one percent of infectious cases (n=35) were asymptomatic. Ninety-four percent (n=103) of cases were treated with antibiotic regimens appropriate for their clinical stage. Discrepancy in management occurred most often in the early latent and unknown duration categories. Ninety-eight cases (90%) completed the full 12 months serological follow-up period and 97% (n=92) of those had an adequate serological response to treatment. There were no treatment failures in patients with HIV infection.

Conclusion Current care of patients with syphilis at Auckland Sexual Health Service is achieving acceptable outcomes. Criteria for diagnosing infectious syphilis cases need to be standardised as it has implications for management and disease surveillance. MSM are a major risk group for acquisition of infectious syphilis and regular serological screening is recommended as a large proportion will be asymptomatic.

The incidence of infectious syphilis has increased in recent years in New Zealand, particularly in the Auckland region. Published data indicates that the majority of New Zealand acquired cases of infectious syphilis occur in men who have sex with men(MSM). However because syphilis is not a notifiable condition the real incidence is unknown, as Institute of Environmental and Research Science (ESR) surveillance is limited to voluntary reporting from sentinel sites such as public sexual health clinics.

An Auckland pilot study of enhanced surveillance found that 22% of 61 identified cases of infectious syphilis would not have been reported to ESR as they were treated and diagnosed at non-sentinel clinical sites (unpublished data). The management of syphilis depends in part on whether cases are classified as infectious or not as this determines duration of antibiotic therapy and whether contact tracing is required. This also has implications for disease surveillance as only infectious cases are notified to ESR.
It may be difficult to determine whether a case of latent (asymptomatic) syphilis is infectious or not if the patient has not had previous serological tests for syphilis (STS). It has been proposed by some experts that classifying asymptomatic cases according to non-treponemal test results as either high titre (infectious) or low titre (not infectious), could simplify management.

A retrospective audit of data for patients recently diagnosed and treated for syphilis was undertaken at Auckland Sexual Health Service (ASHS) to determine whether management of syphilis was conforming to treatment guidelines and whether acceptable outcomes were being achieved as there is no New Zealand data. This study was approved by the Northern X Regional Ethics Committee.

Methods

Cases were initially identified from a review of LabPlus laboratory data from the whole of 2007. LabPlus is the laboratory for Auckland District Health Board and carries out all serological testing for syphilis for ASHS.

In order to exclude individuals with possible false positive serology, cases were only included if they had recorded positive STS on at least 2 occasions and had been coded with a diagnosis of syphilis in the electronic medical record. In addition all cases were required to have both a reactive treponemal enzyme immunoassay (EIA) (Bioelisa syphilis 3.0, Spain) and a reactive treponemal particle (TPPA) agglutination test (Serodia, Japan).

Laboratory results were retrieved electronically from the Lab Plus laboratory database. The electronic case notes were then examined and each case was categorised as being either infectious or non-infectious according to pre-defined clinical and laboratory data. As ASHS is a regional service covering 3 different district health boards there are 6 different clinical sites in operation.

Patient information at ASHS is recorded in both paper files and an electronic database. The paper files contain more complete clinical data than the electronic medical record (EMR) which is used more as a back-up as it can be accessed by staff working at all the different clinical sites. Retrieving all the paper notes would have been impractical so these were only reviewed if there was important clinical information missing from the electronic record.

Determining infectiousness of unknown duration latent cases was based on recommendations by Peterman et al, by using rapid plasma reagin (RPR) titres with the following qualifications: the unknown duration category differed in that there was no age restriction, and early latency was defined by a 2-year instead of a 1-year time frame, as ASHS follows the United Kingdom convention in this respect.

Categorisation criteria—

- Primary and secondary syphilis cases: case presented with compatible clinical symptoms and signs such as genital ulceration or rash confirmed by examination.
- Early latent syphilis cases: case had no clinical symptoms or signs of syphilis and one of the following: a history of primary or secondary syphilis symptoms within the previous 2 years; known recent sexual contact with a case of infectious syphilis; a documented four-fold or greater rise in RPR titre; or documented seroconversion to positive STS within the previous 2 years.
- Unknown duration: cases had no clinical signs or symptoms of syphilis, no previous documented STS and an RPR titre greater than 1:16.
- Late latent syphilis cases: cases had no clinical signs or symptoms of syphilis, no previous documented STS and an RPR titre of 1:16 or less. Late latent cases also had to have a sexual history incompatible with recent acquisition of syphilis.

