Management of the preterm neonate

Recent advances in UK practice

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Aims of this session

- Interactive talk
  - Not a didactic lecture
- Neonatal medicine is still an emerging field
  - Clinical trials
  - Evidence-based medicine
- Case-based discussion

Objectives

- By the end of this session, we should be able to:
  - Recognise the sick preterm neonate
  - Describe some of the problems faced by preterm neonates
    - Respiratory
    - Neurology
    - Gastrointestinal
  - Be aware of the trends in the UK practice in the management of the preterm neonate in the delivery room, the first hour of life, and beyond.

Let's talk about geography!

Case 1

Baby A

Mum A

- Emergency crash call on a night shift at 1.10a.m to the delivery unit
- Primigravida who had ruptured her membranes at 22 weeks gestation
  - Given dexamethasone 4 weeks ago
  - Now in active labour at 28+6 weeks

Antenatal steroids

- Antenatal steroids
  - Well known to be beneficial to preterm neonates
  - Reduce the incidence of respiratory distress syndrome
  - Decrease the risk of an intraventricular haemorrhage
- Maximal effect if delivery happens within 24h to 7 days

Baby A

- Baby A was born at 01.19
- Thermoregulation
  - placed in a plastic bag
- Gasped, with a heart rate of >100- APGAR at 1 min was 4
- Inflations breaths
  - With good chest rise
  - Ongoing poor respiratory effort
- Intubated and surfactant was administered for presumed respiratory distress syndrome
- Birth weight 1.35kg (75^{th} centile)

Within the first hour of life

- Baby A was transferred to the neonatal unit
- Respiratory
  - Placed on Synchronised Intermittent Mandatory Ventilation
  - With volume-guarantee at 4ml/kg
- Circulation
  - Peripheral cannula
  - Umbilical lines
- Fluids- She was started on 10% IV dextrose at 60ml/kg/day
- Haematology
  - IM vitamin K
- Sepsis
  - benzylpenicillin and gentamicin

Is the hard work over?

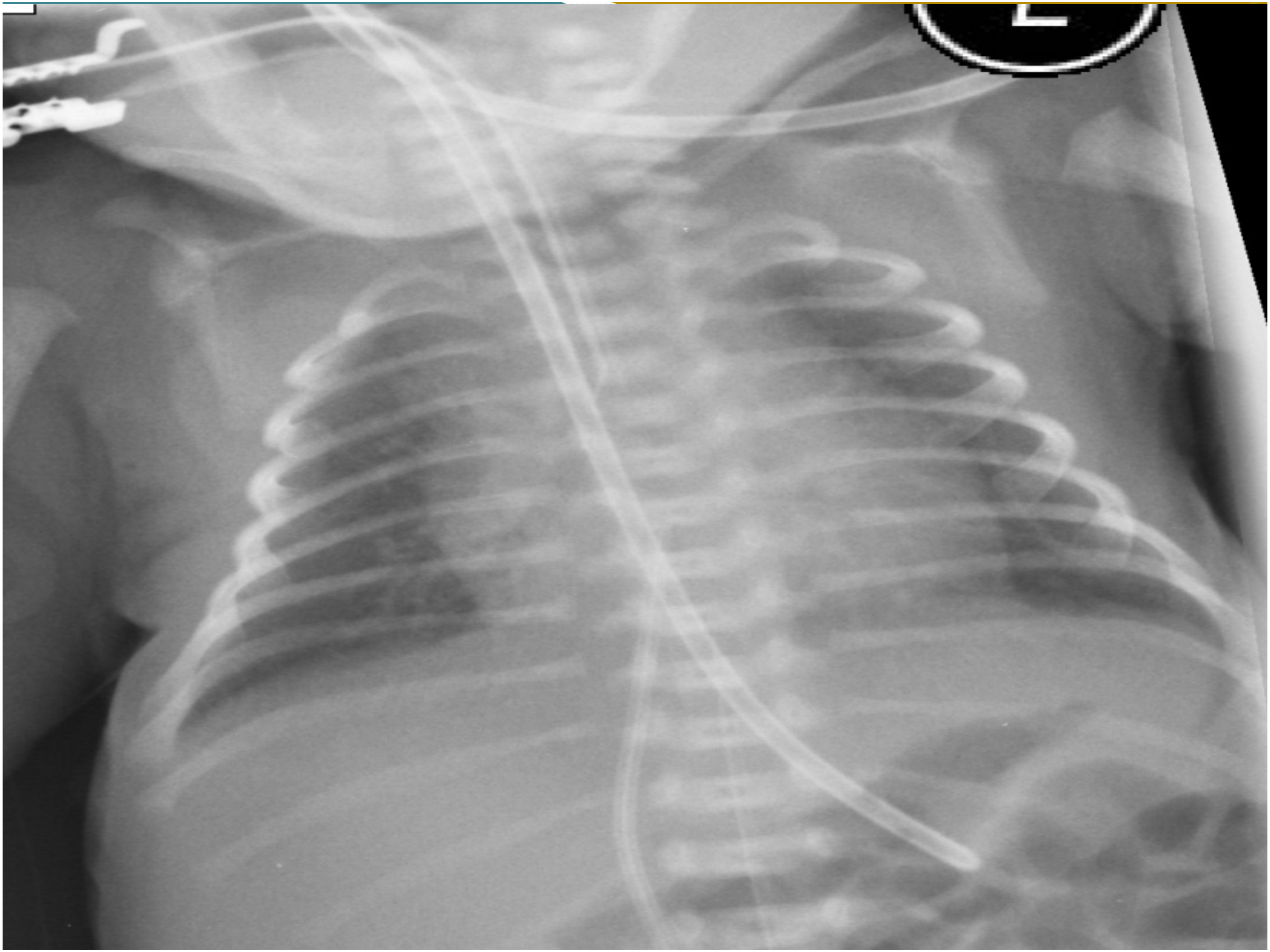
- We soon realised that baby A was much sicker than the average preterm baby that we admit onto our very experienced tertiary neonatal unit.
- Her oxygen requirements on conventional ventilation went up to 100%
- There was a difference of over 10% in her pre and post ductal saturation.
- Dropping of pre-ductal oxygen saturations down to 20%.
- Maternal history in more depth
  - Mum had received a course of antenatal steroids with dexamethasone at 24 weeks.
  - Scan showed profound oligohydramnios
  - Maternal CRP was 52 and mum was also being treated for sepsis

