Haemolytic Disease of the Newborn

HDN

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Objectives

- Rhesus hemolytic disease of the newborn
- Aetiology and effect on the fetus and newborn
- Severity of disease
- Prevention
- Rh immune globulin
- Tests for feto-maternal hemorrhage
- Treatment
  - Inutero
  - Exutero
- Other causes of HDN
- New developments

Rhesus Haemolytic Disease of the Newborn

- Used to be a major cause of fetal loss and death in newborn infants
- HDN was ?first described in 1609 by a midwife who delivered twins
  - One baby was swollen and died soon after birth
  - The twin became jaundiced and died several days later
- Many similar cases were described over the following 300 years

Rhesus HDN

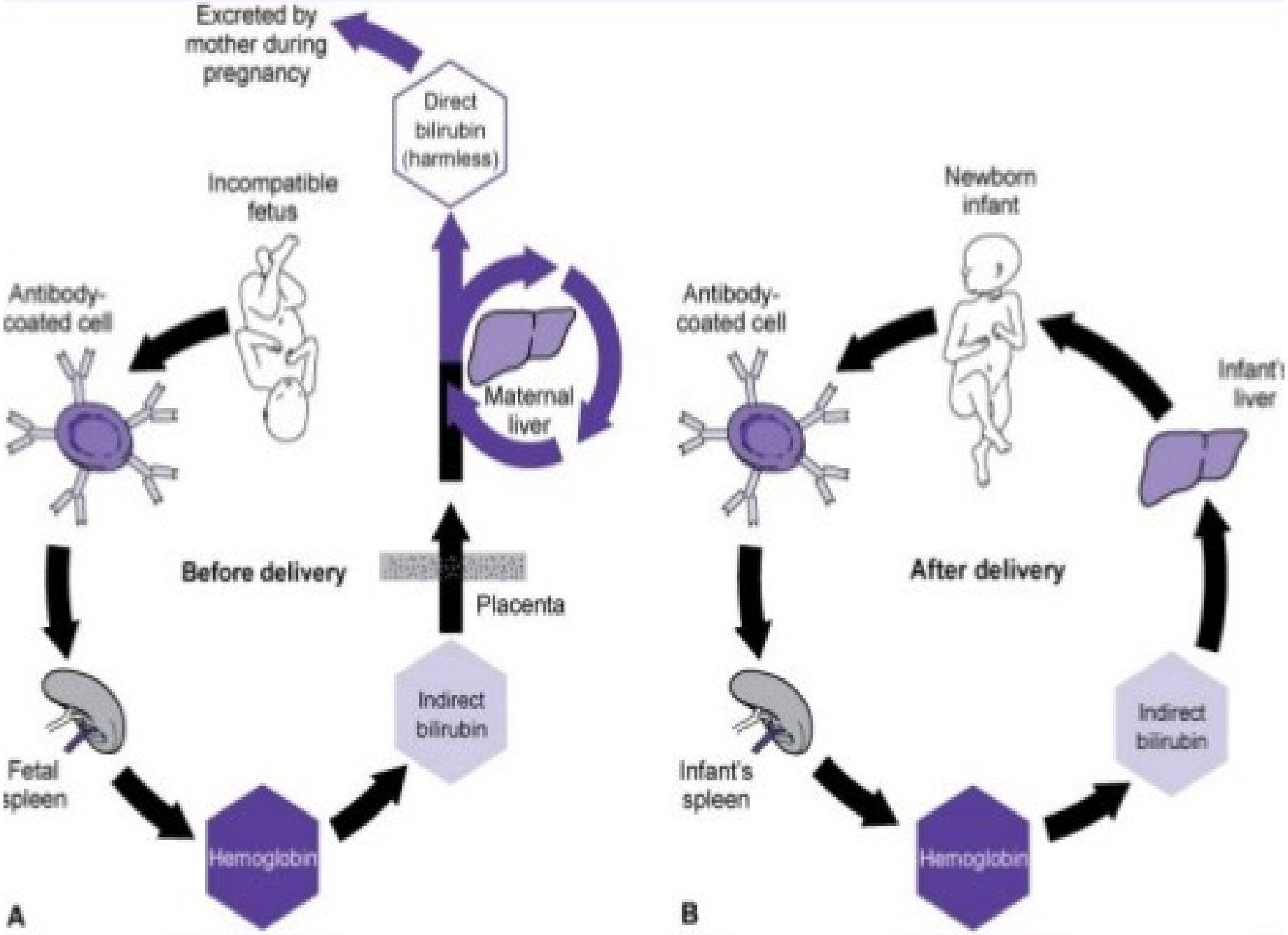
- Disorder of the fetus or newborn where fetal red cells are destroyed by maternal IgG antibodies
- The IgG antibodies cross the placenta and shorten red cell survival
- The premature red cell destruction results in disease varying from mild anaemia to death in utero

