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# **Respiratory Distress and Management Strategies in the Newborn**

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Additional information is available at the end of the chapter

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## **Abstract**

Approximately 10% of neonates require respiratory support immediately after delivery due to transitional problems or respiratory disorders, and up to 1% of neonates are in need of resuscitation. Respiratory distress is the most frequent cause of neonatal intensive care unit (NICU) admission, and the individual management strategies should be the main task in NICUs for these infants. Regardless of the cause, if not recognized and managed in advance, respiratory distress can escalate to respiratory failure and cardiopulmonary arrest. This chapter explores the evaluation and differential diagnosis of respiratory distress in neonates and presents an update on management strategies according to the protocol of Ankara University Children's Hospital Neonatal Intensive Care Unit.

**Keywords:** respiratory distress, newborn, transient tachypnea, respiratory distress syndrome, neonatal pneumonia, management

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## **1. Introduction**

Approximately 10% of neonates require respiratory support immediately after delivery due to transitional problems or respiratory disorders, and up to 1% of neonates are in need of resuscitation. Respiratory distress is the most frequent cause of neonatal intensive care unit (NICU) admission, and the individual management strategies should be the main task in NICUs for these infants. Fifteen percent of term infants and twenty-nine percent of late preterm infants admitted to the NICU develop significant respiratory morbidity; this is even higher for infants born before 34 weeks' gestation.

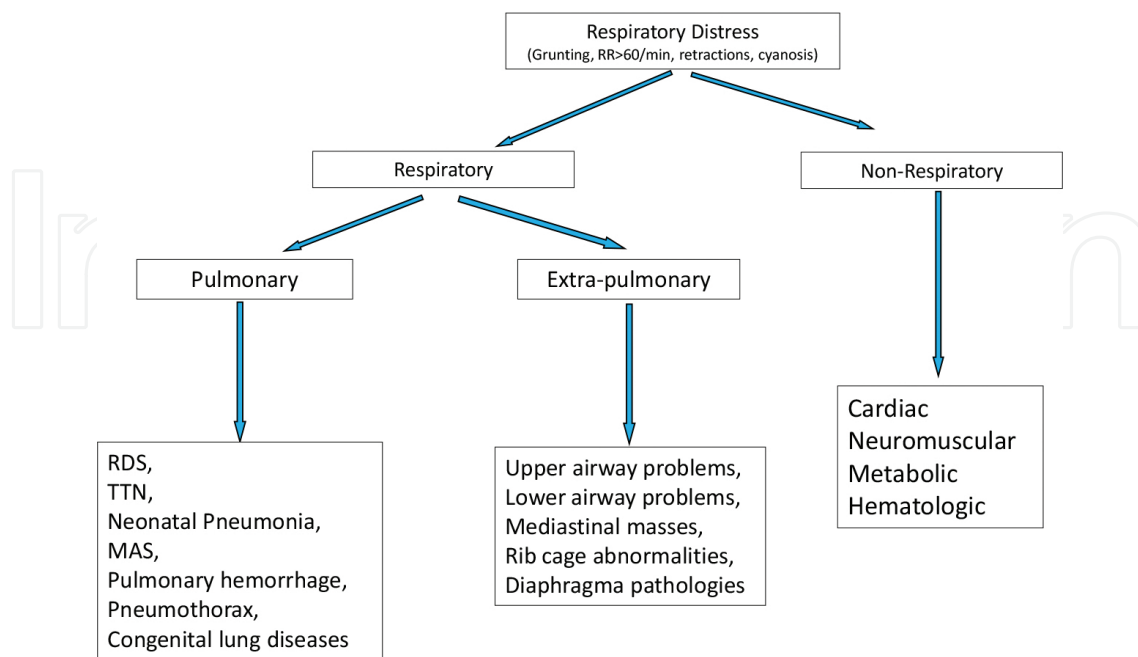
Regardless of the cause, if not recognized and managed in advance, respiratory distress can escalate to respiratory failure and cardiopulmonary arrest. Therefore, it is imperative that any health care practitioner caring for newborn infants can readily recognize the signs and symptoms of respiratory distress, differentiate various causes, and initiate management strategies to prevent significant complications or death. [1]

## 2. Evaluation of the newborn infant’s respiratory status

Respiratory distress is recognized as any signs of labored breathing in the neonate. Recognition of these signs and symptoms is important for both diagnosis and evaluation of the response to treatment [2].

A thorough history may guide in identifying risk factors associated with common causes of neonatal respiratory distress. Together with former and present obstetric history, gestational age, birth weight, presence of fetal distress, maternal diseases, medications, exposure to antenatal steroid, mode and duration of delivery, need for resuscitation, timing, and severity of signs and symptoms are all important for initial evaluation and decision making.

A detailed physical examination should focus beyond the lungs to identify non-pulmonary causes, such as airway obstruction, abnormalities of the chest wall, and cardiovascular or neuromuscular disease that may initially present as respiratory distress in a newborn [1]. Careful inspection and auscultation are important. Signs of increased work of breathing (WOB) [1], such as tachypnea, nasal flaring, retractions, bilateral and equal aeration of the lung and breath sounds, and the presence of cyanosis, should be evaluated. Noisy breathing may



**Figure 1.** Etiologies of respiratory distress in the newborns.

indicate increased airway resistance, and the type of noise auscultation such as grunting, stridor, and wheezing may help to localize airway obstruction [1].

Non-invasive pulse oximetry is recommended by the American Heart Association (AHA) guideline for neonatal resuscitation in 2015 [3] and the American Academy of Pediatrics (AAP) to screen infants for hypoxemia, and saturation oxygen (SpO<sub>2</sub>) values less than 85% are considered normal before 5 minutes of age [3, 4]. The partial pressure of transcutaneous CO<sub>2</sub> (PtCO<sub>2</sub>) is considered as an accurate estimate of both arterial and venous CO<sub>2</sub> tension in newborn [5]. Blood pressure, heart rate follow, and frequent assessment of capillary refill time also give clues about the infants' well being.

Chest X-ray can reveal congenital malformations, and intrathoracic space-occupying lesions, such as pneumothorax, mediastinal mass, and congenital diaphragmatic hernia (CDH), can compromise lung expansion [1].

Blood gas analysis may vary according to gestational age and underlying disease of the newborns. Targeted arterial blood gas values are shown in **Table 1** [6].

Gestational age	Arterial blood gas values				
	pH	PaO <sub>2</sub> (mm Hg)	PaCO <sub>2</sub> (mm Hg)	HCO <sub>3</sub> (mEq/L)	BE
<30 weeks	7.27–7.32	45–60	45–60	19–22	±4
30–36 weeks	7.30–7.35	50–70	45–55	22–25	±3
>36 weeks	7.32–7.38	60–80	35–45	24–26	±3
Term with PPHT	7.35–7.45	80–100	30–45	24–26	±3
BPD	7.35–7.45	50–80	55–65	22–25	±3

**Table 1.** Range of acceptable arterial blood gas values according to gestational age. Adapted from Ref. [4].

Neonatal respiratory distress is not due to respiratory origin. Thus, after initial resuscitation and stabilization, it is important to attain a detailed history, physical examination, and radiographic and laboratory analyses to determine a more specific diagnosis and tailor an appropriate individual management as soon as possible (**Figure 1**).