Differential diagnoses for the low oxygen saturations

- Respiratory distress syndrome (RDS)
- Congenital pneumonia
- Sepsis
- Congenital cardiac disease
- Pulmonary hypertension of the newborn (PPHN)

Investigations

- Blood gas- showed hypoxia
- Oxygenation Index (OI)
  - OI= $\frac{\text{mean airway pressure(cm } H_2O) \text{ x } FiO_2 \text{ (\%)}}{PaO_2\text{(mmHg)}}$
- CXR
  - Done at the end of the first hour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CXR findings

- ET tube position
- Lines position
- Clear lung fields

What is going through our minds?

- In view of the oligohydramnios, baby A was likely to have dry lung syndrome
- A clinical diagnosis of persistent pulmonary hypertension of the newborn was made
- She was switched to high frequency oscillation ventilation and despite an FiO2 of 90%, her saturation were in the 50%s

Further intervention

- Nitric oxide was started at 20ppm
- This helped to improve her saturation to the mid 70s
- She received muscle paralysis with pancuronium in an attempt to improve her oxygenation

Confirmation of clinical diagnosis

- An echocardiogram confirmed features consistent with PPHN
- Despite fluid boluses, she remained hypotensive and she needed quadruple inotopes with dopamine, dobutamine, adrenaline and hydrocortisone
  - The target blood pressure was 30.

Baby A's progress

- Baby A was very unstable from a respiratory and cardiac point of view for the first 5 days of her life
- But after this period, her clinical condition markedly improved
- She came off inotropic support on day 7 of life
- Nitric oxide was gradually weaned down and it was stopped on day 8 of life

What next?

- She was successfully extubated onto biphasic positive airway pressure non-invasive ventilation (BiPAP) on day 9 of life.
- Since then, Baby A went on to have an incredibly smooth neonatal course.
- She was transferred to a neonatal unit closest to her parents' house on day 16 of life on CPAP
- There she was gradually weaned off respiratory support and was self-ventilating in air since day 33 of life.
- Her cranial ultrasound scan was noted to be normal.
- She established full enteral feeds, initially via a nasogastric tube and then bottle feeds.
- She was discharged home, as a well infant, on day 54 of life at a corrected gestational age of 36+2 weeks gestation.

Persistent pulmonary hypertension of the newborn in the preterm neonate

- Persistent pulmonary hypertension of the newborn
  - Occurs when pulmonary vascular resistance (PVR) remains abnormally elevated after birth, resulting in right-to-left shunting
  - This in turn leads to severe hypoxemia that may not respond to conventional respiratory support
  - Co-existing factors like prematurity and sepsis make the management of this condition even more difficult
  - Dry lung syndrome secondary to preterm, premature rupture of membranes is a recognised cause of PPHN in preterm neonates

Nitric oxide in PPHN in the preterm neonate

- From the current literature, it appears that the outcome for preterm babies with PPHN is still poor
- The efficacy of nitric oxide as a pulmonary vasodilator in preterm infants is the subject of many studies
  - Decreases perfusion-ventilation mismatch in the lungs
  - Decreases ductal shunting
  - Minimises lung inflammation
  - Decreases the risk of bronchopulmonary dysplasia (BPD)

Day 1	• Intubated and ventilated on HFOV, started on nitric oxide and inotropic support
Day 7	• Stopped all inotropes and started weaning of nitric oxide
Day 8	• Stopped nitric oxide
Day 9	• Extubated to Biphasic Positive Pressure Ventilation (BiPAP)
Day 16	• Changed to Continuous Positive Pressure Ventilation (CPAP)
Day 33	• Self-ventilating in air
Day 54	• Discharged home

Case 2

- Baby B

Mum B- Antenatal history

- Mum's 3rd pregnancy
  - 2 previous healthy children
- Dating scan at 13 weeks at her local hospital
  - Monochorionic, monoamniotic twins
- Referred to a specialist centre for 2 weekly fetal scans
- Detailed fetal echo at 19 weeks- normal

Antenatal scans

- Antenatal scan at 26 weeks shows:
- Twin 1 estimated 851g
- Twin 2 estimated 905g
- 6% weight discrepancy

Antenatal scans- cont

- Repeat scan at 28+6 weeks
- Acute **Twin-to-twin transfusion syndrome**
- Twin 1: 1160g, anhydramnios
- Twin 2: 1410g, polyhydramnios
- 18% difference in foetal weight
- Umbilical dopplers normal
- But increased Peak Systolic Velocity(PSV) in Middle Cerebral Artery (MCA) in Twin 1, decreased PSV in MCA in twin 2

The next day

- 29+0 weeks
- Poor trace on CTG
- Emergency c-section in the local hospital
- Twin 1- stillbirth
- Twin 2- live birth

Twin 2

- Recipient twin
- BW 1.38kg (50th to 75th centile)
- Intubated, given surfactant and ventilated at the local hospital- before being transferred to Cambridge

