ankura hospital
for women & children

MEDICAL INSIGHTS

EDITION-3

SPECTRUM OF RESPIRATORY DISTRESS SYNDROME IN PRETERM NEONATES

Case-Based Discussions

Founder's Note

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Greetings,

As I write this note today, I feel very optimistic about the year ahead. The COVID-19 vaccination drive is underway and thousands of healthcare workers are receiving protection against the virus as we speak. More good news came in the form of our yearly budget as our government announced a 137% increase in healthcare expenditure. These developments have been a confidence booster for Ankura Hospital, especially as we prepare for the inauguration of our tenth and newest branch at LB Nagar on February 15th.

Our vision of providing a complete healthcare experience for women and children nation-wide is being realized, and at a healthy pace! An important part of this pursuit is to achieve clinical excellence. Two months back, we have started our monthly newsletter, Medical Insights, with the idea of discussing significant cases and to enable a free exchange of knowledge and ideas between peers in our medical fraternity. I'd like to thank Dr Srinivas Jakka for spearheading this and leading the editorial responsibilities. The overwhelming response that we received for the 1st and 2nd editions has only strengthened our commitment to our goals!

Thank you for your support in all of our endeavours.

Looking forward to a COVID free world, and many more such insightful newsletters.

Best Wishes,
Dr Krishna Vunnam

Message From The Editor

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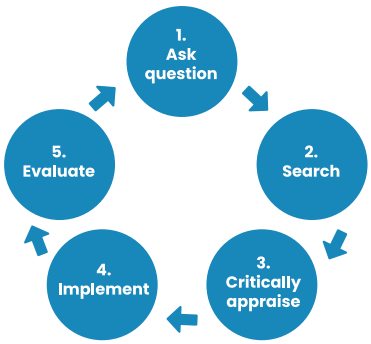

Dear friends,

In the previous edition, we have discussed the various steps involved in evidence-based practice. The steps involved include:

1. Asking a question
2. Finding information/evidence to answer question
3. Critically appraise the information/evidence
4. Integrate appraised evidence with own clinical expertise and patient's preferences
5. Evaluating our effectiveness and efficiency in executing Steps 1-4 and seeking ways to improve them

Let us now discuss the first step. It involves converting the information we need into an answerable question. PICO is a usefultool for asking focused clinical questions.

P - patient/population/problem
I - intervention/exposure
C - comparison
O - outcome

Once you have formulated a focused clinical question using PICO, it is also useful to decide what type of question it is. Does it deal with the aetiology, diagnosis, investigations, treatment, patient experience, or prognosis of a given clinical condition? This will help you decide what type of clinical studies to look for in the next step, namely, finding evidence for the clinical question.

The current edition includes case-based discussions on respiratory distress syndrome (RDS) in newborn babies by our experienced neonatologists.

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Case 1

RDS IN AN EXTREME PRETERM NEONATE

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Case 2

RDS IN A LATE PRETERM NEONATE

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Case 3

RDS WITH SECONDARY PPHN

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CASE-1
SPECTRUM OF RESPIRATORY DISTRESS SYNDROME IN PRETERM NEONATES

A female baby was born at 27 weeks gestation with a birth weight of 950g to a 25 year old primi by LSCS (indication: severe PIH). The pregnancy was otherwise uncomplicated. Mother received one complete course of antenatal steroids and Magnesium Sulphate was given for neuro protection. Baby cried at birth and was received in a plastic bag. Delayed cord clamping was done after 1 minute and was shifted to pre-warmed resuscitaire. She soon developed respiratory distress in the form of tachypnea, retractions and grunt.

Q1. Will you intubate this baby?

Evidence from three high-quality randomized controlled trials (COIN, SUPPORT, and VON DRM trials) showed that early CPAP when initiated in delivery room was associated with significant reduction in need for intubation, mechanical ventilation, and surfactant usage when compared to the conventional approach of 'mechanical ventilation with or without surfactant'.