Significant tachypnea without increased work of breathing (WOB) should prompt additional laboratory investigation to identify metabolic acidosis or sepsis [1].

Most of the time it may be difficult to distinguish cardiovascular diseases from pulmonary causes of respiratory distress. Most congenital heart defects present with cyanosis, tachypnea, or respiratory distress from cardiac failure. Timing of the symptoms is an important clue for most of the conditions as very few congenital heart defects present immediately after birth [1]. Cardiac pathology should be suspected especially when there is persistent cardiomegaly, abnormal pulses, or a postductal SaO<sub>2</sub> drop.

Regardless of the cause, it is vital to recognize symptoms and act quickly. Non-specific treatment and respiratory support started even before the specific underlying diagnosis. If the

newborn cannot sustain the extra WOB to meet its respiratory needs, respiratory failure follows. This failure may manifest as impaired oxygenation (cyanosis) or ventilation (respiratory acidosis). Without prompt intervention, respiratory arrest is imminent.

### 3. Common diseases causing neonatal respiratory distress

#### 3.1. Transient tachypnea of neonate

Transient tachypnea of neonate (TTN) is a benign self-limited, common respiratory disease of term and late preterm infants due to impaired clearance of lung liquid. Rapid clearance of fetal lung fluid is a key aspect of the transitional period in the delivery room [7]. Hooper et al. [8], who used phase contrast X-ray imaging to observe the rate and spatial pattern of lung aeration at birth in rabbit pups delivered by cesarean section, found the close association of residual liquid clearance from the airways with the present inspiratory activity. They detected no significant distal movement of the air/liquid interface between breaths. These findings indicate that the transpulmonary pressure generated by inspiratory effort also plays a critical role in the airway fluid clearance [8]. The clearance of fetal lung fluid mainly depends on two mechanisms: amiloride-sensitive sodium transport through epithelial sodium channels in lung and mechanical forces created during vaginal delivery. Actually, lungs of preterm infants are less responsive to this sodium reabsorption, leading to less efficient lung fluid clearance [9]. Pathophysiology of TTN and RDS is assumed to be related to the disruption of this process [7]. In our study, we suggested the possible relationship of lower cord levels of cortisol, adrenocorticotrophic hormone, and free triiodothyronine in TTN group with fetal lung fluid clearance and hormonal modulatory effect on postnatal pulmonary adaptation [10]. Thus, interruption of this process at any step such as delivery before onset of labor or delay in the first breath may result in transition problems including TTN.

Delivery following elective cesarean section (C/S) is the main risk factor for TTN. The usual mechanisms present with the onset of labor for the clearance of lung fluid in vaginal delivery are often inadequate after elective C/S, resulting in TTN [11]. Other risk factors are delivery prior to 39 weeks of gestation, precipitous delivery, fetal distress, male sex, low birth weight and macrosomia [12], multiple gestations and maternal sedation, and maternal diseases such as gestational diabetes and asthma [13].

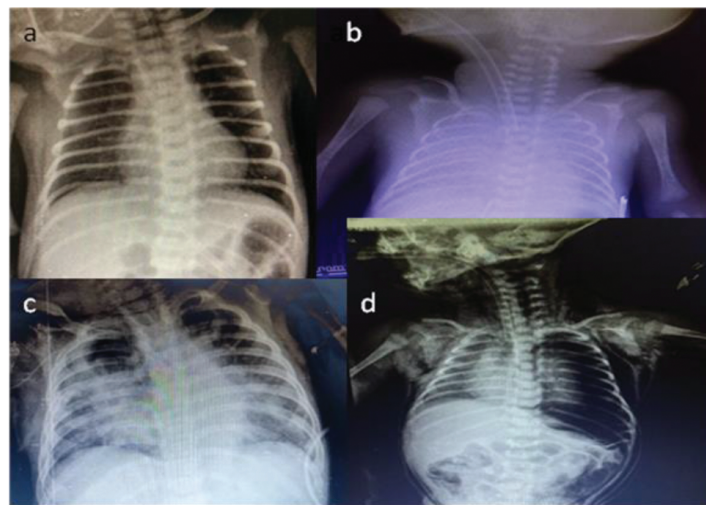
Incidence of TTN requiring ventilation is significantly reduced to each extra week in utero decreasing from 34% at 37 weeks to 0.5% at 41 weeks of gestation [14]. In European Consensus Guidelines on the Management of Neonatal Respiratory Distress Syndrome in Preterm Infants – Update 2013 [15], antenatal steroids are also considered for women undergoing a C/S prior to labor up to term. As the long-term effects are currently unknown, at present, the best course is to avoid elective C/S prior to 39 weeks wherever possible.

The infant is usually term, near term or large, and premature, and shortly after delivery or within the first 6 hours of delivery has tachypnea. It usually presents with grunting and other mild signs of respiratory distress because lung liquid inhibits gas exchange, which persists for up to 48 hours.

Continuous pulse oximetry follow-up is needed. Blood gases often reveal some degree of mild to moderate hypoxemia. Partial CO<sub>2</sub> pressure is usually normal due to tachypnea but sometimes either hypocarbia or mild hypercarbia may exist resulting in mild respiratory acidosis [16].

Complete blood count (CBC) is needed for differentiation of sepsis, neonatal pneumonia, and polycythemia because CBC is normal in TTN.

Chest radiographs reveal hyperinflation, which is a hallmark of TTN. There are excess diffuse parenchymal infiltrates due to fluid in the interstitium, fluid in the interlobar fissure, and occasionally pleural effusions. Mild to moderate cardiomegaly with flattened diaphragm and prominent pulmonary vascular markings may also be present (**Figure 2a**).



**Figure 2.** Chest X-ray of a newborn with (a) transient tachypnea of the newborn, (b) respiratory distress syndrome, (c) meconium aspiration syndrome, and (d) pneumothorax.

### 3.2. Neonatal pneumonia

Among newborns with respiratory distress, the third most likely cause after RDS (46%) and TTN (37%) is pneumonia. The incidence of pneumonia/sepsis in preterm infants with birth weight 1500–2500 g is only 0.28%, whereas in patients with birth weight <1000 g, the incidence is severalfold higher at 1.9% [17].

Respiratory infections in the newborn may be bacterial, viral, fungal, spirochetal, or protozoan in origin. Infants may acquire pneumonia transplacentally (congenital pneumonia), through infected amniotic fluid, through colonization at the time of birth, from the community or nosocomially [18]. Perinatal pneumonia is the most common form of neonatal pneumonia and is acquired at birth. Common pathogens include Group B streptococcus (GBS), gram-positive bacteria, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Listeria*, and gram-negative enteric rods (e.g. *E. coli*); and viruses, such as herpes simplex virus, respiratory syncytial virus, and influenza A & B viruses; atypical organisms, such as chlamydia; and fungi [19]. Risk factors for perinatal pneumonia include prolonged rupture of membranes (PROMs), maternal



infection (maternal fever or raised white cell count), and prematurity [19]. Birth weight and age of onset are both strongly associated with the mortality risk from pneumonia. Pneumonia can occur secondary to invasive mechanical ventilation but is largely confined to preterm infants who receive prolonged ventilation. Prevention of neonatal pneumonia and its complications focuses on maternal GBS screening, intrapartum antibiotic prophylaxis, and appropriate follow-up of newborns at high risk after delivery [20, 21]. On the other hand, the most important and easiest method of preventing nosocomial pneumonia is hand washing to prevent cross-infection and avoiding invasive ventilation [19–21].