Aetiology in the Fetus

- The mother is exposed during her first pregnancy
- In subsequent pregnancies the IgG antibodies cross the placenta
- The antibodies bind to the antigens on the fetal red cells destroying the cells and releasing haemoglobin
- This results in anaemia which if severe leads to fetal death

Aetiology in the Newborn

- After delivery red cell destruction continues
- Haemoglobin is broken down
- Newborn liver is immature and is unable to produce enough glucuronyl transferase to convert unconjugated (indirect) to conjugated (direct) bilirubin
- High levels of unconjugated bilirubin are neurotoxic

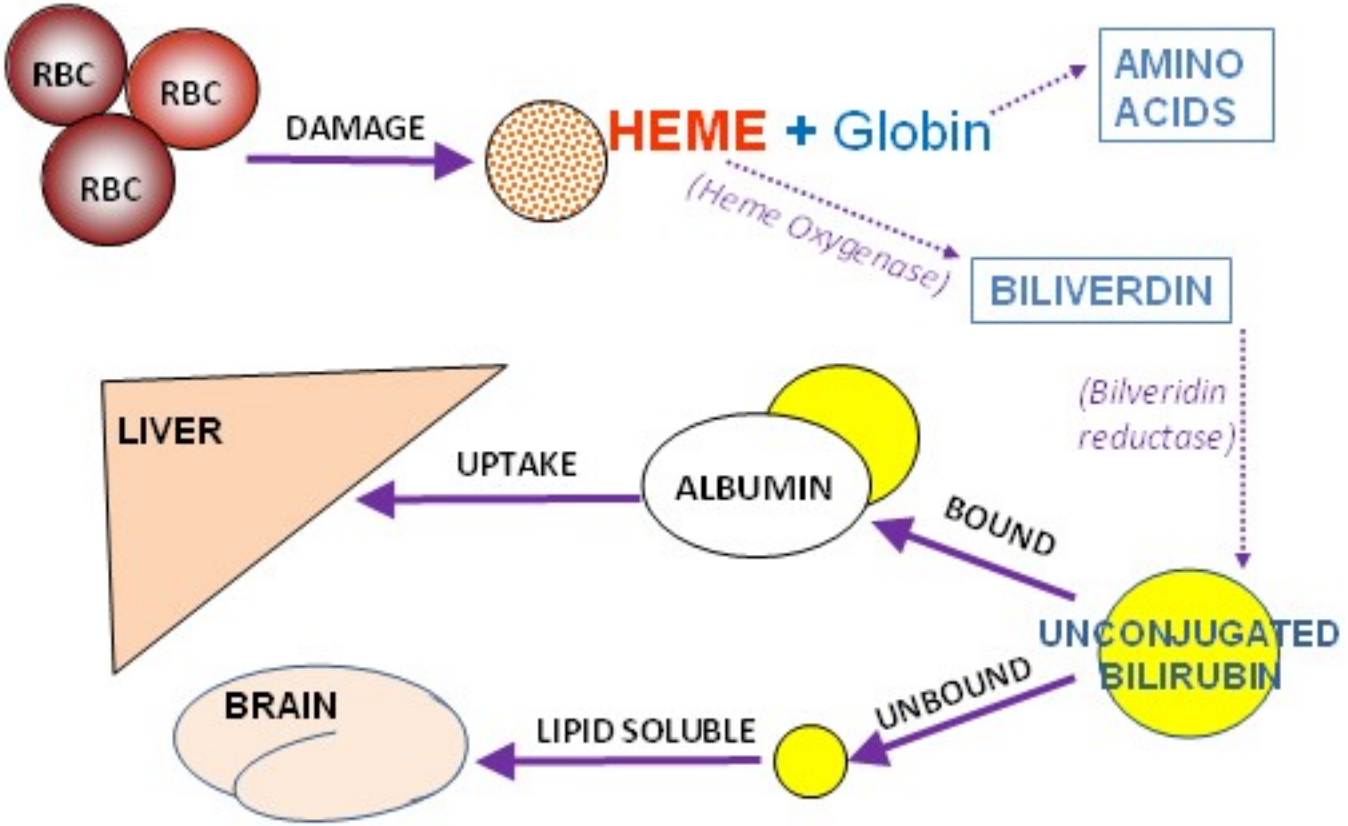

Excreted by mother during pregnancy
Direct bilirubin (harmless)
Incompatible fetus
Antibody-coated cell
Maternal liver
Before delivery
Placenta
Indirect bilirubin
Fetal spleen
Hemoglobin
A
Newborn infant
Antibody-coated cell
Infant's liver
After delivery
Indirect bilirubin
Infant's spleen
Hemoglobin
B

