NEONATAL RESPIRATORY DISTRESS SYNDROME

CHI Formulary Development Project

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM- November 2023

To the CHI Original Neonatal Respiratory Distress Syndrome

Clinical Guidance- Issued April 2020

Contents

Related Documents

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Abbreviations

BiPAP	Bilevel Positive Airway Pressure
BPD	Bronchopulmonary Dysplasia
CHD	Congenital Heart Disease
CHI	Council of Health Insurance
CPAP	Continuous Positive Airway Pressure
CPG	Clinical Practice Guideline
EMA	European Medicines Agency
ESPR	European Society for Pediatric Research
FDA	Food and Drug Administration
HFNC	High Flow Nasal Canula
HMD	Hyaline Membrane Disease
IDF	CHI Drug Formulary
IVH	Intraventricular Hemorrhage
LISA	Less-Invasive Surfactant Administration
LMA	Laryngeal Mask Airway
MAS	Meconium Aspiration Syndrome
MIST	Minimally Invasive Surfactant Treatment
MV	Mechanical Ventilation
NEC	Necrotizing Enterocolitis
NICHD	National Institute of Child Health and Human Development
NICU	Neonatal Intensive Care Unit
NIPPV	Noninvasive Positive Pressure Ventilation
NIV	Non-invasive Ventilatory Support
NRDS	Neonatal Respiratory Distress Syndrome
SFDA	Saudi Food and Drug Authority
TTN	Transient Tachypnoea of the Newborn
UENPS	Union of European Neonatal and Perinatal Societies

Executive Summary

Neonatal respiratory distress syndrome (NRDS), also known as infant respiratory distress syndrome and hyaline membrane disease[1], is a respiratory disorder of neonates that manifests itself within few hours after delivery. It is one of the most common causes of admission to neonatal intensive care unit (NICU) and respiratory failure in neonates[2].

NRDS applies to all forms of abnormal gaseous exchange at the level of the lung of a neonate irrespective of the cause[3]. It is an inability to maintain respiratory homeostasis, leading to impairment of gaseous exchange, ventilation-perfusion mismatch, and cerebral anoxia.

NRDS is a common neonatal emergency worldwide[4]. It occurs in about 24,000 infants born in the United States annually[5], and it is the most common complication of prematurity leading to significant morbidity in late preterm neonates and even mortality in very low birth weight infants[6]. In one recent study, 1.9% of premature babies who had NRDS later developed cerebral palsy, compared with 0.5% of premature babies who did not have NRDS[7]. Another study published in 2018 found that premature infants had a higher risk of childhood epilepsy[8].

Moreover, Mechanical ventilation, which helps keep infants alive, also puts them at risk for bronchopulmonary dysplasia (BPD). An estimated 5,000 to 10,000 newborns develop BPD or other form of chronic lung disease[1]. While prognosis of RDS depends on the severity and underlying cause[9], a center in China reported a mortality rate of 3.9% in full term neonates with RDS[10]. Another study showed that the neonatal mortality rate due to NRDS (case fatality rate) in low- and middle-income countries (LMICs) was higher compared with high-income countries[4,11,12].

The most important risk factors for NRDS are prematurity and low birth weight. The incidence of NRDS increases with decreasing gestational age at birth. In one study of babies born between 2003 and 2007 at various National Institute of Child Health and Human Development (NICHD) Neonatal Research Network centers, 98% of babies born at 24 weeks had RDS, while at 34 weeks, the incidence was 5%, and at 37 weeks was less than 1%[13] . Other risk factors include white race, male gender, late preterm delivery, maternal diabetes, perinatal hypoxia, and ischemia, chorioamnionitis, and multiple pregnancies[10,14–17].

Respiratory distress (RD) is a challenging problem and one of the most common causes of admission in neonatology intensive care units (NICU), it may occur due to respiratory or non-respiratory diseases (Kresimir et al 2017). Incidence of RDS ranges from 1.5 cases per 100,000[19] to nearly 79 cases per 100,000[20], with European countries reporting a lower incidence than USA. A scoping review published in 2020 showed that the prevalence of NRD ranged from 0.21 to 84.8% and the highest prevalence rates were observed in Saudi Arabia (78.5%) and other countries[13]. Another local study from Altayef reported a prevalence of 0.15% in infants born at more than 37 weeks gestation[21].

Several studies have been published related to the cost of care in neonatal units including NRDS, where 76% of the cost were due to NICU management excluding surfactants and other drugs to manage complications[22,23]. Main cost was associated with the progress in the level of technologies available for the treatment of neonates with RDS that has undergone prominent changes. Neonatal intensive care units (NICUs) providing care for infants with RDS have increased but have impacted the cost of therapy.

According to the relevant sources, this report gathers all the clinical and economic evidence pertaining to NRDS. The primary goal of the Council of Health Insurance in issuing NRDS guidelines is to incorporate the most up-to-date clinical and economic evidence regarding drug therapies into the IDF (CHI Drug Formulary). This objective aims to ensure that patients with NRDS in Saudi Arabia have timely and secure access to appropriate treatments while prioritizing their safety. The focus of the review was on Saudi, American, European and England guidelines issued within the last three years.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) reflecting specific drug class role in the management of neonatal respiratory distress syndrome.

This report functions as an addendum to the prior CHI NRDS disease report and seeks to offer guidance for the effective management of NRDS.

Regarding the management of Neonatal RDS, one new surfactant was mentioned in updated guidelines, however, no market authorization was obtained yet from the European medicine agency. No changes or modifications were made to existing drugs and no drugs were withdrawn from Saudi FDA.

