EPIQ Lung Health Group Journal Club

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

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ABSTRACT

Respiratory distress syndrome (RDS) care pathways evolve slowly as new evidence emerges. We report the sixth version 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. Optimising outcome for babies with RDS includes prediction of risk of preterm delivery, appropriate maternal transfer to a perinatal centre, and appropriate and timely use of antenatal steroids. Evidence-based lung-protective management includes initiation of non-invasive respiratory support from birth, judicious use of oxygen, early surfactant administration, caffeine therapy, and avoidance of intubation and mechanical ventilation where possible. Methods of ongoing non-invasive respiratory support have been further refined and may help reduce chronic lung disease. As technology for delivering mechanical ventilation improves, the risk of causing lung injury should decrease, although minimising time spent on mechanical ventilation by targeted use of postnatal corticosteroids remains essential. The general care of infants with RDS is also reviewed, including emphasis on appropriate cardiovascular support and judicious use of antibiotics as being important determinants of best outcome. We would like to dedicate this guideline to the memory of Professor Henry Halliday who died on November 12, 2022. These updated guidelines contain evidence from recent Cochrane reviews and medical literature since 2019. Strength of evidence supporting recommendations has been evaluated using the GRADE system. 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 Paediatric Research (ESPR) and the Union of European Neonatal and Perinatal Societies (UENPS).

COMMENTARY (EPIQ Lung Health Group)

This publication highlights the European Consensus Guidelines for the management of RDS. It was developed by a panel of experts in perinatal and neonatal medicine. It is the sixth version of these guidelines, and the previous update was done in 2019. You will find at the end of the commentary a table comparing the latest CNN Lung Health Group (LHG) BPD bundle (updated in 2020) and the European Consensus Guidelines side-by-side.

The guidelines have been divided in 4 sections: prenatal care, delivery room stabilization, respiratory support and surfactant, and supportive care. To make the comparison with the current LHG clearer the same categories have been kept for comparison. *It is important to note that the authors of the European Guidelines mention that these do not apply to premature babies <25 weeks GA*. It is important to note that admissions <25 weeks GA now represent about ¼ admissions of babies <29 weeks GA and 1/10 admissions of babies <32 weeks in the CNN.

1. *Prenatal care*

The Prenatal care section of the guideline is more developed than the LHG BPD bundle, partly because of the collaboration already in place within the different groups of the CNN and CPTBN. In the prenatal care section, the authors highlight some important points that are not part of the BPD bundle – for example, the *in-utero* transfer of babies at-risk of being born premature. Many of the prenatal care recommendations should be discussed with our OBGYN colleagues to improve the outcomes for these babies.

2. *Delivery room stabilization*

Both the BPD Bundle and the European Consensus Guidelines recommend the use of CPAP for stabilization of spontaneously breathing preterm infants. The European Consensus Guideline provides a direct recommendation with regards to reserving intubation for infants who do not respond to positive pressure ventilation as a strategy to reduce BPD that is not present in the BPD bundle. Additional differences in this section can be attributed to the presence of the NRP guidelines in Canada which cover recommendations such as T-piece device, FiO_2 recommendations at delivery and are not addressed in the BPD bundle.

