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**An audit on the management and outcomes
of infants at risk of congenital syphilis in the
Top End of the Northern Territory, Australia,
2005-2013**

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An audit on the management and outcomes of infants at risk of congenital syphilis in the Top End of the Northern Territory, Australia, 2005-2013

Natalia B.A. Rode, Nathan Ryder, Jiunn-Yih Su

Abstract

Introduction

Congenital syphilis (CS) remains a condition of serious clinical and public health importance, particularly in the Aboriginal populations of northern Australia, which have seen a recent resurgence in cases. In 2005, the Northern Territory (NT) Centre for Disease Control (CDC) published guidelines for management of infants at risk of CS. We audited the management and outcomes of infants at risk of CS who were born between 2005 and 2013 in the Darwin and Katherine regions of the NT.

Methods

Data, including serology, clinical examination, treatment, follow-up and infant outcomes at 12 months, were extracted from the Syphilis Register, medical and pathology records to assess clinician compliance with the CDC guidelines.

Results

Thirty-three infants were identified as being at risk of CS, 26 low risk and 7 high risk. Hospital management at birth conformed well with the guidelines, with 85% of low risk, and 100% of high risk infants receiving treatment and 92% of low risk and 86% of high risk having appropriate serology. Follow-up was poorly compliant, with only 48% of infants completing serological follow-up and less than 15% undergoing clinical examination. No definitive case of CS was identified among the at-risk children.

Conclusion

Overall, peri-natal management of infants was performed well, but follow-up was poor. Effective systems to transfer care from hospitals to primary care are required to improve this. The fact that no infant had direct evidence of syphilis infection suggests consideration should be given to modifying the Australian surveillance case definition.

Introduction

Congenital syphilis is caused by mother-to-child-transmission of the bacterium *Treponema pallidum*. Recent studies estimated that over half of untreated or inadequately treated syphilis infections during pregnancy result in adverse outcomes, including stillbirths and fetal death during second or third trimester, neonatal deaths, premature and low birth weight infants and infants with serious disabilities, such as deafness, blindness and intellectual disability.^{1, 2} Globally, in 2008, an estimated total of 1.36 million pregnant women had probable active syphilis, which resulted in over half a million adverse pregnancy outcomes.³ Congenital syphilis-related morbidity and mortality should be preventable as a public health problem if all pregnant women receive appropriate antenatal care and infected women are detected and treated adequately by 20 weeks of gestation.⁴

The rate of congenital syphilis in Australia declined from 8.6 per 100,000 live births in 1995 to 0.32 in 2012, a low rate by international standards (calculated using surveillance data from Australian Department of Health website⁵ and birth data from website of Australian Bureau of Statistics^{6, 7}). However, the national rate data calculated using national live birth numbers as the denominator masks far higher rates occurring in Aboriginal and Torres Strait Islander people (henceforth respectfully referred to as Aboriginal people), especially those residing in remote areas of northern and central Australia. The notification rate of infectious syphilis in the Northern Territory (NT) was by far the highest among all jurisdictions in Australia in the 1990s⁸⁻¹² and early to mid-2000s,¹³ and the rates were especially high in the Aboriginal population. Consequently, there were comparatively high numbers of congenital syphilis cases reported during this period, with the NT accounting for 17 of 21 and 13 of 19 cases of congenital syphilis notified across Australia in 2000 and 2001 respectively.⁵ While notifications of congenital syphilis have declined considerably from their peak since then, there has been a recent resurgence in northern Australia and the rate of congenital syphilis for the Aboriginal

population in 2015 was 16.2 per 100,000 live births¹⁴, substantially higher than the same rate for the non-Aboriginal population in Australia. Congenital syphilis remains a condition of ongoing and serious clinical and public health importance in Australia.

In order to enhance the management and control of syphilis, the NT Centre for Disease Control (CDC) employs a team of nurses to maintain a computerised register of syphilis testing, treatment and follow-up (Syphilis Register Information System, SRIS). The register receives notification of all positive syphilis results and provides clinical and information support to clinicians in the management of all syphilis cases, including congenital syphilis. The management of confirmed and at-risk cases of congenital syphilis in the NT is guided by the locally developed guidelines (hereafter referred to as the CDC guidelines)¹⁵ released in July 2005 broadly based on the guidelines of the Centers for Disease Control and Prevention of the United States.¹⁶ The guidelines follow a risk based approach with infants classified as “no risk”, “low risk” or “high risk” and recommend a management protocol according to the level of risk. In particular, the guidelines recommended that presumptive treatment be given to all infants assessed to be at risk of congenital syphilis (both low and high risk infants).

