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# Pathophysiology of respiratory distress syndrome

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## Abstract

Respiratory distress syndrome (RDS) is a major cause of neonatal mortality and morbidity, especially in preterm infants. Its aetiology includes developmental immaturity of the lungs, particularly of the surfactant synthesizing system. Surfactant is produced, stored and recycled by type II pneumocytes and is detectable from about 24 weeks' gestation. It is a mixture of phospholipids, neutral lipids and proteins and is spread as a film over the alveolar surface to lower surface tension and to prevent alveolar collapse. The resulting clinical correlates of RDS can be predicted from the immature lung structure and atelectasis which occur due to surfactant deficiency. Various clinical factors are known to dysregulate surfactant production and function, leading to the development of RDS. Apart from preventing the incidence of prematurity, antenatal steroids and prophylactic surfactant are of proven benefit in reducing the incidence of RDS.

**Keywords** alveoli; infant; newborn; preterm birth; pulmonary surfactant; respiratory distress syndrome

## Introduction

Respiratory distress syndrome (RDS) is the dominant clinical problem faced by preterm infants. It remains a major cause of neonatal mortality and morbidity despite advances in perinatal care. The incidence of RDS decreases with advancing gestational age, from about 60–80% in babies born at 26–28 weeks, to about 15–30% in those born at 32–36 weeks.<sup>1,2</sup> The syndrome is also more frequent in male infants and infants of diabetic mothers. RDS is caused by developmental insufficiency of surfactant production and function, as well as by structural immaturity of the lungs. It can also result from surfactant protein genetic disorders. This review discusses the pathogenesis of RDS in relation to fetal lung growth and surfactant metabolism. Risk factors for RDS and preventative approaches will also be reviewed.

## Lung growth and development

Some understanding of lung growth and development may be useful in understanding why RDS occurs. Normal lung development,

which occurs as a series of complex, tightly regulated events, can be divided into five stages (Table 1). During the *embryonic stage* (fetal weeks 0–7), the lung develops as a ventral diverticulum from the foregut endoderm and, after divisions, the main bronchi and five lobes are formed. The pulmonary arteries develop and accompany the developing airways.<sup>3</sup> The embryonic stage is followed by the *pseudo-glandular stage* (weeks 7–17). Branching of the airways and vessels continues and by the end of this stage the terminal bronchioles and primitive acini are formed. During the *canalicular stage* (weeks 17–27), further development of the distal airways into definitive primary acini occurs and the alveolar capillary barrier is formed. Differentiation into type I and II pneumocytes occurs and surfactant components produced by type II cells are detectable in the form of lamellar inclusion bodies by 24 weeks' gestation. Thus, a possible but immature platform for gas exchange is established.<sup>4</sup>

With advances in perinatal medicine and ever increasing survival of extremely preterm infants, this is an important landmark in lung growth and development. However, surfactant deficiency leading to RDS is inevitable if preterm delivery occurs at this stage.<sup>4</sup> In the *saccular stage* (weeks 28–36), the gas-exchanging surface area increases as the airways wall thins out. Lamellar bodies in type II cells increase and further maturation of type II into type I cells occurs. Capillaries are closely associated with type I cells, thus reducing the distance between the future air–blood interface. The *alveolar stage* (36 weeks' gestation–2 years post-natally; although controversy remains regarding the exact timing

### Stages of lung growth

Stage	Time	Structural changes
Embryonic	0–7 weeks	Formation of trachea, right and left main bronchi and segmental bronchi. Blood vessels connect to the heart
Pseudoglandular	7–17 weeks	Differentiation of epithelial cells, formation of conduction airway and terminal bronchioles, formation of pulmonary arteries and veins
Canalicular	17–27 weeks	Formation of respiratory bronchioles, alveolar ducts and primitive alveoli; differentiation of type I and type II pneumocytes
Saccular	28–36 weeks	Increment in gas exchange areas; further differentiation of type I and type II cells
Alveolar	36 weeks–2 years	Septation and multiplication of alveoli

Table 1

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of the alveolar phase) is characterized by alveolar formation and maturation. The result is a great increase in gas-exchanging surface area and maturation of cells, which will enable adaptation to the postnatal environment. Other major determinants for lung growth and development include maintenance of an adequate fetal lung fluid volume and fetal breathing movements, which appear to be essential for normal lung growth.<sup>5</sup>

### Development of type II pneumocytes

Type II pneumocytes are at the centre of surfactant production and function. Flattening of the acinar epithelium at 22–24 weeks marks the initial differentiation of type II pneumocytes, from which type I pneumocytes will be derived later.<sup>4</sup> Type II pneumocytes have a cuboidal shape and comprise 10–15% of the cells of the mature distal lung. They produce surfactant and their characteristic feature is the lamellar bodies which store surfactant. Lamellar bodies are first observed between 22 and 24 weeks' gestation. Surfactant is secreted from these cells by exocytosis into the lining of the alveoli and appears in the future air spaces at 23–24 weeks' gestation. Type II pneumocytes mature more rapidly between 32 and 36 weeks' gestation, thereby promoting functional maturity of the lung.

Type II cells are also important in maintaining structural integrity of the pulmonary alveolus as they proliferate after lung injury and serve as precursors for gas-exchanging type I cells. Type I pneumocytes are flat and elongated and cover the majority of the alveolar surface. Their shape is designed to aid effective gas exchange. These cells are however vulnerable to oxidant damage, that is due to hyperoxia because of their large surface area and reduced anti-oxidant capacity compared to type II alveolar cells which are more resistant to such injury.

### Surfactant

Surfactant, which is a major determinant of alveolar wall surface tension, is a complex mixture of phospholipids, neutral lipids and proteins. Its major constituents are dipalmitoylphosphatidylcholine (DPPC or lecithin), phosphatidylglycerol, cholesterol and apoproteins (surfactant proteins SP-A, -B, -C and -D). DPPC is the principle component responsible for reducing surface tension. The other phospholipids and proteins aid spreading and re-absorption of surfactant along the alveolar wall.

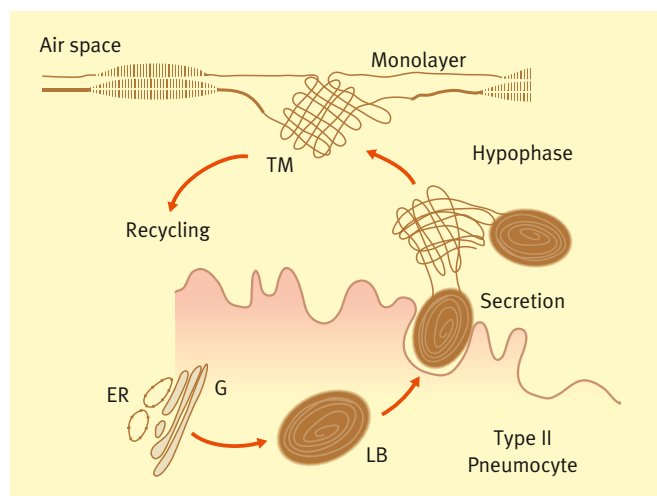
Four apoproteins have been identified. The hydrophobic SP-B and SP-C play a major role in the surface-active properties of surfactant and are essential for lung function and pulmonary homeostasis after birth. These proteins enhance the spreading, adsorption and stability of surfactant lipids required to reduce surface tension in the alveolus.<sup>6</sup> Hydrophilic SP-A and SP-D are lectins. Their primary role is in host defence and in surfactant clearance and metabolism.<sup>7</sup> Despite many commercial attempts, none of the currently available surfactant preparations for treatment of RDS contains either SP-A or SP-D.

The normal alveolar pool size of surfactant phospholipids in a full-term neonate has been estimated at about 100 mg/kg, which is about ten times greater than the amount noted in the lungs of a newborn infant with RDS.<sup>8</sup> Surfactant deficiency due to decreased production and secretion is the primary cause of RDS and is more severe in the structurally immature lung of the preterm infant.

### Surfactant metabolism

Surfactant proteins and phospholipids are produced in the smooth endoplasmic reticulum of type II pneumocytes then transported via the Golgi apparatus to the lamellar bodies which are the intracellular stores for surfactant (Figure 1). From these, surfactant is secreted by exocytosis into the liquid lining of the alveoli. In the alveolus, the phospholipids undergo transition to an extracellular form, tubular myelin, in association with SP-A and SP-B. SP-B and SP-C are responsible for liberating the phospholipids from this structure and ordering them into a monolayer at the air–liquid interface. Subsequently, most of the phospholipid and protein components of surfactant are recycled by endocytosis from the alveolar lumen in the form of small vesicles by the type II pneumocytes. Alternatively, a small proportion (~10%) is phagocytosed and degraded by alveolar macrophages. A single transit of the phospholipid components of surfactant through the alveolar lumen normally takes only a few hours. The phospholipids in the lumen are recycled by type II cells and reutilized approximately ten times before being degraded.

The cycle of surfactant synthesis and metabolism is tightly regulated to ensure maximal economy and function, especially in the neonatal period. There is negative feedback of surfactant production mediated by SP-A binding to type II cells. Surfactant secretion, at least to some extent, is triggered by stretch receptors and by  $\beta$ -adrenergic receptors on type II pneumocytes, with receptor numbers increasing towards the end of gestation. Several other mechanisms which stimulate the synthesis and release of surfactant into the alveolar space have been also identified.<sup>9</sup> Some of these pathways involve catecholamines, cyclic adenosine monophosphate (cAMP), adenosine triphosphate (ATP), calcium and prostaglandins.



**Figure 1** Surfactant recycling. The location and movement of surfactant from the type II pneumocyte to the alveolus is shown. Surfactant is synthesized from precursors in the endoplasmic reticulum (ER) and transported via the Golgi apparatus (G) to lamellar bodies (LB) where it is stored. From there it is secreted into the liquid lining of the alveolus where it forms tubular myelin (TM), which generates the surface tension reducing monolayer. Subsequently, surfactant components are taken up by the type II pneumocytes again in the form of small vesicles. A small proportion of surfactant is also taken up by alveolar macrophages. (Redrawn with permission from McCabe et al.<sup>29</sup>)

### Pathophysiology of surfactant deficiency

Surfactant is spread as a thin film at the air–liquid interface of the alveolar surface, lowering its surface tension and thereby preventing alveolar collapse, especially at the low alveolar volumes reached at end-expiration. It also reduces the pressure required for subsequent alveolar inflation and maintains a satisfactory functional residual capacity.

It is therefore clear that in the absence of an adequate amount of mature pulmonary surfactant, infants with RDS will progressively develop atelectasis and abnormalities of lung function. The alveoli tend to collapse at end-expiration, resulting in a low functional residual capacity. The pressure needed to inflate the lungs will be high, the lung compliance will be decreased and the work of breathing greatly increased. Infants with RDS have a low tidal volume and a large physiological dead space. Minute ventilation may be increased due to an increased respiratory rate in an attempt to sustain alveolar ventilation, but alveolar ventilation remains inadequate.

Atelectasis with other areas of over inflation may co-exist, especially in an infant receiving mechanical ventilation and thus leading to ventilation–perfusion mismatching and right-to-left intrapulmonary shunting. This limits the excretion of carbon dioxide and oxygen saturation of pulmonary venous blood, leading to respiratory acidosis and hypoxaemia. Persistent hypoxaemia leads to metabolic acidosis, reduced cardiac output and hypotension. Arterial blood gases in severe RDS thus reflect a mixed metabolic and respiratory acidosis. Acidosis will further reduce surfactant production and may also increase pulmonary vascular resistance.

The increased work of breathing is manifested by intercostal and subcostal recessions as the infant generates higher negative pleural pressure to maintain alveolar ventilation. Most preterm babies are born with poor reserves of surfactant and the characteristic deterioration in the early phase of RDS is in part due to the disappearance of these small quantities together with fatigue as the neonate struggles to sustain adequate ventilation. Proteins leak into the alveolar spaces during the early stages of acute lung injury and will further inhibit the small amount of surfactant present. Hypoxaemia and acidaemia will also affect surfactant function and synthesis.

In the untreated infant, endogenous surfactant production commences from 2–3 days of age and heralds clinical recovery from respiratory distress. By reducing surface tension, surfactant allows the alveoli to re-expand with inspiration. Therefore, optimum gas exchange is achieved through matching of ventilation and perfusion. Clinically, the functional residual capacity improves and the work of breathing decreases markedly due to the decreased airway resistance and improved lung compliance.

**Pathological findings:** on macroscopic examination a surfactant deficient lung appears poorly inflated, has the consistency of liver and does not float in water. Microscopically, the initial finding is of alveolar epithelial cell necrosis, which can develop within half an hour of birth. The epithelial cells become detached from the basement membrane and small patches of hyaline membrane form on the denuded areas. Hyaline membranes are composed of fibrin, cellular debris, red blood cells, neutrophils and macrophages. They appear as an eosinophilic, amorphous material, lining or filling the alveolar spaces and thus adversely affecting gas

exchange. In the initial stages, these changes are rather patchy, but by about 24 hours of age more generalized hyaline membrane formation occurs. After 24 hours, the repair phase begins and cells of resolution, mainly macrophages, appear within the airway lumen. After 5–7 days, the hyaline membranes start to disappear and the remnants are phagocytosed by the macrophages. The architecture of the lung returns to normal. In the prolonged inflammatory processes of many preterm infants, the disease may progress to chronic lung disease of prematurity (CLD).

### Risk factors for the development of respiratory distress syndrome

Many risk factors of RDS have been described (Table 2). Some of the common ones are described below.

#### Prematurity

The greatest risk factor for RDS is low gestational age and the development of the disease begins with the impaired synthesis of surfactant associated with prematurity. About 50% of infants born before 30 weeks' gestation will develop RDS<sup>10</sup> and the incidence decreases with advancing gestational age, from about 60–80% in babies born at 26–28 weeks, to about 15–30% of those born at 32–36 weeks.<sup>1,2</sup> As described above, RDS is the result of both surfactant deficiency and structural immaturity of the lungs.

#### Gender

Boys are more likely than girls to develop RDS (male-to-female ratio ~1.3:1).<sup>11</sup> These differences are thought to be partly due to androgenic actions on type II pneumocytes delaying the production of mature surfactant.<sup>12</sup>

#### Race

There are ethnic differences in the incidence of RDS with higher rates observed in Caucasian compared to black infants. In a study of preterm infants born between 23 and 32 weeks' gestation, the incidence of RDS was 75% in Caucasian infants, 54% in infants of Caribbean origin and 40% in infants of African origin.<sup>13</sup>

### Risk factors for respiratory distress syndrome

#### Maternal factors

Multiple pregnancy  
Elective caesarean section  
Gestational diabetes  
Intrahepatic cholestasis of pregnancy

#### Infant factors

Prematurity  
Male gender  
Familial disposition  
Hypothermia  
Caucasian ethnicity  
Intrapartum asphyxia  
Pulmonary infections  
Pulmonary haemorrhage  
Meconium aspiration syndrome  
Congenital diaphragmatic hernia  
Pulmonary hypoplasia

Table 2

### Multiple pregnancy

In twin pregnancies, the second twin is usually at greater risk of developing RDS. This risk of developing RDS in the second twin increases with gestation and is most significant after 29 weeks.<sup>14</sup> It is not clear whether this increased risk is due to delayed maturation of the lungs or an increased risk of hypoxia/acidosis in the second twin.

### Caesarean section

At any given gestational age the incidence of RDS is greater for infants born by caesarean section, especially without established labour, than for those born by vaginal delivery.<sup>15</sup> The combination of elective caesarean section and delivery before term significantly increases the risk of RDS.<sup>16</sup> The reasons for the increased risk of respiratory morbidity are probably a combination of delayed removal of lung fluid and a lack of cortisol response associated with spontaneous labour.

### Maternal diabetes

Infants of diabetic mothers are more likely to develop RDS compared to infants of non-diabetic mothers of equivalent gestational age. These babies have an abnormal pattern of surfactant synthesis with delayed appearance of phosphatidylglycerol.<sup>17</sup> Insulin has been shown to delay the maturation of type II pneumocytes and decreases the proportion of saturated phosphatidylcholine in surfactant. However, delivery at term rather than at 36–37 weeks reduces the risk of severe RDS in infants of diabetic mothers.

### Genetic disposition

Cases of familial RDS in term babies have been reported and it is now clear that some of these are due to genetic reasons, such as partial or complete deficiency of SP-B.<sup>18</sup> In cases where SP-B is completely absent, death is inevitable despite intensive care and surfactant treatment.<sup>19</sup> Partial deficiency of SP-B has also been reported and this may be compatible with survival. Similar genetic defects of other components of surfactant are increasingly being described.

### Intrahepatic cholestasis of pregnancy

It has recently been shown that maternal intrahepatic cholestasis of pregnancy is significantly associated with the occurrence of RDS in the newborn. It has been hypothesized that bile acids can cause surfactant depletion in the alveoli.<sup>20</sup>

### Other risk factors

Secondary surfactant deficiency may occur in infants with intra-partum asphyxia, pulmonary infections (e.g. Group B  $\beta$ -haemolytic streptococcal pneumonia), pulmonary haemorrhage, meconium aspiration syndrome, congenital diaphragmatic hernia or pulmonary hypoplasia. RDS is further exacerbated by treatable and preventable factors, including hypothermia, hypoxia and acidosis, which impair surfactant production and secretion.

### Prevention

Most important in decreasing the incidence of RDS is prevention of prematurity, including avoidance of unnecessary and poorly timed caesarean sections. Maternal narcotic addiction, smoking and alcohol intake all reduce the incidence of RDS in preterm

babies.<sup>21,22</sup> The mechanism is probably due to stimulation of surfactant production, but the significant adverse effects of these drugs clearly prohibit their use in pregnancy.

The two major management approaches to prevent the development of RDS are the use of antenatal treatment of women in preterm labour with glucocorticoid hormone to accelerate fetal lung maturation and the early use of surfactant replacement therapy.

### Antenatal glucocorticoids

Several randomized controlled clinical trials have been performed on the efficacy of antenatal corticosteroids in preterm birth to decrease the rates of RDS and the first structured review on corticosteroids in preterm birth was published in 1990.<sup>23</sup> A recent Cochrane review showed that treatment with antenatal corticosteroids reduces the risk of neonatal death, RDS, intraventricular haemorrhage, necrotizing enterocolitis, infectious morbidity, need for respiratory support and neonatal intensive care unit admission.<sup>24</sup> Antenatal administration of corticosteroids accelerates lung growth by several mechanisms, including maturation of type II pneumocytes and production of surfactant.<sup>25</sup> However, repeated doses to the mother in threatened preterm labour may affect the final numbers of alveoli and somatic growth; this has been shown at least in animal models.

### Thyrotropin-releasing hormone

Thyroxine increases surfactant production and lung maturation. However, unlike T3 and T4, thyrotropin-releasing hormone (TRH) readily crosses the placenta and increases the amount of surfactant phospholipid. TRH in combination with corticosteroids has been used in the past. However, some studies have shown that receiving surfactant in addition to TRH does not decrease the incidence of RDS in infants.<sup>26</sup> In follow-up studies, there was an increased risk of motor delay in surviving infants. Therefore, antenatal administration of TRH to women in preterm labour is not routinely used in practice.

### Prophylactic surfactant administration

Prophylactic, or preventive, surfactant administration is defined as endotracheal intubation and surfactant administration to infants at high risk of developing RDS. For infants at high risk for RDS, prophylactic surfactant replacement therapy is preferable to later rescue therapy for established RDS as survival, CLD or death and air leak are significantly decreased.<sup>27,28</sup> Together with antenatal corticosteroid treatment, the use of prophylactic surfactant has made the greatest contribution to decreasing the incidence of RDS and its associated mortality and morbidity.

### Summary

RDS is caused by developmental insufficiency of surfactant production and structural immaturity of the lungs. The incidence is therefore inversely related to the gestational age and RDS remains the leading cause of death in premature infants. The lack of surfactant, which is produced in type II pneumocytes from 24 weeks' gestation, leads to a reduction in lung compliance. The alveoli tend to collapse, giving rise to atelectasis and a reduced functional residual capacity. Apart from prematurity, several factors contribute to the development of RDS. The risk of



developing RDS is markedly reduced with the administration of antenatal steroids and prophylactic surfactant. ◆

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## Practice points

- RDS is caused by developmental immaturity of the lung, particularly the surfactant-producing type II pneumocytes
- Surfactant reduces surface tension at the alveolar surface and its lack leads to atelectasis
- The greatest risk factor for RDS is prematurity but there are many others
- Antenatal steroids and prophylactic surfactant administration have been shown to be of the greatest benefit in reducing the incidence of RDS

# Management of respiratory distress syndrome

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## Abstract

Respiratory distress syndrome is the most common pathology of preterm infants managed in neonatal intensive care units worldwide. Advances in neonatal intensive care, prenatal interventions, especially corticosteroid therapy, and postnatal respiratory support have considerably increased the survival of extremely premature infants. Despite these advances, epithelial lung injury and inflammation secondary to surfactant deficiency and as a consequence of mechanical ventilation ultimately leading to bronchopulmonary dysplasia has not significantly reduced. Animal studies have confirmed that the pathological cascade of inflammation is initiated within the first few breaths of life, more so in a surfactant-deficient lung. Hence early management is aimed at minimizing lung injury, starting in the delivery suite. Although a number of different modalities of ventilation are available for ongoing support, the principle is to administer controlled ventilation, avoiding overinflation, and to give just enough end expiratory pressure to prevent collapse of surfactant-deficient alveoli. Non-invasive ventilation is an invaluable tool both in the treatment of mild-to-moderate RDS and the prevention of post-extubation respiratory failure. Supportive treatment contributes equally to the outcome.

**Keywords** CPAP; neonatal delivery room management; neonatal respiratory distress syndrome; neonatal resuscitation; neonatal ventilation; preterm infant; RDS; surfactant

## Introduction

Respiratory distress syndrome (RDS) is the commonest single condition managed in neonatal intensive care units. It is the commonest pathology of preterm infants born at less than 32 weeks' gestation, and the disease and its complications still account for substantial mortality and long-term morbidity.

Initial disease severity is associated with lower gestational age, perinatal asphyxia, male gender, hypothermia, absence of maternal pre-delivery corticosteroid treatment and, probably, delivery by caesarian section.<sup>1</sup> The role of perinatal infection in relation to disease severity is still to be elucidated. Without exogenous surfactant treatment, symptoms develop shortly after birth and usually increase in severity over the first 2 days of life. Without

ventilatory support, infants present with grunting, cyanosis, tachypnoea and subcostal and intercostal recession, and less frequently with apnoea and circulatory collapse.<sup>2</sup> Recovery usually starts after 48–72 h and is associated with a diuresis which coincides with clearance of excess lung fluid, decreasing oxygen and ventilatory requirements and improvement in functional residual capacity (FRC). Lung compliance improves later.<sup>3</sup>

## Aetiology and pathophysiology

The initial pathology of RDS is due to physiological and anatomical immaturity of the neonatal lung. Both synthesis and secretion of surfactant are deficient and the lungs are incompletely alveolarized and vascularized. Effective lung function requires not only surfactant, but also an efficient system for gas exchange, development of the diaphragm and chest wall rigidity, along with a mature respiratory drive.<sup>3</sup> A complex secondary pathological cascade of tissue damage and inflammation follows the first breaths, leading to the characteristic clinical syndrome which may either resolve or progressively evolve into bronchopulmonary dysplasia (BPD).<sup>2,3</sup>

## Pulmonary functions

**Lung volume:** FRC is the volume of lung gas at normal tidal expiration. This is the volume available for gas exchange and is determined by the balance of expanding and collapsing forces from lung and chest wall. In RDS alveolar gas volume may be further displaced by vascular congestion, interstitial oedema and proteinaceous exudate. Improvement in FRC is clinically reflected by a decrease in oxygen requirement, and may be facilitated by application of positive airways pressure (or negative intrathoracic pressure), the presence of surfactant and clearance of oedema and exudates.<sup>1</sup>

**Lung compliance** is the change in lung volume with the application of a unit change in airway pressure. As the chest walls of premature infants are pliable, the lungs are the major determinants of thoracic elasticity. High surface tension associated with surfactant deficiency increases the pressure increment needed to expand the surface area of the gas–liquid interface between expiration and inspiration. This is the major determinant of poor lung compliance in RDS. Hyaline membrane formation and interstitial oedema may be secondary factors.