The first three categories were considered infectious in this audit. Adequate treatment response for infectious cases was considered to be a four-fold or greater decline in RPR titre by 12 months. Non-infectious cases were considered adequately treated if they remained serofast over the 12 month follow-up period—i.e. their RPR titres did not change by more than 1 dilution from pre-treatment.
levels. Treatment response was categorised as not known if the patient had not completed the total 12 months follow-up.

**Statistical methods**—In order to investigate whether there was a difference in the demographic characteristics of those who were infectious compared to who were not; a logistic regression was fitted with infectious or not as the outcome (modelling infectious) and age, ethnicity, sexual behaviour and HIV status as explanatory variables. Gender could not be included along with sexual behaviour and HIV status, so was investigated separately including gender, age and ethnicity as explanatory variables.

**Results**

109 cases of syphilis were identified from the 2007 laboratory data. Sixty-eight (62%) of these cases were considered to be infectious: 12 primary, 19 secondary, 26 early latent and 11 of unknown duration. The remaining 41 cases were categorised as having late latent syphilis. There were no cases of neurosyphilis.

**Demographic data**—The total age range of cases was 18 to 70 with a median age of 34. The median age for infectious cases was lower (32) than for non-infectious cases (37). There was a predominance of men diagnosed (79%, n= 86) as has been previously reported.2,3

**Table 1 Summary of demographic and clinical data**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Infectious Cases (n=68)</th>
<th>Non-Infectious Cases (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>18 to 66</td>
<td>25 to 70</td>
</tr>
<tr>
<td>Median</td>
<td>32</td>
<td>37</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>58 (85%)</td>
<td>28 (68%)</td>
</tr>
<tr>
<td>Female</td>
<td>10 (15%)</td>
<td>13 (32%)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>31 (45%)</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>Pacific</td>
<td>6 (9%)</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>NZ Māori</td>
<td>4 (6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Indian</td>
<td>14 (20%)</td>
<td>21 (51%)</td>
</tr>
<tr>
<td>Other</td>
<td>10 (15%)</td>
<td>12 (29%)</td>
</tr>
<tr>
<td>declined</td>
<td>3 (5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Sexual behaviour</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterosexual</td>
<td>24 (35%)</td>
<td>39 (95%)</td>
</tr>
<tr>
<td>MSM</td>
<td>44 (65%)*</td>
<td>2 (5%)*</td>
</tr>
<tr>
<td><strong>Symptoms or signs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>35 (51%)</td>
<td></td>
</tr>
<tr>
<td>Ano-genital ulceration</td>
<td>11 (16%)</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>18 (26%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4 (6%)</td>
<td></td>
</tr>
<tr>
<td><strong>HIV Serostatus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>60 (85%)</td>
<td>40 (98%)</td>
</tr>
<tr>
<td>Positive</td>
<td>8 (15%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td><strong>Treatment response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>60 (88%)</td>
<td>35 (85%)</td>
</tr>
<tr>
<td>No</td>
<td>3 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Not known</td>
<td>5 (7%)</td>
<td>6 (15%)</td>
</tr>
</tbody>
</table>

*P <0.0001.
The majority of cases were of European ethnicity (32%, n=35), followed by Indian (32%, n=35), Other (20%, n=22), Pacific (9%, n=10) and New Zealand Māori (4%, n=4). Three cases (3%) declined to provide ethnicity data on registration at ASHS (Table 1). Indians were over-represented compared to 2006 Auckland population census data while Europeans, Māori and Pacific were under-represented.

There was only weak evidence of an association between infectiousness and age (p=0.11, OR 0.96 [95% CI 0.02–1.01]) or ethnicity [p=0.13, OR European vs Māori/Pacific 0.16 (0.03–0.99) OR Indian vs Māori/Pacific OR 0.27 (0.06–0.29)].

