Differential Diagnosis and Management of Respiratory Distress

Mary Beth Bodin, DNP, CRNP, NNP-BC
Lead Academic Faculty and Clinical Instructor
Acute & Continuing Care Neonatal Nurse Practitioner Track
University of Alabama at Birmingham
Neonatal Nurse Practitioner
DCH Health System, Tuscaloosa, AL

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Session Summary

This presentation will provide an overview of airway issues, diseases, mechanical, structural, obstructive, and iatrogenic causes of neonatal respiratory distress. The speaker will review the key characteristics, stabilization, and treatment options for the conditions discussed.

Session Objectives

Upon completion of this presentation, the participant will be able to:

- review the differential diagnosis for neonatal respiratory distress;
- determine appropriate clinical assessments with radiographic and laboratory studies for neonates in respiratory distress;
- discuss stabilization measures indicated for neonates in respiratory distress.

Test Questions

1. Which of the following measures are imperative for the infant with Choanal Atresia?
   a. Intubate and place on mechanical ventilation
   b. Place a # 8 NG Tube into the stomach
   c. Place an oral airway

2. Radiograph findings of generalized ground-glass appearance may indicate all of the following except:
   a. GBS pneumonia
   b. MAS
   c. Pulmonary hemorrhage
   d. RDS
3. An Arterial Blood Gas from an infant with early RDS typically shows:
   a. Profound alkalosis
   b. Metabolic acidosis
   c. Mild to moderate Respiratory acidosis

4. Nitrogen wash-out treatment for neonatal pneumothorax is accomplished by:
   a. Placing the infant in 100% oxygen
   b. Placing the infant on iNO for 8 hours
   c. Lung lavage with nitrogen solution

5. Permissive hypercapnia is indicated for all ventilated infants.
   a. True
   b. False

6. Side effects associated with long-term therapy with Lasix is:
   a. Excessive bone growth
   b. Nephrocalcinosis
   c. Speech impediments

References*


Session Outline

See presentation handout on the following pages.
DDx for Respiratory Distress in the Neonate

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Objectives:

- Upon completion of this presentation, the participant will be able to:
- Review the differential diagnoses for neonatal respiratory distress;
- Determine appropriate clinical assessments with radiographic and laboratory studies for neonates in respiratory distress;
- Discuss stabilization measures indicated for neonates in respiratory distress.

Differential Diagnosis

Structural anomalies – non-pulmonary

- Airway obstruction:
  - Nasal or pharyngeal: choanal atresia, nasal edema, blood, meconium, secretions, etc.
  - Oral cavity: macroglossia, micronathia, Pierre Robin Syndrome, teratoma
  - Neck: congenital goiter, cystic hygroma, malposition
  - Trachea: tracheomalacia, TEF, tracheal stenosis, bronchial stenosis

Choanal Atresia

- The nasal passages (choanae) are separated from the nasopharynx by a structure known as the buccosal membrane.
- Failure of the buccosal membrane to normally perforate during gestation.
- Bilateral in 50% of cases.
- Most affected infants are female.
- Half have associated anomalies such as CHARGE association.
Macroglossia

- Enlargement of the tongue which can be congenital or acquired.
- Most likely secondary to congenital hemangioma if localized.
- Can be seen with Beckwith's syndrome:
  - macroglossia, gigantism, omphalocele and severe hypoglycemia.
- Can be seen with Pompe's disease:
  - glycogen storage disease

Micrognathia: Pierre Robin Syndrome or Sequence

- Major feature is micrognathia (small mandible)
- The hypoplasia of the mandible.
- Obstructive respiratory distress and cyanosis.
- If placing the infant prone does not relieve the distress, a nasal airway device will be needed.
- Good prognosis for survival if non-syndromic.

Micrognathia: Other causes: DDx

- Many syndromes (e.g. Stickler or Catel-Manzke) have the craniofacial features associated with Pierre Robin.
- If non-craniofacial features are the primary defects, a MCA (multiple congenital anomaly) syndrome other than Pierre Robin is present.

Oral Teratoma

- Teratoma: benign and malignant tumors.
- Most common germ cell tumor.
- Consist of more than one embryonic layer.
- Airway stabilization and surgical resection of the lesion.
- Prognosis is generally excellent with non-malignant tumors. Mortality is generally the result of airway obstruction.
Cystic Hygroma

- Cystic hygroma
  - Neurogenic tumor
  - Neuroblastoma
  - Ganglioneuroma
  - Neurofibroma
- Derived from lymphatic tissue, is the most common lateral neck mass in the newborn period.
- Can be quite disfiguring and leave residual deformity if large.
- Airway patency is major concern.

Tracheomalacia

- Abnormal collapse of the tracheal walls.
- May be isolated or in combination with other lesions that cause airway compression or damage to the airways.
- Usually benign with symptoms related to airway obstruction during expiration (majority of cases).
- Definitive diagnosis is made by bronchoscopy.

Tracheomalacia: Management

- The safest and most effective treatment is allowing time to pass.
- Bronchodilators do not help and may worsen the symptoms.
- Chest physiotherapy may be helpful if heavy secretions are present.
- Pharmacotherapy for GER if present.
- Systemic corticosteroids may be helpful during an acute RTI.
- Tracheostomy with internal stenting for complicated cases.

