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Educational Case

Educational Case: Neonatal respiratory distress syndrome

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see https://www.journals.elsevier.com/academic-pathology/news/pathology-competencies-for-medical-education-pcme.[1]

Keywords: Pathology competencies, Organ system pathology, Respiratory system, Respiratory disorders, Fetus, Infant, Lung development, Neonatal respiratory distress syndrome, Hyaline membrane disease, Bronchopulmonary dysplasia

Primary learning objective

Objective RS6.1: Respiratory Disorders of the Fetus and Infant. Explain the pathogenesis and clinicopathologic features of congenital and acquired disorders affecting the airways and lungs of the fetus and infant.

Competency 2: Organ System Pathology; Topic: Respiratory System (RS); Learning Goal 6: Respiratory Disorders of the Fetus and Infant.

Patient presentation

A newborn male infant is delivered along with his twin via unplanned cesarean section to a 30-year-old now G1P0202 woman at 26 w and 4 d gestation due to chorioamnionitis and preterm prelabor rupture of membranes (PPROM). Prior to delivery, the mother received tocolytic indomethacin to allow time for betamethasone administration and transfer from a community hospital to a facility with a NICU. In addition to indomethacin and betamethasone, she also received magnesium sulfate for fetal neuroprotection.[2] The mother has type 2 diabetes mellitus, an AB-positive blood type, and a negative antibody screen. The father has an unremarkable medical history. Apgar scores were 5 and 5 at 1 and 5 min, respectively. The infant weighs 910 g and measures 34 cm in length. The other twin is larger and was born first. Within the first 15 min of life, the pediatrician notices that the skin around the newborn's mouth has started to appear blue, and he makes a noise that resembles singing when he exhales.

Diagnostic findings, Part 1

On a physical exam, the infant exhibits expiratory grunting, nasal flaring, and forceful intercostal and subcostal retractions. He has a temperature of 97.6 °F and a respiratory rate of 81 breaths/min. The infant is cyanotic and has weak peripheral pulses. Lung auscultation reveals diminished breath sounds with a harsh, tubular quality and scattered crackles on inspiration.

Question/discussion points, Part 1

Based on the clinical presentation, what is the differential diagnosis?

This infant displays several signs of increased work of breathing, including tachypnea, grunting, nasal flaring, and retractions. If a newborn displays one or more signs of increased work of breathing, causes of respiratory distress must be considered in the differential diagnosis.

Neonatal respiratory distress may be the result of pulmonary, cardiovascular, metabolic, or systemic diseases. Therefore, the differential diagnosis for this patient based on clinical presentation alone is broad and includes neonatal respiratory distress syndrome, transient tachypnea of the newborn, bacterial pneumonia, air leak syndrome, cyanotic congenital heart disease (CHD), congenital lung diseases, interstitial lung diseases, hypoglycemia, polycythemia associated with maternal diabetes,

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and severe anemia.[3] Another potential underlying diagnosis is pulmonary hypoplasia secondary to oligohydramnios caused by autosomal recessive polycystic kidney disease, obstructive uropathy, or renal hypoplasia.[4]

In view of the differential diagnosis, what would be the next steps in management to confirm the underlying diagnosis or underlying diagnoses?

A chest radiograph may be obtained to evaluate the underlying pulmonary etiology. In neonatal respiratory distress syndrome (RDS), the radiograph of the preterm infant will demonstrate low lung volumes with diffuse hazy opacities, representing subsegmental atelectasis related to alveolar collapse from a lack of surfactant.[5] In contrast, the radiograph of a patient with transient tachypnea of the newborn (TTN) will demonstrate normal lung volumes with interstitial edema, which may be seen as perihilar streaking, patchy infiltrates, and increased interstitial markings. There are also associated small bilateral pleural effusions.[5] In an infant born with meconium aspiration, lung volumes are expected to be large, with cord-like opacities in the lung, which represent the meconium plugs in the bronchi. Small pleural effusions may be seen, and pneumothorax is an associated complication.[6] Both of these conditions are more common in term infants.[5]

Other clinical considerations include perinatal pneumonia, which may appear as diffuse bilateral consolidations on a radiograph, while later infections may appear as lobar consolidations. Air leak syndrome, which includes a pneumothorax or pneumomediastinum, may be visualized on chest radiographs as air outlining the pleural space or mediastinum, respectively.[5] Respiratory distress related to congenital malformations may be suspected based on radiographic findings.[3] A newborn with a history of oligohydramnios and a chest radiograph displaying opaque lung fields typical of pulmonary hypoplasia may have a Potter sequence. Further imaging may demonstrate renal abnormalities, such as bilateral renal agenesis with absence of visible kidneys on radiograph and ultrasound, autosomal recessive polycystic kidney disease with nephromegaly or visible cysts on ultrasound, or a tumor demonstrated on a radiograph causing obstructive uropathy.[4] Congenital diaphragmatic hernia may result in hypoplastic lungs due to the mass effect.[3] On radiography, the small bowel is displaced into the thorax, with a characteristic bubbly appearance. Other congenital abnormalities, such as sequestrations or congenital pulmonary airway malformation (CPAM), may be seen on radiographs. In the immediate postnatal period, these malformations may appear as well-defined opacities as the cysts remain filled with fluid. Eventually, the cysts may become aerated, appearing more lucent than the remainder of the lung.[7]

To determine the degree of hypoxemia and the acid/base status of the patient, an arterial blood gas analysis should be ordered. In neonatal RDS, infants demonstrate respiratory acidosis and hypoxemia. Later in the course of neonatal RDS, these patients may progress to metabolic acidosis. Newborns with TTN demonstrate variable hypoxemia with normo- or hypercapnia.[3] Measuring arterial blood gases is also crucial to distinguish cyanotic CHD from pulmonary disease because neonates with cyanotic CHD usually cannot significantly raise their arterial blood partial pressure of oxygen (PaO2) during administration of 100% oxygen. This is known as the hyperoxia test.[8]

A complete blood count (CBC) with differential and a blood culture should also be ordered to evaluate this patient for pneumonia and sepsis. Although a CBC is not sensitive or specific in diagnosing early-onset sepsis, the presence of marked neutropenia has been associated with an increased risk of sepsis. A positive blood culture is the gold standard for the diagnosis of sepsis.[5] Interestingly, neutropenia in the first 30–90 min of life may also be indicative of neonatal RDS as inflammation allows neutrophils to exit circulation and enter the airway and distal lung.[9] A CBC may also be helpful for ruling out hematologic causes of respiratory distress, as a low hemoglobin level is indicative of anemia, whereas an elevated hemoglobin level is indicative of polycythemia.[3]

