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Review Article

# Neonatal Respiratory Distress Disorders: comparative pathologies review and diagnosis suspicion algorithm proposal

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## ABSTRACT

Respiratory pathologies, along with congenital cardiac diseases, represent the main etiologies of neonatal disorders. Neonatal respiratory distress syndrome embraces several pathologies that share respiratory impairment as its main clinical manifestation. Epidemiological and risk factors for respiratory disorders, such as weeks of gestation accomplished before birth and maternal comorbidities, have been identified during the last decades. However, similar acute clinical manifestations, as well as laboratory and radiological findings, lack comprehension, which might lead to an incorrect diagnosis and delayed optimal treatment. Hyaline membrane disease, transient tachypnea of the newborn, and meconium aspiration syndrome represent the three most frequent types of neonatal respiratory distress syndrome. In this paper, we describe the risk factors and pathophysiology of each disease and compare clinical manifestations, as well as laboratory and radiological findings between them. For this purpose, we analyzed a key termed based literature review which include Systematic Reviews, Metanalysis, case reports and book chapters as well as private hospitals epidemiologic statistic reports. Finally, we present a differential diagnosis algorithm which can be used to identify which respiratory distress syndrome the newborn manifests and consequently give prompt and optimal treatment.

**Key words:** neonatal respiratory distress syndrome; hyaline membrane disease; transient tachypnea of the newborn; meconium aspiration syndrome; differential diagnosis.

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## RESUMEN

Las patologías respiratorias junto con las cardiopatías congénitas representan las principales etiologías de las enfermedades neonatales. El síndrome de distrés respiratorio neonatal engloba varias patologías que comparten la insuficiencia respiratoria como principal manifestación clínica. Durante las últimas décadas se han identificado factores epidemiológicos y de riesgo para trastornos respiratorios, como semanas de gestación cumplidas antes del nacimiento y comorbilidades maternas; sin embargo, la similitud de manifestaciones clínicas así como la mala comprensión de hallazgos de laboratorio y radiológicos puede conducir a un diagnóstico incorrecto y retrasar el tratamiento óptimo. La enfermedad de la membrana hialina, la taquipnea transitoria del recién nacido y el síndrome de aspiración de meconio representan los tres tipos más frecuentes de síndrome de dificultad respiratoria neonatal. En este trabajo se describen los factores de riesgo de cada enfermedad, la fisiopatología, y de igual forma, se comparan las manifestaciones clínicas así como hallazgos de laboratorio y radiológicos entre ellos. Finalmente, presentamos un algoritmo de diagnóstico diferencial que puede utilizarse para identificar qué síndrome de dificultad respiratoria presenta el recién nacido y, en consecuencia, ofrecer un tratamiento óptimo y oportuno.


**Palabras clave:** síndrome de dificultad respiratoria neonatal; enfermedad de la membrana hialina; taquipnea transitoria del recién nacido; síndrome de aspiración meconial; diagnóstico diferencial.

## INTRODUCTION

Neonatal respiratory distress syndrome (NRDS) is a medical term that encompasses acute pathologies manifesting as respiratory distress in newborns.[1] These diseases exhibit certain clinical and pathological characteristics, such as an onset within the first 72 hours of extrauterine life, inadequate pulmonary distention, varying degrees of cyanosis, pulmonary hypertension, and a strong correlation with the week of gestation in progress at the time of birth.[1,2] While there are several diseases that can cause this syndrome, its incidence and potential complications have led the literature to focus on the description of three main pathologies: Hyaline membrane disease (NRDS Type 1), Transient tachypnea of the newborn (NRDS Type 2), and Meconium aspiration syndrome (NRDS type 3).[3]

Hyaline membrane disease (HMD) is primarily caused by deficient production and poor quality of pulmonary surfactant. Transient tachypnea of the newborn (TTN) results from a delay in the reabsorption of fetal lung fluid. Lastly, Meconium aspiration syndrome (MAS) occurs when newborns produce meconium while still in the uterus, leading to its aspiration and intrapulmonary deposition.[2,3] Despite the different pathophysiological mechanisms, without optimal and timely detection and treatment, pulmonary incapacity, incomplete alveolar distension, and hypoperfusion can lead to respiratory acidosis and pulmonary hypertension. These conditions can lead to extrapulmonary consequences affecting organs such as the heart, kidney and brain, significantly compromising both present and future proper functioning and development.[1,3]

