Haemolytic disease of the fetus (HDF)

Condition for which Ig use is in exceptional circumstances only

Specific Conditions	• Haemolytic disease of the fetus
Indication for Ig Use	• Haemolytic disease of the fetus with high risk of early fetal hydrops or death
Level of Evidence	Conflicting evidence of benefit (Category 2c)
Description and Diagnostic Criteria	Haemolytic disease of the fetus and newborn (HDFN) is characterised by a breakdown of red blood cells (RBCs) by maternal antibodies. During pregnancy, some of the mother's antibodies are transported across the placenta and enter the fetal circulation. Antibodies to the RhD, RhC and Kell antigen are the most common causes of severe HDFN in Australia. Anaemia is the most significant problem in utero because excess fetal bilirubin crosses the placenta and is eliminated by the mother. However, bilirubin levels can rise rapidly after birth, leading to the need for intensive phototherapy and exchange transfusion. Exchange transfusions are associated with an increased risk of neonatal morbidity and mortality. In newborns with haemolytic disease (HD), the use of IVIg is not recommended (Recommendation 7, Patient Blood Management Guidelines (PBM) Module 6 - Paediatric and neonatal). Infants at risk of HD should be promptly assessed after birth. Those at high risk of severe jaundice should receive intensive phototherapy. (Practice point 34, PBM, Module 6). In maternity patients with a fetus affected by HDFN who is at high risk of early fetal hydrops or death, a course of weekly IVIg should be considered. (Expert opinion point 6, PBM Module 6).
Justification for Evidence Category	Since IVIg can compete with alloantibodies for Fc receptors on cells that mediate red blood cell (RBC) breakdown (Hammerman et al, 1996), it has been proposed that it can reduce the incidence of exchange transfusion. One good quality systematic review in 2014 by Louis et al, (including 12 randomised control trials [RCTs]) reported that while combined results of all trials suggested that IVIg can reduce the incidence of exchange transfusion (ET) in infants with haemolytic disease of the fetus and newborn (HDFN), the earlier trials were generally of low quality. When only the trials at low risk of bias were considered, there was no effect of IVIg on reducing incidence of ET or any other outcome of importance (e.g. peak bilirubin, duration of phototherapy or need for top-up transfusion). None of the trials were powered to assess rare (but potentially life-threatening) adverse effects such as transfusion related acute lung injury (TRALI), the risk of which is likely to increase with transfusion of plasma products. The recent, high-quality trials specified the use of intensive phototherapy, which is the most effective neonatal treatment to reduce the need for ET. Although the review suggested a benefit of IVIg in reducing ET for jaundice due to ABO incompatibility, the studies were also of low quality. It seems unlikely that IVIg would be of benefit in ABO haemolysis (which is typically milder) if there is no benefit in RhD HDFN. For preterm and term infants with alloimmune haemolytic disease, the effect of IVIg compared with no IVIg on ET incidence is uncertain. In infants with alloimmune haemolytic disease, the effect of IVIg compared with no IVIg on mortality is also uncertain.
Diagnosis Requirements	A diagnosis must be made by a Haematologist, Maternal-Fetal Medicine Specialist, General Medicine Physician or an Obstetrician.

Qualifying Criteria for Ig Therapy	• Maternal antibodies against fetal antigens in severe haemolytic disease of the fetus AND • High risk of early fetal hydrops or death
Exclusion Criteria	Haemolytic disease of the newborn
Review Criteria for Assessing the Effectiveness of Ig Use	**Review is not mandated for this condition however the following criteria may be useful in assessing the effectiveness of Ig therapy.** • Live birth and clinical outcome post delivery
Dose	• **Dose during pregnancy (IVIg)** - 1 g/kg (up to a maximum weight of 100 kg) weekly throughout pregnancy. The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient. Refer to the current product information sheet for further information on dose, administration and contraindications.

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Generated on: 20 March 2020