Initial stabilization on CPAP should be the preferred approach even in preterm neonates ≤ 28 weeks of gestation.[1]

Case: Baby was started on CPAP of 5 cm/ FiO_2 0.25 with T-piece resuscitator in delivery room on which she maintained saturation of 91-95%. She was then transferred to NICU in a pre-warmed transport incubator. Admission temperature was 36.7°C.

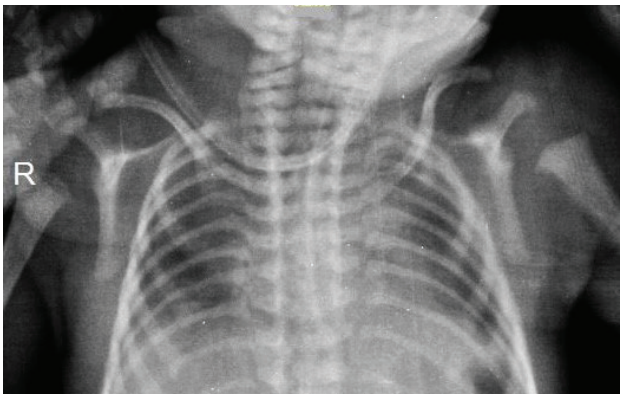
Q2: What respiratory support will you start this baby on, CPAP or NIPPV?

In a meta-analysis of 10 trials, early NIPPV showed significantly reduced risk of respiratory failure, need for intubation and also reduced risk of CLD, as compared to early CPAP in preterm neonates with RDS.[2]

NIPPV delivered by a ventilator using synchronised or non-synchronised methods may be used as the primary mode in preterm neonates with RDS where equipment and its expertise are available.[1]

Case continued: Baby was started on bubble CPAP of 6 cm of H_2o, FiO_2- 0.25, on which she maintained saturations.

Venous Blood gas at admission: pH 7.22, pCO_2 56, pO_2 45, HCO_3- 18.8, BE -6



Chest X-ray at admission
Low volume lungs
Reticulo-granular pattern both lung fields

Q3: How do you diagnose Respiratory Distress Syndrome in preterm? Is there a need of chest X-ray for diagnosing or for initiating treatment?

The diagnosis is RDS is primarily based on the

clinical presentation supported by certain historic information (incomplete / no antenatal steroids) and a chest X-ray.[1]

Clinical features: early onset respiratory distress (usually within the first 6 hours of life) in a preterm neonate. Chest X-ray findings: low volume lungs, reticulo-granular opacities, air bronchograms, ground glass appearance.

Chest X-ray is desirable for diagnosis, but is not essential for the initiation of treatment.

Case: This baby was diagnosed to have RDS based on clinical presentation and supported by chest X-ray evidence. She maintained saturation of 91-95% on CPAP of 6 cm of H_2O and FiO_2 of 0.25.

Q4: Does this baby need surfactant? Is there a role of prophylactic surfactant?

Surfactant prophylaxis is traditionally defined as surfactant administration on the basis of gestational age and/or expected high risk of RDS.

A systematic review of studies that compared prophylactic surfactant administration (through intubation) with stabilization on CPAP and early rescue surfactant (if required) showed that infants initiated on CPAP were at lower risk of broncho-pulmonary dysplasia or death. Preterm neonates with RDS should be stabilized on CPAP and if indicated selective surfactant replacement therapy should be administered.[3]

There is a subgroup of preterm neonates who might require intubation in the delivery room for stabilization. The European Consensus Guidelines on the management of Respiratory Distress Syndrome – 2019 Update recommends the use of surfactant in such neonates in the delivery room. Clinicians may consider delivery room surfactant in this subgroup of neonates.

Prophylactic surfactant administration should not be used to treat preterm neonates < 28 weeks gestation with RDS.

Case continued: Over next 1 hour baby had worsening respiratory distress and the increase in FiO_2 to 0.35.