**Role of surfactant in pulmonary function and blood flow:** surfactant forms a thin film at the gas–liquid interface within the terminal saccules or alveoli and reduces surface tension.<sup>4</sup> Reduced surface tension facilitates expansion of the terminal airways and reduces collapse at end-expiration during the first breaths of life, thus allowing the establishment of an FRC. Establishment of an FRC may be impaired both by surfactant deficiency and by the preterm infant's impaired ability to clear fetal lung fluid.<sup>2</sup> Once FRC is established, reduced surface tension improves lung compliance and reduces the work of breathing with each tidal breath.

Improvements in gas exchange, particularly oxygenation, result in pulmonary vasodilation and a significant fall in pulmonary arteriolar pressure, facilitating pulmonary blood flow. The pressure change reverses the pulmonary-to-systemic pressure relationship, usually leading to a bi-directional or left-to-right shunt until the duct closes.<sup>1</sup>

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Infants born prematurely are likely both to be surfactant deficient and to have a limited ability to clear lung fluid.<sup>3</sup> Thus, they fail to establish an optimal FRC and also have decreased lung compliance. This may lead to hypoxia and acidosis, pulmonary vasoconstriction, pulmonary hypertension and decreased pulmonary blood flow.<sup>2</sup> This in turn may lead to right-to-left shunting, endothelial and epithelial cell injury, pulmonary oedema and right heart failure.

The synthesis and release of surfactant are pH, temperature and perfusion dependent. Hypoxia, asphyxia, pulmonary ischaemia and cold stress are strong inhibitors of surfactant production.<sup>3</sup> High oxygen concentrations<sup>5</sup> and overdistension of alveoli result in a further reduction in surfactant production.<sup>3</sup>

## Management

Postnatal management of the preterm infant may be regarded as supportive care while the immature physiology and anatomy adapt to the postnatal environment independent of the placental circulation. Intact survival demands that for the respiratory and associated cardiovascular systems, this transition to tissue oxygen delivery and carbon dioxide elimination has to take place very rapidly. In general, with increasing gestational age, particularly at gestations greater than 32 weeks, most premature infants are capable of making the transition with minimal help. Below 32 weeks' gestation the increased propensity to develop more severe RDS frequently requires some means of respiratory support.<sup>6,7</sup> While many alternative or complementary respiratory supports exist, the evidence base for their comparative effectiveness individually and for clinical strategies underlying their deployment is limited. Similarly there is concern over potential but uncertain long term respiratory and neurological sequelae of the various treatment strategies and modalities, particularly should they be applied over zealously.<sup>7</sup> Advances in neonatal intensive care and the widespread use of antenatal steroids, surfactant and ventilatory support have considerably increased the survival of extremely premature infants.<sup>8</sup> Despite these advances, the consequence of surfactant deficiency and its management (epithelial lung injury and inflammation ultimately leading to BPD) has not significantly reduced.<sup>8</sup>

Discussion of antenatal prevention of prematurity and RDS is beyond the scope of this review. Evidence in experimental animals for the initiation of the pathological cascade of RDS within the first few breaths of life and a general observation that most clinical interventions are more effective the earlier they are applied suggest that efforts to support respiration while minimizing injury need to focus on very early management. The relative contributions to the evolution of lung injury of such innate factors as molecular genetics, vertically transmitted infection and prenatally disordered lung development – as opposed to postnatal respiratory support strategies – is still unclear. However, pragmatically, there is now increasing emphasis on minimizing ventilation-induced lung injury (VILI) and its consequence, chronic lung disease (CLD), starting in the delivery suite.<sup>9–11</sup>

## Delivery room management

A preterm delivery under 30 weeks' gestation requires skilled personnel trained in the resuscitation and stabilization of premature infants.<sup>9</sup> Currently, the evidence for best practice for supporting preterm neonates in the delivery room remains weak.

**Intubation:** it is known that premature lungs are surfactant deficient, so a rational approach is to replace deficient surfactant and inflate lungs with just enough distending pressure to achieve adequate gas exchange. Surfactant delivery currently requires endotracheal intubation. There is evidence that early surfactant administration is more effective than later administration.<sup>12</sup> While it remains controversial for which preterm group elective endotracheal intubation for the sole purpose of administering early surfactant has advantages, it has been suggested that infants below 27 weeks' gestation are most likely to benefit from this approach (see Surfactant section below).<sup>9</sup> In premature infants whose clinical condition requires emergency intubation or in whom elective intubation has been chosen, it is good practice to administer exogenous surfactant as early as possible.<sup>9,11,12</sup> The advantage of giving surfactant early is to help establish an FRC before lung damage starts, to reduce barotrauma and vascular injury from mechanical ventilation and to prevent damage-related protein leak.

**Oxygen and resuscitation:** oxygen is a potentially toxic gas which can cause direct damage to respiratory epithelium. There is good evidence that 100% oxygen is harmful to most neonates<sup>5</sup> and potentially more so in extremely preterm infants, in whom hyperoxia results in a 20% decrease in cerebral blood flow and a much worse alveolar–arterial oxygen gradient.<sup>5</sup> On the other hand, hypoxia can be detrimental too.

Pulse oximetry at resuscitation can be a useful way of providing immediate feedback on both oxygen saturation and heart rate, although evidence of long-term benefit of its use during delivery suite resuscitation is lacking.<sup>9,13</sup> In contrast, pulse oximetry may help to wean inspired oxygen and prevent hyperoxic peaks.<sup>13</sup>

It is important to be aware of the relatively low fetal intrauterine arterial oxygen concentration of 30–40%<sup>13</sup> and to avoid an obsession with rapidly achieving the high arterial oxygen saturations characteristic of adults. Care should be taken to avoid rapid swings in oxygen saturation. In the absence of evidence to the contrary it is suggested that inspired oxygen concentrations should start with air and be slowly increased to achieve saturations around 90% over no less than 5 min duration.<sup>13</sup> It is no longer acceptable not to have air/oxygen mixed gas available for neonatal resuscitation in delivery suites.

**Continuous positive airway pressure (CPAP) and resuscitation:** there is increasing awareness from animal studies and observational studies in human infants that positive pressure ventilation is capable of inducing lung injury and triggering an inflammatory cascade within minutes of birth, especially in a surfactant-deficient lung.<sup>3,11</sup>

CPAP support has re-emerged as a potentially 'gentler' and less invasive modality to stabilize preterm neonates in the delivery room.<sup>10</sup> This modality appears to be beneficial for infants born with a good heart rate but who are slow to establish an FRC and effective spontaneous respiration. CPAP support with a pressure of at least 5–6 cm H<sub>2</sub>O<sup>9</sup> helps stabilize expanded or recruited alveoli and also works in synergy with endogenous surfactant by conserving the surfactant on the alveolar surface.<sup>3,10</sup>

A large international multicentre randomized controlled trial, the COIN trial,<sup>14</sup> investigated whether commencing nasal CPAP (nCPAP) in spontaneously breathing babies by 5 min of age as opposed to elective intubation and ventilation would reduce the



rate of death or BPD in preterm infants born between 25 and 28 weeks' gestation. The results of this study were inconclusive, showing no reduction in the primary outcome measure of death or BPD in the early CPAP group. In this group there was an increase in pneumothoraces but a decreased use of surfactant, fewer days on ventilation and a lower incidence of oxygen requirement or death at 28 days. This study did demonstrate that nCPAP initiated in the delivery suite in infants of 25–28 weeks' gestation is an effective strategy, but the evidence to recommend routine use in this group over elective intubation, ventilation and surfactant administration is weak.

**Positive pressure ventilation:** If positive pressure breaths are required during resuscitation, either by mask or endotracheal tube, peak inspiratory pressure limiting or monitoring devices should be used to help avoid excessive tidal volumes.<sup>9,11</sup> Uncontrolled pressure inflations may result in lung damage, capable of triggering an exaggerated inflammatory reaction and of reducing the effectiveness of both endogenous and exogenous surfactant.<sup>3</sup> 'Controlled ventilation' that avoids overinflation (volutrauma) is essential. It is desirable to administer just enough peak end expiratory pressure (PEEP) to prevent collapse of surfactant-deficient alveoli (as the amount of pressure required is greater to open atelectatic alveoli than it is to ventilate already open alveoli) and to prevent generation of shear forces that can disrupt respiratory epithelium.<sup>3</sup>

**Thermal control:** hypothermia in preterm infants decreases endogenous surfactant production, increases the incidence and severity of RDS and is associated with decreased survival. Avoiding early hypothermia is essential secondary management of RDS.<sup>15</sup> Measures should include avoidance of draughts and nearby cold surfaces (e.g. windows), elevation of the short-term environmental temperature, use of radiant heat sources and use of an occlusive plastic bag to reduce heat loss by evaporation – this is more effective than attempting to dry the infant. There should be appropriate thermal control during transfer to the neonatal unit and the route from delivery suite to neonatal unit should preferably be short.<sup>15</sup>

### Exogenous surfactant therapy

Since exogenous surfactant's first use in the 1980s by Fujiwara for the management of neonatal RDS, many randomized controlled trials have been undertaken; making surfactant the most extensively studied pharmacological agent in neonatal medicine. These studies have helped determine the type (natural versus synthetic), optimal dosage, timing (prophylactic versus early rescue) and method of administration of surfactant to maximize its usefulness. Its clinical efficacy is immediately suggested by sometimes dramatic improvements in gas exchange. Meta-analyses of surfactant trials demonstrate a 40% reduction in odds of neonatal mortality and a 30–50% reduction in odds of pulmonary air leaks.<sup>12</sup>

**Types of surfactant:** human surfactant is a complex and poorly understood mixture of surface tension reducing and spreading components. Exogenous surfactant used therapeutically may be primarily derived from animal sources (natural) or chemically constituted (synthetic). Both natural and synthetic surfactants are effective in the management of neonatal RDS (Table 1). Despite some theoretical advantages of artificial surfactants (lack of viral risk and of immunogenicity, and better availability of the phospholipid component for recycling by the type II alveolar cells), meta-analysis of randomized controlled trials comparing different types of surfactants have favoured natural surfactants in reducing neonatal mortality (RR 0.86, NNT 50) and pulmonary air leaks (RR 0.63, NNT 25). Natural surfactants are the treatment of choice not only for their rapid onset of action, but also for their sustained effect in maintaining lower mean oxygen requirements for the first 72 h following their first administration.<sup>9</sup>

**Timing of surfactant administration:** surfactant should be administered as early as possible. There is a considerable body of evidence to support prophylactic use of surfactant (Table 2). Despite convincing evidence, many clinicians are still hesitant to use prophylactic surfactant as the standard care for infants at high risk of RDS, on the grounds that intubation and surfactant administration is an invasive, expensive and potentially unnecessary procedure.

### Types of surfactants (adapted from Sweet et al<sup>9</sup>)

Generic name	Trade name	Origin	Composition
<i>Natural surfactants</i>			
Calfactant	Infasurf (USA)	Bovine	Apoproteins SP-B and SP-C
Bovactant	Alveofact (Germany)	Bovine	Apoproteins SP-B and SP-C
BLES	BLES (Canada)	Bovine	Apoproteins SP-B and SP-C
Surfactant TA	Surfacten (Japan)	Enriched bovine	Apoproteins SP-B and SP-C
Beractant	Survanta (USA)	Enriched bovine	Apoproteins SP-B and SP-C
Poractant $\alpha$	Curosulf (Italy)	Porcine	Apoproteins SP-B and SP-C
<i>Synthetic surfactants</i>			
Colfosceril palmitate	Exosurf (USA)	Synthetic	No proteins
Pumactant	ALEC (UK)	Synthetic	No proteins
Lucinactant	Surfaxin (USA)	Synthetic	SP-B analogue (sinapultide)
(less inhibited by meconium and serum components)			

Table 1

However, it is currently recommended that all preterm infants born under 27 weeks' gestation should be electively intubated and given surfactant at birth, especially where prenatal steroids have not been administered.<sup>9</sup> Surfactant should in addition be considered for infants under 30 weeks' gestation who require intubation in the delivery room. A dose of 100–200 mg/kg of phospholipid is recommended. The higher dose may allow time for the endogenous surfactant pool to recycle and replenish, whilst the exogenous surfactant continues to reduce surface tension. Exogenous surfactant should be given as a bolus to assist in rapid and equal distribution through both lungs. A repeat dose of surfactant is recommended if there is an ongoing oxygen requirement on mechanical ventilation 12 h after the initial dose. There is an uncertain evidence base for earlier or additional doses.

### Oxygen therapy

In mild RDS, increasing the inspired oxygen concentration may suffice to elevate arterial oxygen concentrations. Much of the oxygen desaturation in RDS is caused by failure to establish and maintain an adequate FRC and associated atelectasis, so this approach has severe limitations and will usually need to be supplemented by pressure support if the oxygen requirement exceeds 30% or there is significant costal or intercostal recession. Oxygen therapy has no impact on the hypercapnia and respiratory acidosis of RDS.

### Further/ongoing management

There is now a wide range of available pressure support modalities including:

- CPAP (using a variety of techniques to generate airway pressure)
- nasal positive pressure ventilation (BIPAP)
- intermittent positive pressure ventilation (IPPV)
- intermittent mandatory ventilation (IMV)
- patient triggered ventilation (PTV)

### Timing of surfactant administration (adapted from Soll and Morley<sup>24</sup> and Enhorning et al<sup>25</sup>)

Timing	Advantages	Disadvantages
<i>Prophylactic</i> (treatment within minutes after birth, regardless of respiratory status) NNT in <30 weeks 17	Avoid barotrauma and vascular injury Reduction in mortality (RR 0.61, NNT 20) and air leaks (RR 0.62, NNT 50) Aid in re-absorption of lung fluid Homogeneous distribution	A number of infants are subjected to unnecessary treatments Side effects of endotracheal intubation (hypoxia and trauma)
<i>Early rescue</i> (administration of surfactant to symptomatic infants before 2 h of life)	Reduction in mortality (RR 0.87) and air leaks (RR 0.7)	Careful clinical monitoring required

Table 2

- volume limited ventilation
- volume guarantee ventilation (VGV)
- pressure support ventilation (PSV)
- high frequency oscillatory ventilation (HFOV) (using a variety of techniques to generate the high frequency energy within the airway).

Each of these modalities may be deployed in a variety of ways during both acute and weaning phases of RDS. Evidence from large randomized multicentre clinical trials for superiority of one modality over another is largely missing. Such trials are notoriously difficult to design due to the many variables influencing medium- and long-term respiratory outcomes. It is beyond the scope of this review to discuss each modality in detail, but there are generally accepted principles for pressure support interventions for RDS and a hierarchy of interventions for increasing disease severity, with many variations of application between different centres and clinicians depending on personal experience and preferences.

### Non-invasive ventilation

#### Continuous positive airway support

CPAP is a technique of respiratory support useful in infants with respiratory distress who are spontaneously breathing, and is widely used both in the early acute and late weaning/recovery phases of RDS. The continuous distending pressure applied to the lung improves oxygenation by decreasing atelectasis, helping establish an FRC and eliminating fetal lung fluid, controlling excessive pulmonary blood flow and pulmonary plethora in the presence of a patent ductus arteriosus (PDA) and left-to-right shunt, and improving ventilation–perfusion matching.<sup>6,16</sup> It may also reduce airways resistance by supporting the non-surfactant dependent upper airways. The effect of CPAP on lung compliance is variable from infant to infant and time to time in the same infant, depending on disease severity and the pressure used. At higher pressures, the work of breathing against the positive pressure may increase and so the impact of CPAP on carbon dioxide elimination is variable. CPAP is also useful in reducing apnoea of prematurity which commonly coexists with RDS.

Potential disadvantages of CPAP tend to be common to most methods of respiratory pressure support and include increased risk of pneumothorax and decreased pulmonary perfusion. Effectiveness may also be limited by technical difficulties in maintaining an adequate airway pressure. Effective use of CPAP requires considerable nursing and medical skill. Excessive hypercapnia due to increased airways pressure, and insufficiently improved oxygenation (required FiO<sub>2</sub> more than 40%) generally herald the need to progress to tidal or high frequency oscillatory pressure support.

Cochrane reviews of trials of the early use of CPAP in the pre-surfactant era failed to demonstrate clear clinical benefit over intubation and ventilation. More recent trials comparing early use of CPAP with early positive pressure ventilation have demonstrated that many infants can be satisfactorily supported on CPAP alone, although evidence of resultant decrease in BPD or mortality is disappointingly absent.<sup>14</sup>

It is suggested that early intubation for the administration of surfactant followed by immediate extubation and CPAP may have benefits over early use of CPAP alone or early intubation,

surfactant administration and ongoing positive pressure ventilation. Evidence from trials is still awaited.<sup>6,11</sup>

In the weaning/recovery phase of RDS, CPAP is invaluable after extubation from positive pressure ventilation by reducing the need for re-intubation due to respiratory failure.<sup>9,17</sup>

### **Nasal positive pressure ventilation (BiPAP/SiPAP)**

Nasal ventilation (NV) through prongs is a non-invasive way of delivering positive pressure throughout the respiratory cycle (like CPAP) with additional phasic increases in airway pressure that can be synchronized with the infant's respiratory effort. NV could be used as a non-invasive alternative to CPAP both in early RDS and post-extubation. This modality could potentially be more effective than CPAP by decreasing the work of breathing and thus hypercapnia, and in reducing apnoea. One trial has shown that use of NV produced fewer failed extubations than use of CPAP in infants weighing less than 1251 g. The use of NV in the acute phase of RDS lacks an evidence base at present.<sup>18</sup>

### **Invasive ventilation**

Indications for invasive ventilation include failure of non-invasive ventilation (see above) or a policy of initial intubation and ventilation for the high-risk preterm infant.

### **Intermittent positive pressure ventilation**

IPPV delivered by constant flow, time-cycled, pressure limited ventilators is the most frequently used and familiar modality of neonatal ventilation. A constant flow of gas through the circuit allows the infant to take their own spontaneous breaths. Adjustable inspiratory and expiratory valves control the pressures within the circuit for the two phases of the ventilatory cycle. Depending on lung compliance, gas flows through the T-piece into the infant's lungs during the inspiratory phase; during the lower pressure expiratory phase, elastic recoil of lung and chest wall allows gas to leave the lungs. It is usual to maintain a PEEP of between 4 and 6 cm H<sub>2</sub>O – the equivalent of CPAP – to avoid alveolar de-recruitment during expiration.

Higher PEEP may be desirable in the presence of large left-to-right ductal shunts, pulmonary haemorrhage or severe RDS and high oxygen requirement. Lower PEEP may be advantageous if there is radiographic evidence of air trapping and this sometimes helps carbon dioxide elimination. Higher inspiratory pressures improve lung inflation and oxygenation but carry the risk of lung damage and pulmonary air leak. Tidal volume and therefore carbon dioxide elimination is generally proportional to the difference between inspiratory and expiratory pressures.

Many modern neonatal ventilators allow not only the monitoring of proximal airway pressure, but also flow within the T-piece. This has many potential advantages, including an ability to target desired tidal or minute volumes by adjusting inspiratory and expiratory pressures and times, to display pressure–volume loops and assess dynamic lung compliance, to detect gas leaks from around the endotracheal tube and to detect spontaneous respiratory effort and synchronize the ventilator to the infant. Most neonatal ventilators allow manipulation of the pressure–time waveform either through varying the circuit flow rate or controlling the release of the inspiratory valve. It is unclear what constitutes an optimal pressure waveform – a squarer waveform

is likely to be more effective both in terms of oxygenation and carbon dioxide elimination for given pressures and rates, but may increase pulmonary shear forces and lung damage.

Time-cycling is generally achieved through adjustable electronic timer control of the opening and closing of the inspiratory valve, to deliver variable inspiratory and expiratory times and the resultant ventilator rate. Shorter inspiratory times (0.2–0.35 s) are generally favoured for better carbon dioxide elimination with very stiff lungs. Longer inspiratory times may improve oxygenation but carry the risk of air trapping. Longer expiratory times allow extra spontaneous breaths during weaning but in general lead to poorer oxygenation and carbon dioxide elimination. Conversely, within limits, shorter expiratory times and thus faster ventilator rates improve both oxygenation and carbon dioxide elimination.

There is little definitive outcome-related evidence for varying styles of IPPV ventilator settings, although current practice favours faster rates (shorter expiratory times), which may reduce the incidence of pulmonary air leak<sup>7,19</sup> and help achieve entrainment of the infant's spontaneous respiratory effort leading to improved ventilator synchrony (see below).

### **Patient-triggered ventilation**

It is customary to ventilate preterm infants without muscle relaxant medications (see below). The unselected use of muscle relaxants has been associated with the need for higher ventilatory pressures, longer ventilation and increased BPD. As a result, most infants will breathe spontaneously while ventilated. When the spontaneous breathing pattern is totally dissociated from that of the mechanical ventilator, the efforts of infant and ventilator may intermittently conflict. This is liable to lead to a need for higher ventilator settings, a higher incidence of pulmonary air leak and worse BPD. Patient-triggered ventilation attempts to introduce a degree of synchrony between infant and ventilator.<sup>20</sup> All modern neonatal trigger ventilators detect infant ventilatory effort through spontaneous inspiratory flow through the T-piece and attempt to synchronize mechanical inflation with the infant's own effort. There are several modes of ventilation which use PTV principle, including synchronized intermittent mandatory ventilation (SIMV), assist/control (A/C), pressure support ventilation (PSV) and flow cycling. The modes differ in respect to the available trigger time window during the ventilation cycle, the presence of back-up ventilator breaths when spontaneous respiration is not detected, the level of pressure support provided for spontaneous breaths, and whether the inspiratory and/or expiratory phases of ventilation are triggered.<sup>16</sup>

Short-term benefits of PTV have been well recorded, and there is some evidence for shorter periods of ventilation requirement but there is a lack of clear evidence for reduction in BPD, probably due to methodological difficulties and underpowering of trials.