Epidemiology of these diseases varies depending on prenatal support and care programs in each country, nevertheless, it is clear that worldwide the incidence of this syndrome has a negative proportional relation with the weeks of gestation of the newborn, particularly in NRDS types 1 and 2.[2] Different guidelines that consider clinical manifestations and imaging criteria serve as orientation resources for the diagnosis of each type of syndrome.[1] In this paper, we present a comparative review of NRDS types 1, 2 and 3 epidemiology, risk factors and pathophysiology, and propose a differential diagnosis algorithm that can be used as a synthesized information resource that aids in the comprehension of this syndrome and the practical decision-making.

## METHODOLOGY

In order to retrieve actualized information about Neonatal Respiratory Syndromes, we performed a key words/terms based search on PUBMED, Cochrane and Google Scholar online servers. *Neonatal Respiratory Distress Syndrome, Hyaline Membrane Disease, Transient Tachypnea of the Newborn, Meconium Aspiration Syndrome,* and *Differential diagnosis* were used to mark off our research. English or Spanish written Systematic Reviews, Metanalysis, case reports and book chapters published over the last 10 years were selected for this paper. Any other sources published before 2013 or written in a language besides English or Spanish were excluded. We obtained more than 50 different publications matching our searching criteria, 22 were excluded for having been published before 2013, 6 were excluded because they were written in languages

not included in our inclusion criteria, and 1 was excluded for being a Spanish transcription of an already included English-written article. Finally, we selected a total 21 publications for the making of this paper.

## RESULTS

### Hyaline Membrane Disease (NRDS Type 1)

HMD is one of the most common respiratory disorders in newborns, especially in preterm newborns. This condition is caused by a deficient quantity and quality of pulmonary surfactant due to an immaturity of type two pneumocytes, leading to acute respiratory distress.[4] Despite epidemiological efforts to estimate the approximate incidence of HMD, data remains uncertain since it largely depends on the rate of preterm births in each country or region studied. However, it is clear that this disease primarily affects newborns born before 37 weeks of gestation (WOG), and its occurrence is inversely proportional to the number of WOG completed prior to birth. International estimates allow us to calculate the probability of suffering from HMD; newborns between 31 and 36 WOG have a 10 to 20% chance of developing HMD, 20-40% for newborns at 28-30 WOG, 50-70% for those at 26-27 WOG and 80 to 95% probability for newborns between 24 and 25 WOG.[5] Additional risk factors associated with HMD include male sex, Caucasian ethnicity, twin pregnancy, fetal hydrops, poorly controlled diabetes in the mother, and maternal hypothyroidism.[1]

HMD has its pathophysiological basis in the deficiency of pulmonary surfactant, a surface-active agent composed of lecithin, sphingomyelin, phosphatidylglycerol, and apoproteins. This surfactant fulfills essential functions for adequate pulmonary activity, such as decreasing alveolar pressure, stabilizing alveoli, optimizing gas exchange, maintaining functional respiratory residual capacity, and serving as an anti-edematous and protective agent against infections.[3,5] Pulmonary surfactant is produced by type two pneumocytes starting from the 20th WOG. However, lung maturation, as well as the correct production and functioning of the surfactant, do not occur until 34th WOG. At birth, especially in preterm infants, the absence of surfactant and the lack of maturation of its components cause poor alveolar expansion and an imbalance in the oxygen uptake, leading to the establishment of SDRRN.[6,7] Poor gas exchange results in respiratory acidosis and pulmonary vasoconstriction, damaging endothelial integrity and promoting the leakage of protein exudate, as well as the formation of hyaline membranes. Alveolar atelectasis commonly forms, leading to the generation of perfused but not ventilated lung areas. This, in turn, induces pulmonary hypertension with a right-to-left shunt. Finally, the high concentration of oxygen received by the failing lungs can damage lung epithelium and aggravate the deficiency of surfactant.[7]

Clinical manifestations include acute respiratory distress, tachypnea, intercostal shots, nasal flaring, progressive cyanosis, grunting, xiphoid retraction, and poor response to oxygen. These patients usually have high Silverman Anderson scale results and decreased on the APGAR scale due primarily to poor respiratory function.[6]