Pneumonia in newborn infants is often difficult to diagnose and distinguish from other causes of respiratory distress including RDS and TTN. Infants present with increased WOB and oxygen requirement. In contrast to older infants and children, neonatal pneumonia is part of a generalized sepsis illness; thus, obtaining investigations including blood white cell counts, CRP even though they lack the necessary sensitivity and specificity to accurately diagnose pneumonia, blood, and cerebrospinal fluid cultures and initiating broad-spectrum antibiotic therapy is recommended for any symptomatic infant [19, 20]. Unlike TTN, RDS, and MAS, bacterial infection takes time to develop with respiratory consequences occurring hours to days after birth.

Chest radiography helps in the diagnosis with bilateral diffuse parenchymal infiltrates with air bronchograms or lobar consolidation suggesting in utero infection. Pleural effusions are present in two thirds of cases [22].

### 3.3. Respiratory distress syndrome

Respiratory distress syndrome (RDS), formerly called hyaline membrane disease, is caused by a deficiency of surfactant and is often, which strictly speaking, a histological diagnosis. The Vermont Oxford Network definition for RDS requires an arterial oxygen tension ( $\text{PaO}_2$ )  $<50$  mmHg and central cyanosis in room air, a requirement for supplemental oxygen to maintain  $\text{PaO}_2 >50$  mmHg, or a requirement for supplemental oxygen to maintain a pulse oximeter saturation over 85% and a characteristic chest radiographic appearance within the first 24 hours of life [23].

The EuroNeoNet figures for 2010 show an incidence of 92% at 24–25 weeks' gestation, 88% at 26–27 weeks, 76% at 28–29 weeks, and 57% at 30–31 weeks [24]. However, published data have shown that infants with a birth weight of  $>2500$  g account for 9.9–11.5% of infants with RDS, and those with gestational age of 37 weeks' gestation account for 7.8% [12].

Pathophysiologic mechanisms include as follows:

**A-** Surfactant deficiency increases surface tension in alveoli, resulting in microatelectasis and widespread alveolar collapse. In the absence of surfactant, the small airspaces collapse; each expiration results in progressive atelectasis. Exudative proteinaceous material and epithelial debris, resulting from progressive cellular damage, accumulate in the airway and directly decrease total lung capacity.

**B-** In the presence of a weak, compliant chest wall secondary to prematurity, the large negative pressures generated to open the collapsed airways cause retraction and floppy chest wall instead of proper inflation and stability [23].

**C-** The presence or absence of a cardiovascular shunt through a patent ductus arteriosus (PDA) may change the presentation or course of the disease.

Decreasing gestational age is inversely related to the RDS risk. Dani et al. reported the main risk factors for RDS as gestational age, low birth weight, maternal age, elective and emergency C/S, and male sex [12]. Type II cells responsible for surfactant synthesis are sensitive to asphyxia. Their maturation can be delayed with the presence of fetal hyperinsulinemia. On the contrary, administration of antenatal corticosteroids, chronic intrauterine stress due to pregnancy-induced hypertension, intrauterine growth restriction, or twin gestation enhances their maturity [23].

Preventing premature birth will lower the incidence of RDS. Prenatal steroids decrease the risk of RDS and additionally decrease the risk of intraventricular hemorrhage and NEC [24]. Twenty-four milligrams of betamethasone therapy is recommended in all pregnancies with threatened preterm labor below 35 weeks' gestation. The optimal time period between the treatment and delivery is more than 24 hours and less than 7 days after the first dose of steroid [24]. After 14 days, benefits are diminished. A single repeat course a week after the first course reduces not only RDS and other short-term problems but also birth weight [25]. Using antibiotics in the case of preterm prelabor rupture of the membranes can delay delivery [26]. Tocolytics are mainly used to allow safe transfer to a suitable perinatology center and/or enable steroid effect [27, 28].

The clinical course of the disease varies with the presence of antenatal steroid, severity of disease, size of the infant, use of surfactant, the presence of infection, and degree of shunting of blood through PDA. With modern early management, classical definition of RDS may not be achieved, and making the diagnosis on the basis of having administered surfactant may be an overestimate [23].

Infants with RDS typically present within the first several hours of life, often immediately after delivery or in the first hours of life with marked respiratory distress and significant need of supplemental oxygen. The course of RDS is self-limited and typically improves by age 3–4 days in correlation with the aforementioned diuresis phase and as the infant begins to produce endogenous surfactant.

Blood gas sampling reveals hypoxemia with hypercarbia. Without intervention, worsening of blood gases will correlate the clinical status of the patient.

Complete blood count and blood culture should be obtained from each infant as early onset sepsis can be indistinguishable from RDS.

Chest radiography typically shows uniform reticulogranular pattern, referred to as a ground-glass appearance with peripheral air bronchograms (**Figure 2b**).



### 3.4. Persistent pulmonary hypertension of the neonate

Persistent pulmonary hypertension (PPHN) is a condition characterized by marked pulmonary hypertension resulting from elevated pulmonary vascular resistance (PVR) and altered pulmonary vasoreactivity, leading to right-to-left shunting of blood through intra or extrapulmonary shunts (foramen ovale or PDA) [29]. It can be either primary or secondary due to conditions leading to hypoxemia such as RDS, congenital diaphragmatic hernia (CDH), MAS, and pneumonia. Events such as perinatal stress, hemorrhage, aspiration, hypoxia, and hypoglycemia may lead to PPHN. On the other hand, PPHN may be the result of underdevelopment of the lung together with its vascular bed (e.g., CDH and hypoplastic lungs) [19, 29]. Right-to-left shunting of blood through foramen ovale or PDA due to high PVR further contributes to systemic hypoxemia and metabolic acidemia, both of which contribute to ongoing increased PVR. Ventilation perfusion mismatching is also likely to be present compounded by conditions such as MAS [19]. Risk factors can be classified as conditions related to lungs such as MAS, RDS, pneumonia, pulmonary hypoplasia, and CDH and conditions related to other systemic disorders (such as polycythemia, hypoglycemia, hypoxia, acidosis, hypocalcemia, hypothermia, and sepsis) or some of the congenital heart diseases (total anomalous venous return and hypoplastic left heart). Perinatal asphyxia, CNS disorders, and neuromuscular diseases can also result in PPHN [29]. Resuscitation and support from birth may presumably prevent or ameliorate, to some degree, PPHN when it may occur superimposed on a preexisting condition.

Pulmonary hypertension needs to be considered in any infants with respiratory distress and cyanosis. This may occur despite adequate ventilation. It is often challenging to manage and usually presents in the first few hours of life but may present later especially when secondary to the other conditions. It is also associated with significant mortality especially if associated with CDH [30]. When PPHN occurs without concurrent pulmonary disease, differentiating from cyanotic heart disease is difficult. In an infant with pulmonary disease, PPHN should be suspected as a complicating factor when there is marked hypoxemia and liability in oxygenation. These infants may have significant decrease in pulse oximetry readings with routine nursing care or minor stress [29]. The response to ventilation with 100% oxygen (hyperoxia test) can help distinguish the two conditions. In some neonates with PPHN, the  $\text{PaO}_2$  will increase above 100 mmHg, whereas it will not increase above 45 mmHg in infants with cyanotic heart defects that have circulatory mixing [29].