### **Volume-targeted ventilation**

Conventionally, the volume of gas delivered with each ventilator breath is clinician controlled by adjusting inspiratory pressure and time. The volume is monitored directly on the ventilator by integrating flow and time. Much of the lung damage represented by BPD is thought to be mediated through excessive volume delivery – volutrauma. Arguably it might be advantageous to allow the ventilator to deliver pre-set volumes rather than pre-set pressures. This would allow the ventilator to respond to rapid

changes in lung compliance without clinician intervention and is potentially a self-weaning modality of ventilation, possibly facilitating faster weaning from mechanical ventilation.<sup>21</sup> Although there is early promising work, the relative advantages of this form of ventilation over conventional techniques remains unproven.

### High-frequency oscillatory ventilation

HFOV utilizes different physical principles from conventional tidal IPPV to achieve gas exchange. Very small tidal volumes are delivered at rapid rates, while alveolar recruitment is achieved by the application of a continuous distending pressure similar but usually higher than conventional CPAP. This has proven to be an effective mode of ventilation in infants who have severe carbon dioxide retention or pulmonary hypertension. Because the airway pressure excursion at alveolar level is very small, it has been thought that this style of ventilation might cause less lung damage.

Strategies for applying HFOV have polarized between 'low volume' where the mean airways pressure is minimized and therefore required inspired oxygen concentrations are liable to be high, and 'high volume' where sufficient distending pressure is applied to achieve near full alveolar recruitment and low inspired oxygen concentrations. High volume strategies are considered to offer the best hope for minimizing lung damage as oxygen toxicity is also avoided. Lower pressures and volumes may be more appropriate in the presence of air leak or cardiovascular compromise.

Treatment strategies are further polarized between use of the modality as rescue treatment for infants failing conventional ventilatory management at moderate pressures and first-line treatment with the objective of avoiding early lung damage associated with conventional ventilation.

The diverse trials of early use of HFOV with varying designs and case mixes have reported diverse outcome. On balance, early HFOV has been shown to be an effective ventilation modality for RDS but there is no good evidence for a reduction in BPD. Clinical experience of 'rescue' treatment is that many infants with RDS who are unstable with escalating oxygen requirements on conventional ventilation do well on transfer to HFOV, providing that any associated cardiovascular compromise is addressed. A Cochrane review<sup>22</sup> of rescue HFOV use showed reduction in new pulmonary air leaks (NNT 6), but increased risk of intraventricular haemorrhage in preterm infants.

### Permissive hypercapnia

Whatever style of ventilation, it has been argued that allowing carbon dioxide to run at supra-physiological levels will reduce ventilatory requirements and thus CLD. Randomized controlled trials<sup>23</sup> have shown that permissive hypercapnia decreases the duration of mechanical ventilation and reduces the hypocapnia-associated decreased cerebral blood flow. Unfortunately, there is no evidence of reduction in incidence of CLD. The relative safety, acceptable range of hypercapnia and long-term neurodevelopmental outcome are not yet known and require further studies.<sup>23</sup>

### Sedation and muscle relaxants

Endotracheal ventilation of unsedated patients of any age is likely to be unpleasant and it is now considered good practice for all intubated ventilated infants to receive some sedation, at least

until extubation is contemplated and respiratory drive needs to be optimized.

Muscle relaxants are widely used in other intensive care scenarios, but preterm infants often have relatively weak respiratory muscular effort and there is evidence that routine unselected use of paralysing agents is associated with delayed ventilatory weaning and extubation. In addition, even weak respiratory effort may help support respiration while on a ventilator as evidenced by the acute need for higher inspiratory pressures in some infants on starting muscle relaxant therapy. However, other ventilated infants with dys-synchronous breathing on ventilation – 'fighting the ventilator' – benefit from acute muscle relaxation through reduced oxygen requirement and probable reduced risk of air leak. Muscle relaxation should be considered for infants on very high pressure ventilation or when oxygenation is difficult in association with dys-synchronous breathing, but its duration of use should probably be minimized.

### Respiratory stimulants

Caffeine has several pharmacological effects, including improved respiratory drive, and it may help earlier extubation following mechanical ventilation.

### Antibiotics

Group B streptococcus (GBS) infection carries the risk of mortality and adverse neurological sequelae in preterm infants. Symptoms of early-onset GBS chest infection may be indistinguishable from RDS. It is therefore good practice to screen infants with respiratory distress for sepsis and to commence antibiotic treatment until infection is excluded.<sup>9</sup>

The role of other infective organisms (e.g. *Ureaplasma ureolyticum*) and their antimicrobial treatment in the pathology of RDS and its evolution to BPD remains unclear.

### Patent ductus arteriosus

The management of PDA in RDS remains controversial and detailed discussion of this is beyond the scope of this review. Despite theoretical respiratory benefits, unselected prophylactic pharmacological closure of the PDA does not improve long-term outcome. Similarly, there is insufficient evidence for benefit from routine pharmacological or surgical closure of established PDAs, and decisions on whether and when to attempt closure need case-by-case assessment of the clinical impact of the left-to-right shunt on respiratory performance and progress.

### Supportive treatment

Other supportive management of infants with RDS (fluid and nutritional management, cardiovascular support, thermal control, etc) is likely to be important in determining both mortality and morbidity in these infants, but these issues constitute general care of preterm infants and are beyond the scope of this review.

### Conclusions

The management of RDS in preterm infants has contributed to major improvements in survival, but the legacy in the most



preterm survivors is a high level of lung damage and chronic respiratory impairment. There is now a very wide and constantly increasing range of available supportive technologies, but because of the multiple factors influencing respiratory outcome, study design is difficult and the evidence base for relative effectiveness, safety and improved long-term outcomes for many is weak or non-existent. Because of the pathological cascade which characterizes RDS, the most effective therapeutic interventions are likely to be those instituted at the very beginning of life. ♦

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## Practice points

- At resuscitation, initially use air or low oxygen concentrations. Only increase oxygen concentration if the heart rate remains less than 100 bpm or oxygen saturation remains unacceptably low after 5 min. Pulse oximetry is useful to monitor heart rate and to avoid hyperoxia
- If positive pressure ventilation is required at resuscitation, use pressure limiting devices to avoid large tidal volumes. For infants at risk of RDS but not requiring intubation, commence CPAP support of at least 5–6 cm H<sub>2</sub>O via prongs to establish alveolar recruitment and a functional residual capacity
- In premature infants whose clinical condition requires emergency intubation or in whom elective intubation (less than 27 weeks) has been chosen, it is good practice to administer exogenous surfactant as early as possible
- Although the development of BPD is multifactorial and poorly understood, techniques and strategies that reduce the duration of mechanical ventilation are likely to be helpful in preventing lung injury
- Non-invasive ventilation (CPAP and BiPAP) following extubation reduces the need for re-intubation. Caffeine therapy may facilitate successful extubation
- Supportive aspects of clinical management of the preterm baby – thermal, fluid and nutritional care, sepsis treatment and cardiovascular support – may be just as important in determining respiratory outcome as direct respiratory interventions



# Causes and management of pulmonary air leak in newborns

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## Abstract

Pulmonary air leaks are usually complications of mechanical ventilation, although they can occur spontaneously. The reported incidence varies from 1% in term infants to 20% in preterm infants. The incidence has decreased in recent years. Ventilatory manoeuvres which increase mean airway pressure are associated with increased air leaks. Use of higher ventilatory rates, shorter inspiratory times and surfactant are known to reduce the incidence. Pulmonary interstitial emphysema presents as a slow deterioration of the infant during ventilation. Pneumothorax is usually associated with sudden deterioration. The diagnosis of a tension pneumothorax is clinical and emergency management should not be delayed for a confirmatory X-ray. A ventilatory strategy allowing for permissive hypercapnia with lowest possible pressures, shorter inspiratory times and higher ventilatory rates may aid in the management of pulmonary air leaks. High frequency ventilation may help when conventional ventilation fails. Sedation and paralysis may be helpful when the infant fails to synchronize with the ventilator. Pulmonary air leaks are associated with increased mortality and morbidity and a higher incidence of intraventricular haemorrhages.

**Keywords** air leak; infant; neonate; pneumothorax; pulmonary interstitial emphysema

## Introduction

Pulmonary air leak is a well recognized complication of mechanical ventilation, causing significant morbidity and occasionally mortality. The overall incidence of air leaks in term infants is about 1%, although only about 10% of these are symptomatic.

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The incidence in preterm infants is higher. The incidence of pneumothorax from 1990 to 2002 was 13% in babies weighing less than 750 g and 2% in babies weighing 1251–1500 g in a large North American study.<sup>1</sup> The incidence of pneumothorax at Liverpool Women's Hospital in mechanically ventilated babies was approximately 2% in the years 2005 and 2006.

## Definition

Pulmonary air leak refers to accumulation of air outside the pulmonary space. Pulmonary interstitial emphysema (PIE) and pneumothorax are most common, followed by pneumomediastinum and pneumopericardium.

## Pathophysiology

Air leak is caused by alveolar overinflation which causes the alveoli to rupture. Poor compliance of the lungs may contribute to this as it results in unequal ventilation and some alveoli becoming over distended and some remaining collapsed. This is further accentuated by a reduced number of pores of Kohn in preterm neonates (which normally allow redistribution of air between well and poorly ventilated alveoli). The overinflated alveoli may rupture and free air can escape into the interstitial spaces of the lung, causing PIE. This is worsened in the preterm lung by the increased interstitial water, resulting in air being trapped in the interstitium.<sup>2</sup> Air from the ruptured alveoli can also dissect along the perivascular spaces toward the hilum to reach the root of the lung. This can subsequently rupture into the pleural space leading to pneumothorax, into the mediastinum resulting in pneumomediastinum, or into the pericardium leading to pneumopericardium.

## Aetiology

**Spontaneous pneumothoraces** can occur soon after birth due to the high pressures generated by the baby taking their first breaths or at resuscitation. Familial spontaneous pneumothoraces are rare.<sup>3</sup>

**Lung diseases** such as respiratory distress syndrome (RDS), meconium aspiration syndrome, congenital bullous lesions and pulmonary hypoplasia: these can all result in uneven lung compliance leading to alveolar overdistension and rupture.

**Direct injury** can result from suctioning through the endotracheal tube (ETT), use of introducers through the ETT for their placement or central venous catheter placement.

**Mechanical respiratory support** can be associated with air leak when using a prolonged inspiratory time,<sup>4</sup> a high mean airway pressure (MAP)<sup>5</sup> or poor patient synchronization with the ventilator (where infants actively expire during the inspiratory phase of mechanical ventilation).<sup>6</sup> Continuous positive airway pressure (CPAP) may also be associated with an increased risk of air leak.<sup>7</sup>

## Prevention

Surfactant administration has been shown to significantly reduce the incidence of pneumothorax (OR 0.35; 95% CI 0.26–0.49).<sup>8</sup>

Optimizing the respiratory support offered to mechanically ventilated babies can reduce the risk of air leak syndromes. Strategies include using the minimum necessary peak inspiratory and end expiratory pressure and inspiratory time to achieve adequate oxygenation and ventilation, and employing faster ventilator rates to prevent the baby breathing out of phase with the ventilator. The following is a summary of the current evidence regarding which ventilator strategies can reduce the risk of pneumothorax.

- A meta-analysis of three randomized controlled trials (RCTs) comparing high rate positive pressure ventilation (rate more than 60/min) with conventional mechanical ventilation at lower rates showed a decrease in air leak in the high rate group (RR 0.69; 95% CI 0.51–0.93).<sup>9</sup>
- A meta-analysis of five RCTs evaluating a long versus a short inspiratory time (Ti) using conventional mechanical ventilation in neonates with RDS showed that a long Ti (more than 0.5 s) was associated with an increased risk of pneumothorax (RR 1.56; 95% CI 1.24–1.97).<sup>10</sup> However, all these studies were done in the pre-surfactant era and prior to the introduction of antenatal steroids.
- Elective high frequency oscillatory ventilation has not been shown to be effective in reducing air leaks. Compared to conventional ventilation, it showed a significant increase in air leaks in the high frequency group (RR 1.23; 95% CI 1.06–1.44).<sup>11</sup>
- Meta-analysis of six trials of patient-triggered ventilation (PTV) has not shown that PTV reduces the incidence of air leaks when compared to conventional ventilation (RR 1.03; 95% CI 0.8–1.34).<sup>9</sup>
- Retrospective studies have shown that maximal peak inspiratory pressures during the 24 h before diagnosis, number of suction procedures during the previous 8 h before diagnosis and ETT displacements have been associated with an increased incidence of air leaks.<sup>12,13</sup>
- Providing 'routine' paralysis to abolish the baby's respiration does not prevent pneumothorax when compared to synchronous ventilation.<sup>14</sup> Hence, synchronizing the baby's ventilation by increasing the respiratory rate up to 60–80/min can prevent the need for paralysis. If the baby's oxygenation does not improve and if obvious respiratory effort continues in spite of high rates, paralysis may be beneficial.<sup>15</sup>

### Pulmonary interstitial emphysema (Figure 1)

#### Incidence

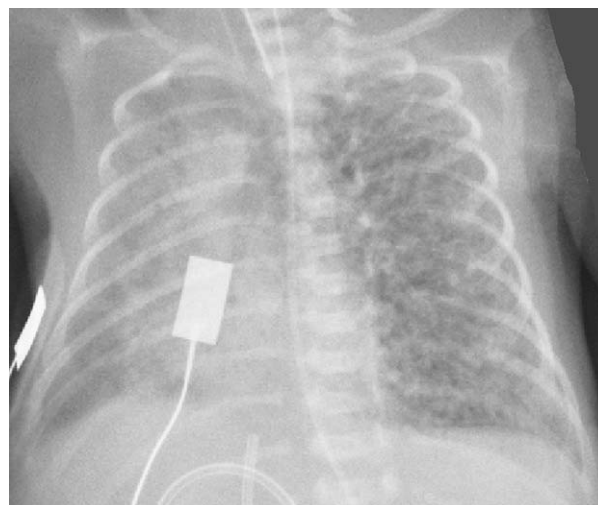
The incidence of PIE in the pre-surfactant era in mechanically ventilated babies under 1500 g was approximately 20%.<sup>16</sup> It is likely that this complication now occurs much less frequently, although there are no recent population-based studies to support this.

#### Pathophysiology

PIE occurs more commonly in neonates with RDS and less frequently in neonates with meconium aspiration syndrome and sepsis.<sup>16</sup> PIE causes air trapping in the interstitial spaces of the lung. This compromises the blood flow in the lungs, leading to ventilation perfusion mismatch and then hypercapnia and hypoxia.

#### Presentation

PIE often presents with a slow, progressive deterioration of the blood gases with the need for increasing ventilatory support.



**Figure 1** Pulmonary interstitial emphysema of the left lung.

Rarely, the neonate has a sudden deterioration with profound respiratory acidosis and hypoxaemia.

#### Diagnosis

Transillumination of the chest in diffuse PIE reveals hyperlucency, similar to pneumothorax. The diagnosis is confirmed on a chest radiograph (CXR) which reveals hyperinflation and small cysts, either localized or diffuse. There are linear radiolucencies which are variable in length and do not branch. In extreme cases, large bullae may appear which may mimic congenital lobar emphysema or cystic adenomatoid malformation.

### Pneumothorax (Figure 2)

#### Pathophysiology

Pneumothorax occurs when air leaks between the visceral and parietal pleural surface. Pneumothorax may develop spontaneously in non-ventilated neonates. It occurs at delivery when high opening pressure is needed to open up the alveoli, either by the baby taking breaths or at resuscitation. In the ventilated neonate it may occur after alveolar overinflation secondary either to using high initial ventilatory pressures or to failure to wean pressures once compliance is achieved (e.g. after surfactant administration).

#### Presentation

Neonates with spontaneous pneumothorax are usually asymptomatic or have mild signs of tachypnoea with an oxygen requirement. Occasionally, severe respiratory distress (grunting, nasal flaring and intercostal retractions) may occur. In the ventilated neonate, pneumothorax may result in a rapid clinical deterioration, resulting in cyanosis, hypotension, hypoxaemia, hypercapnia and respiratory acidosis. There may be decreased breath sounds on the affected side with heart sounds shifted to the opposite side, asynchronous chest movement and abdominal distension due to displacement of the diaphragm. With a right-sided pneumothorax, the liver can be displaced downwards.

#### Diagnosis

A high index of suspicion is needed to diagnose pneumothorax. Transillumination (whilst awaiting the CXR) with a



**Figure 2** Right-sided tension pneumothorax with mediastinal shift to the left.

fibre-optic light source placed on the neonate's chest will illuminate the affected hemithorax. CXR remains the gold standard for diagnosing pneumothorax and should be performed unless the neonate's condition needs emergency intervention. CXR appearances vary depending on the severity of the pneumothorax.<sup>2</sup> A small pneumothorax is recognized by a difference in translucency between the two sides. CXR of a large pneumothorax or one under tension will display the following:

- air in the pleural cavity (the area appears hyperlucent with absent pulmonary markings)
- collapse of the affected lung
- displacement of the mediastinum and heart shadow to opposite side
- bulging intercostal spaces
- downward displacement of the diaphragm on the affected side.

Often, in ventilated babies, anteroposterior films of the chest may not show the classic radiographic appearance if free air is situated anteriorly. In such cases, a lateral decubitus X-ray film with the affected side up will show free air.

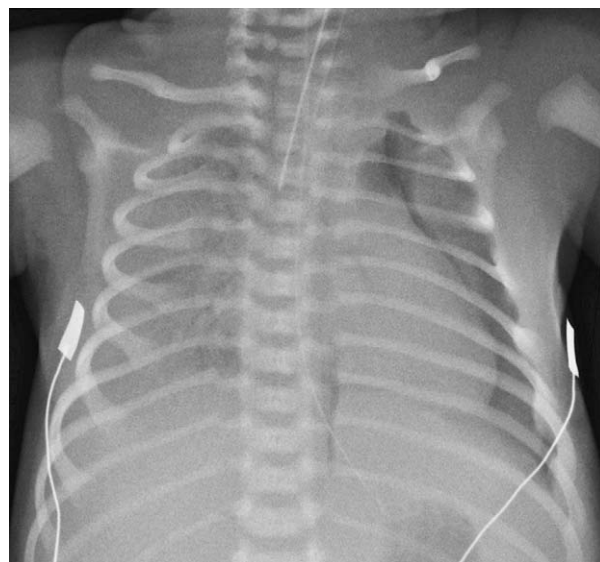
### Pneumomediastinum (Figure 3)

#### Incidence

Pneumomediastinum in the pre-surfactant era has been reported to occur in up to 3% of ventilated babies,<sup>16</sup> although anecdotally, now, the incidence seems to be much less.

#### Pathophysiology

Pneumomediastinum is preceded by PIE in most instances, when after alveolar rupture, air traverses the fascial planes and passes into the mediastinum.



**Figure 3** Pneumomediastinum.

#### Presentation

Isolated pneumomediastinum may not be clinically apparent. Clinical signs range from mild respiratory distress to other features associated with more severe coexisting air leak syndromes (pneumothorax or PIE). Physical signs include tachypnoea, muffled heart sounds and an increase in anteroposterior diameter of the chest.

#### Diagnosis

CXR shows a halo around the heart border, excluding the diaphragmatic surface of the heart, or a lateral view may show a retrosternal translucency. The mediastinal air can elevate the thymus away from the pericardium, resulting in a 'spinnaker sail' appearance.<sup>2</sup>

### Pneumopericardium (Figure 4)

#### Incidence

The incidence of pneumopericardium in extremely low birth weight ventilated neonates in the pre-surfactant era has been reported as being approximately 2%,<sup>16</sup> although in current practice it is seen much less often.

#### Pathophysiology

Pneumopericardium occurs secondary to passage of air from the pleural space or mediastinum into the pericardial sac through a defect located at the reflection near the ostia of the pulmonary veins.<sup>2</sup>

#### Presentation

Pneumopericardium usually causes pericardial tamponade with sudden hypotension or a decrease in pulse pressure, bradycardia and cyanosis. Heart sounds are muffled and rarely a friction rub may be heard.

#### Diagnosis

CXR is confirmatory. There is air completely surrounding the heart, including the inferior diaphragmatic surface of the heart,



**Figure 4** Pneumopericardium in an 8-month-old infant post cardiac surgery.

outlining the base of the great vessels and contained within the pericardium. The presence of air inferior to the diaphragmatic surface of the heart differentiates this condition from a pneumomediastinum. In severe cases, the transverse diameter of the heart can be reduced.<sup>2</sup>

### Situations where the diagnosis may not be clear-cut

Congenital lobar emphysema causes hyperinflation of one lobe of the lung (usually the left upper). Compensatory hyperinflation with atelectasis on the contralateral side mimics a pneumothorax. Cystic adenomatoid malformation, usually diagnosed antenatally, may mimic PIE radiologically if the cysts are small but is usually confined to one lobe and is usually unilateral.

## Management

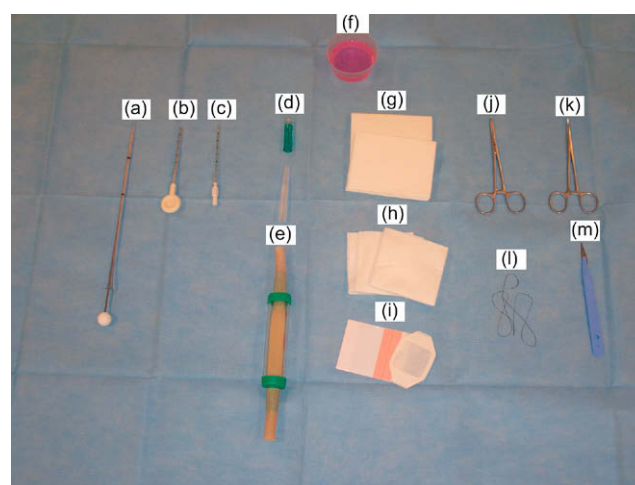
### Pneumothorax

Asymptomatic pneumothoraces can usually be managed conservatively with close observation for any clinical deterioration.<sup>2</sup> Mildly symptomatic pneumothoraces in term infants can be managed by increasing the inspired concentration of oxygen to near 100%, which helps in the resorption of air from the pleural spaces by nitrogen washout. This strategy should be avoided in preterm infants because of the risk of oxygen toxicity, mainly retinopathy of prematurity.

**Emergency management** of a pneumothorax is warranted if the baby has severe impairment of gas exchange and cardiovascular compromise. This is usually caused by a tension pneumothorax. Management is by needle thoracocentesis and this should not be delayed pending a CXR. This is carried out using a butterfly needle and sterile container with sterile water as an underwater seal. The skin surface should be cleaned with an antiseptic and a 21–25 gauge butterfly needle should be inserted perpendicular to the skin in the second intercostal space on the affected side and in the midclavicular line just above the lower rib.<sup>17</sup> After

insertion into the skin, the needle and skin should be shifted laterally before piercing the deeper muscle and pleura so as to avoid making a direct tract. The extension tubing of the butterfly needle is placed in the container of water below the level of the needle end. Drainage of air can be detected by bubbling in the water. Alternatively, a 50 ml syringe attached to the end of the butterfly needle with a three-way tap in between can be used. The air can be emptied from the syringe with the tap closed to the lung and opened to the air.<sup>17</sup> The needle should be inserted with caution and the advancement stopped as soon as air is aspirated. Aspirating all the air with the needle risks further iatrogenic lung injury should the needle come into contact with lung tissue. Once the baby is stabilized with needle aspiration, a chest drain should be inserted.