Below is a table summarizing the major changes based on the different NRDS guidelines used to issue this report:

Table 1. General Recommendations for the Management of Neonatal Respiratory Distress Syndrome (NRDS)

Management of NRDS		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
The aim of modern RDS management is to maximize survival while minimizing complications such as air leaks and Bronchopulmonary dysplasia (BPD).	Not graded	European Consensus Guidelines on the Management of Respiratory Distress Syndrome: 2022 Update
Neonatal care settings where CPAP is routinely used to stabilize preterm infants, and when the rate of antenatal corticosteroid administration has been high (>50%), prophylactic surfactant is no longer recommended.	Grade A	Guidelines for surfactant replacement therapy in neonates, Canadian pediatric society, 2021
Noninvasive respiratory support (e.g., CPAP) should be provided to preterm infants with RDS from birth. Early surfactant should be provided for newborns with increasing severity of RDS, demonstrated by escalating or sustained levels of oxygen requirement and other clinical or radiological indications.	Grade B	Guidelines for surfactant replacement therapy in neonates, Canadian pediatric society, 2021
If a preterm baby <30 weeks of gestation requires intubation for stabilization, they should be given surfactant (A2). Babies with RDS needing treatment should be given an animal-derived surfactant preparationA1.	A1	European Consensus Guidelines on the Management of Respiratory Distress Syndrome: 2022 Update
Surfactant therapy improves survival and reduces	Not graded	European Consensus Guidelines on the

pneumothorax and therefore plays an essential role in management of RDS.		Management of Respiratory Distress Syndrome: 2022 Update
Use of surfactant before inter-facility transport of preterm infants was found to be associated with lower oxygen requirement during transport and shorter duration of ventilation support, compared with controls.	Level 4 evidence	Guidelines for surfactant replacement therapy in neonates, Canadian pediatric society, 2021
Repeated dosing of surfactant should be provided to infants only when there is evidence of ongoing moderate to severe RDS.	Grade A	Guidelines for surfactant replacement therapy in neonates, Canadian pediatric society, 2021
Animal-derived and the newer generation synthetic surfactants are both effective for treating RDS and improving survival without BPD.	Level 1a evidence	Guidelines for surfactant replacement therapy in neonates, Canadian pediatric society, 2021
Three natural (animal derived) surfactants are currently available in Europe: Beractant (Survanta®), Bovactant (Alveofact®) and Poractant alfa (Curosurf®).	Not graded	European Consensus Guidelines on the Management of Respiratory Distress Syndrome: 2022 Update
When comparing different animal-derived surfactants, emerging evidence suggests that porcine minced lung extract, especially in higher dose, may be superior to bovine surfactant for improving acute respiratory status and reducing mortality or BPD in infants with RDS.	Level 1a evidence	Guidelines for surfactant replacement therapy in neonates, Canadian pediatric society, 2021

Section 3 lists the key recommendations synthesis for NRDS treatment.

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI NRDS report, and the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This part contains the updated versions of the guidelines mentioned in the 2020 CHI NRDS report and the corresponding recommendations.

Three guidelines were used in the last version of NRDS. Updates were only found on the European Consensus Guidelines on the Management of Respiratory Distress Syndrome, published in 2022 in comparison with European Guidelines on NRDS in 2019.

Table 2. Guidelines Requiring Revision

Guidelines requiring revision	
Old versions	**Updated versions**
European Consensus Guidelines on the Management of Respiratory Distress Syndrome – **2019 Update**	**European Consensus Guidelines** on the Management of Respiratory Distress Syndrome: **2022 Update**
American family physician: Newborn Respiratory Distress guidelines 2015	N/A*
Joint Guideline for the Management of Respiratory Distress Syndrome of the Newborn **2019**	N/A*

**: No updated version available:* the existing version is the most recent one and no further updates or revisions have been made or released.

1.1.1 European Consensus Guidelines on the Management of Respiratory Distress Syndrome: 2022 Update

Respiratory distress syndrome (RDS) care pathways evolve slowly as new evidence emerges. Six versions were reported of "European Guidelines for the Management of RDS" by a panel of experienced European neonatologists and an expert perinatal obstetrician based on available literature up to end of 2022.

There are changes to some of the previous recommendations as well as some changes to the strength of evidence supporting recommendations that have not changed.

This guideline has been endorsed by the European Society for Pediatric Research (ESPR) and the Union of European Neonatal and Perinatal Societies (UENPS)[24].

Until more evidence is available, these guidelines apply mainly to management of RDS in infants with gestational ages of greater than 24 weeks.

Definition: RDS is caused by pulmonary immaturity and surfactant deficiency, resulting in respiratory insufficiency from soon after birth.

The aim of modern RDS management is to maximize survival while minimizing complications such as air leaks and Bronchopulmonary dysplasia (BPD).

Lack of antenatal care increases risk of death or severe morbidity. General measures to reduce preterm birth include prevention of teenage pregnancies, adequate pregnancy spacing, prevention of unnecessary caesarean sections, early screening for preeclampsia and treatment with low-dose aspirin in women at risk, and single embryo transfer when in vitro fertilization is used.

In asymptomatic pregnant women at risk of spontaneous preterm birth, due either to previous preterm birth or where a shortened cervix has been identified, use of progesterone is associated with a reduced rate of preterm birth and lower perinatal mortality.

Prenatal Care

There is often warning of impending preterm delivery and a need to consider interventions to prolong gestation or reduce risk of adverse outcomes by "preparing" the fetus.

Mothers at high risk of preterm birth < 28–30 weeks of gestation should be transferred to perinatal centers with experience in management of RDS (B1).

In women with a singleton pregnancy and a short cervix in mid-pregnancy or previous preterm birth, vaginal progesterone treatment should be used to increase gestational age at delivery and reduce perinatal mortality and morbidity (A1).

In prenatal pre-labor rupture of membranes, antibiotics can delay preterm delivery and reduce neonatal morbidity, although co-amoxiclav should be avoided because of its association with increased risk of necrotizing enterocolitis (NEC).

Magnesium sulphate, given to women with imminent preterm delivery before 32 weeks, reduces incidence of cerebral palsy (A1).

In women with symptoms of preterm labor, cervical length and accurate biomarker measurements should be considered to prevent unnecessary use of tocolytic drugs and/or antenatal steroids (B2).

Clinicians should offer a single course of prenatal corticosteroids to all women at high risk of preterm delivery, from when pregnancy is considered potentially viable up to 34 completed weeks of gestation, ideally at least 24 h before birth (A1).

A single repeat course of steroids may be given in threatened preterm birth before 32 weeks of gestation if the first course was administered at least 1–2 weeks earlier (A2).

MgSO4 should be administered to women in imminent labor before 32 weeks of gestation.

Clinicians should consider short-term use of tocolytic drugs in very preterm pregnancies to allow completion of a course of prenatal corticosteroids and/or in utero transfer to a perinatal center (B1).

Delivery Room Stabilization

Personnel attending birth should know how to identify infants who require urgent airway management and lung inflation in the first minutes after birth in order to establish gas exchange and restore cardiac output.

Spontaneously breathing preterm infants should be stabilized using CPAP (A1). If apnoeic or bradycardic, start giving ventilation breaths. Expert consensus is to start with CPAP pressure at least 6 cm H2O and peak inspiratory pressures 20–25 cm H2O (D2)

Oxygen for resuscitation should be controlled using a blender. Use an initial FiO2 of 0.30 for babies <28 weeks of gestation and 0.21–0.30 for those 28–31 weeks, 0.21 for 32 weeks of gestation and above. FiO2 adjustments up or down should be guided by pulse oximetry (B2). SpO2 of 80% or more (and heart rate >100/min) should be achieved within 5 min (C2).

