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Horizon Scanning Technology Prioritising Summary

Perinatal Hepatitis C Screening

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PRIORITISING SUMMARY

REGISTER ID: **000300**

NAME OF TECHNOLOGY: **PERINATAL HEPATITIS C SCREENING**

PURPOSE AND TARGET GROUP: **UNIVERSAL SCREENING OF INFANTS FOR HEPATITIS C VIRUS.**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

- ☒ Yet to emerge
- ☐ Experimental
- ☐ Investigational
- ☐ Nearly established
- ☐ Established
- ☐ Established *but* changed indication or modification of technique
- ☐ Should be taken out of use

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- ☐ Yes — ARTG number
- ☐ No
- ☒ Not applicable

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
European Multicentre	✓		
USA	✓		

IMPACT SUMMARY:

Although Australian guidelines recommend screening all infants of high-risk mothers, screening in Australia is determined by individual institution policies and is not performed uniformly. This prioritising summary examines the controversies in screening neonates for Hepatitis C.

BACKGROUND

Recently, there has been a call for a standardised approach to, and nationwide dissemination of, clinical practice guidelines regarding Hepatitis C virus (HCV) screening in infants born to women who are HCV positive (Hardikar et al 2006). Internationally, there has been an ongoing debate of whether to test universally, selectively or not at all (Pembrey et al 2005; Resti et al 2003). Several factors have contributed to this debate, including: the lack of available therapy for the infant; low

prevalence in the general population; the general lack of symptoms in HCV infected children; the social stigma of being HCV positive; lack of consensus on whether to perform antenatal (i.e. on the mother) HCV tests selectively or universally. The general consensus is beginning to favour selective testing of infants of mothers who are HCV positive, especially mothers who are HCV RNA positive (i.e. experiencing a period of viraemia and the highest risk of vertically transmitting HCV). Currently RANZCOG recommends "All pregnant women should also be offered Hepatitis C screening and those at high risk should be actively encouraged to undergo screening." (RANZCOG 2006). No Australian recommendations for neonatal-HCV screening could be identified.

CLINICAL NEED AND BURDEN OF DISEASE

In Australia, a cumulative total of 225,000 diagnoses of HCV infection were reported to the end of 2005, with 9,700 new HCV infections occurring in 2005. The HCVPWG estimated that there were actually 264,000 people living with HCV antibodies in 2005. The discrepancy between the reported and estimated HCV cases is due to reporting of HCV by all states only beginning in 1995; the low levels of testing in high risk populations; and, the generally asymptomatic nature and long latency of HCV infection. It is estimated that around 80 percent of HCV infections result from injecting drug use. In the general Australian population HCV prevalence ranges from 1 - 2.3 per cent (HCVPWG 2006). About 80 percent of HCV infections are chronic and can lead to sequelae including cirrhosis, liver failure and hepatocellular carcinoma. Of every 1,000 people with chronic HCV infection approximately 200 will develop cirrhosis and of those 2-8 will develop hepatocellular carcinoma per year (Giles et al 2003).

The prevalence in antenatal patients is approximately 1 percent (Garner et al 1997; Spencer et al 2003). One study reported a prevalence of 1.45 percent (95% CI [0.97, 2.1]) in 2,000 consecutive antenatal patients in Melbourne (Sfameni et al 2000). The rate of vertical transmission of HCV is around 4-6 percent and 13-22 percent for mothers positive for both HCV and HIV (Conte et al 2000; Dore et al 1997; Yeung et al 2001; EPHN 2001). Assuming a prevalence of 1.3 percent, it is estimated that in Australia, 134 children are infected perinatally with HCV each year (HCVPWG 2006).

Drug-based therapy for infants with HCV is not recommended (Davison et al 2006) but identifying the individuals that are HCV positive is important for monitoring and treatment later in childhood. Childhood treatment trials have reported moderate success with some children tolerating therapy better than adults. Sustained virus rates[1] of 36 percent for interferon monotherapy (Jacobson et al 2002) and 46-61 percent for interferon and ribavirin combination therapy (Suoglu et al 2002; Wirth et al 2002; Gonzalez-Peralta et al 2005) were reported.

