Leading Article

Respiratory distress syndrome of the newborn

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Neonatal respiratory distress syndrome (NRDS) primarily occurs in premature infants and is one of the commonest causes of respiratory failure of the newborn[1].

Epidemiology and risk factors

The incidence and severity of NRDS is inversely related to gestational age and birth weight[2]. Whilst 60-80% of neonates born earlier than 28 weeks of gestation and 15-30% born at 32-36 weeks of gestation develop NRDS, it is rare in those more than 36 weeks of gestational age[2]. The incidence of NRDS is 80% for infants weighing <750g at birth and 55% for infants weighing 750–1000g[1]. Other risk factors include maternal diabetes, caesarean delivery, asphyxia, multiple births, precipitous delivery, cold stress and a maternal history of previous affected infants[2]. In contrast, incidence of NRDS decreases with prolonged rupture of membranes, chronic pregnancy associated hypertension and antenatal corticosteroid prophylaxis[2].

Patho-physiology

The primary cause of NRDS is impaired surfactant synthesis and secretion, which leads to atelectasis, ventilation-perfusion (V/Q) mismatch and hypoventilation resulting in hypoxaemia and hypercarbia[2]. The relative deficiency of surfactant decreases lung compliance and functional residual capacity with an increase in the dead space[2]. The combination of hypercapnia, hypoxia, and acidosis cause pulmonary arterial vasoconstriction, leading to shunting of blood from right to left[3]. Progressive injury from atelectrauma, volutrauma, ischaemia and oxygen toxicity results in impaired endothelial and epithelial integrity with leakage of proteinaceous exudate and formation of hyaline membranes[2]. Severe NRDS has been associated with an increased incidence of chronic lung disease, retinopathy of prematurity (ROP) and neurological impairment[4].

Diagnosis

Clinical features

Clinical manifestations of NRDS present within minutes to hours of life. If left untreated, progressive worsening is noted over the first 48 hours[2]. Increased work of breathing manifests as grunting, tachypnoea, nasal flaring, intercostal and subcostal recessions, along with diminished breath sounds on auscultation[2]. Cardiovascular manifestations, including cyanosis due to right-to-left shunting, pallor and reduced pulse volume may also be seen[3]. Apnoea and irregular respiration are ominous signs which require immediate intervention[2]. Untreated patients may also have ileus and oliguria[2]. Death can result from severe impairment of gas exchange, pneumothorax, interstitial emphysema, pulmonary haemorrhage or intraventricular haemorrhage (IVH)[4]. Diuresis is typically noted if there is improved lung function[3].

Laboratory findings

Arterial blood gas analysis may reveal hypoxaemia and hypercapnia, which worsen with delayed treatment and lead to mixed respiratory and metabolic acidosis[2]. Hyponatraemia is noted in the background of oliguria due to increased free water[3].

Radiological findings

Characteristic radiographic features are found on the chest radiograph (CXR)[5]. A normal CXR at 6 hours of age excludes the diagnosis of NRDS[5]. In the past, a grading system was used to classify the severity of the disease[6,7]. This included five stages; Stage 0: clear lungs, normal condition. Stage 1: nonspecific; greater than normal appearance of air bronchogram involving at least two lobes. Stage 2: diffuse air bronchogram accentuated by peri bronchial atelectasis involving all lobes. Stage 3: diffuse air bronchogram with definite alveolar opacification; a dense reticular pattern involving more than 50% of total lung field. Stage 4: total white-out of the lungs, alveolar opacification involving majority of lung fields. However,

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currently most centres use a simpler classification system[5]. This method incorporates a radiological spectrum ranging from mild, moderate to severe, which correlates with clinical findings[5,8]. It is well established that ultrasound scan of the chest has high diagnostic sensitivity although infrequently used[9]. It is able to detect lung consolidation, atelectasis and alveolar interstitial syndrome or white-lung changes[5].

Management

Any baby delivered preterm is at risk of developing NRDS. Therefore, these babies should be delivered at centres with appropriate equipment and experience in managing NRDS[10]. Management strategies are aimed at preventative interventions, in addition to specific and general measures to improve short as well as long term outcomes.