Intubation should be reserved for babies not responding to positive pressure ventilation via face mask or nasal prongs (A1).

Plastic bags or occlusive wrapping under radiant warmers and humidified gas should be used during stabilization for babies <32 weeks of gestation to reduce the risk of hypothermia. Hyperthermia should also be avoided (A1).

Surfactant Therapy

Surfactant therapy improves survival and reduces pneumothorax and therefore plays an essential role in management of RDS.

Since 2013, recommendations have been to only use surfactant in infants showing clinical signs of RDS.

If a preterm baby <30 weeks of gestation requires intubation for stabilization, they should be given surfactant (A2).

Babies with RDS needing treatment should be given an animal-derived surfactant preparation (A1).

Most preterm infants will transition successfully on CPAP, but those with RDS will develop progressively worsening lung disease, clinically presenting as increased work of breathing, sternal recession, and increasing oxygen requirements to maintain normal saturations.

More than one dose of surfactant may be needed. Many infants can continue Non-invasive Ventilatory Support (NIV) even when surfactant is required. If poractant alfa is used, the need for re-dosing can be minimized by using a larger initial dose of 200 mg/kg.

Three natural (animal derived) surfactants are currently available in Europe:

- Beractant (Survanta®) at recommended dose of 100 mg/kg requires surfactant dose volume of 4 mL/kg.
- Bovactant (Alveofact®) at recommended dose of 50 mg/kg requires volume of 1.2 mL/kg.
- Poractant alfa (Curosurf®) at recommended dose of 100– 200 mg/kg requires dose volume of 1.25–2.5 mL/kg.

Head-to-head trials show similar efficacy among surfactants when used in similar doses; however, there is a survival advantage when poractant alfa at the higher dose of 200 mg/kg is compared to 100 mg/kg of poractant alfa or beractant (1A).

Rescue surfactant should be given early in the course of the disease (A1). Suggested protocol would be to treat worsening babies with RDS when FiO2 > 0.30 on CPAP pressure ≥6 cm H2O or if lung ultrasound suggests surfactant need (B2).

A second and occasionally a third dose of surfactant should be given if there is ongoing evidence of RDS such as persistent high oxygen requirement and other problems have been excluded (A1).

Oxygen Supplementation beyond Stabilization

There are no relevant changes since 2019 in terms of refining previous recommendations for oxygen saturation targeting based on data from the NeOProm Collaboration.

In preterm babies receiving oxygen, the saturation target should be between 90 and 94% (B2).

Alarm limits should be set to 89% and 95% (D2).

Protocols for screening and treating preterm babies for ROP should be in place (A1).

Non-Invasive Respiratory Support

CPAP or Noninvasive Positive Pressure Ventilation (NIPPV) should be started from birth in all babies at risk of RDS, such as those <30 weeks of gestation who do not need intubation for stabilization (A1).

NIV with early rescue surfactant by LISA technique is considered optimal management for babies with RDS (A1).

The system delivering CPAP is of little importance; however, the interface should be short binasal prongs or mask with a starting pressure of about 6–8 cm H2O

(A2). Ability to escalate to NIPPV will reduce the need for invasive MV in some infants (A1).

Bilevel positive airway pressure (BIPAP) devices confer no advantage over CPAP alone (A2). However, synchronized NIPPV, if delivered through a ventilator, can reduce need for ventilation or need for re-ventilation following extubation and may reduce BPD (A2).

HFNC can be used as an alternative to CPAP for some babies, with the advantage of less nasal trauma, provided centers have access to CPAP or NIPPV for those failing this mode (B2).

Mechanical Ventilation (MV) Strategies

Around half of babies <28 weeks will require MV and those that do have worse outcomes.

The aim of MV is to provide "acceptable" blood gases by ventilating at optimal lung volumes (open lung concept) while avoiding over-distension and atelectasis.

MV should be used in babies with RDS when other methods of respiratory support have failed (A1). Duration of MV should be minimized (B2).

Lung-protective modes such as VTV or high-frequency oscillation ventilation should be the first choice for babies with RDS who require MV (A1).

When weaning from MV, it is reasonable to tolerate a modest degree of hypercarbia, provided the pH remains above 7.22 (B2). Avoid pCO_2 < 4.7 kPa (35 mm Hg) when on MV to reduce brain injury (C1).

Caffeine Therapy:

Methylxanthines are respiratory stimulants, and caffeine therapy is now a well-established aspect of newborn respiratory care.

Caffeine (20 mg/kg loading, 5–10 mg/kg maintenance) should be used to facilitate weaning from MV (A1). Early caffeine can be considered for babies at high risk of needing MV such as preterm babies on NIV (C1).

Permissive Hypercapnia: The concept of facilitating earlier extubation by tolerating mild hypercapnia is long-standing.

Postnatal Steroids

Despite best efforts, some infants are difficult to wean from MV with an apparent cycle of MV-induced lung inflammation and increased risk of BPD. Systemic corticosteroids have a role in breaking this cycle to facilitate extubation and improve outcomes.

steroids are powerful drugs, increasing risk of gastrointestinal perforations, and have potential to increase risk of long-term neurological problems, particularly if used within the first week of life**.**

A short tapering course of low-dose dexamethasone should be considered to facilitate extubation in babies who remain on MV after 1–2 weeks (A2).

Pain and Sedation

Preterm babies can clearly experience pain and discomfort. There is a balance between appropriate analgesia and the negative effects of sedation, particularly when there is an emphasis on minimizing duration of MV.

Routine sedation for ventilated infants is not recommended.

Opioids should be used selectively when indicated by clinical judgement and evaluation of pain indicators (D1). The routine use of morphine or midazolam infusions in ventilated preterm infants is not recommended (A1).

Monitoring and Supportive Care

Core temperature should be maintained between 36.5°C and 37.5°C at all times (C1).

Most babies should be started on intravenous fluids of 70–80 mL/kg/day in a humidified incubator, although some very immature babies may need more (C2). Fluids must be tailored individually according to serum sodium levels, urine output, and weight loss (D1).

Parenteral nutrition should be started from birth. Amino acids 1.5–2 g/kg/d should be started from day 1 and quickly built up to 2.5–3.5 g/kg/d (B2). Lipids 1–2 g/kg/d should be started from day 1 and quickly built up to 4.0 g/kg/day as tolerated (C2).