Physical findings may include a prominent right ventricular impulse, a single second heart sound, and a murmur of tricuspid insufficiency. In extreme cases, there may be hepatomegaly and signs of heart failure [29].

In the presence of right-to-left shunting of blood through the PDA, a difference  $>10\text{--}15$  mmHg of the  $\text{PaO}_2$  is present between the preductal blood (from the right radial artery) and the postductal blood (obtained from other extremities or umbilical artery).

The chest X-ray differs according to the cardiac functions and the presence of pulmonary disease. Normal or decreased pulmonary vascularity and normal-sized heart or cardiomegaly can be observed [29].

Echocardiography is essential in distinguishing cyanotic congenital heart disease from PPHN because the latter frequently is a diagnosis of exclusion.

### 3.5. Meconium aspiration syndrome

Meconium is composed of lanugo, bile, vernix, pancreatic enzymes, desquamated epithelia, amniotic fluid, and mucus. Meconium is present in the gastrointestinal tract as early as 16 weeks' gestation but is not present in the lower descending colon until 34 weeks' gestation; therefore, meconium stained amnion fluid (MSAF) is seldom seen in infants younger than 37 weeks' gestation [31]. In the compromised fetus, hypoxia or acidosis may result in a peristaltic wave and relaxation of the anal sphincter, resulting in meconium passage in utero. The passage of meconium in utero results in MSAF, which may be aspirated by the fetus especially if already compromised, during gasping [19]. Any infant who is born through MSAF and develops respiratory distress after delivery, which cannot be attributed to another cause, is diagnosed as having MAS. Meconium aspiration syndrome is essentially a disease of term and post-term born infants, but an infective etiology especially from *Listeria* should be suspected in preterm deliveries associated with MSAF [19]. Meconium can cause mechanical obstruction of the airways leading to mismatched ventilation/perfusion. Meconium is toxic to the newborn lung, causing inflammation and epithelial injury as it migrates distally. The pH of meconium is 7.1–7.2. The acidity causes airway inflammation, chemical pneumonitis, and infection, which inhibits surfactant function and leads to inflammation and swelling, which also can block small airways with release of cytokines [1, 31]. As meconium reaches the small airways, partial obstruction occurs, which results in air trapping and hyperaeration. Thick MSAF, post-term gestational age, fetal distress, male sex, APGAR score <7 at 5 minutes, and oligohydramnios are the main risk factors. Previously, many post-term infants (>42 weeks' gestation) developed MAS. Reducing post-term deliveries has been shown to reduce the incidence of MAS [32]. In addition, advances in fetal heart rate monitoring have identified compromised fetuses, allowing for timely obstetric intervention that may help to prevent in utero aspiration of meconium. Amnioinfusion or transcervical infusion of saline into the amniotic cavity has been proposed, but best evidence does not indicate a reduced risk of moderate to severe MAS or perinatal death [33].

Endotracheal suctioning immediately after birth was a routine practice for all meconium-stained infants until a large randomized controlled trial found that intubating and suctioning vigorous infants born through MSAF had no benefit and increased the rate of complications [34]. This finding has been confirmed by additional, well-designed studies [35], prompting a change in practice guidelines in 2000. And recently, in the last quarter of 2015, ILCOR changed the ongoing practice of immediate endotracheal suctioning of the depressed infant (<100 beats per minute), poor muscle tone, and no spontaneous respiratory effort before positive pressure ventilation with prompt initiation of ventilation support. Intubation is considered when there is airway obstruction with no special relevance to MSAF [3].

Most of the infants with MSAF do not exhibit any sign of respiratory distress, but MAS can result in respiratory distress of varying severity immediately after birth or in the transition period. Umbilical cord staining takes 15 minutes with thick meconium and 1 hour with light

meconium. Four-to-six-hour exposure leads to staining of nails, while nearly 12 hours are needed for vernix caseosa staining [36].

Large amounts of thick meconium can result in airway obstruction, which results in apneic or gasping respirations at first, and then as it is driven down to distal airways, respiratory distress secondary to increased resistance, decreased compliance, and air trapping develop [36].

Arterial blood gas is hypoxemic. In mild cases, hyperventilation may result in respiratory alkalosis, while in severe ones, just the opposite is true with respiratory acidosis progressing into mixed acidosis.

The typical chest radiograph initially appears streaky with diffuse parenchymal infiltrates (**Figure 2c**). In time, lungs become hyperinflated with patchy areas of atelectasis, due to inactivated surfactant by the bile acids within the meconium, and alveolar distension. Pneumomediastinum, pneumothorax, and PPHN are common in MAS [1].

Pulmonary hypertension commonly develops in severe cases and should be aggressively treated. Echocardiography helps confirm PPHN.

### 3.6. Pneumothorax

Pneumothorax is an abnormal accumulation of air or gas between the visceral and parietal pleura. It develops secondary to an underlying disease process such as pneumonia, meconium aspiration, ventilation, or congenital abnormalities of the lungs. It can also occur spontaneously in 1% of newborns around the perinatal period, although only about 10% of these are symptomatic [37]. On the other hand, traumatic pneumothorax can occur due to either positive pressure ventilation (PPV) or accidental insult during a central line placement [38]. Tension pneumothorax is the life-threatening condition, requiring immediate medical attention and intervention. When the air is trapped in the pleural cavity and lung volume is decreased and increased pleural pressure causes a mediastinal shift [38].

Patients with TTN, RDS, MAS, pneumonia, pulmonary hypoplasia, urinary tract anomalies, perinatal asphyxia, and infants who were resuscitated at birth or infants receiving CPAP, PPV cardiopulmonary resuscitation, and male infants are under risk [38].

The clinical presentation may vary from mild or severe signs of respiratory distress to a gradual decline in respiratory function. In non-tension pneumothorax, signs can be variable in severity such as mild-to-moderate tachypnea, apnea, irritability, grunting, pallor, and cyanosis. In tension pneumothorax, clinical findings are very severe with definite cyanosis, hypoxia, tachypnea, a sudden decrease in heart rate with bradycardia, a sudden increase in systolic blood pressure followed by narrowing pulse pressure and hypotension, an asymmetric chest, decreased breath sounds, and shift of the cardiac apical pulse away from the affected side [38].

Blood gas can reveal hypercarbia and hypoxia with respiratory acidosis and metabolic acidosis, which may accompany in tension pneumothorax.