The infant's blood glucose should be measured, especially as his mother is diabetic, in order to rule out hypoglycemia as the cause of the infant's respiratory distress.[3]

Some neonates may have chronic respiratory disorders encompassed by the group of diseases known as childhood interstitial lung diseases (chILDs) or diffuse lung disease (DLD). Some examples of chILDs include acinar dysplasia, alveolar capillary dysplasia with misalignment of the pulmonary veins caused by *FOXF1* mutations, pulmonary interstitial glycogenosis (PIG), surfactant protein B deficiency due to homozygous *SFTPB* mutations or *ABCA3* gene mutations (deficiency caused by mutation rather than prematurity), pulmonary hemorrhage syndromes, and pulmonary lymphangiectasia. The causes of these diseases are varied and include surfactant function abnormalities, persistent tachypnea of infancy, and neuroendocrine cell hyperplasia. Interstitial lung diseases are diagnoses of exclusion and may be diagnosed if the results of the tests listed above are unremarkable. A neonate or infant with DLD is considered to have chILD syndrome if at least three of the following four criteria are met: (1) respiratory symptoms such as cough or difficulty breathing; (2) respiratory signs such as retractions or failure to thrive; (3) hypoxemia; and (4) abnormalities on a chest radiograph or computer tomography (CT). A CT of the chest should be obtained with a high-resolution protocol for further evaluation. Genetic testing may also be beneficial for diagnosis in select patients.[3]

Diagnostic findings, Part 2

A chest x-ray (Fig. 1), CBC (Table 1), arterial blood gas (Table 2), glucose level, and blood cultures are obtained. The glucose level is 50 mg/dL (reference range 40–180 mg/dL up to 24 hours after birth), and blood cultures are negative at 48 hours of life.

Question/discussion points, Part 2

What is the most likely diagnosis based on the chest radiograph and lab results?

Neonatal RDS is the most likely diagnosis. The patient's chest radiograph shows low lung volumes with diffuse, bilateral, and symmetrical granular opacities. In addition, the newborn's arterial blood gas analysis demonstrates hypoxemia and an uncompensated respiratory acidosis. These characteristic neonatal RDS findings, coupled with his unremarkable CBC, normal blood glucose level, and negative blood culture, are indicative of a diagnosis of neonatal RDS.

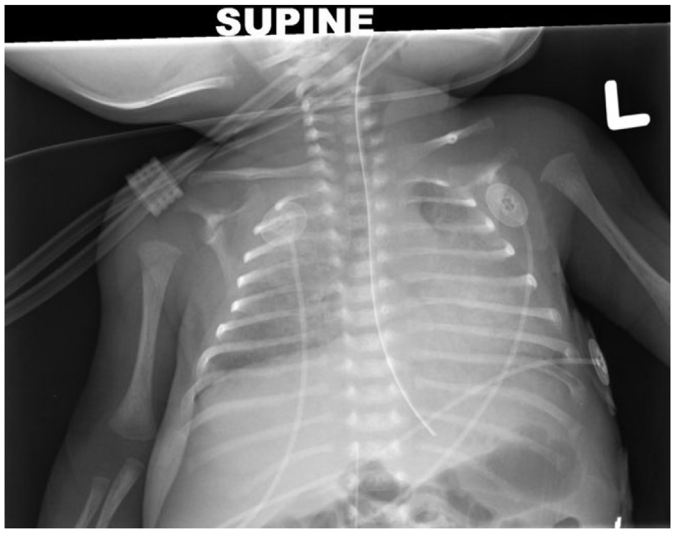

Fig. 1. anteroposterior supine radiograph obtained portably demonstrates low lung volumes with diffuse, bilateral, symmetrical granular opacities throughout the lungs.

Table 1
Complete blood count (limited).

Test	Result	Reference range (Preterm neonates)
Total WBC	10,000 mm^3	6000–19,000 mm^3
Neutrophils	6000 cells/mm^3	4000–20,000 cells/mm^3
Hgb	14.8 g/dL	10–18 g/dL (26–27 wks GA)
Hct	45%	30%–55% (26–27 wks GA)
Platelet count	221 x 10^9/L	104.2-400 x 10^9/L (<32 wks GA)

Table 2
Arterial blood gas results (limited).

Test	Result	Reference range
pH	7.26	7.35–7.45
$PaCO_2$	55 mmHg	35–45 mmHg
HCO_3^-	25 mEq/L	22 - 26 mEq/L
PaO_2 (preterm)	39 mmHg	45–65 mmHg

What are the risk factors for neonatal respiratory distress syndrome?

Preterm birth is the strongest risk factor for developing neonatal RDS, also referred to as hyaline membrane disease in the literature. Preterm birth is defined as any birth before 37 w gestational age, and it is further subdivided based on gestational age: extremely preterm (less than 28 w gestation), early preterm (28 to less than 32 w gestation), moderate preterm (32 to less than 34 w gestation), and late preterm (34 to less than 37 w gestation).[10] The risk of neonatal RDS increases with decreasing gestational age. This is evidenced by a study that found the incidence of neonatal RDS is approximately 5% in late preterm neonates, 30% in early preterm neonates, and 60% in extremely preterm neonates.[3] The risk of neonatal RDS also increases with decreasing birth weight. Extremely low birth weight (ELBW) neonates are born weighing less than 1000 g, very low birth weight (VLBW) neonates are born weighing less than 1500 g, and low birth weight (LBW) infants weigh less than 2500 g at birth.[11] Compared to neonates weighing more than 2500 g at birth, the relative risk estimates of neonatal RDS are 1.4 for neonates weighing 2000–2500 g, 4.5 for neonates weighing 1500–2000g, 8.8 for VLBW neonates, and 39.3 for ELBW neonates. Risk is also increased in males compared to females.[12] Interestingly, there is a well-known increased risk of RDS in a twin born second compared with the first-born twin. This was previously thought to be due to the asphyxia of the second twin during birth. However, during a matched case-control study of 221 preterm twin pairs, it was determined that second birth order was an independent risk factor only in vaginal deliveries, and second twins delivered via cesarean section did not have an increased risk of RDS when compared with first-born twins. In this study, malpresentation of the second twin was found to be a more predictive risk factor of RDS than birth order. Therefore, predisposition to respiratory depression at birth cannot explain the increased risk of RDS in twins, and it is more likely that the second-born twin does not receive as much benefit from the stress of labor as the first-born twin.[13]

What is the pathogenesis of neonatal respiratory distress syndrome?

