PREMATURITY

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Introduction

- About 7–8% of all births are born preterm (<37 weeks' gestation).
- Preterm births account for the majority of work on most neonatal intensive care units (NICUs).
- Preventing preterm birth has become the foremost challenge for obstetric practice today.
- They require an expert and careful intervention to support in the immediate neonatal period.

Gestational age

Table 11.1 Gestational age bands and their incidence.

Gestational age (weeks after LMP)	Terminology	Approximate incidence (as % singleton live births)[a]
>42 weeks	Post term	4
37–42 weeks	Term	90
<37 weeks	Preterm	6–8
34–36 weeks	Late preterm[b]	4.9
32–34 weeks	Moderately preterm[b]	0.8
28–32 weeks	Very preterm[b]	1.3
<28 weeks	Extreme preterm[b]	0.4
≤24 weeks	Threshold of viability	0.14

[a] The frequency of preterm birth is much higher in multiples (twins, triplets, etc.).

[b] The definitions of these gestation bands vary between different countries and authors.

Risk factors for preterm labour

Table 11.2 Risk factors for preterm labour and prematurity.

Factor	Comment
Maternal age	Extremes of age (<18 yrs or >35 yrs) are associated with preterm labour
Maternal ethnicity	Afro-Caribbean mothers have a 15% incidence of preterm labour
Multiple pregnancy	The higher the multiple, the greater the chance of preterm delivery
Infection	Chorioamnionitis is strongly associated with extreme preterm labour
Hypertension, PET	Labour often induced early to maintain maternal health
Cervical weakening	Previous midtrimester pregnancy loss or cervical surgery (e.g. cone biopsy
Uterine malformation	Bicornuate uterus or massive fibroids
Antepartum haemorrhage	Abruption or placenta praevia
Amniotic fluid volume	Polyhydramnios and oligohydramnios are both risk factors
Maternal substance abuse	Alcohol, cocaine and cigarette smoking all associated with preterm labour
Fetal abnormality	Congenital anomalies and trisomies are associated with preterm delivery

Clinical management of preterm labour

- **Magnesium sulphate** does not delay delivery but has been shown to reduce the risk of cerebral palsy in the preterm infant and is recommended below 30 weeks gestation.

- **Betamethasone** has been shown to be associated with fewer adverse effects than dexamethasone.

- Corticosteroids **given for 48 h before delivery significantly reduce**

1. **The incidence and severity of respiratory distress syndrome (RDS),**
2. **The incidence of intraventricular haemorrhage (IVH),**
3. **Risk of NEC**
4. **Neonatal mortality**
5. **Possibly improve neurodevelopmental outcome**.

Survival and outcome for the preterm infant

Table 11.3 Survival rates to discharge home by gestational age and birthweight for babies admitted alive into Australian and New Zealand intensive care nurseries in 2013. Note that these data do not include babies who die before admission or who are not resuscitated.

Gestation at birth (weeks)	Survival (%)	Birthweight (g)	Survival (%)
<24	43	400–499	56
24	66	500–749	73
25	84		
26	88	750–999	90
27	94	1000–1249	95
28–32	97	1250–1500	95

Source: Chow, S.W. (2015) *Reports of the Australian and New Zealand Neonatal Network* 2013. ANZNN, Sydney.

Survival and outcome for the preterm infant

Long-term outcomes

- It is clear that there is an **additional hidden burden of subtle neurodisability occurring in the most preterm babies (<26 weeks).** This can occur **even in the absence of obvious central nervous system (CNS) damage or haemorrhage**, and may be related to a subtle disruption of the normal neuronal pathways that are developing in the third trimester.

- There is a higher than expected incidence of

1. **Attention deficit hyperactivity disorder (ADHD),**
2. **Autistic features**
3. **Subtle learning difficulties** than in term-born controls.
4. **Lower Final stature,**
5. **Lower IQ,**
6. **Hearing and visual function**.

Stabilization at birth and management in the ‘golden hour’

- Ideally, the baby will have been **transferred *in utero* to a perinatal center with a suitable NICU**.
- In general, these **babies are fragile, and usually not severely asphyxiated**.
- They benefit from a **calm transition** and **avoidance of trauma** or **hyperoxygenation**.
- Once in the NICU they should have **vascular access secured** and from then on have ‘**minimal handling**’.

Stabilization at birth and management in the 'golden hour'

Table 11.5 Approach to stabilization of a preterm infant ≤28 weeks.

Factor	Comment
Personnel	Experienced staff required – usually two neonatal doctors/practitioners and a neonatal nurse to attend
Thermoregulation	The room must be warm. An overhead heater should be turned on. Place the baby in a clear plastic bag/wrap immediately at delivery (without drying first) and place under the overhead heater. Put a bonnet over the head. Monitoring of the heart rate can take place through the plastic bag. Do not remove until the baby is in a warm, humidified incubator. Hypothermia <36 °C massively increases the mortality in preterm babies
Airway	As at term, keep the head in the neutral position. You will need a small face mask and should have a small laryngoscope and ET tubes (2.0, 2.5 and 3.0 mm) available
Breathing	Use lower peak pressures (20–25 cmH_2O) to prevent lung damage. PEEP (5–6 cmH_2O) is very important and must be maintained throughout the stabilization. Use an air–oxygen mix and be prepared to increase the oxygen concentration. Use a saturation monitor and avoid hyperoxia (see below). Give surfactant early, once the ET tube has been confirmed clinically to be correctly located. If attempting CPAP (see below), it is vital that PEEP is maintained throughout
Circulation	A rise in heart rate is a valuable sign of effective lung aeration, as chest movement is harder to see than at term. Saturation monitoring or ECG leads can measure the pulse.
Drugs	These are rarely indicated. If there has been sufficient asphyxia that the heart rate does not respond to lung inflation, a senior doctor should consider whether it is in the best interests to continue aggressive resuscitation as the prognosis will be poor. A lower dose of prophylactic vitamin K is required than at term.
Parents	Transfer the baby to the NICU as soon as possible, but try to allow the mother to see her baby, even if only briefly, before you leave the room.
Vascular access	Once the baby is in a warm, humidified incubator, a skilled operator should insert an umbilical venous and arterial line (see CLINICAL TIP above).