Anteroposterior chest radiography may show shift of the mediastinum away from the affected side, depression of the diaphragm on the same side, and displacement of the lung on the

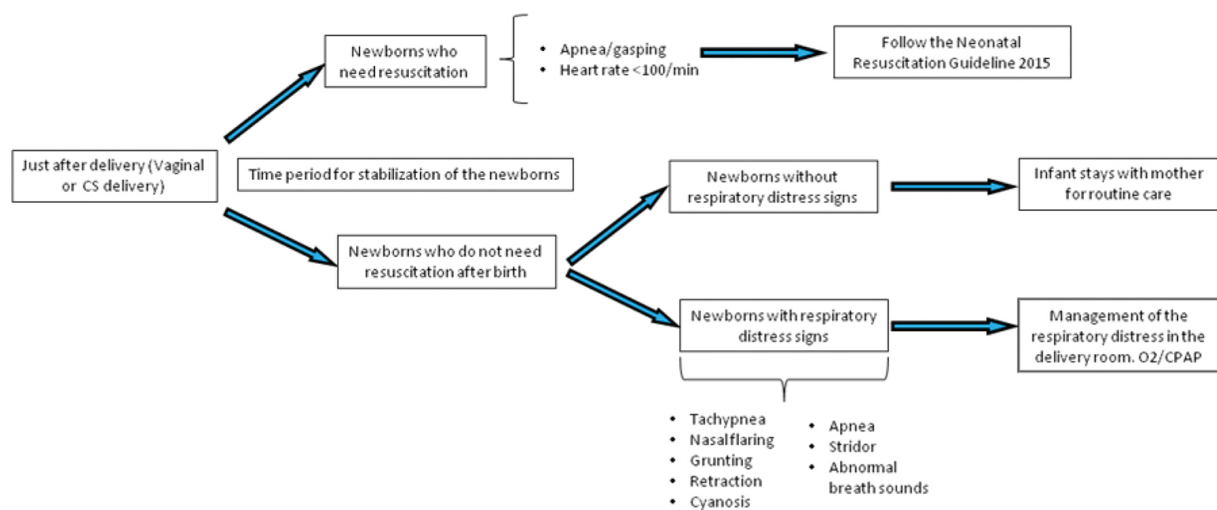
affected side away from the chest wall by a radiolucent band of air (**Figure 2d**). In cases of confusion, lateral decubitus view will detect even a small pneumothorax. The infant should be positioned so the side of the suspected pneumothorax is up [38].

## 4. Management of respiratory distress

### 4.1. Stepwise approach for newborn infants with respiratory distress in the delivery room

AHA guideline for neonatal resuscitation should be followed for newborns who need resuscitation in the delivery room [3]. In 2015 update, there were major management differences and new recommendations compared to 2010 guideline [3].

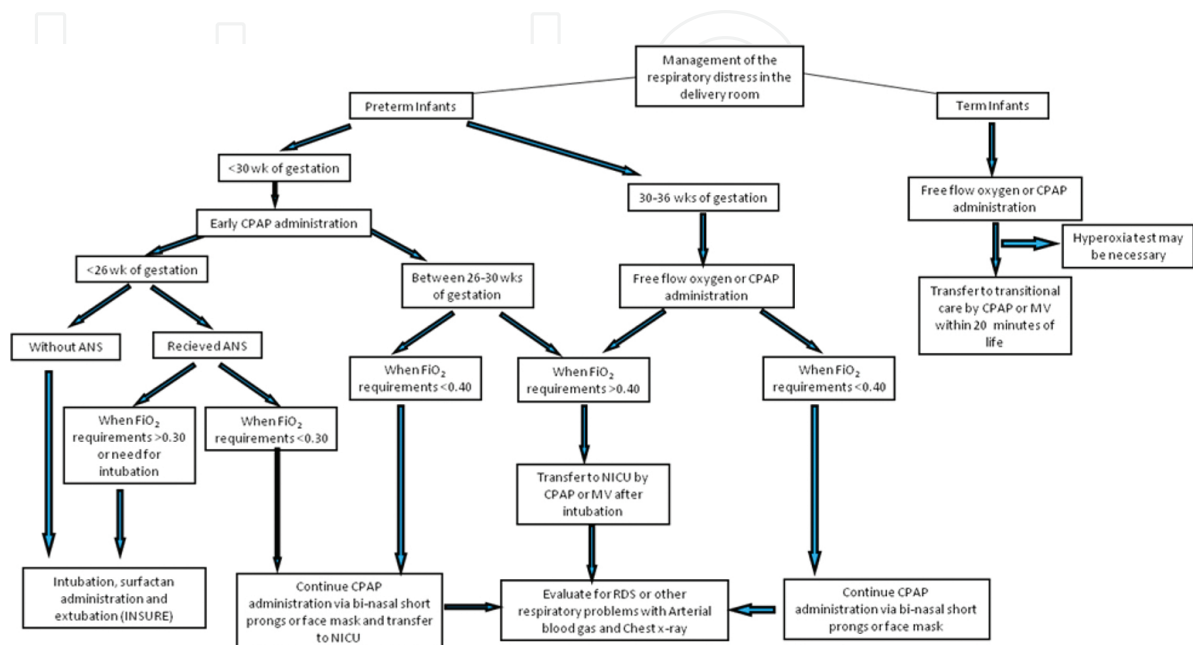
Spontaneously, breathing preterm infants with respiratory distress may be supported with CPAP initially rather than with routine intubation for administering PPV.



**Figure 3.** Practical AUCH approach for newborns in the delivery room. CS: cesarean section; AUCH: Ankara University Children's Hospital.

Practical approach for spontaneously breathing infants who do not need resuscitation but have respiratory distress signs—that is to say labored breathing (tachypnea, apnea, grunting, flaring of the nostrils, retractions) or persistent cyanosis in relevance with ILCOR 2015—in the delivery room at Ankara University Children Hospital (AUCH) is summarized in **Figures 3** and **4**. Delivered oxygen concentration to reach the targeted saturation and gestational age is a key point for practical approach to newborns with respiratory distress in our delivery room (**Figure 4**). For some newborns whose respiratory distress improves, follow-up is continued up to 20 minutes of life in the delivery room. If their respiratory signs worsen or not resolve

after 20 minutes, infants should be admitted to the transitional care. On the other hand, if the infants  $\geq 34$  weeks gestation and otherwise healthy whom respiratory distress improve (the absence of clinical sign of respiratory distress, transcutaneous oxygen saturation of  $>90\%$  without oxygen, respiratory rate  $< 60/\text{min}$ ) within 2 hours in the transitional care units, they can stay with the mother.



**Figure 4.** Practical AUCH approach for spontaneously breathing infants who have respiratory distress signs (tachypnea, apnea, grunting, flaring of the nostrils, retractions, cyanosis, etc.). AUCH: Ankara University Children’s Hospital; CPAP: continuous positive airway pressure; ANS: antenatal steroid;  $\text{FiO}_2$ , fraction of inspired oxygen; MV: mechanical ventilation; NICU: neonatal intensive care unit; RDS: respiratory distress syndrome.

