Great Ormond Street Hospital for Children NHS Trust

Medical Neonates

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Associated clinical guidelines/protocols:
- Jaundice
- PPHN guidelines
- Pentoxyfilline
- PH study guide

Fundamental Knowledge:

List of topics relevant to PIC that will have been covered in membership examinations.
They will not be repeated here.

- Apgar scoring
- Thermoregulation in the neonate
- Consequences of prematurity on: lung function, gastrointestinal tract, neurological development, immunity
- Lung development in the fetus, factors affecting lung growth
- Neonatal nutrition, neonatal rickets

Information for Year 1 ITU Training (basic):

> **Year 1 ITU curriculum**
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> **ITU Management of the following clinical conditions:**
> - PPHN: Basic physiology, causes, treatment
> - Neonatal RDS: surfactant.
> - Intraventricular haemorrhages: causes, prognosis, severity, hydrocephalus monitoring & treatment, CUSS appearances
> - Hypoxic-ischaemic encephalopathy
> - Neonatal hypoglycemia, investigation and treatment
> - Neonatal sepsis: differences, immunoglobulin, pentoxyphyllin

Curriculum Notes for Year 1:
PPHN: Basic physiology, causes, treatment

Persistent pulmonary hypertension of the newborn (PPHN) is the result of elevated pulmonary vascular resistance to the point that venous blood is diverted to some degree through fetal channels (i. e. the ductus arteriosus and foramen ovale) into the systemic circulation and bypassing the lungs, resulting in systemic arterial hypoxemia.

This disorder can be classified into three forms dependent on the likely etiology of the pulmonary hypertension:

1. **PPHN associated with pulmonary parenchymal disease**, such as hyaline membrane disease, meconium aspiration, or transient tachypnea of the newborn as the cause of alveolar hypoxia
   o known as secondary PPHN or appropriate PPHN
   o alveolar oxygen tension appears to be the major determinant of pulmonary artery vasoconstriction.
2. **PPHN with radiographically normal lungs** and no evidence of parenchymal disease
   o frequently called Persistent Fetal Circulation (PFC), or primary or inappropriate PPHN

3. **PPHN associated with hypoplasia of the lungs**
   o most often in the form of diaphragmatic hernia
   o associated with an anatomic reduction in capillary number in addition to the pathophysiology listed below

Several factors are thought to play a role in maintaining high fetal pulmonary vascular resistance.

1. Hypoxia is a potent vasoconstrictor - especially below 40-45 mmHg. Fetal PaO_2 averages 20-25 mmHg, so that persistent hypoxemia exists producing persistent active pulmonary vasoconstriction.
2. Because the lungs are not fully expanded in utero, an element of mechanical compression of the vessels exists. During lung expansion, the arteries straighten out and become less resistant to blood flow.
3. Carbon dioxide appears to play a minor role in maintaining vasoconstriction. However, hypocapnia ($PaCO_2$'s less than 30 mmHg) is known to blunt hypoxic vasoconstriction.

Treatment
Basic treatment goals ;
Improve alveolar oxygenation
Minimize pulmonary vasoconstriction
Maintain systemic blood pressure and perfusion
Consider induction of an alkalotic state
Consider a trial of vasodilatation
Consider extracorporeal membrane oxygenation support

Improving alveolar oxygenation with supplemental oxygen (FiO2).
This is especially important when pulmonary parenchymal disease exists, as improvement in alveolar oxygenation will often result in a normal relaxation of the pulmonary arteries and improved pulmonary blood flow.

Minimize "inappropriate" pulmonary vasoconstriction
By overventilating an infant and producing hypocapnia, hypoxic vasoconstriction can be blunted allowing pulmonary blood flow to increase. This may result in improvement in oxygenation. However, use of mechanical ventilatory support to achieve hypocapnic alkalosis can result in pulmonary trauma. Since vasoconstriction appears related to intracellular pH rather than pCO_2 levels use of alkalinising agents such as sodium bicarbonate has become commonplace. Controlled trials of alkalosis do suggest a positive benefit in some infants, but not all.
Maintenance of systemic arterial blood pressure and, by inference, pulmonary perfusion, appears to have some benefit. Theoretically, increasing system arterial pressure may result in decreased right-to-left shunt flow across a patent ductus arteriosus, increased pulmonary blood flow, and hopefully, improved oxygenation. Dopamine and dobutamine are frequently used to improve cardiac output and systemic blood pressure.

Vasodilators are effective in a certain proportion of infants. However, these agents are nonspecific and frequently result in vasodilatation of both the pulmonary and systemic vascular beds.

Nitric Oxide Inhaled nitric oxide has been studied intensively as therapy for Persistent Pulmonary Hypertension of the Newborn. This gaseous free-radical compound was previously known as endothelial-derived-relaxation-factor. Inhaled nitric oxide directly activates soluble guanylate cyclase resulting in increased levels of cyclic-GMP in vascular smooth muscle cells. This results in vascular relaxation by prohibiting myosin protein cross-bridge formation in smooth muscle. Multiple controlled trials have demonstrated that inhaled nitric oxide improves oxygenation in many infants with PPHN. A controlled trial of inhaled nitric oxide in infants with congenital diaphragmatic hernia demonstrated no efficacy. Nitric oxide was FDA approved 12/23/99 for use in term and near-term infants with hypoxic respiratory failure requiring ventilatory support who have clinical and/or echocardiographic evidence of pulmonary hypertension.