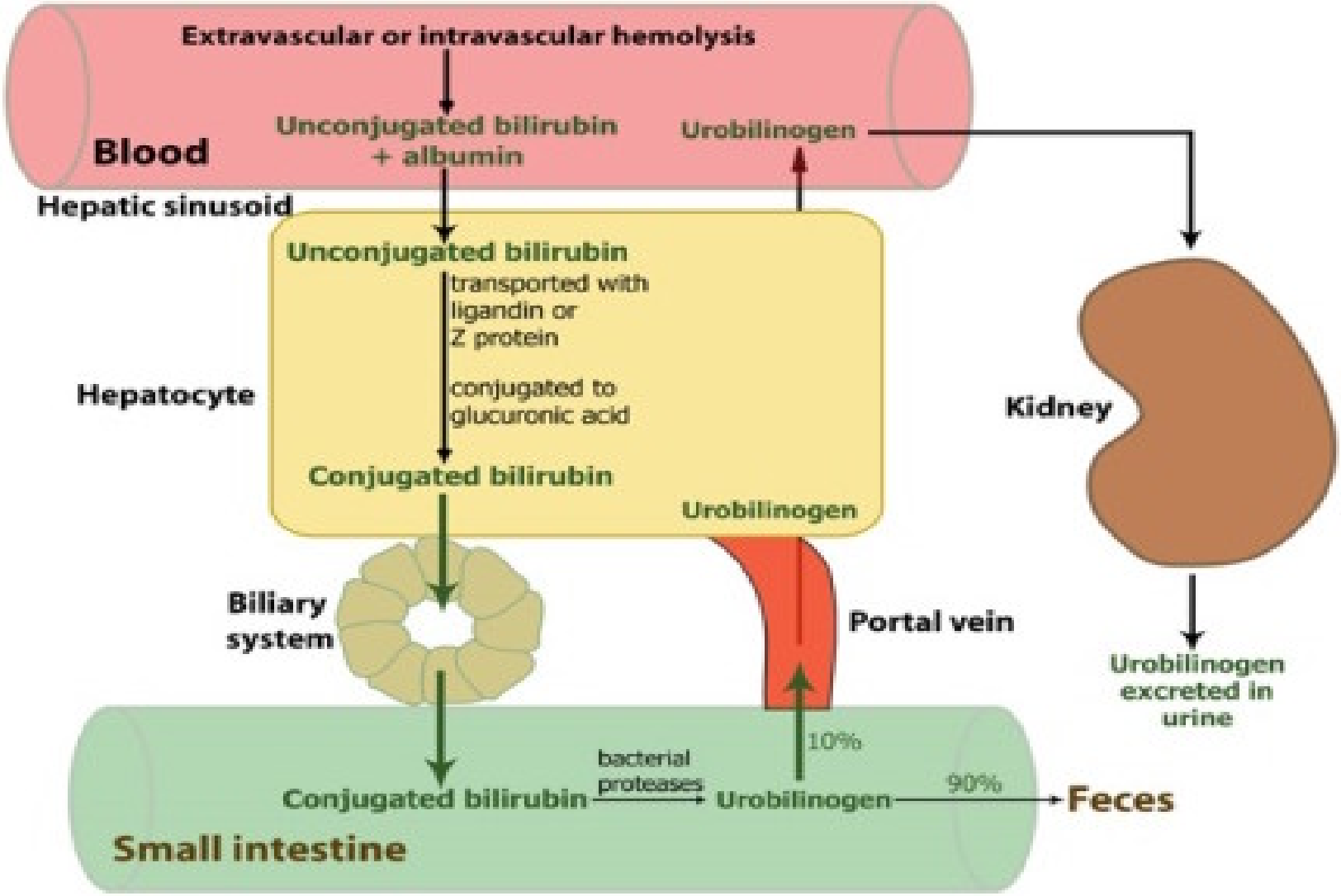
Bilirubin physiology

- Bilirubin derived from breakdown of haem proteins which are present in Haemoglobin
- Bilirubin is bound to albumin for transport in the blood (bound bilirubin is non toxic)
- In the liver bilirubin enters the liver cell is bound to ligandin to help transport to the site of conjugation
- Bilirubin conjugates with glucuronic acid which produces a water soluble compound

- Conjugated bilirubin is transported to the gut in bile
- Newborn baby's guts contain an enzyme B glucuronidase which converts the conjugated bilirubin to unconjugated which is then reabsorbed into the circulation

Bilirubin Metabolism




Extravascular or intravascular hemolysis
Blood
Unconjugated bilirubin
+ albumin
Urobilinogen
Hepatic sinusoid
Unconjugated bilirubin
transported with
ligandin or
Z protein
Hepatocyte
conjugated to
glucuronic acid
Conjugated bilirubin
Urobilinogen
Kidney
Biliary
system
Portal vein
Urobilinogen
excreted in
urine
10%
bacterial
proteases
Conjugated bilirubin
Urobilinogen
90%
Feces
Small intestine

Rh HDN

- Anti –D is responsible for the most severe cases of HD of the fetus and newborn
- Alloimmunisation occurs during first pregnancy in a Rhesus D positive mother carrying a Rhesus D negative fetus
- This rarely resulted in clinical symptoms
- Subsequent pregnancies where fetus was Rh D+ are affected

Rh Immune Globulin

- Introduced in 1968
- Dramatic reduction of the incidence of Rh haemolytic disease .

When to give antiD IgG

- Need to prevent Rh neg women becoming sensitised.
- During pregnancy and after if baby is Rh +
- Following miscarriage or threatened miscarriage, ectopic pregnancy and termination
- Invasive prenatal diagnosis eg amniocentesis
- External cephalic version
- Abdominal trauma
- Fetal death