3. *Respiratory support and surfactant therapy*

a) *Surfactant therapy:* The recommendations of both groups are similar with regards to the use of CPAP and early selective surfactant at a threshold of > 30% oxygen on CPAP, with a new recommendation in the 2022 RDS guideline to utilize lung ultrasound as an alternative way to guide early treatment with surfactant as well as emphasis on the impact of MAP on utilizing FiO_2 thresholds and the need to utilize lower FiO_2 thresholds for extremely preterm infants. In terms of the method of surfactant administration to spontaneously breathing infants, both documents recommend the use of LISA/MIST, however a new recommendation in the 2022 version of the European Consensus Guidelines is the use of the laryngeal mask (LM) as an alternative method for surfactant administration in babies >1kg. This recommendation may address issues related to the ability to deliver early surfactant non-invasively for units that may not have competence in the MIST/LISA techniques. This recommendation is based on 2 RCTs. One was a RCT of LM surfactant administration vs CPAP (no surfactant)[1] and the other was a RCT of LM administration vs traditional (ETT) administration of surfactant with premedication[2].
b) *Mode of ventilation:* Both the BPD Bundle and the European Consensus Guidelines recommend the use of volume targeted ventilation with minor differences in terms of the initial tidal volume setting varying from 4.5-5.5ml/ kg and both acknowledging the need for higher tidal volume delivery with later post-natal ages. High frequency ventilation is included as an alternative option in both the BPD bundle and European Guidelines as a mode that can be used to facilitate lung protection. Both guidelines emphasize the importance of limiting the duration of invasive ventilation through early extubation.
c) *Nitric Oxide*: The BPD Bundle does not provide recommendations for use of Nitric Oxide (NO) whereas the updated version of the European Consensus Guidelines provides some guidance that NO use should be limited to a therapeutic trial in preterm infants with evidence of pulmonary hypertension and severe respiratory distress.
d) *Steroid use*: Both recommendations address the use of postnatal steroids with slightly different conclusions. The European Consensus Guidelines warrants caution for the use of prophylactic hydrocortisone in the first days of life especially in the babies <26 weeks GA due to the risk of negative interactions seen in infants with high baseline endogenous cortisol levels which may increase risk of severe IVH and gastrointestinal perforation published in 2021. The BPD bundle recommends the use of prophylactic hydrocortisone in select high risk populations with the caution of an increased risk of late onset sepsis, however these recommendations were based on evidence available prior to 2020 and may need to be revised to reflect the current body of evidence. The European Consensus Guidelines do not discuss the use of late hydrocortisone, and make a similar recommendation as the EPIQ LHG regarding the use of dexamethasone to facilitate extubation in infants who remain on mechanical ventilation after the first week of life. Both the BPD bundle and the updated European Guidelines do not recommend the routine use of inhaled steroids.

4. Supportive care

The European Guidelines specifically addresses areas related to early nutrition, thermoregulation and hemodynamic considerations of the preterm infant which are not specifically covered in the BPD Bundle but are covered under NRP guidelines or other EPIQ bundles in Canada.

Overall, the recommendations between the updated 2022 European Consensus Guideline for RDS management and the EPIQ Lung Health Group BPD bundle released in early 2020 are fairly consistent. The differences in recommendations that exist can be mostly attributed to evidence that has been published since 2019 which was not available when the updated Lung Health BPD bundle was released in 2020. The European Consensus Guidelines includes a larger number of recommendations when compared to the EPIQ BPD bundle as it addresses in detail prenatal and obstetrical management and additional recommendations regarding delivery room stabilization that are largely covered in the NRP guidelines. The 2022 update to the European Consensus Guidelines for the Management of RDS is in its 6th version and highlights the need to continually update and revise recommendations to help improve the lung health of preterm infants as new evidence emerges.

	EPIQ LHG Bundle	**European Consensus Guidelines**
Prenatal care	Antenatal steroid administration	Transfer of mother to perinatal centers
		Offer a single course of antenatal steroids A single repeat course may be given if the first course was administered 1-2 weeks earlier (<32 wks)
		MgSO4 should be administered in imminent labor (<32 wks)
		Consider tocolytics to complete steroids or and/or in utero transfer
Delivery		Delay clamping the umbilical cord for at least 60s, especially in stable preterm infants
		Use a T-piece device rather than bag and mask