Prostaglandin I2 (prostacyclin) This is a complex molecule made from arachadonic acid and is one of the major endogenous vasodilators in the lung. It is normally produced by the lung when lung vessels are in a constricted state, thereby relaxing them. Whether PPHN is the result of faulty PGI2 production is not known. Administration of pharmacologic doses of PGI2 to babies with persistent pulmonary hypertension has proven successful.

Other therapies proposed as beneficial in Persistent Pulmonary Hypertension of the Newborn include magnesium sulphate

When other therapies have failed to result in patient improvement, Extracorporeal Membrane Oxygenation (ECMO) support has been used with good success.

Outcome
If this syndrome is severe, it can result in death. Prior to the introduction of extracorporeal membrane oxygenation support, mortality rates were reported from 12 to 50% in 1989. Although extracorporeal membrane oxygenation support has increased survival to about 85% in infants with severe Persistent Pulmonary Hypertension of the Newborn, it may be associated with significant morbidity in 10-45% of patients. "Spontaneous" resolution of this condition may occur 36 hours to several weeks after birth.

Neonatal RDS: surfactant
A disorder affecting newborn infants (usually premature) characterised pathologically by the development of a hyaline-like membrane lining the terminal respiratory passages. Extensive atelectasis is attributed to the lack of surfactant. an acute lung disease of the newborn (especially the premature newborn); lungs cannot expand because of surfactant deficiency; characterised by rapid shallow breathing and cyanosis and the formation of a glassy hyaline membrane over the alveoli

Surfactant
Surfactant is surface-active lipoprotein complex formed by type II alveolar cells. The proteins and lipids that comprise surfactant have both a hydrophilic region and a hydrophobic region. By adsorbing to the air-water interface of alveoli with the hydrophilic headgroups in the water and the hydrophobic tails facing towards the air, the main lipid component of surfactant, dipalmitoylphosphatidylcholine, reduces surface tension.

Surfactant production in humans begins in Type II cells during the canalicular stage of lung development. Lamellar bodies appear in the cytoplasm at about 20 weeks gestation. These lamellar bodies are secreted by exocytosis into the surface water layer lining the alveolar airspace, where the surfactant forms a meshwork of tubular myelin. Term infants are estimated to have an alveolar storage pool of approximately 100mg/kg of surfactant, while preterm infants have an estimated 4-5mg/kg at birth. This alveolar surfactant can be both broken down by macrophages and/or reabsorbed into the lamellar structures of type II cells. Up to 90% of surfactant phosphatidylcholine is recycled from the alveolar space in the newborn.

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Intraventricular haemorrhages

This is a significant cause of morbidity and mortality in infants who are born prematurely. Neurological complications include life-long seizures, developmental delay and cerebral palsy. IVH is uncommon in term infants.

Occurs in 60-70% of neonates weighing 500-750g and 10-20% of those weighing 1,000-1500g. There is an inverse relationship between the severity of the haemorrhage and the likelihood of survival.

It is classified on radiological appearance on cranial ultrasound (CUSS)
- **Grade I**: Bleeding confined to germinal matrix/subependymal region. Bleed occupies <10% of ventricle - approx. 35% of cases.
- **Grade II**: Bleed fills 10-50% of ventricle - approx. 40% of cases.
- **Grade III**: Dilated ventricles that are > 50% full of blood.

- 10-15% have hydrocephalus that may not appear for 2-4 weeks.
- Infants with massive haemorrhage often rapidly deteriorate and die.
- Significant proportion show motor and cognitive deficits.
- Extremely low birth weight infants with grades I-II IVH have poorer neurodevelopmental outcomes at 20 months' than infants with normal cranial ultrasound.

Hypoxic-ischaemic encephalopathy

Damage to cells in the central nervous system from inadequate oxygen. Hypoxic-ischemic encephalopathy allegedly may cause death in the newborn period or result in what is later recognised as developmental delay, mental retardation, or cerebral palsy.

Hypoxic ischemic encephalopathy (HIE) is a term for brain damage caused by lack of oxygen and lack of blood flow to the brain. Damage can occur within minutes. Once brain damage occurs, it is irreversible.

Very often the injury occurs during birth, due to birth accidents such as uterine rupture, knot in the umbilical cord, cord wrapped around the baby's neck, breech birth or other difficult births. However, HIE can also be a result of stroke, drowning, hanging, or any other event which would cut off oxygen and blood flow to the brain. The damage can also occur in utero. In some instances of babies born with HIE, the cause is never determined.

Children who are diagnosed with HIE can range from mild to severe in the amount of damage that has occurred. EEGs, MRIs and CAT scans are used to determine the severity and location of the brain injury. Three types of HIE, mild, moderate and severe are described and gives an explanation of each.

This damage can be an underlying cause of cerebral palsy, mental retardation, dysphagia, cortical vision impairment or blindness, hearing impairment or deafness, microcephaly, temperature instability, chronic lung disease, and seizures. Prognosis given is often bleak in terms of the child's future abilities or quality of life.

