Specialist Working Group for Haematology

Proposed changes to the *Criteria for the clinical use of intravenous immunoglobulin in Australia, Second Edition*

ITEM	CRITERIA FOR THE CLINICAL USE OF INTRAVENOUS IMMUNOGLOBULIN IN AUSTRALIA, SECOND EDITION (CRITERIA)	PROPOSED REVISIONS TO THE CRITERIA	SWG RATIONALE FOR PROPOSED CHANGE (A) Administrative) (B) Progressive (C) Programmed
Condition Name	**Neonatal haemochromatosis (NH)**	**Neonatal haemochromatosis (NH)**	
Specialty	Haematology	Haematology	
Chapter	5	5	
Specific Conditions			
Level of Evidence	Evidence of probable benefit (Category 2a).	Evidence of probable benefit (Category 2a).	
Justification for Evidence Category	A trial compared the impact of IVIg on pregnancy outcome of women whose most recent pregnancy had resulted in NH with historical controls (randomly selected previously affected pregnancies). All 15 pregnancies resulted in live births. NH was diagnosed in 11 but responded to medical treatment. By contrast, there were 2 successful outcomes in controls (Biotext 2004).	A trial compared the impact of intravenous immunoglobulin (IVIg) on pregnancy outcome of women whose most recent pregnancy had resulted in NH with historical controls (randomly selected previously affected pregnancies). All 15 pregnancies resulted in live births. NH was diagnosed in 11 but responded to medical treatment. By contrast, there were two successful outcomes in controls (Biotext 2004). Rand et al (2009) describes successful treatment of NH in neonates using exchange transfusion and IVIg.	Addition of evidence with successful use of IVIg together with exchange transfusion. (A)

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Description and Diagnostic Criteria	NH manifests in the foetus and newborn and is characterised by abnormal accumulation of iron in the liver and extra-hepatic tissues. Affected neonates present with fulminant liver failure, usually in the context of a history of prematurity, intrauterine growth retardation and oligohydramnios. NH differs from most other causes of neonatal liver disease, other than congenital infections, in that the condition begins in utero and fulminant liver disease is manifested in the first few days of life. The aetiology and pathogenesis remains uncertain. The NH phenotype may be the outcome of numerous disease processes. There is also evidence, however, that NH is an alloimmune disorder. First, there is an approximate 80% likelihood of NH once a woman has an affected baby. Second, mothers can have affected babies with different fathers. It has not been described that fathers can have affected half-siblings with different mothers. **Symptoms and signs** Affected neonates present with signs of liver failure, including extreme cholestasis,	NH manifests in the foetus and newborn, and is characterised by abnormal accumulation of iron in the liver and extra-hepatic tissues. Affected neonates present with fulminant liver failure, usually in the context of a history of prematurity, intrauterine growth retardation and oligohydramnios. NH differs from most other causes of neonatal liver disease, other than congenital infections, in that the condition begins in utero and fulminant liver disease is manifested in the first few days of life. The aetiology and pathogenesis remains uncertain. The NH phenotype may be the outcome of numerous disease processes. There is also evidence, however, that NH is an alloimmune disorder. First, there is an approximate 80% likelihood of NH once a woman has an affected baby. Second, mothers can have affected babies with different fathers. It has not been described that fathers can have affected half-siblings with different mothers. **Symptoms and signs** Affected neonates present with signs of liver failure, including extreme cholestasis,	