Pregnancy monitoring plays an essential role in fetal development. Timely detection of problems, such as the threat of preterm labor or any other situation that may predispose to fetal distress, is important for the correct prophylaxis of conditions such as NRDS type 1. In this case, when a situation involving fetal distress is encountered, the use of corticosteroids, which accelerate the maturation of type 1 and 2 pneumocytes, is recommended.[8] The constant concern remains as to which steroid should be applied in these cases, but the two most widely accepted for this therapy are betamethasone and dexamethasone, since they are the steroids that suffer least from placental metabolism by 11 beta-hydroxysteroid dehydrogenase.[9] A consensus of experts comprised of European neonatologists who convene every 3 years to develop updates on the latest techniques for the management and prevention of premature or at-risk infants, mention that a cycle of prenatal corticosteroids administered to pregnant patients at risk of preterm birth improves survival, reduces the likelihood of developing NRDS, necrotizing enterocolitis, and ventricular hemorrhage. Furthermore, it appears to have no adverse effects on the mother or the newborn. On the other hand, it has been observed that these prenatal steroids reduce mortality in patients with pregnancies at 22 WOG and even in patients with pregnancies at 34-36 WOG. It has been shown that prenatal steroid administration decreases the risk of short-term respiratory morbidity. It has also been observed that the optimal time between the initiation of steroid administration and childbirth should be between 24 hours and 7 days, as beyond this timeframe, the beneficial effects begin to diminish.[10]

### Transient Tachypnea of the Newborn (NRDS Type 2)

TTN, also known as pulmonary maladaptation, is a benign, non-infectious respiratory distress condition primarily caused by a delay in the reabsorption of fetal lung fluid.[1] This disease is considered the second type of the NRDS and


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is the most common presentation of respiratory distress in term newborns.[3] Its incidence worldwide is approximately 11% of live newborns, but in Mexico, it is estimated to affect 0.3-2% of term or late preterm newborns. However, it constitutes up to 50% of cases of respiratory distress admitted to pathological nurseries or neonatal intensive care units. Risk factors include birth by cesarean, maternal gestational diabetes or asthma, male sex, being small for gestational age and macrosomia.[11,12]

TTN possesses a multifactorial pathophysiology that combines pre- and post-natal conditions leading to respiratory distress. Excess lung liquid, electrolyte imbalances (mainly sodium and chloride ions), alveolar edema, as well as fluid in lymphatics and interstitium, result in hypoxemia, hypercapnia, air entrapment, and, finally, compensatory taquipnea.[9] Generally, in the final weeks of gestation, fetal lungs produce lung liquid and surfactant at an approximate rate of 5 ml/kg/h, generating an internal lung pressure of 1 to 2 mmHg greater than the amniotic fluid. This pressure differential is essential for normal lung development. At the time of birth, lung liquid needs to be cleared out and reabsorbed so lungs can function as an air reservoir and oxygen interchange chamber. The main mechanism for doing so is Na+ uptake across the airway epithelium (by Na+ channels previously activated by fetal epinephrine and glucocorticoids), which reverses the osmotic gradient leading to airway liquid reabsorption.[1,12] Absence of mechanical squeezing of vaginal delivery (which diminishes alveolar pressure natural birth increase) as well as a prolonged time lapse between birth and first breath are considered as factors that negatively impact TTN.[3]

Clinical manifestations of TTN include respiratory distress, which might be present since birth or begin in the next 2 hours. The main finding is evident tachypnea, typically with a respiratory rate above 60, which can even reach 100-120 breaths per minute. Other occasional findings can include cyanosis, tachycardia, and barrel-shaped chest.[8,13] The common duration of TTN is usually 48 hours until resolution of the clinical picture. Various treatments have been proposed to support correct resolution, which have been evaluated by different reviews published in Cochrane. These treatments include fluid restriction, administration of furosemide, salbutamol, and even epinephrine. However, it has been observed that none of these have been reported as effective. Finally, an agreement has been reached that the treatment is based on supportive measures such as oxygen therapy, suspension of enteral feeding, and the initiation of intravenous fluids. Additionally, assisted ventilation might be needed, although the percentage of cases requiring it is very low. As mentioned earlier, the condition will resolve within 48-72 hours, but it is highly likely that the newborn will need to be admitted to a neonatal intensive care unit.[13,14]