There is no treatment for HIE per se. Treatment in the form of therapies can help with muscle tone and control, oral muscle development, and vision in the case of cortical vision impairment. Traditional therapies include physical therapy for gross motor control, occupational therapy for small muscle control, and speech and language therapy. Oral stimulation is a form of therapy that is done by either the OT or the SLT depending on their particular qualifications. There are many alternative therapies that can be attempted as well, although the benefits of these are not considered to be proven.

Neonatal hypoglycemia, investigation and treatment

Neonatal hypoglycemia is a common in the newborn infant. Serum glucose levels less than 2.2 mmol/L in the first 24 hours of life and 2.6 mmol/L thereafter are considered low. 5-6 mmol/L is considered normal. The level at which this potential for long-term injury is reached is controversial. There is a normal dip in blood glucose 2-4 hours postnatally so the challenge is to be able to recognize a normal dip from true metabolism errors.

INFANTS AT RISK
- Preterm
- Small for Gestational Age
- Macrosomic babies (may have hyperinsulinism)
- Infants of poorly controlled diabetic mothers
- Infant who suffers perinatal asphyxia
- Growth restricted babies

Treatment
Give a bolus of 2 ml/kg of IV Dextrose 10% slowly . Follow-up by an infusion of glucose at 4-6 mg/kg/min (72ml/kg/day D10%) Keep nil by mouth. Repeat glucometer after 1/2 to 1 hour and increase the infusion as necessary to 6-8 mg/kg/min (90 ml/kg/day D10%) If infection is suspected or there is no alternative explanation for hypoglycaemia take Blood C&S and treat as sepsis. Once the blood glucose normalised, feeds can be reintroduced gradually and infusion tailed off

If Hypoglycaemia persists
Take Blood C&S and treat as sepsis if not done yet. Increase the rate of dextrose infusion if possible (i.e. do not increase beyond daily requirement). Increase the concentration of dextrose. Concentrations of 12.5% to 15% may be needed. If concentration of 12.5% is used, a central line is required. If glucose infusion rates of more than 12mg/kg/min are required,

Neonatal sepsis: differences, immunoglobulin, pentoxyphyllin
Neonatal sepsis is invasive bacterial infection occurring in the 1st 90 days of life. Signs are multiple and include diminished spontaneous activity, less vigorous sucking, apnea, bradycardia, temperature instability, respiratory distress, vomiting, diarrhea, abdominal distention, jitteriness, seizures, and jaundice. Diagnosis is clinical, with extensive laboratory testing. Treatment is initially with ampicillin plus either gentamicin or cefotaxime, narrowed to organism-specific drugs as soon as possible.

Neonatal sepsis occurs in 0.5 to 8.0/1000 births. The highest rates occur in low-birth-weight (LBW) infants, those with depressed respiratory function at birth, and those with maternal perinatal risk factors. The risk is greater in males (2:1) and in neonates with congenital anomalies.

A neonate may be predisposed to sepsis by obstetric complications, eg, premature rupture of membranes (PROM) occurring ≥ 18 h before birth or maternal bleeding (placenta previa, abruptio placentae), toxemia, precipitous delivery, or maternal infection (particularly of the urinary tract or endometrium, most commonly manifested as maternal fever shortly before or during parturition).

Early-onset sepsis (ie, within 7 days of birth) usually results from organisms acquired intrapartum. In > 50% of cases, early-onset sepsis appears within 6 h of birth, and most cases occur within 72 h. Late-onset sepsis (after 7 days) is often acquired from the environment.

Group B streptococcus (GBS) and gram-negative enteric organisms (predominantly *Escherichia coli*) account for 70% of early-onset sepsis. Vaginal or rectal cultures of women at term may show GBS colonization rates of up to 30%. At least 35% of their infants also become colonized. The density of infant colonization determines the risk for invasive disease, which is 40 times higher with heavy colonization. Although only 1/100 of those colonized develop invasive disease due to GBS, > 50% of those present within the 1st 6 h of life. Nontypeable *Haemophilus influenzae* sepsis has been increasingly identified in neonates, especially premature neonates.

Other gram-negative enteric bacilli (eg, *Klebsiella* sp) and gram-positive organisms—*Listeria monocytogenes,* enterococci (eg, *Enterococcus faecalis*, *E. faecium*), group D streptococci (eg, *Streptococcus bovis)*, α-hemolytic streptococci, and staphylococci - account for most

other cases. *Streptococcus pneumoniae, H. influenzae* type b, and, less commonly, *Neisseria meningitidis* have been isolated. Asymptomatic gonorrhea occurs in 5 to 10% of pregnancies, so *N. gonorrhoeae* may be a pathogen.

Staphylococci account for 30 to 50% of late-onset cases and are most frequently due to intravascular devices (particularly umbilical artery or vein catheters). Isolation of *Enterobacter cloacae* or *E. sakazakii* from blood or CSF suggests contaminated feedings. Contaminated respiratory equipment is suspected in outbreaks of hospital-acquired *Pseudomonas aeruginosa* pneumonia or sepsis.

The role of anaerobes (particularly *Bacteroides fragilis*) remains unclear, although deaths have been attributed to *Bacteroides* bacteremia. Anaerobes may account for some culture-negative cases in which autopsy findings indicate sepsis.

Candida sp are increasingly important causes of late-onset sepsis, occurring in 12 to 13% of very LBW infants.