Premature infants are born with immature type II pneumocytes, which are the specialized lung surface epithelial cells that produce surfactant, a complex of phospholipids and proteins that coats the alveoli to decrease surface tension and prevent alveolar collapse, following the onset of respirations.[14]

Deficient surfactant production by immature pneumocytes results in increased alveolar surface tension and alveolar collapse upon expiration.[15] The infant is unable to maintain functional residual capacity (FRC), which is the volume of air that remains in the lungs with passive expiration. Premature infants have cartilage chest walls that are highly compliant and therefore less likely to resist the natural tendency of the lungs to collapse, so air volume approaches the residual volume with end-expiration.[5] Because there is increased resistance to reinflating the lungs with each subsequent breath, the newborn tires easily.[15] This leads to generalized atelectasis, resulting in decreased tidal volume and increased dead space.[16] The collapsed alveoli are perfused by blood but not ventilated by air, resulting in hypoxia, acidosis, and hypercapnia. These effects all contribute to alveolar epithelial damage and pulmonary arterial vasoconstriction. Pulmonary arterial vasoconstriction results in increased right-to-left shunting through the foramen ovale and ductus arteriosus, and the increased amount of deoxygenated blood in the systemic circulation results in cyanosis. Pulmonary arterial vasoconstriction also contributes to pulmonary ischemia, or insufficient blood flow to the lungs to provide adequate oxygenation to the lung tissue itself. Pulmonary ischemia exacerbates the ongoing damage to alveolar epithelial cells and the pulmonary endothelium within the capillaries.[15]

The damage to the epithelium and endothelium of the lung described above results in inflammation and interstitial edema. When plasma components, such as fibrinogen and albumin, leak into the airspaces with edema, they bind surfactant and further increase its deficiency in the neonate. This exacerbates respiratory distress, resulting in worsening atelectasis, further injury to the endothelium and epithelium, and severe hypoxia.[15]

Gross examination of the lungs of a neonate with RDS, also referred to as hyaline membrane disease in the literature, reveals lungs that are dark red, solid, airless, and firm, resembling the liver in appearance and consistency due to atelectasis and perfusion of blood.[15] They may sink when placed in water (Fig. 2).[5]

Microscopic examination demonstrates focally atelectatic and hemorrhagic parenchyma with dilated terminal and respiratory bronchioles lined by eosinophilic, smooth "hyaline membranes" composed of necrotic debris and a plasma protein exudate (Figs. 3 and 4).[5] The hyaline membrane develops within the first 12–24 h after the onset of symptoms and is reabsorbed within three to four days.[5]

What is surfactant, and when does it typically appear at mature levels in the growing fetus?

Surfactant is a macromolecular complex of phospholipids and apoproteins that is synthesized by type II pneumocytes and stored in

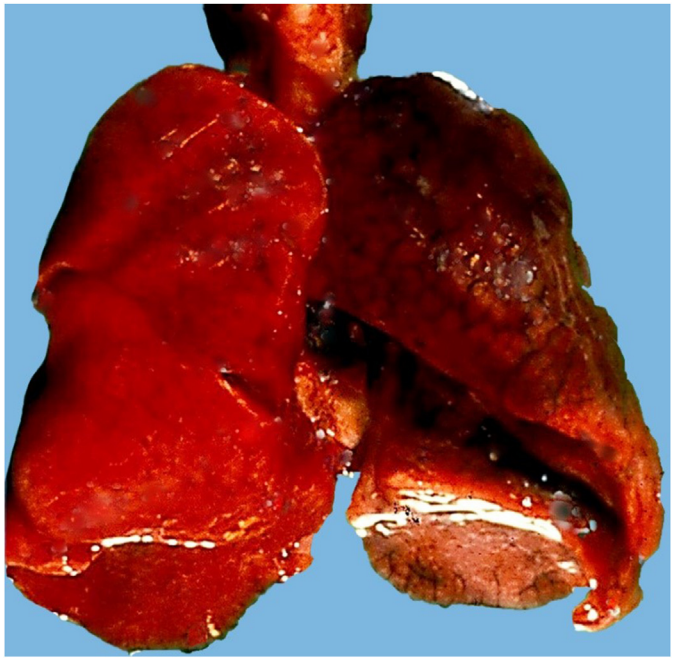

Fig. 2. Stiff lungs in this premature infant at autopsy resemble the liver in their consistency and are difficult to ventilate.

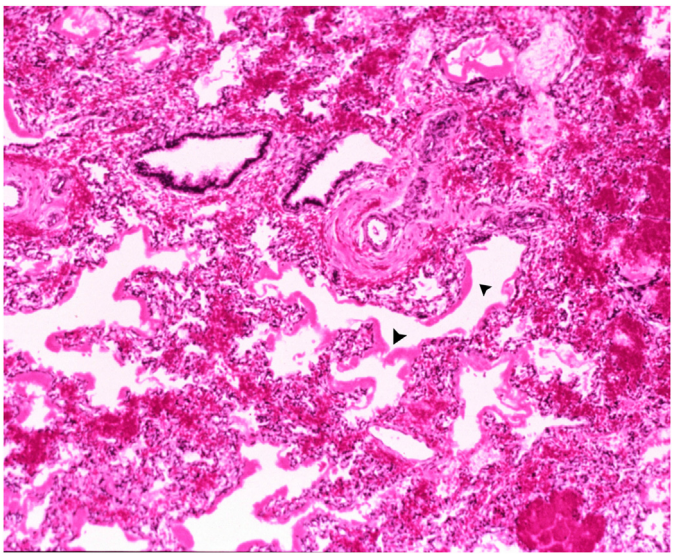

Fig. 3. Hyaline Membrane Disease. This section of lung from an infant with RDS displays thick hyaline membranes (arrowheads) throughout the pulmonary acinus, atelectasis, and hemorrhage. (H&E, intermediate magnification). RDS, respiratory distress syndrome.

