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Review Article

Review of Neonatal Respiratory Distress Disorder

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Abstract

Introduction: Transition from fetal life to neonatal life at the time of delivery involves major and rapid changes in the cardiorespiratory system physiology. These changes are essentially due to the shifting the site of gas exchange from placenta to lungs. About 10 percent of neonates fail the process of transition by their own and demand resuscitative efforts.

The aim of work: Clinical features and general guide for evaluation and management of common causes of respiratory distress in neonates will be provided.

Methods: This article is a review based upon a comprehensive search of medical literature regarding respiratory distress in neonate.

Conclusion: The presumptive clinical diagnosis depends mainly on the course of the presentation (history) and radiographic findings rather than the presentations themselves. The initial step in management of neonate with respiratory distress is the use of continuous positive airway pressure (CPAP) regardless of the cause. Low supplemental oxygen could be added to relieve the distress or cyanosis, if needed. The recommended target of oxygen saturation is between 90 and 95 percent. If PPHT is the suspected cause of distress, SpO2 level should be maintained at 95, at least.

Keywords: *Neonatal Respiratory Distress; RD Evaluation; Diagnosis; Management; Oxygen Therapy*

Introduction

Transition from fetal life to neonatal life at the time of delivery involves major and rapid changes in the cardiorespiratory system physiology. These changes are essentially due to the shifting the site of gas exchange from placenta to lungs. Successful shift requires, and involves, replacement of alveolar fluid with air, onset of regular breathing, and Increase in pulmonary blood flow [1]. The increase in lungs blood flow is a consequent of increased systemic vascular resistance (SVR) and decreased pulmonary vascular resistance (PVR). As a results, arterial oxygen tension (PaO_2) raises from 25 to 60 - 80 mm Hg during the first minutes of neonatal life [2].

About 10 percent of neonates fail the process of transition by their own and demand resuscitative efforts. Failure of transition leads to respiratory distress immediately after birth, which is mainly attributed to abnormal respiratory function during the transition. Clinically, this appears as tachypnea, nasal flaring, intercostal or subcostal retractions, audible grunting, and/or cyanosis. These could be transient that resolve quickly with no sequelae, or persistent, which necessitate a rational diagnostic and therapeutic approach to optimize out-

come and minimize morbidity. Although the failure of transition may be caused by several disorders, there are three main conditions frequently encountered in delivery room and neonatal units: respiratory distress syndrome (RDS), transient tachypnea of the newborn (TTN), and persistent pulmonary hypertension of the newborn (PPHN).

In this review, clinical features and general guide for evaluation and management of common causes of respiratory distress in neonates will be provided. Detailed management of distinct disorders is not the focus of this article.

Methods

This article is a review based upon a comprehensive search of medical literature. The main databases used in search were PubMed and google scholar. Crossruff was used to check the result of search. The output of search were screened; only relevant studies were included. The terms used in the search include Neonatal respiratory distress, evaluation, diagnosis, management, treatment, oxygen therapy.

Pathophysiology

Pulmonary surfactants promote alveolar stability by decreasing the required pressure to keep the alveoli inflated. In respiratory distress syndrome (RDS), pulmonary surfactants are deficient and the infant is unable to generate higher pressure to maintain alveolar inflation. Hence, progressive and diffuse atelectasis occurs [3]. Diffuse atelectasis leads to low compliance and low functional residual capacity which lead to hypoxemia and distress. Failure of adequate fluid clearance may also play a role in RDS pathogenesis, especially in preterm [4]. Genetic predispositions were also proposed [5].

Normally, fluid clearance from the lungs should occur at birth to ensure successful transition. For clearance, fluids moves from the air spaces into interstitial space whereby it is cleared by the lymphatic or vascular circulation. Failure of adequate fluid clearance is believed to be the main pathology of transient tachypnea of the newborn (TTN). The exact pathogenesis is uncertain, however, several hypothesis were proposed to explain failure of fluid clearance. Inadequate activation of amiloride-sensitive sodium channels may leads to insufficient osmotic gradient across the pulmonary epithelium essential for water move [6]. Preterm infants are more affected by low activity of airway epithelial sodium channels as it appears later in fetal life [4]. Another normal mechanism that may be impaired is hydrostatic pressure gradient caused by lung inflation.