Q5: Does this baby require surfactant now? What is early rescue?

Early selective surfactant administration showed reduction in the risk of neonatal mortality, BPD, reduction in BPD or death at 36 weeks, risk of pneumothorax, pulmonary interstitial emphysema and overall air leak syndromes.[2]

Early rescue (within 2 hours) surfactant should be administered along with CPAP in preterm neonates with RDS. Outcomes are best if surfactant is reserved for infants showing clinical signs of RDS.

Suggested protocol would be to give surfactant to preterm babies less than 34 weeks gestation if FiO_2 requirement is more than 0.3 on CPAP of at least 6 cm.[1]

Q6: What is the optimal preparation? Bovine (Survanta) or Porcine (Curosurf)?

Evidence has shown that 200 mg/kg poractant-α (a porcine surfactant) was associated with lower BPD/mortality, BPD, retreatment, air leaks, pulmonary haemorrhage.[4]

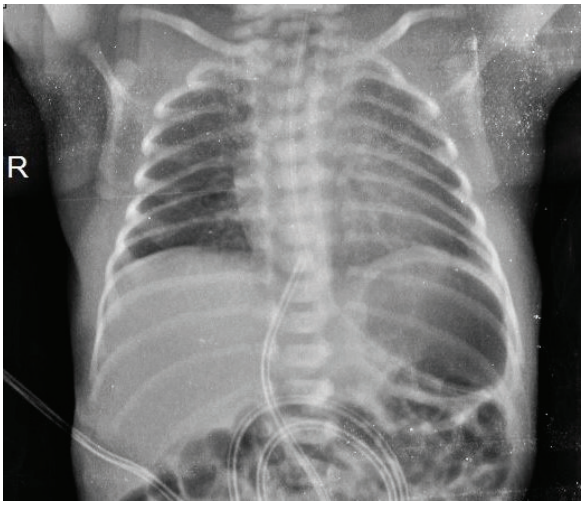
Q7: How will you give surfactant - INSURE or LISA?

Recent meta-analyses demonstrated reduction in composite outcome of death or BPD at 36 weeks, BPD at 36 weeks among survivors, need for mechanical ventilation within 72 hours of birth, need for mechanical ventilation anytime during the NICU stay, in infants who were treated with LISA/MIST technique.[5] However LISA requires special expertise especially in extremely low gestational age neonates and there are also some limitations like failure to insert the catheter through the vocal cords at first attempt, significant surfactant reflux, acute desaturations, bradycardia and/or need for manual ventilation during the procedure.

INSURE is the method of choice. LISA can be tried in case of expertise and availability.[1]

Case: As this baby had worsening respiratory distress with increase in FiO_2 requirement > 0.3, **Porcine surfactant (200mg/kg) was given via MIST at 1 HOL.**

Post surfactant FiO_2 requirement came down to 0.25 and bubble CPAP of 6 cm of H_2O was continued. At 4 HOL baby again had increase in subcostal retractions and FiO_2 requirement increased to 0.4. Repeat chest X-ray was done to look for severe RDS, pneumothorax, selective surfactant administration in to the right lung (inadvertently).



Low volume lungs
(better than the initial X-ray)
Reticulo-granular pattern both lung fields

As baby had worsening retractions and chest X-ray showed evidence of low volume lungs, CPAP was increased to 7 cm of H_2O. However baby continued to deteriorate with worsening respiratory distress on CPAP of 7 cm of H_2O and had frequent desaturation needing FiO_2 of 0.45.

Q8: Does this baby need a repeat dose of surfactant? How early second dose of surfactant can be given after the first dose?