**Chest drain insertion:** a chest drain should be inserted as the primary treatment for a significant pneumothorax that is not under tension, or following needle drainage for a tension pneumothorax. All units caring for sick infants should have essential equipment prepared for a chest drain insertion (Figure 5). The largest possible chest drain that can pass through an intercostal space should be used. The sizes of chest drains used in newborns range usually from 8F for the extremely preterm to 14F in larger babies.<sup>3</sup> If using a drain with a trocar, it is advisable to remove the trocar prior to insertion because of the risk of injury to the lungs and deeper structures. The side of insertion should be re-checked prior to insertion and the baby positioned with the affected side elevated to approximately 45° from horizontal, with a support under the shoulder blade, and the ipsilateral arm positioned above the head. The chest drain should be placed in the fifth or sixth intercostal space in the mid or anterior axillary line. Rarely, it may have to be inserted more anteriorly in the second intercostal space for anterior pneumothoraces which have proved difficult to drain with the lateral approach. A wide area of skin around the insertion site should be cleansed with antiseptic. If time permits, the skin and subcutaneous tissue should be injected with 1% lignocaine. If the infant is ventilated, a bolus



**Figure 5** Instruments for a chest drain insertion. **a–c** Chest tube (sizes 12F, 10F, 8F); **d** connector; **e** connector extension tube; **f** antiseptic; **g** sterile towels; **h** sterile swabs; **i** transparent dressing; **j** straight artery forceps; **k** curved artery forceps; **l** suture; **m** scalpel.



dose of opioid may be used. A 1–2 cm incision parallel to the ribs should be made above the lower rib in the space, avoiding the breast tissue. The subcutaneous tissue and muscle should be bluntly dissected with forceps. The pleura may be nicked with the tip of the scalpel or with a clamp. The tip of the chest drain should be inserted with artery forceps through the opening for 2–3 cm pointing anteriorly.<sup>18</sup> The distal end of the chest drain should then be connected to a flutter (Heimlich) valve or underwater seal with an appropriate extension. Though some authors do not recommend Heimlich valves except for transport, on our unit we have found them to work satisfactorily in most settings. The chest drain should be secured in place with sutures on one or either side of the tube to snugly close the wound. The site then should be covered with gauze and dressed with transparent dressings. Although not always necessary, it may be useful to apply low pressure suction (5–10 cm H<sub>2</sub>O) to either the Heimlich valve or underwater seal to help lung re-expansion. The drain position should then be checked with a CXR. Once a chest drain is inserted, it is prudent to leave it for 72–96 h or at least 24 h after there is no air leak (confirmed by lack of fluttering of the Heimlich valve or bubbling of the underwater seal together with clinical and radiological expansion of the affected lung).<sup>18</sup> It should then be clamped for 24 h and removed, provided that there is no re-accumulation of pleural air. The complications of chest drain insertion include haemorrhage, infection, damage to breast tissue and damage to deeper structures including the diaphragm, phrenic nerve, pericardium and thoracic duct.

Air leaks, including bronchopleural fistulae, which persist more than a few days after adequate placement of chest drains may need to be treated surgically. Alternatively, some success has been reported with conservative management, including instillation of fibrin glue or selective bronchial intubation of the contralateral side.<sup>2,18</sup>

### Pulmonary interstitial emphysema

PIE may be global in both lungs or localized to single lobes of the lung. It can occur in isolation or may be associated with pneumothoraces, pneumomediastinum, pneumopericardium and pneumoperitoneum. Isolated PIE without extrapulmonary air leak can be managed conservatively by modifying ventilator management. When using conventional ventilation, the pressures should be kept at the minimum compatible with acceptable blood gases (pH more than 7.25, PaO<sub>2</sub> 45–52 mm Hg) with a degree of permissive hypercapnia.<sup>17</sup> Higher ventilatory rates up to 100–120/min that ensure a short inspiratory time may be beneficial. If conventional ventilation fails, high frequency oscillation may improve gas transfer. In unilateral PIE, ventilating the baby with the affected lung in a dependent position or selectively intubating the contralateral bronchus may facilitate resolution.<sup>2,17</sup> If an infant fails to improve with these ventilatory strategies, a pneumothorax may have to be created to release the interstitial air with lung scarification using a 21 gauge needle through the chest wall or by rupture of the blebs at thoracotomy. Fortunately, these interventions are very rarely required and should be performed only by experienced personnel.

### Pneumomediastinum

Pneumomediastinum often occurs in conjunction with a pneumothorax and draining the latter usually adequately treats the

pneumomediastinum. A pneumomediastinum occurring in isolation is difficult to drain because of multiple loculations and management should focus on the underlying condition. Multiple needle drainage and tube placements are theoretically possible but have never been used by the authors. Giving a term infant 100% oxygen may aid resolution but this strategy should be avoided in preterm infants at risk of retinopathy of prematurity.

### Pneumopericardium

A pneumopericardium very rarely occurs in isolation. It is usually associated with other significant air leaks in preterm infants with severe lung disease requiring ventilatory support. A pneumopericardium which does not cause cardiovascular compromise can be treated conservatively.<sup>19</sup> If cardiovascular compromise is present, a pericardial tap via a sub-xiphoid route, maintaining continuous cardiorespiratory monitoring, should be performed only by an experienced practitioner. Surgical placement of a catheter may be required if air re-accumulates.

### Pneumoperitoneum

A pneumoperitoneum may rarely be associated with an intrathoracic air leak due to air tracking down through the diaphragmatic foraminae. It usually resolves with adequate management of the lung pathology and intrathoracic air leaks. If the accumulation of air in the peritoneal cavity causes respiratory embarrassment, it may need needle drainage or placement of a catheter.

### General management of babies with air leak

The general principles of management of an ill, ventilated infant apply. A minimum touch policy should be used. No randomized trials of sedation in ventilated infants have been shown to alter any long-term outcomes.<sup>20</sup> However, it seems prudent to sedate and give adequate analgesia using opioids to babies receiving mechanical ventilation who have an air leak. Although a meta-analysis has shown a trend towards reduced air leaks in babies receiving neuromuscular paralysis, the indication for its use after an air leak has occurred is unclear.<sup>21</sup> Fluid balance, nutrition and cardiovascular support should be managed appropriately. It seems logical to adopt a ventilatory strategy aimed at achieving acceptable gas exchange with the least amount of mean airway pressure possible to prevent further barotrauma and volutrauma leading to worsening of the air leak.

### Prognosis

Pulmonary air leaks in newborn babies are associated with increased mortality and morbidity. In a prospective cohort study in infants born weighing less than 1500 g there was a 13-fold increase in the composite outcome of death or bronchopulmonary dysplasia if a pneumothorax occurred in the first 24 h.<sup>22</sup> Air leaks are also associated with an increased risk of intraventricular haemorrhage.<sup>23</sup> ◆

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### Practice points

- Pulmonary air leaks are caused by alveolar overdistension and ventilatory strategies which reduce mean airway pressure and improve synchrony (lower peak inflation pressure and positive end-expiratory pressure, shorter inspiratory times and higher ventilatory rates) can reduce the risk of occurrence
- Surfactant use in preterm infants with RDS significantly reduces the incidence of air leaks
- There is no evidence that sedation and paralysis prevent air leaks, but these may be used if an infant fails to synchronize with the ventilator despite maximum possible optimization of ventilation
- Asymptomatic air leaks can be managed with close clinical observation
- PIE usually presents with slow deterioration of a ventilated infant, whereas pneumothoraces present with acute deterioration
- Tension pneumothoraces should be diagnosed clinically and managed as an emergency using needle thoracocentesis
- Pulmonary air leaks are associated with increased morbidity, including intraventricular haemorrhages, and mortality

# Pulmonary haemorrhage in the neonate

R Narasimhan

S Papworth

## Abstract

Pulmonary haemorrhage (PH) in a sick neonate is a life-threatening complication and is often associated with a high mortality. It is now often seen in extreme preterm and very low birth weight infants who are growth restricted and have received surfactant with significant respiratory distress syndrome. The mainstay of treatment includes ventilation and vigorous resuscitation of a shocked and critically ill infant. This review aims to give an overview of the pathogenesis, aetiology and management of PH in a neonate.

**Keywords** low birth weight; pulmonary haemorrhage; surfactant

## Introduction

Pulmonary haemorrhage (PH) is an acute, catastrophic event characterized by discharge of bloody fluid from the upper respiratory tract or the endotracheal tube (ETT). It is a form of fulminant lung oedema with leakage of red blood cells and capillary filtrate into the lungs. It commonly occurs in babies weighing less than 1500 g, who often have a patent ductus arteriosus (PDA), have been treated with surfactant and are ventilated.

## Incidence

The incidence of PH in infants with a birth weight less than 1500 g and treated with surfactant was reported to be 11.9%.<sup>1</sup>

## Pathogenesis

PH must be clearly differentiated from the common occurrence of a small amount of blood-stained material aspirated from the ETT of a ventilated baby as a result of trauma. The antecedents of PH are mostly conditions associated with hypoxia or pulmonary oedema in which an acute rise in lung capillary pressure can be expected. The most likely explanation is that massive PH represents the build-up of the capillary filtrate in the pulmonary interstitial space. It bursts through the pulmonary epithelium into the air spaces. There is an association between PH and significant

left-to-right ductal shunting and resultant high pulmonary blood flow.<sup>2</sup>

## Aetiology

Massive PH represents the extreme end of the spectrum of pulmonary oedema in the neonate. This has four main causes (Table 1).

The risk factors for pulmonary haemorrhage include:

- intrauterine growth restriction
- surfactant therapy
- PDA
- coagulopathy.

## Surfactant therapy

PH is thought to occur as a complication of exogenous surfactant therapy but the exact mechanism is not clear. It is thought that surfactant therapy, by increasing pulmonary blood flow as PaO<sub>2</sub> increases, with reduction in pulmonary vascular resistance as the lung function improves, worsens any existing pulmonary oedema and leads to PH. A Cochrane systematic review of seven RCTs in a total of 1583 premature infants concluded that prophylactic treatment with synthetic surfactant increased the risk of PH, meta-analysis showing a RR of 3.28 (95% CI 1.50–7.16).<sup>4</sup> In a case-control study of 787 very low birth weight infants treated with surfactant, 11.9% developed PH. In these infants, this was associated with increased risk of death (OR 7.8, 95% CI 2.6–28) and short-term morbidity if moderate or severe.<sup>1</sup> In a similar case-control study of 1011 very low birth weight infants, 5.7% developed PH with a mortality of 50%.<sup>5</sup> Significantly more infants who developed PH had received surfactant therapy compared with matched controls, despite a similar severity of lung disease. Meta-analysis of 29 trials demonstrated an association of PH with synthetic, but not natural, surfactant use.<sup>6</sup> The risk of PH associated with prophylactic and rescue surfactant therapy has been addressed in two Cochrane reviews. Rescue surfactant therapy was not demonstrated to have a significant effect on PH,<sup>7</sup> but prophylactic surfactant increased the risk (RR 3.28; 95% CI 1.5–9.2).<sup>4</sup>

## Patent ductus arteriosus

Preterm infants with echocardiographic evidence of a large left-to-right shunt across a PDA and a high pulmonary blood flow have a high incidence of PH.<sup>2</sup> In addition, the neonate with severe respiratory distress syndrome (RDS) on intermittent positive pressure ventilation (IPPV) in a high oxygen concentration and with heart failure secondary to a large pulmonary blood flow from a PDA may suffer a PH.

## Intrauterine growth restriction

Infants who are small for gestational age are more likely to suffer a PH, the association being independent of other factors.<sup>8</sup>

## Coagulopathy

PH is rarely seen in babies with disseminated intravascular coagulation (DIC), but does not usually occur in babies with thrombocytopenia, haemorrhagic disease of the newborn or haemophilia. However, it is not uncommon for secondary DIC to occur following a massive PH.

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### Causes of pulmonary oedema.<sup>3</sup>

Increased pulmonary microvascular pressure	Reduced intravascular oncotic pressure	Reduced lymphatic drainage	Increased microvascular permeability
Heart failure	Prematurity	Pulmonary interstitial emphysema	Sepsis
Hypoxia	Hydrops	Pulmonary fibrosis	Endotoxaemia
Transfusions	Fluid overload	Raised central venous pressure	Emboli
Intravenous fat	Hypoproteinaemia		Oxygen toxicity
Increased pulmonary blood flow			
Pulmonary hyperplasia			

Table 1

### Clinical features

PH commonly occurs between the second and fourth day of life. Clinically, the onset of massive PH is heralded by sudden deterioration of the infant with pallor, cyanosis, bradycardia or apnoea. Pink or red frothy liquid drains from the mouth or can be suctioned through an ETT. The baby usually is hypotensive and is frequently limp and unresponsive, although term babies may occasionally be active and restless secondary to hypoxaemia and fight the ventilator. Occasionally collapse antedates the overt haemorrhage by an hour or two and rarely the baby looks surprisingly well despite the production of copious blood-stained pulmonary oedema. As the condition is commonly secondary to heart failure, the infant may have a tachycardia and the murmur of a PDA is frequently heard. Other signs include hepatosplenomegaly, peripheral oedema and a triple rhythm. Auscultation of the chest reveals widespread crepitations with reduction in air entry.

### Investigations

**Haematological:** although the haematocrit of the oedema fluid is usually less than 10%,<sup>9</sup> considerable quantities of blood can be lost and the baby can become severely anaemic. Secondary DIC can develop.

**Biochemical:** infants with PH usually have the same problems as those with severe RDS, namely hypoglycaemia, hypocalcaemia, hypoalbuminaemia and renal failure, and these should be sought and remedied.

**Chest X-ray:** infants with a massive PH show a virtual 'white out' with just an air bronchogram visible (Figure 1). As the condition improves with IPPV, the changes may clear or merge into those of bronchopulmonary dysplasia (BPD). Rarely, a lobar pattern of consolidation is found, suggesting that the haemorrhage has just occurred in a part of the lung.

**Blood gases:** all components of the blood gas deteriorate rapidly with severe hypoxia, hypercarbia and metabolic acidosis.

**Septic screen:** the possibility of infection should be considered and the infant should have a blood culture taken and be commenced on antibiotics.

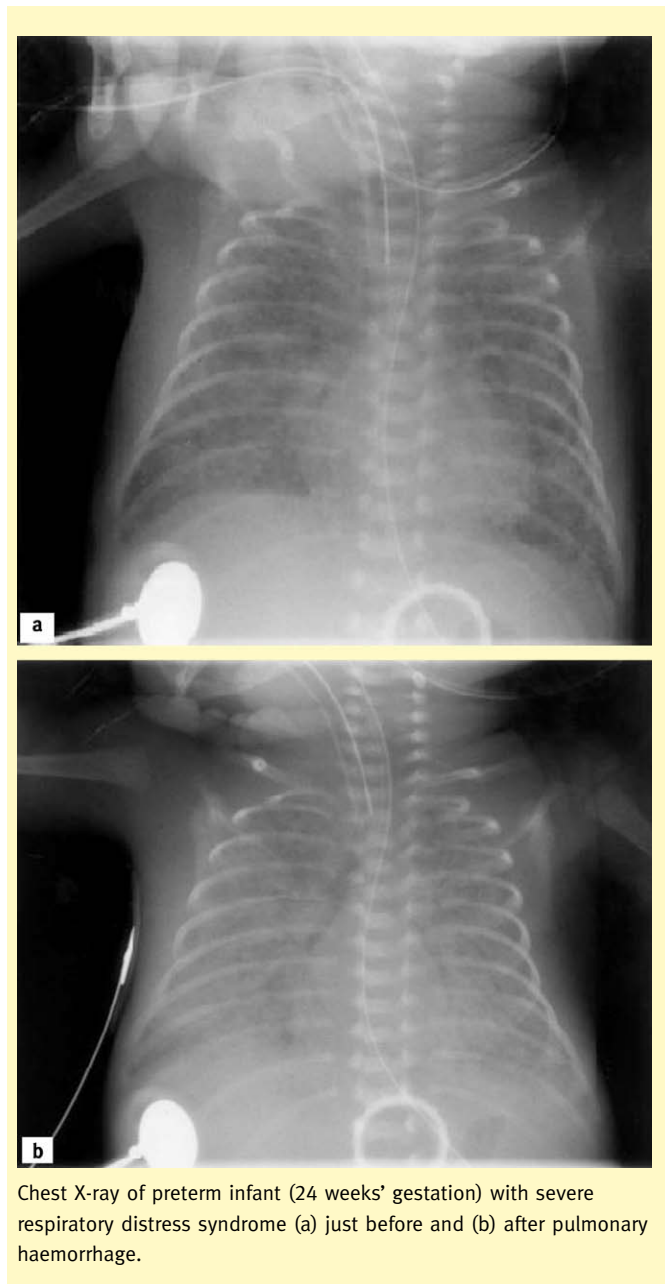


Figure 1

## Treatment

### Resuscitation

Initial resuscitation is the priority. The airway should be cleared with suction, and the infant should be intubated and ventilated and/or the ventilator pressures increased. The circulatory volume should be restored with boluses of colloid 20 ml/kg, a combination of fresh frozen plasma, blood and platelets, with regular re-assessment.

### Ventilation

All babies with massive PH should be intubated and ventilated. They usually have severe lung disease, and a peak inflating pressure above 30 cm H<sub>2</sub>O may be required. A ventilation strategy of high positive end-expiratory pressure (PEEP) (up to 6–7 cm H<sub>2</sub>O) is used with a long inspiratory time (0.4–0.5 s). Although in experimental studies this does not reduce the total lung water, it redistributes it back into the interstitial space, improving oxygenation and ventilation–perfusion balance. Frequent suctioning may be required to keep the ETT clear.

### Surfactant

Paradoxically, although surfactant may precipitate PH, after stabilizing the baby on the ventilator, a single dose of surfactant has been suggested to improve oxygenation.<sup>10</sup>

### Circulation

Once the initial circulating volume is restored, the infant needs re-assessing for signs of cardiac failure and pulmonary oedema. Intermittent colloid infusions and inotropes are often required to maintain the blood pressure and cardiac contractility. Blood transfusions may be required to correct anaemia and fresh frozen plasma for clotting derangements. Diuretics may be required if there is significant fluid overload.

### Antibiotics

Sepsis is a recognized cause of PH, thus broad-spectrum antibiotics should be started after taking cultures.

## Complications

These babies are susceptible to all the major complications of respiratory failure. High pressure ventilation predisposes to air leaks and BPD is a common sequelae. At the time of collapse they are susceptible to neurological damage and major intraventricular haemorrhage (OR 3.1; CI 1.5–6.4 in surfactant-treated very low birth weight infants<sup>1</sup>). However, survivors who could be assessed at 2 years did not differ significantly in neurodevelopmental outcomes when compared to controls.

### Mortality

In the modern era of intensive care, survival is improved; but affected infants are the sickest and most immature and their mortality rate is of the order of 38%.<sup>11</sup> ♦

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## Practice points

- PH remains a catastrophic complication in an already sick, ventilated preterm neonate
- It should be distinguished from the common occurrence of a small amount of traumatic bleeding aspirated from the ETT
- Risk factors for developing PH are extreme prematurity, growth restriction, surfactant therapy and PDA
- The mainstay of treatment includes ventilation and vigorous resuscitation of a shocked and a critically ill infant

# Management of meconium aspiration syndrome

Benjamin J Stenson

Allan D Jackson

## Abstract

Meconium aspiration syndrome (MAS) affects 0.43–2.1 in 1000 live births and can be life-threatening. A variety of treatment strategies is used, many of which do not have a solid evidence base to support them, but do appear to be effective. Routine suction of the fetal pharynx prior to delivery of the shoulders is not effective in reducing the incidence of MAS and neither is routine suction of the trachea after birth in vigorous infants. Tracheal suction after birth is still recommended for infants who are not vigorous. After delivery close attention must be paid to the management of the respiratory status of these infants. Some will require ventilation, and surfactant, inhaled nitric oxide and high frequency oscillatory ventilation may all be of benefit in some cases. For the most severely affected, extracorporeal life support has been shown to be effective in reducing the mortality of this condition.

**Keywords** extracorporeal membrane oxygenation; high frequency ventilation; infant; labour, induced; meconium aspiration syndrome; newborn; nitric oxide; persistent fetal circulation syndrome; pulmonary surfactant

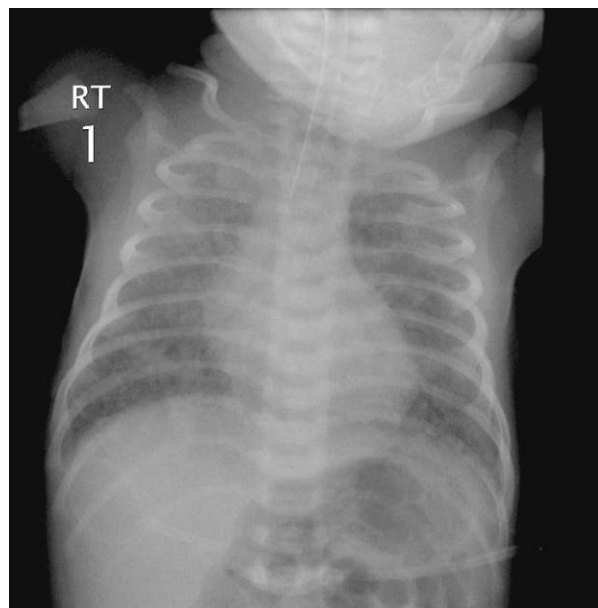
## Introduction

Meconium aspiration syndrome (MAS) remains one of the most challenging conditions faced by neonatologists. There is no universal definition, but it is generally accepted that MAS is present when there is respiratory distress associated with the passage of meconium before birth, with characteristic radiological changes (Figure 1) and without an alternative aetiology for the respiratory symptoms. In the developed world, 0.43–2.1 in 1000 live births require mechanical ventilation for MAS,<sup>1–3</sup> the majority being term or post term. A recent study showed a mortality of 2.5%, representing 0.96 in 100,000 live births.<sup>1</sup>

Meconium staining of the amniotic fluid (MSAF) is observed in 4.3% of deliveries before 37 weeks' gestation,<sup>4</sup> increasing with advancing gestation beyond 37 weeks to be present in approximately 12% of all deliveries.<sup>5</sup> In most of these cases, the passage of meconium is not associated with any demonstrable adverse fetal conditions and probably reflects developing fetal gut maturity.

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**Figure 1** Chest X-ray of a ventilated infant with meconium aspiration syndrome showing typical appearances of hyperinflation and patchy interstitial shadowing.

However, the fetus also passes meconium in response to stress, such as hypoxia–ischaemia. The commonly accepted model<sup>6</sup> of the pathogenesis of MAS is that meconium is passed in utero in response to stress such as hypoxia–ischaemia. The stress also provokes reflex fetal gasping, which causes meconium to be aspirated into the fetal upper airway. The meconium is then able to enter the distal airways. The extent to which the meconium enters the distal airways before delivery or after delivery with the onset of breathing is unclear and remains a source of controversy in deciding the appropriate airway management at birth. The four main pulmonary characteristics of MAS are mechanical airway obstruction, chemical pneumonitis, surfactant inhibition and pulmonary vasoconstriction. These features reflect both the direct effects of meconium in the airways and the prenatal hypoxic–ischaemic insult that is often associated. Typically, respiratory signs of tachypnoea, cyanosis and chest hyperinflation are present from soon after birth, though in a proportion of cases they develop over some hours after delivery.