Despite the relatively high numbers of congenital syphilis cases in the NT, no previous study has been conducted to examine the management and outcomes of infants at risk of congenital syphilis. Nor, to our knowledge, has one been conducted elsewhere in Australia. In this audit study, we aimed to investigate if the management of infants at risk of congenital syphilis had been carried out in compliance with the CDC guidelines and to ascertain the outcomes of these infants at 12 months of age. It is hoped that the findings of the audit will provide practical information and evidence for improving the prevention and management of congenital syphilis.

Methods

The audit period was from the implementation of the CDC guidelines in August 2005, to December 2013. Cases were defined as infants born to mothers residing in the Katherine and Darwin districts of the Top End of the NT who were classified as being at low or high risk of congenital syphilis according to the CDC guidelines and as recorded in the SRIS.

The CDC guidelines define an infant to be at “low risk” of congenital syphilis if the mother was diagnosed with syphilis in pregnancy and received adequate treatment for her syphilis at least 30 days prior to delivery. If the treatment was inadequate or not completed at least 30 days prior to delivery, the infant is deemed to be at “high risk”. Immediately after birth all “at-risk” (i.e. low or high risk) infants require, at a minimum, full physical examination, syphilis serology and a penicillin course of varying duration, depending on the categorised risk. The infant then requires follow-up at 3 and 6 months with repeat clinical examination and syphilis serology. If the syphilis serology remains reactive at 6 months, it is to be repeated at 12 months of age.

Data was extracted from a variety of sources for this audit. From SRIS we first identified the infants at low or high risk on the basis of antenatal diagnosis and treatment of maternal syphilis. For these infants we collected any recorded paired maternal and infant serology at birth, neonatal clinical examination findings and treatment, records of subsequent follow-up at 3, 6 and 12 months of age and the outcome in terms of clinical signs of congenital syphilis and serology results, including both treponemal and non-treponemal tests. In the cases where the information was not available in the SRIS, we also collected data from the medical records at Royal Darwin Hospital (RDH), Katherine District Hospital and via the Shared Electronic Health Record (SEHR, an opt-in online clinical information system connected to a patient’s NT computerised hospital and community health records, enabling sharing of health information) and Primary Care Information System (PCIS), a shared clinical database used by NT

government-serviced remote health clinics. Finally, laboratory results for syphilis serology for the infants and mothers were retrieved from the private pathology laboratory that provides laboratory testing to the vast majority of primary care services in the two districts included in this study. Follow-up requirements were defined as those required for the original risk categorisation recorded at the time of diagnosis, regardless of whether that classification was retrospectively determined to be correct by the investigators.

We examined the management of each at-risk infant against the CDC guidelines’ recommendations, to assess the level of clinician compliance with regards to serological testing, clinical examination and treatment. Additionally, we assessed the clinical outcomes, with a focus on the follow-up serology results.

This audit was supported by the CDC and approved by the Human Research Ethics Committee of NT Department of Health and Menzies School of Health Research (HREC 2014-2,258).

Results

A total of 33 infants were identified from the SRIS database as being at risk of congenital syphilis in the Darwin and Katherine districts during the study period, including 26 categorised as low risk and 7 as high risk.

A. Compliance with CDC guidelines (summarised in Table 1)

Treatment

All low risk infants require a single dose of intramuscular benzathine penicillin at 37.5mg/kg. High risk infants should receive intravenous benzyl penicillin 50mg/kg/dose, 12 hourly for 10 days. Four (57%) of the high-risk infants and 19 (73%) of the low-risk infants received treatment as per the guidelines. The remaining three high-risk infants (43%) received alternative treatment regimens with either 3rd generation cephalosporins or intramuscular penicillin replacing part of the treatment course. A further three low

risk (11.5%) infants were treated as high risk, receiving a 10 day course of intravenous and/or intramuscular benzyl penicillin.