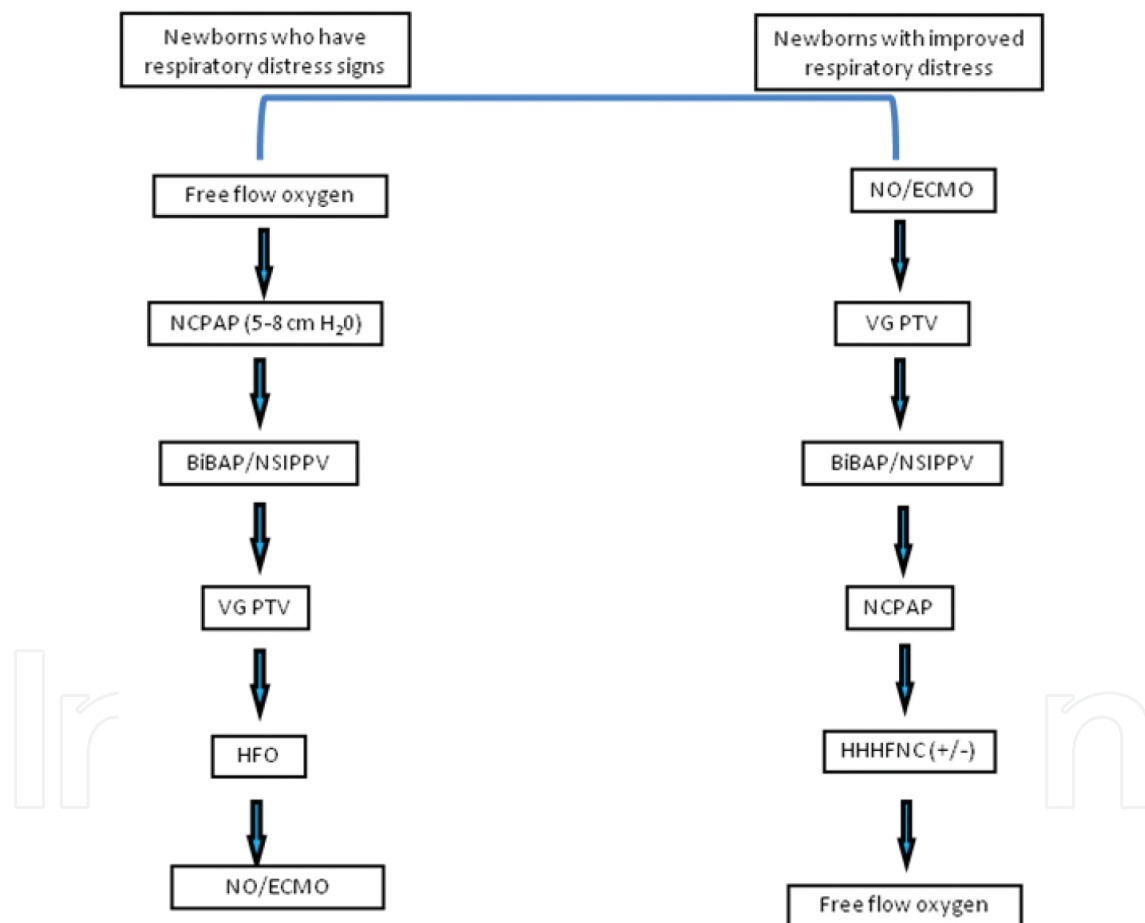
#### 4.2. Treatment modalities for newborn infant’s respiratory distress in the NICU

Infants with respiratory distress may need only supplemental oxygen, whereas those with respiratory distress and apnea require non-invasive or invasive mechanical ventilation [2]. Although the survival of infants with respiratory problems has dramatically improved with the treatment modalities, they may also lead to harmful side effects especially for immature infants. Avoiding lung injury and adverse effects of these treatments is the main challenge for the modern NICUs. Flow chart for newborns with respiratory distress who need assisted ventilation or who are in recovery period in our NICU is showed in **Figure 5**.

*Oxygen treatment* with hoods, face mask, and nasal cannulas is commonly used in the delivery room and NICUs to achieve targeted  $\text{SpO}_2$  values or to decrease WOB. Very mild cases of respiratory distress may be successfully managed by 21–30% ambient  $\text{O}_2$  in the incubators [2]. Optimizing oxygenation allows efficient use of respiratory muscles. Any sign of increased WOB or increasing oxygen requirement more than 40% suggests the need for early institution of positive pressure support. Babies should not be allowed to become significantly acidotic ( $\text{pH} < 7.25$ ) without escalating support [39].



Oxygen is a therapeutic gas, and insufficient or excessive oxygen can be harmful for all newborns. A non-invasive monitoring device to measure oxygen saturation by pulse oximetry should be used continuously in infants, especially in preterm ones receiving any supplemental oxygen. Although, in preterm babies receiving oxygen, the saturation target should be between 90% and 95%, the appropriate saturation ranges remain controversial [15]. Both lower (85–89%) and higher (91–95%) oxygen-saturation targets have been associated with severe morbidity and mortality in preterm infants. More recently, the trial from the BOOST-II Australia and the United Kingdom Collaborative Groups concluded that the use of an oxygen-saturation target range of 85–89% versus 91–95% resulted in significantly increased risks of death or disability at 2 years in infants born before 28 weeks' gestation. In addition, fluctuations in SpO<sub>2</sub> should be avoided in the postnatal period for avoiding retinopathy of prematurity (ROP) [15].



**Figure 5.** AUCH flow chart for newborns with respiratory distress who need assisted ventilation or who are in recovery period. NCPAP: nasal continuous positive airway pressure; BiBAP: bi-level nasal CPAP; NSIPPV: nasal synchronized intermittent positive pressure ventilation; VG PTV: volume-guarantee patient triggered ventilation; HFO: high frequency oscillatory ventilation; ECMO: extra corporeal membrane oxygenation.

*Non-invasive ventilation (NIV)* support can be defined as any form of respiratory support that is not delivered through an endotracheal tube [40]. Nasal CPAP (nCPAP) is a well-known

useful strategy for NIV<sup>34</sup> [15]. Among new modes of NIV, alternating nasal positive pressures in the form of either nasal intermittent positive pressure ventilation (NIPPV) or bi-level nasal CPAP and heated humidified high-flow nasal cannula (HHHFNC) gain increasing popularity [41].

CPAP provides stabilization of the airway and allows alveolar recruitment. Flow for CPAP delivery can be continuous or variable. A warmed and humidified gas is continuously provided by ventilators and bubble CPAP devices. Infant flow CPAP system device allows expiration, provides variable flow, and reduces WOB [2].

Nasal CPAP provides end-expiratory pressure, which reduces atelectasis, maintains higher FRC, and improves lung function by reducing workload and minimizing ventilation/perfusion (V/Q) mismatch. It reduces obstructive and central apnea and improves synchronization of respiratory movements. If there is evolving signs of respiratory distress, nCPAP is best used early rather than waiting for babies to deteriorate and has been associated with a significant reduction in the need for intubation [39].

Recent randomized clinical trials demonstrated that, in comparison with prophylactic or early use of surfactant, the use of CPAP decreases the need for invasive mechanical ventilation (MV) and the combined outcome of death or BPD [42]. Although all randomized trials to date have shown a high rate of CPAP failure in the most immature infants (24–25 weeks' gestational age), these infants also may benefit most from this strategy [43].

CPAP should be started from birth in babies who is lower than 30 weeks' gestation if they do not need MV. The interface should be short binasal prongs or mask for delivering CPAP, and a starting pressure of 5–6 cm H<sub>2</sub>O should be applied. According to European Consensus Guideline, CPAP with early rescue surfactant should be considered the optimal management for babies with RDS [15].