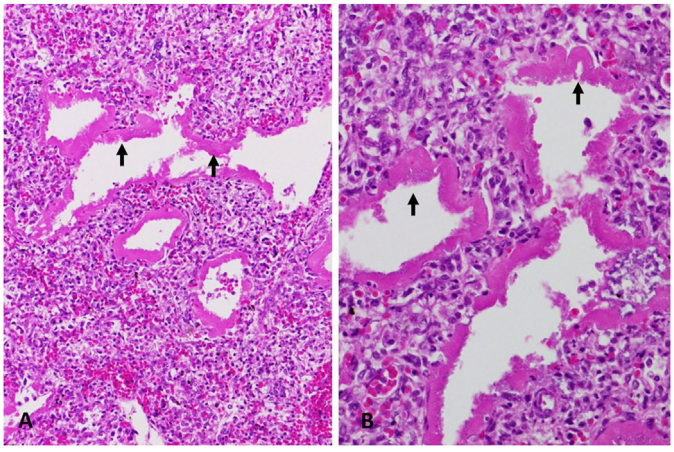

Fig. 4. A. Hyaline Membrane Disease. This section of lung from an infant with RDS displays atelectasis and thick hyaline membranes within the pulmonary acinus (arrows). (H&E, intermediate power). B. Higher magnification displays thick hyaline membranes composed of fibrin, plasma transudate, and necrotic bronchiolar and alveolar cellular debris (arrows). Atelectasis of the alveoli and capillary congestion are also evident. (H&E, intermediate magnification). RDS, respiratory distress syndrome.

intracellular inclusions known as lamellar bodies until it is secreted extracellularly in a multitude of forms: lamellar bodies, highly organized tubular myelin, and monolayered and multilayered sheets and vesicles. In this variety of forms, surfactant molecules form hydrophobic lipid-rich films that coat the surfaces of epithelial cells in alveoli to protect against environmental enzymes and optimize gas exchange by lowering the surface tension that creates collapsing forces. It is essential that surfactant consists of both phospholipids and proteins, as phospholipids alone at 37 °C are rigid and cannot maintain a film against the expansion and compression of the lungs during the respiratory cycle. Apoproteins, especially hydrophobic surfactant proteins B (SP-B) and C (SP-C), increase phospholipid fluidity, allowing surfactant to rapidly form a film on the epithelium and remain stable during the respiratory cycle. SP-B or SP-C alone, or a mixture of the two, is sufficient to confer these properties on phospholipids in surfactant. Of note, full-term newborns may develop neonatal RDS due to a genetic mutation resulting in a deficiency of SP-B and/or SP-C. Surfactant is recycled and degraded by alveolar macrophages and respiratory epithelial cells.[17]

Surfactant consists of approximately 70% saturated and unsaturated dipalmitoylphosphatidylcholine (DPPC, also known as lecithin), 8% phosphatidylglycerol, and 16% neutral lipids, other phospholipids, and cholesterol. Six percent of surfactant is composed of the apoproteins SP-A, SP-B, SP-C, and SP-D. Mature surfactant consists of at least two groups of surfactant-associated proteins.[5]

High concentrations of surfactant are present in fetal lung homogenates by 20 w gestational age. However, surfactant has not reached the surface of the lung at this point in development. It is detectable in amniotic fluid between 28 and 32 w of gestational age. Surfactant only reaches mature levels in the developing fetus after 35 w of gestation.[5]

What lab tests are commonly used for assessing fetal lung maturity prior to birth?

Obstetricians may order lab tests to assess fetal lung maturity prior to birth and predict the risk of RDS in an infant who requires premature delivery. Of note, the frequency of testing to determine fetal pulmonary maturation has significantly decreased in clinical practice in recent years as the American College of Obstetricians and Gynecologists (ACOG) and the National Institute of Child Health and Human Development (NICHD) have recommended more stringent indications for late preterm and early term births (between 37 w and 1-d gestational age and 38 w and 6-d gestational age). The 2011 NICHD guidelines state that if there is a significant risk to the mother or if abnormal antepartum fetal tests indicate a risk of fetal death, prompt delivery should occur regardless of whether the fetus is biochemically mature. In addition, the presence of surfactant does not indicate the maturity of other organ systems or take into account the ability of the preterm neonate to adapt to life outside the uterus.[18]

Available methods to assess fetal pulmonary maturity rely on amniocentesis and measure either the presence and quantity of surfactant components or surfactant function. In current practice, tests used to determine the presence of surfactant components are more common and reliable, but neither method has data showing it is more effective at predicting fetal lung maturity.[18]

One test that quantifies pulmonary surfactant is the determination of the lecithin/sphingomyelin (L/S) ratio. Lecithin, also known as DPPC, is the primary component of surfactant. Its levels rise as the lung matures, and its presence indicates the production of surfactant by the fetal lung. The L/S ratio is a good measure of fetal lung maturity because the quantity of sphingomyelin exceeds the quantity of lecithin until 26 w gestation. When the quantity of lecithin is twice the quantity of sphingomyelin, making the L/S ratio 2:1, the lung is considered mature, and the neonate has a low risk of developing neonatal RDS. However, this does not occur until 35 w of gestation. Determination of the L/S ratio takes hours to perform, is technically difficult to perform and interpret, and may be influenced by the presence of blood or meconium in the amniotic fluid sample. Another method to determine the quantity of surfactant present in the fetal lung is a test for the presence of phosphatidylglycerol, another phospholipid present in surfactant. The phosphatidylglycerol assays are not affected by the presence of blood or meconium. Alternative quantification methods include measurement of a surfactant/albumin ratio, visual inspection of fluid, optical density at 650 nm, and a foam stability index.[18]

An alternative test is the assessment of lamellar body count (LBC). Recall that lamellar bodies are intracellular inclusions that represent the storage form of surfactant. This test of an amniotic fluid sample directly measures the ability of type II pneumocytes to produce surfactant. This test is performed with a standard hematology analyzer, as lamellar bodies are about the same size as platelets. Fetal lung maturity is suggested by a LBC greater than 50,000/μL. A count of 15,000/μL suggests immaturity. A count between 15,000/μL and 50,000/μL is indeterminate.[19] Of note, a study of 435 amniotic fluid samples determined that the fiftieth

percentile of LBC was 3000 at 30 w, 4000 at 31 w, 10,000 at 32 w, 22,000 at 33 w, 34,500 at 34 w, and 48,500 at 35 w, with plateauing of the LBC at mature levels at gestational ages greater than 35 w.[20] This method is quicker and easier to perform than the methods indicated above.[18]

How do hormones regulate surfactant synthesis?