Serology

At birth

All mothers and neonates require paired serology at delivery. Six of 7 high-risk infants had paired serology done at the time of delivery. All infants had Rapid Plasma Reagin (RPR) levels lower than their mother's, but remained categorised as high risk due to inadequate maternal treatment of syphilis. In the low risk group, 24 of 26 (92%) had paired serology taken at birth. Five of these infants (21%) were incorrectly classified in SRIS. Three should have been classified as not being at risk, as both they and their mothers had non-reactive RPRs at the time of delivery and file review suggests that reactive treponemal tests in pregnancy were due to past treated infection. Two should have been classified as high risk on the basis of inadequate maternal treatment, although both had paired RPR levels lower than their mother's at the time of delivery. One infant incorrectly had cord rather than venous blood specimen taken with subsequent discrepancy in SRIS classification (low risk) and treatment by the paediatric team (as high risk).

At 6 months

Both high and low risk infants require repeat syphilis serology at 6 months of age. Two high risk infants (29%) had 6 month syphilis serology performed. For one of these infants their serology was non-reactive and they did not require further serological follow up. The other had a persistently reactive treponemal result and insufficient blood for RPR. Five of the low risk infants (19%) had 6 month serology performed, of which three had non-reactive results and did not require further serological testing.

At 12 Months and subsequently

Three of the 6 high risk infants requiring repeat serology at 12 months had this performed.

Two (8.7%) of the 23 low risk infants requiring repeat serology at 12 months had it performed at this time. A further six (26%) had serology done within 24 months from birth. One child had serology performed at nearly 8 years of age. For all of these children their treponemal tests were negative and they do not require further serological follow-up. Serology results remain outstanding for three high risk (43%) and 14 low risk infants (61%).

Clinical examination

All infants at risk of congenital syphilis require full clinical examination by a paediatrician at birth and by their local doctor at 3 and 6 months of age. High risk infants must be reviewed by a paediatrician at 6 months of age.

At birth

All seven high-risk and 25 of 26 low-risk infants were examined at birth. One low risk infant was found to have skin desquamation, a potential cutaneous manifestation of syphilis, however as this resolved by day two it was not thought to indicate congenital syphilis. Two of the high-risk infants were of low birth weight but there were no other abnormal clinical findings to indicate congenital syphilis.

3 months

One of the 7 high-risk infants was followed up specifically to review congenital syphilis risk. Of the low-risk infants, three of the 26 (11.5%) were followed up by a paediatrician at 3 months of age specifically because of their risk of congenital syphilis. One low-risk infant was seen by the paediatrician for other concerns, but the issue of congenital syphilis was addressed. Three high risk and four low risk infants were seen by health professionals for other reasons and the congenital syphilis risk was not addressed. There was no documentation of the three remaining high risk infants (43%) and 18 remaining low risk infants (69%) having been reviewed.

6 months

At 6 months of age, one of the 7 high-risk infants had clear documentation of having been seen by a paediatrician to follow up congenital syphilis risk. One other high-risk infant had documentation on the SEHR of having been reviewed, but it is unclear if this was by a paediatrician or not. Of the 26 low risk infants, four (15%), were seen by a paediatrician specifically for congenital syphilis risk. Three children were seen by paediatricians for other reasons and it was unclear if their syphilis risk was addressed. Five high risk (71%) and 22 low risk (85%) infants have outstanding clinical examination as per the guideline recommendations.

B. Clinical outcomes

No definitive diagnosis of congenital syphilis was made during the study period, on the basis of no infant having RPR at least 4-fold maternal, clinical lesions or positive *T pallidum* PCR. Nor

was any infant found to have abnormal clinical findings suggestive of congenital syphilis during follow-up.

Discussion

Our audit found that while the assessment and management at birth had almost always been completed in all identified cases in line with the CDC guidelines, the subsequent clinical and serological follow-up was performed poorly. Interestingly and notably, our audit did not find any confirmed case of congenital syphilis out of the 33 at-risk infants examined.

The majority of infants received serology, physical examination and treatment as per the guidelines at birth. For the high risk infants who received alternative treatment, this was most commonly because of failure of the intravenous cannula and an appropriate intramuscular antibiotic (penicillin or 3rd generation cephalosporin) was given instead. Those low risk infants who received alternative treatment usually did

Table 1: Audit results on clinician compliance with the Centre for Disease Control guidelines for managing infants at risk of congenital syphilis, Top End, NT, 2005-2013

Category	High Risk (n=7)		Low Risk (n=26)	
Treatment				
First line treatment	4	(57%)	19	(73%)
Alternative treatment	3	(43%)	3	(11.5%)
Total treated	7	(100%)	22	(85%)
Serology				
At birth	6	(86%)	24	(92%)
6-months	2	(29%)	5	(19%)
12-months	3	(50%)*	2	(8.7%)**
> 12 months	0		7	(30%)
Outstanding serology	3	(43%)	14	(61%)
Clinical examination				
at birth	7	(100%)	25	(96%)
3 months***	1	(14%)	3	(11.5%)
6-months***	1	(14%)	4	(15%)

* n = 6, as one infant had negative serology at 6 months of age and did not require further follow-up.