The use of very early (prophylactic) CPAP in spontaneously breathing preterm infants is already studied by multicenter large trials and recommended as described above. But, there is only one trial about the role of prophylactic CPAP administration to the late preterm and term infants who have a higher risk for TTN. It is found that prophylactic CPAP administration decreases the rate of NICU admission without any side effect in late preterm and early term infants delivered by elective C/S [44].

Nasal masks lead to less nasal trauma than short binasal prongs. CPAP of 5–7 cm H<sub>2</sub>O is recommended. Babies with RDS need considerably higher PEEP than a baby with TTN or sepsis due to the noncompliant lungs. Excessive PEEP can lead to pneumothorax and may reduce cardiac output [2]. The increase in PEEP or O<sub>2</sub> requirements (especially greater than 40%) may suggest the further escalation of therapy.

Clinical report from the Committee on fetus and newborn for non-invasive respiratory support concluded that (a) synchronized NIPPV reduces the frequency of postextubation failure than NCPAP. (b) There is no difference between nonsynchronized NIPPV and BiPAP for postextubation failure. (c) Data do not support the advantage of NIPPV/BiPAP over nCPAP for the management of babies with RDS. (d) There is no published evidence of benefit of NIPPV or

BiPAP for apnea of prematurity. (e) Committee suggest that further research is needed before recommending NIPPV or BiPAP instead of nCPAP in RDS or apnea [41].

Heated humidified high flow nasal cannula devices used in preterm neonates should precondition inspiratory gases close to normal tracheal gas conditions (37°C and 100% relative humidity) without causing the excessive airway drying, mucosal damage, bleeding, and increased risk of infection that can complicate conventional high flow nasal oxygen. Committee on fetus and newborn also suggested that HHHFNC devices that precondition the inspiratory gas mixture and deliver 2–8 L/minute flow may be an effective alternative to nCPAP for postextubation failure. Unlike CPAP, HHHFNC can cause unpredictably high nasopharyngeal pressures and may lead to traumatic injury in the airways of the infants. An appropriate size of the prongs, detection of an adequate air leak between the prongs and the nares, and using air flow rates as low as possible will reduce the risk of harmful effects of HHHFNC [39, 41]. Despite its emerging popularity, the evidence that HHHFNC is as effective as nCPAP is largely anecdotal or retrospective [39].

In our NICU, primary modes of respiratory support are nCPAP, BiPAP, or NIPPV for infants who have spontaneous breaths. In our daily practice, infants with signs of respiratory distress as tachypnea, grunting, retractions, or need of  $\text{FiO}_2$  greater than 21% at 20 minutes were started nCPAP (5–7 cm  $\text{H}_2\text{O}$ ) in the delivery room and transferred to NICU on nCPAP. They were kept on nCPAP unless they required nCPAP >7 cm  $\text{H}_2\text{O}$  or  $\text{FiO}_2 \geq 0.4$  and if so, their positive pressure respiratory support was switched to BiPAP with the same device. BiPAP was started as 5 and 8 cm  $\text{H}_2\text{O}$  for the lower and higher CPAP levels, respectively. BiPAP pressures were increased to maximum of 7 and 10 cm  $\text{H}_2\text{O}$  for the lower and higher CPAP levels, respectively, and the pressure exchange rate was increased to maximum of 40 per minute for clinical stability and a blood gas analysis within normal ranges. Treatment is usually escalated to NIPPV if the need for  $\text{FiO}_2$  of more than 0.4, or respiratory acidosis ( $\text{pH} \leq 7.25$ ), or insufficient respiratory effort, or excessive work of breathing before intubation. After de-escalation of NIV support, it was stopped when patients showed no signs of respiratory distress with nCPAP of 4 cm  $\text{H}_2\text{O}$  and BiPAP of 6–4 cm  $\text{H}_2\text{O}$  and  $\text{FiO}_2 < 0.30$ .

The pressure gradient between the airway opening and lungs generated through mechanical ventilation produces a flow of gas into the lung. Conventional ventilators for newborns are either pressure or volume controlled ones [6].

Pressure-controlled ventilators deliver a preset peak inspiratory pressure (PIP), thus delivering a variable tidal volume depending largely on lung compliance. A constant flow of gas passes through the ventilator. Pressure is limited to the desired magnitude. This ventilation is usually used with the technique of synchronized intermittent mandatory ventilation (SIMV), which allows spontaneous breathing between ventilator breaths [6] and patient triggered ventilation (PTV).

Volume-controlled ventilators deliver a preset tidal volume with a variable PIP, depending largely on lung compliance. When this gas has been delivered by the piston, inspiration is terminated. Infants' tidal volume is set between 4 and 8 ml/kg. PIP may change in response to patient's effort, and historically, this mode of ventilation was not safe enough for neonates.

However, in the volume-guarantee (VG) modes, the clinician sets both a maximum PIP and a desired target volume for mechanical breaths. As recent evidence suggests that lung injury is most likely related to volutrauma, volume guarantee modes are being accessed in the newborn respiratory management. In addition, volume ventilation results in reductions or trend for reductions in duration of ventilation, pneumothorax, intracranial hemorrhage, and BPD [6]. In summary, it is known that lung injury is most directly related to excessive tidal volumes and, conversely, that an inadequate tidal volume increases work of breathing and promotes atelectasis and V/Q mismatch [39]. Volume targeted ventilation provides an open lung strategy and reduces the frequency of excessive tidal volumes, decreasing inadvertent hyperventilation. There has not, however, been conclusive evidence of improved long-term outcomes [39].

*High-frequency ventilation (HFV)* refers to various ventilator strategies and devices designed to provide ventilation at rapid rates and very low tidal volumes. Rates during HFV are expressed in hertz (Hz). There are two types of high frequency ventilators (high frequency jet ventilator – HFJV and high frequency oscillatory ventilator – HFOV), which are frequently used in neonatal medicine. Oscillatory ventilation is unique because exhalation is actively generated, as opposed to other forms of high frequency ventilation, in which it is passive [6].

Cochrane 2015 analysis revealed that the evidence to use elective HFOV instead of conventional ventilation for reduction in the risk of BPD is small, and the evidence is weakened by inconsistency of this effect across trials. In addition, the benefit could be counteracted by an increased risk of acute air leak [45]. More recently, Iscan et al. suggested that HFOV with a VG option resulted in constant tidal volume delivery and less fluctuant CO<sub>2</sub> levels compared to HFOV alone in premature infants with RDS [46].