The most important risk factor in late-onset sepsis is prolonged use of intravascular catheters. Others include associated illnesses (which may, however, be only a marker for the use of invasive procedures), exposure to antibiotics (which selects resistant bacterial strains), prolonged hospitalization, and contaminated equipment or IV or enteral solutions. Gram-positive organisms (eg, coagulase-negative staphylococci and *Staphylococcus aureus*) may be introduced from the environment. Gram-negative enteric bacteria are usually derived from the patient's endogenous flora, which may have been altered by antecedent antibiotic therapy or populated by resistant organisms transferred from the hands of personnel (the major means of spread) or contaminated equipment. Therefore, situations that increase exposure to these bacteria (eg, crowding, nurse:patient ratios > 1:1, inadequate hand washing) result in higher rates of hospital-acquired infection. Risk factors for *Candida* sp sepsis include prolonged (> 10 days) use of central IV catheters, hyperalimentation, use of antecedent antibiotics, necrotizing enterocolitis, and previous surgery.

Diagnosis

- CBC, differential, and smear
- Lumbar puncture (LP)
- Unrinalysis and cultue
- Other tests for infection and inflammation:

Pentoxifylline for neonatal sepsis.

Two RCTs enrolled a total of 140 preterm (< 36 weeks) neonates with suspected late onset (> 7 days) sepsis to evaluate the effect of pentoxifylline on neonatal outcomes. However, the two studies reported outcomes of only the 107 randomised patients with confirmed sepsis. The results showed a reduction in 'all cause mortality during hospital stay' following pentoxifylline treatment [typical RR 0.14 (95% CI 0.03, 0.76), RD -0.16 (95% CI -0.27, - 0.04), NNT 6 (95% CI 4, 25)]. No adverse effects due to pentoxifylline were observed in the two included trials.

Current evidence suggests that the use of pentoxifylline as an adjunct to antibiotics in neonatal sepsis reduces mortality without any adverse effects.

References.
Haque K, Mohan P. Pentoxifylline for neonatal sepsis. Cochrane Database Syst Rev. 2003;(4):CD004205.

Information for Year 2 ITU Training (advanced):

> ### Year 2 ITU curriculum
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> #### ITU Management of the following clinical conditions:
> - PPHN: advanced physiology, causes, treatment
> - Meconium aspiration
> - Chronic lung disease.
> - Neonatal abstinence syndrome
> - Neonatal seizures
> - Retinopathy of Prematurity: screening and treatment

Curriculum Notes for Year 2:

PPHN: advanced physiology, causes, treatment

Physiological determinants of pulmonary vascular resistance

Pulmonary endothelium plays a crucial role in the adaptation and regulation of pulmonary vascular tone in both the normal and hypertensive circulations. There are a number of physiological factors which influence pulmonary artery pressure (PAP) and pulmonary vascular resistance and there are a number of specific manoeuvres which have been used to reduce PVR when elevated.

Carbon dioxide and hydrogen ion concentration

Carbon dioxide tension and hydrogen ion concentration are important determinants of PVR. Alkalosis produces pulmonary vasodilatation and acidosis results in pulmonary vasoconstriction. For some time it was unclear whether the stimulus for vasoconstriction was an elevated carbon dioxide tension or resultant changes in hydrogen ion concentration. In an elegant study of children with trisomy 21 and increased propensity to pulmonary hypertension; following atrio-ventriular valve repair Chang and his colleagues patch allowed the arterial carbon dioxide tension to rise to >7.3 kPa resulting in PHT which then decrease with intravenous administration of a sodium bicarbonate despite allowing the $paCO_2$ to stay elevated. PVR decreased in spite of a high $paCO_2$, confirming hydrogen ion concentration to be the primary determinant of PVR.

Oxygen

In normal lungs a sufficiently large reduction in alveolar oxygen tension will provoke hypoxic pulmonary vasoconstriction (HPV). The relationship between alveolar oxygen tension and PVR is not linear. An increase in PVR occurs only below an alveolar oxygen tension of about 60mmHg. Furthermore, this response is pH dependent. As the pH is reduced, the increase in PVR in response to a given reduction of paO_2 is greater. The HPV response appears to be mainly due to changes in alveolar oxygen tension rather than pulmonary arterial or pulmonary venous oxygen tension.

Hypoxic pulmonary constriction is a fundamental mechanism to instantaneously match pulmonary perfusion to ventilation. The patho-physiological mechanism of HPV is thought to be due to the Redox regulation of O_2-K-sensitive channels of mitochondrial sensors in resistance artery, and smooth muscle cells (SMC). Similarly, the low PO_2 environment favours *in utero*, pulmonary vasoconstriction, whereas increased alveolar PO_2 secondary to the first few breathes instantaneously vasorelaxes the pulmonary circulation.

Lung volume

During anaesthesia or resuscitation, at low lung volumes PVR increases due to the surrounding un-inflated lungs compressing intra-pulmonary blood vessels. As the lungs are expanded PVR falls and is lowest at the functional residual capacity (FRC). However, with over-distension PRV increases again as a result of stretching the intrapulmonary vessels.