## Meconium Aspiration Syndrome (NRDS type 3)

MAS is a cause of NRDS commonly found in patients born between weeks 38 and 42 of gestation, particularly in undeveloped countries. At the same time, 3-12% of those born with Meconium-stained amniotic fluid (MSAF) will develop MAS. According to Monfredini and others, this number could be up to 52% in those beyond the 42 WOG.[15]

MAS possesses a multifactorial pathophysiology.[3] The first important factor is antenatal inflammation/infection. It is recognized that the presence of endotoxins, bacteria, and inflammatory mediators in MSAF causes an increase of intestinal peristalsis and meconium aspiration by the fetus. Another physiopathology factor is the mechanical airway obstruction, which will be caused most of the times by meconium plugs.[8] Those meconium plugs lead to a high resistance and air trapping whose intensity depends on the consistency and quantity of the meconium-stained liquid. In fact, this factor has been considered the most common physiopathology mechanism of MAS. Mechanical airway obstruction could be partial or total. If the obstruction is partial, hyperinflation will be caused because of valve effects.[15] On the other hand, if the obstruction is total, patchy areas of atelectasis can be caused. The third factor in the pathophysiology of MAS is the inactivation of pulmonary surfactant due to the presence of meconium fatty acids. This inactivation leads to atelectasis, resulting in ventilation-perfusion mismatch. Despite not being completely understood, it is known that meconium can alter the surfactant function through direct toxicity on type II pneumocytes.[15,16]

Finally, there is an activation of the inflammatory cascade due to chemotactic action for neutrophils substances contained by meconium, this activates the complement, has a vasoactive function and is a source of pro-inflammatory mediators as well.[12] Nowadays it is not well known the cellular mechanism that causes the activation of the inflammatory cascade, however, it is known that meconium induces inflammation and apoptosis, besides that, it can cause chemical pneumonia during the first 48 hours of life of the newborn. Moreover, persistent pulmonary hypertension has been identified in 15-20% of MAS patients and has been associated with pulmonary vasoconstriction, capillary hypertrophy and pulmonary hyperexpansion.[16,17]

Timely diagnosis of NRDS is essential for a quick medical response and a better prognosis, for this intention there exist several general newborn state scales, however there is one that particularly helps in the detection of respiratory pathologies.[2] The Silverman Anderson scale is a tool that allows us to identify respiratory signs and symptoms thereby determine the severity of distress present in the neonate, as presented in Figure 1. It evaluates 5 respiratory distress signs and grades them in a scale from 0 to 2 depending on the severity. A higher score indicates a more severe respiratory problem while lower scores suggest a more respiratory functional newborn.[18]