Routine Antenatal Prophylaxis

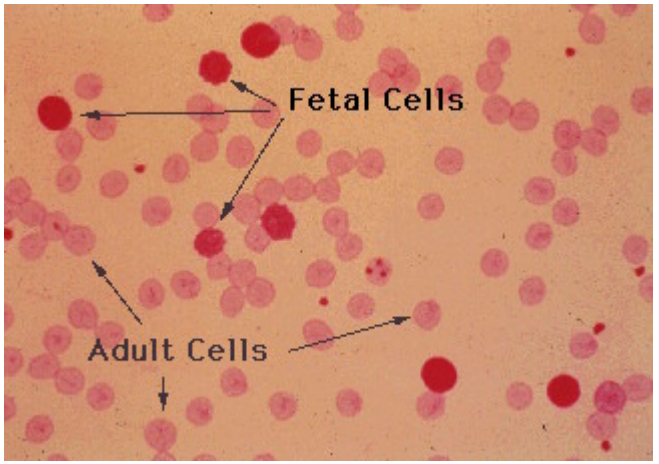
- All non sensitised Rh D negative women
- One larger dose or 2 smaller doses
- Routine antibody screening test at 28 weeks must be taken before Anti -D Ig prophylaxis is given

Postnatal Prophylaxis for the Mother

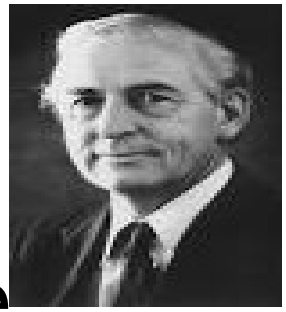
- Anti-D Ig prophylaxis should be given within 72 hours if the baby is Rh D +
- A blood test from the mother is required to estimate the amount of fetal blood in the maternal circulation.
- If estimated greater than 4 ml additional anti-D will be required to prevent sensitisation.

Kleihauer Test

- Used to measure the amount of fetal Hb transferred from the fetus into the maternal circulation
- It is performed in Rh negative mothers
- It quantifies the amount of blood that has crossed into the maternal blood stream
- It uses the fact that fetal Hb is resistant to acid



Sir William Liley
1929-1983



- First introduced concept of intrauterine transfusion
- He heard that red cells transfused into the peritoneum of children with sickle cell disease appeared to migrate into the circulation and correct the anaemia

Inutero treatment

- Intrauterine transfusion of fetal RBCs
- Choice of access (no comparison RCT)
  - Peritoneal cavity
  - Intravascular transfusion
    - Umbilical cord vein
    - Intrahepatic umbilical vein
- Combined approach

Neonatal Management

- Cord bloods for Hb, DAT and bilirubin
- Phototherapy
  - Blue light spectrum 420-475 nm
  - Single, double or triple
- Exchange transfusion
  - Irradiated leucodepleted CMV negative blood
- Follow up
  - Top up transfusion
  - Folic acid replacement

Threshold table

Consensus-based bilirubin thresholds for management of babies 38 weeks or more gestational age with hyperbilirubinaemia

Age (hours)	Bilirubin measurement (micromol/litre)			
0	–	–	> 100	> 100
6	> 100	> 112	> 125	> 150
12	> 100	> 125	> 150	> 200
18	> 100	> 137	> 175	> 250
24	> 100	> 150	> 200	> 300
30	> 112	> 162	> 212	> 350
36	> 125	> 175	> 225	> 400
42	> 137	> 187	> 237	> 450
48	> 150	> 200	> 250	> 450
54	> 162	> 212	> 262	> 450
60	> 175	> 225	> 275	> 450
66	> 187	> 237	> 287	> 450
72	> 200	> 250	> 300	> 450
78	–	> 262	> 312	> 450
84	–	> 275	> 325	> 450
90	–	> 287	> 337	> 450
96+	–	> 300	> 350	> 450
Action	 Repeat bilirubin measurement in 6–12 hours	 Consider phototherapy and repeat bilirubin measurement in 6 hours	 Start phototherapy	 Perform an exchange transfusion unless the bilirubin level falls below threshold while the treatment is being prepared