In response to the presence of a physiologic concentration of corticosteroids, the glucocorticoid receptors of the fetal lung signal downstream to activate genes that induce the production of lipogenic enzymes and surfactant apoproteins, increasing the production of surfactant. During labor and intrauterine stress, including fetal growth restriction, corticosteroid production is increased, which increases surfactant production and decreases the risk of neonatal RDS.[21] Cesarean sections with no prior onset of labor are associated with a higher incidence of RDS, as the fetus does not experience an increase in corticosteroids in response to the stress of labor.[16]

Interestingly, thyroid hormone has also been shown to accelerate lung development and surfactant production in a study of the lung tissue of animals after treatment with thyroid hormones in vivo. T3 binds nuclear receptors in different biochemical sites of glucocorticoids to enhance phosphatidylcholine synthesis and stimulate surfactant production in the fetal lung. However, because T3 and T4 do not transfer across the placenta, maternal administration of thyroid hormones along with glucocorticoids prior to preterm delivery has not been demonstrated to benefit the fetus. Therefore, the administration of antenatal glucocorticoids remains the standard of care in preterm labor.[22]

Insulin counteracts the effects of corticosteroids and is associated with an increased risk of neonatal RDS. As such, infants of diabetic mothers are at higher risk of neonatal RDS as they may suppress surfactant synthesis by increasing the production of insulin in response to intrauterine exposure to elevated serum glucose.[16]

What therapies are recommended for the prevention and treatment of neonatal respiratory distress syndrome?

Tocolytics may be administered short-term to a mother at risk for preterm birth or early term birth in order to delay delivery to allow time for administration of antenatal corticosteroids and/or to allow time for transfer to a facility with a higher level of care for both mother and neonate.[23] Administration of a single dose of antenatal corticosteroids (e.g. betamethasone or dexamethasone) is recommended for pregnant women between 24 0/7 w and 36 6/7 w gestation at risk of preterm delivery within 7 d.[24] Exposure of the fetus to exogenous corticosteroids at a level similar to that seen physiologically allows near-maximal occupancy of glucocorticoid receptors and induction of target proteins that accelerate the development of lung and other tissue, thus promoting fetal lung maturity before delivery.[21] A single course of antenatal corticosteroids has been demonstrated to reduce the risk of perinatal death, neonatal death, and RDS. Similar effects are seen in both twin and singleton births.[25] Repeat courses are not recommended unless the mother is less than 34 0/7 w gestation at risk for preterm delivery within 7 d and had her previous course of corticosteroids more than 14 d beforehand.[24] Although treatment with antenatal corticosteroids causes a transient suppression of maternal and fetal adrenal function, treated neonates demonstrate a normal cortisol surge in response to newborn stress.[21] As administration of antenatal corticosteroids has become increasingly routine in clinical practice, there is a decreased need for fetal lung maturity testing prior to preterm and early term deliveries.[18]

After delivery, if the newborn demonstrates signs of respiratory distress, the neonate should be stabilized with 21–30% oxygen until oxygen saturation gradually reaches greater than 85%, using a pulse oximeter on the right wrist as a guide. Of note, it is preferential to start all neonates at high risk for RDS (i.e. those born at less than 30 w gestational age) on continuous positive airway pressure (CPAP) at birth until clinical status is assessed. Exogenous surfactant may then be administered to the neonate as prophylaxis or rescue treatment.[23] Administration of prophylactic exogenous surfactant to infants born at less than 28 w gestational age has made it much less common for infants to die from acute RDS.[16] Early rescue surfactant should be administered to infants born at less than 26 w gestational age who require FiO_2 greater than 0.3 and infants born at greater than 26 w gestational age who require FiO_2 greater than 0.4. Repeat doses of exogenous surfactant may be administered if the infant demonstrates persistence of RDS, such as a continued need for oxygen or mechanical ventilation.[23] Exogenous surfactants may be animal-derived or synthetic with SP-B-like activity. Both types of surfactant have been demonstrated to decrease acute respiratory morbidity and mortality in preterm infants with RDS.[26] For preterm infants who are spontaneously breathing and receiving nasal continuous positive airway pressure (nCPAP), it is advised to deliver the surfactant via the less invasive surfactant administration (LISA) technique using a thin catheter rather than delivering the surfactant via endotracheal intubation because this results in a lesser need for mechanical ventilation. For other infants, the INSURE technique (Intubate--SURfactant-Extubate) should be used to deliver surfactant.[27]

Infants with neonatal RDS require respiratory support via minimally invasive ventilation and optimal positive end-expiratory pressure (PEEP) to optimize ventilation/perfusion match. Spontaneously breathing neonates should be stabilized with CPAP via mask or nasal prongs. Intubation should be reserved for neonates who demonstrate continued labored breathing with the use of CPAP via mask. The goal for patients who require mechanical ventilation is to ventilate for as short a duration as possible to avoid hyperoxia, hypocapnia, and volutrauma.[23] The FiO_2 should be adjusted so pH is maintained between 7.25 and 7.40, PaO_2 is maintained between 50 and 70 mmHg, and $PaCO_2$ values lie between 45 and 65 mmHg.[5] A moderate degree of hypercapnia is acceptable as long as the pH remains above 7.22. Arterial blood gas analysis and chest x-rays may be repeated as clinically indicated. The oxygen saturation target following stabilization is between 90% and 95%. After surfactant administration, it is often necessary to rapidly reduce FiO_2 in order to avoid fluctuations in SaO_2.

Caffeine may be used for the treatment of apnea or to facilitate weaning from mechanical ventilation.[23] These agents increase the central respiratory drive by lowering the threshold of response to hypercapnia (i.e. promoting an increased respiratory rate at a lower $PaCO_2$) and prevent fatigue by enhancing the contractility of the diaphragm. The use of caffeine has been demonstrated to reduce the rate of bronchopulmonary dysplasia and improve neurodevelopmental outcomes.[5]

Neonates with RDS are often treated prophylactically with antibiotics for treatment of sepsis until the diagnosis of sepsis is excluded via laboratory testing (i.e. negative blood culture) or after 48 h if the infant is stable.

Supportive care is critical in the care of a newborn with neonatal RDS. It is important to avoid hypothermia and maintain the infant's body temperature between 36.5 °C and 37.5 °C by using plastic bags or occlusive wrapping under radiant warmers. Fluid balance should be tightly controlled, with an early focus on aggressive nutritional support via parenteral nutrition. The neonate should be started on the mother's breast milk as soon as possible, if feasible and desired by the mother. Blood pressure should be monitored regularly to ensure adequate perfusion. As always, it is important to encourage parental bonding and family support.[23]

What are some complications of neonatal RDS?