[1] HCV RNA becoming undetectable during and after drug therapy

DIFFUSION

No established programs for routine perinatal screening of infants were identified, either in Australia or internationally. The UK National Screening Committee recommends "Antenatal screening for Hepatitis C should not be offered" (UK NSC 2006). The UK Department of Health recommends offering HCV testing to "Babies born to mothers known to be infected with HCV" (UK DH 2004).

A recent editorial in the Medical Journal of Australia recommended the establishment and dissemination of a program for perinatal HCV screening (Hardikar et al 2006).

COMPARATORS

HCV testing can be requested by patients at their general practitioner.

EFFECTIVENESS AND SAFETY ISSUES

A small study (level IV screening evidence)(Mok et al 2005) was designed to find the time of transmission from the mother to child. The site of vertical transmission was found to be intra-uterine in 31 percent (17/54; 95% CI [19, 46]) of cases and peripartum in 50 percent (27/54; 95% CI [36, 64]) of cases. It was concluded that transmissions of postnatal origin were unlikely.

In a study involving HCV and, HCV plus HIV-1 co-infected pregnant women, it was found that transmission of HCV to the infant occurred in 3.7 percent (3 of 80; 95% CI [0.4, 7.9]) HCV infected cases, and also in 15.1 percent (25 of 165; 95% CI [9.6, 20.6]) of HCV plus HIV-1 co-infected cases (level IV screening evidence). The overall transmission rate was 11.4 percent (28 of 245; 95% CI [0.4, 7.9]). This study also found that there was a small benefit to caesarean delivery compared to vaginal delivery, a 5.6 percent chance of HCV transmission for caesarean compared to a 13.9 percent chance for vaginal delivery. Intravenous drug use, prematurity, and low birth weight were not associated with transmission of HCV. Testing in this study was performed using a second-generation enzyme-linked immunosorbent assay (EIA) and a recombinant immunoblotting assay (RIBA II or RIBA III) for HCV-seropositivity, and reverse transcriptase polymerase chain reaction (RT-PCR) to detect HCV RNA. No information was given as to the sensitivity or specificity of the diagnostic assay used in this study (Tovo et al 1997).

A study published in 2005 (level IV screening evidence)(Mast et al 2005) found that the transmission rate from HCV infected mother to child was 3.8 percent, and from HCV plus HIV-1 co-infected mother to child was 25 percent. Transmission only occurred if the mother was HCV-RNA positive. Noting inconsistent results in other studies the study authors recommended that the mother's HCV RNA level cannot be used to predict the risk of transmission to the infant. Breast feeding and other post-natal modalities were not responsible for transmission to the infant. The study recommended testing using RT-PCR as all infants that were confirmed HCV positive were found to be positive with respect to HCV RNA. Conversely, they reported that

anti-HCV antibody testing of infants was more likely to give false positive results, potentially due to passively acquired maternal antibodies, unless delayed until after 18 months of age. Other factors increasing the risk of transmission were prolonged time between membrane rupture and delivery and, intra-uterine foetal monitoring. Infected infants were followed up over 5 years and although none displayed clinical hepatitis, there were indications of mild liver disease (raised serum alanine aminotransferase levels).

A large study in 2000 (level IV screening evidence)(Conte et al 2000) examined the vertical transmission of HCV in 15,250 consecutive pregnant women, of which, 370 (2.4 percent) women were found to be HCV reactive. The highest risk factor for HCV positivity in the women was past intravenous drug (heroin) usage (118/370; 32 percent), past blood contact accounted for 88/370 (24 percent) cases. Forty percent of infected women were found to have an unidentified source of HCV infection. From the 370 infected women, 366 newborns were delivered alive, all were anti-HCV antibody positive at birth, declining to 25 positive at 12 months, indicating the lack of positive predictive power of this diagnostic test. 18 newborns were HCV-RNA positive at birth and this declined to, and subsequently stayed at, 8 positive after 4 months of age. A rate of transmission was reported at 5.1 percent (8 of 155 infants followed up at 12 months were infected). Testing of cord blood for HCV RNA was not found to be of value as there was frequent contamination with maternal blood. It was found that testing at 4 months for HCV RNA was the most efficient test timing, having the earliest and best positive predictive value, although no testing was performed between 0-4 months.