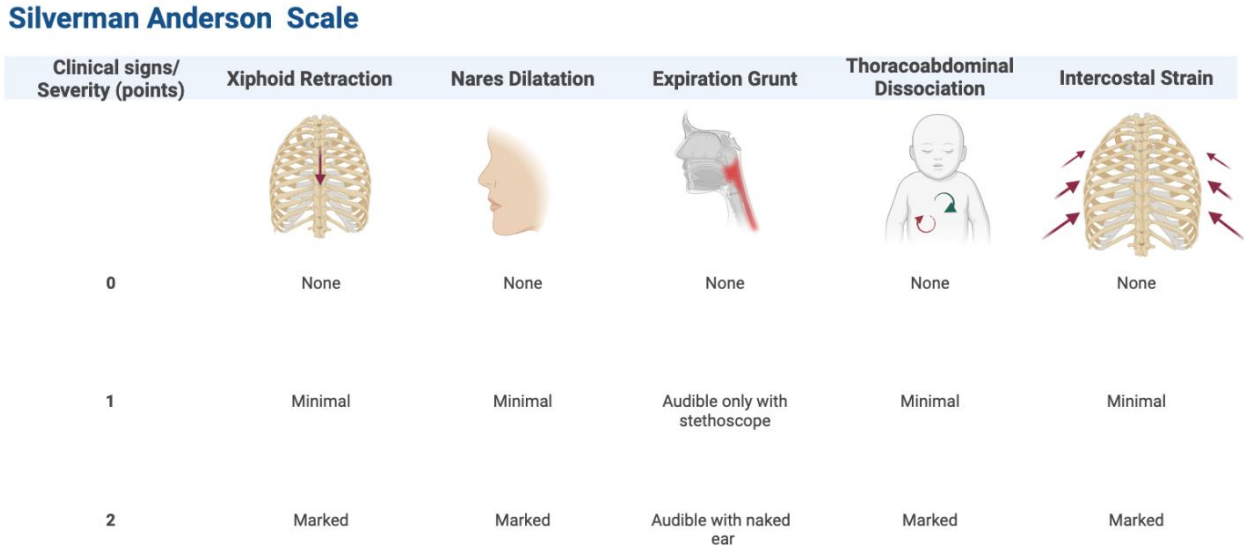


**Figure 1.** Silverman Anderson scale recreation.

## Differential diagnostic approach

The first step in the diagnosis is suspicion. As mentioned before, the main risk factor involved in any type of NRDS is the week of gestation at birth. Clinical manifestations can sometimes be shared between pathologies, mainly tachypnea, respiratory retractions, and progressive cyanosis.[2] Thus, additional laboratory tests and imaging information are frequently required to confirm or rule out a possible diagnosis. Hypoxemia, hypercapnia, and clear respiratory acidosis are common gasometrical findings, particularly in HMD and MAS. These results can be absent or slightly notable in TTN. However, when TTN or MAS is suspected, blood culture and a complete blood count can be requested to identify possible infections.[1,3]

Radiological imaging (chest X-ray) is of great support not only for confirming diagnosis but to identify damage extent and severity. Accentuated radiopacity, fine granular infiltrate, as well as a "ground glass" pattern are characteristic of HMD, while intercostal space overdistension, vascular plot reinforcement and pulmonary fissures effusions are more commonly seen in TTN. Lastly, diffuse opaque collections, as well as vascular plot reinforcement can be seen in MAS radiographs.[19] Table 1 summarizes risk factors, clinical manifestations, laboratory, and imaging findings presented so far. Nevertheless, it's important to emphasize that there are no 100% pathology specific signs and that due to their pathophysiology complexity, any manifestation (clinical or paraclinical) can be present in any type of NRDS.


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**Table 1.** Comparison of NRDS Type 1,2 and 3 risk factors, clinical manifestations, and laboratory and radiological outcomes

| | Hyaline Membrane Disease | Transient Tachypnea of the Newborn | Meconium Aspiration Syndrome |
|---|---|---|---|
| **Risk Factors** | • Preterm child (less WOG, higher incidence)<br>• Male sex<br>• Caucasian ethnicity<br>• Twin pregnancy<br>• Fetal hydrops<br>• Poorly controlled diabetic mother/ hypothyroid mother | • Cesarean delivery<br>• Prolonged time lapse between birth and first breath<br>• Mother with gestational diabetes or maternal asthma<br>• Male sex<br>• Macrosomia | • Post term child<br>• Been born in an undeveloped country<br>• Been born with Meconium-stained amniotic fluid (MSAF) |
| **Clinical Manifestations** | • Start 4-6 hours after birth<br>• Taquipnea (above 60 bpm)<br>• Nasal flaring<br>• Respiratory grunting<br>• Intercostal retraction<br>• Xiphoid retraction<br>• Progressive cyanosis<br>• Poor response to oxygen<br>• Decreased vesicular murmur<br>• Altered pulse (if there is persistence of ductus arteriosus) | • Start 2-6 hours after birth<br>• Marked taquipnea (above 100 bpm)<br>• Nasal flaring<br>• Intercostal retraction<br>• Xiphoid retraction<br>• Slight cyanosis | • Cyanosis<br>• Encephalopathy<br>• Heart failure<br>• Poor peripheral perfusion<br>• Reduction of urine output.<br>• Tachypnea<br>• Nasal flaring<br>• Respiratory retractions |
| **Laboratory Findings** | • Hipoxemia<br>• Hypercapnia<br>• Clear respiratory acidosis | • Hipoxemia<br>• Slight hypercapnia<br>• Slight respiratory acidosis (might be absent)<br>• *Blood count and culture might be requested | • Hipoxemia<br>• Respiratory acidosis<br>• *Blood count and culture might be requested |
| **Radiological Findings** | • Accentuated radiopacity<br>• Fine granular infiltrate<br>• “Ground glass” pattern | • Intercostal space overdistension<br>• Vascular plot reinforcement<br>• Pulmonary fissures effusions<br>• Reticulogranular pattern<br>• Notable pleural liquid at bases might be present | • Diffuse cottony alveolar condensations<br>• “Honeycomb” pattern<br>• Chest hyperinflation<br>• Possible neumotrax |