Some early complications of neonatal RDS are pneumothorax, apnea, intraventricular hemorrhage, anemia, hypoglycemia, hypernatremia, patent ductus arteriosus, necrotizing enterocolitis, and renal failure. Later complications include gastrointestinal reflux disease, feeding intolerance, growth failure, apnea, sudden death, bronchopulmonary dysplasia, and developmental and neurologic deficits. Infants who recover from neonatal RDS are often followed by an interdisciplinary team, including a primary care pediatrician, developmental pediatrician,

nutritionist, social worker, physical therapist, and other specialty physicians and surgeons.[3]

Complications of neonatal RDS associated with exposure to high concentrations of ventilator-administered oxygen for a prolonged period include retrolental fibroplasia and bronchopulmonary dysplasia (BPD). Retrolental fibroplasia, also known as retinopathy of prematurity, develops in two phases. In phase one, hyperoxia from ventilator use results in reduced expression of vascular endothelial growth factor (VEGF), resulting in endothelial cell apoptosis. In phase two, VEGF levels rebound after the neonate is weaned from the hyperoxic ventilator to relatively hypoxic room air. This VEGF rebound results in retinal neovascularization, producing characteristic lesions in the retina. Gentler ventilation techniques, antenatal corticosteroid administration, and the administration of exogenous surfactant have all reduced the incidence of both retinopathy of prematurity and BPD.[16]

The complications of neonatal RDS associated with anoxia and acidosis include IVH, persistent patent ductus arteriosus, and necrotizing enterocolitis.[15]

Diagnostic findings, Part 3

The patient remains oxygen-dependent in the NICU for 77 d. At 36 w postmenstrual age, he is on effective oxygen >30% with an oxygen saturation of 97%, so he undergoes a room air challenge with continuous observation and oxygen saturation monitoring. However, he fails the room air challenge as his oxygen saturation drops to 83% after weaning. A chest radiograph and CT are obtained (Figs. 5 and 6, respectively).

Question/discussion points, Part 3

What diagnosis is indicated by the clinical signs and diagnostic imaging above?

This patient meets the diagnostic criteria for both the clinical and physiologic definitions of new bronchopulmonary dysplasia (BPD). The strongest predictors of BPD are prematurity and low birth weight.[28] As gestational age at birth increases, the risk of BPD decreases. This is demonstrated by a study that shows that around 80% of infants born at 22–24 w gestational age are diagnosed with BPD, whereas only around 20% of infants born at greater than or equal to 28 w gestational age are ultimately diagnosed with BPD. Similarly, 95% of infants who develop BPD are VLBW.[11]

An infant born at less than 32 w gestational age who is oxygen-dependent for at least 28 d meets the clinical definition for new BPD.[28] This patient was born at 26 w and 4 d gestational age and has been oxygen dependent for 77 d.

The physiologic definition of new BPD is more complex. A premature neonate meets the physiologic definition of new BPD if he/she is on positive pressure support or receiving greater than 30% supplemental oxygen with SaO_2 between 90% and 96% at what would have been 36 w gestational age. If the neonate is on less than 30% FiO_2 or receiving greater than 30% FiO_2 with SaO_2 greater than 96%, a room air challenge with continuous observation and oxygen saturation monitoring should be conducted. If the neonate's SaO_2 remains greater than or equal to 90% during weaning and in room air for 30 minutes, the neonate does not have BPD. If the SaO_2 drops below 90%, the infant has BPD.[29] This infant was on greater than 30% FiO_2 with SaO_2 equal to 97% when he reached what would have been 36 w gestational age. However, he failed the room air challenge because his SaO_2 dropped to 83% after weaning. Therefore, he meets the physiologic definition of BPD.[28]

This patient's chest radiograph shows characteristic features of BPD: mild bilateral hyperexpansion with coarse lung markings and patchy parenchymal opacities interspersed with areas of hyperlucency due to air trapping. Of note, characteristic radiographic findings are no longer required to diagnose an infant with BPD.[28]

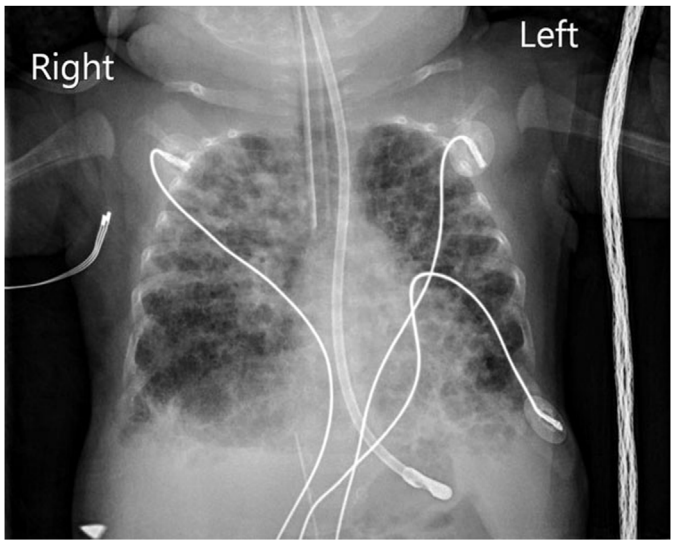

Fig. 5. anteroposterior supine radiograph obtained portably demonstrates mild bilateral pulmonary hyperexpansion with coarse lung markings. Patchy parenchymal opacities are interspersed with areas of hyperlucency. The patient is intubated, with the tip of the endotracheal tube just above the carina.

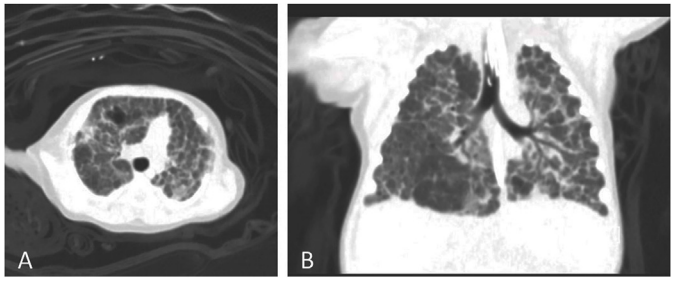

Fig. 6. CT of the chest without contrast, axial (A) and coronal (B) demonstrate mild hyperinflation of the right greater than left lung with a mosaic lung parenchymal pattern. Areas of low attenuation and focal air trapping are noted, along with associated bronchial wall thickening. Small subpleural triangular/linear opacities are also seen. CT, computer tomography.