Baby B

Respiratory system

- Difficult ventilation
- Initially on SIMV(synchronised intermittent mandatory ventilation)
- Required high frequency oxygenation ventilation (HFOV) for 5 days
- Extubated onto nasal Continuous Positive Airway pressure(CPAP)
- Switched to high flow nasal cannula (HFNC) O2 on day 6
- Self-ventilating in air (SVIA) on day 9

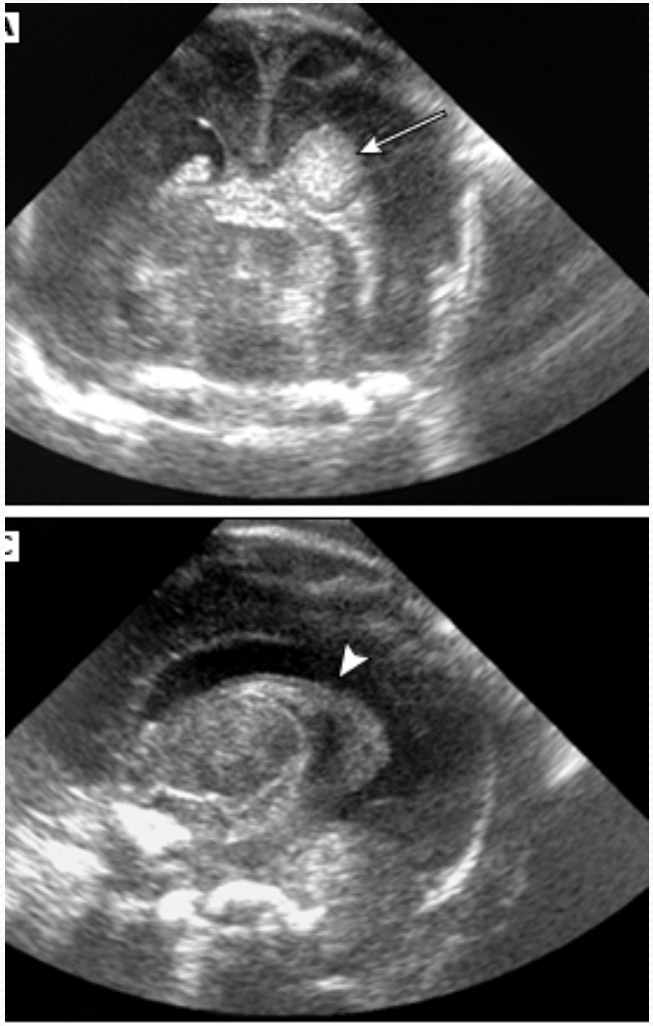
Other systems

- Cardiovascular- no concerns
- Feeds/fluids- on parenteral nutrition and gradually established feeding as per the high risk protocol
- Haematolgy- Hb 188
- Metabolic- jaundice. DAT negative

Cranial ultrasound scans

<28 Weeks	**28-32 Weeks**
Admission	Admission
Day 2	
Day 3	
Day 7	Day 7
Day 14	Day 14
Day 21	Day 21
Monthly to 36 weeks	
Discharge	Discharge

Cranial ultrasound scan



Neurology

- Left-sided intraventricular haemorrhage(IVH)


Quiz

True or false

- Monochorionic, diamniotic twins are always identical twins

- Dichorionic, diamniotic twins are always non-identical twins

Timing of division post-fertilization in monozygotic twins

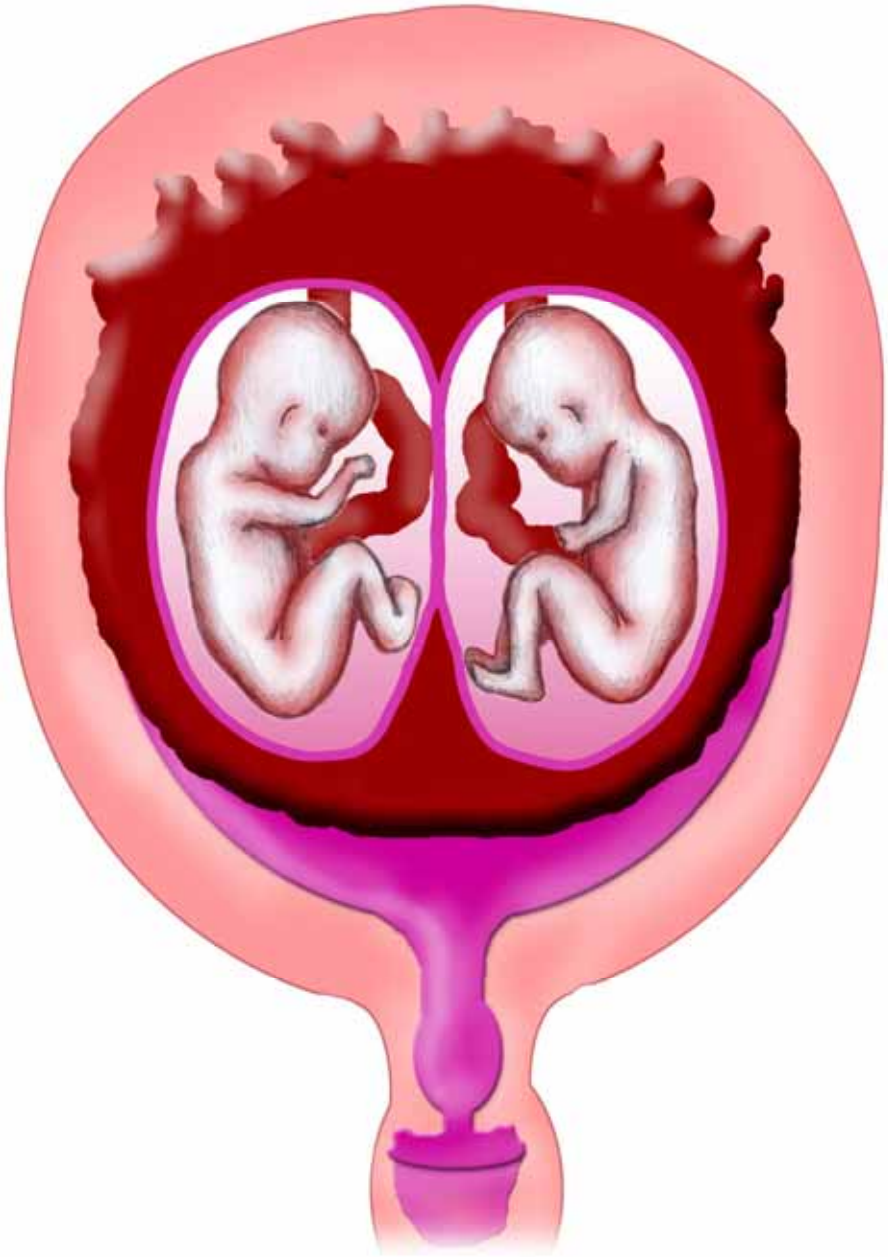
- Diamniotic, dichorionic placentation occurs with division within 3 days post fertilization.
- Diamniotic, monochorionic placentation occurs with division between days 4 and 8 post fertilization.
- Monoamniotic, monochorionic placentation occurs with division between days 8 and 12 post fertilization.
- Division at or after day 13 results in conjoined twins.