Gender (p=0.30, 0.59 [0.21–1.71]) and HIV status (p=0.60, OR 0.44 [0.02–9.45]) were also not associated with the probability of being infectious. There was however very strong evidence of an association with sexual behaviour; men who had sex with men being far more likely to be classified as infectious (p<0.0001, OR 41.8 [95% CI 7.0–250.1]). The lack of association with any other variables is probably due to the small numbers of cases in this audit.

Clinical presentation—Just over half of the cases classified as infectious had no clinical symptoms or signs (n=35, 51%). Of those who had symptoms, eleven (33%) had anogenital ulceration and 18 (55%) had a rash. Nine cases (8%) had HIV infection, the majority of whom were MSM (n=8) and nearly all had infectious syphilis (n=8) (Table 1).

Eight of the HIV positive cases had been previously diagnosed and the remaining case was diagnosed simultaneously at the time of his syphilis diagnosis. Two MSM seroconverted to become HIV positive several months after their diagnoses and treatment for syphilis.

Concordance with treatment guidelines—ASHS treatment guidelines are closely based on Centres for Disease Control (CDC) guidelines, that recommend either benzathine penicillin G 2.4 mega units (MU) stat as an intramuscular injection (IMI) or doxycycline 100mg bd orally for 14 days for treatment of early infectious syphilis (primary, secondary, early latent).

Longer courses of antibiotics are recommended for treatment of late syphilis; either benzathine penicillin 2.4 G MU IMI weekly for 3 doses (total 7.2 MU) or doxycycline 100mg bd orally for 28 days. Accordingly the majority of cases (93%, n=101) in this audit had been treated with benzathine penicillin.

Discrepancy with treatment guidelines occurred most often in the early latent and unknown duration categories (both classified as infectious in this audit). The majority (73%, n=19) of the early latent cases were treated with regimens recommended for early infectious syphilis while 7 were over-treated (Table 2). Most of the unknown duration category (82%, n=9), were treated with regimens recommended for late syphilis although most (n=8) had been entered in the electronic medical record as having a diagnosis of infectious syphilis.

In contrast all of the cases of late latent syphilis (non-infectious) and primary and secondary syphilis (infectious) received the recommended treatment for their classification category (Table 2). Reassuringly none of the cases in this audit were under-treated and all were treated with antibiotic regimens recommended in the treatment guidelines.
Table 2. Treatment regimens according to category

<table>
<thead>
<tr>
<th>Category</th>
<th>Benzathine penicillin 2.4 MU</th>
<th>Doxycycline 14 days</th>
<th>Benzathine penicillin 7.2 MU</th>
<th>Doxycycline 28 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>11</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Secondary</td>
<td>18</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Early latent</td>
<td>18</td>
<td>1</td>
<td>6*</td>
<td>1*</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>0</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Late Latent</td>
<td>0</td>
<td>0</td>
<td>37</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>49</td>
<td>3</td>
<td>52</td>
<td>5</td>
</tr>
</tbody>
</table>

*Over-treated.

Treatment response and follow-up—Ninety-eight (90%) cases completed the 12 month follow-up period and in 11 cases outcome was not known (Table 1). Two of the 11 cases who did not complete follow-up were known to have moved out of the area and the remainder (n=9) did not respond to recall attempts for follow-up blood tests. Ninety-seven per cent of those who completed 12 months of serological follow-up had an adequate treatment response within that time-frame (n= 95).

Eight of the non-infectious cases (late latent) remained serofast at RPR titres of 1:8 and one was serofast at a titre of 1:16 following treatment (Figure 1). Only 39(57%) infectious cases attended for all the recommended follow-up blood tests. However the majority (88%, n=60) did have sufficient blood tests to ascertain that they had had an adequate serological response to treatment.

ASHS treatment guidelines recommend a baseline RPR test on the day of treatment for infectious cases, then follow-up tests at 1 month, 2 months, 3 months, 6 months and 12 months after treatment. Late latent cases are recommended to have a baseline RPR test and then repeat tests at 6 and 12 months.

For public health reasons, ascertaining serological response to treatment is more important for infectious cases than non-infectious cases. In this audit, only 51 (47%) cases had had an RPR titre performed on the day of treatment, 35(32%) had had one within 7 days of treatment and the remainder had not had an RPR for 8 days or longer before treatment.