Nitric oxide

Nitric Oxide (NO) is synthesised in the vascular endothelium by nitric oxide synthase (NOS), via the oxidation of the terminal guanidino nitrogen atom of the amino acid L-arginine (LA). Nitric oxide relaxes smooth muscle cells by activating the soluble enzyme guanylate cyclase increasing intracellular cyclic guanosine 3'-5' monophosphate concentrations initiating a cascade that results in relaxation of the arterial smooth muscle It relaxes smooth muscle under normal conditions. Perhaps more usefully it also causes relaxation under hypoxic, and hypercapnic conditions.

Endothelins

Endothelins (ET) are a family of potent vasoactive modulators which also mediate smooth muscle cell proliferation in the vascular wall. ET1 is found in the highest concentration and acts on both Endothelin A (ET-A) and Endothelin B (ET-B) receptors. ET-A receptors are responsible for vasoconstriction, whereas ET-B receptors are responsible for vasodilatation and clearance of ET1. Increased concentrations of ET1 have been demonstrated in children with pulmonary hypertension. Studies have demonstrated that ET1 concentrations correlated with pulmonary reactivity in response to hypoxia. Endothelin antagonists, both non-specific blockers of ET-A and ET-B receptors, and specific ET-A antagonists reduce PVR and improve symptoms.
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PRIMARY PULMONARY HYPERTENSION

Primary or idiopathic pulmonary hypertension occurs without a specific cause in children and results in intractable pulmonary hypertension with mean PAP ≥ 25mmHg at rest or ≥ 30mmHg on exercise, In some children abnormalities of NO production may be implicated as they respond with a reduction in PVR to supplemental L-Arginine infusions, to the same extent as the maximally tolerated doses of prostacyclin.

PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

Persistent pulmonary hypertension of the newborn (PPHN) is seen in newborns and is characterised by central cyanosis due to right to left shunting of blood secondary to increased pulmonary vascular resistance. This syndrome has previously been described as persistent fetal circulation. PPHN occurs in 1-6/1000 live births and is a major cause of morbidity (15-25% neurological handicap) and mortality (20-25%) in the term and near term infant. The exact pathogenesis of PPHN continues to be undefined although there is a suggestion that this syndrome may be due to an imbalance between vasoconstricting and vasorelaxing factors. Factors which may contribute to this increased pulmonary vascular resistance include a maladaptation to extra uterine life with a failure of the normal postnatal pulmonary vasodilatation, abnormal muscularisation of pulmonary acinar arteries or an underdevelopment with decrease both in size and number of pulmonary arterioles. The pulmonary vascular transition that occurs at birth depends on a cascade of both structural and biochemical interactions of which the stimuli that initiate and maintain this change are not fully understood. These interactions seem to be disrupted by factors such as prematurity, hypoxia or parenchymal lung disease. Another possible mechanism is due to a disruption in the transition from fetal to normal circulation due to alterations in vasoactive mediator levels. Elevated levels of endothelin-1, a recognised vasoconstrictor and reduced levels of cGMP plasma concentrations in infants with PPHN have also been described. Infants with PPHN have also been shown to have abnormal arginine metabolism and several studies have shown reduced pulmonary adenosine concentrations in fetal as compared to newborn lambs and in patients with pulmonary hypertension. Loss of NO activity seems to be implicated in the pathogenesis of PPHN. Inhaled NO has been used as a pulmonary vasodilator in neonates with PPHN to improve oxygenation. Animal studies have shown peak levels of NOS immediately after birth indicating a high level of NOS is necessary for postnatal adaptation. Infants with PPHN have been shown to have a decreased gene expression of endothelial nitric oxide synthase.

THERAPEUTIC OPTIONS

In the management of PHT, the aim is to maintain sufficient pulmonary blood flow and avoid complications, until resolution of the raised PVR. The aim of treatment is to: improve alveolar oxygenation, minimize pulmonary vasoconstriction, and maintain systemic pressure and perfusion. Complications may result either from hypoxia or barotrauma. The degree of hypoxia depends upon the ratio of PVR to systemic resistance. The mortality in this group is

about 10%. The optimal approach to PHT remains uncertain. As alkalosis reduces PVR, an approach using muscle relaxants, sedation and aggressive hyperventilation to render the infant alkalotic has been used. Rapid ventilation rates with high peak pressures produce a higher minute volume with low arterial carbon dioxide, producing a respiratory alkalosis. Drummond, in a study of children with PPHN, demonstrated a sudden precipitate increase in PaO_2 once a pH of 7.55 was reached. However, this pH required a $PaCO_2$ between 20 to 30 mmHg. Although PVR may be lowered by alkalosis, lung injury may result from the relatively hard ventilation that is required, worsening the long term outcome.

Nitric Oxide
This toxic gas is an effective pulmonary vasodilator, although it does not have pulmonary specificity. Inhaled NO has made a dramatic difference to the outcome of children with PPHN. Initially improvement of oxygenation was described with iNO in doses of 80 ppm. Experience has shown that lower concentrations (5-10ppm) are as effective as higher concentrations, and are less likely to cause problems with toxicity. In randomised controlled trials iNO reduced the need for ECMO by 48%, though no effect on overall mortality was demonstrated.