## Management

### General supportive measures

Most babies born through meconium-stained liquor do not require any resuscitation at birth and remain well. Infants with MSAF who are born in good condition, are free of respiratory distress and have no other perinatal risk factors should receive routine postnatal care. Those who develop respiratory distress require further management, with admission to a neonatal unit. There are little objective data on the optimal general management of babies developing MAS, but standard monitoring and treatment should generally include:

- close observation and monitoring of oxygen saturation, heart rate and respiratory rate
- avoidance of excessive handling
- use of intravenous fluids until the respiratory difficulty diminishes



- monitoring of blood glucose as the infant may be at increased risk of hypoglycaemia after a hypoxic-ischaemic insult
- use of oxygen therapy to maintain saturation in the upper 90s in order to minimize pulmonary hypertension
- monitoring of pCO<sub>2</sub> to detect worsening respiratory acidosis.

It is usual practice to give any newborn with respiratory symptoms antibiotics pending the results of blood cultures, even though in the majority of cases cultures are eventually negative. As meconium is sterile, there is no specific rationale for the use of antibiotics in the treatment of MAS, more a general concern that the meconium may not be the cause of the infant's symptoms or that infection triggered the stress response and passage of meconium. Studies have shown that in those without predisposing risk factors for infection, antibiotics do not appear to influence the outcome of MAS.<sup>7</sup> Before abandoning antibiotic treatment, however, it should be borne in mind that, although sepsis is relatively infrequent, it is potentially devastating, so studies with large numbers of cases will be needed before it can be concluded reliably that antibiotics should not routinely be given.

Current practice for the management of MAS can be divided into perinatal and postnatal management.

### Perinatal management

**Management of the 'post dates' pregnancy:** there is a clear association between advancing gestation and the incidence of MAS, particularly beyond 40 weeks' gestation. This may partly explain the variations in incidence of MAS as management of 'post dates' delivery varies.<sup>3</sup> MAS is reduced after induction of labour post dates in comparison with expectant management.<sup>8</sup> The relative risk of MAS after induction versus expectant management is 0.29 (95% CI 0.12–0.68) at 41 weeks and 0.66 (95% CI 0.24–1.81) at 42 weeks (not significant). However, the absolute risk is small and this in isolation is not considered an indication for induction of labour beyond term.

**Amnioinfusion:** the infusion of fluid transcervically during a labour complicated by meconium-stained liquor has been considered to be of possible benefit in reducing MAS, either by diluting thick meconium or by providing support to the umbilical cord and so reducing the risk of hypoxia-ischaemia due to cord obstruction. In a systematic review of published studies, Xu et al. concluded that the practice may be of benefit in settings where close electronic intrapartum monitoring is not available, but does not prevent MAS in settings where close monitoring could be achieved.<sup>9</sup> These findings have been questioned, with discussion around the inclusion of trials in the analysis,<sup>10</sup> but the practice of amnioinfusion has not been widely adopted.

**Pharyngeal suction before delivery of the shoulders:** until recently it was common practice to recommend intrapartum suctioning of the fetal oropharynx at the maternal perineum, before delivery of the fetal shoulders, with the aim of removing meconium from the upper airway before the onset of breathing. A large multicentre randomized trial has shown that this is not effective in reducing the incidence of MAS,<sup>11</sup> the need for mechanical ventilation or the risk of mortality. This practice is no longer recommended in neonatal resuscitation guidelines.<sup>12,13</sup> Other practices aimed at promoting effective upper airway suction, such as chest

splinting to prevent breathing before suction has been carried out, have not been studied properly and are not recommended.

### Postpartum management

**Tracheal suction:** there is still some uncertainty about the value of attempting to suction meconium directly from the trachea. The practice of suctioning the trachea immediately after birth was previously believed to reduce the incidence of MAS.<sup>14</sup> However, another large multicentre trial has shown that in *vigorous* infants (defined as having a heart rate more than 100 beats/min, as well as presence of spontaneous respirations and reasonable tone), there is no benefit from routine suction of the trachea.<sup>15</sup> It is still recommended that infants who are not vigorous at delivery undergo laryngoscopy and tracheal suction before the use of positive pressure ventilation,<sup>12</sup> but the value of this practice has not been established with a definitive randomized study.

**Nasal continuous positive airway pressure (nCPAP)** is often used as an intermediate level of support in infants with impaired respiratory function. Although its use has been described in MAS,<sup>1,7,16</sup> it has not been studied systematically and shown to be of benefit. As MAS is associated with gas trapping and air leaks due to airway obstruction, some would consider nCPAP to be contraindicated. The use of nCPAP in MAS should be considered experimental until better evidence defines whether it has a role.

### Ventilation:

**Conventional** – ventilating infants with MAS can be difficult and the indications for commencing ventilation are not established. As there can be different disease patterns, with some infants having very patchy disease and others a more homogenous problem, no single approach to ventilation is optimal. The most commonly described pattern is to use a low level of positive end expiratory pressure (PEEP) and a long expiratory time, to avoid worsening any gas trapping,<sup>17</sup> though this approach may well need to be adapted depending on the response of the infant. Pulmonary flow graphics can be of use in tailoring the expiratory time to the mechanics of a particular infant's lungs to ensure that expiration is complete.

Infants with MAS are often severely ill, with a requirement for a high FiO<sub>2</sub> and airway pressures, and it is common for both sedation and paralysis to be used to optimize infant-ventilator interaction.

**High frequency oscillatory ventilation (HFOV)** – because the disease can be severe and high pressures are often required when conventional ventilation is used, HFOV is also a commonly used mode.<sup>1,16,18</sup> Again, the role of HFOV in MAS has not been defined through good quality trials, though in a sub-group of a larger trial,<sup>19</sup> the use of HFOV led to short-term improvements in gas exchange.

### Surfactant:

**Replacement** – meconium is a potent inhibitor of surfactant function.<sup>20</sup> Clinical trials have not demonstrated a reduction in mortality with the use of surfactant replacement, but in a meta-analysis of two trials which enrolled 208 infants,<sup>21</sup> the need for extracorporeal life support (ECLS) was significantly reduced (RR 0.64, 95% CI 0.46–0.91; NNT 6, 95% CI 3–25). The mortality of infants with MAS when treated with ECLS is now so low that it is unlikely that controlled trials of surfactant therapy in this condition could use mortality as an outcome. Most would now consider

surfactant treatment to be an integral part of the treatment of MAS.<sup>22</sup> The response to a single dose of surfactant can be blunt and several doses can be required before the desired response is seen.<sup>23</sup> It is not uncommon for treatment to be followed by a mild deterioration in condition for a few minutes, with reduced saturations and a mild increase in pCO<sub>2</sub>, but this is usually short lived.

**Lavage** – an alternative to surfactant replacement therapy is to use lavage with relatively large volumes of diluted surfactant to facilitate removal of meconium from the lungs, whilst maintaining sufficient surfactant function.<sup>24</sup> This technique has shown promise in small preliminary studies but some infants do not tolerate it well. Experimental work is ongoing to establish the most effective treatment schedules and preparations.<sup>25</sup> Larger clinical trials will be required to establish the place of this treatment. Given the evidence from controlled trials for the efficacy of ‘conventional’ surfactant therapy in MAS, lavage should probably not be compared to no surfactant treatment in future trials.

**Nitric oxide:** many infants with MAS have a degree of persistent pulmonary hypertension of the newborn (PPHN) and consequently have disproportionate difficulty with oxygenation in relation to their apparent degree of lung disease. Close attention to basic homeostasis, including maintenance of a generous systemic blood pressure, control of acidosis and avoidance of hypercarbia, should help to minimize this problem. Inhaled nitric oxide (iNO) has emerged as the treatment of choice for PPHN in term or near-term infants due to its efficacy in reducing the number of infants who go on to require ECLS<sup>26</sup> and its relatively selective action on the pulmonary vasculature. As iNO is delivered as an inhaled gas, good alveolar recruitment is required to maximize its effectiveness and it may be more effective in combination with HFOV if the lung disease is severe.<sup>19</sup> As a sub-group within larger studies of iNO in term and near-term infants with severe respiratory failure and or PPHN, infants with MAS represent a large proportion of the infants studied but they have not been studied in isolation or reported separately in sufficient numbers to enable definitive conclusions about the relative efficacy of iNO in MAS. A review<sup>26</sup> did not show any reduction in mortality with the use of iNO, but did demonstrate a reduction in the need for ECLS, a technique discussed below. Avoidance of the need for this invasive and not universally available technique is viewed as a benefit of iNO therapy, so it has been widely adopted in the treatment of MAS-related PPHN.

**Corticosteroids:** meconium produces a chemical pneumonitis as a major part of MAS. Despite this, a Cochrane review of two small studies of corticosteroids in MAS showed no benefit from steroid therapy.<sup>27</sup> Infants treated with steroids remained oxygen dependent for longer. A further two small studies have since contradicted this finding.<sup>28,29</sup> Infants treated with steroids showed a reduction in the duration of oxygen dependence and improved X-ray appearances. Further studies are required and, with the concerns that have arisen from the use of steroids to treat bronchopulmonary dysplasia about the possible effects of high dose steroids on infant growth and development, speculative treatment should best be avoided in the interim. Given the complexity and expense of some of the other treatment modalities, it would be helpful to determine more reliably whether steroids have any role, particularly in settings where resources are more limited.

**Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS):** the effects of MAS on the lung are mostly reversible, so it is an ideal candidate disease for rescue therapy with ECLS in severe cases. The mortality of severe MAS was reduced by ECLS treatment in the UK collaborative ECMO trial<sup>30</sup> and outcome data from ECLS registries indicate that the mortality rate of infants with MAS who are treated with ECLS is extremely low. Despite this, the use of ECLS in MAS has fallen over time,<sup>31,32</sup> a decline that may be attributable to increased use of HFOV, iNO and surfactant. This trend has meant that the population of infants receiving ECLS for MAS are at the sicker end of the disease spectrum, and potentially at greater risk of an adverse outcome.<sup>33</sup> There is concern that ECLS should be being used earlier, particularly as newer ECLS techniques have reduced complication rates.<sup>34</sup> A call has been made for more relaxed entry criteria for ECLS in MAS.<sup>35</sup> It is very important to ensure that infants who have or are developing severe disease are discussed with an ECLS centre early so that the timing of transfer can be optimized and the risk of death prior to ECLS can be minimized.

## Outcome

MAS produces intense lung inflammation and gives rise to the need for potentially damaging and toxic therapies. Although most infants who survive recover to good health, there are longer term effects on pulmonary function. This has been studied by looking at functional and objective measures, and an increased frequency of respiratory symptoms and abnormal pulmonary function testing has been found.<sup>36,37</sup>

As MAS is closely associated with perinatal hypoxia-ischaemia, there is an accompanying risk of adverse neurological outcome, which will no doubt be compounded by postnatal cardiorespiratory compromise and exposure to therapies which in themselves may increase the risk of adverse outcome.

## Conclusions

As with much in neonatal medicine, the management of MAS has evolved over time, resulting in a group of treatment strategies being used that are seen individually to be effective, but have not been subjected to adequate clinical study to determine their optimal place in the therapy of the condition. Considerable challenges remain in improving the outcome from this condition, both in its prevention and management, which should be achieved through well-designed clinical trials. ♦

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### Practice points

- MAS occurs more commonly in post dates pregnancies and is reduced when labour is induced, in comparison with continued expectant management
- The role of amnioinfusion is uncertain
- Routine suction of the pharynx at delivery and of the trachea in vigorous infants does not reduce the incidence of MAS. It is still recommended that non-vigorous infants have tracheal suction performed before positive pressure ventilation is given
- In ventilated infants with severe hypoxaemic respiratory failure, surfactant replacement, high frequency oscillatory ventilation and inhaled nitric oxide are effective strategies
- Extracorporeal life support (ECLS) has been shown to reduce mortality in the most severely affected infants
- In infants with significant disease, early discussion with an ECLS centre should be considered

# Congenital cytomegalovirus: new progress in an old disease

Suzanne Luck

Mike Sharland

## Abstract

Congenital cytomegalovirus (CMV) is the commonest congenital infection in the developed world with an estimated prevalence of 0.18–6.2% of all births. Despite recognition for many decades of CMV as an important contributor to neurodevelopmental and hearing impairment in infants, little progress has been made with regards to prevention and treatment of this often overlooked infection. In the past ten years, however, research has addressed many important aspects of diagnosis, prognosis, treatment and prevention of congenital CMV. This review summarizes the more important of these advances as they apply to management of babies born with CMV.

**Keywords** congenital; cytomegalovirus; diagnosis; neurological impairment; sensorineural hearing loss; symptoms; treatment

## Introduction

Cytomegalovirus (CMV) is a betaherpes virus. Acquisition is almost universal by the sixth decade, with seroprevalence varying with age and between populations. Primary infection, which is generally asymptomatic, is followed by the establishment of latency predominantly in cells of myeloid lineage. Reactivation of the virus may subsequently occur at any time in an individual's lifetime but is generally controlled by the host's cellular immune response. Severe morbidity and mortality may be seen in immunocompromised hosts or if infection is transmitted from mother to baby transplacentally, leading to congenital infection.

Congenital infection has traditionally been defined as the isolation of CMV from a sample obtained within the first 3 weeks of life in order to differentiate it from postnatally acquired infection. Postnatal infection does not seem to be associated with the long-term sequelae observed with congenital infection and does not generally give rise to disease in term babies, a phenomenon which is yet to be explained.

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## Epidemiology

Congenital CMV (cCMV) is the most common congenital infection in developed countries. Birth prevalence varies widely both between and within different countries and has been reported to occur in around 0.18–6.2% of live births based on culture-based methods, depending on the cohort being studied. Around 30% of the variability between the reported prevalence can be attributed to variations in maternal CMV seroprevalence and, when seroprevalence is controlled for, maternal age is not important. Social class and ethnicity have also been reported to contribute to variations in cCMV with black populations being reported to have an increased prevalence when compared to Caucasian cohorts in the same geographical area. A recent meta-analysis, which only analysed studies of universal screening for cCMV, reported a combined prevalence of cCMV of 1.2% (0.9–1.3%) in populations with low socioeconomic status (SES) compared to 0.39% (0.3–0.5%) in those studying primarily middle SES populations. Maternal human immunodeficiency virus (HIV) infection, premature birth and neonatal intensive care unit (NICU) admittance have also been established as risk factors for cCMV infection.

The transmission of infection is still possible in pregnant women who have previously been exposed to CMV, albeit at a much lower rate of 1.4% compared to the 32.3% reported to occur following primary infection during pregnancy. Symptomatic infection has also been reported to be less likely in women with pre-existing immunity to CMV (23% versus 11%). However, high rates of symptomatic infection have still been reported in resource poor countries with nearly 100% seropositivity.

Although it was an early concern, no association has been found between women working in day nurseries or paediatric clinics and increased seroprevalence, and there was no overrepresentation of nurses in a case series of cCMV. Being in frequent and prolonged contact with children younger than 2 years of age is, however, associated with a high risk of maternal acquisition of primary CMV.

## Pathology and pathogenesis

CMV is transferred transplacentally, probably with the aid of recognition of complexes of virion and maternal immunoglobulin by placental Fc receptors. This may explain the increased transmission noted later in pregnancy.

Congenital infection itself is generally asymptomatic, with symptomatic infection (historically referred to as CMV inclusion disease (CID)) only being seen in around 12.7% (0–25%) of births in a recent meta-analysis. As described in more detail below, a further 17% of those who are asymptomatic develop signs of CMV disease later in childhood. The reason for this delayed presentation of symptoms is uncertain.

CID was classically confirmed by 'owl's eye' intranuclear inclusion bodies on histopathological specimens. These inclusion bodies and identification of CMV antigens using immunohistochemical staining can be found in many different organs at post-mortem in babies with cCMV.

CMV is also characterized by its variable tropism for different cells. It is thought that initial infection of epithelial and vascular endothelial cells is followed by viraemia, secondary spread to other organs, where infection is seeded, and then systemic



dissemination, although this view has recently been challenged. Although undifferentiated cells initially are more likely to become infected with virus and latency established in these cells, reactivation is hypothesized to be initiated during cellular differentiation both in haematopoietic progenitor cells and neuronal cells.

In mouse models of neuropathogenesis neural stem/progenitor cells in ventricular zones are most susceptible to infection with mouse CMV. These infected cells are then seen to migrate to cortical zones as they differentiate. Lytic infection of immature glial cells is then postulated to disrupt brain development. Persistent infection in neuronal cells may also have a role, leading to neuronal dysfunction subsequently.

CMV inclusion bodies have been noted in the stria vascularis and vestibular (Reissner's) membrane but not other critical structures in post-mortem studies. However, a wider distribution of viral antigen throughout the inner ear is seen if immunofluorescence is used, including staining of cells in the organ of Corti and spiral ganglion. Studies in animal models may implicate the immune response to CMV in the inner ear as being a more important factor in the development of hearing loss. Therefore, whether the characteristic long-term effects of CMV on hearing, described in more detail below, are caused by direct lytic damage of cells due to repeated reactivation of latent CMV or host immune response to these latently-infected cells is still debated.

## Diagnosis

Historically, the laboratory diagnosis of CMV was based on a classical cytopathic effect (CPE) seen in cell culture systems from which CMV derives its name (the cells – cyto, become larger – megalos). In the case of CMV this often takes 2 weeks or more to develop and led to the now disproved theory that CMV was a slow-growing virus. In the past two decades the diagnosis of CMV has advanced considerably and will be discussed below.

## Serology

IgG is usually passively acquired from seropositive mothers. IgG avidity (a measure of stickiness as the antibody response matures) has become useful in diagnosing acute infection in adults with a move from IgG of low to high avidity being observed in the first 4 months of infection. No data exist relating to CMV IgG avidity in neonates. IgM is reasonably specific but has only around 70% sensitivity for diagnosing cCMV in newborns.

Serology obtained from older children who present with problems such as sensorineural hearing loss (SNHL) will give a diagnosis of past CMV infection but will not establish when this infection occurred (congenitally or postnatally) unless IgG of low avidity is found, thus implicating recent infection.

## Rapid culture techniques

These techniques enable detection of CMV within 24–48 h. After adding a diagnostic sample to cell monolayers, immunofluorescent- or immunoperoxidase-labelled antibodies are then added in order to detect early antigens produced by CMV during infection of cells. Toxicity of urine specimens to the cell layers, as with traditional culture methods, can be problematic.

## Polymerase chain reaction

Polymerase chain reaction (PCR) detecting areas of the CMV genome are now widely used by many laboratories. Sensitivity and specificity depends on the area of the CMV genome being probed (with probes for areas of high genetic variability between CMV strains being associated with lower sensitivity) and the method used. Nested PCR, while more sensitive, increases the risk of false-positive results being reported due to background contamination and is generally more labour intensive. Urine can cause inhibition of some of the enzymes used in the PCR mixture so internal controls should be used or other means for minimizing false negatives.

Studies report similar sensitivity and specificity of PCR compared to rapid detection methods.

**Qualitative versus quantitative:** in addition to qualitative detection of CMV, the use of quantitative PCR has emerged. This diagnostic method has gained interest for use both prognostically and for monitoring treatment. However, viral loads reported from different laboratories are not reproducible and can vary by up to 3 log<sub>10</sub>, depending on the technique used.

**Urine versus saliva versus blood:** the gold standard specimens for diagnosis are saliva and urine. Studies comparing these methods have found similar sensitivity and specificity. Although easier to obtain, saliva specimens usually require transport in viral transport medium which is not always readily available in clinical areas.

Prolonged excretion in urine has been well documented. In one study, CMV was still detectable in the urine of 98% of congenitally infected babies at the age of 2 and median duration of excretion was 3 years in symptomatic babies. Therefore, detection of CMV in urine of children is not an indication of recent infection.

Not all babies are viraemic at birth but the presence of viraemia has been associated with poor hearing outcome. Detection in blood may occur earlier than in urine and an earlier cut-off for diagnosis of congenital infection of around 10 days may be more appropriate if blood is being used diagnostically.

**Dried blood spots (DBS)** can be used to retrospectively diagnose congenital CMV. Quality control data indicate that sensitivity can vary widely depending on the gene being amplified and the technique being used for DNA extraction from cards. The marked difference in sensitivity and specificity reported between laboratories has led to a call for increased quality control of this diagnostic method. A diagnostic algorithm has been suggested which may decrease unnecessary retrieval of cards and the number of false-positive results reported.

As noted earlier, not all babies will be viraemic in the newborn period and as only around 50–100 µl of blood is spotted onto cards, detection is somewhat limited by sample volume; a negative result does not therefore exclude cCMV.

## History

cCMV should be considered if there is a history of any flu-like illness in a mother during pregnancy and a baby has symptoms in keeping with cCMV. Obstetricians are increasingly aware of the



possibility of congenital CMV if abnormalities are identified on antenatal scans such as intrauterine growth restriction (IUGR), microcephaly, echogenic bowel and cerebral calcification, but these abnormalities are non-specific for congenital CMV. Serological evidence of maternal primary CMV infection increases the suspicion of congenital CMV and PCR of amniotic fluid may have been carried out antenatally.

### Clinical findings: signs and symptoms

Classical features of CID are thrombocytopenia, blueberry muffin rash, petechiae, IUGR, microcephaly, hepatosplenomegaly and jaundice.

Other CNS features include seizures, focal neurological findings and abnormalities in tone and posture, which may be more difficult to identify clinically. Ocular abnormalities reported include chorioretinitis (which is indistinguishable from that seen in toxoplasmosis), optic atrophy, pigmentary retinopathy and strabismus. Hearing loss seen in cCMV is described in more detail below.

Pneumonitis and myocarditis are less common. The frequency with which each of these features is reported in babies with symptomatic CMV varies somewhat between studies and is summarized along with the frequency of abnormal investigations in Table 1.

### Investigations

#### Confirmation of infection

It is important that the diagnosis is confirmed at birth as not all babies born to mothers with positive amniotic fluid will be positive for CMV at birth.

Urine and/or saliva are the most reliable samples diagnostically. PCR of blood can also be helpful prognostically but if negative, it does not exclude cCMV. If a sample is not available from within the first few weeks of life, then retrieval of the DBS should be arranged.

#### Identification of disease

Most important will be samples for full blood count (FBC) and liver function tests (LFTs), including a measurement of conjugated bilirubin and renal function (both as a measure of a neonate's general condition and as a baseline if treatment is being considered). Coagulation studies should be performed if hepatomegaly is present.

**Neuroimaging:** referral for a cranial ultrasound scan (Cr USS) should be carried out as a minimum. More detailed neuroimaging should be considered, although a balance has to be struck between the risks of carrying out these procedures, which often require sedation, and the likelihood of identifying abnormalities.