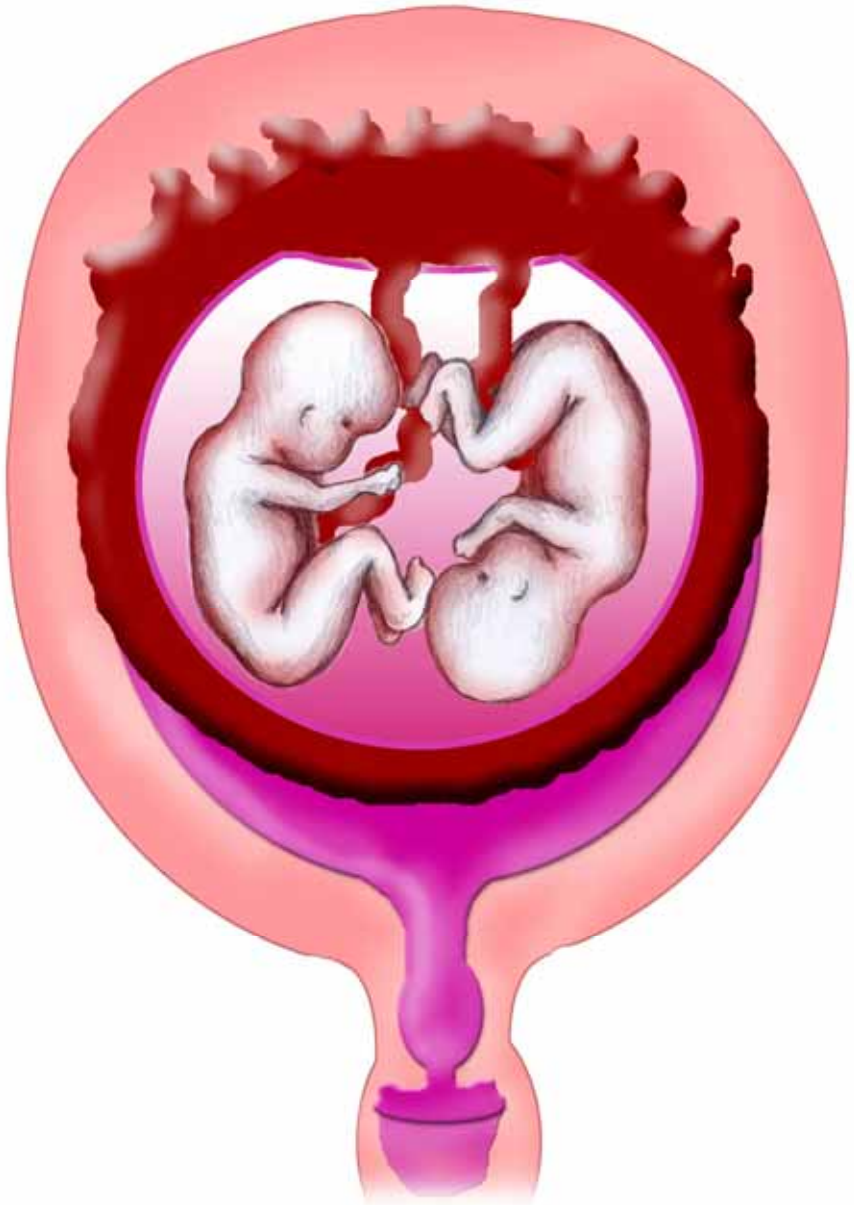
Multiple choice

- Which of the following are at risk of Twin-to-Twin transfusion syndrome (TTTS)?
  - A. Monozygotic twins with monochorionic, diamniotic placentation (MCDA)
  - B. Monozygotic twins monochorionic, monoamniotic placentation (MCMA)
  - C. Monozygotic twins with dichorionic, diamniotic placentation (DCDA)
  - D. Dizygotic twins with dichorionic, diamniotic placentation (DCDA)
  - E. All of the above

Twin-to-twin transfusion syndrome(TTTS)