Enteral feeding with mother's milk should be started from the first day if the baby is hemodynamically stable (B2).

In infants with RDS, antibiotics should be used judiciously and stopped early when sepsis is ruled out (D1).

Managing Blood Pressure and Perfusion

Treatment of hypotension is recommended when there is evidence of poor tissue perfusion such as oliguria, acidosis, and poor capillary refill (C2). Treatment will depend on the cause.

When a decision is made to attempt pharmacologic closure of hemodynamically significant PDA, indomethacin, ibuprofen, or paracetamol can be used with a similar efficacy (A2).

Paracetamol is preferred when there is thrombocytopenia or concerns about renal function (B2).

Thresholds for red blood cell transfusion in infants can be set at 12 g/dL (HCT 36%) for those with severe cardiorespiratory disease, 11 g/dL (HCT 30%) for those who are oxygen dependent, and 7 g/dL (HCT 25%) for stable infants beyond 2 weeks of age (A2).

Miscellaneous

Surfactant can be used for RDS complicated by congenital pneumonia (C2).

Surfactant therapy can improve oxygenation following pulmonary hemorrhage (C1).

Surfactant can improve oxygenation in infants with severe meconium aspiration syndrome (B2).

1.2 Additional Guidelines

This part includes the added guidelines to the previous CHI Neonatal RDS report, along with their recommendations.

Table 4. List of Additional Guidelines

List of additional guidelines
Canadian Pediatric Society Guidelines for Surfactant Replacement Therapy in Neonates (**2021**)
Neonatal Respiratory Distress Syndrome, a Review Article (**2023**)
The epidemiology, risk factors, mortality rate, diagnosis, etiologies, and treatment of neonatal respiratory distress: a scoping review (**2020**)

1.2.1 Canadian Pediatric Society Guidelines for Surfactant Replacement Therapy in Neonates (2021)

Surfactant replacement therapy (SRT) plays a pivotal role in the management of neonates with respiratory distress syndrome (RDS) because it improves survival and reduces respiratory morbidities.

With the increasing use of noninvasive ventilation as the primary mode of respiratory support for preterm infants at delivery, prophylactic surfactant is no longer beneficial. For infants with worsening RDS, early rescue surfactant should be provided.

While the strategy to intubate, give surfactant, and extubate (INSURE) has been widely accepted in clinical practice, newer methods of noninvasive surfactant administration, using thin catheter, laryngeal mask airway, or nebulization, are being adopted or investigated.

Use of SRT as an adjunct for conditions other than RDS, such as meconium aspiration syndrome, may be effective based on limited evidence[25].

Prophylactic versus selective surfactant treatment

Prophylactic use of surfactant refers to a strategy of providing exogenous surfactant at birth to infants at risk for RDS, with the aim of preventing severe RDS from developing.

Selective use of surfactant refers to a strategy of providing exogenous surfactant to infants with established RDS.

Both strategies have been shown to be effective, but with increasing use of continuous positive airway pressure (CPAP) in the delivery room stabilization of preterm infants, the benefit of prophylactic surfactant is being questioned.

Early versus delayed surfactant

Use of surfactant before inter-facility transport of preterm infants was found to be associated with lower oxygen requirement during transport and shorter duration of ventilation support, compared with controls (level 4 evidence)

What type of surfactant is preferable—natural or synthetic?

Surfactant, no matter which form, has been shown to be efficacious in the treatment of RDS.

Surfactant is a complex structure that is mainly composed of di-palmitoyl phosphatidyl choline (DPPC) and surfactant protein (SP-) A, B, C, and D.

Synthetic surfactants

First-generation synthetic surfactants are composed of DPPC without surfactant proteins, and they are less effective in reducing ventilation support, pneumothorax, and mortality compared with animal-derived surfactants.

The only second-generation synthetic surfactant ever tested in infants is lucinactant (Surfaxin), which contains two phospholipids, and it was withdrawn from the market in 2015 preceding trials of its aerosolized form.

Animal-derived surfactants

A wide variety of animal-derived or natural surfactants are available for use.

Two types of bovine surfactant preparations were comparable in reducing death or BPD:

- Meta-analysis showed that porcine surfactant was more effective than bovine surfactant in reducing mortality before discharge, death or BPD at 36 weeks, and need for redosing.
- Benefit of porcine surfactant was only observed when given in the higher dose (>100 mg/kg) range.
- One recent trial comparing bovine lipid extract surfactant to porcine minced lung extract (poractant), found that poractant was more effective in reducing duration of supplemental oxygen and appeared to trend toward less BPD in survivors.
- However, a trend toward increased mortality associated with the use of poractant was also noted, although these deaths were not respiratory-related.

In summary, animal-derived and the newer generation synthetic surfactants are both effective for treating RDS and improving survival without BPD.

When comparing different animal-derived surfactants, emerging evidence suggests that porcine minced lung extract, especially in higher dose, may be superior to bovine surfactant for improving acute respiratory status and reducing mortality or BPD in infants with RDS (Level 1a evidence).

Dosing and re-dosing surfactant

A generally accepted practice at the present time is to repeat doses of surfactant only when there is evidence of ongoing RDS based on ventilation and oxygen requirements.

Delaying re-dosing of surfactant until the infant requires escalated respiratory support is acceptable, except when RDS is complicated by sepsis or perinatal hypoxic-ischemic injury.

The size of the initial dose might be an important factor to consider in this context. One study involving poractant showed that a higher initial dose (200 mg/kg) was more effective in reducing oxygen requirement, need for re-dosing, and mortality by 36 weeks corrected GA.

Poractant is the only product that is concentrated enough to create such a high dose in a reasonable intratracheal volume (Level 1b evidence).

Newer techniques of surfactant administration

Less-invasive surfactant administration (LISA) methods (specifically thin catheter, laryngeal mask airway (LMA), pharyngeal route, and nebulization demonstrated that there is growing clinical interest in techniques that avoided mechanically ventilating infants with RDS.

Less-invasive surfactant administration and minimally invasive surfactant treatment (MIST): administering surfactant through a thin catheter instead of an endotracheal tube (ETT) may combine the avoidance of mechanical ventilation with the benefits of early surfactant.

A new approach using the LMA to guide a catheter for LISA or MIST has been described and shown to be feasible without overt adverse effect (Level 2b evidence).