Adequate transition to neonatal life should encompass marked decrease in pulmonary vascular resistance (PVR). Hence, as suggested by its name, persistent pulmonary hypertension (PPHN) entails abnormal persistence of elevated PVR. High PVR, in the presence of foramen ovale and patent ductus arteriosus, causes right-to-left shunt of deoxygenated blood, which is reflected by hypoxemia. Failure of decrease in PVS could be attributed to a combination of underdevelopment, maldevelopment, or maladaptation of the pulmonary vascular bed.

Clinical features

Despite considerable overlap, characteristic clinical features may aid distinguishing the three common causes of respiratory distress: respiratory distress syndrome (RDS), transient tachypnea of the newborn (TTN), and persistent pulmonary hypertension (PPHN).

Respiratory distress syndrome (RDS) occurs almost always in preterm neonate. The features of distress start to appear at birth, or shortly after. Typical signs include grunting, nasal flaring, and intercostal and subcostal retractions. The early interventions render typical features and course of RDS less frequent. These include antenatal glucocorticoid, surfactant therapy, and/or administration of continuous positive air pressure (CPAP) or positive end-expiratory pressure (PEEP) in the delivery room [7].

On the other hand, late preterm neonates delivered by elective caesarean section between 34 and 37 weeks of gestation are the classic cases of TTN [8]. This does not eliminate the possibility of TTN in term and postterm neonates. Usually, TTN manifests within two hours

after delivery. The most prominent finding is tachypnea with a respiratory rate ≥ 60 per minute. Nasal flaring, intercostal and subcostal retractions, and expiratory grunting may also present; but mild and resolve earlier than tachypnea. Mils cyanosis may be also observed and usually disappears with low concentrations of supplemental oxygen. Transient tachypnea of the newborn frequently resolves within 24 hours; longer course up to 72 is less frequently seen.

Persistent pulmonary hypertension (PPHN) classically affects term infants. Nevertheless, late preterm and postterm neonates could be affected as well. Very low birth weight (VLBW) infants, when birth weight is < 1500, are rarely affected by PPHN. Tachypnea, cyanosis, and differential pre- and postductal saturation are common findings. Blatant metabolic acidosis may occur when PPHN is associated with sepsis, meconium aspiration syndrome, and congenital diaphragmatic hernia; due to lactic acidosis from poor perfusion or severe hypoxemia.

Evaluation and diagnosis

The presumptive clinical diagnosis depends mainly on the course of the presentation (history) and radiographic findings rather than the presentations themselves; due to overlap in clinical findings among the different conditions.

By history, the infant's gestational age, mode of delivery, risk of infection, and associated complications could be obtained and greatly aid the process of diagnosis. The risk of RDS increases with the decrease in gestational age. Infants of diabetic mothers are especially at higher risk compared with control infants. TTN typically affects preterm infant delivered by caesarean delivery. This could be explained by the lack of physiologic mechanisms facilitate fluid clearance from the lungs, which occur with labor. History of meconium-stained amniotic fluid and perinatal depression is suggestive PPHN. Additional risk factors for PPHT include bacterial infection, poor intrauterine growth, abnormal patterns of fetal heart rate, and inadequate placental function. Echocardiography is essential to distinguish cyanosis due to PPHT from that of congenital heart disease, even with suggestive features of PPHT.

Chest radiographic imaging is essential tool in evaluating neonatal respiratory distress and aids differentiating incriminated disorders. Chest image in infant with RDS classically shows a diffuse ground glass appearance with air bronchograms, and low lung volume. These finding are caused by atelectasis occurred with RDS. Infants with TTN usually demonstrates characteristic perihilar linear streaking bilaterally; caused by engorged lymphatic or blood vessels. Fluid retention may also appear as patchy infiltrates and usually clear within 24 to 48 hours. Sometime, these infiltrates render the distinction between TTN and pneumonia challenging. Lung ultrasound has been proposed as an imaging technique for reliable early diagnosis and differentiation of TTN [9]. Chest radiograph of infant with PPHT differs according to precipitating lung disease and may show normal size or large heart. If there is no other lung condition, the lung fields usually clear with decreased pulmonary vascularity.