- Only occurs in monozygotic (identical) twins with a monochorionic placenta
- Intrauterine blood transfusion from one twin (donor) to another twin (recipient)
- Occurs through placental vascular anastomoses
  - most common vascular anastomosis is a deep, artery-to-vein anastomosis through a shared placental cotyledon





Epidemiology

- Monozygotic twins occur in 3-5 per 1000 pregnancies
- Approximately 75% of monozygotic twins are monochorionic
- TTTS occurs in 5-38% of monochorionic twins
- Severe TTTS has a 60-100% fetal or neonatal mortality rate
- Fetal demise of one twin is associated with neurologic sequelae in 25% of surviving twins

Clinical signs of TTTS

- Rapidly increasing fundal height over 2-3 weeks
  - polyhydramnios develops in the amniotic sac of the recipient twin

Antenatal echo

- 20% difference in weight
- Donor twin becomes hypovolaemic and oliguric/anuric
  - Oligohydramnios
  - foetal bladder not visualised because of absent urine.
- Recipient twin becomes hypervolaemic and polyuric
  - Polyhydramnios
- Either twin can develop hydrops fetalis.
- The donor twin can become hydropic because of anaemia and high-output heart failure.
- The recipient twin can become hydropic because of hypervolaemia

Grading of TTTS

Stage	Oligohydramnios/ Polyhydramnios	Absent Urine in Donor Bladder	Abnormal Doppler Blood Flows	Hydrops Fetalis	Fetal Demise
I	+	-	-	-	-
II	+	+	-	-	-
III	+	+	+	-	-
IV	+	+	+	+	-
V	+	+	+	+	+

Treatment in utero

- Reduction amniocentesis
  - draining the amniotic fluid from around the recipient twin
  - may improve circulation in the donor twin
- Fetoscopic laser photocoagulation of chorionic plate vessels
  - reserved for more severe cases, especially those that do not respond to amnioreduction
  - In pregnancies treated with fetoscopic procedures, the overall survival is 75% with 85% having at least 1 fetus survive
- Timing of delivery depends on multiple factors
  - ideal would be for delivery at term

Presentation of TTTS at birth

- Donor twin
  - More than 20% smaller than recipient twin
  - Pallor
  - Poor peripheral perfusion
- Recipient twin
  - More than 20% larger than donor twin
  - Plethoric
  - Jaundice
- Hydrops fetalis can be present in either twin in TTTS. These infants have subcutaneous oedema, a distended abdomen, and respiratory distress.

Systemic evaluation

- Cardiovascular:
  - The recipient twin may develop hypertension or hypertrophic cardiomegaly
- Respiratory
  - Both may need respiratory support
- Gastrointestinal
  - In hydrops fetalis- ascites
- Metabolic
  - Recipient: hyperbilirubinemia after birth

Systemic examination- cont

- Haematology:
  - The donor twin is anaemic at birth
  - The recipient twin is polycythaemic at birth
  - Disseminated intravascular coagulation
  - Thrombocytopenia
- Electrolytes
  - Hypocalcaemia in the donor twin
- Renal
  - Either twin may have evidence of renal dysfunction

Treatment of infants with TTTS

- Medical care of twins after birth is directed toward problems related to prematurity
- Severely anaemic donor twins may require packed RBC transfusions
- Polycythaemic recipient twins may require partial exchange transfusion to lower serum haematocrit levels
- Newborns with hydrops fetalis may require mechanical ventilation, thoracocentesis, pericardiocentesis, and paracentesis.

Neurological outcome

- Intrauterine demise of one twin can result in neurologic sequelae in the surviving twin
- Acute exsanguination of the surviving twin into the relaxed circulation of the deceased twin can result in intrauterine CNS ischemia

Altered Fetal Cerebral and Cerebellar Development in Twin-Twin Transfusion Syndrome. T.Tarui et al. *American Journal of Neuroradiology*. 2012 33: 1121-1126