Antenatal corticosteroid (ACS) administration

Females at an increased risk of preterm delivery should be given ACS. This may be any time during 24 to 34 weeks of POA. The optimal effect of ACS is noted from 24 hours up to 7 days post administration[11,12]. Ideally birth should be delayed to allow maximum benefit of ACS treatment[10]. Though repeated doses of ACS reduce NRDS and morbidity from chronic lung disease, concerns regarding development of cystic periventricular leukomalacia, neuro-developmental abnormalities at 2 years of age and reduced water content of solid organs of the fetus remain to be rectified[13]. Therefore, RCOG guidelines recommend a single course of antenatal corticosteroids between 24 0/7 weeks and 34 6/7 weeks and to all patients for whom an elective caesarean is planned prior to 38 6/7 weeks[14].

Delivery room stabilization

Current practice emphasizes stabilization rather than resuscitation of the preterm infant[11]. The 2016 European Consensus Guidelines on management of NRDS recommend that training courses on newborn resuscitation be designed to stress the importance of allowing for gradual transition of the preterm infant to extra-uterine life, instead of using aggressive interventions that are usually performed on term infants born in terminal apnoea due to prolonged hypoxia[11]. Delayed cord clamping allows for smoother transition of the baby[14]. Umbilical cord milking is now an accepted alternative method in preterm infants[11]. The baby should be delivered into a plastic bag if born less than 32 weeks of gestation[15]. This method, followed by keeping the baby under a radiant warmer, ensures the maintenance of temperature[15,16]. If there is a need to deliver inflation breaths, air or blended air/oxygen (30-40%) is better than the use of 100% oxygen[11,15]. Following stabilization, oxygen saturation should be maintained between 90 and 95%[10].

Assisted ventilatory support

Respiratory support is invariably required once a preterm baby is delivered and it should not be delayed in order to prevent atelectasis[17]. Although various modes of assisted ventilatory techniques exist, non-invasive modes are the recommended means of initial intervention. These non-invasive modes maintain positive end expiratory pressure (PEEP) in a spontaneously breathing preterm infant requiring respiratory support[16]. This includes providing nasal continuous positive airway pressure (nCPAP) of 6-8 cm H_2O using a T-piece device[11]. CPAP initiated at the delivery room is considered to be superior to intubation and surfactant administration within the first hour of birth, with regards to long-term respiratory morbidity[18,19]. Therefore, nCPAP should be started from birth to all babies at risk of NRDS[10]. Additionally, early nCPAP delivery is found to have a lower incidence of air leak, grade III and IV intraventricular haemorrhage (IVH) and mortality rate[20].

Alternatively, the use of nasal intermittent positive pressure ventilation (NIPPV) is utilized as an initial treatment modality, as this method has the extra benefit of delivering ventilator driven mandatory breaths, while avoiding the possibility of trauma if intubated. In addition to providing PEEP, this method is beneficial in a preterm infant with poor respiratory drive and effort. If a baby remains apnoeic or bradycardic, gentle positive pressure ventilation (PPV) should be administered. Mechanical ventilation (MV) during the stabilization phase is reserved only for preterm infants who do not respond to positive pressure ventilation[10].

Once stabilized, the infant with NRDS may require continuation of respiratory support. This can be provided by non-invasive methods such as nCPAP, high flow nasal cannulae (HFNC) and NIPPV or various invasive ventilation modes. HFNC has high failure rates compared to nCPAP[21,22]. NIPPV has been shown to have a reduced risk of respiratory failure and the need for intubation when compared to nCPAP, but no difference in reducing bronchopulmonary dysplasia (BPD)[23]. Intubation and ventilation is indicated when non-invasive measures fail. The aim of MV is to avoid hyper or hypocarbia, induce acceptable blood gas levels and minimize lung injury[11]. It was earlier thought that a moderate degree of hypercarbia is acceptable, provided the pH remains above 7.22[10]. However, most recently this concept has been questioned, as hypercarbia is found to be associated with adverse neuro-developmental outcomes[24,25]. Hypocarbia is

associated with increased risks of BPD and periventricular leukomalacia and therefore should be avoided[10]. Volume targeted ventilation (VTV) is the mode of choice as it shortens the duration of ventilation and reduces BPD as well as IVH[11]. Auto-weaning of pressure, as lung compliance improves, is an added benefit in VTV. When comparing different ventilator modes, a systematic review and meta-analysis disclosed that time cycle pressure limited ventilation (TCPL), high frequency oscillatory ventilation (HFOV), synchronized intermittent mandatory ventilation plus volume guarantee (SIMV + VG), and volume controlled (V-C) ventilation modes were associated with lower mortality in comparison to synchronized intermittent mandatory ventilation plus pressure support ventilation (SIMV + PSV) mode[26]. However, this volume targeted mode is still widely used as therapy for NRDS. After extubation, shifting to a non-invasive mode of ventilation such as nCPAP (with or without pressure support) is recommended as it is effective in preventing extubation failure after MV[27].