Treatment threshold graph for babies with neonatal jaundice

NHS National Institute for Health and ClinicalExcellence

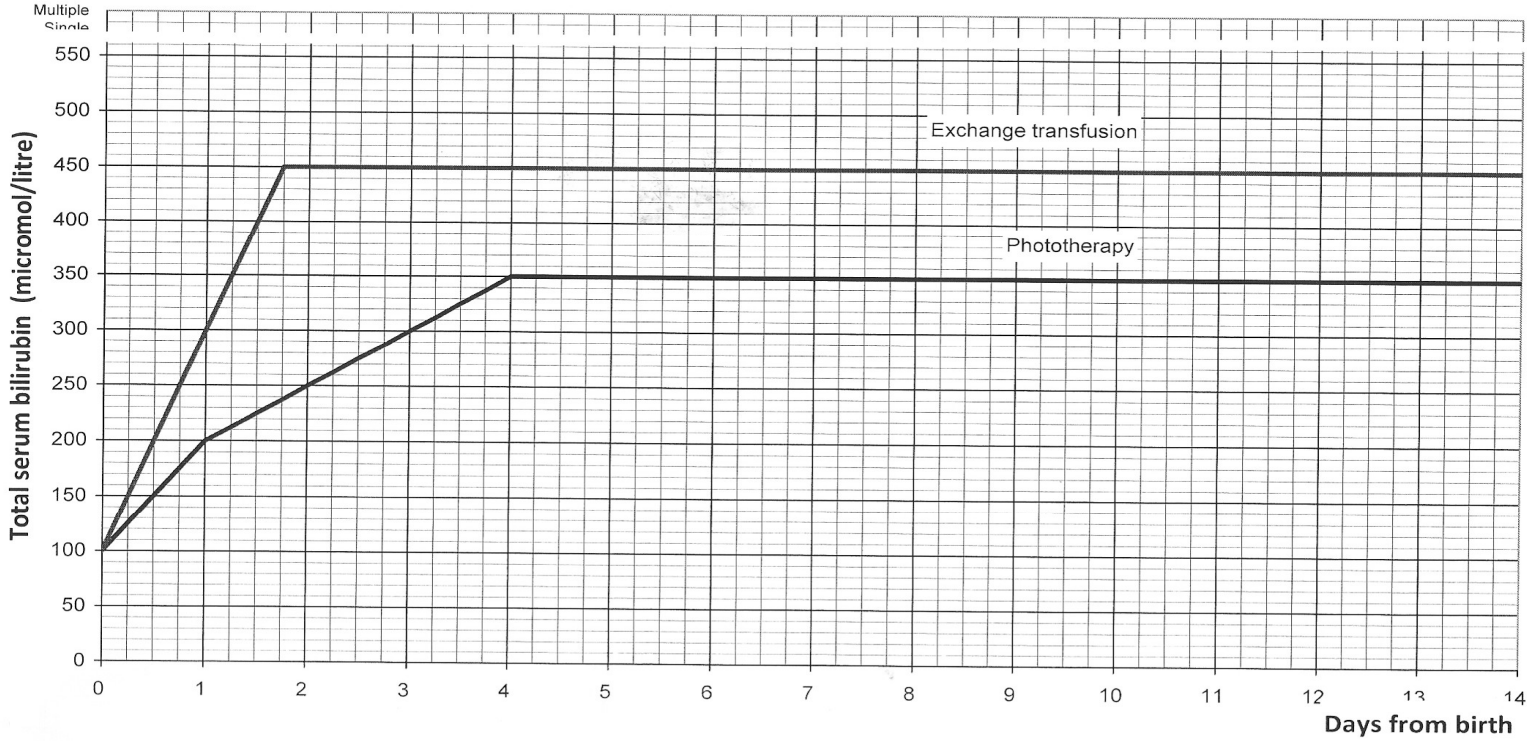
Baby's name _____ Date of birth _____

Hospital number _____ Time of birth _____ Direct Antiglobulin Test _____

Shade for phototherapy Baby's blood group _____ Mother's blood group _____

Click below and choose gestation

>=38 weeks gestation



Bilirubinometer

Phototherapy

- Phototherapy converts bilirubin into lumirubin via structural isomerization that is not reversible .
- Lumirubin, a more soluble substance than bilirubin, is excreted without conjugation into bile and urine.
- This is the principal mechanism by which phototherapy reduces bilirubin concentration.