Pharyngeal surfactant administration allows distribution of surfactant to the air–fluid interface during spontaneous breathing. Study results were confounded by a significant number of infants from both groups who required subsequent intubation and surfactant, making it difficult to draw definite conclusions regarding the benefit of this approach of surfactant administration (Level 2b evidence).

The only truly noninvasive method of SRT is via nebulization.

The effect of nebulized surfactant depends on a number of important factors, including optimal particle size, stability of the substance after nebulization, and the loss of particles in relation to an effective dose.

Earlier clinical studies using jet nebulizers did not show significant clinical benefits.

Surfactant replacement for infants with MAS or pulmonary hemorrhage may be considered at clinicians' discretion (Grade B).

1.2.2 Neonatal Respiratory Distress Syndrome: A Review article (2023)

Neonatal respiratory distress syndrome is a frequent cause of increased morbidity and mortality in neonates. This review describes the etiology, epidemiology, pathophysiology, evaluation, and management of respiratory distress syndrome in neonates, and discusses the role of the interprofessional team in evaluating and treating patients with this condition[5].

Neonatal respiratory distress syndrome, or RDS, is a common cause of respiratory distress in a newborn, presenting within hours after birth, most often immediately after delivery.

The incidence of RDS is inversely proportional to the gestational age of the infant, with more severe disease in the smaller and more premature neonates.

Etiology:

Neonatal respiratory distress syndrome (RDS) occurs from a deficiency of surfactant, due to either inadequate surfactant production, or surfactant inactivation in the context of immature lungs.

Prematurity affects both these factors, thereby directly contributing to RDS.

Monozygotic twins have a higher incidence of RDS compared to dizygotic twins, and an increased incidence of RDS has also been reported in families, thus supporting an underlying genetic predisposition.

Pathophysiology

Neonatal respiratory distress syndrome is caused by surfactant deficiency, especially in the context of immature lungs.

The deficiency of surfactant increases the surface tension within the small airways and alveoli, thereby reducing the compliance of the immature lung.

The delicate balance of pressures at the air-fluid interface is essential to prevent the collapse of the alveolus or the filling of the alveolus with fluid. As the surface tension increases at the alveolar level, the amount of pressure required to maintain alveolar shape increases.

With reduced surfactant production, atelectasis occurs throughout the lung, causing reduced gas exchange. Widespread and repeated atelectasis eventually damages the respiratory epithelium, causing a cytokine-mediated inflammatory response.

Pulmonary edema develops as a result of the inflammatory response, increasing amounts of protein-rich fluid from the vascular space to leak into the alveoli, which further inactivate surfactant. Furthermore, many infants with RDS require mechanical ventilation, which may have deleterious effects on the lung.

RDS can cause hypoxemia through alveolar hyperventilation, diffusion abnormality, ventilation-perfusion mismatch, intrapulmonary shunting, or a combination of these mechanisms.

Diagnosis

Prompt diagnosis and treatment require an overall assessment of prenatal and delivery history to identify perinatal risk factors, clinical presentation, radiographic findings, and evidence of hypoxemia on blood gas analysis.

Clinical presentation consists of non-specific respiratory symptoms, including tachypnea, nasal flaring, grunting, retractions, and cyanosis, with decreased air entry on auscultation.

Chest radiography findings pathognomonic of RDS include homogenous lung disease with diffuse atelectasis, classically described as having a ground-glass reticulo-granular appearance with air bronchograms, as well as low lung volumes.

Arterial blood gas analysis may show hypoxemia that responds to increased oxygen supplementation and hypercapnia.

An echocardiogram may show the presence of a patent ductus arteriosus that might complicate the clinical course of RDS.

Complete blood counts may show evidence of anemia and abnormal leukocyte counts, suggesting infection.

At times, a workup for infectious etiologies may be necessary, including blood, cerebrospinal fluid, and tracheal cultures (when appropriate).

Treatment / Management

The goals of optimal management of neonatal RDS include decreasing incidence and severity using antenatal corticosteroids, followed by optimal management using respiratory support, surfactant therapy, and overall care of the premature infant.

Monitoring Oxygenation and Ventilation: Serial blood gas monitoring may be necessary to optimize oxygenation and ventilation. Partial pressure of arterial oxygen (PaO2) on an arterial blood gas is maintained between 50 to 80 mmHg, and partial pressure of arterial carbon dioxide (PaCO2) is maintained between 40 to 55 mmHg, with the pH >7.25.

Assisted Ventilation of the Neonate: to reduce atelectasis by providing a constant distending positive airway pressure. The current preferred strategy is the early initiation of continuous positive airway pressure (CPAP) with selective surfactant administration.

In most institutions, non-invasive modalities are preferred over invasive ventilation as they decrease the risk of mortality, and bronchopulmonary dysplasia (BPD) compared to invasive ventilation with or without surfactant.

Continuous Positive Airway Pressure (CPAP): Nasal CPAP is an initial intervention in preterm infants with RDS or risk of RDS without respiratory failure.

Non-invasive Respiratory Support: Nasal Intermittent Positive Pressure Ventilation (NIPPV) appears superior to CPAP alone for decreasing extubation failure, the need for intubation in preterm infants, but the same in cost and safety.

High Flow Nasal Canula: Heated humidified high-flow nasal cannulas (HFNC) are also used in some centers as an alternative to CPAP to provide positive distending pressure ventilation to neonates with RDS.

Mechanical Ventilation: Patients who do not respond to CPAP, develop respiratory acidosis (PH < 7.2 and PaCo2 > 60-65 mm of Hg), hypoxemia (PaO2 < 50 mm of Hg or Fio2 > 0.40 on CPAP), or severe apnea are managed with endotracheal intubation and mechanical ventilation.

The goals of mechanical ventilation include providing adequate respiratory support while balancing the risks of barotrauma, polytrauma, and oxygen toxicity.

Exogenous Surfactant Therapy

The targeted treatment for surfactant deficiency is intratracheal surfactant replacement therapy via an endotracheal tube.

Surfactant administered within 30 to 60 minutes of the birth of a premature neonate is found to be beneficial.

Surfactant hastens recovery and decreases the risk of pneumothorax, interstitial emphysema, intraventricular hemorrhage (IVH), BPD, and neonatal mortality in the hospital and at one year.

Neonates who receive surfactant for established RDS, have an increased risk of apnea of prematurity.

According to European census guidelines, the surfactant is administered to immature babies with FiO2 > 0.3, and mature babies with FiO2 > 0.4.