The diagnostic accuracy of tests for HCV RNA were assessed in 547 HCV exposed infants. The recommendations were to delay the first PCR based HCV test until after 1 month of age, after which the sensitivity of the test rose to 79 percent (95% CI [58, 93]) and the specificity was 98 percent (95% CI [94, 99]). It was also recommended that negative results should be confirmed by anti-HCV antibody tests between 9 to 15 months (level III-2 diagnostic evidence) (Polywka et al 2006).

A study on the effects of HCV infection in 80 children reported that, although the children were clinically asymptomatic, liver biopsy detected high grade hepatitis in 17 (21.2 percent) children; mild or moderate fibrosis in 44 (55 percent) and 13 (16.2 percent) children respectively; and, cirrhosis in 1 child. Fibrosis increased with duration of HCV infection, indicating clinical disease symptoms may commence in early adulthood (level IV prognostic evidence)(Guido et al 1998).

In conclusion, HCV risk factors could not be identified for 40 percent of mothers infected with HCV. Transmission from mother to infant occurs in approximately 5 percent of cases where the mother is HCV-RNA positive. This transmission is unlikely to occur postnatally. HIV-1 and HCV co-infection increases the likelihood of transmission of HCV to the infant. Accurate testing of the infant can be performed at

one month of age using HCV-RNA PCR based detection methods, and at 18 months using anti-HCV antibody tests (the gold standard for HCV infection). No interventions, either drug based or surgical, were identified to lower the vertical transmission rate. Infants that are HCV positive are generally in good health and suffer from sub-clinical manifestations of the disease. There is some indication that HCV infected infants may progress to clinical disease in early adulthood.

COST IMPACT

No cost effectiveness studies were found for perinatal HCV screening.
A study on asymptomatic pregnant women found providing HCV screening plus therapy or HCV screening plus therapy plus caesarean was not cost effective versus the current US recommendation of no HCV testing for asymptomatic women (Plunkett & Grobman 2005).

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

The significant stigma and discrimination attached to being HCV positive (DHA 2000) together with: the current lack of interventions to prevent vertical transmission; the relatively low rate of vertical transmissions; the lack of effective or safe therapies for the infant; and, the low rate of clinical disease in infants, could lead to a positive HCV test being overall detrimental to the infant. These factors should be considered when determining whether to screen all infants.

OTHER ISSUES

The Australasian Society for Infectious Diseases recommends that infants of HCV infected mothers be screened at 12-18 months, with positive tests being repeated before confirmation of HCV infected status is given. PCR based tests are optional if there is reason to warrant earlier testing for HCV (Palasanthiran et al 2002).

CONCLUSION:

The number of HCV infected infants in Australia is low, but the potentially chronic and serious sequelae of HCV warrant their identification through screening. HCV screening in Australia is not standardised and the screening approach is determined by the institute or practitioner. The establishment of a standardised methodology for HCV screening would identify more infected infants than are currently identified. Due to the low prevalence in Australia, universal screening is not recommended. Conversely, there is evidence suggesting that screening only those “at risk” would miss approximately 40% of HCV infected mothers, and by inference, their offspring. Evidence is beginning to emerge as to the best times and methods to screen infants for HCV, although this evidence is not strong due to the low numbers of cases.

HEALTHPACT ACTION:

With the advent of more effective treatment of children with polymerase inhibitors within the next few years, screening infants for hepatitis C will be of growing importance. However, HealthPACT can not assess the effectiveness of pharmacological therapies and have therefore recommended that further assessment of this technology is no longer warranted.

SOURCES OF FURTHER INFORMATION:

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Plunkett, B. A. & Grobman, W. A. (2005). 'Routine hepatitis C virus screening in pregnancy: a cost-effectiveness analysis', *Am J Obstet Gynecol*, 192 (4), 1153-1161.

Polywka, S., Pembrey, L. et al (2006). 'Accuracy of HCV-RNA PCR tests for diagnosis or exclusion of vertically acquired HCV infection', *J Med Virol*, 78 (2), 305-310.

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LIST OF STUDIES INCLUDED

Total number of studies	
Level IV screening evidence	4
Level III-2 diagnostic evidence	1
Level IV prognostic evidence	1

SEARCH CRITERIA TO BE USED:

Disease Transmission, Vertical
Hepatitis C/ diagnosis/prevention & control/ transmission
Infant, Newborn
Neonatal Screening
Pregnancy
RNA, Viral/blood
Hepatitis C/ transmission/virology