Sildenafil
In an animal model of PPHN, induced with meconium aspiration, intravenous sildenafil reversed the increase of PAP, which inhaled NO at 20ppm only attenuated[26]. In adults undergoing cardiac catheterisation Sildenafil (75mg) decreased the pulmonary wedge pressure and reduced PAP to a greater extent than inhaled NO (80ppm). In a small case series, oral Sildenafil when given in combination with intravenous prostacyclin improved haemodynamics and symptoms in adults with pulmonary PHT. Inhaled iloprost in combination with oral sildenafil produced a greater and more prolonged fall in PAP than either agent alone.[29] Sildenafil, a selective inhibitor of type-5 phosphodiesterase, is available as 25 mg tablets. Dosage should start at 0.1 mg/kg, with stepwise increases by 0.1 mg/kg up to 0.5 mg/kg 6 hrly. However, in cardiac patients, initial dosage may be as high as 0.5 mg/kg, with stepwise increases by 0.5mg/kg up to 1.0 – 1.5 mg/kg. Intravenous dose has been started at 0.2 mg/kg/hr though currently only available as part of clinical trials. As the effects of sildenafil are not selective to the pulmonary circulation, at higher concentrations it may lead to a fall in systemic pressure. Furthermore, due to a longer half-life than iNO, its effects are maintained for several hours.

Endothelin Antagonists
Endothelin receptor antagonists have been investigated for the treatment of PHT. Bosentan, a dual ET-A and ET-B antagonist, improves symptoms and haemodynamics acutely and over three months but may cause significant hepatotxicity. Bosentan has been used successfully in children). Sitaxsentan, an ET-A antagonist, is effective but has significant hepatotoxicity. Bosentan, a non-selective blocker of endothelin receptors ET-A and ET-B, is available as 62.5 and 125mg tablets. It has been approved for use in adults for the treatment of primary pulmonary hypertension. However, it is still experimental therapy in children. Dosage is 1-2 mg/kg q 12 hrs, up to 2-4 mg/kg 12hrly, (Actelion Pharmaceuticals). AST enzymes should be monitored. A multicentre clinical trial (BREATHE-2) is in progress (Actelion).

Magnesium
Magnesium is a powerful smooth muscle relaxant acting as a calcium antagonist. It is also an effective skeletal muscle relaxant, sedative and controls dysrhythmias. Magnesium may also attenuate the effect of hypoxia on PVR. A magnesium infusions aiming for serum concentrations between 3-5.5mmol/L has been effective in reducing hypoxia induced PPHN. Improvements in oxygenation were seen contemporaneous with the increase in serum magnesium.

Prostacyclin
Prostocyclin is an effective vasodilator but does not have pulmonary specificity. Doses of 2-20μg/kg/min produce pulmonary vasodilatation, but may also cause systemic hypotension. Prostacyclin may be delivered into the pulmonary arteries or nebulised to improve pulmonary specificity. Long-term reduction of pulmonary vascular resistance in primary pulmonary hypertension by intravenous prostacyclin can exceed the acute reduction in PVR[32]. The complications of long term prostacyclin therapy and the serious complications relate to the

vascular access. Hence other delivery routes have been used. Iloprost is a more stable analogue, with a longer half-life and may be delivered by nebuliser 2-3 hourly; Beraprost is stable in gastric juices and has a biological half-life of one hour. Trespostinil, another analogue, may be given by continuous subcutaneous infusion .

Adenosine
In a placebo-controlled trial, infused at 25-50 µg/kg/min improved oxygenation in infants with PPHN. No systemic haemodynamic consequences were seen. As adenosine is rapidly metabolised by the endothelium, its half-life is short.

Atrial Naturetic Peptide (ANP)
Plasma ANP and BNP reflect pressure and volume loads to the pulmonary artery and right ventricle and may help to identify children with ventricular septal defect complicated by PHT that demands early intervention. BNP measurements may also be used to guide therapy e.g., pulmonary vasorelaxants in PAH since upregulation of the natriuretic peptide pathway has been shown to reduce cardiac hypertrophy and PAH. There may also be therapeutic potential via recombinant BNP or neutral endopeptidase inhibitors in RV dysfunction and PAH.

High frequency oscillatory ventilation (HFOV)
In a randomised clinical trial of neonates with severe PPHN HFOV was as effective as inhaled NO. In the presence of severe lung diseases HFOV was more effective than inhaled NO. In the absence of parenchymal lung disease inhaled NO was more effective than HFOV. Combining inhaled NO and HFOV was more successful than either alone.

ECMO
Finally, for intractable PHT, which fails to respond to all the available therapeutic modalities, extracorporial membrane oxygenation (ECMO) should be considered[38]. An oxygenation index of >40 should be a trigger for considering ECMO. However, in a unit with HFOV and iNO a higher OI of 60-80 may be tolerated particularly if ECMO is near or on site. With the addition of the vasodilators described the need for ECMO is declining. The rate of increase in OI reflects the speed of deterioration and also indicates urgent consideration of ECMO.

Management Strategy
Any management strategy should be based upon an attempt to selectively dilate the pulmonary vascular bed thereby increasing pulmonary blood flow and enhancing gas exchange. If this is not possible the next best option is to try and alter the balance between pulmonary (PVR) and systemic vascular resistance (SVR) preferentially increasing SVR while not altering PVR to the same degree.