Currently, there are no clinically significant advantages of using one type over another when used in similar doses:

- Beractant: This is a modified natural surfactant prepared from minced bovine lungs with the additives
- Poractant alfa: This is a modified natural surfactant derived from minced porcine lung extract
- Calfactant: This is a natural surfactant obtained from lavaging calf lung alveoli and contains 80% phosphatidylcholine with only 1% protein

Synthetic surfactant: Clinical trials are ongoing

The standard technique of surfactant administration by endotracheal intubation and mechanical ventilation may result in transient airway obstruction, pulmonary injury, pulmonary air leak, and airway injury.

Emerging evidence shows that the LISA technique is associated with a lower rate of BPD, death, and need for mechanical ventilation compared to surfactant administration through endotracheal intubation.

Supportive Care

Preterm infants with apnea of prematurity may require caffeine therapy.

Caffeine can also be administered to preterm infants < 28 weeks with extremely low birth weight (BW <1000 g) to increase respiratory drive and enhance the use of CPAP.

Optimal fluid and electrolyte management is critical in the initial course of RDS. Some neonates may require volume resuscitation using crystalloids as well as vasopressors for hypotension.

1.2.3 The epidemiology, risk factors, mortality rate, diagnosis, etiologies, and treatment of neonatal respiratory distress: a scoping review (2020)[1]

Neonatal respiratory distress (NRD) remains an emergency until its etiology is diagnosed and appropriate treatment is delivered to the neonate.

The objective of this scoping review is to synthesize contemporary studies on the prevalence, risk factors, etiologies, and diagnosis of NRD[13].

Factors associated with neonatal respiratory distress:

Studies have demonstrated that respiratory distress of any cause is more common in preterm neonates than in term and post-term neonates. Similarly, to gestational age (GA), NRDS is inversely related to birth weight.

Advanced maternal age has been cited as well as a risk factor for NRDS due to increased incidence of maternal diseases (hypertension, diabetes, placenta praevia or abruptio placentae), high preterm deliveries or cesarean deliveries in older women.

Several studies showed a significant risk of NRDS when a mother had been a chronic smoker than not.

Infectious anamnestic risk factors have been shown to predispose a neonate to NRD due to neonatal infection.

Maternal diabetes mellitus, whether chronic diabetes or gestational diabetes mellitus, has been reported as a major risk factor for NRDS in several countries.

Many studies have proven placenta praevia and abruptio (independent of caesarean section as a confounder) to be risk factors for NRDS. As well as hypertensive disorders.

[1] Although the title of this review mentions treatment, no treatment section was described in the manuscript. Yet the importance of this review is that it delignates severity assessment and complications of NRDS.

Diagnosis:

The most frequent diagnosis in the majority of studies was either the presence of at least one or two of the elements of the following three signs:

- An abnormal respiratory rate: tachypnoea [respiratory rate above 60 breaths/minute], bradypnea [respiratory rate less than 30 breaths/minutes], Respiratory pauses [an absence of breathing movements for a period less than 20 seconds], and apnea [an absence of breathing movements for a period greater than 20 seconds])
- Signs of laboured breathing (expiratory grunting, nasal airing, intercostal recessions, xiphoid recession and thoraco-abdominal asynchrony)
- And generalized or localized cyanosis.

Investigations include leukocytosis, leucopoenia, raised C-reactive proteins (CRP), elevated procalcitonin and a positive blood, urine or cerebrospinal fluid culture confirm the diagnosis of a neonatal infection.

Low blood glucose level may be indicative of hypoglycemia as the cause of NRDS and low hemoglobin level may suggest anemia as the etiology.

A chest x-ray ideally carried out at the neonate's bedside in the anteroposterior view taken in inspiration with a gastric tube in situ.

An echocardiography would help confirm the diagnosis of CHDs and a trans fontanel ultrasound is not diagnostic of perinatal asphyxia but may help diagnose its complications such as intracranial hemorrhage, periventricular leukomalacia which may indirectly suggest the presence of perinatal asphyxia.

Severity of NRDS

Severe NRDS can be identified by the following. Silverman score ≥ 7, cyanosis refractory to supplementary oxygen, and hemodynamic instability; tachycardia above 160/min, capillary refill time (CRT) >3 sec, hypotension, hypoxemia, respiratory acidosis, hypercapnia, low ejection fraction, pulmonary hypertension, severe congenital heart defect.

The table below represent the criteria for Silverman score calculation:

Table 3. Silverman Score

Signs	Points	0	1	2
Inspiration	Nasal flaring	Absent	Mild	Marked
	Intercostal retraction	Absent	Mild	Marked
	Xiphoid retraction	Absent	Mild	Marked
	Thoracoabdominal movement	Synchronous	Chest lags on inspiration	See-saw movement

Expiration	Expiratory grunting	Absent	Heard only with stethoscope	Heard with Naked ear

Score 0 – 3: Mild NRD, Score 4 – 6: Moderate NRD, Score > 6: Severe NRD with impending respiratory failure

Causes of NRDS

Neonatal Infection NRD is frequently the clinical manifestation of pathological processes by microorganisms trans placentally through the ascending route from the birth canal or from the birth canal (vagina) during childbirth.

Transient Tachypnoea of the Newborn (TTN) is a benign condition and one of the most common causes of NRDS, irrespective of GA and it is due to delayed in the resorption of pulmonary fluid after birth.

Hyaline Membrane Disease (HMD) is also called respiratory distress syndrome (RDS). It is NRDS due to a structural and functional pulmonary immaturity stemming from a deficiency in pulmonary surfactant. Thus, usually more common in pre-term newborns.

Meconium Aspiration Syndrome (MAS) is defined as respiratory distress due to inhalation of Meconium. Another cause is perinatal asphyxia.

Congenital Heart Diseases CHD could be cyanotic or a cyanotic heart disease. In both cases, the newborn can present with NRD, a heart murmur, cardiomegaly and/or signs of heart failure depending on the severity of the CHD.

Choanal Atresia It is a congenital malformation caused by partial or complete imperforation of the posterior nasal cavity into the rhino pharynx. This pathology is important because the newborn breaths exclusively through the nostrils.

Other causes include congenital diaphragmatic hernia and esophageal atresia with or without tracheoesophageal fistula.

Complications

Early complications include pneumothorax and pneumomediastinum, usually seen in neonates on artificial ventilation with high pressures.

Late complications include bronchopulmonary dysplasia (BPD), retinopathy of prematurity (due to oxygen toxicity and can be prevented by avoiding PaO2 above 75mmHg in the newborn), persistent ductus arteriosus and sequelae of cerebral anoxia such as cerebral palsy.