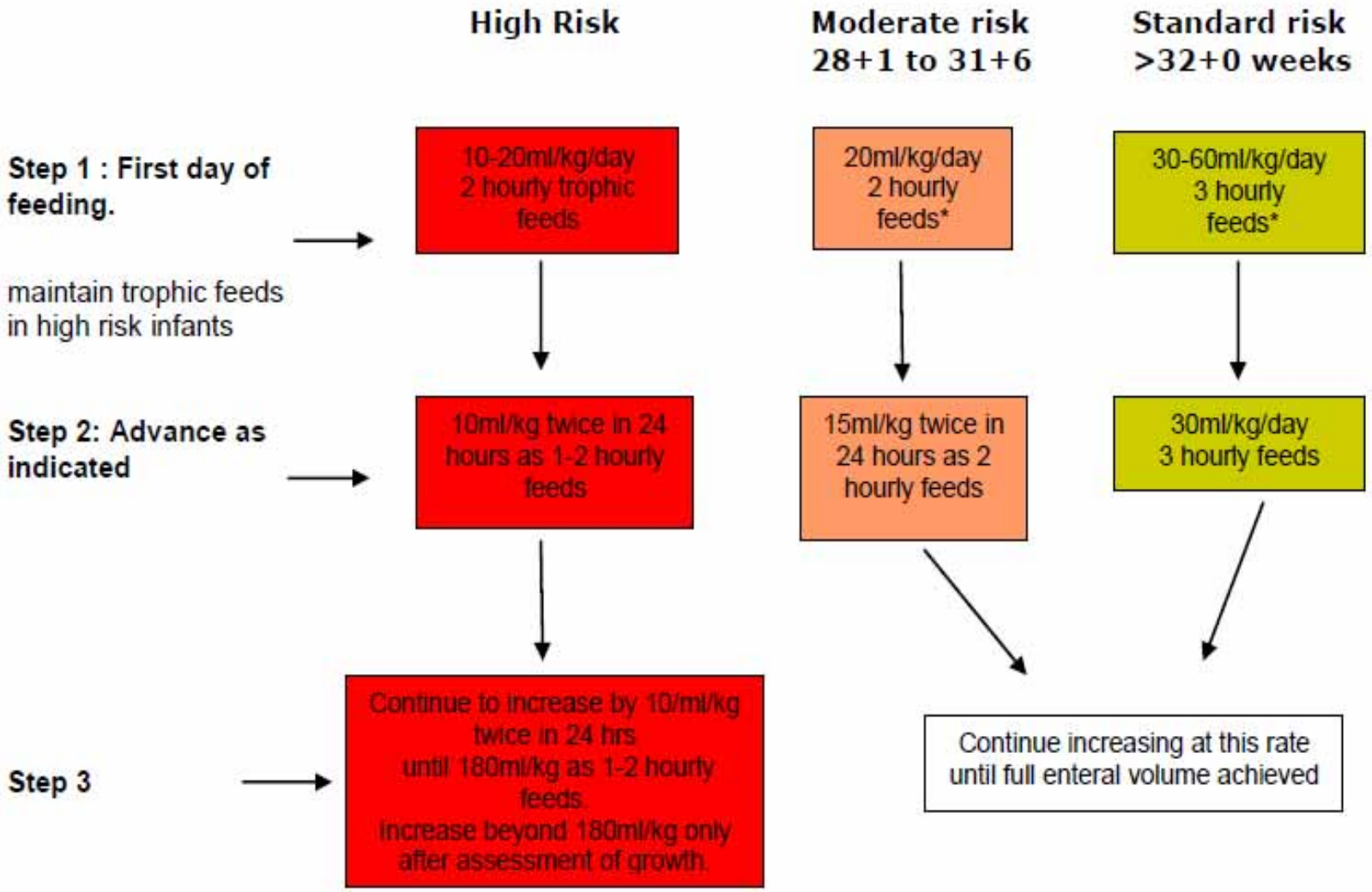
- Review of foetal brain MRI of 33 twin pairs with TTTS
- Ventriculomegaly
  - Most common anomaly(63%) in both donor and recipient
  - Likely secondary to cardiovascular instability
- Foetuses with TTTS may have subtle global structural abnormalities such as gray and white matter volume reduction and altered growth
  - late-emerging neurodevelopmental abnormalities, such as impairment of language and learning

Case 3

- Baby C

Baby C

- Born at 28+4 days, birth weight 1.05kg (50th centile)
- Now 20 days old- 31+4 days corrected
- “Well baby”
- Respiratory system
  - “In and out” surfactant
  - BiPAP
  - Currently self-ventilating in air
- Cardiovascular system- no concerns
- Metabolic- jaundice- phototherapy
- Gastrointestinal- fed as per the moderate risk feeding protocol
  - Now fully enterally fed via a nasogastric tube using expressed breast milk


High Risk
Moderate risk
28+1 to 31+6
Standard risk
>32+0 weeks
Step 1 : First day of feeding.
10-20ml/kg/day
2 hourly trophic feeds
20ml/kg/day
2 hourly feeds*
30-60ml/kg/day
3 hourly feeds*
maintain trophic feeds in high risk infants
Step 2: Advance as indicated
10ml/kg twice in 24 hours as 1-2 hourly feeds
15ml/kg twice in 24 hours as 2 hourly feeds
30ml/kg/day
3 hourly feeds
Step 3
Continue to increase by 10/ml/kg twice in 24 hrs until 180ml/kg as 1-2 hourly feeds
Increase beyond 180ml/kg only after assessment of growth
Continue increasing at this rate until full enteral volume achieved

At the start of the shift

- Asked to review
  - Desaturations (with bradycardia)- correcting with stimulation

- What goes through your mind?

Further information

- History:
  - Large gastric aspirate ?bilious
- On examination
  - Distended abdomen + appears shiny