Effectiveness of Phototherapy depends on

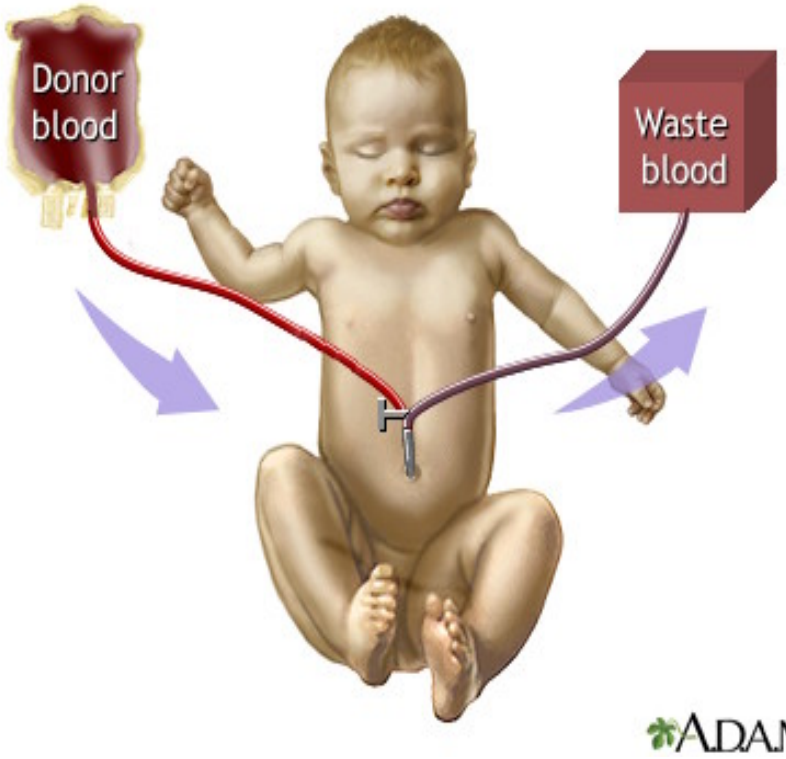
- Spectral quantities of delivered light (optimal wavelength range 400-520nm with peak emissions at 460nm)
- Irradiance (intensity of light)
- Surface area deceiving phototherapy
- Skin pigmentation
- Total SBR at start of phototherapy
- Duration of exposure

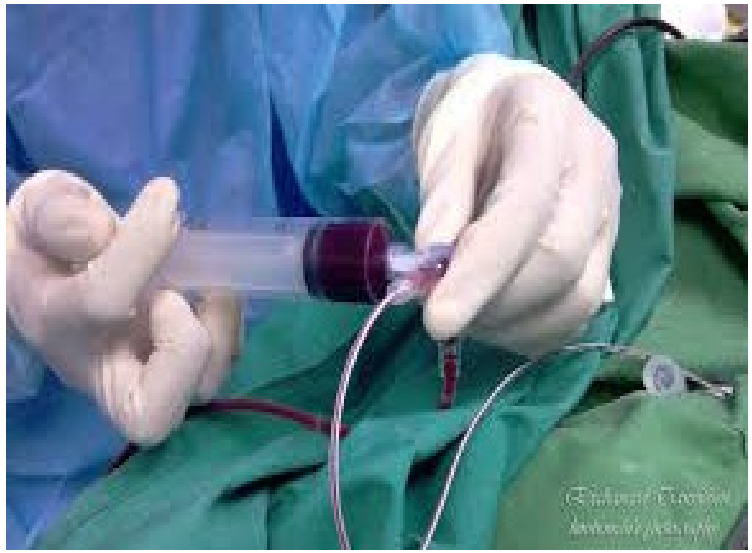
Traditional Guidelines for Exchange Transfusion