** n = 23 as 3 low risk infants had negative serology at 6 month and did not require follow-up at 12 months.

*** Please see limitations described under Discussion.

so because they were being treated conservatively as high risk cases and therefore received more-than adequate treatment. However, the subsequent community follow-up was very poorly compliant with the guidelines, with 52% of all at risk infants still requiring follow-up of outstanding serology and less than 15% undergoing the required clinical examination. Given that the CDC guidelines do not require the comprehensive investigation of every high risk infant, such as lumbar puncture and long bone x-rays, as recommended in other guidelines,^{17, 18} adherence to follow-up recommendations is vital to ensuring no cases of congenital syphilis are missed.

The high level of compliance with recommended assessment and treatment at birth may reflect the role of active support by Syphilis Register staff and the broad awareness of congenital syphilis among local hospital obstetric and paediatric teams. In considering reasons behind poor community completion of the follow-up components of the CDC guidelines, we explored communication between the hospitals and the primary care clinics and found that documentation of this was frequently missing. Discharge summaries are the primary mode of communication between hospitals and primary care clinics, and they need to be completed accurately and delivered in a timely fashion. On examining these, we found that while most infants had discharge summaries completed, many were not addressed to a primary care clinic, and the majority did not specify that the infant was at risk of congenital syphilis and that follow-up was required. It is therefore not surprising that correct follow-up failed to occur for so many at-risk infants. Because of this finding, the Syphilis Register has revised its operation protocol to ensure clinicians are aware of infants returning to their community who require follow-up management. The Register also monitors the results of follow-up serology and actively alerts primary care clinics if further management is required. Arrangement has been made by the Register staff to undertake the outstanding follow-up for the audited children.

While all 7 high risk cases met the Australian congenital syphilis surveillance case definition,¹⁹ no infant was found to have evidence of congenital syphilis infection when applying the clinical criteria outlined in Australian Management of Perinatal Infections Guideline.²⁰ The Australian surveillance case definition does not require evidence of actual infection of the neonate, as inadequate treatment of the mother in conjunction with a reactive non-treponemal test is sufficient evidence to define a probable case. By comparison, the US and European case definitions both require evidence of infection of the neonate in the form of either clinical features or direct detection of *T pallidum* organisms by nucleic acid amplification, dark field microscopy or histological stain.^{21,22} The Australian case definition may reflect the assumption behind the CDC clinical guidelines, that is that full assessment and follow-up is impractical in the remote setting, where most congenital syphilis cases occur in Australia. This audit demonstrates that the birth assessment is performed reliably and should allow for a stricter case definition requiring direct clinical and/or laboratory evidence of infection of the neonate to be applied.

The key limitation of our data relates to assessing patient files to determine community follow-up. We used PCIS and SEHR to view primary health centre records. The individual NT government-run remote health clinics joined up to the PCIS system, and concurrently to SEHR, at various times from 2004 to 2010. Some, but not all, old files were transferred to the new system. The non-government health services, such as the Aboriginal Medical Services, use their own clinical database systems rather than PCIS, but offer SEHR to all their patients. As SEHR is an opt-in system, not all patients may have joined up. In most cases, if serology had been performed in the community, we should have been able to access those results through the private pathology laboratory servicing the two districts included in this audit. Had the children been seen by a visiting paediatrician, we expected that there would have been documentation of this in the RDH or Katherine Hospital files. Taking into account other common limitations of assessing medical records, such as quality and

completeness, we believe the number of children who had received follow-up complying with the guidelines but for whom we could not find any documentation should be small.

In conclusion, compliance with the assessment and presumptive treatment of infants at risk of congenital syphilis was very good in the at-risk children audited; however the subsequent follow-up was poor. Better and more effective systems to transfer care from hospitals to primary care services are required to improve the follow-up of infants at risk of congenital syphilis. Finally, the current Australian congenital syphilis case definition appears to capture a high proportion of cases that do not have evidence of actual neonatal infection and consideration should be given to modifying the definition to require direct clinical or laboratory evidence in the neonate.

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