There were only 3 possible serologically defined treatment failures among those who were followed up for 12 months (Figure 1). None of these 3 cases had HIV infection. One was a pregnant woman with syphilis of unknown duration who was treated at 30 weeks gestation with benzathine penicillin 7.2 MU over 3 weeks (pre-treatment RPR was 32). She was subsequently delivered of a healthy infant (the baby’s RPR was 4 at birth) and she remained serofast with an RPR of 16, 12 months after completing her treatment so in retrospect she was probably misclassified as infectious.
One woman with early latent syphilis also did not have an adequate decline in her RPR titres by 12 months after treatment. However she was re-treated half-way through her 12 month follow-up as there was a possibility of re-infection from an untreated partner and she did not respond to attempts at recall for serology after her second treatment.

The third case of possible treatment failure was a male with syphilis of unknown duration and he subsequently had an adequate decline in RPR after 2 years follow-up without requiring re-treatment. The first 2 cases had not had an RPR titre taken on the day of treatment and this may have impacted on assessment of treatment response.

**Outcome of partner notification**—Complete documentation at ASHS on outcome of partner notification at ASHS is available only from the paper files however as noted in the methods section it was impractical to pull all the full clinical notes. Therefore
this data is only derived from what was recorded in the electronic medical record and so should be interpreted with appropriate caution.

In 17 of the audit cases (15.5%) there was no documentation in the EMR about outcome of contact tracing. However 8 of these 17 cases had reported multiple anonymous contacts, 3 reported contacts who lived overseas, 2 had left the Auckland area and 1 lived overseas. So for the majority (82%) of these 17 cases contact tracing was not possible. For the remaining cases, 109(68.5%) out of 159 possible contacts documented in the EMR had apparently been notified they were a contact of syphilis. However what proportion of these contacts actually presented to a health practitioner for screening and treatment is unknown. This is because it is not usually possible to link someone who presents to ASHS as a syphilis contact to a particular index case unless they are identified as a regular partner of the index case.

Also some contacts may choose to go to their GP or another health service for screening and treatment. (For recommendations regarding contact tracing look back periods for syphilis the reader is referred to either the UK National guidelines for syphilis or the CDC guidelines for the management of sexually transmitted diseases).

Discussion

Adequate follow-up was achieved for 90% of patients treated and diagnosed with syphilis at ASHS and nearly all of those had a satisfactory serological response to treatment (97%). As noted above, there were only 3 possible serologically defined treatment failures; all in patients with latent syphilis. Of these cases-one may have been re-infected, one was pregnant (pregnancy can affect specificity of non-treponemal tests due to production of anti-phospholipid antibodies) and the third had an adequate serological response after 2 years of follow-up.

Data from non-randomised trials report re-treatment is required in 5% to 11% of patients treated for infectious syphilis because of inadequate decline in RPR titre but this situation appears to be uncommon at ASHS. It is acknowledged that a small number of patients did not return for follow-up and so treatment success may have been over-estimated in this audit.

ASHS 12-month follow-up rates(90%) were better than those reported in 3 audits published from the UK in which adequate follow-up ranged from 32.5% to 74% of treated patients. However it is acknowledged that our patient population may not be directly comparable to the populations in those audits.

Adherence to treatment guidelines by ASHS staff was also better than that reported in an audit of early syphilis management by specialist genito-urinary medicine clinics in the UK, in which 14% of clinics did not routinely use recommended antibiotic regimens. ASHS partner notification outcomes appear to be satisfactory when compared to international recommendations, with 68% of contactable partners recorded as having been notified. However as stated above there are limitations as to the accuracy of this data. UK national guidelines recommend that at least 60% of contactable partners should attend for screening and treatment, although they comment that this standard may not be achievable for all settings.
Three cases of syphilis of unknown duration in this audit had a diagnosis of non-infectious syphilis entered into the electronic medical record and so would not have been reported to ESR. Assessment of infectiousness of syphilis in latent (asymptomatic) cases is problematic particularly if there has been no previous testing or if previous results are inaccessible. The clinician frequently has to make a judgement based on sexual history, clinical examination and titres of non-treponemal (RPR/VDRL) tests.