In infants with established RDS, a policy of multiple doses of animal derived surfactant resulted in greater improvements regarding oxygenation and ventilatory requirements, a decreased risk of pneumothorax and a trend toward improved survival.[6]

Evidence from a single RCT (Kattwinkel et al) which compared the relative efficacy of administering second and subsequent

doses of a natural surfactant at low (FiO_2 > 0.30, still requiring intubation) & high (FiO_2>0.40, MAP>7cm H_2O) thresholds after a minimum of 6 hours showed no benefits from retreating at the lower threshold, except in those babies with complicated RDS (evidence of perinatal compromise or sepsis) who had a lower mortality with low threshold retreatment.[7]

AAP recommends a gap of 12 hours between the doses. The CPS suggests using the second dose as early as 2 hours and subsequent doses at 4-6 hourly intervals.

Clinicians can use a higher threshold (MAP/ CPAP of > 7 cm of H2O, FiO_2 of > 0.4) for repeat doses of surfactant in preterm less than 34 weeks of gestation.
Repeat dose may be given as early as 2 h after the initial dose or, more commonly, 4 h to 6 h after the initial dose.[8]

Case continued: As this baby had worsening respiratory distress and desaturation on CPAP of 7 cm and FiO_2 of 0.45, second dose of Porcine surfactant was given at a dose of 100 mg/kg (1.25 ml/kg of Curosurf) via MIST. After second dose of surfactant, respiratory distress improved and FiO_2 requirement came down to 0.3. CPAP was decreased to 6 cm of H2O after 4 hours (8 hours of life) as the baby had minimal retractions and FiO_2 requirement was 0.25.
As baby continued to improve, CPAP was weaned gradually to 5 cm of H_2O and then to 4 cm of H_2O over next 12 hours. On day of life 3, baby was started on heated humidified high flow at 5 L/min,FiO2-0.21.

Take-Home Messages:

- Preterm neonates with RDS should be stabilized on CPAP and selective surfactant replacement should be given only if indicated. No role of prophylactic surfactant.
- Early Rescue surfactant to be given in preterm babies less than 34 weeks gestation if FiO_2 requirement is more than 0.3 on CPAP of at least 6 cm of H_2O.
- Poractant-α (200 mg/kg) may be used for preterm < 34 weeks gestation with RDS.
- INSURE is the method of choice. LISA can be tried in case of expertise &availability.
- For repeat doses of surfactant in preterm less than 34 weeks of gestation, higher threshold (MAP/CPAP of > 7 cm of H_2O, FiO_2 of > 0.4) may be used.
- Repeat dose may be given as early as 2 h after the initial dose.

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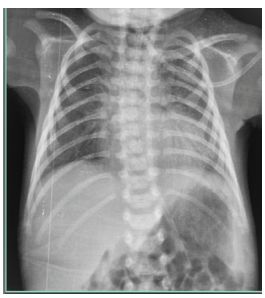
CASE-2
RDS IN A LATE PRETERM NEONATE

A 34^{+6} week male neonate with birth weight 2200gm was born to a G2P1L1 mother by emergency LSCS with indication being fetal hypoxia on MCA Doppler. Maternal morbidities were gestational diabetes on insulin therapy and hypothyroidism. She didn't receive any antenatal corticosteroids. Baby didn't cry after birth and required PPV for about 90 seconds. However, exact details of Apgar scores were not documented. Baby developed respiratory distress soon after the birth and started on bubble CPAP support. Antibiotics were started in view of clinical sepsis. At 48 hours of life, baby had worsening of respiratory distress and was transported to level III NICU for further management. Admission temperature was noted to be 37.2°C & had Respiratory distress of 7/10 on Silverman Anderson score. Baby was started on bubble CPAP and required PEEP of 7cm of H_2O and FiO_2 of 60%. Chest X-ray was suggestive of RDS.

Chest X-ray at admission:



Q1: How will you manage?

Baby was given bovine surfactant by Less Invasive Surfactant Administration (LISA) technique. Antibiotics were upgraded to cover Gram negative bacteria and GBS. Echocardiography was also done to rule out PPHN, congenital heart diseases like TAPVC. Baby responded well to the surfactant therapy and FiO_2 requirements came down.