Cr USS has been reported to have a good positive predictive value with regards to subsequent neurological abnormalities. Although computed tomography (CT) had a better sensitivity for detecting intracerebral calcifications in one recent study, it added nothing diagnostically to Cr USS. Conversely, magnetic resonance imaging (MRI) has been shown in a number of studies to find abnormalities, such as neuromigrational disorders, not detected on Cr USS. However, there is currently no literature

### Clinical features of congenital cytomegalovirus (data taken from Kylat et al, Boppana et al and Noyola et al)

	Percentage
<i>Clinical</i>	
Intrauterine growth restriction	26–43
Microcephaly	19.5–53
Hepatosplenomegaly	45–70
Petechiae	45–75
Jaundice	41–70
Pneumonitis	7.3
Chorioretinitis	14–17
Seizures	7.3–13
Other neurological abnormalities	19–37
Dental enamel defects	11
<i>Laboratory</i>	
Thrombocytopenia	50–77
Anaemia	7.3
Raised ALT/AST	48–83
Conjugated hyperbilirubinaemia	47–81
CSF abnormalities	46
<i>Imaging</i>	
Abnormal cranial ultrasound	56
Abnormal CT	71–80
Abnormal MRI	89
<i>Other</i>	
Abnormal visual evoked potential*	43
Abnormal somatosensory evoked potentials*	71
Abnormal electroencephalogram*	67

\*Only reported in Kylat et al.

Table 1

evaluating the prognostic benefit of carrying out MRI in asymptomatic babies in addition to Cr USS.

**Ophthalmological evaluation** for retinal scars should be carried out as a baseline by ophthalmologists with experience of examining neonates.

**Audiological testing:** a formal assessment of hearing should be carried out as early as possible. An abnormal hearing test early in the course of disease may lead to the baby being considered for antiviral treatment as discussed below.

### Course of disease/progression

#### Acute course

Quoted mortality rates vary from 3.6% to 12%.

The duration of hospital stay has been reported to be 13–24 days in symptomatic babies and is probably dependent on prematurity amongst other factors. The platelet count reached its nadir during the second week of life in one study; however, another reported that the median time for resolution of thrombocytopenia

was 9.5 days. In contrast, abnormalities in alanine aminotransferase (ALT) have been reported to persist for more than a month.

### Long-term sequelae

Long-term sequelae are mainly in the form of SNHL, chorioretinitis and neurodevelopmental delay.

Studies have shown that those infants who are symptomatic at birth have a 40–58% risk of permanent sequelae compared to a 13.5% risk in those who have no symptoms at birth. In addition, the sequelae reported in babies who are symptomatic at birth are generally more severe, although features are very heterogeneous. Around 50% of symptomatic babies are described as having both neurological and hearing impairment.

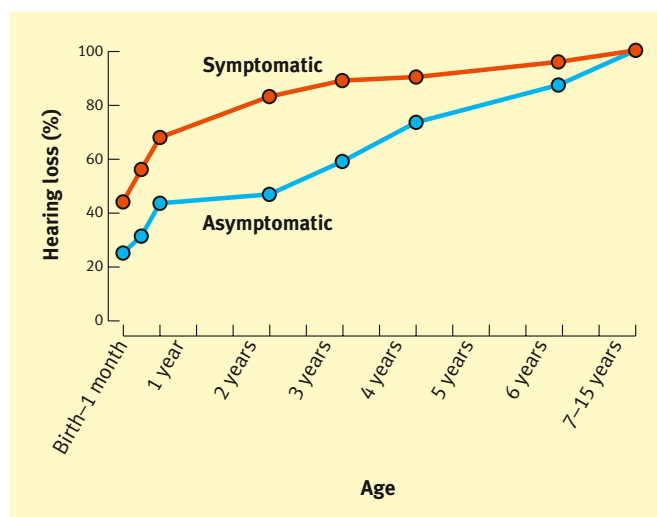
**Hearing loss:** many prospective studies have been carried out to characterize the nature of the hearing loss observed in congenital CMV. Some of the largest cohorts followed up are those studied by the University of Alabama (UAB) in the US. These studies have found a hearing loss in 22–65% of babies with symptomatic CMV versus 6–23% in asymptomatic infants. It should be noted, however, that the UAB population has a high proportion of black and low-income mothers, groups known to be associated with a high risk of cCMV. This population may therefore not be representative of the situation worldwide. However, a meta-analysis of studies found hearing loss in 11–12% of babies born with asymptomatic cCMV and around 35% of those born with symptoms, which is in keeping with the UAB figures.

Hearing loss can occur at any frequency but characteristic of CMV has been the discovery that hearing loss may be progressive in 54% of cases and of late onset in 27.1% and 37.5% of babies symptomatic and asymptomatic at birth for hearing loss, respectively. In addition a fluctuation in the hearing loss (defined as deterioration in hearing followed by subsequent improvement in hearing assessments with no other obvious cause for this change in measurements) has been noted in 29.4% of symptomatic and 54.1% of asymptomatic babies.

If cumulative hearing loss is plotted, the majority of SNHL can be seen to occur in the pre-lingual phase of development with symptomatic babies having a slightly earlier onset of hearing loss when compared to those who are asymptomatic (Figure 1). Of babies with symptomatic CMV, 67.1% have been reported to have bilateral SNHL compared to 47.9% of those with asymptomatic infection. A severe or profound hearing loss has been documented in around 70% of both groups (68% versus 74% respectively) (Figure 2).

**Neurological progression:** some kind of long-term cognitive deficit was noted in 6.5% of asymptomatic babies assessed for this outcome, and around 42% of symptomatic babies when studies of long-term outcome are amalgamated. Seizures are common and have been reported in 13% of babies younger than 6 months of age and a further 16% later in childhood.

**Visual loss:** studies from the 1970s identified that CMV could cause chorioretinitis not only in those with symptoms at birth (5 of 8) but also in those who were asymptomatic initially (2 of 35). As with other sequelae, symptomatic babies are more likely to have long-term visual impairment than those who are asymptomatic at birth, with 22–50% reported to have significant visual



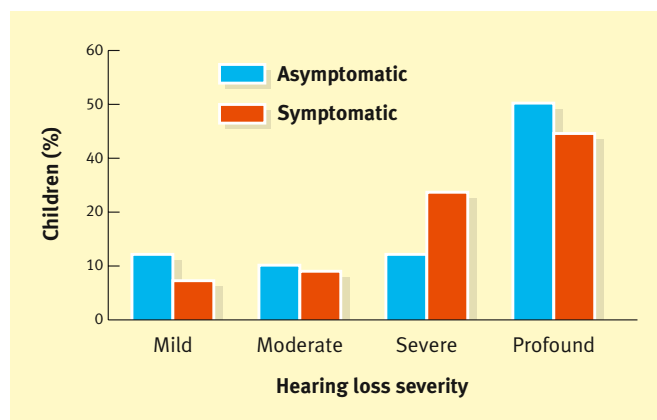
**Figure 1** Cumulative sensorineural hearing loss in babies with symptomatic ( $n = 85$ ) and asymptomatic ( $n = 48$ ) congenital cytomegalovirus by age (data taken from Dahle et al).

impairment on long-term follow-up. Although ophthalmological disease is generally thought to be stable in immunocompetent children infected with CMV, case studies reporting delayed onset, reactivation and progression of CMV chorioretinitis would seem to refute this.

**Dental abnormalities** have been seen in 40% of symptomatic and 5.6% of asymptomatic children on follow-up. This can manifest as discoloured teeth, defects in enamel and teeth that generally wear easily with some fracturing to give an irregular outline. A more recent study reported dental enamel defects in only 11% of children with symptomatic CMV at birth.

### Differential diagnosis

It is important to ensure that CMV has been congenitally acquired as opposed to postnatally acquired, given that long-term sequelae have not been documented in case-control studies following up postnatally infected neonates. Other congenital infections, such as



**Figure 2** Severity of hearing loss in a cohort of children with symptomatic and asymptomatic congenital cytomegalovirus at last hearing test (data taken from Dahle et al).

toxoplasmosis, rubella, syphilis, HIV, Epstein–Barr virus (EBV), varicella zoster virus (VZV) or lymphocytic choriomeningitis virus should also be excluded. The type of rash observed, if present, can be helpful in differentiating between some of these congenital infections.

If thrombocytopenia is the only finding, then other causes of neonatal thrombocytopenia should be considered. If other features of congenital infection are present, however, then an infectious cause is most likely.

Isolated hepatosplenomegaly should raise the suspicion of haemolytic disorders, Beckwith Wiedemann syndrome and Zellweger, in addition to congenital infection.

If abnormal neurological and neuroradiological abnormalities are the primary finding, with no other features to indicate congenital infection, then the differential diagnosis can include toxoplasmosis, Sturge–Weber disease, tuberous sclerosis, venous sinus thrombosis (if calcification is present) and neurometabolic diseases, genetic disorders and congenital muscular dystrophy (if white matter changes are found) amongst others.

If SNHL is the primary presentation, then a full aetiological work-up should be carried out as genetic causes are still the commonest cause of this presentation and asymptomatic CMV infection may occur in combination with another underlying pathological process.

## Management

### Supportive

Resolution of any abnormal results should be monitored and symptomatic treatment initiated as per local protocol. Hepatitis may require administration of vitamin K and the input of paediatric hepatology specialists. If hepatitis is the only sign of cCMV, then other diagnoses should be considered given the high frequency of asymptomatic CMV.

### Antiviral treatment

Intravenous (IV) ganciclovir is the drug most commonly used, although evidence is currently only available to support its use in babies with evidence of central nervous system (CNS) disease. A randomized controlled trial of 6 weeks' ganciclovir treatment commenced in babies aged younger than 30 days showed prevention of deterioration of hearing at both 6 and 12 months of age. In addition, these babies had fewer developmental impairments at 1 year of age.

Other studies have also shown a trend towards better neurological outcome with antiviral treatment, although randomized placebo-controlled trials in this area are essential to draw proper conclusions. A more rapid resolution of liver function tests has been noted with ganciclovir treatment in one study, although evidence that this offers any benefit to long-term outcome is lacking. Ganciclovir treatment has been reported to improve active retinal changes.

Oral valganciclovir is now available and licensed for use in older children and adults. Pharmacokinetic studies have been carried out in the neonatal age group, reporting a dose of 16 mg/kg twice daily of oral valganciclovir solution as giving equivalent ganciclovir exposure to the 6 mg/kg dose of IV ganciclovir established as being optimal in earlier studies. Whether levels achieved in CNS will result in comparable neurological

outcomes to the earlier study is unknown. There are theoretical benefits in treating all symptomatic babies and in giving longer treatment courses, which are now potentially justifiable with the availability of an oral preparation. A placebo-controlled, double blind, randomized study comparing 6 weeks versus 6 months of oral valganciclovir has just commenced in the US, aiming to address some of these issues. Solution made extemporaneously may not be homogeneous and should therefore be used with caution.

If treatment is commenced, careful monitoring for side effects should be carried out; neutropenia and anaemia are the commonest reported in the acute phase. In addition, the theoretical risk of carcinogenicity and decreased spermatogenesis in the longer term should not be dismissed.

## Follow-up

### Neurological

Screening by general paediatricians is probably sufficient in the first instance. More formal review at 1 year may be helpful and are not only reassuring to parents but also enable early intervention with supportive measures if abnormalities are identified.

### Ophthalmological

If the initial screen is normal in an asymptomatic baby, then repeated eye examinations are probably not indicated. In symptomatic babies, however, reports of delayed onset and progression of chorioretinitis would suggest that follow-up should continue until an age when children are able to report visual disturbance. We would therefore advocate yearly follow-up until the age of 5 years in the first instance. More regular follow-up should be carried out if there are pre-existing retinal lesions.

### Hearing

Recent guidance published by the National Deaf Children's Society (NDCS) recommends that testing should be carried out every 3–6 months in the first year, every 6–9 months until age 3 and then yearly until age 6 years. This enables early identification of any hearing impairment and appropriate measures to be instituted to optimize hearing during the period of language acquisition in these children, including cochlear implantation if indicated.

## Prognosis and explanation to the patient

### Disease associations

Thrombocytopenia and IUGR have been established as independent risk factors for subsequent hearing impairment in one study. Another study has reported microcephaly (taking into account whether head circumference (OFC) was appropriate for weight) as being the most specific predictor for neurological outcome, whereas normal CT and head circumference were associated with a good outcome.

### Viral load

Viraemia was first reported to be associated with a poor hearing outcome in 2005. Subsequently, investigators have reported an

association between quantitative CMV viral load and symptoms in urine, blood and DBS. Duration of CMV excretion in urine has not, however, been helpful in predicting the subsequent course of disease.

Although a low viral load has been reported to have a very high negative predictive value for subsequent sequelae of CMV, values of viral load measurements between labs can vary widely and clinicians should be clear about the limitations of extrapolating results from such research when counselling parents.

### Counselling for treatment

It is important that parents are aware that studies to date have examined very restricted groups of babies. Further studies are in progress but results of small non-randomized studies need to be interpreted with caution given the known natural fluctuation in hearing outcomes seen over time in cCMV. Parents also need to be fully aware of the potential side effects of treatment, including the theoretical risk of cancer and decreased fertility. Too few numbers of treated babies have been followed up long term to be able adequately to examine this link, although, to date, problems have not been documented in young children and babies treated with ganciclovir for other reasons.

### Prevention

#### Primary prevention

**Mother:** prevention of primary CMV infection during pregnancy is based largely on maternal hand washing after changing the nappies of any older child. Infants have high rates of acquisition of CMV in day care and can then excrete the virus in their urine, passing the infection to a non-immune pregnant mother. The Centers for Disease Control (CDC) has made recommendations for pregnant women to decrease primary infection.

**Baby:** a number of research initiatives are in progress addressing the prevention of antenatal transmission of CMV. A detailed summary is outside the scope of this review but CMV hyper-immune IgG has been shown to prevent transmission in a non-randomized study, while further studies are in progress. Valaciclovir treatment of mothers during pregnancy has been shown to decrease blood viral load in the fetus, and studies of its efficacy in decreasing CMV infection at birth are in progress.

**Vaccination** would be the ultimate preventative measure and Phase II trials of the Group B subunit vaccination are nearing completion. Other vaccine strategies are in varying stages of development but we are some years away from knowing how any of these might impact on the development of cCMV.

#### Prevention of hearing and neurological sequelae

Treatment has been addressed above and has shown promise with regards to preventing hearing loss and neurological impairment in symptomatic babies. The use of treatment in babies who are asymptomatic at birth has not yet been evaluated. The optimal duration of treatment or suppression of viral load to be achieved has also not been established for this disease. Prevention of long-term problems is therefore largely dependent on

identifying problems early through regular follow-up to provide early input for any impairments identified.

### Conflict of interest statement

Dr Luck and Dr Sharland have no financial or personal relationships with other people or organizations that could inappropriately influence the content of this review. ◆

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### Practice points

- Diagnosis should be made from identification of CMV in urine or saliva before 21 days of age and in blood before 10 days of age
- Two-thirds of babies with long-term impairments from CMV infection will have been asymptomatic at birth
- MRI can pick up more abnormalities than cranial USS in symptomatic babies and can be helpful prognostically
- Viral load can be helpful in combination with clinical scenario for counselling parents on outcome
- Treatment may prevent hearing loss in symptomatic neonates
- There is no evidence to date for treating asymptomatic babies
- Follow-up of hearing and vision should continue during early childhood to detect any deterioration

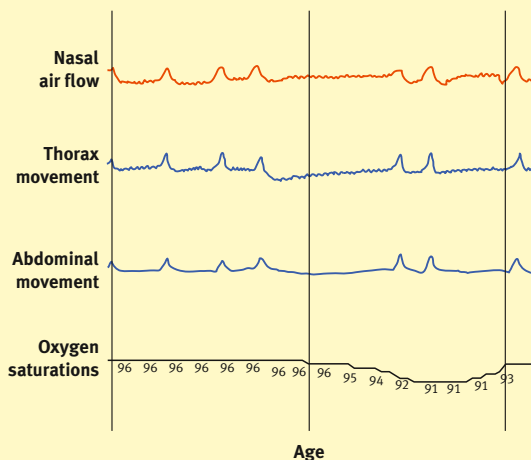
# Self-assessment

## Questions

### Case 1

A 5-day-old term infant presents with a history of multiple apnoeic episodes during which she was noted by her parents to have blue lips and appeared not to be breathing. On examination the infant was alert, afebrile and not dysmorphic; heart sounds were normal at 110/min. The chest was clear with good air entry and the fontanelle was flat and soft with a slight pulsation noted; neurological and abdominal examination was normal. The infant continued to have frequent desaturations and a full septic screen was performed but no organism was found. Chest X-ray, head ultrasound, echocardiogram and pH studies were normal. A capillary blood gas showed an elevated  $p\text{CO}_2$  of 7.5–8.2 kPa.

A sleep study was performed and a section of this is shown below. Each epoch represents 15 s. Multiple similar episodes were seen throughout the study.



- Which of the following is the most likely diagnosis? Choose ONE answer ONLY from the following:
  - Obstructive sleep apnoea
  - Congenital hydrocephalus
  - Infantile spasms
  - Congenital central hypoventilation syndrome
  - Benign periodic breathing

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- Which of the following investigations would be most likely to confirm the diagnosis? Choose ONE answer ONLY from the following:
  - Genetic studies
  - Electroencephalogram
  - Flexible bronchoscopy
  - 24-h ECG
  - Echocardiogram
- Which of the following would be the most appropriate management option for this infant? Choose ONE answer ONLY from the following:
  - Corticosteroid therapy
  - Invasive positive pressure ventilation
  - Non-invasive positive pressure ventilation
  - Surgical intervention
  - Home oxygen therapy

### Case 2

A 3-year-old boy presents with an acute history of breathlessness and right-sided chest pain. On examination he was found to have signs consistent with a pneumothorax and a chest drain was inserted. In addition he had a long history of a productive cough and recurrent infected eczema. He had received six courses of oral antibiotics in the last year, which helped the cough for a short period before it recurred. He went on to have the following investigations performed.

#### Full blood count

Haemoglobin	11.1 g/dl
White cell count	$9.3 \times 10^9/\text{L}$
Neutrophils	40%
Lymphocytes	36%
Eosinophils	15%
Platelets	$786 \times 10^9/\text{L}$

#### Immunoglobulins

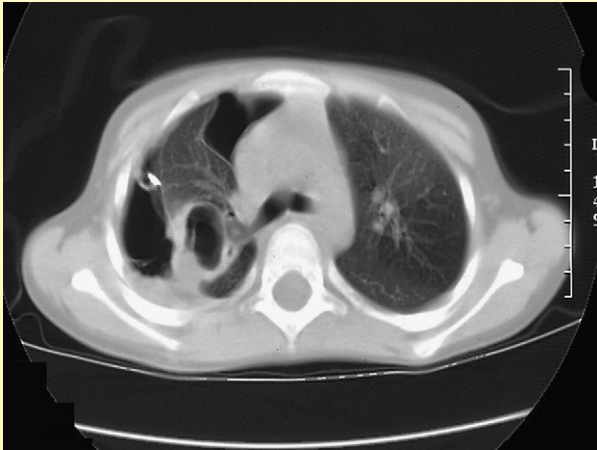
IgG	6.27 g/L	(4.2–12.4)
IgM	0.55 g/L	(0.35–1.55)
IgA	1.02 g/L	(0.25–1.85)
IgE	10,350 IU/ml	(< 120)

#### Sweat test

Chloride	40 mmol/L
Weight of sweat	131 mg

Nitroblue tetrazolium (NBT) test was negative.

Below is a thoracic CT scan of the chest taken following pneumothorax and chest drain insertion.



- In addition to the pneumothorax and chest drain, what anomaly is shown on the CT scan? Choose ONE answer ONLY from the following:
  - Pneumatocoele
  - Bronchiectasis
  - Pulmonary lobar emphysema
  - Congenital cystic adenomatous malformation
  - Pulmonary sequestration
- Which of the following organisms is most likely to be responsible for the lung pathology seen? Choose ONE answer ONLY from the following:
  - Mycobacterium tuberculosis*
  - Aspergillus fumigatus*
  - Escherichia coli*
  - Pseudomonas aeruginosa*
  - Staphylococcus aureus*
- Which of the following options is the most likely underlying diagnosis? Choose ONE answer ONLY from the following:
  - Cystic fibrosis
  - Job syndrome
  - Wiskott-Aldrich syndrome
  - Primary ciliary dyskinesia
  - Chronic granulomatous disease

### Case 3

A 4-year-old boy presented to his local hospital with a 5-day history of cough, abdominal pain, pyrexia, malaise and poor oral intake. He was noted to have a respiratory rate of 35 breaths/min with intercostal recession, oxygen saturations of 91% in air and decreased air entry in the left lower region. A chest X-ray was performed which showed opacification of the left lower lobe. The patient was admitted for intravenous antibiotics and oxygen therapy. Blood tests taken on admission gave the following results:

#### Electrolytes

Na <sup>+</sup>	126 mmol/L	(135–145)
K <sup>+</sup>	3.5 mmol/L	(3.5–5.6)

Chloride	101 mmol/L	(95–110)
Bicarbonate	28 mmol/L	(18–26)
Urea	3.0 mmol/L	(2.5–6.0)
Creatinine	36 µmol/L	(18–40)
CRP	283 mg/L	(< 7)

#### Full blood count

Haemoglobin	12.8 g/dl
White cell count	$24.3 \times 10^9/L$
Neutrophils	92%
Lymphocytes	6%
Platelets	$247 \times 10^9/L$

Over the next 4 days, the patient's symptoms persisted and, on examination, the chest became stony dull to percussion. Repeat chest X-ray showed a 'white out' of the left side, with apparent scoliosis. A chest ultrasound demonstrated a loculated, parapneumonic effusion. The child was referred to the paediatric tertiary referral centre for further management.

- Which of the following is the most likely cause of his hyponatraemia? Choose ONE answer ONLY from the following:
  - Low sodium intake
  - Increased renal sodium excretion
  - Hyponatraemic dehydration
  - Increased sodium dilution
  - High sweat sodium concentrations
- Which of the following organisms is most likely to be responsible for his symptoms? Choose ONE answer ONLY from the following:
  - Staphylococcus aureus*
  - Streptococcus pneumoniae*
  - Klebsiella pneumoniae*
  - Mycobacterium tuberculosis*
  - Mycoplasma pneumoniae*
- On arrival at the paediatric tertiary centre, which of the following actions is the most appropriate next step in management? Choose ONE answer ONLY from the following:
  - Surgical decortication
  - Conservative management and observation for 48 h
  - Small bore chest drain insertion with intrapleural fibrinolytics
  - Large bore chest drain insertion
  - Chest drain insertion (small or large bore) with intrapleural antibiotics

### Case 4

A 15-year-old boy presents with a recurrent dry cough and breathlessness with activity which has become more obvious over the previous 6 months. Of note in his past medical history, at age 6 he was diagnosed with stage IV neuroblastoma and completed treatment consisting of chemotherapy,

radiation and an autologous stem cell graft. Prior to this, he was well; however, he was prescribed a salbutamol inhaler to use before exercise.

On examination he was noted to have fine crepitations audible throughout both lung fields and there was good air entry bilaterally. The rest of the clinical examination was normal.