Section 2.0 Drug Therapy

This section comprises four subsections: the first contains the newly recommended drugs, the second covers drug modifications, the third outlines the drugs that have been withdrawn from the market, and the fourth details drugs that have been approved by the FDA and/or EMA but have not been registered by the SFDA.

2.1 Additions

There have been no new SFDA registered drugs since the last CHI report issued in 2020.

2.2 Modifications

There are no new modifications regarding the prescribing edits mentioned in the previous CHI report.

2.3 Delisting

None of the previous medications were withdrawn from Saudi FDA.

2.4 Other Drugs

Two surfactants were mentioned in the European Consensus Guidelines on the Management of Respiratory Distress Syndrome (2022 update): Poractant alfa which was approved by FDA in 1999, and Bovatcant (Alveofact®) which was designated as an orphan medicine for the treatment of respiratory distress syndrome in the European Union on 24 February 2022. Poractant is not registered by SFDA as well.

Section 3.0 Key Recommendations Synthesis

NRDS applies to all forms of abnormal gaseous exchange at the level of the lung of a neonate irrespective of the cause. It is an inability to maintain respiratory homeostasis, leading to impairment of gaseous exchange, ventilation-perfusion mismatch and cerebral anoxia.

NRDS is a common neonatal emergency worldwide. In one recent study, 1.9% of premature babies who had NRDS later developed cerebral palsy, compared with 0.5% of premature babies who did not have NRDS. Another study published in 2018 found that premature infants had a higher risk of childhood epilepsy.

Incidence of RDS ranges from 1.5 cases per 100 000 to nearly 79 cases per 100 000. A scoping review published in 2020 showed that the prevalence of NRD ranged from 0.21 to 84.8% and the highest prevalence rates were observed in Saudi Arabia (78.5%) and other countries.

The aim of modern RDS management is to maximize survival while minimizing complications such as air leaks and Bronchopulmonary dysplasia (BPD).

Neonatal care settings where CPAP is routinely used to stabilize preterm infants, and when the rate of antenatal corticosteroid administration has been high (>50%), prophylactic surfactant is no longer recommended.

Noninvasive respiratory support (e.g., CPAP) should be provided to preterm infants with RDS from birth. Early surfactant should be provided for newborns with increasing severity of RDS, demonstrated by escalating or sustained levels of oxygen requirement and other clinical or radiological indications.

If a preterm baby <30 weeks of gestation requires intubation for stabilization, they should be given surfactant (A2). Babies with RDS needing treatment should be given an animal-derived surfactant preparation (A1).

Use of surfactant before inter-facility transport of preterm infants was found to be associated with lower oxygen requirement during transport and shorter duration of ventilation support, compared with controls.

Repeated dosing of surfactant should be provided to infants only when there is evidence of ongoing moderate to severe RDS.

Animal-derived and the newer generation synthetic surfactants are both effective for treating RDS and improving survival without BPD.

Two surfactants were mentioned in the European Consensus Guidelines on the Management of Respiratory Distress Syndrome: 2022 Update, Poractant alfa which was approved by FDA in 1999 and Bovatcant (Alveofact®) which was designated as an orphan medicine for the treatment of respiratory distress syndrome in the European Union on 24 February 2022. Poractant is not registered by SFDA as well

Section 4.0 Conclusion

This report serves as **an annex to the previous NRDS report** and aims to provide recommendations to aid in the management of NRDS. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with NRDS. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

Section 5.0 References

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Section 6.0 Appendices

Appendix A. Prescribing Edits

Some covered drugs may have additional requirements, rules or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age Edit):	Coverage may depend on patient age
CU (Concurrent Use Edit):	Coverage may depend upon concurrent use of another drug
G (Gender Edit):	Coverage may depend on patient gender
MD (Physician Specialty Edit):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limit):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another Drug
EU (Emergency use only):	This drug status on Formulary is only for Emergency use.
PE (Protocol edit)	Use of drug is dependent on protocol combination, doses and sequence of therapy

Examples:
Age edit: Desmopressin in Nocturnal Enuresis should not be prescribed for children < 5 years.
Concurrent Use Edit: Flavoxate in Nocturnal Enuresis should be used as add on to desmopressin after desmopressin failure and cannot be used alone.
Gender Edit: Exemestane in Endometriosis should be used only by Females.
Physician Specialty Edit: Fentanyl in Endometriosis should be prescribed by a gynecologist or pain management specialist.
Prior Authorization: Desmopressin in Nocturnal Enuresis: The prescriber must check the following before prescribing:

- Failure of combination of behavioral and alarm therapy.

Quantity Limit: Idarubicin in Acute Leukemia: Cumulative dose should not exceed 150 mg/m2. Please note that this Quantity Limit is different than the one based on maximum daily dose as this is not necessary based on Maximum Daily Dose
Step Therapy: Aripiprazole in Social Anxiety: should be used as third line after:
First-line: Escitalopram, fluvoxamine, fluvoxamine CR, paroxetine, paroxetine CR, pregabalin, sertraline, venlafaxine XR
Second-line: Alprazolam, bromazepam, citalopram, clonazepam, gabapentin
Emergency use only: Furosemide IV form in Hypertension is used only in emergency setting.
Protocol edit: Bendamustine Hydrochloride, Cyclophosphamide, Ifosfamide, Dacarbazine should be used in Lymphoma as per the following protocol

I. Adult and Pediatric Quantity Limit?

This is either the adult or pediatric maximum amount of a drug that can be administered per day based on a maximum daily dose.
If there is no clinical evidence supporting the quantity limit for that relevant indication, this column will be left as Blank.

II. What information are available in the notes?

“Notes” section provides details of the prescribing edits, extra important drug information and special warning and precautions.