ET, endotracheal; PEEP, positive end-expiratory pressure; CPAP, continuous positive airway pressure.

Table 11.6 Common problems in the preterm infant.

Problem	Impact
Pulmonary immaturity	Apnoea, RDS, and chronic lung disease of prematurity (bronchopulmonary dysplasia) are common. Pneumothorax and pneumonia can occur.
Fragile capillary network in the subependymal area	High risk of IVH, especially in response to swings in cerebral perfusion pressure and carbon dioxide level. Large IVH can cause venous infarction or hydrocephalus (see Chapter 22)
White matter injury	Periventricular white matter susceptible to ischaemic damage, especially if sensitized by fetal inflammation (infection). Preterms are less able to tolerate perinatal asphyxia. High risk of periventricular leukomalacia (PVL) – see Chapter 22)
Thermal instability	Hypothermia exacerbates RDS and increases mortality. If environmental temperature is too low the baby will expend energy keeping warm at the expense of growth
Feed intolerance and lack of suck-swallow reflexes	Immature or absent suck–swallow and gag reflex. Need NG feeding. Poor gut motility may cause feed intolerance. Prematurity is also the main risk factor for necrotizing enterocolitis (NEC) – see Chapter 17.
Patent ductus arteriosus (PDA)	Risk of congestive heart failure and risk factor for NEC and IVH
Immature visual system	Risk of ROP (see Chapter 23) and myopia/strabismus
Jaundice	High red cell mass and poor liver conjugation makes hyperbilrubinaemia almost inevitable. Acidosis and a poor blood–brain barrier increases the risk of kernicterus (see Chapter 19)
Renal immaturity	Inability to concentrate urine, and to excrete an acid load with a low renal bicarbonate threshold, resulting in late metabolic acidosis which may be associated with failure to gain weight satisfactorily. Treatment with sodium bicarbonate and feeding with breast milk or appropriate preterm formula feeds usually improves the acidosis
Metabolic disturbance	Hypoglycaemia, hypocalcaemia, hypomagnesaemia, hyponatraemia, hypernatraemia, hyperkalaemia are all common and must be anticipated
Infection	Relative immunodeficiency and breech of natural barriers (e.g. by central venous lines) predispose to infection, which may be nosocomial or maternal in origin
Haematological disorders	Disseminated intravascular coagulation, vitamin K deficient bleeding and iatrogenic or iron-deficient anaemia are more common, but not inevitable
Surgical problems	Undescended testes, inguinal and umbilical hernias

Complications and Supportive care on the NICU

Monitoring

- Heart rate, respiratory rate, blood pressure and temperature must be monitored continuously, with appropriate alarm signals. An apnoea monitor is often used in the special care nursery.

Thermoregulation

- Body temperature must be maintained in the normal range by nursing the preterm infant in a closed, humidified incubator.

Complications and Supportive care on the NICU

Oxygen therapy

- Oxygen is a potentially **toxic substance** in the preterm infant, and may cause **retinopathy of prematurity (ROP) and chronic lung disease.**

- It must therefore be administered with the utmost care and the response continuously monitored with **regular measurements of PaO2 (through blood gas, pulse oximeter or transcutaneous monitor.**

- Oxygen can be administered directly into the incubator or by nasal prongs but nasal continuous positive airway pressure (CPAP) or high-flow humidified oxygen therapy (HFNT) are usually used in the immediate newborn period and even intubation with mechanical ventilation maybe required.

- Oxygen should be warmed and humidified.


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Complications and Supportive care on the NICU

Birth Asphyxia or HIE.

- is the **most common cause** of neonatal seizures in both **full-term and preterm infants** and causes up to 50% of seizures in the first 48 hours of life (more common first 24 hours of life).
- MRI studies suggest the period around birth accounts for >75% of the causative period.
- It can be secondary to prenatal, perinatal, and postnatal causes.

- **Neonatal signs**
  - **Apgar score <5 at 5 minutes and 10 minutes.**
  - **Fetal umbilical artery acidemia** pH <7 and base deficit >12 mmol/L or both.
  - **Neuroimaging evidence of acute brain injury** seen on brain (MRI) consistent with HI.
  - **Presence of multisystem organ failure** consistent with HIE (renal, cardiac, pulmonary, hepatic, GI, hematological and metabolic) .

- **Developmental outcome is spastic quadriplegia or dyskinetic cerebral palsy.**

Sarnat scale for HIE

Features	Stage I	Stage II	Stage III
Severity	Mild degree	Moderate degree	Severe degree
Consciousness	Hyper alert and irritable	Lethargic and obtunded	Comatosed
Pupils	Dilated	Constricted	Dilated
Tone	Normal tone	Marked hypotonia	Flaccidity
Reflexes	Normal or increased	Sluggish	Absent
Seizures	No seizures and symptoms usually resolve in less than 24 hours	Seizures are common	Seizures are frequently seen and more resistant to treat with anticonvulsants
EEG	Normal	Abnormal	abnormal with decreased background activity
Apgar score	5 to 7	3 to 4	1 to 2

Therapeutic Hypothermia as management for HIE

Complications and Supportive care on the NICU

Respiratory distress syndrome (RDS)

- Even with the advent of **antenatal corticosteroids and postnatal surfactant**, which have radically reduced mortality and morbidity, RDS remains the major problem for the preterm baby in the first week of life.

- Nowadays the challenge has moved from preventing death from RDS to preventing chronic lung disease of prematurity.

- There has been a recent shift towards the early use of **non-invasive ventilation (CPAP or high-flow nasal therapy; HFNT), even in the most extreme preterm infants, with the aim of avoiding mechanical ventilation**.

Complications and Supportive care on the NICU

Respiratory distress syndrome (RDS)

- For **infants less than 32 weeks' gestation, airway stabilization at birth with CPAP** is the standard of care.