Q2: Can surfactant be given in late preterm neonates with respiratory distress?

Studies on surfactant therapy in late preterm and early term population are very scarce. Evidence from three RCTs have shown beneficial effects of surfactant therapy in late preterm neonates with RDS in relation to decreased incidence of invasive mechanical ventilation, air leak and PPHN. Hence, it is suggested that surfactant may be given in late preterm neonates with RDS who satisfy the criteria for surfactant therapy.

Q3: What is the cut off for surfactant therapy in late preterm neonates with RDS?

The FiO_2 and PEEP thresholds for surfactant instillation in preterm neonates of lesser gestational ages are 0.30 and 6 cm H_2O. Most studies have used a FiO_2 cut off of 0.4 in the late preterm and term age group. Hence, it is appropriate that late preterm and early term neonates with RDS and requiring a PEEP of more than or equal to 7 cm H_2O & FiO_2 of more than 0.4 be considered for surfactant therapy, provided other causes of respiratory distress are unlikely.

Q4: In the above baby, surfactant was given late. What is the role of surfactant administration beyond 72 hours in preterm neonates?

Surfactant administration beyond 72 hours might not be beneficial in improving outcomes of preterm babies with RDS. The three RCTs comparing the effect of delayed surfactant beyond the first 72 hours did not show any substantial benefits. All these studies were done in developed countries. However, there are scenarios where surfactant might have to be given at a later stage of the disease process. This is especially true in developing nations where delay in transfer of the neonate to a referral centre might result in not receiving even single dose of surfactant until later stage. Surfactant therapy may be considered in such neonates even beyond 72 hours of life.

Q5: What is the role of surfactant in neonates with bacterial pneumonia?

Role of surfactant in neonates with bacterial pneumonia is not established. Evidence from studies suggest that surfactant use in neonatal pneumonia might decrease the risk of combined outcome of mortality or ECMO, reduce the duration of invasive mechanical ventilation as well as hospital stay. But these studies were of low quality. Hence, routine use of surfactant therapy may not be used in neonates with bacterial pneumonia.

Take-Home Messages:

- RDS is one of the most common causes of respiratory failure in late preterm neonates.
- Surfactant may be given in late preterm neonates with RDS who satisfy the criteria.
- PEEP of more than or equal to 7 cm H_2O and a FiO_2 of more than 0.4 may be used as cut-off for surfactant therapy in late preterms.
- Delayed surfactant beyond 72 hours may be considered in babies with severe RDS with no prior surfactant use.
- Routine use of surfactant therapy is not indicated in neonates with bacterial pneumonia.

References:

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CASE-3
RDS WITH SECONDARY PPHN

A $34^{6/7}$ weeks female neonate was born via emergency LSCS to a primigravida mother. The indication for C-section was fetal distress. There were no risk factors for sepsis in the mother. Mother did not receive antenatal corticosteroids. Baby did not cry immediately after birth and required positive pressure ventilation for 1 minute. APGAR at 1 and 5 min were 6 and 8 with normal cord arterial blood gas values. Baby had respiratory distress since birth with a Silverman-Anderson score of 6/10. She was stabilized on delivery room CPAP and shifted to NICU for further management. At admission, the core body temperature was 36.7^0C and baby was on CPAP, with increasing FiO_2 requirement. At $1^{1/2}$ HOL the neonate was on CPAP 7 cm H_2O & FiO_2 – 50%. She was given surfactant replacement therapy at $1^{1/2}$ HOL through INSURE. Post surfactant the neonate had a transient decrease in FiO_2 requirement followed by increasing distress as well as FiO_2 requirement (100%). She was intubated at 4 HOL & put on conventional mechanical ventilation with volume guarantee (volume- 5 ml/kg) with PIP of 24-26 cm H_2O, PEEP – 7 cm H_2O, FiO_2 – 85%, rate – 50 bpm, Ti – 0.35 seconds.