In our practice we start by ensuring the baby is adequate fluid resuscitated and will give up to 30ml/kg fluids, crystalloid or colloid. We then ensure that the arterial pH is as normal as possible with an arterial carbon dioxide tension of around 4-4.5kPa and a high serum bicarbonate resulting in a serum pH of 7.45-7.50. We achieve this in two ways. We institute HFO at a very early stage and use a wide span and low oscillator frequency, down to 5Hz, to clear carbon dioxide. To ensure a relative alkalosis we will give boluses of sodium bicarbonate or set up an infusion to achieve normal to high serum bicarbonate levels. While adjusting the pH we will simultaneously introduce inhaled NO at 20ppm. If pre-ductal saturations remain low our next step is to raise the mean arterial pressure to 60-70mmHg, recognising that this is considerably higher than normal for a neonate. This is achieved with a noradrenaline infusion. We deliberately attempt to increase the SVR. There is some evidence to suggest that noradrenaline has more of a peripheral action on the systemic vasculature than on the pulmonary vascular bed.[39] These few simple measures often result in success and no further interventions are necessary. If we are still having problems with increased PVR at this stage, then we use agents with less evidence base but which in our experience have proved very useful. We introduce a bolus of magnesium and raise serum magnesium level to the upper limits of the normal range. Finally we will introduce adenosine. With this stepwise approach we have been able to successfully manage neonates with OIs higher than normally indicated for ECMO yet without recourse to ECMO. Our median OI in the last five years in the group of neonates referred to ECMO was 49 rising to 65 in the group that also received adenosine, with no difference in mortality. So with iur current management strategy we have

been able to delay the commencement of ECMO and improve those neonates with much higher OI levels.

Conclusion

There is no single magic bullet for the successful treatment of PHT. Recent efforts have been devoted to understanding the cellular mechanisms underlying the pathophysiology of pulmonary hypertension, concentrating on endothelial cell dysfunction and defects in vasodilatation in order to fine tune the treatment of pulmonary hypertension. A better understanding of the regulation of pulmonary vascular tone will lead to the appropriate use of the new drug therapies available and a combination of any or all of the above therapies may be useful when treating this life threatening condition.

Meconium aspiration

Meconium aspiration syndrome occurs when a neonate inhales meconium. Most meconium deliveries involve some meconium staining of the liquor but needing no further intervention. However, significant aspiration of thick meconium can induce 3 major pulmonary effects: airway obstruction , surfactant dysfunction, and chemical pneumonitis.

Incidence The figure quoted for infants born with meconium-stained liquor is 5-10% of births. However, improvements in obstetric practice have resulted in a reduction in the incidence of meconium aspiration syndrome (MAS) over recent years.

Management

- *Intubation* - if the baby is showing weak or no respiratory effort, an endotracheal tube should be inserted. However, tracheal suctioning of vigorous infants is not recommended.
- *Oxygen* - depending on the degree of respiratory distress, respiratory support should be provided with oxygen via a nasal cannula, continuous positive pressure ventilation, conventional mechanical ventilation, or high-frequency oscillatory ventilation.
- *Surfactant* - meconium flowing into the lung deactivates the activity of surfactant, causes a rise in surface tension, and the onset of respiratory distress. Surfactant lavage combats this effect and significantly improves infant mortality and morbidity.
- *Inhaled nitric oxide* - this is useful in the management of pulmonary hypertension associated with MAS. It is thought to act by relaxing smooth muscles in the pulmonary vessels causing vasodilatation, as well as promoting bronchodilation. It is often more effective when combined with high-frequency oscillatory ventilation.
- *Extracorporeal membrane oxygenation (ECMO)* - this uses a heart-lung machine to take over the work of the lungs. Veno-venous ECMO seems as effective as veno-arterial ECMO

Complications and Prognosis

In mild cases, respiratory distress usually subsides in 2-4 days, although tachypnoea can persist for longer. Rarely, more prolonged respiratory damage can occur which can persist for many years.This is more likely if ventilation has been required. Cerebral hypoxia may lead to long-term neurological damage[2] The mortality rate is approximately 5%. Risk factors for mortality include resuscitation outside hospital, first born babies, shock, pneumothorax, pulmonary hypertension, and renal failure.

Chronic lung disease

Chronic lung disease (CLD) is a general term for long-term respiratory problems in premature babies. It is also known as bronchopulmonary dysplasia (BPD).

CLD results from lung injury to newborns who must use a mechanical ventilator and extra oxygen for breathing. The lungs of premature babies are fragile and are easily damaged. With injury, the tissues inside the lungs become inflamed and can break down causing scarring.

Some of the causes of lung injury include the following:

- prematurity - the lungs, especially the air sacs, are not fully developed
- low amounts of surfactant (a substance in the lungs that helps keep the tiny air sacs open)
- oxygen use (high concentrations of oxygen can damage the cells of the lungs)

- mechanical ventilation - the pressure of air from breathing machines, suctioning of the airways, use of an endotracheal tube.

It is diagnosed when a premature baby with respiratory problems continues to need additional oxygen after reaching 36 weeks gestational age. Chest x-rays compared with previous x-rays may show changes in the appearance of the lungs. The x-ray of lungs with CLD often have a bubbly, sponge-like appearance.