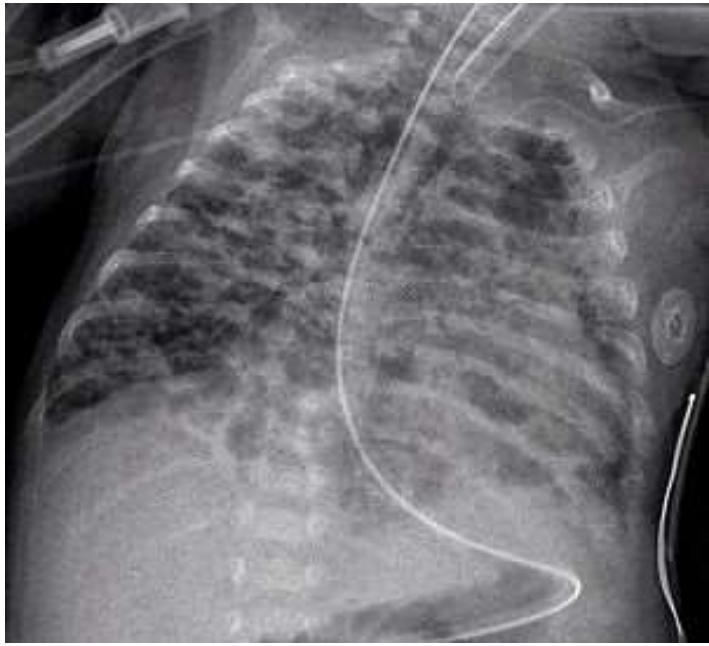
- **If the baby is intubated, exogenous 'prophylactic' surfactant should be administered as soon after birth as possible**.

- 'Rescue' surfactant treatment for those babies who do not cope on CPAP or HFNT may be delivered by the **'InSurE' technique**: Intubation, Surfactant, Extubation.

- A modification of this is to instill surfactant into the trachea via a fine catheter while the baby remains breathing on CPAP. This is known **as minimally invasive surfactant therapy (MIST) or less invasive surfactant administration (LISA).**

Complications and

Bronchopulmonary Dysplasia (BPD)



- BPD defined as **persistent oxygen dependency up to 28 days of life**.

- The severity of BPD-related pulmonary dysfunction and neurodevelopmental impairment in early childhood is more accurately predicted by an **oxygen dependence at 36 weeks' postmenstrual age (PMA) in infants <32 weeks' gestational age (GA) and at 56 days of age in infants with older GA**.

Apnea of prematurity

Central apnea - total cessation of respiratory movements, and consequent cessation of airflow in the upper airways.

Obstructive apnea - cessation of airflow in the upper airways in the presence of active respiratory movements.

Mixed apnea - episode of central apnea followed by obstructive episode (respiratory movements without airflow in the airways) or obstructive episode followed by central apnea.

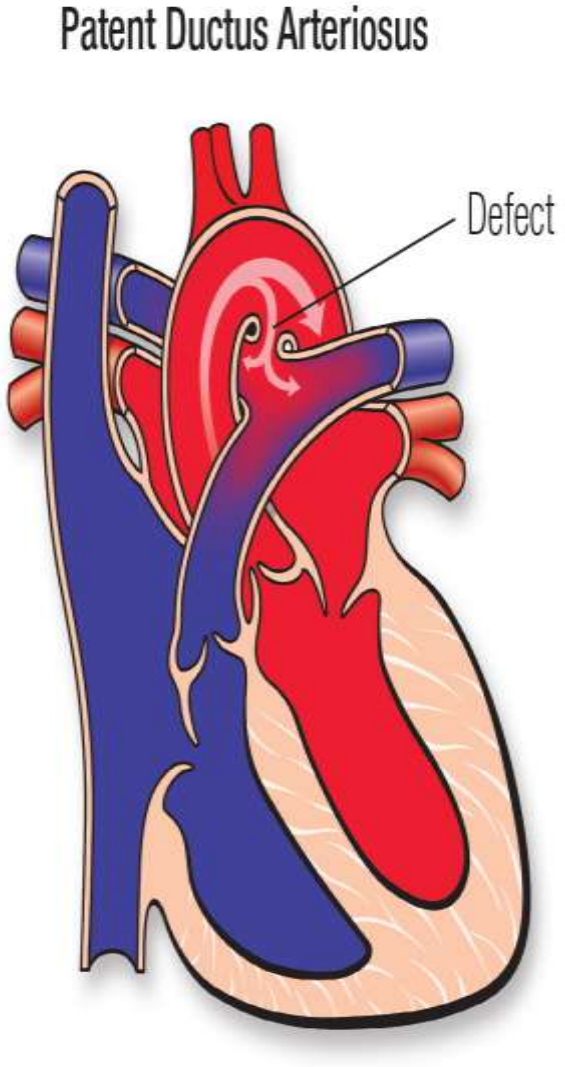
Figure 1 - Classification of neonatal apneas

Mechanism of action	Treatment
Reduction of work of breathing	• Prone, head elevated position • nCPAP or nIPPV/nSIPPV
Increased respiratory drive	• Oxygen administration • Red blood cell transfusion (increases tissue oxygenation) • Caffeine • Doxapram (not a standard treatment due to side effects)
Increased diaphragm contractility	• Caffeine • Branched-chain amino acids (there is still a lack of evidence)

Complications and Supportive care on the NICU

Patent ductus arteriosus (PDA)

- The arterial duct **usually closes within hours of birth but in preterm babies can remain open for weeks**.
- The PDA **causes a left to right shunt** from the aorta to the pulmonary artery. This causes **pulmonary congestion and a reduction in systemic blood flow during diastole**.
- **It is a risk factor for NEC, CLD and IVH.**
- Close the duct using anti-inflammatory agents (ibuprofen or paracetamol) or surgical closure.