Similar clinical manifestations between NRDS types 1,2 and 3 might produce confusion and difficulty for reaching a successful diagnosis, hence, the importance of a sequential differential diagnosis strategy is crucial. Figure 2 represents our diagnostic suspicion algorithm. It considers gestation week at time of birth as the main risk factor for these diseases and clinical manifestations, serving not only as a staring point once the baby has been born, but as information needed before birth to prevent and have all the necessary materials for a quick response. As seen in section B, once the baby has been born, respiratory distress suspicion starts with clinical manifestations, onset time can lead to an specific type of NRDS, however we suggest that laboratory tests, particularly gasometry is performed to confirm oxygenation disturbance as well as to identify and treat potential metabolic and hydroelectrolyte imbalance. Finally, we suggest the usage of chest radiography if diagnosis is still unclear or, if MAS is suspected, localize potential sites of lung injury or meconial collection.

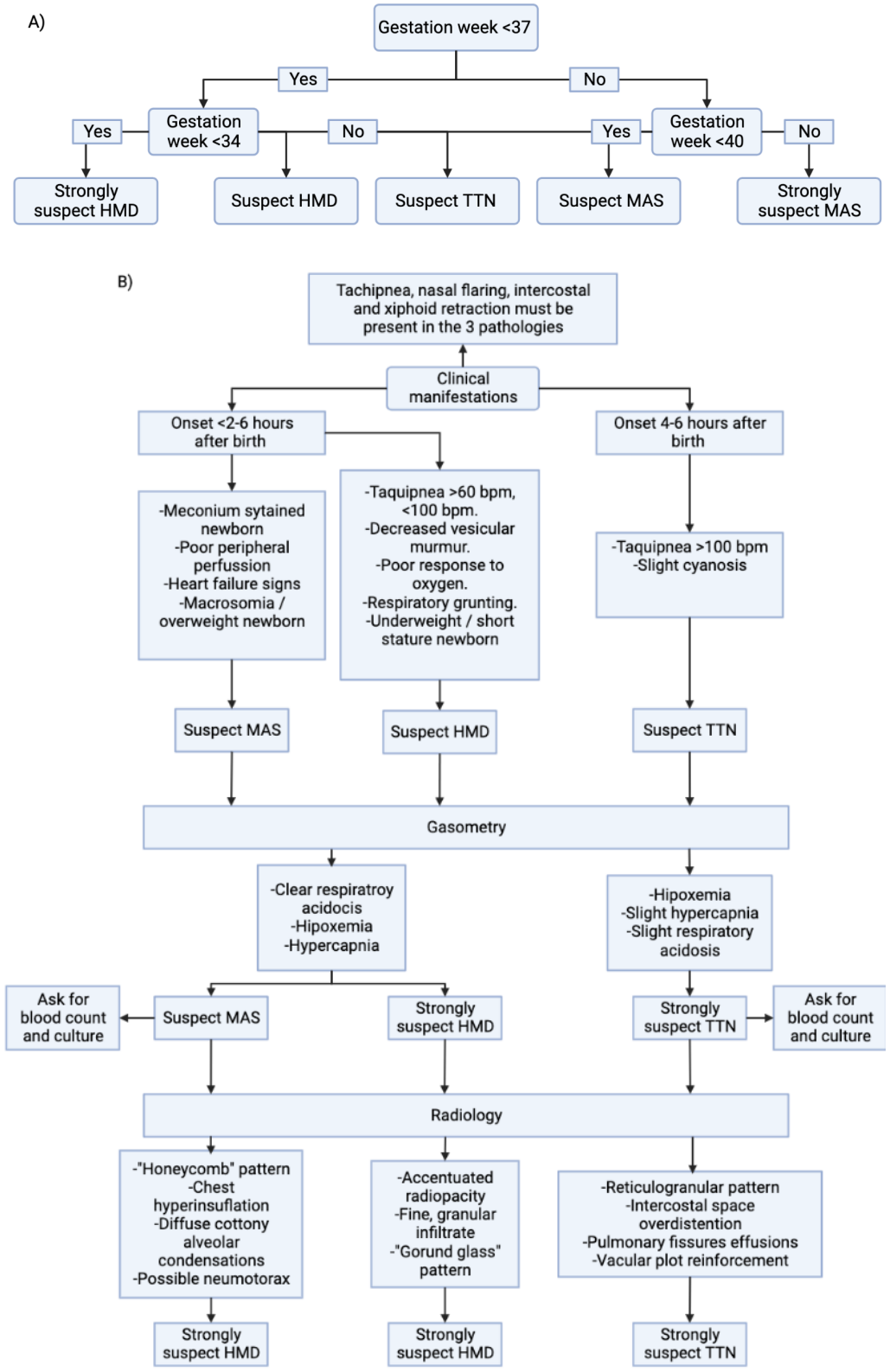


**FIGURE 2.** Differential NRDS diagnosis suspicion algorithm. A) Algorithm based on gestation week at time of birth. B) Algorithm based on clinical manifestations, and laboratory and radiological outcomes.


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## Possible treatment routes

Once a specific type of NRDS has been identified, prompt treatment care is crucial for limiting respiratory distress etiology and avoiding potential complications. For HMD, guidelines indicate exogen pulmonary surfactant administration. Natural exogen surfactant (derived from cattle or pig) are preferred over synthetic surfactant (mixture of tensioactive agents and phospholipids).[1] It is important to highlight that for HMD, the best treatment is prevention, intramuscular betamethasone or dexamethasone administration serve as fetal lungs maturing promoter and can be used 72 hours before an inevitable premature birth.[4] Regarding TTN, a systematic review studied the use of diuretic therapy as a potential medication to help the lung fluid clearance, the review included two randomized groups comparing furosemide with placebo and showed no changes in the severity of symptoms or the duration of hospital stay.[14] Similarly, other clinical studies concluded that there is not enough evidence to determine the efficacy of beta-agonists in the management of TTN.[12] It is necessary to provide respiratory support or administer oxygen to maintain oxyhemoglobin saturations between 90 - 95%.[17]

