NICE 2015
Intravenous Immunoglobulin therapy for HDFN

Rebecca Davidson
The Mother – Mrs H

- 1st baby 2011

- Blood group A Rh(D) Negative

- Prophylactic anti-D given at 28/40, 34/40 & postpartum

- Never transfused
The Mother – Mrs H

- Found to be isoimmunised early in 2\textsuperscript{nd} pregnancy $\rightarrow$ anti-D
- Anti-D titre at 23/40 $\rightarrow$ 64
- Anti-D titre at 27/40 $\rightarrow$ 1024
  (6 weeks prior to birth)
  (Analysis on the Ortho AutoVue)
- IUT not performed
- LUSCS at 33/40
The baby – Miss H

- Born 5 August 2015
- Delivered at 33/40 weeks gestation, IUGR (below 1\textsuperscript{st} centile), 1.58kg
- Mildly acidotic and hypoglycaemic at birth, fully corrected within 4 hours
- First bilirubin levels at 7 hours old
  Total bilirubin = 154\,\mu\text{mol/L}
- O Rh(D) Positive
- DAT Positive score 4 (0-4 score scale)
- DiaCidel elution showed Anti-D specificity
Haemolytic disease

- Maternal IgG antibody reaches the foetus by transplacental movement
- Haemolysis of immunoglobulin coated neonatal erythrocytes leads to raised plasma bilirubin levels and foetal anaemia (varying degree)
- The neonate's liver is unable to produce sufficient conjugating enzymes and there is enterohepatic circulation of bilirubin leading to deposition of bilirubin in dermal and subcutaneous tissue and clinical jaundice
- High concentrations of unconjugated bilirubin create a risk of kernicterus (brain damage)
CONVENTIONAL MANAGEMENT

- Intensive phototherapy (excretion by alternative pathways)
- Maintain hydration & increase feeds (decreases enterohepatic circulation)
- Exchange transfusion (mechanical removal)
Treatment of hyperbilirubinaemia

- Phototherapy at 460-490nm of varying intensity (oxidation of bilirubin to hydrophilic form)
- Red cell exchange transfusion removes bilirubin & haemolytic antibody/ies & corrects anaemia
- Intravenous immunoglobulin – mechanism of action not understood
Risks of exchange transfusion

- Hypocalcaemia, hypoglycaemia, hyperkalaemia, acidaemia
- Thrombocytopenia
- Transmission of infectious agents
- TACO, TRALI
- Catheter related complications
  (infection, sepsis, air emboli, thrombosis haemorrhage)
Why use IVIg?

• Alternative to red cell exchange transfusions
• May reduce duration of phototherapy
• May reduce length of stay
• When access to appropriate blood for exchange is not possible
• Parental preference
• What evidence exists that IVIg for treatment of HDFN is efficacious?
How does IVIg work?

- Infused immunoglobulin occupies Fc receptor sites in the neonates RE system (macrophages) thus preventing uptake and lysis of antibody-coated neonatal erythrocytes
- Infused immunoglobulin competes for Fc receptors on neonates erythrocytes
- Infused immunoglobulin may increase IgG catabolism resulting in a shorter half life of antibodies
- The presence of anti-idiotypic antibodies in infused immunoglobulin neutralises anti-Rh antibodies
Miss H – bilirubin levels

- Total Bili
- Unconjugated bili

Bilirubin conc µmol/L

- 0
- 50
- 100
- 150
- 200
- 250

Date and Time:
- 05/08/15 2330
- 06/08/15 0655
- 06/08/15 1000
- 06/08/15 1630
- 07/08/2015 2215
- 08/08/15 0615
- 09/08/15 0650
- 10/08/15 1810
- 11/08/15 0600
- 12/08/15 0445
- 13/08/15 0500
- 14/08/15 0545
- 14/08/15 0600

Monash Health
Miss H

- Intravenous immunoglobulin therapy given 6 August 2015.
- Baby was 24 hours old
- Intragam P given 1g/kg (total 1.5g)
- Hb 175g/L on day of birth and 143g/L 7 days later
- Required red cell transfusion late August 2015
• Conditions for which IVIg use is in exceptional circumstances only include haemolytic disease of the newborn (HDN)

• IVIg may be used in selected cases in consultation with experts in foetomaternal medicine and transfusion medicine.
Recommendation – haemolytic disease (IVIg)
Recommendation 7 (Grade B)

• In infants with HDFN, the *routine* use of IVIg is not recommended.

NHRMC definition:
• *Grade B* – Body of evidence can be trusted to guide practice in most situations
3.5.2 Preterm and term infants – effects of IVIg for haemolytic disease on outcomes

Evidence Statement 4.3

• In infants with alloimmune haemolytic disease, the effect of IVIg compared with no IVIg on exchange transfusion incidence is uncertain.

Evidence Statement 4.4

• In infants with alloimmune haemolytic disease, the effect of IVIg compared with no IVIg on mortality is uncertain.
References

- [http://www.rch.org.au/uploadedFiles/Main/Content/neonatal_rch/EXCHANGE_TRANSFUSION.pdf](http://www.rch.org.au/uploadedFiles/Main/Content/neonatal_rch/EXCHANGE_TRANSFUSION.pdf)
References


• Exchange transfusion incidence

The systematic review assessed the effect of IVIg on the incidence of exchange transfusion in term and preterm neonates with HDFN secondary to Rh or ABO incompatibility. It performed separate meta-analyses in Rh and ABO incompatible patients. A significant reduction in exchange transfusion incidence following IVIg was reported (p<0.00001); however, in a sensitivity analysis that included only RCTs assessed to have an overall low risk of bias, the significant difference was not observed (p=0.37). In a subanalysis of RCTs involving preterm neonates only, there was no significant difference between treatment groups for the incidence of exchange transfusions.