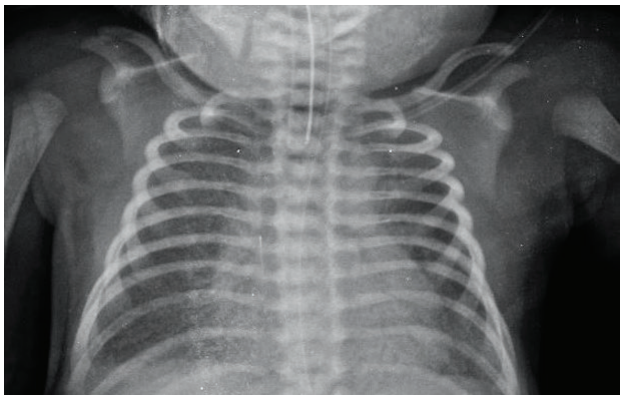
Q1: What are possible causes of respiratory deterioration post surfactant in this neonate and how will you proceed?

The possible causes for deterioration include –

	Differential diagnoses	Comments
1.	Air leak	Lung compliance improves post-surfactant, the PIP used during INSURE and the PEEP delivered during CPAP needs to be titrated to avoid delivering excessive pressures.
2.	Severe RDS disease pathology	In a late-preterm, this is quite unlikely as there were no other significant antecedent history such as gestational diabetes, severe perinatal asphyxia and hypothermia, all of which can cause or worsen surfactant dysfunction in RDS.
3.	Inadvertent selective surfactant instillation into right lung	This can occur if the endotracheal tube is accidentally inserted deeper than required during INSURE. Such neonates are prone for right sided pneumothorax due to increased right lung compliance, and alveolar de-recruitment, collapse of left lung due to surfactant deficiency.
4.	PPHN, TAPVC	PPHN can be primary or secondary. Late preterm neonates are more prone for primary PPHN. Secondary PPHN can be due to many causes such as RDS, pneumonia, sepsis, lung collapse, hypoxia, acidosis etc. TAPVC can also have a CXR picture similar to RDS.
5.	Pulmonary hemorrhage	The occurrence of pulmonary hemorrhage post surfactant is postulated to be due to increased lung compliance which would in turn increase the left to right shunting across PDA resulting in flooding of lungs and hence pulmonary hemorrhage.
6.	Bacterial pneumonia	This would be kept as the last of the differential diagnoses. Mother had no risk factors for sepsis. GBS pneumonia can mimic RDS, however it is rare in India.

Further investigations – Chest radiography, Echocardiography

Figure 1: Chest radiography at 4 HOL



Chest radiography findings –

- Well expanded lungs (due to recruitment by ventilation and surfactant)
- Grade II-III RDS
- Causes 1 and 3 listed in the table are ruledout. No blood in the ET while intubating – massive pulmonary hemorrhage (cause 5) ruled out.

Figure 2A: Echo Apical view showing dilated right ventricle (RV) (yellow arrow) **with a tricuspid jet** (velocity 3 m/sec) (red arrow)