Differentials

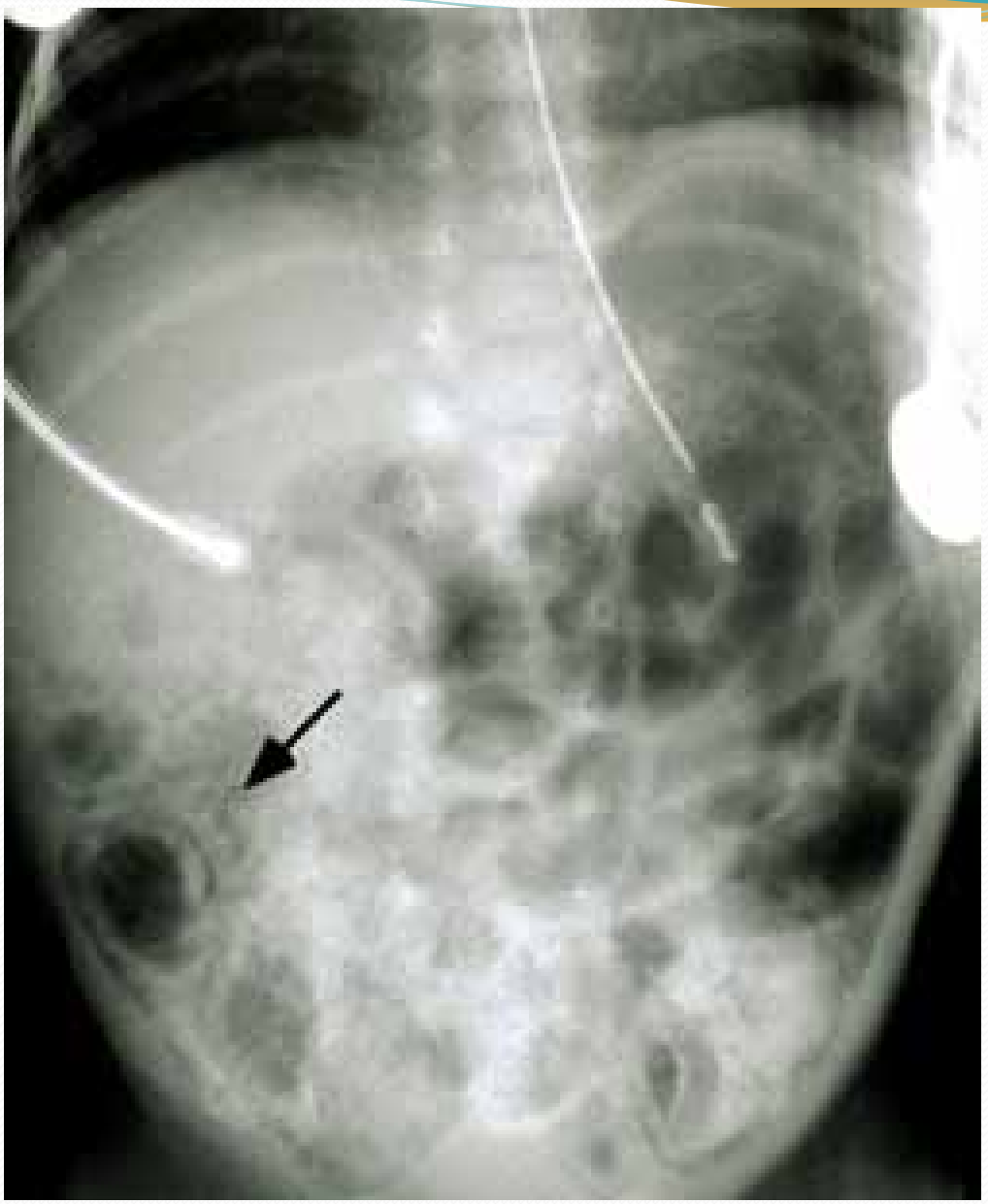
- Sepsis
- Necrotising enterocolitis
- Intestinal malrotation
- Intestinal volvulus

Clinical findings in NEC

- Suspect the diagnosis if there is:
- Abdominal distension.
- Bilious aspirates.
- PR Blood.
- Systemic signs of sepsis

Investigations

- Blood gas
- Full blood count
- Cross-match
- Urea and electroytes
- CRP
- Blood cultures
- Abdominal x-ray (AXR)



AXR findings in NEC

- Abnormal gas pattern with dilated loops of bowel
- Pneumatosis intestinalis appears as bubbles of gas in the small bowel wall
- Pneumoperitoneum typically appears when bowel perforation
  - "football" sign- a large hypolucent area in the central abdomen with markings from the falciform ligament
  - Portal vein gas
- Sentinel loops, a loop of bowel that remains in fixed position, is suggestive of necrotic bowel

Our initial management

- Feeds stopped- kept nil by mouth
- NG tube on free drainage
- IV access
- Triple antibiotics- benzylpenicillin, gentamicin, metronidazole
- Started on IV fluids

Keeping an eye on Baby C

- Monitor clinical status
- Laboratory studies (white cell and platelet count, lactate, serum bicarbonate and glucose)
- Repeat AXR to assess the response to medical management

Deterioration in Baby C's condition

- Profound apnoeas
  - Intubated and ventilated
- Worsening abdominal distention
- PR bleeding
- Bilious NG aspirates
- Lactate- 5
- Surgical team asked to urgently review Baby C
  - Took her to theatre the next day

In theatre

- Open laparotomy
- Necrotic small and large bowel
- Extensive bowel resection
- Left with 2 cm of jejunum and a jejunostomy

Modified Bell staging criteria for necrotizing enterocolitis (NEC) in neonates

Stage	Classification of NEC	Systemic signs	Abdominal signs	Radiographic signs
IA	Suspected	Temperature instability, apnea, bradycardia, lethargy	Gastric retention, abdominal distention, emesis, heme-positive stool	Normal or intestinal dilation, mild ileus
IB	Suspected	Same as above	Grossly bloody stool	Same as above
IIA	Definite, mildly ill	Same as above	Same as above, plus absent bowel sounds with or without abdominal tenderness	Intestinal dilation, ileus, pneumatosis intestinalis
IIB	Definite, moderately ill	Same as above, plus mild metabolic acidosis and thrombocytopenia	Same as above, plus absent bowel sounds, definite tenderness, with or without abdominal cellulitis or right lower quadrant mass	Same as IIA, plus ascites
IIIA	Advanced, severely ill, intact bowel	Same as IIB, plus hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis, DIC, and neutropenia	Same as above, plus signs of peritonitis, marked tenderness, and abdominal distention	Same as IIA, plus ascites
IIIB	Advanced, severely ill, perforated bowel	Same as IIIA	Same as IIIA	Same as above, plus pneumoperitoneum

Indications for surgery in NEC

- Necrosis extending through the bowel wall and resulting in perforation.
  - pneumoperitoneum on AXR
- However peritonitis, extensive necrosis, or perforation can occur without evidence of free air on the radiograph
  - As a result, other signs that indicate peritonitis must be considered (clinical deterioration, presence of an abdominal mass, ascites, or intestinal obstruction)
- Surgical procedures performed for NEC
  - either exploratory laparotomy with resection of the affected intestinal region
  - or primary peritoneal drainage (PPD)

Baby C grows!!!