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	hypoalbuminaemia, coagulopathy, ascites and hypoglycaemia. Diagnosis of neonatal haemochromatosis is made after other causes of neonatal liver failure have been ruled out. In addition to extensive iron deposition (siderosis), liver biopsy would show cirrhosis with diffuse fibrosis, bile duct proliferation, and giant cells. Siderosis is also present in other tissues and viscera (e.g. epithelial tissues and the heart) but not in reticuloendothelial cells. **Occurrence** NH is a rare disease but the rate of recurrence after the index case in a sibship is up to 80%. **Prognosis** About 20% survival with medical treatment.	hypoalbuminaemia, coagulopathy, ascites and hypoglycaemia. Diagnosis of neonatal haemochromatosis is made after other causes of neonatal liver failure have been ruled out. In addition to extensive iron deposition (siderosis), liver biopsy would show cirrhosis with diffuse fibrosis, bile duct proliferation, and giant cells. Siderosis is also present in other tissues and viscera (e.g. epithelial tissues and the heart), but not in reticuloendothelial cells. **Occurrence** NH is a rare disease but the rate of recurrence after the index case in a sibship is up to 80%. **Prognosis** About 20% survival with medical treatment.			
Diagnosis is required		No	Which Speciality		
Diagnosis must be verified		No	Which Specialty		

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Exclusion Criteria			
Indication for use	Pregnant women who have had a previous pregnancy affected by neonatal haemochromatosis.	**Pregnant women who have had a previous pregnancy affected by neonatal haemochromatosis.** **Neonate with neonatal haemochromatosis.**	SWG recommend the addition of an indication for the treatment of neonates with IVIg and exchange transfusion. **Please note - the formal addition of this group of patients will require specific approval by governments.** (B)
Qualifying Criteria	Women who are pregnant or attempting to conceive and their most recent pregnancy ended in delivery of a foetus shown to have had NH.	**Pregnant women who have had a previous pregnancy affected by NH.** • Pregnant woman or woman attempting to conceive with a previous pregnancy ending in delivery of a fetus shown to have had NH. **Neonate with NH.** • A diagnosis of NH confirmed in a neonate by exclusion of other causes of neonatal liver failure and findings of high ferritin in liver biopsy, and MRI demonstration of iron overload.	Qualifying Criteria aligned with current criteria however, SWG recommends wording in the current version is too restrictive to limit to the 'most recent' pregnancy (Qualifying criteria) and the wording of the original indication should be used (previous pregnancy). (A) Qualifying criteria and evidence items defined to confirm Neonatal NH diagnosis. (B)
Review Criteria	• Occurrence of NH, or evidence of liver disease (serum ferritin and a-fetoprotein levels, coagulopathy) in the offspring of women who have previously given birth to an NH-affected neonate. • Requirement for liver transplantation in	**Pregnant women who have had a previous pregnancy affected by NH.** Review is not mandated for this indication however the following criteria may be useful in assessing the effectiveness of therapy. • The occurrence of NH, or evidence of liver disease in the offspring of women	While the maximum term would be 42 weeks for a normal pregnancy, these pregnancies are likely to be induced earlier. SWG confirmed that the maximum time of 5 months treatment (i.e. treat from 18 until 38 weeks pregnant) was sufficient. (A)

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	these neonates. • Survival and development of infants following maternal IVIg therapy during pregnancy.	who have previously given birth to an NH-affected neonate. **Neonate with NH.** Review is not mandated for this indication however the following criteria may be useful in assessing the effectiveness of therapy. • Evidence of liver disease in the neonate • Requirement for liver transplantation in the neonate	Outcome data have been defined. (A)
Dose	1 g/kg body weight weekly from the 18th week until the end of gestation. **Refer to the current product information sheet for further information.** **The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.**	**Pregnant women who have had a previous pregnancy affected by NH.** **Maintenance** - 1 g/kg body weight (to a maximum of 100 kg) weekly from the 18th week until the end of gestation. **Neonate with NH.** **Maintenance** - 1- 2 g/kg following exchange transfusion in the first 7 days and then 1 g/kg weekly, as required. The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient. Dosing above 1g/kg per day is contraindicated for some IVig products. **Refer to the current product information sheet**	Dosing in pregnant women consistent with current version with the addition of defining a maximum maternal weight of 100Kg given the high incidence of obesity in the pregnant population. (B) Dosing for neonates consistent with literature. (B)

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		for further information.	

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