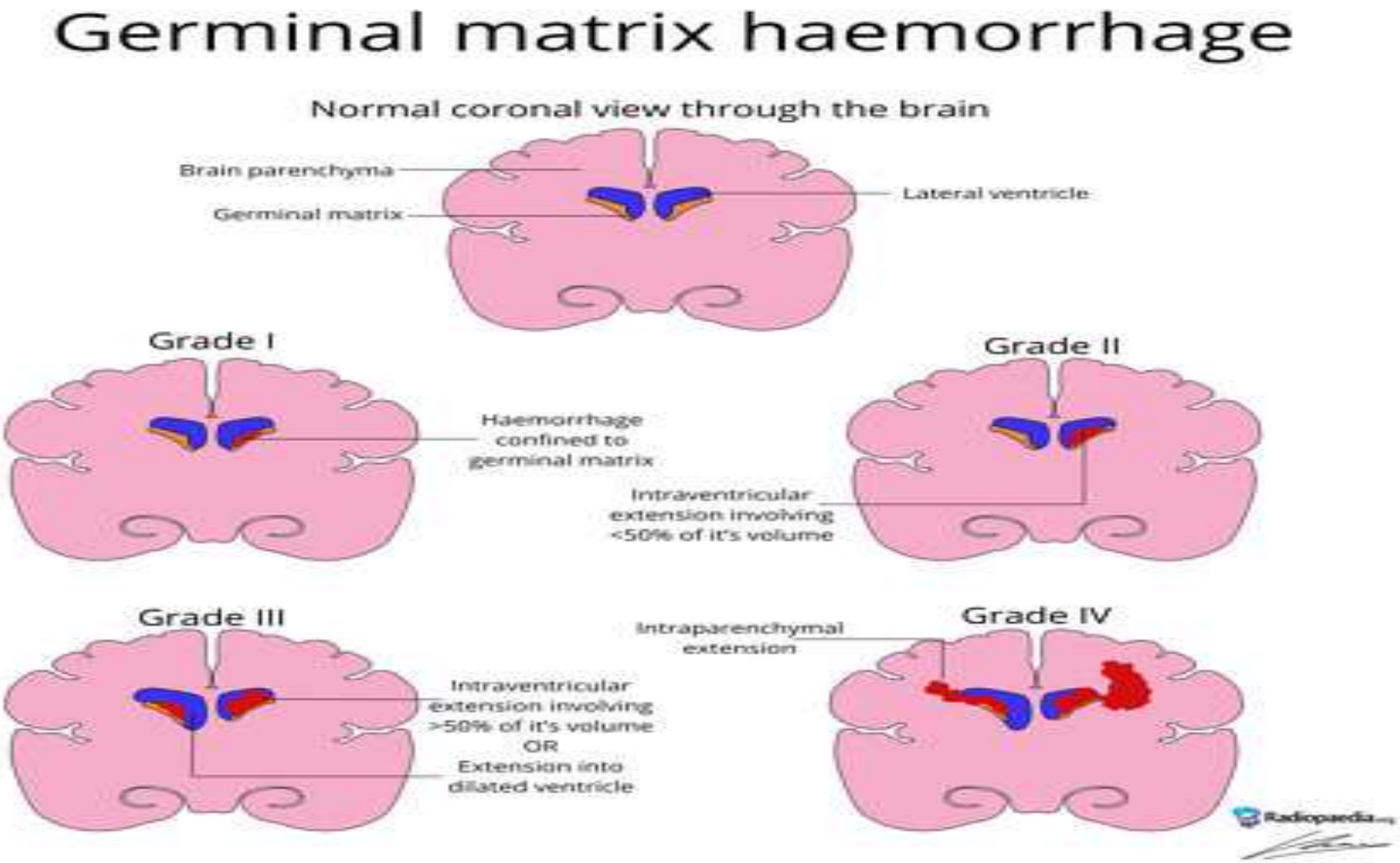


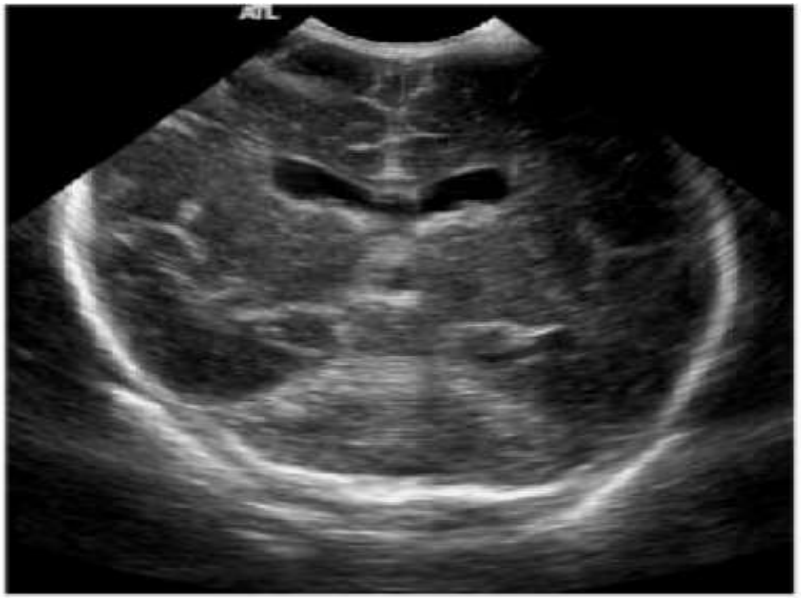
Complications and Supportive care on the NICU

Intraventricular haemorrhage (IVH)

- The preterm brain contains a **germinal matrix**, just outside the lateral ventricles, from which new brain cells migrate to the cortex.
- This area is **highly vascular** with a network of capillaries that are vulnerable to changes in cerebral perfusion pressure due to **mechanical ventilation, fluctuations in pCO2 and complications such as hypotension, PDA and pneumothorax**.
- Bleeding from these capillaries can cause a sub-ependymal or IVH that occurs in about 15–20% of all extreme preterms.
- Present with anemia and hypoxia at day 3 mostly.
- Follow up with serial cranial ultrasound.