His full blood count showed the following result:

Haemoglobin	13.1 g/dl
White cell count	$5.8 \times 10^9/L$
Neutrophils	45%
Lymphocytes	40%
Platelets	$214 \times 10^9/L$

His pulmonary function tests are shown below.

	Normal range	Pre-salbutamol value	Post-salbutamol value
<i>Spirometry</i>			
Forced expiratory volume in 1.0 s (L)	1.89–2.92	1.10	1.15
Forced vital capacity (L)	2.31–3.44	1.22	1.32
FEV <sub>1</sub> /VC (%)	77–92	90	87
Peak expiratory flow rate (L/s)	214–394	198	205
<i>Plethysmography</i>			
Slow vital capacity (L)	1.27–3.44	1.34	1.41
Functional residual capacity (L)	2.41	1.66	1.64
Residual volume (L)	0.52–1.39	0.5	0.49
Total lung capacity (L)	2.98–4.43	2.48	2.53
Transfer factor (mmol/min kPa)	4.83–8.39	3.1	

- Which one of the following options is best demonstrated by the pulmonary function tests shown? Choose ONE answer ONLY from the following:
  - Obstructive airway disease with significant reversibility
  - Obstructive airway disease with no significant reversibility
  - Restrictive lung disease
  - Air trapping
  - Poor technique
- Which of the following investigations would be most useful in determining the diagnosis? Choose ONE answer ONLY from the following:
  - Histamine challenge
  - High-resolution CT chest

- Bone marrow aspirate
- MRI chest
- Bronchoscopy and lavage

- What is the most likely cause of these results? Choose ONE answer ONLY from the following:
  - Asthma
  - Interstitial lung disease
  - Mediastinal mass causing large airway obstruction
  - Bronchiectasis
  - Pneumocystis pneumonia

## Answers

### Case 1

- D
- A
- B

Congenital central hypoventilation syndrome (CCHS) is a rare genetic condition characterized by significant under breathing, particularly during quiet sleep, and a lack of response to hypoxia and hypercarbia. Unrecognized this condition can be fatal or result in hypoxic brain injury. Infants present with apnoeic episodes or cyanosis, with respiratory studies showing poor respiratory air flow associated with a lack of chest and abdominal wall movement, hypoxia and progressive hypercarbia. CCHS is a lifelong condition, which is associated with multiple abnormalities in the autonomic nervous system, including reduced heart rate variability, reduced ability to produce a febrile response to illness and oesophageal dysmotility, and 10–15% have Hirschsprung disease. In 90% of CCHS patients the PHOX2b gene has been identified and genetic studies are widely available. The gene is located on chromosome 3p12 and codes for a homeobox transcription factor.

All patients require mechanical ventilatory support whilst sleeping and 35% require long-term 24-h ventilation. In infants this is best delivered as positive pressure mechanical ventilation via tracheostomy, although in some older children, who only require night-time ventilation, non-invasive bi-level pressure ventilation can be used; diaphragmatic pacing has also been used in some patients.

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- Weese-Mayer DE, Berry-Kravis EM. Genetics of congenital central hypoventilation syndrome: lessons from a seemingly orphan disease. *Am J Respir Crit Care Med* 2004; **170**: 16–21.



**Case 2**

1. A
2. E
3. B

Job syndrome (also called the hyper IgE-syndrome) is a rare multisystem disorder of immunity and connective tissue. Children usually have recurrent pneumonias and infected eczema, with *Staphylococcus aureus* being the most common pathogen, leading to the development of pneumatoceles in the lung and skin abscesses, which are frequently 'cold' in nature. In addition, there are a number of skeletal symptoms, including hyperextensible joints, scoliosis, retained primary dentition and coarse facial features in older children. Laboratory investigations demonstrate extremely elevated IgE levels (more than 2000 IU/ml) and raised eosinophil counts.

Job syndrome has been identified in all ethnic groups and is found equally in both sexes. It may be sporadic in nature and, although most pedigrees are consistent with an autosomal dominant inheritance, this may vary. Recent studies have identified mutations in the signal transducer and activator of the transcription 3 (STAT3) gene. The underlying mechanism of Job syndrome is still not clear but theories include an imbalance in the normal T helper 1 cell (Th-1)/T helper 2 cell (Th-2) cytokine response, leading to increased IgE production.

There is no specific therapy available, although aggressive treatment of active infection and antistaphylococcal prophylaxis is important. Immune modulators such as interferon- $\gamma$ , cyclosporine A and intravenous immunoglobulin infusions have been used with limited response; bone marrow transplantation has not been shown to be curative.

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- Holland SM, DeLeo FR, Elloumi HZ, et al. STAT3 mutations in the hyper-IgE syndrome. *N Engl J Med* 2007; **357**: 1608–19.

**Case 3**

1. D
2. B
3. C

The hyponatraemia was due to syndrome of inappropriate antidiuretic hormone (SIADH). ADH is usually secreted in response to rising plasma osmolality in order to increase reabsorption of water in the distal tubules and the collecting ducts of nephrons. In certain pathological situations, including lower respiratory tract infections, too much ADH is secreted, leading to excess water retention and hyponatraemia, with fluid restriction being the most appropriate treatment.

The incidence of empyema has been steadily increasing since the mid 1990s and this appears to be unrelated to any increase in cases of pneumonia. Empyema is more common

in males and the highest incidence is seen between the ages of 1 and 4 years. Seventeen per cent of cases yield a positive organism, with *Streptococcus pneumoniae* serotype 1 being responsible for 50% of these cases. Blood cultures, sputum cultures and pleural fluid should be sent for analysis. Identification yields may be increased by using polymerase chain reaction and latex agglutination techniques.

All children with empyema or loculated parapneumonic effusion should be managed in the respiratory unit of a tertiary referral centre. Delay in diagnosis leads to increased morbidity and a prolonged hospital stay, due to the difficulties in treating advanced, organized empyemas. Early intervention with chest drain insertion reduces the period of illness and hospital stay.

A small bore chest drain should be inserted under ultrasound guidance. There is no evidence that large bore drains are preferable; small bore drains allow for more patient movement and are better tolerated. Intrapleural fibrinolytics (such as urokinase) have been shown to reduce hospital stay. In some centres a mini-thoracotomy or video-assisted thoracotomy (VATS) are used prior to chest drain insertion. If symptoms continue, a thoracic surgeon should be consulted as decortication may be required.

In contrast to adults, the long-term outcome for children with empyema is extremely good, with the majority of children being clinically back to full health by 4 weeks and with most chest radiographs returning to near normal in 3–6 months. The majority of children who develop empyema will have been in good health prior to the acute infection and will have no long-term clinical consequences; provided the chest X-rays return to normal, further follow up investigations are unnecessary.

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- Roxburgh CS, Youngson GG, Townend JA, Turner SW. Trends in pneumonia and empyema in Scottish children in the past 25 years. *Arch Dis Child* 2008; **93**: 316–8.

**Case 4**

1. C
2. B
3. B

Spirometry shows a proportional reduction in both forced expiratory volume in 1 s (FEV<sub>1</sub>) and forced vital capacity (FVC), with the FEV<sub>1</sub>/FVC ratio being within normal limits, excluding obstructive airways disease. Plethysmography demonstrates a reduced total lung capacity and residual volume, which indicates a restrictive lung disease. Transfer

factor is a measure of how readily carbon monoxide crosses the interstitium and is reduced if infiltrates or fibrosis are present within the lung parenchyma, as found in interstitial lung disease.

High-resolution CT is the most sensitive imaging modality to confirm the diagnosis of interstitial lung disease and demonstrates the extent of parenchymal lung disease; it may also determine suitable biopsy sites should a tissue diagnosis be required.

Restrictive lung disease may be secondary to the following causes:

- intrinsic lung disease (e.g. primary interstitial lung diseases, infectious and post-infectious disorders)
- extrinsic disorders (e.g. scoliosis, neuromuscular disorders such as Duchenne muscular dystrophy, morbid obesity)
- secondary to systemic disease (e.g. sarcoidosis, histiocytosis)
- drug induced (e.g. chemotherapy agents, radiation).

Paediatric interstitial lung disease is rare. The types, causes and prognosis are ill-defined, and do not follow the patterns seen in adults. In approximately half of cases, the aetiology is unknown. In this case, the restrictive defect is most probably a consequence of treatment of the stage IV neuroblastoma. Many of the treatments used to treat childhood cancer can result in pulmonary fibrosis in subsequent years,

including alkylating agents such as busulfan, bleomycin and cyclophosphamide. Radiotherapy can also cause pulmonary fibrosis, particularly if used in combination with alkylating agents. The prognosis of pulmonary fibrosis in cancer survivors is variable and symptoms may improve, remain unchanged or worsen with time. Any child at risk of developing restrictive lung disease should have baseline pulmonary function tests performed at the end of therapy and repeated if clinically indicated.

The treatment of interstitial lung disease in children is dependent upon the aetiology. Steroids remain the primary therapeutic option, with other immunosuppressive agents such as azathioprine, cyclophosphamide or hydroxychloroquine being of benefit in some patients.

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# Abstracts from the Paediatric Research Society and the British Association of General Paediatricians autumn meeting

Royal Shrewsbury Hospital, 2nd and 3rd October 2008

Edited by: Dr Ragbir S Thethy

## The impact of the National Patient Safety Agency intravenous fluid alert on iatrogenic hyponatraemia in children

**Drysdale S**, Coulson T, Cronin N, Piyasena C, Fox A, Ford-Adams M, Broughton S

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**Introduction:** In March 2007, the National Patient Safety Agency issued an alert regarding intravenous fluid (IVF) prescription to hospitalised infants and children, to be implemented in UK hospitals by September 2007. Previously the most common IVF (0.18% saline/4% dextrose) has been associated with iatrogenic hyponatraemia, resulting in four deaths and one near miss since 2000. The alert recommended 0.45% (or 0.9%) saline/5% dextrose as maintenance fluids and banned 0.18% saline/4% dextrose. We audited practice and outcome before and after the implementation of the IVF guideline for hospitalised infants and children.

**Methods:** Prior to the guideline implementation we audited data from June 2007 on 102 patients, retrieving notes and data on 69. Prospective data was then collected from 186 patients admitted in June 2008 after guideline implementation. We recorded demographics, serum sodium levels and IVF prescriptions.

**Results:** Prior to the guideline implementation 46 (66%) were prescribed IVF (median age 4.5 (0.02-15) years, median weight 17.4 (2.2-73.0)kg). Seven received hypotonic IVF, and one became hyponatraemic (Na<sup>+</sup> 123). After guideline implementation 57 of 186 (30.6%) received IV fluids (6.9 (0.001-17) years and 22.2 (3.2-65.0)kg). One received hypotonic IVF and became hyponatraemic (Na<sup>+</sup> 123). The median change in serum sodium levels for all children who received hypotonic fluids (-6 (0 to -15) mmol/L), was significantly greater than those who did not (0 (-7 to +7) mmol/L)  $p=0.007$ . Children receiving 0.45% or 0.9% saline had a median maximum serum sodium of 140 (range 136-150) mmol/L. The value of 150 mmol/L was in a child with diabetes insipidus.

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**Conclusion:** Implementation of a new IVF guideline has been associated with less use of hypotonic IVF solutions and less iatrogenic hyponatraemia. The only children who became hyponatraemic received hypotonic IVF. Prescription of 0.45% or 0.9% saline was not associated with hypernatraemia.

## New patient referrals to the paediatric cardiology clinic

**Mascarenhas S**, Hammill B, Wyllie J

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**Introduction:** Congenital heart disease is found in 8-10/1000 live births. Cardiac murmurs are a common finding in asymptomatic paediatric patients. The most common causes are innocent murmurs and minor structural heart disease. With an increase in awareness of CHD, referrals to paediatric cardiology services have also increased. A previous audit in 1998 demonstrated that almost 75% of the patients referred with murmurs had normal echo's with two-thirds of them discharged following initial consultation. A potential way of avoiding unnecessary referrals would be to develop guidelines so as to enable general practitioners identify those that require specialist review. We set out to analyze current referral patterns to the clinic and determine patient outcomes with regards to symptomatology and the need for onward referral.

**Methods:** A retrospective review of all new patients referred to the PSIC's (Paediatrician with special interest in Cardiology) over an 18-month period (January 2004 to June 2005). Data was obtained by review of referral letters and clinic notes.

**Results:** 387 new referrals were received in 52 clinics. 30 patients were excluded. (11 -DNA, 13-non cardiac referral, 2-known CHD, 4-case notes could not be traced) Therefore, 357 eligible case notes were reviewed with a mean age of 3 years 8months (range 1 day to 15 yrs 2 months). Almost half of the referrals came from general practitioners who referred them for murmurs (60%), palpitations (7%), chest pain (4%), syncope (3%) cyanosis (2%) family history of CHD (11%) and other causes (13%). Of those referred for murmurs, 73% were still audible in clinic with 25.7% of those having had an abnormal echo. In infants < 6 weeks of age, 34% had structurally abnormal hearts, 37% needed onward referral. In infants between 6 weeks - 1 year, 22% had structurally abnormal hearts, half of them needed onward referral while in those > 1 year, only 9.7% had abnormal Echo's and one third needed onward referral. Of those referred with chest pain, ECG was normal in all of them. 68% of those with chest pain underwent an echo, which did not show significant abnormal findings in any of them 7.2% referred with palpitations; all but one underwent an echo, which was normal. 22% had definite or suspected tachyarrhythmia and were referred to tertiary cardiologist. Overall, 72.7% of all new referrals were discharged and 18.1% were given follow up appointments between 4months and 2 years. 7.2 % were referred to the tertiary cardiologist and 1.8% to other tertiary specialists

**Conclusions:** Asymptomatic heart murmurs in children > 1 yr are more likely to be innocent in nature. Newborns and infants with murmurs are likely to need specialist referral.

## Paediatricians' understanding of anogenital warts in children

**Gandhi A**

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**Introduction:** Anogenital warts (AGW) are common in adults and are invariably sexually transmitted. Not surprisingly their presence in a prepubertal child is often thought to indicate sexual abuse. However presence of warts alone without supporting clinical, laboratory and social information is not diagnostic of sexual abuse.

**Aims:** To evaluate understanding and approach of paediatricians to a child presenting with AGW.

**Methods:** A multiple response (Likert 5 point scale) questionnaire based on a real case of AGW was distributed to the delegates attending a paediatric scientific meeting at Newport. Completed questionnaires were collected at the end of the meeting and responses analysed.

**Results:** Of the 44 people who responded, more than half (23/44) had never managed a child with AGW. Their paediatric experience ranged from 0.5 to 30 years (median 9 years). 18% incorrectly indicated AGW as a definite sign of child abuse. Another 16% felt that AGW should be reported as child sexual abuse as a priority. 66% had knowledge of perinatal transmission while only 43% accepted non-sexual contact as a mode of transmission. Nearly 39% wrongly believed that viral DNA typing can identify the perpetrator. Open question asking for helpful clinical features or investigations received several sensible responses but none comprehensive enough to resolve the issue.

**Conclusions:** A significant number of paediatricians consider AGW as a definite sign of child sexual abuse and many appear to lack understanding regarding other modes of transmission. Clear guidance in dealing with this challenge needs to be developed and made available locally.

## Self-harm in children and young people: do we think we follow the NICE Guidelines?

**Harrop AJ, Powell CVE**

*Department of Paediatrics, University Hospital of Wales, Cardiff*

**Introduction:** Staff training, general care of and attitudes towards children and young people who have self-harmed, is often sub-optimal. The aim of this study was to compare staff attitudes to our practice with the recommendations made by the NICE Clinical Guideline for Self Harm 16 (July 04).

**Method:** A self-completed questionnaire was issued to doctors and nurses (all grades) involved with acute paediatric care. Staff from paediatric intensive care and child and adolescent mental health were excluded. The study occurred between August and November 2006. The 31 questions were developed using the key recommendations from the NICE Guideline.

**Results:** There were 104/262 (40 %) questionnaires returned. Only 29% were aware of the NICE guidelines. 64.4% were not confident in treating and caring for those with self-harm. Only 4.8% reported good formal training and 33.6% had some training in adolescent self-harm management. Awareness of the 'logistics' surrounding admission (overnight admission, paediatrician overall responsibility, assessment by mental health team and consent for mental health assessment) was poor.

**Conclusion:** There was minimal awareness of the existence and content of the NICE guidelines. There was low confidence in most staff treating and caring for those with self-harm. Numbers of staff with formal training was inadequate. Although there was a poor return rate, this study has highlighted an area of clinical and educational weakness surrounding an important group of patients who are frequently admitted under our care.

## NICE traffic light approach to managing feverish illness in children: compliance and likely impact on outcome

**Rao S, Gandhi A**

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**Introduction:** NICE had recently introduced guidelines using the traffic light system to facilitate assessment and initial management of children with feverish illness: green (low risk) category - managed in community and blood tests not required; amber (moderate risk) category - blood tests performed unless deemed unnecessary; red (high risk) category - blood tests mandatory. This audit was conducted to assess compliance and practical adaptability of these guidelines.

**Methods:** 70 children aged under 5 years, referred to our hospital between November 2007 and January 2008, were included and classified using NICE criteria into 3 categories: Green (n = 34), Amber (n = 25) and Red (n = 11).

**Results:** 8 (23%) children under the green category were admitted (5 for observation; 3 for intravenous antibiotics). Blood tests were performed in 6 children (not in accordance with NICE guidelines). 11 (44%) under amber category required admission and blood tests were not performed in 21 (87.5 %) as this was deemed unnecessary. Six (55%) children in the red category required admission and 5 were discharged following 6 hours of observation. 4 children who had non blanching rash did not have any blood tests. There was no documentation of appropriate discharge advice for 29 % (green), 12 % (amber) and 18 % (red). A safety net was not provided to 16 % under amber and 36.4 % under red category.

**Conclusions:** The traffic light approach could be an effective triaging system to identify sick children requiring admission. Provision of discharge advice and safety net needs to be improved. The majority of children categorised as amber can be managed successfully without the need for laboratory tests and adoption of guideline in its entirety may lead to a significant increase in the number of investigations in children presenting with a febrile illness.



### Are middle grade doctors trained in formal assessment of other trainees?

**Schwarz A**, Satish HP, Thompson B, Sackey AH  
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**Introduction:** Workplace- based assessment and feedback are important in foundation and specialist training. Middle grade doctors are expected to help in these assessments using DOPS (Direct Observation of Procedural Skills), CBD (Case-based Discussion), mini-CEX (Mini Clinical Evaluation Exercise) and mini-PAT (mini Peer Assessment Tool). Our aim was to determine training status of these doctors in our hospital.

**Method:** This is a questionnaire survey in district general hospital over 4 weeks in June 2008. Out of a total of 80 middle grade doctors, questionnaires were personally handed out to 38 middle grade doctors (from various departments) who were available during the study period. Data were analysed with SPSS.

**Results:** Completed questionnaires were collected from all 38 middle grade doctors. 16 were SpRs, 9 ST3, 1 ST4, 8 Staff Grades and 4 clinical fellows. 71% (27/38) had assessed junior doctors for more than one year. 89% (34/38) had used DOPS, CBD and mini-CEX at least once. 58% (22/38) had used the mini-PAT at least once. 53% (18/34) had used DOPS, 44% (15/34) CBD, 50% (17/34) mini-CEX and 41% (9/22) mini-PAT on more than 10 occasions. 66% (25/38) had training in DOPS, CBD, mini-CEX and 49% (18/38) had training in mini-PAT. 26% (10/38) had face-to-face training, 11% (4/38) had read guidelines in addition to the course and 32% (12/38) had only read guidelines. 29% (11/38) had no training on assessment. 49% (18/38) reported feeling "fully confident". 68% (26/38) would appreciate further formal training.

**Conclusion:** This survey has shown that in our hospital most middle grade doctors have not had face-to-face training in workplace- based assessment. Most reported need for further formal training. Efforts should be made to provide for this training.

### Parental diabetes knowledge and glycaemic control of their children: a questionnaire study

**Joseph L**, Bentley A, Mathew V  
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**Aim:** Management of type 1 diabetes in children is a complex process. A good parental understanding of diabetes and its management would be considered a prerequisite for their involvement in the care of their children's diabetes. The aim of this study was to explore the relationship between parental knowledge of diabetes self management and glycaemic control of their children.

**Design:** A diabetes knowledge questionnaire was used to assess the parental diabetes knowledge in the paediatric outpatient clinic. HbA1c was used as an indicator of the glycaemic control of their diabetic children. Parents of children with type 1 diabetes aged between 5 years and 15 years filled the diabetes

knowledge questionnaire. Data on parental education was also collected. Children who had diabetes for less than 3 years and those with co-morbidities like hypothyroidism and coeliac disease were excluded from the study. The study was done over a 3 month period in 2007. Ethics approval was obtained from the local research and ethics committee.

**Results:** Parents of 48 children were included in the study. No relationship between parental knowledge scores and glycaemic control was found [Spearman's correlation coefficient:  $-0.126$ ]. There was no relationship between parental knowledge scores and their level of education [Spearman's correlation coefficient:  $-0.205$ ]. Glycaemic control of the diabetic children was not related to the educational level of the parents [Spearman's Correlation coefficient:  $0.097$ ].

**Conclusions:** This study did not show any relationship between parental diabetes knowledge score and the glycaemic control of their children. However this does not mean that parental diabetes knowledge is not required for successful day to day management of their children's diabetes. There are other factors like behaviour, attitudes, empowerment and family dynamics which could have considerable impact on the active participation of the child and family in the management of type 1 diabetes in children.

### Fact and fiction: the use of *House MD* as a teaching tool for medical students

**Isba R**, Costigan WS, Byrne G, O'Neill P  
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**Introduction:** Medical education is undergoing significant changes, with the responsibility for learning increasingly shifting to the learner.

Recent innovations such as problem based learning (PBL) have encouraged students to seek out their own information sources – traditionally textbooks. More recently, however, use of other sources such as the internet, has become more widespread.

TV drama may also be an under-recognised source of student knowledge.

This study looks at how much information medical students learned from an episode of the TV drama "*House M.D.*".

**Method:** In the pilot study, 25 students were randomised into three groups:

- Group 1 watched an episode of "*House M.D.*"
- Group 2 read written materials
- Group 3 received no intervention

All students completed a purpose-written, 16-item MCQ test immediately after the intervention and again 2 weeks later.

**Results:** Group 1 achieved the highest mean score in both sets of tests, and there were significant differences between groups 1 ("*House*") and 3 (no intervention) in test 1 ( $p = 0.02$ ) and a trend towards differences between the groups in test 2 ( $p = 0.073$ ). Further analysis was limited by small group size.

The study was re-run with a second group of students, and these data are currently being analysed.

**Conclusion:** TV drama has the potential to be used as a supplementary teaching tool, and the use of a larger cohort will help further elucidate this.

### Do picture charts improve the accuracy of asthma medication history given by parents? a prospective cohort study

**Williams LM**, Nickson CL, Deshpande SA, Rees JHM  
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**Introduction:** Accurate medication history is essential for assessment of children with asthma, yet inaccuracies or uncertainty over drug, dose and device are frequent. Posters have been marketed for use with other chronic diseases (e.g. diabetes and insulin devices) but none for the wide range of asthma medications currently available. Neither have the practical benefits and accuracy of such a tool been documented.