Ultrasonography on chest has been proposed to differentiate RDS from TTN, and to predict failure of noninvasive CPAP ventilation [10]. Sever hypoxia and cyanosis prompt the use of echocardiography to exclude structural heart disease.

Management: general approach

The initial step in management of neonate with respiratory distress is the use of continuous positive airway pressure (CPAP) regardless of the cause. Low supplemental oxygen could be added to relieve the distress or cyanosis, if needed. Pulse oximetry should be applied continuously to monitor oxygen saturation. The recommended target of oxygen saturation is between 90 and 95 percent. If PPHT is the suspected cause of distress, SpO_2 level should be maintained at 95, at least. Assisted ventilation, via CPAP or endotracheal intubation, may be needed should respiratory failure developed. Respiratory failure is evident with hypoxia (arterial PaO_2 < 50 mmHg) despite oxygen supplementation, respiratory acidosis (arterial pH < 7.2 and $PaCO_2$ > 60 mmHg), and severe apnea.

Clinician should be aware of the harming effects of high oxygen concentrations and hyperoxia. Excessive management with oxygen contributes to oxygen toxicity, which causes bronchopulmonary dysplasia (BPD) and retinopathy. Hence, the goal is to fulfill the metabolic needs of the infant (avoid hypoxia), and to limit the concentration to sufficient level (avoid hyperoxia). It is worthwhile mentioning that the optimal range of SpO_2 for different gestational age remains controversial, despite several trials [7,11]. In 2000, the Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) trial suggested that oxygen saturation between 96 and 99 in preterm infants was associated with greater morbidity compared with a lower range of 89 to 95 [12]. Other large trials had included thousands of infant and compared similar protocol of oxygen therapy (91-95 versus 85-89) to determine the optimal goal of SpO_2 for extremely preterm infants [13-15]. Low SpO_2 target was associated with a higher incidence of necrotizing enterocolitis (NEC), higher risk of patent ductus arteriosus requiring surgery, and lower incidence of ROP requiring treatment, according to systematic reviews on these trials [16-18]. However, no difference in the combined outcome of death and major disability at 24 months corrected age was observed between the two ranges of oxygen saturation [16,18,19]. Some experts argue that the conclusion of the systematic reviews should be interpreted carefully because there was significant overlap in the oxygen saturation between the two groups despite the design of the trials specifying separation between the target ranges.

Blood gases should be ordered to check for respiratory or metabolic acidosis. Complete blood count (CBC) and blood culture are routinely ordered. Chest imaging assists the diagnosis and is essential for the follow-up to identify complications. The infant should be kept in a neutral thermal environment to reduce energy and oxygen consumption and avoid hypothermia. Fluid infusion maintain the hydration status of the infant until feeding is possible.

The presence of risks factor for infection or sepsis and progressive respiratory distress despite oxygen should prompt empirical antibiotics. Typically, ampicillin and gentamicin are the agent of choice. Subsequently, the results of blood culture, the definite diagnosis, and the clinical course should guide antibiotic therapy. The dose of antibiotic should be tailored with gestational age.

Management: Specific consideration of RDS

Certain procedures and techniques are applied for reducing the severity of RDS or avoid it. These techniques include antenatal corticosteroid administration (ACS), positive airway pressure delivery, and surfactant therapy replacement.

Antenatal corticosteroid therapy

It is highly recommended to administer ACS for high-risk preterm delivery pregnants at 23 to 34 gestational weeks to protect preterm infants from RDS development or progress. ACS importance is related to promoting the synthesis and release of the surfactant, which is essential for fetal lung maturity.

Assisted ventilation techniques

Respiratory support is necessary to apply for the preterm infants at the greatest risk of RDS. The best way to provide positive end-expiratory pressure (PEEP) by nasal continuous positive airway pressure (nCPAP) modality, then nasal intermittent positive pressure ventilation (NIPPV). Both (nCPAP and NIPPV) are considered less invasive methods that endotracheal intubation and mechanical ventilation, which help in reduce the risk of complications as atelectasis. However, some cases do not respond to (nCPAP) or (NIPPV) for that intubation and mechanical ventilation with PEEP may be required.