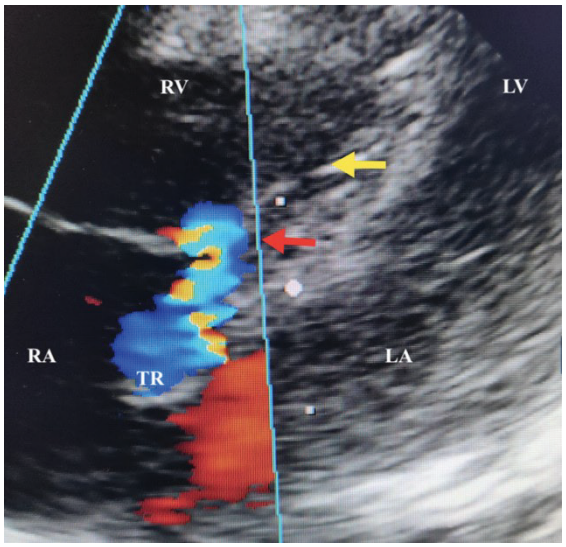
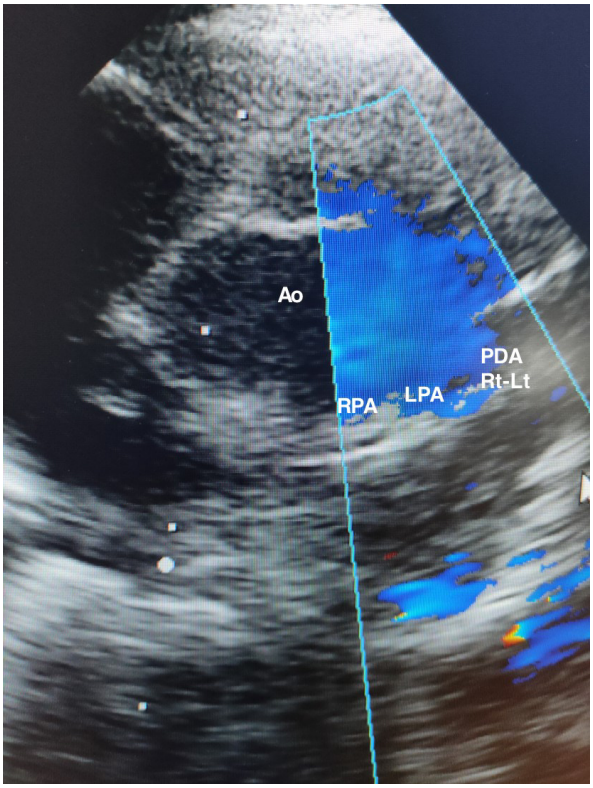


Figure 2B: Short axis view showing right to left shunting at PDA



Echocardiography findings –

- Raised pulmonary pressures (right ventricular systolic pressure = systemic systolic blood pressure)
- Left ventricular dysfunction, dilated right ventricle
- Right to left shunting at PDA and PFO
- All pulmonary veins traced into left atrium

Q2: What is the most probable diagnosis after these investigations?

Based on chest radiography and echocardiography findings, the most likely diagnosis is severe RDS with secondary PPHN with left ventricular dysfunction. Possibility of congenital pneumonia (GBS) could not be ruled out.

Q3: How will you manage?

Adequate ventilation to recruit the lung

In view of high mean airway pressure (MAP) and FiO_2 requirement on conventional ventilation, the baby was started on HFOV at 4 HOL. Recruitment maneuver was attempted to achieve adequate lung expansion. Final MAP was kept at 16 cm H_2O with FiO_2 requirement at 75% (not responding to lung recruitment).

Second dose surfactant

The neonate satisfies the criteria for second dose surfactant (MAP ≥ 7 cm H_2O and FiO_2> 40%). The next question is how early the second dose can be repeated? Different national guidelines suggest different intervals between two doses of surfactant. The Canadian Pediatric Society recommends giving it as early as 2 hours after the prior dose.[1] Since the baby is critically ill, we can give the second dose of surfactant at this juncture.

Cardiac dysfunction

Dobutamine at 10 ug/kg/min was started.

Possible GBS?

Started on high dose ampicillin (300 – 400 mg/kg/day) with an intention to stop if sepsis parameters and blood culture indicate otherwise.

Case continued: The baby is at 6 HOL, on HFOV with MAP of 16 cm H_2O and requiring a FiO_2 of 75% post second dose. Post ductal ABG reveals pH – 7.21, $PaCO_2$ – 48 mmHg and PaO_2 – 40 mm Hg. Repeat echo shows persisting left ventricular dysfunction with PPHN.

Q4: How will you proceed?

Assess and address the cardiac dysfunction first.