IVH grades


Germinal matrix haemorrhage
Normal coronal view through the brain
Brain parenchyma
Germinal matrix
Lateral ventricle
Grade I
Haemorrhage confined to germinal matrix
Grade II
Intraventricular extension involving <50% of it's volume
Grade III
Intraventricular extension involving >50% of it's volume OR Extension into dilated ventricle
Grade IV
Intraparenchymal extension
Radiopaedia



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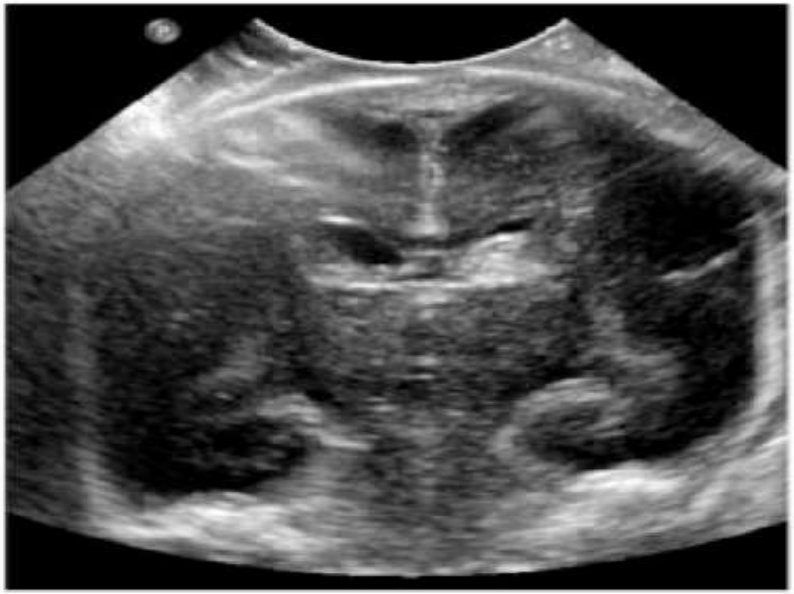

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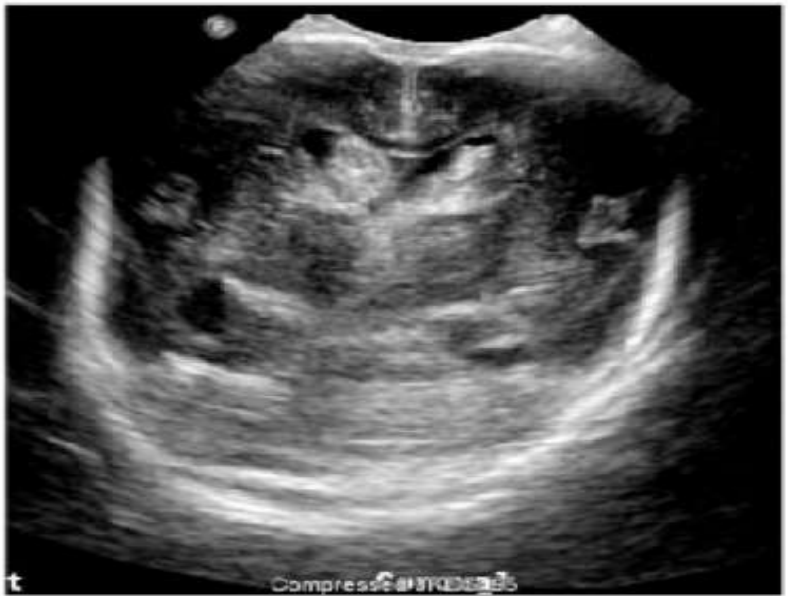

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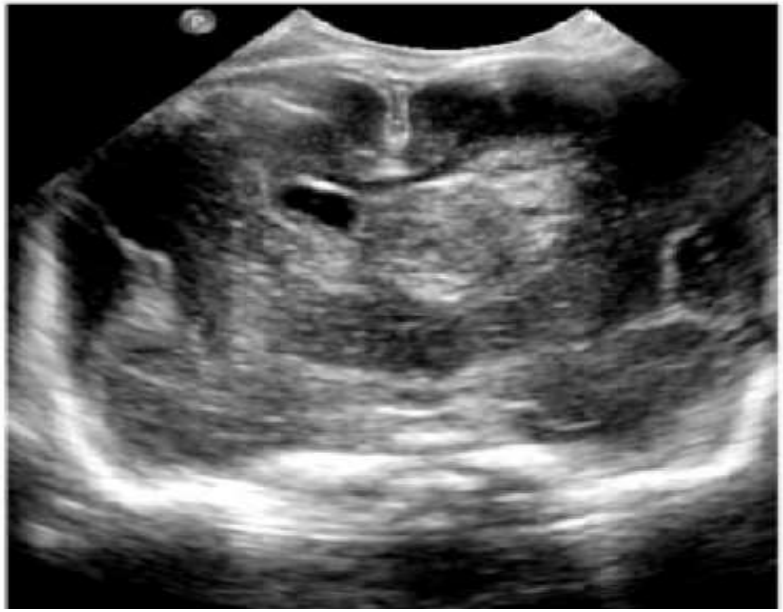