		Stabilize spontaneously breathing preterm infants with CPAP. If apneic, start mask ventilation/inflations, at initial pressure of 6-8 cmH2O and PIP 20-25 cmH2O
	Initiate resuscitation using FiO2 0.21-0.3 and titrate O_2 to achieve pre-ductal saturation >85% by 7-10 minutes of age	Use an oxygen blender, start with FiO2 - 0.3 for <28 weeks - 0.21-0.3 for 28-31 weeks - 0.21 for 32 and above Adjust FiO_2 guided by pulse oximetry Aim for SpO_2 of 80% or more by 5 min of age
		Intubation should be reserved for babies not responding to PPV via face mask or nasal prongs
		Plastic bag or occlusive wrapping, radiant warmers, and humidified gas should be used during stabilization for babies <32 weeks of gestation to reduce the risk of hypothermia
Respiratory support and surfactant	MIST or LISA is the preferred mode of surfactant administration for spontaneously breathing babies ≥ 26 weeks GA provided that clinicians are experienced with this technique	Use natural surfactant given by LISA technique where possible
		Laryngeal mask surfactant can be used for more mature infants >1000g
	Preterm infants with clinical or radiological evidence of RDS who require intubation for initial stabilization or early in the neonatal period should be given surfactant	If intubated for stabilization <30 wks, give surfactant
	Preterm infants with RDS who are managed with non-invasive respiratory support as an initial mode should receive early selective surfactant with a FiO2 threshold of greater than 0.3 and no later than 0.5	Treat worsening RDS with surfactant when FiO_2>0.3 on CPAP pressure ≥ 6 cmH_2O or if Lung US suggest surfactant deficiency
		Consider lower FiO_2 thresholds for very immature infants

	Infants with evidence of RDS on chest X-Ray and who have persistent or recurrent oxygen (>0.3) and ventilatory requirements within the first 72h of life should have repeated doses of surfactant	A second and third dose of surfactant can be given if there is ongoing evidence of RDS
	Maintain consistent CPAP to prevent lung de-recruitment Continue use of appropriate distending pressure to maintain FRC Volume targeted ventilation is recommended. over pressure limited ventilation to minimize risk of BPD	Start CPAP of (s)NIPPV as soon as possible in all babies at risk of RDS, HFNC can be used as an alternative, provided centres can provide CPAP or NIPPV for those failing HFNC If MV is required, use lung protective modes such as VTV or HFO
	Appropriate use of High Frequency Ventilation (HFV) – criteria to be developed locally	

	Extubate as early as clinically appropriate Tidal Volume Targets **Birth weight less than 800g: VT = 4.5 – 5.5 ml/kg** with the higher VT for smaller infants (fixed flow sensor dead space). **Larger preterms: VT = 4 - 5 ml/kg** **Preterms with evolving BPD (2+ weeks old): 5.5 - 6.0 ml/kg** (increased anatomical and alveolar dead space). In infants with evolving BPD, selection of mode of ventilation should follow careful assessment of clinical status and radiological findings such as presence of atelectasis or pulmonary interstitial emphysema. High frequency oscillatory or jet ventilation are frequently used in those infants. Conventional ventilation might be used as well; however, some observational studies showed older preterm infants have increased alveolar dead space and may require VT > 6 ml/kg with reduced work of breathing with VG of 7 ml/kg. BPD rates were not reported with this strategy.	Minimize the duration of MV
		When weaning from MV, tolerate moderate hypercarbia but maintain pH > 7.22
		Use iNO only where there is strong evidence of PHN such as pre- and post-ductal saturation difference

	Preterm infants who cannot be treated with MIST/LISA and require intubation solely for surfactant administration should be evaluated for rapid extubation back to non-invasive respiratory support (INSURE) as opposed to routine mechanical ventilation to reduce duration of MV	Spontaneously breathing babies on MV should be extubated to CPAP, HFNC, or NIPPV immediately following surfactant BiPAP[3] confers no advantage over CPAP; however (s)NIPPV can reduce need for ventilation or need for re-ventilation following extubation
	Non-invasive positive pressure ventilation (NIPPV) or CPAP should be used as post extubation support to reduce risk of re- intubation in preterm infants If using CPAP as primary post extubation support; use higher CPAP levels (greater than 6cmH20) with escalation to NIPPV (via a ventilator) as rescue therapy to reduce risk of re-intubation. Do not use HFNC in the immediate post extubation period, insufficient evidence on use in infants less than 28 weeks gestation	
	Caffeine for apnea of prematurity Early Caffeine	Use caffeine routinely in infants <32 weeks GA to minimize need for MV
	Clinicians may consider prescribing a course of low-dose hydrocortisone (physiologic replacement dose) beginning in the first 24-48h after birth, for 10 days, to selected infants at the highest risk of BPD (e.g.: <28weeks GA, exposure to chorioamnionitis). There may be an increased risk of LOS associated with this practice. Hydrocortisone should not be combined with indomethacine prophylaxis.	