A recent CDC audit found that misclassification of latent syphilis was common with only 48.4% agreement for early latent cases and 49.7% for those of unknown duration. Those results had important implications in terms of treatment, partner notification and disease surveillance. The authors proposed that the current system of staging latent syphilis be dropped in favour of reporting cases as either having low or high titres on non-treponemal tests (VDRL and RPR), with high titre cases being managed as infectious and low titre cases being managed as non-infectious.

There is a clear relationship between duration of infection and the titre of non-treponemal tests. The natural course of untreated disseminated syphilis is to resolve spontaneously, however relapses can occur within the first 2 years of infection but after this time the person is non-infectious to sexual contacts. Non-treponemal test titres rise rapidly after initial infection with syphilis, remain high during the first year and then gradually decline even if the person is untreated.

Sensitivity of non-treponemal tests is much lower in late syphilis (approximately 70%) because of sero-reversal and this correlates with lack of infectiousness. A four-fold or greater decline in titre after treatment also correlates with a high probability of treatment success, however positive low-level titres in the VDRL (<1:16) or the RPR test (≤1:16) sometimes persist despite adequate treatment. This was demonstrated with this data, with 9 cases of late latent syphilis remaining serofast with RPR titres of 1:8 or higher at 12 months. There is little evidence to convincingly indicate that patients such as these harbour replicating treponemes.

Clinical judgement plays a large role in management of latent syphilis with most clinicians preferring to over-treat than under-treat. Fifty-one per cent of cases of infectious syphilis in this audit lacked symptoms and it is recommended that advice be sought from a specialist experienced in managing syphilis when treating such cases, particularly with respect to contact management.

MSM are a known high-risk group for acquisition of syphilis in New Zealand and it is worrying that both the incidence of syphilis and HIV is continuing to increase. Syphilis can enhance both transmission and acquisition of HIV, although the proportion of MSM with HIV co-infection (18%) was relatively low in this sample compared with international data. Two men did however seroconvert to HIV during follow-up and it is strongly recommended that all cases of syphilis be tested for HIV infection.

There is some clinical debate about the management of people with syphilis and HIV co-infection because of the concern that immune deficiency may increase the risk of developing neurosyphilis or increase risk of relapse of syphilis in these individuals. Early neurosyphilis-type syndromes such as syphilitic meningitis and...
meningovascular syphilis have been reported as being more common in HIV infected individuals.\textsuperscript{17,18}

Prospective studies comparing the outcome of HIV infected and HIV negative individuals treated with standard therapy have found that HIV infected individuals have similar serological responses to treatment\textsuperscript{19–24} although one of these studies\textsuperscript{19} was limited by poor follow-up rates. The number of syphilis cases with HIV co-infection in this audit is small, however all those who completed 12 months of follow-up did have an adequate serological response to standard therapy. Most international guidelines do not recommend different management of HIV infected patients with early infectious syphilis.\textsuperscript{5,6}

In conclusion current management of syphilis at ASHS is largely conforming to treatment guidelines and has good outcomes in terms of treatment response and follow-up although more care needs to be taken in ensuring that cases of infectious syphilis in particular, have an RPR test on the day of treatment. Assessment of latent syphilis can be difficult even for experienced clinicians and expert advice is recommended when managing syphilis so that correct treatment and follow-up occurs.

MSM are a high-risk group for acquisition of infectious syphilis and HIV although New Zealand rates of co-infection are lower than some international data. As a large proportion of infectious cases in this audit were asymptomatic it is recommended that STS should be part of routine STI testing particularly for MSM.

\textbf{Competing interests:} None known.

\textbf{Author information:} Sunita Azariah, Sexual Health Physician, Auckland Sexual Health Service, Greenlane Clinical Centre, Auckland District Health Board, Auckland

\textbf{Correspondence:} Dr Sunita Azariah, Auckland Sexual Health Service, Greenlane Clinical Centre, Private Bag 92024, Auckland, New Zealand. Fax: +64 (0)9 6309783; email: SunitaA@adhb.govt.nz

\textbf{References:}

1. Sexually Transmitted Infection in New Zealand: Annual Surveillance Report 2008. Institute of Environmental Science and Research Ltd.\textsuperscript{1}


6. Centres for Disease Control. Sexually Transmitted Diseases Treatment guidelines 2006.\textsuperscript{6}


9. Chauhan M, Srisha B, Sankar KN, et al. Audit of the use of benzathine penicillin, post-