This patient's axial nonenhanced CT of the chest showed scattered cysts, parenchymal bands, and triangular subpleural opacities. CT scan findings are positively correlated with pulmonary function and help to assess the severity of BPD.[28]

What are the differences between old/classical bronchopulmonary dysplasia and new bronchopulmonary dysplasia?

Old/classical BPD is a ventilator-induced injury that occurs in neonates diagnosed with neonatal RDS who receive high-inspired oxygen. With the adoption of more gentle ventilation techniques and the new standard of administering antenatal steroids and surfactant therapy in the hopes to prevent the need for aggressive ventilation, this form of BPD is rarer than it historically was. Long-standing healed BPD demonstrated hyperexpanded alveoli intermixed with areas of atelectasis. Diffuse alveolar sepal fibrosis is present in pulmonary acini exposed to barotrauma and elevated oxygen tensions (Fig. 7).[5]

New BPD typically affects earlier preterm infants who survive neonatal RDS. It is associated with the disruption of lung development, resulting in the arrest of alveolar septation and vascular development in the distal lung (Fig. 8).[5]

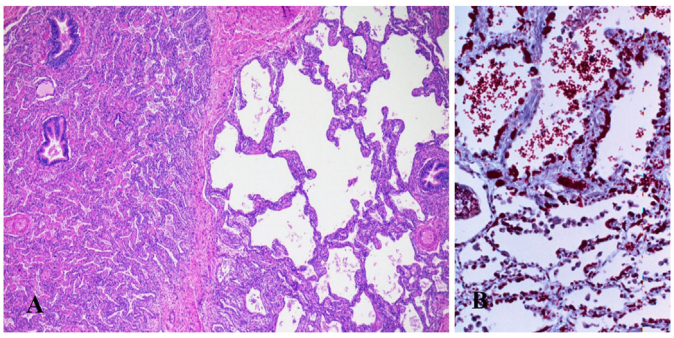

Fig. 7. Premature infants treated with oxygen and mechanical ventilation before the advent of surfactant replacement often developed a chronic lung disease called bronchopulmonary dysplasia BPD, now known as "old BPD." A. Acini, protected from high ventilatory pressures and high oxygen concentrations due to airway occlusion, shows collapsed alveoli (left side). Acini exposed to high ventilatory pressures and high oxygen concentrations show expanded alveoli with various degrees of alveolar septal fibrosis (right side). (H&E, intermediate magnification). B. Thickened alveolar septa due to alveolar septal fibrosis is seen in areas exposed to high ventilatory pressures and high oxygen concentrations (Masson stain, intermediate magnification). BPD, bronchopulmonary dysplasia.

What is the pathogenesis of new bronchopulmonary dysplasia?

Neonatal RDS is characterized by inflammation in the premature lung. This inflammation can cause an imbalance between proinflammatory and antiinflammatory cytokines, resulting in increased apoptosis of the premature lung with varying degrees of repair. The repeating cycles of apoptosis and repair prevent normal lung maturation due to impaired alveolarization and angiogenesis, resulting in the hallmarks of BPD: large, simplified alveoli and inadequate pulmonary vasculature. The cause of BPD may be multifactorial. Other insults that may contribute to the development of BPD include intrauterine and postnatal infection, trauma due to resuscitation/ventilator techniques, oxygen-induced injury, or inadequate nutrition.

Infants with neonatal RDS who develop BPD have a marked V/Q mismatch. Due to interstitial edema secondary to inflammation, fibrosis secondary to repair, and thickening of the alveolar basement membranes, these patients also have decreased lung compliance. On a chest x-ray, areas of hyperinflation interspersed with areas of atelectasis may be visible as the disease progresses. These infants may also develop hyperplasia of the bronchiolar epithelium, with squamous metaplasia present in the bronchi and bronchioles.[3]

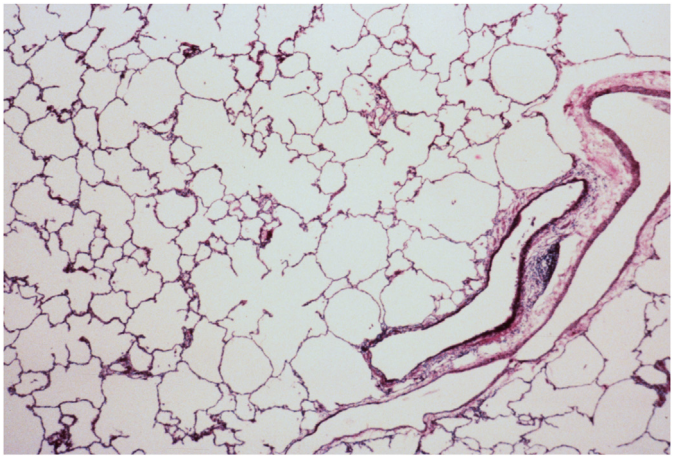

Fig. 8. BPD seen in immature and premature infants who have been treated with exogenous surfactant consists largely of "arrested" lung development with acini containing fewer numbers of alveolar saccules and alveoli, now known as "new BPD." (H&E, intermediate magnification). BPD, bronchopulmonary dysplasia.

How are infants with bronchopulmonary dysplasia managed?

Infants diagnosed with BPD in the NICU are administered supplemental oxygen in order to maintain an oxygen saturation between 90% and 94%. Invasive ventilation techniques are avoided in order to minimize pressure-induced lung damage.[3] These patients are often fluid--restricted to minimize the buildup of pulmonary edema associated with BPD.[5] Nutrition is closely monitored to ensure that there are sufficient nutrients available to fuel lung growth and maturation. These infants are fed fortified breast milk or formula, and gastrostomy tube placement should be considered prior to discharge for patients at risk for aspiration or for patients with inadequate oral intake. Careful planning and coordination with the patient's family members, home health, and outpatient specialists is required before discharge from the NICU. The care team should teach the parents how to administer medications and feeds under nursing supervision, especially if the patient will be discharged on supplemental oxygen or with a gastrostomy tube. If a patient will be discharged on chronic ventilator support, it is necessary to follow protocols to determine medical readiness for discharge, assess family proficiency in respiratory care, and help the patient's family schedule follow-up appointments with pulmonology for ventilator titration and/or otolaryngology for tracheostomy care and decannulation.[30]

An infant with BPD should be administered Respiratory Syncytial Virus (RSV) prophylaxis, and all of the patient's close contacts who are older than six months should receive the seasonal influenza vaccination. Exposure to secondhand smoke may worsen the patient's respiratory symptoms. An infant with BPD should avoid exposure to upper respiratory infections and daycare. Frequent handwashing by caregivers is essential to limit the spread of disease to the infant.[3]