- She is now 1 year old
- A delightful child

- But with complications from her surgery for NEC in her early life

Late complications of surgery

- Stricture formation
- Short bowel syndrome

Short bowel syndrome

- Short bowel syndrome occurs in approximately 9% of infants who undergo surgery for NEC
- Results in significant malabsorption
- Macronutrient and micronutrient deficiency
- NEC is the 2nd most common cause of neonatal onset intestinal
- Total parenteral nutrition(TPN) dependent
- TPN places her at risk of sepsis, cholestasis, and liver failure.
- Intestinal and hepatic transplantations have been performed as life-saving procedures in patients with these complications

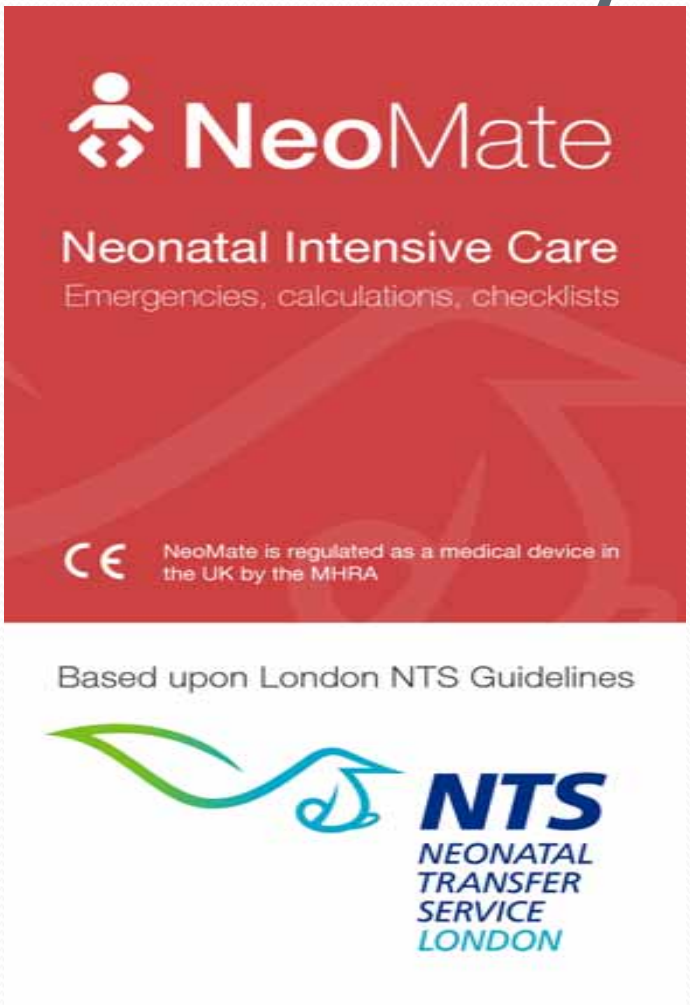
Prognosis with NEC

- Prognosis of NEC has improved with earlier recognition and treatment
- Survival rates- 70 to 80%
- Half of the survivors are normal
- Long-term sequelae
  - short bowel syndrome
  - intestinal strictures
  - increased frequency of bowel movements with loose stools
  - impairment of growth and neurodevelopmental outcome.

In summary

- Case-based discussion of the management of preterm neonates in the current UK setting
- Identified a range of problems faced by these preterm infants
- Discussed about useful investigations in these settings
- Explored the management strategies employed

And in today's era…



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Thank You!

Any questions?

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References

- Aikio O, Metsola J et al. Transient defect in nitric oxide generation after rupture of fetal membranes and responsiveness to inhaled nitric oxide in very preterm infants with hypoxic respiratory failure. *J Pediatr.* 2012 Sep;161(3):397-403
- Chung-Hua Fu Chan Ko Tsa Chih. Perinatal outcome of monochorionic twin pregnancies. *Chinese Journal of Obstetrics & Gynecology* 2013, vol./is. 48/6(405-10)
- Cincotta RB, Gray PH, Gardener G, Soong B, Chan FY. Selective fetoscopic laser ablation in 100 consecutive pregnancies with severe twin-twin transfusion syndrome. *Aust N Z J Obstet Gynaecol*. Feb 2009;49(1):22-7
- Elimian A, Verma U et al. Effectiveness of antenatal steroids in obstetric subgroups. *Obstet Gynecol*. 1999 Feb;93(2):174-9
- Kenton AB, O'Donovan D, Cass DL, et al. Severe thrombocytopenia predicts outcome in neonates with necrotizing enterocolitis. *J Perinatol* 2005; 25:14.
- Kinsella JP, Cutter GR et al. Early Inhaled Nitric Oxide Therapy in Premature Newborns with Respiratory Failure. *N Engl J Med* 2006; 355:354-364
- Kumar VH, Hutchison AA et al. Characteristics of pulmonary hypertension in preterm neonates. *J Perinatol.* 2007 Apr;27(4):214-9
- Sehgal A, Francis J et al. Dry Lung Syndrome: A Distinct Clinical Entity. *The Indian Journal of Paediatrics* 2010; Volume 77, Issue 9, pp 1029-1031
- Pourcyrous M, Korones SB, Yang W, et al. C-reactive protein in the diagnosis, management, and prognosis of neonatal necrotizing enterocolitis. *Pediatrics* 2005; 116:1064..
- Sekar K. Inhaled nitric oxide in term and preterm infants. *Journal of Perinatology* 2006; 26, S4–S7
- Subhedar N, Dewhurst C. Is nitric oxide effective in preterm infants? *Arch Dis Child Fetal Neonatal Ed* 2007;92:337–341
- Teng RJ, M.D. Wu TJ. Persistent pulmonary hypertension of the newborn. *Formos Med Assoc.* April 2013; 112(4): 177-184