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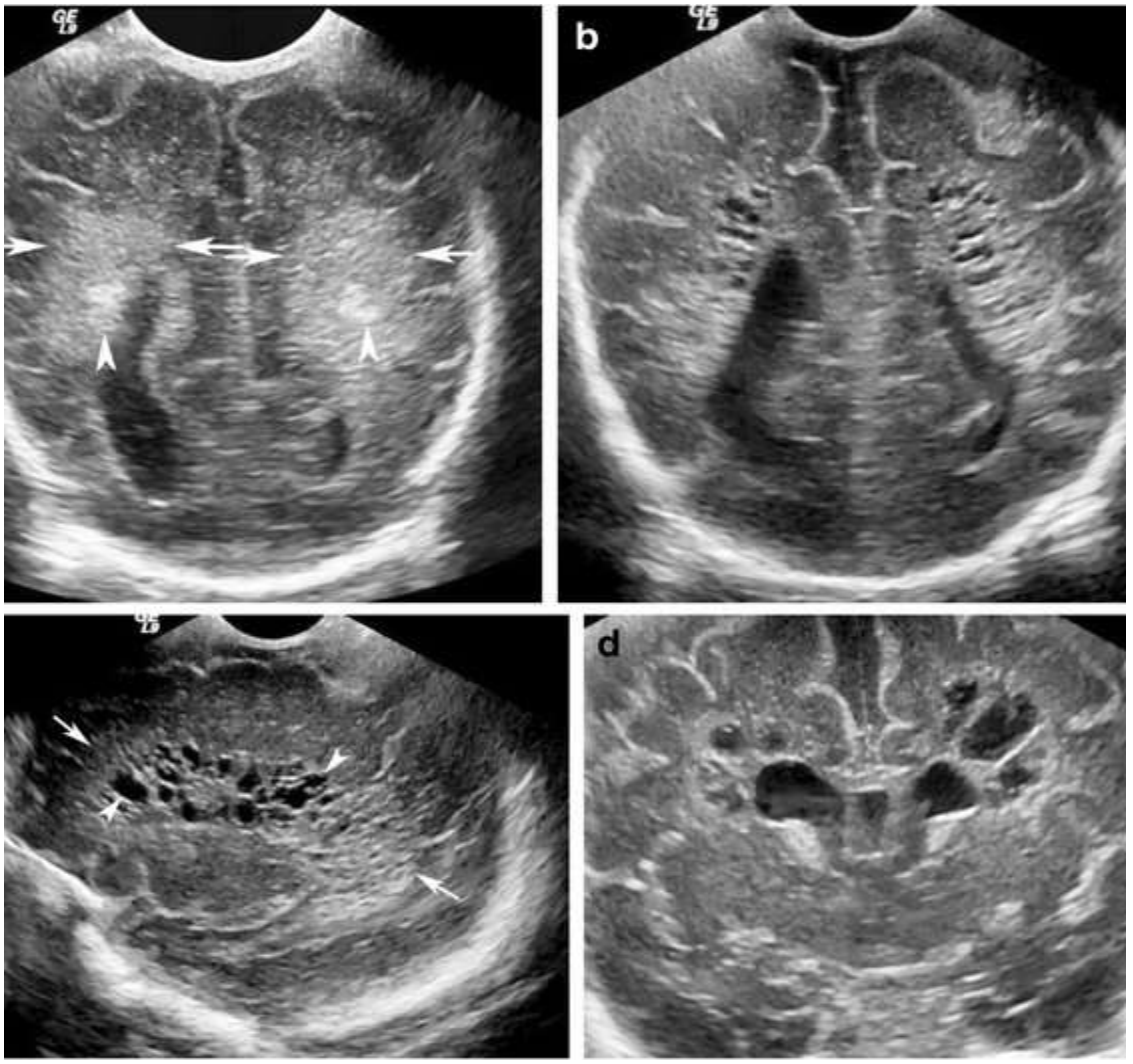
Complications and Supportive care on the NICU

Periventricular leukomalacia (PVL)

- PVL is a necrosis and gliosis of white matter (injury) occurring in preterm babies usually **less than 32 weeks** and triggered by **inflammation, cerebral ischaemia or hypoxia**.

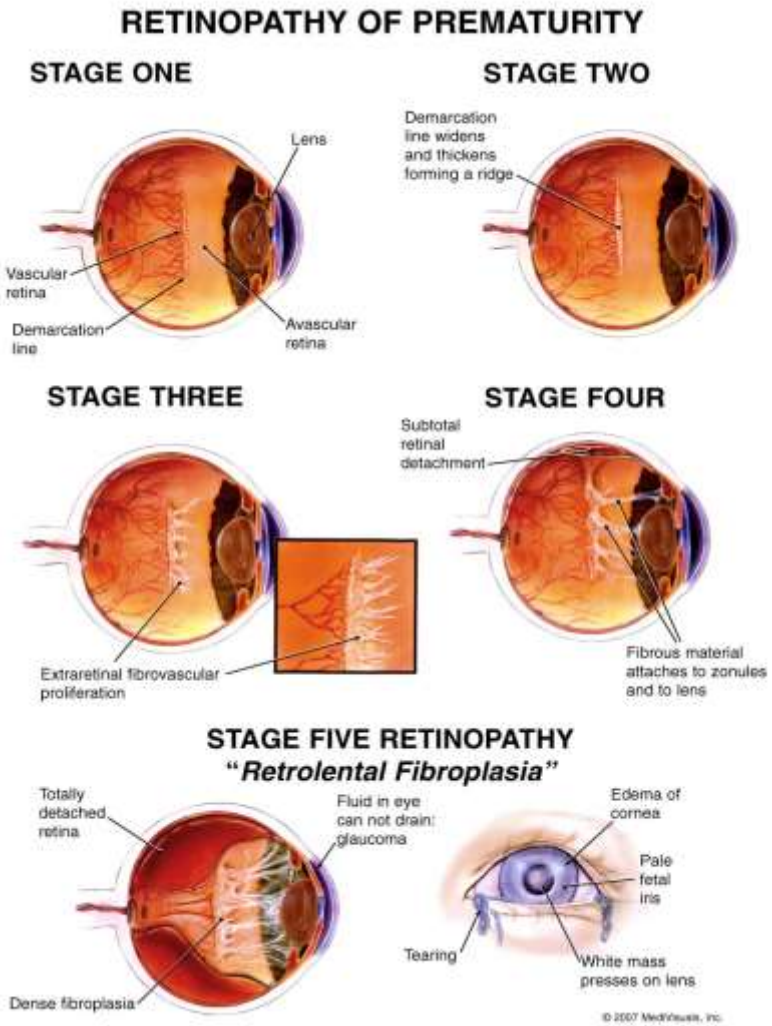
- It can have devastating consequences, with **a high risk of cerebral palsy (**spastic diplegic or quadriplegic CP**).**



Complications and Supportive care on the NICU

Retinopathy Of Prematurity (ROP)

- is a disorder resulting from the disruption of the normal development of retinal vasculature.
- White pupillary reflex
- Advanced stages may lead to blindness.