There are no standard guidelines for the management of an infant with BPD after discharge from the NICU. Diuretics are commonly used for the treatment of associated pulmonary edema, but there is limited data regarding the efficacy of diuretic use in the outpatient setting. The target SaO2 for these patients is greater than or equal to 92%. If an infant has pulmonary function tests indicative of obstructive small airway disease, symptoms may be only partially responsive to bronchodilators due to a fixed obstructive component. Inhaled corticosteroids and beta-agonists may treat symptoms like wheezing or a chronic cough. Leukotriene-modifying agents may be used as adjunctive therapy. Some infants with BPD may have recurrent respiratory symptoms or pneumonia in the absence of an infectious etiology because their fragile respiratory status makes them unable to tolerate even minimal amounts of aspiration from gastroesophageal reflux disease (GERD) or dysphagia. In this setting, antireflux therapy with histamine-2 blockers, proton pump inhibitors, and/or motility agents may be indicated.

Most infants diagnosed with BPD are weaned from supplemental oxygen therapy in the first year of life. However, patients requiring mechanical ventilation at home after discharge from the NICU may require support into childhood. Some patients improve by school age, while others have symptoms that persist into adulthood. Respiratory symptoms that persist manifest as an asthma-like phenotype in early childhood.[30] These patients may also have delayed development, learning disorders, and neurological difficulties requiring a diverse care team, including a general pediatrician, a subspecialist, and community support agencies.[3]

If a patient has severe BPD, it is necessary to discuss end-of-life care with the child's parents. Categorization of BPD as severe is less likely if the patient maintains SaO2 greater than 92% during wakefulness, sleep, and feeding. A complication of BPD that increases the risk of sudden death is pulmonary hypertension (PH).[3] PH in a patient with BPD is considered a class 3 disorder (PH due to lung diseases and/or hypoxia) according to the classification of PH by the symposium at Dana Point in 2008. The exact etiology of PH in BPD patients is not

known, but proposed mechanisms describe both anatomic and physiologic abnormalities of lung circulation as contributors to the development of PH. Anatomic abnormalities include reduction of small pulmonary arteries and altered distribution of pulmonary arteries within the interstitium, resulting in further reduction of alveolar-capillary surface area in patients who already have reduced alveolarization secondary to BPD. This impairs gas exchange, prolongs oxygen treatment requirements, and results in decreased vascular growth and structure, which contributes to the cardiopulmonary sequelae of BPD. BPD may also result in systemic-to-pulmonary collateral vessels that may result in significant shunt flow to the lung and cause pulmonary congestion, also contributing to the development of PH. Physiologic abnormalities that assist in the development of PH include increased vascular tone and reactivity and hypertensive remodeling. A marked elevation of pulmonary artery pressure on cardiac catheterization may occur in preterm infants with BPD with only mild hypoxia.[31] It is necessary to screen patients diagnosed with BPD for PH via transthoracic echocardiogram. Pulmonary hypertension may improve with adequate lung growth. Oral sildenafil is also used to treat PH, but the response in patients is variable. Other complications of BPD that contribute to morbidity and mortality are worsening respiratory failure and cor pulmonale.[3]

Teaching points

- The differential diagnosis of respiratory distress in a newborn is broad and includes pulmonary, congenital, metabolic, and hematologic causes. Some of the congenital and acquired pulmonary disorders include neonatal respiratory distress syndrome, transient tachypnea of the newborn, bacterial pneumonia, air leak syndrome, interstitial lung diseases, congenital pulmonary airway malformation and sequestration, and meconium aspiration. A chest x-ray, arterial blood gas analysis, blood glucose, and complete blood count may be used to narrow the differential diagnosis of respiratory distress in the newborn and, along with the clinical course, can assist in the diagnosis of neonatal RDS.
- Neonatal RDS develops due to deficient surfactant production by immature type II pneumocytes in premature infants, resulting in increased alveolar surface tension that causes alveolar collapse upon expiration. The high energy necessary to overcome cell-cell affinity in the collapsed alveoli makes each subsequent breath more difficult for the newborn patient, and the newborn tires easily, resulting in generalized atelectasis. Generalized atelectasis of the newborn lungs leads to a ventilation-perfusion mismatch, where collapsed alveoli are perfused but not ventilated, resulting in hypoxia, acidosis, and hypercapnia.
- Damage to the alveolar epithelium and pulmonary endothelium in neonatal RDS results in inflammation and edema that allow for necrotic debris to form eosinophilic, smooth hyaline membranes that line the bronchioles of the premature lung.
- Frequency of testing to determine fetal pulmonary maturation has significantly decreased in clinical practice in recent years because ACOG and NICHD have increased the stringency of indications for late-preterm and early-term births. If there is a significant risk to the mother or if abnormal antepartum fetal tests indicate a risk of fetal death, prompt delivery should occur regardless of whether or not the fetus is biochemically mature.
- Endogenous glucocorticoids produced in response to physiologic stress during labor and delivery increase surfactant production and decrease the risk of neonatal RDS. Obstetricians aim to decrease the risk of neonatal RDS during preterm births by administering a course of antenatal corticosteroids.
- Infants with neonatal RDS require respiratory support via minimally invasive ventilation and optimal PEEP to optimize ventilation/perfusion match while simultaneously aiming to avoid hyperoxia and volutrauma. Intubation should be reserved for neonates who demonstrate continued labored breathing with the use of CPAP via mask.
- Complications of neonatal RDS include retrolental fibroplasia, BPD, intraventricular hemorrhage, persistent patent ductus arteriosus, and necrotizing enterocolitis.
- Old/classical BPD is a ventilator-induced injury that occurs in neonates diagnosed with neonatal RDS who receive high-inspired oxygen. New BPD is associated with the disruption of lung development, resulting in the arrest of alveolar septation and vascular development in the distal lung.
- Inflammation during neonatal RDS can cause an imbalance between proinflammatory and anti-inflammatory cytokines, resulting in increased apoptosis of the premature lung with varying degrees of repair. The repeating cycles of apoptosis and repair prevent normal lung maturation due to impaired alveolarization and angiogenesis, resulting in the hallmarks of BPD: large, simplified alveoli and inadequate pulmonary vasculature.
- A complication of BPD that increases the risk of sudden death is pulmonary hypertension. Other complications of BPD that contribute to morbidity and mortality are worsening respiratory failure and cor pulmonale.

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Declaration of competing interest

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