III. Drug interactions

- A: No known interaction
- B: No action needed
- C: Monitor therapy
- D: Consider therapy modification
- X: Avoid combination

IV. Defined Daily Dose

The Defined Daily Dose (DDD) is to be set based on the WHO recommendations https://www.whocc.no/ddd/definition_and_general_considera/

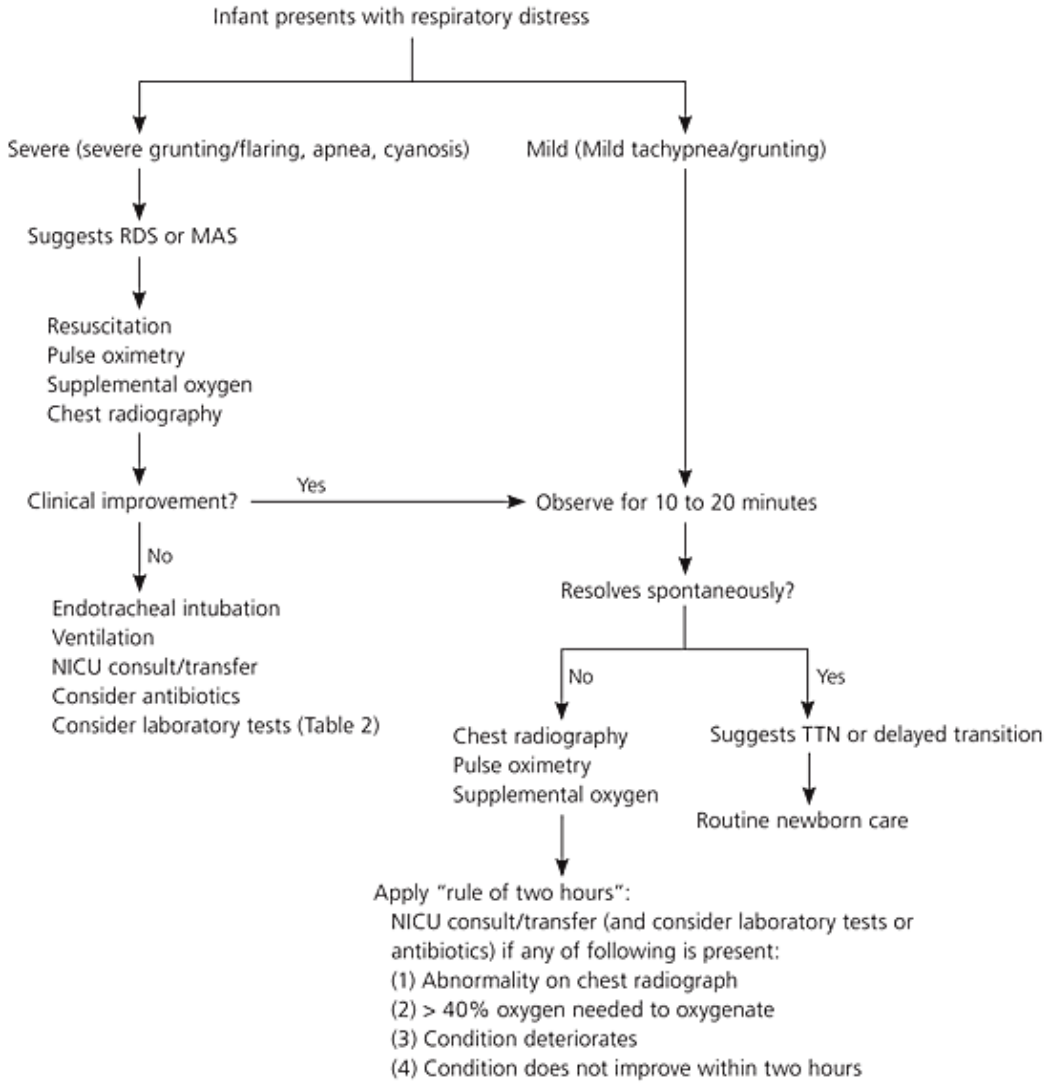
V. REMS

A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks.

Appendix B. Level of Evidence Adopted

Grade of research[26]	
A	Strongly recommend; Good evidence
B	Recommend; At least fair evidence
C	No recommendation for or against; Balance of benefits and harms too close to justify a recommendation
D	Recommend against; Fair evidence is ineffective, or harm outweighs the benefit
E	Evidence is insufficient to recommend for or against routinely; Evidence is lacking or of poor quality; Benefits and harms cannot be determined.
Level of evidence	
Level I	Meta-analysis of multiple studies
Level II	Experimental studies
Level III	Well-designed, quasi-experimental studies
Level IV	Well-designed, non-experimental studies
Level V	Case reports and clinical examples

Appendix C. Management of Neonatal Respiratory Distress Algorithm



RDS = respiratory distress syndrome; MAS = meconium aspiration syndrome; NICU = neonatal intensive care unit; TTN = transient tachypnea of the newborn.

Figure 1. *Treatment Algorithm for the Management of Neonatal Respiratory Distress (Adapted from American family Physician[27])*

Appendix D. Scope

2020 Version	Changes Performed	2023 (Current version)	Rationale/Description
Not available	New section	Scope	Summarize the main changes and updates between the 2020 and 2023 versions
Executive Summary	New section	Background	A general overview covering pathophysiological and epidemiological aspects was added.
Section 1. NRDS CLINICAL GUIDELINES			
European Consensus Guidelines on the Management of Respiratory Distress Syndrome – 2019 Update	**Updated**	European Consensus Guidelines on the Management of Respiratory Distress Syndrome: 2022 Update	Sweet DG, Carnielli VP, Greisen G, Hallman M, Klebermass-Schrehof K, Ozek E, Te Pas A, Plavka R, Roehr CC, Saugstad OD, Simeoni U, Speer CP, Vento M, Visser GHA, Halliday HL. European Consensus Guidelines on the Management of Respiratory Distress Syndrome: 2022 Update. Neonatology. 2023;120(1):3-23. doi: 10.1159/000528914. Epub 2023 Feb 15. PMID: 36863329; PMCID: PMC10064400.
Not available	New section	Neonatal Respiratory Distress Syndrome, 2023	Yadav S, Lee B, Kamity R. Neonatal Respiratory Distress Syndrome. [Updated 2023 Jul 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560779/#

Not available	New section	Guidelines for surfactant replacement therapy in neonates, Canadian pediatric society, 2021	Ng EH, Shah V. Guidelines for surfactant replacement therapy in neonates. Paediatr Child Health. 2021 Feb 1;26(1):35-49. doi: 10.1093/pch/pxaa116. PMID: 33552321; PMCID: PMC7850281.
Not available	New section	The epidemiology, risk factors, mortality rate, diagnosis, etiologies and treatment of neonatal respiratory distress: a scoping review, 2020	Joel Noutakdie Tochie, Aurelie T. Sibetcheu, Celestin Danwang et al. The epidemiology, risk factors, mortality rate, diagnosis, etiologies and treatment of neonatal respiratory distress: a scoping review, 30 December 2020
Section 2. DRUG THERAPY FOR NRDS			
None			
Not existing	**New section**	**Section 4. Key Recommendations Synthesis**	
Not existing	**New section**	**Section 5. Conclusion**	
References	Updated	**Section 6. References**	
Appendices	Updated	**Section 7. Appendices**	