Complications and Supportive care on the NICU

Feeding

- Infants of less than 33–34 weeks' gestational age do not have a good suck or swallow reflex and should usually be **fed via an orogastric or nasogastric tube**.
- Premature infants with small gastric capacity **require frequent feeding**.
- **The ideal milk is mother's freshly expressed breast milk (EBM**). If this is not available, stored (frozen) EBM or sometimes donor EBM may be used.
- **This provides immunity, is easily absorbed, and reduces the risk of NEC.**
- If formula is used it should be a specialized **preterm formula**.

Complications and Supportive care on the NICU

Necrotizing enterocolitis (NEC)

- This occurs in about 10% of all extremely preterm infants and carries a high mortality.

- It is an **ischaemic inflammation of the gut associated with translocation of bacteria (mixed organisms and involve anaerobic infection)** into the gut wall.

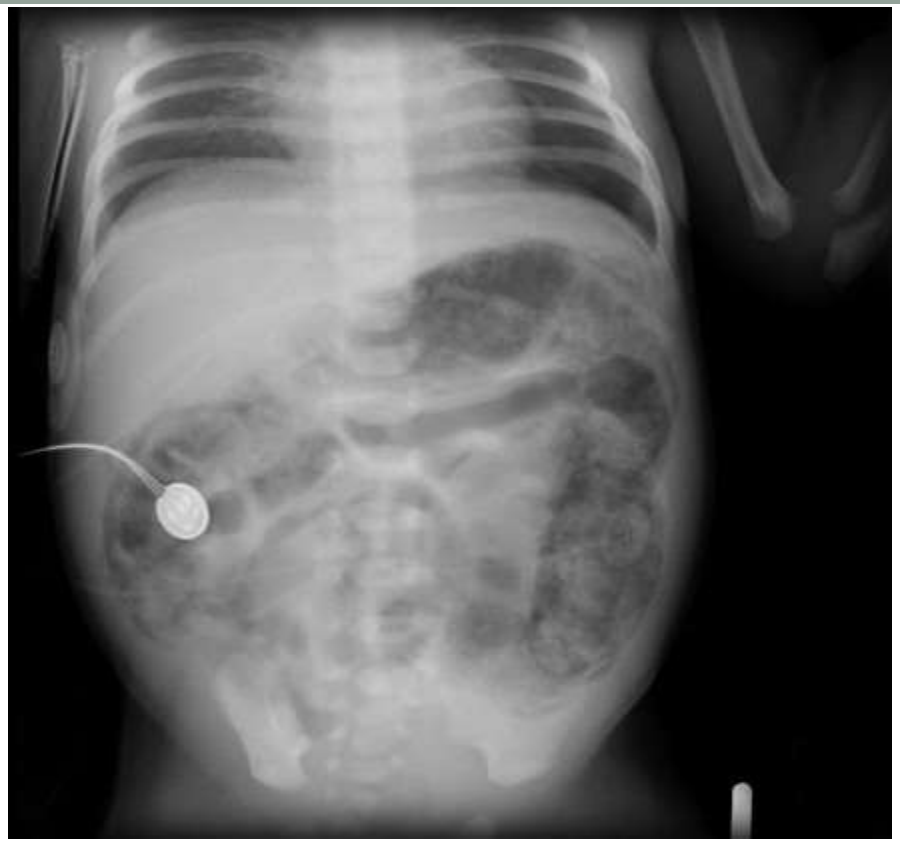
- There are a number of risk factors, including **low gestational age, hypotension, PDA and absence of breast milk feeds. Excessively aggressive increase of feed volumes and use of formula feeds** may lead to NEC.

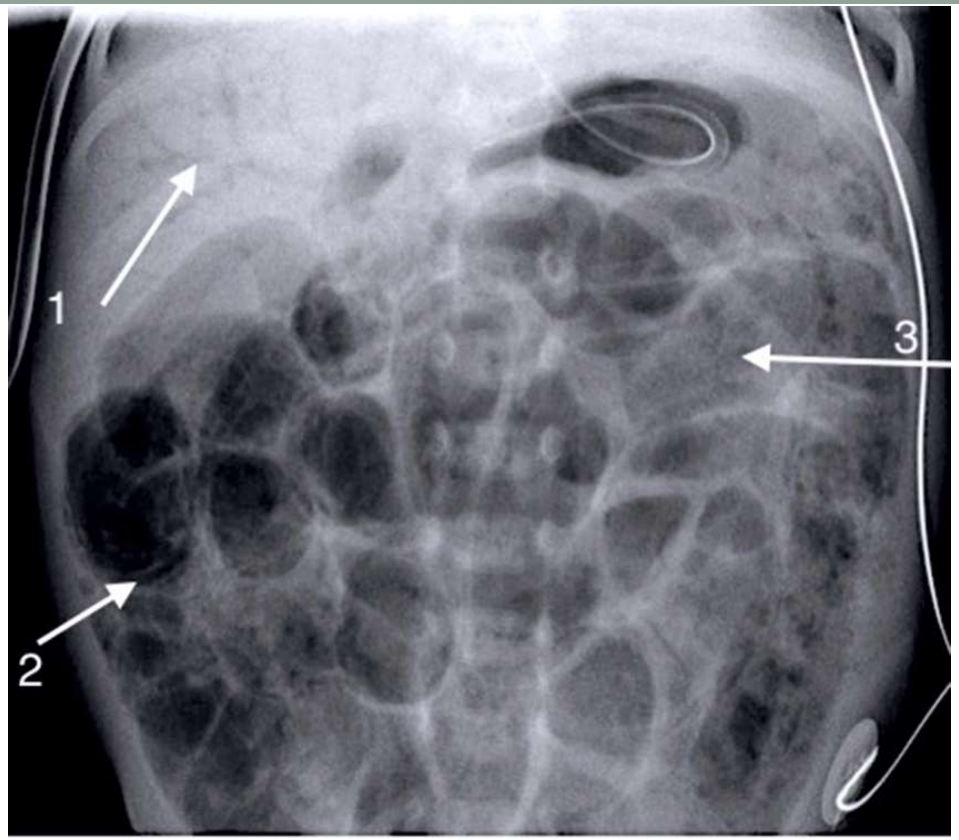
- The use of **probiotics (e.g. *Lactobacillus* and *Bifidobacter* species) from birth to 34 weeks can reduce the risk of NEC**.