The most likely cause for LV dysfunction is PPHN. However, starting inhaled nitric oxide (iNO) amidst LV dysfunction in PPHN can be counter productive.[2] In the event of PPHN with LV dysfunction, the physiology is akin to hypoplastic left ventricle one where the systemic circulation is supported by high pulmonary pressures and ensuing right to left shunting at PDA. If iNO is started at this point, there might be circulatory collapse due to rapid reduction in pulmonary pressures and change of shunting at PDA to left to right, resulting in systemic hypoperfusion. Milrinone is an alternative to dobutamine which would not only improve cardiac dysfunction, but also result in pulmonary vasodilation. Hence, in this neonate milrinone was initiated and dobutamine weaned off. It is emphasized that unlike other inotropes, milrinone has a high volume of distribution, longer half-life, and if started without a loading dose, the inodilator effect would be seen only after some hours.

Treat PPHN once LV dysfunction improves.

Once LV function is supported, iNO can be considered. The oxygenation index in this baby is {[FiO_2/PaO_2(post-ductal)] X MAP = [75/40] X 16 = 30]. iNO is indicated at an OI > 15 - 20. iNO was started at 20 ppm in this neonate. The baseline FiO_2 decreased by 20% within one-hour of iNO initiation to 55%, considered a complete response.

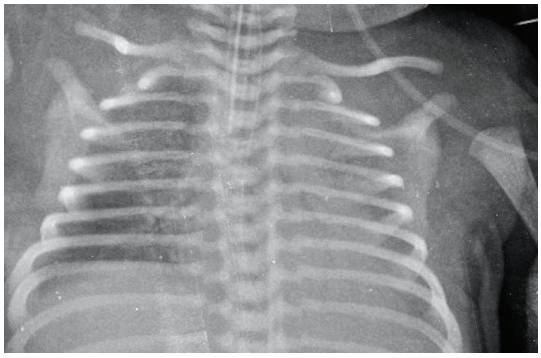
Why not start iNO prior to second dose surfactant?

As discussed earlier, the PPHN component was secondary to RDS and lung de-recruitment. Our aim must be to first address the cause of PPHN, which was RDS through lung recruitment (HFOV, surfactant). Following adequate recruitment, if the OI is still high, we can consider iNO. High quality evidence and strong recommendation indicate that routine or rescue iNO should not be used in preterm neonates< 34 weeks gestation.[3]

However in our case, the neonate was of late-preterm gestation where iNO has been found to be of some benefit in RDS associated with secondary PPHN & not responding to adequate ventilation.[4]

Case continued : At 24 HOL, the neonate was on MAP–10 cm H_2O with rising FiO_2 requirement (70% compared to three hours prior which was 40%). Inhaled nitric oxide was tapered to 5 ppm from 10 ppm four hours prior. The chest radiograph is given below in Figure 3.

Figure 3 – Chest radiography at 24 HOL



Q5: What would be your next step?

Recruit lungs by increasing MAP using recruitment manoeuvres.

There is derecruitment and loss of lung volume compared to previous chest radiograph. This can happen if HFOV is interrupted due to repeated suctioning or if MAP is weaned off rapidly. The most appropriate step would be to recruit the lung by maneuvers in HFOV and assess again. If FiO_2 > 40% persists despite lung recruitment by increasing MAP, repeat surfactant is indicated. Also, possibility of rebound PPHN due to tapering of iNO be kept.

Take-Home Messages:

- RDS can be severe even in late preterm neonates.
- Secondary PPHN associated with severe RDS and not responding to lung recruitment might require iNO therapy.
- LV dysfunction in PPHN needs to be treated with an inotropic agent, preferably Milrinone prior to pulmonary vasodilator therapy (iNO, Sildenafil).
- Lung volume needs to be frequently assessed while a neonate is on HFOV. Repeated suctioning and rapid weaning of MAP from HFOV should not be done, unless indicated.

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