**Methods:** A prospective cohort study of parents of asthmatic children attending paediatric asthma out-patient clinics in a district general hospital. Verbal information on asthma medication was first obtained from parents using standard methods of recall and memory via specific and standardised questioning. Information was then obtained using a specially designed photographic poster depicting all the commonly prescribed asthma medications and spacer devices. Follow-up information was also obtained during a telephone interview when the parents had the child's inhalers with them at home, if such inhalers had not already been brought to the outpatient clinic. Data analysis by Fisher Exact Test.

**Results:** 51 parents were recruited to the study, of which only 27% (14) brought their inhalers with them to the clinic. 59 reliever and 60 preventer preparations were in use for 51 children.

Reliever medications:

- Incorrect recall of medication name for 85% (50/59) improved to 100% with poster,  $p=0.003$ . Incorrect recall of dose for 69% (41) increased to 100% with poster,  $p=0.02$ .

Preventer medications:

- Incorrect recall of medication name for 42% (25/60) improved to 92% (55/60),  $p=0.0001$ .
- Incorrect recall of inhaler device for 85% (51/60) improved to 100%,  $p=0.0001$ .
- Incorrect recall of medication dose 52% (31/60) improved to 95% (57/60),  $p=0.0001$ .

Telephone interviews did not lead to correction of data obtained by use of poster.

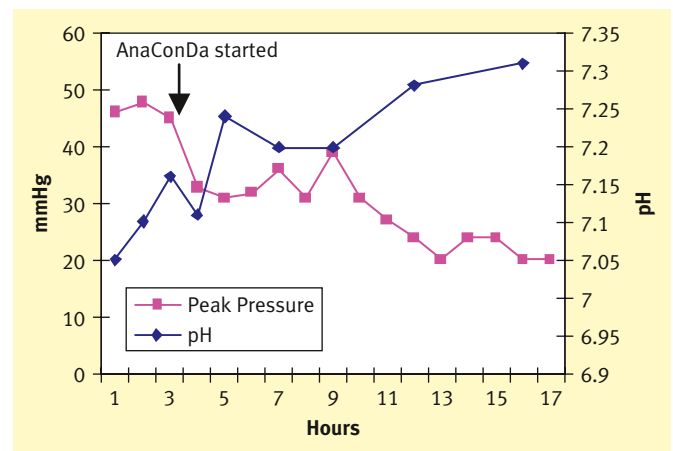
**Summary:** Parental recall of medication name, dose and device is understandably often poor and potentially misleading. The use of a photograph poster depicting the range of asthma treatments available provides highly accurate information. Such posters should be made routinely available in all clinical settings that see children with asthma.

### Use of the AnaConDa® device in life-threatening asthma

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**Introduction:** The AnaConDa® device is a modified HME filter which allows for the administration of volatile anaesthetic agents into a standard ventilator circuit in the critical care environment. Using this device, volatile anaesthetic agents may be administered to provide sedation to mechanically ventilated patients or for specific therapeutic effect such as for bronchodilation in severe asthma.

**Method:** We describe for the first time the use of the AnaConDa® device in a case series of children with life-threatening asthma. The cases of three children are described, all of whom were unresponsive to maximal standard therapy. In each case, administration of Isoflurane via the AnaConDa® device was associated with rapid improvement of ventilatory parameters and blood gases.



**Figure 1** Typical results demonstrating improvement in ventilatory parameters and blood gases following the administration of Isoflurane via the AnaConDa® device.

**Conclusion:** The AnaConDa® device provides a simple route of administration for volatile anaesthetic agents in the critical care environment which can be life-saving in the most severe cases of asthma.

### Use of continuous positive airway pressure (CPAP) in infants admitted with bronchiolitis in West Midlands

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**Aim:** To study the use of CPAP in infants with bronchiolitis and to assess the failure rate in terms of intubation and transfer to intensive care unit (ICU).

**Method:** We conducted a prospective audit on infants requiring CPAP in High Dependency Unit (HDU) in five district general hospitals (DGH) in West Midlands from October 2007 to February 2008. Control data was used from a retrospective audit performed in Birmingham Heartland's Hospital (BHH)(1).

**Results:** 1147 infants were admitted for bronchiolitis and 4% (48) required CPAP. Less than 1% (0.6%) of admissions and

15% of those requiring CPAP (7) were intubated and transferred to ICU. Data from BHH suggest that 5% were admitted to ICU for bronchiolitis in 2001 (before HDU was set up) and 2% in 2002 (before use of CPAP). This had decreased to <1% (0.7-0.9%) in 2003-2006 (1). Median corrected age of infants requiring CPAP was 2 weeks (range -4 to 15 weeks). 25 (52%) were born prematurely and 3 (6%) had congenital heart disease. Their gas values are given below:

	Mean pH ( $\pm$ SD)	Mean pCO <sub>2</sub> ( $\pm$ SD)
Before CPAP	7.245 ( $\pm$ 0.12)	9.26 ( $\pm$ 2.9)
After CPAP	7.339 ( $\pm$ 0.05)	7.22 ( $\pm$ 1.4)
P value	0.025	0.038

Median corrected age of 7 infants who failed CPAP and required intubation was 6 weeks (range 2-15 weeks). 5 (17%) were born prematurely including 1 with Trisomy 21 and congenital heart disease. The reasons were apnoea in 3 cases, increasing respiratory distress in 3 and worsening gas in 1. Mean pH (before CPAP) was 7.096 ( $\pm$ 0.18) and mean pCO<sub>2</sub> was 12.79 ( $\pm$ 5.2). They are significantly different from those who didn't require intubation. Median duration of CPAP before intubation was 6 hours.

**Conclusion:** CPAP improves respiratory acidosis in infants with bronchiolitis. There has been reduction in ICU admission since the use of CPAP in HDU setting. We recommend considering CPAP earlier for bronchiolitis especially in infants who have underlying problems and uncompensated respiratory acidosis.

## REFERENCE

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## EEG referrals from a district general hospital

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**Introduction:** EEG is commonly used to investigate epilepsy in children. However, its inappropriate use can lead to misdiagnosis. NICE guidelines published in October 2004 state that EEG should be performed only to support clinical diagnosis of epilepsy and it may also be useful to diagnose epilepsy syndrome. It should not be used to confirm or refute the diagnosis of epilepsy. An audit was conducted to assess the appropriateness of EEG referrals.

**Methods:** It was a retrospective audit of patients referred for EEG, from Royal Albert Edward Infirmary, Wigan to the Royal Manchester Children's Hospital from January to December 2006. Patients were identified from the records at the department of Neurophysiology at Royal Manchester Children's Hospital. All the notes and EEG referral letters were manually scrutinised by the Paediatrician with special interest in Epilepsy to assess the appropriateness of referrals.

**Results:** 55 EEG referrals were made for 51 patients during the study period. Repeat EEG was done in 4 patients in the same

year. 51 routine EEGs, 2 video EEGs and 2 sleep EEGs were performed. 34 EEGs were normal and 19 were reported as abnormal. EEG was inconclusive in 2 patients and they were treated with antiepileptic drugs based on history. Out of 19 abnormal EEGs, 6 patients were not treated (31.5%) and 9 patients were treated out of 34 normal EEGs (26.5%).

**Conclusion:** Forty five (82%) EEG referrals were appropriate. All patients with inappropriate referrals had normal EEG. The commonest cause of inappropriate referrals was syncopal episodes in the teenage group. Paroxysmal non-epileptic disorders like Syncope, Reflex anoxic seizures can be confused with epileptic seizure but EEG is not indicated in these conditions. Referrals can be improved by enhancing the clinical history and re-educating the paediatricians to adhere to the EEG guidelines in clinical practice.

## Electrocardiographic abnormalities in children with suspected epilepsy

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**Introduction:** National Institute for Health and Clinical Excellence recommends that a 12 lead electrocardiogram (ECG) should be considered in children with suspected diagnosis of epilepsy. However there are relatively few data on the value of ECG in these children.

**Aim:** To investigate the prevalence of electrocardiographic abnormalities and their clinical significance in children with suspected epilepsy.

**Methods:** Retrospective case notes review of all children with a possible diagnosis of epilepsy between January 2004 and June 2007, who were referred to a paediatrician with an interest in epilepsy. All the ECGs (for the purpose of this study) were reviewed by a paediatrician with expertise in cardiology.

**Results:** Of the 96 children included, 85 had an ECG done in the outpatient clinic. However ECG could be located in only 77 case notes. ECG abnormalities were noted in 26% of patients. The commonest abnormality was incomplete right bundle branch block (9%), followed by prolonged corrected QT interval (5%) and probable left ventricular hypertrophy (4%). Other significant abnormalities included first degree heart block (2.6%), low atrial rhythm and abnormal QRS axis.

The epilepsy team was able to correctly identify all 57 normal ECGs and 12 of the 20 abnormalities. The remaining 8 abnormal ECGs had minor abnormalities, but prompted further clinical review.

**Conclusion:** Electrocardiographic abnormalities are relatively common in children with suspected epilepsy. They are however usually minor and not always clinically significant. Correct identification of such abnormalities requires a good understanding of ECGs in children.

## The role of stiripentol in the treatment of Lennox Gastaut syndrome

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**Introduction:** Stiripentol is an antiepileptic drug used most frequently in the treatment of Severe Myoclonic Epilepsy in Infancy (SMEI). Published data on the efficacy of Stiripentol in the treatment of other epilepsy syndromes are limited; no United Kingdom (UK) data are available. We investigated the efficacy of Stiripentol in the small number of children we have treated.

**Method:** Children who had received Stiripentol were identified by searching for the word 'Stiripentol' on computerised records and by checking pharmacy prescriptions. The case notes of individuals who were identified by the search were reviewed; data were recorded when Stiripentol was used and follow up data were available.

**Results:** Four patients received Stiripentol as an add-on therapy following the failure of treatment with the full range of traditional anti epileptic drugs (AEDs). Two children (one with migratory partial epilepsy of infancy and another with refractory epilepsy secondary to hypoxic ischaemic encephalopathy) did not respond to Stiripentol treatment; the progress of two children with Lennox Gastaut syndrome (LGS) who did respond is described. None of the children experienced side-effects. Child 1: An eight year old female child received Stiripentol whilst concurrently treated with sodium Valproate. Introduction of Stiripentol resulted in the reduction of atonic and myoclonic seizure frequency from 10 to 0.2 seizures per day (80% reduction). Child 2: Treatment of a male child aged 13 yrs concurrently treated with Ethosuximide and Vigabatrin resulted in the eradication of frequent tonic, myoclonic and atonic seizures, although atypical absence seizures persisted.

**Conclusion:** In our limited experience, Stiripentol treatment does lessen seizure frequency in patients with LGS; further data are required about its long term efficacy. Stiripentol should be considered as an 'add on' AED in children with LGS and epilepsy syndrome associated with myoclonus

## Incidental neutropenia in children: should we routinely investigate further?

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**Introduction:** Neutropenia can be discovered incidentally in otherwise healthy children. It is often identified during investigation for an acute infection. Repeat blood tests are often performed to ensure resolution.

**Aim:** The aim of the study was to identify children with neutropenia and to review our follow-up practice. In particular we assessed the necessity for a repeat full blood count.

**Methods:** All children with an episode of neutropenia during a 12-month period at our district general hospital were included in the study. We used the cut-off level of  $1.5 \times 10^9/l$  to define neutropenia. Case notes were reviewed and data were collected on patient age, gender, clinical examination, diagnosis and full blood count results. The necessity for a repeat full blood count was assessed retrospectively based on clinical findings and full blood count parameters.

**Results:** A total of 48 patients were included. Male:24 Female:27. Mean age: 5.4yrs. Three patients had hepatomegaly. A diagnosis of viral infection was made in 30 cases. One patient was diagnosed with EBV infection on serology. Two patients were diagnosed with bacterial pneumonia. One patient was diagnosed with aplastic anaemia. One patient had a post-operative infection. A total of 36 patients had a repeat FBC performed. There was partial resolution of neutropenia in 13 patients and complete resolution in 21.

**Conclusions:** The clinical significance of incidental neutropenia in previously healthy children is not clear from current literature. In our study, most cases of neutropenia resolved with resolution of infection. We propose that repeat full blood counts for neutropenia associated with viral infection are of limited value and should not be performed routinely. However, a full blood count should be repeated if there is severe neutropenia, serious bacterial illness or a low haemoglobin or platelet count. Associated clinical features of severe stomatitis or hepatosplenomegaly should also prompt further investigation.

## Copying clinic letters to parents – Current views and practices

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**Introduction and Aims:** The department of health (April 2004) has recommended that patients should receive a copy of clinical letters following attendance at outpatient clinics. Previous studies have shown that parents were in favour of receiving letters and this improved parent satisfaction and compliance.

In this study, we examine the current practice amongst paediatricians regarding copying letters to parents and identify factors hindering its implementation.

**Methods:** We conducted a questionnaire survey of all consultants and specialist registrars in general paediatrics and paediatric subspecialties. The areas covered included frequency of copying letters to parents, obtaining consent and clinician's views on the benefits and disadvantages of forwarding letters.

**Results:** We evaluated 30 completed questionnaires (81% response rate) with an equal mix of consultants and specialist registrars. Only 33% of respondents routinely copied letters to parents while 47% would do so under special circumstances. Most (80%) of them were unaware of the need for consent prior to copying letters and 20% obtained consent only in special circumstances. 25% of those who copied letters, wrote a separate letter to parents from that to the GP.



Majority believed that this may improve communication (77%) and parental satisfaction (70%) while 50% expected that compliance with medical advice may improve. However, 46% opined that it would increase workload and parental anxiety and 50% believed that there was potential for breach of confidentiality. These factors seemed to deter them from copying letters to parents.

73% of the trainees were unaware of DOH guidelines and none had received formal training on written communication with parents/patients.

**Conclusions:** We should increase our efforts to provide clear and prompt written information to parents. Awareness on the need for obtaining consent needs to be raised amongst clinicians. As written communication is an essential and sensitive aspect of our practice, formal training needs to be facilitated by introducing it in paediatric curriculum.

### Yes, breast is the best but only if attachment is the best

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**Introduction:** Breastfeeding is advocated as the best feeding for newborns all over the world. The failure of breastfeeding has been attributed to various reasons. One major factor is the incorrect attachment of the babies on the breast resulting in sore and cracked nipples and hungry babies and anxious parents.

**Aim:** To see whether mothers were using a correct method of breastfeeding and if not, to intervene and teach them. To see whether the intervention helped. To see if there were any differences between the primigravida and multigravida mothers.

**Methods:** Observational and interventional. Breastfed babies were observed by a doctor/nurse while being fed. The latching of the baby on the breast was observed and if incorrect attachment was observed, mothers were explained the correct method. Following this intervention, the feeding was again observed by another doctor/nurse. 84 mothers were involved in the study, 44 primigravida and 40 multigravida.

**Results:** Not surprisingly, incorrect method of attachment was noted in 80% of the primigravida mothers as compared to 25% in multigravida. Following the teaching of the correct method over the next 2 days, figures dropped to 36% in primigravida group and 5% in multigravida group. So, the intervention was helpful in the mothers to continue with the breastfeeding.

**Conclusion:** All mothers, especially first time mothers require additional support during the first few days to successfully establish breastfeeding.

### Estimation of endotracheal tube size and insertional length in neonates

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**Background:** Optimal positioning of the endotracheal tube (ETT) plays a vital role in management of the neonate. Mal-positioning of ETT can be associated with endo-bronchial intubation or accidental extubation<sup>1, 2</sup>. A variety of methods have been reported for predicting insertional length<sup>3</sup>. In our unit no consistent predictor was being used.

**Aim:** To audit the proportion of neonatal unit staff who could correctly predict the insertional length and size of ETT in preterm babies of various gestational age.

**Methods:** A questionnaire was distributed to all the neonatal unit staff. Results were compared with Leeds Neonatal Transport Network standard for correct intubation. A correct response of >80% was interpreted as satisfactory.

**Results:** 45 completed questionnaires were returned by nurses and doctors. 28% of junior doctors and 40% of middle grade doctors estimated the correct ETT insertional length. 50% of senior nurses and 33% of junior nurses estimated the correct ETT insertional length. Nearly 90% of the nurses and 40% of the doctors got the correct ETT size.

**Conclusion:** The overall response in predicting ETT length and size was variable. Nursing staff performed better than medical staff. This highlights the need for a consistent chart which rapidly estimates ETT length and size for various gestational ages at the time of delivery. Easy access to this was achieved by laminating and attaching them to every resuscitaire.

### REFERENCES

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### Hepatic pharmacovigilance at 36 weeks corrected gestational age among babies born <1500g or <32 weeks: a scoping study using routinely collected data

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**Introduction:** Pharmacovigilance (PV) for preterm infants has been identified as a priority by the European Medicines Agency. We aimed to assess the feasibility of using routinely collected aspartate transaminase (AST) measurements in neonatal PV by exploring the extent to which AST measurements are affected by clinical circumstances.

**Methods:** Details of all infants born < 32 weeks or <1500g admitted to our Regional Neonatal Unit in 2007 were extracted from the unit database including results of blood tests closest to 36 weeks corrected gestational age.

**Results:** Of 155 eligible infants, AST was available between 35 and 36<sup>+6</sup> weeks for 34 (22%) – 16 had died, 76 were discharged

or transferred before 35 weeks and AST was not measured in 29 inpatients during the sampling period. Median AST was 27 IU/L, IQR 21-65, range 20-274. 8 (24%) infants had a level above 73 IU/L, the age-adjusted normal range for our laboratory. AST was inversely correlated with gestational age at birth ( $r_s = -0.47$ ,  $p < 0.01$ ) and weight at measurement ( $r_s = 0.42$ ,  $p < 0.05$ ) and directly correlated with CRIB score ( $r_s = 0.57$ ,  $p < 0.005$ ) and days of ventilation ( $r_s = 0.519$ ,  $p < 0.005$ ). A regression model which explained about 25% of the variance in AST showed that only days of ventilation was independently related to AST.

**Conclusions:** AST levels reflect the extent of neonatal intensive care but are likely to be influenced by other factors, including medication.

### Congenital adrenal hypoplasia presenting as sudden death: implication for siblings

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**Introduction:** Congenital adrenal hypoplasia is an uncommon cause of primary adrenocortical failure with an incidence of approximately 1 in 10-15 000 births worldwide. Transmission is either autosomal recessive or x-linked recessive by a mutation/deletion of the DAX-1 gene. The condition typically presents in the neonatal period with symptoms of adrenal insufficiency including salt wasting, failure to thrive, hyperpigmentation and hypoglycaemia. We describe two cases with a more unusual presentation.

**Case 1:** This neonate was born by normal vaginal delivery with no complications. He presented at 27 hours of age with sudden collapse and apnoea. He was extensively resuscitated, including being given intravenous dextrose and hydrocortisone. A cardiac output was achieved an hour after the initial collapse, however, after a difficult course on the neonatal unit, intensive care was withdrawn at 62 hours of age. The diagnosis of congenital adrenal hypoplasia was made on post mortem examination.

**Case2:** This newborn was delivered by caesarean section due to failure to progress. He was initially tachypnoeic and was started on antibiotics in view of maternal pyrexia. At eleven hours of age he became apnoeic. The cardiac arrest team was called but despite vigorous resuscitation he was declared dead at twelve hours of age. His blood cultures were negative and post mortem revealed the diagnosis.

**Conclusion:** As this condition is eminently treatable, the importance of diagnosing congenital adrenal hypoplasia in existing and future siblings is paramount. We have, therefore, made suggestions on how to manage these siblings from birth and what investigations are necessary to confirm or refute the diagnosis based on our experiences.

### Association of necrotising enterocolitis with elective packed red cell transfusion for anaemia of prematurity: does it exist?

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**Objectives:** A recently published study (1) suggested an association between elective packed red blood cell transfusion and necrotising enterocolitis in stable, growing preterm infants. The aim of the study was to explore this association further.

**Methods:** A retrospective data analysis was conducted on all admissions to our tertiary referral unit between January 2001 and July 2006 who had a diagnosis of definite (Stage  $\geq$  II) necrotising enterocolitis (NEC). Ethical approval was obtained prior to the study being undertaken.

**Results:** 7935 infants were admitted to our unit over the 67 month study period, 4833 (61%) preterm (< 37 weeks gestation). Definite NEC was diagnosed in 37 (0.8%) preterm infants. 793 preterm infants received a total of 2191 packed red cell transfusions (median 2, range 1-12) during the study. Seven babies developed NEC within 48 hours of a packed red cell transfusion, but only 1 was a stable, growing infant in our high dependency unit.

**Conclusion:** It is unlikely that an association exists between NEC and blood transfusion. Prospective observational studies are warranted given the significance of this issue.

### REFERENCE

- 1 Mally P, Golombek SG, Mishra R et al. Association of necrotising enterocolitis with elective packed red blood cell transfusion in stable, growing, premature neonates. *Am J Perinatol* 2006; **23**: 451-58.

### Transfusion-associated neonatal necrotising enterocolitis: a case control study

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**Introduction:** A particularly fulminant form of necrotising enterocolitis (NEC) has been anecdotally reported following elective red blood cell transfusions in babies but is poorly characterised. We describe the epidemiological and clinical features of NEC developing soon after transfusion.

**Methods:** All cases of NEC at the Royal Shrewsbury Hospital (5100 births per annum) between January 2006 and June 2008 were identified from the discharge records. NEC was defined by the presence of characteristic symptoms and signs plus at least one of the following features - pneumatosis intestinalis, portal venous air, persistent sentinel loop or surgical evidence of bowel necrosis. We compared the demographic, clinical and haematological features of babies with transfusion-associated NEC (NEC occurring within 48 hrs of a transfusion -TaNEC) with those with nontransfusion NEC (no transfusion within preceding 48 hrs of onset of NEC - non-TaNEC). In a separate case-control study, clinical and haematological features of infants with TaNEC were compared with contemporaneous gestation-matched infants receiving transfusions but without occurrence of NEC.

**Results:** During the study period, 12 infants met the study criteria for NEC, 3 (25%) of whom had TaNEC. During the same period, 74 babies received 189 transfusions. There were no statistically significant demographic differences between TaNEC and non-TaNEC infants, although NEC tended to be late-onset in the former. Median (range) transfusion-to-NEC interval was 6.3 h (2.1-10.5) in TaNEC group compared to 113 h (81.5-471.5) in non-TaNEC cohort ( $p=0.03$ ). The median (range) pre-transfusion haemoglobin (g/dl) was 8.6 (6.7-10.5) among TaNEC infants compared to 10.2 (5.8-11.2) among non-TaNEC infants, and 9.6 (6.7-13.9) among non-NEC transfused infants. All transfusions in non-TaNEC and matched transfused control

group were for specific symptomatic indications whilst 2 of the 3 TaNEC asymptomatic infants developed NEC following elective transfusion purely for haemoglobin replacement. Two infants with TaNEC and 3 with non-TaNEC died.

**Conclusions:** Transfusion-associated NEC occurred in 4.1% of transfused infants, and accounted for 25% of all NEC during the study period. Asymptomatic stable growing preterm infants transfused solely for low haemoglobin seem particularly at risk of this fulminant disease. A very short transfusion-to-NEC interval among TaNEC infants suggests a possible widespread gut shock. ◆