Exogenous surfactant therapy

It has long been established that surfactant is effective in reducing mortality of NRDS[28,29]. Traditionally, prophylactic surfactant was used in preterm babies, but it is no longer recommended, as nCPAP is used routinely from birth[30]. Instead, early selective surfactant administration is recommended for infants with signs of NRDS. Natural surfactant preparations are superior to synthetic ones, as it has been shown to be associated with a need for lesser FiO_2 and pressures, as well as reduced mortality due to NRDS[31]. Surfactant should be given early to any baby who develops NRDS with a FiO_2 requirement of more than 30% (if <26weeks) or more than 40% (if >26weeks) at 2 hours of age while on nCPAP[11].

For mature babies who do not require MV, the INSURE technique (INtubate—SURfactant—Extubate to CPAP) was advocated until recently, but newer and safer methods have now been introduced[10,32-34]. Less invasive surfactant administration (LISA) by using a fine flexible catheter placed in the trachea and minimally invasive surfactant treatment (MIST) which uses a more rigid catheter, are newer methods currently used widely in Europe and Australia. However, the feasibility of either of these methods in the local set-up is rather doubtful. In low income countries it is far more cost-effective to administer surfactant after the baby is stabilized in the NICU, intubated and tube placement confirmed on CXR. After the initial rescue dose, surfactant can be repeated if there is ongoing evidence of NRDS.

Other therapeutic measures

Administration of caffeine citrate for babies with apnoea or to facilitate weaning from MV is standard practice in countries where the drug is available[10]. The standard dose of caffeine citrate is 20 mg/kg loading dose and 5–10 mg/kg/day maintenance. Although previously used as a treatment modality, most recent evidence based studies show inhaled nitric oxide is not beneficial to extreme preterm infants in managing NRDS[35].

Supportive care

Optimal supportive care to maintain homeostasis is of paramount importance for a favourable outcome in NRDS. Prevention of hypothermia by maintaining body temperature between 36.5-37.5^{o}C, providing adequate cardiovascular stability by avoiding high pressures delivered through positive pressure ventilation which can hinder venous return, monitoring blood pressure and maintaining mean arterial pressures, sustaining a careful fluid balance towards a slightly negative equilibrium are areas in management which need special attention[10]. Intake of sodium should be restricted over the first few days of life to improve outcome and it may be withdrawn when NRDS status improves which is heralded by the onset of diuresis[11]. Antibiotics should be started but it must be stopped when sepsis has been excluded[9]. Aggressive nutritional support through parenteral nutrition need to be commenced from birth with the introduction of breast milk as early as possible.

Prognosis

Although mortality and morbidity due to NRDS has improved over time, complications which arise due to PPV and oxygen supplementation still persist. Pulmonary air leaks which occur from over-distended alveoli is a common acute complication of NRDS. Atelectasis with contralateral lung hyperinflation from improper endotracheal tube placement and IVH due to aggressive PPV and hypocarbia are also notable complications in the acute setting[18,37]. The main long-term complication remains BPD with many studies focusing on management strategies to reduce its incidence[35,36]. By linking concepts of gentle ventilation to avoid volutrauma and barotrauma along with steps to minimize oxygen toxicity, current practices hope to achieve best outcomes for infants with respiratory distress syndrome.

In summary, NRDS remains as the commonest acute respiratory problem faced by preterm infants. Current practices aim at early identification of babies at risk of developing NRDS in order to provide the best treatment. Management strategies include preventative measures, specific treatments and supportive care. Preventative actions are aimed

at optimum timing and dosing of ACS administration to the mother, while using various obstetric measures to delay the time of delivery. Specific treatment includes stabilization of the infant at birth rather than resuscitation in order to allow gradual transition into extra-uterine life. This is achieved by delayed cord clamping/cord milking, providing respiratory support via nCPAP from birth onwards and maintaining target FiO2 and body temperatures. Furthermore, once stabilization has been achieved, other specific treatment modalities are focused on providing individualized further respiratory support and surfactant administration. Newer evidence-based treatment strategies are implemented worldwide and local neonatal facilities are improving nationwide in Sri Lanka. Therefore, it is essential for paediatricians to be updated with best practice methods in order to yield better short as well as long term outcomes in neonates who suffer from NRDS.

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