	Dexamethasone in the first week of life to prevent BPD should not be given. The routine use of dexamethasone for all infants who require assisted ventilation after 7 days of age to treat evolving BPD is not recommended The benefits of late (after 7 days of life) dexamethasone therapy appear to outweigh the adverse effects for infants who are at high risk of BPD. In these circumstances, low-dose dexamethasone (initial dose 0.15-0.2 mg/kg/day) should be used in most circumstances in tapering doses over a short course (7-10 days)	Consider low-dose dexamethasone to facilitate extubation in infants ventilated >1-2 weeks
	Hydrocortisone to treat infants at high risk of BPD, after the first week of life, or infants with prolonged ventilator dependence is not recommended	
	The routine use of inhaled corticosteroids to prevent BPD is not recommended	
	Use in-line suction No routine suctioning, suction only as clinically indicated Avoid ventilator disconnect	
	Always use blenders when on oxygen therapy	
	Use daily histogram to guide respiratory support and oxygen therapy to aim for maintaining SpO2 within alarm limits for greater than 70% of time	
	Enforce high alarm setting on monitor when infant is receiving oxygen	
	No absolute recommendations can be given at this time for BPD prevention	Oxygen saturation target should be between 90-94% with alarm limits 89-95%

Supportive care		Maintain body temperature between 36.5-37.5 at all time
	TPN within 4 hours of life if <1500 g	Start TPN from birth, initial fluids around 80 mL/kg/day, restrict sodium intake during the first few days
	Monitor weight change closely in first 7 days to optimize fluid and sodium intake	
		Start enteral feedings with mother's milk from day one if the baby is stable
		Use antibiotics judiciously and stop when early sepsis is ruled out
		Monitor BP regularly, aim for normal tissue perfusion, use inotropes where deemed necessary (ECHO advised), and maintain Hb within acceptable levels
	Routine prophylaxis with macrolides for BPD prevention in preterm infants is not recommended. However , select high risk population/Ureaplasma positive patients may benefit – especially with early treatment with azithromycin/clarithromycin. Currently, optimal dosing remains unknown	
	Vitamin A (availability issue in Canada)	
	Implement standardized practices to reduce unplanned extubation.	
	Daily discussion regarding respiratory management and O2 therapy status	
	Multidisciplinary discussions regarding respiratory management of difficult patients	

CNN: Canadian Neonatal Network
CPTBN: Canadian Preterm Birth Network

FRC: Functional Residual Capacity
MAP: Mean Airway Pressure
GA: Gestational age
HFNC: High flow nasal cannulae
HFO: High frequency oscillation
LOS: Late-onset Sepsis
MV: Mechanical ventilation
NRP: Neonatal Resuscitation Program
(s)NIPPV: (synchronized) Non-Invasive Positive Pressure Ventilation
VTV: Volume targeted ventilation

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[1] Roberts KD, Brown R, Lampland AL, Leone TA, Rudser KD, Finer NN, et al. Laryngeal mask airway for surfactant administration in neonates: a randomized, controlled trial. J Pediatr. 2018 Feb; 193: 40–6. e1.

[2] Gallup JA, Ndakor SM, Pezzano C, Pinheiro JMB. Randomized trial of surfactant therapy via laryngeal mask airway versus brief tracheal intubation in neonates born preterm. J Pediatr. 2022 Oct 12; 3476(22): S002200891–5.

[3] BiPAP in the European Guidelines refers to what the NIPPV vs CPAP CER called Biphasic