As for MAS, all patients should be admitted to the neonatal intensive care unit where they have to receive parental nutrition, keep normothermia (36.5-37.5ºC) and correct the acidosis keeping blood pH in the range 7.25–7.40 and PaCO2 in the range 40–55 mmHg.[17] In the possible scenario of respiratory failure, intubation is indicated to maintain saturation between 92-97%. Although meconium is sterile, it is prone to over-infection in areas of the lung not adequately ventilated, however the use of prophylactic antibiotics is not recommended.[20] Finally, it is important to remark that newborns that suffer continued respiratory distress should be monitored persistently in case they need supplemental oxygen. The oxygen must be applied when the SpO2 is <90%. Newborns with signs of increased work of breathing and/or persistent tachypnea may require continuous positive airway pressure (CPAP) with the objective to maintain functional residual capacity (FRC) and oxyhemoglobin saturations in their normal parameters.[13,21]

## CONCLUSION

Neonatal respiratory distress syndrome encompasses several pathologies, characterized by inadequate respiratory function, impaired gas exchange, and potential lungs and multisystemic complications. HMD, TTN, and MAS are the most studied presentations of this syndrome, and significant signs and symptoms are shared among these pathologies. However, clear risk factors, laboratory findings, and radiological signs can help differentiate respiratory distress presentations. The use of a differential diagnosis algorithm can ease the identification of specific NRDS being presented, leading to prompt and appropriate treatment. The algorithm we present recognizes WOG at time of birth as the main risk factor for any NRDS, moreover, it includes a step-by-step method which starts with clinical suspect, and uses laboratory and radiologic studies to confirm the diagnosis as well as to promptly identify and treat potential hypoxia complications.

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