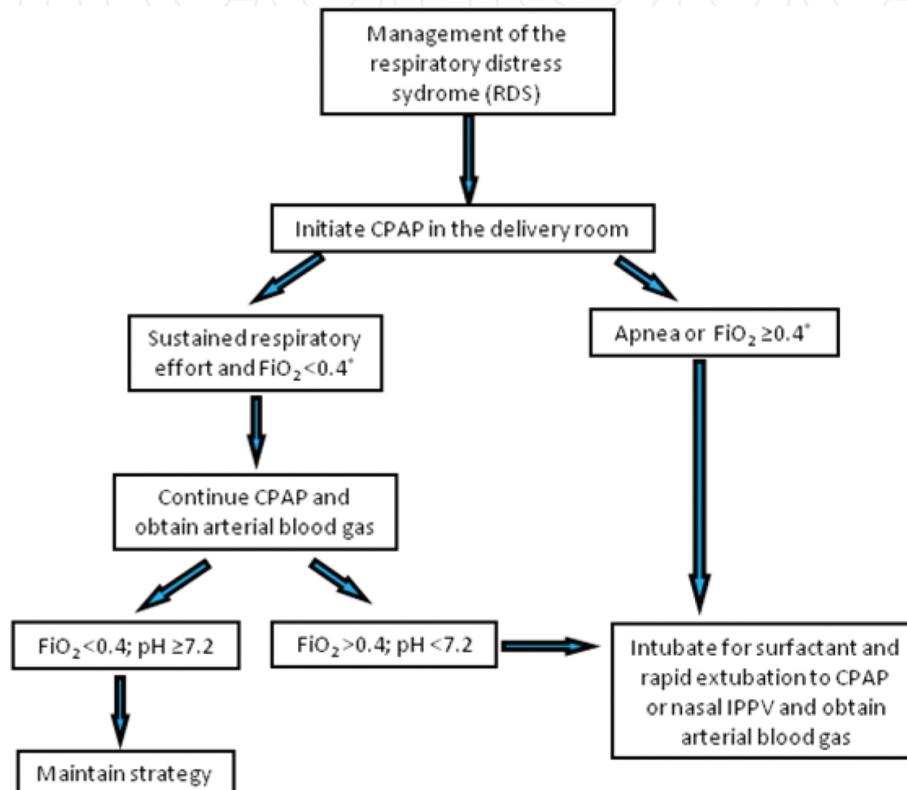
One approach to minimize ventilator-induced lung injury is to tolerate higher levels of pCO<sub>2</sub> (permissive hypercapnia), allowing the use of lower tidal volumes. Unfortunately, prospective trials have not demonstrated a reduction in BPD. On the other hand, low pCO<sub>2</sub> is known to decrease cerebral blood flow. There is a proven association between hypocapnia, neonatal brain injury, and subsequent cerebral palsy. Hypocapnia should therefore be avoided in ventilated infants wherever possible [39].

In our NICU, preferred modes of invasive ventilatory support are volume guarantee-PTV for preterm and term infants to maintain more stable pCO<sub>2</sub> and to avoid over distension and subsequent volutrauma. HFOV is preferred as a rescue strategy, but it is the primary mode for CDH.

There are several different surfactant preparations that have been used in neonates with RDS, including synthetic (protein-free) and natural (derived from animal lungs) products. Natural surfactants are superior to synthetic preparations at reducing pulmonary air leaks and mortality [15]. Natural surfactants contain the hydrophobic surfactant protein, SpB and SpC, although at different concentrations. However, some synthetic surfactant preparations contain only phospholipids [2]. According to Cochrane review, in a trial comparing protein containing synthetic surfactants compared to protein-free synthetic surfactant for the prevention of RDS, no statistically different clinical differences in death and BPD were noted [47].

Some trials, which aim to compare the effect of poractant alfa and the beractant for rescue therapy, demonstrated that more rapid improvement in oxygenation was achieved with poractant alfa [15]. According to European Consensus Guideline, 200 mg/kg dose of poractant alfa has an advantage for overall survival than 100 mg/kg of beractant or 100 mg/kg of poractant alfa to treat RDS [15].

Infants receiving INSURE (intubate, surfactant, extubate) have less need for mechanical ventilation, fewer pneumothorax, and less BPD, but evidence of long-term benefit is limited.



**Figure 6.** \* $\text{FiO}_2$  cut off  $<0.3$  for infants born  $<26$  weeks of gestation. Adapted and modified from Kalus & Fanaroff's Care of the High Risk Neonate.

According to European Consensus Guideline [15]:

1. Infants diagnosed with RDS should be given a natural surfactant preparation.
2. Extremely preterm infants in whom the mother has not had antenatal steroids and infants who require intubation for stabilization surfactant should be administered in the delivery room. Except these situations, early rescue surfactant should be standard.
3. Infants with RDS should be given rescue surfactant as early as possible. A suggested protocol from European Consensus Guideline would be to treat infants  $<26$  weeks' gestation when  $\text{FiO}_2$  needs  $>0.30$  and infants  $>26$  weeks' gestation when  $\text{FiO}_2$  needs  $>0.40$ .
4. When the initial dose of poractant alfa is 200 mg/kg, it would be better for treatment of RDS comparing to 100 mg/kg of poractant alfa or beractant.



5. Consideration of the INSURE technique is important. Because more mature babies can often be extubated to NIV just after surfactant administration, and a clinical judgment needs to be made as to whether an individual infant will tolerate this.
6. If there is evidence of ongoing RDS, a second or sometimes a third dose of surfactant can be administered.

Management of RDS in AUCH has been summarized in **Figure 6**.

There are some limited data about surfactant therapy for disease other than RDS. Preliminary reports of surfactant therapy have been noted in cases of pneumonia, pulmonary hemorrhage, MAS, and PPHN. However, an established protocol for these situations is not present [2].

*Extra corporeal membrane oxygenation (ECMO)* provides oxygen delivery, carbon dioxide removal, and cardiac support in patients who have cardiac and/or respiratory failure. ECMO is used for critically ill term and late preterm infants ( $\geq 32$ –34 weeks or  $\geq 1.6$ –1.8 kg) as a rescue bridge therapy for severe but reversible respiratory and/or cardiac insufficiency in case of failure of other conventional therapies [48].

*Nitric oxide (NO)* is a colorless gas with a half-life of seconds stimulates soluble guanylate cyclase (sGC) to increase intracellular cGMP, which indirectly decreases the free cytosolic calcium, resulting in smooth muscle relaxation. Excess iNO diffuses into the blood stream, where it is rapidly inactivated by binding to hemoglobin and subsequent metabolism to nitrates and nitrites. This rapid inactivation thereby limits its action to the pulmonary vasculature [49].

Inhaled NO is licensed for only term and near-term neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension by the Food and Drug Administration in the USA [50]. Inhaled NO does not improve long-term surfactant function or markers of pulmonary inflammation and oxidative stress [51]. Although the use of iNO has increased over the years and this increase is mostly due to off-label use in premature infants, the treatment of preterm infants is more controversial [50].

*Methylxanthines* have been used as respiratory stimulants to decrease apnea of prematurity and to facilitate successful extubation [15, 39]. Methylxanthines increase minute ventilation, improve CO<sub>2</sub> sensitivity, decrease hypoxic depression, enhance diaphragmatic activity, and decrease periodic breathing [2].

The Caffeine for Apnea of Prematurity (CAP) study evaluated the issue of long-term effects of caffeine therapy in infants who were under 1250 g birth weight. Study infants randomly had caffeine or placebo in the first 10 days of life and continuing until the clinician decision. Babies in caffeine group weaned off ventilation a week earlier and had significant reduction in BPD than placebo group [15]. According to CAP study, the combined outcome of death or neurodisability decreased in caffeine-treated babies at 18 months and also reduced rates of cerebral palsy and cognitive delay [52]. The differences were no longer significant after 5 years but reassuring that there were no long-term adverse effects on development. Infants who were on MV and had started caffeine earliest appeared to provide the most benefit [52].

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