Treatment of CLD may include:
- extra oxygen (to make up for the decreased breathing ability of the damaged lungs)
- mechanical ventilation with gradual weaning as the baby's lungs grow and can do more of the work of breathing
- medications such as:
- bronchodilators (to help open the airways)
- steroids to help reduce inflammation)
- limiting fluids and giving a medication (diuretic) to help reduce excess fluid which can worsen breathing ability
- nutrition (to help the baby and the lungs grow)
- immunization against lung infection by respiratory syncytial virus (RSV) and influenza

Neonatal abstinence syndrome

If mother is known to be heroin dependent, or on methadone treatment, then the neonate should be observed for evidence of the Neonatal Abstinence Syndrome (NAS). Neonatal abstinence syndrome is scored using an NAS score chart (a modified Finnegan Scoring System).
Infants born to narcotic dependent women are evaluated for signs of withdrawal by mean NAS scoring two hours after birth or sooner if signs of withdrawal are evident, and subsequently at 4 hourly intervals. The scoring should be performed 1/2 to 1 hour after baby the baby has been fed. The NAS score chart lists 21 signs most commonly seen in the passively narcotic addicted neonate. Each sign and its associated degree of severity are assigned a score. Higher scores accompany those signs found in babies with more severe abstinence that are at an increased risk of morbidity. The total abstinence score is determined by summation of scores assigned to each sign observed throughout the entire scoring interval.
Due to heroin's short half life, withdrawal often manifests in the first one or two days of life, whereas significant withdrawal from methadone may take up to 7 days to become apparent. Hence, mothers and their babies should be routinely observed as in-patients for at least seven days before being discharged.
Neonates with an abstinence score averaging 8 or more for three consecutive scores should be transferred to the Special Care Nursery for evaluation for morphine therapy. If there are inconsistencies in the scores, the baby may be observed for a period of time to ensure morphine therapy is truly indicated.

Neonatal seizures

Seizures during the neonatal period are relatively common, occurring in approximately 1% of all neonates. Neonatal seizures represent an age-specific seizure disorder, which is usually considered to be in a separate category from epilepsy. While in children seizures often occur in the absence of another neurological disorder, neonatal seizures frequently are a non-specific sign of an underlying disease. Neonatal seizures also have many other characteristics that are quite different from seizures in children and adults.

Neonatal seizures are usually divided into four main categories: clonic, myoclonic, tonic, and subtle.
- Clonic seizures are characterized by rhythmic, repetitive shaking of isolated parts of the body.

- Focal clonic seizures involve one part of the body and multifocal clonic seizures involve several parts simultaneously or in sequence with migration in a random fashion.
- Myoclonic seizures represent very brief isolated jerks of parts of the body. Tonic seizures involve stiffening of parts of the body and can be focal or generalized, although generalized tonic stiffening is usually not due to true electrographic seizure activity.
- Finally subtle seizures consist of other miscellaneous paroxysmal clinical phenomena, such as eye deviation, oral-buccal movements, or patterned movements of the extremities like bicycling.

The most common antiepileptic drugs used in neonates are phenobarbital, phenytoin, and various benzodiazepines. Phenobarbital is especially popular in neonates because of its long half-life and favorable pharmacokinetic properties.

Overall, ~10-50% of patients with neonatal seizures die, mostly during the neonatal period, and ~50% of survivors develop long-term neurological complications, like epilepsy, mental retardation, and cerebral palsy.

Retinopathy of Prematurity: screening and treatment

Retinopathy of prematurity (ROP) is an abnormal vascular proliferative disorder of the immature retina that may acutely threaten vision. In the longer term, even after regression, it can lead to: acuity defects; refractive errors; gaze abnormalities. The median onset of threshold disease (that requiring intervention) is 36 - 37 weeks corrected age - babies must continue ophthalmological followup until there is mature vascularisation of the retina (at least term). Treatment of threshold disease reduces the incidence of retinal detachment by 50%. Whether or not treatment is required, babies with ROP are at increased risk of ophthalmological problems

Screening
The aim of screening is to identify those infants at risk of vision
threatening retinopathy so as to allow effective therapy to prevent poor ophthalmic outcomes (blindness). Screening occurs in babies <1250g who have received supplemental oxygen.
The retinas are checked by an experienced paediatric ophthalmologist at 4-6 weeks of age, with the subsequent frequency depending on the location, extent and severity of the disease.
A more detailed screening plan is outlined in the American Academy of Pediatrics position statement.

Treatment
Treatment of established "threshold" disease was introduced in order to prevent the high risk of blindness in affected eyes. This involved ablation of the peripheral avascular retina, thus preserving central macula vision. Treatment modalities include: transscleral cryoablation (technically easier in infants with hazy vitreous); photocoagulation (laser); cryoablation.
These interventions aim to destroy the avascular retina thought to be responsible for the angiogenic growth factors that drive the neovascularisation. Peripheral retinal ablation, by any means, reduces the incidence of early adverse ophthalmic outcome (retinal detachment) in infants with threshold ROP by 50% (from 47.9 to 28.1%). It is important to note that the risk of blindness in treated eyes remains (though the risk is halved) even after intervention.
The risk of retinal detachment in treated eyes remains stable whereas the risk of detachment continues in untreated eyes with threshold disease. Cryotherapy may produce a small reduction in the visual field.