- Severe anaemia Hb< 100mg/dl at birth
- Severe hyperbilirubinaemia SBR>350 micromols in the first 48 hours

These values are from the era when managing the sick neonate with untreated RhD disease

Exchange transfusion





Risks

- Blood borne infections
- Thrombocytopenia and coagulopathy
- Graft vs Host disease
- NEC
- Portal vein thrombosis
- Electrolyte abnormalities
- Cardiac arrhythmias

Intravenous Immunoglobulins

- Studies have shown the use of IVIG reduces the need for exchange transfusion.
- Avoiding exchange transfusion reduces potential risks of adverse side effects
- Mechanism is uncertain. Possibly IVIG inhibits haemolysis by blocking antibody receptors on the RBCs

Other types of HDN which can be predicted by screening

- Any Ig G antibody is capable of causing HDN if the fetal red cells possesses an antigen that the mother lacks.
- Anti –c is the next most commom
- Other common causes include anti Kell and anti M

Anti Kell Antibodies

- Particularly difficult to manage
- Severity of HDN can change within a week
- Antibody supresses erythropoiesis as well as causing haemolysis
- Accounts for 10% of severely affect fetuses

Causes of HDN presenting as early onset or rapidly progressive hyperbilirubinaemia which will not be predicted by maternal antibody screening

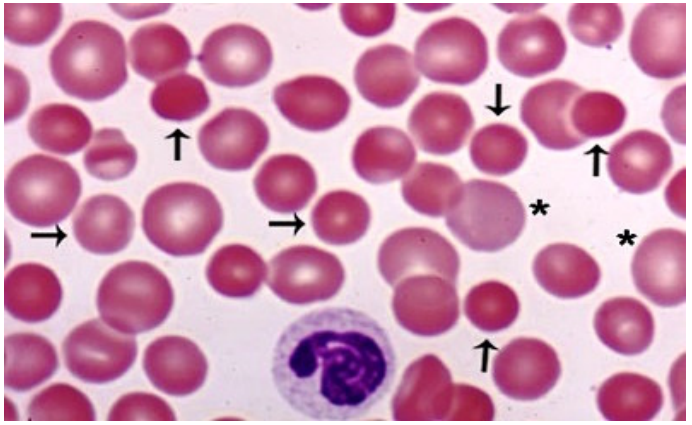
- ABO incompatability
- Red blood cell membrane defects (eg congenital spherocytosis)
- Red blood cell enzyme defects (eg G6PD deficiency)

ABO incompatability

- More common than Rh disease
- Most cases are very mild and require no treatment
- If jaundice develops only treatment required is phototherapy
- Mothers are usually Group O and babies Group A or B
- This can affect first pregnancy

Congenital Spherocytosis

- Most common red cell membrane defect
- Occurs 1 in 5000 live births in parents of northern European extraction
- Presents in neonate with unconjugated hyperbilirubinaemia
- Inherited as autosomal dominant trait with 25% new mutation



G6PD Deficiency

- Seen in all ethnic groups
- More common in people from central Africa (20%)
- Mediterranean (10%)
- Often presents in first few days of life with severe hyperbilirubinaemia and a completely normal blood film
- Diagnosis made by assaying G6PD in peripheral blood
- Counsel parents on what chemicals and foods may precipitate haemolysis .

Follow Up

- Folic acid and iron replacement
- Careful planned Fu tailored to the baby

Free Fetal DNA

- This an exciting new technique
- Can be used for prenatal diagnosis in a number of fetal conditons
- Particularly identifying blood groups of the fetus. If the fetus is Rh-ve then the pregnancy can be managed as a low risk

- Any Question ?