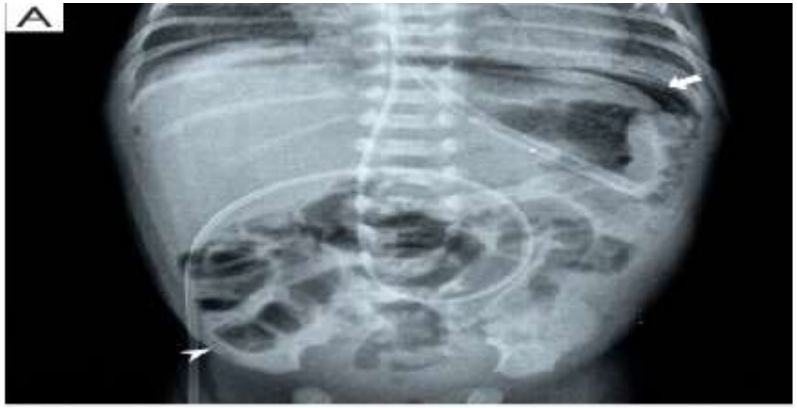
Modified Bell´s Staging Criteria for Necrotizing Enterocolitis (NEC).

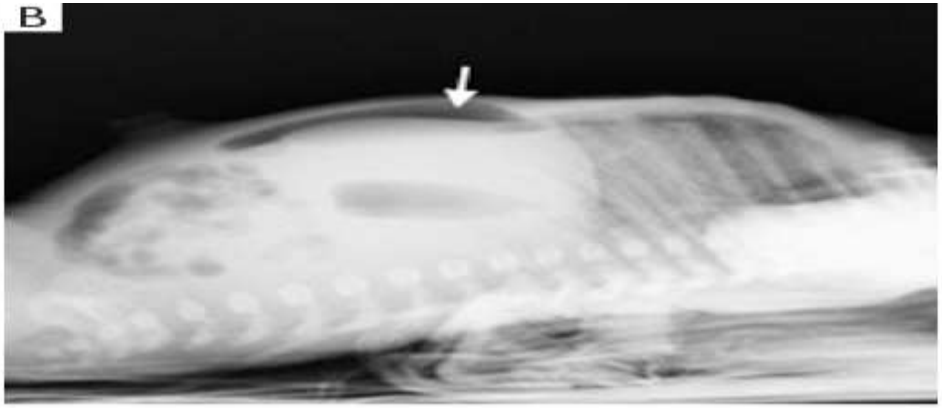
Stage	Systemic signs	Abdominal signs	Radiographic signs	Treatment
IA Suspected	Temperature instability, apnea, bradycardia, lethargy	Gastric retention, abdominal distention, emesis, heme-positive stool	Normal or intestinal dilation, mild ileus	NPO, antibiotics x 3 days
IB Suspected	Same as above	Grossly bloody stool	Same as above	Same as IA
IIA Definite, mildly ill	Same as above	Same as above, plus absent bowel sounds with or without abdominal tenderness	Intestinal dilation, ileus, pneumatosis intestinalis	NPO, antibiotics x 7 to 10 days
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	NPO, antibiotics x 14 days
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	NPO, antibiotics x 14 days, fluid resuscitation, inotropic support, ventilator therapy, paracentesis
IIIB Advanced, severely ill, perforated bowel	Same as IIIA	Same as IIIA	Same as above, plus pneumoperitoneum	Same as IIA, plus surgery

DIC: disseminated intravascular coagulation
NPO: "nil per os" or nothing by mouth









ay of the abdomen in orthostasis: subdiaphragmatic air (arrow) and intestinal pneumatosis (arrow head

Necrotizing enterocolitis (NEC)

Antibiotics choice.

- Frequently used regimen includes **ampicillin, aminoglycoside (eg, gentamicin) or third-generation cephalosporin (cefotaxime), and clindamycin or metronidazole**.

- Variable combinations but the most frequently used Vancomycin, amikacine or meropenem and metronidazole because it is considered as nosocomial late onset sepsis.

Complications and Supportive care on the NICU

Jaundice

- Preterm infants are more prone to bilirubin encephalopathy than term infants(increased risk of kernicterus), and factors that affect the entry of free bilirubin into the brain include low albumin levels, acidosis, hypoxia, hypoglycaemia, hypothermia, certain drugs and starvation.

Complications and Supportive care on the NICU

Anaemia

- Some sick preterm infants will be anaemic at birth or develop anaemia as a result of **frequent blood sampling**, and will require a transfusion with packed red blood cells.

- The venous haematocrit should be maintained at more than 0.35% (**haemoglobin 12 g** dl–1) **in all sick babies during the acute phase of RDS.**

- **During the physiological nadir of anaemia (at 5–7 weeks) preterm infants may tolerate a haemoglobin concentration of 7 g dl–1**, especially if there is an adequate reticulocyte response (>5%).

- To prevent iron-deficiency anaemia, **preterm infants of less than 2000 g birthweight or 34 weeks' gestation are usually prescribed supplemental iron (ferrous sulphate) from 2–6 weeks until fully weaned**, unless they are on formula milk.

Complications and Supportive care on the NICU

Susceptibility to infection.

Term	Preterm
↓ Physical barriers	↓↓↓ Physical barriers
↑ Effectiveness of immune cells to target pathogens	↓ Number of monocytes and neutrophils
	↓ Overall ability to produce cytokines
	↓ T cell activation
	↓ Number of natural killer cells
↓ Bactericidal/permability-increasing protein	↓↓ Bactericidal/permability-increasing protein
	↓ Passive Immunity (level of IgG depends on transplacental transfer and thus increases with gestation age)

↑ indicates increased; ↓ indicates decreased

Preparation for discharge home

Early discharge must

1. at 34–35 weeks
2. weight of >=1800 gram
3. feeding is progressing well,
4. temperature control is good,
5. weight gain is steady,
6. the mother is handling her baby competently
7. the home situation is good.

THANK YOU