Nasal continuous positive airway pressure

According to the American Academy of Pediatrics (AAP), American Heart Association (AHA), International Liaison Committee on Resuscitation (ILOR) guidelines, and the European Consensus Guidelines, initially providing of nCPAP for preterm infants who had RDS or at

risk is a better intervention than the combined regimen of surfactant therapy, endotracheal intubation and mechanical ventilation [20,21]. Several studies have revealed that CPAP is more effective with a lower risk of bronchopulmonary dysplasia (BPD) and lower mortality [22]. It is essential to use nCPAP when patients extubated because it reduces the side effects of intubation as apnea, respiratory acidosis and increased oxygen need; and that the main approach in our center to avoid the need for intubation.

Recent reviews of multicenter have recommended for early administration of caffeine as it increases the respiratory drive for preterm low birth weight infants (BW< 1000g), who are at risk of BPD development. However, a subgroup large multicenter study stated that caffeine treatment did not reduce the risk of CPAP failure [23]. Failure of CPAP is defined as Ph < 7.2 or needs of oxygen supply on FiO2 ≥0.40.

The incidence of death or BPD was increased in neonates, who do not respond to CPAP apart from GA compared with those who respond successfully to CPAP. Nasal intermittent positive pressure ventilation (NIPPV) is a method of PPV delivery through nasal prongs (or nasal mask). According to that, nCPAP is considered less costly as it is administered bubble device, whereas NIPPV needs a ventilator.

Surfactant therapy

It is an effective method to reduce RDS mortality and morbidity in preterm infants (< 30-week gestation). Also, several clinical trials reported that surfactant replacement therapy compared with placebo has shown a reduction of RDS complications such as BPD, emphysema, and pneumothorax [24]. Important issues to be considered when the surfactant therapy is administered include the type of surfactant preparation, indications for surfactant therapy, time to administer surfactant therapy, and technical issues of administration.

There are two types of surfactants, synthetic and natural which is superior to the synthetic one because it contains protein B and C analogs [21]. Subsequently, the use of natural preparations has shown a reduction in oxygen consumption, the mortality rate, and complications of RDS in preterm infants. In the USA and Canada, natural surfactant preparations are obtained from: [25] Poractant alfa (porcine lung minced extract); Calfactant (Bovine lung lavage extract); Beractant (bovine lung minced extract); Bovine lipid extract surfactant (bovine lung lavage extract). Dipalmitoylphosphatidylcholine (DPPC) is the primary surface-active component that lowers alveolar surface tension.

Although the US Food and Drug Administration (FDA) approved the first synthetic peptide-containing surfactant [26], it has not yet been available because of its manufactures had stopped production of it.

A lot of studies and efforts try to produce a developed synthetic surfactant, which contains both protein B and C analogues [27].

According to the 2014 American Academy of Pediatrics (AAP) and the European Consensus Guidelines (ECG) recommendations, the main approach is to provide nCPAP to all patients with RDS. However, infants with persistent severe respiratory distress or apneic are more effective to apply intubation and surfactant replacement [20,21]. The effective time of administered the surfactant therapy must be balanced with the time for into trial of nCPAP.

In patient with a persistent need of FiO2 > 0.30, additional doses of surfactant therapy are administered. However, if the infant is stable and has an FiO2 < 0.30, then no need for additional doses of surfactant and can be extubated to m CPAP [24].

Additionally, surfactant therapy would be highly effective if it is administered with 30 to 60 minutes of life following placement of the pulse oximeter and endotracheal tube correctly [24].

Conclusion

Despite considerable overlap, characteristic clinical features may aid distinguishing the three common causes of respiratory distress. Hence, the presumptive clinical diagnosis depends mainly on the course of the presentation (history) and radiographic findings rather

than the presentations themselves. In addition, early interventions such as antenatal glucocorticoid, surfactant therapy, and/or administration of continuous positive air pressure (CPAP) render features and course of RDS less frequent.

The initial step in management of neonate with respiratory distress is the use of continuous positive airway pressure (CPAP) regardless of the cause. Low supplemental oxygen could be added to relieve the distress or cyanosis, if needed. The recommended target of oxygen saturation is between 90 and 95 percent. If PPHT is the suspected cause of distress, SpO_2 level should be maintained at 95, at least.

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