DDx for symptoms of tracheal wall collapse:

- Bronchogenic cyst, Cystic Fibrosis, GER, Pulmonary Artery Sling, Vascular Ring - Double Aortic Arch, Vascular Ring - Right Aortic Arch
- Consider: Anomalous innominate artery, complete tracheal ring, Tracheal stenosis, Williams-Campbell syndrome.
**Tracheal Agenesis and Atresis**

- Fetus is generally growing and doing well in utero
- Immediate respiratory distress after delivery.
- Inability to pass even the smallest ETT
- Fatal unless there is presence of bronchoesophageal fistula

**Esophageal Atresia & Tracheoesophageal Fistula**

- Can exist as separate congenital anomalies, but most present with both. Most are associated with other congenital anomalies.
- Occurs when the trachea fails to differentiate and separate from the esophagus.
- 1 - 2 /5000 live births
- Predominance in white populations and in males and a disproportional rate of twinning among affected infants

**X-Ray of Esophageal Atresia**

- Chest x-ray shows tube ending in pouch or coiling there.
- Air in bowel indicates distal TEF.
- Airless abdomen indicates no fistula present.
- Contrast studies generally contraindicated but may be necessary if H-type fistula is suspected.
**Presentation**

- Clinically, cannot pass an OG tube or NG tube past 9 - 12 cm.
- As oral secretions and saliva collect in the upper esophageal pouch, the infant will present with large amounts of oral secretions due to lack of ability to swallow.
- Coughing, choking, and cyanosis during feedings is a common presentation with TEF.
- Secretions may be aspirated in cases of fistula.

**Initial Management**

- As with any problem causing respiratory distress in the neonate, airway patency and ventilation is a priority.
- Secretions may be aspirated in cases of fistula.
- The triad of excessive secretions, reflux, and respiratory distress especially in the presence of maternal hx of polyhydramnios indicates TEF until otherwise ruled out.

**Management**

- Surgical repair is the ultimate resolution.
- Pre-operatively, placement of Replogle tube to low suction.
- Humidified air may assist in thinning secretions.
- Elevating the HOB 30 - 40 degrees helps in avoiding aspiration.
- Comfort measures to avoid excessive crying.

**DDx**

**Other non-pulmonary causes of Respiratory Distress**

- Congestive heart failure: CHD
- Metabolic: acidosis, hypoglycemia, hypocalcemia
- PPHN: decreased pulmonary blood flow
- Respiratory depression: maternal narcotics?
- Shock
- Polycythemia
- Hyper or hypothermia
- CNS disorders
### CNS Disorders Causing Respiratory Distress in the Neonate

- Most commonly associated with cerebral edema or intracranial hemorrhage, usually as a consequence of anoxia or birth trauma.
- Wide range of clinical presentations: apnea, cyanosis, irregular respirations, tachypnea with GFR.
- Prognosis depends on cause and severity of the initial and any ongoing insult.

### CNS Disorders: DDx

- Brain: asphyxia
- Spinal Cord: trauma, Wernig-Hoffman disease
- Nerve injury: (phrenic nerve)
- Myasthenia gravis
- Muscular dystrophies

### DDx 

**Pulmonary Causes of Respiratory Distress in the Neonate**

- Aspiration: blood, meconium or amniotic fluid; formula
- Respiratory Distress Syndrome
- Atelectasis
- Air leaks
- TTNB

- Pneumonia
- Pulmonary hemorrhage
- CDH
- Intrathoracic: cyst or tumor, congenital lobar emphysema
- Effusions, chylothorax
- Agenesis or hypoplasia

### TTNB

- TTNB or Transient Tachypnea of the Newborn is also referred to as Retained Fetal Lung Fluid (RFLF).
- Commonly seen in infants delivered by cesarean section - more often in the absence of labor.
- Failure of the infant to adequately "clear" the lungs of fetal lung fluid.
- Most often is self-limiting resolving by 24 to 48 hours of age (may take up to 72 hours).
- Is very different from Amniotic Fluid Aspiration!
Presentation

- Unlabored tachypnea
- Can have GFR
- May have cyanosis
- "Barrel chest" appearance
- May see tachycardia with normal BP

ABG in Room Air

- Some degree of hypoxia is not unusual
- pH usually normal
- Hypocarbia is usual. Hypercarbia, if present is mild.
- Evaluate for need of hyperoxia test.

TTNB

Risk factors

- Elective cesarean delivery
- Male sex (Caucasian?)
- Macrosomia
- Maternal sedation
- Prolonged labor
- Negative PG
- Birth asphyxia

- Maternal fluid overload with oxytocin
- Delayed cord clamping
- Breech delivery
- Fetal polycythemia
- IDM
- Late preterm
- Exposure to B-mimetic agents
Treatment

- Oxygenation – supplemental oxygen if necessary. A few infants will require NCPAP and an even fewer number will require mechanical ventilation.
- Antibiotics – evaluate for sepsis/pneumonia.
- Feeding – Usual recommendations are for NPO if RR >80, OG or NG feeds if RR >60 but <80.
- Fluid and electrolytes – electrolytes usually not needed during 1st 24 hours. Maintain hydration.
- Diuretics – may lose weight but no difference in duration of TTN or decrease in length of stay.

Pneumonia in the Newborn

- Can be acquired transplacentally, during the birth process, or postnatally.
- Can be caused by bacteria, viruses, and fungi.
- Most transplacental infections are viral.
- In U.S. nurseries, GBS pneumonia remains the most frequently identified organism causing neonatal pneumonia.
- The second most common group of organisms causing early-onset pneumonia are the gram-negative enteric bacilli.
- Invasive procedures (intubation) increase the incidence of postnatally acquired infection.

<table>
<thead>
<tr>
<th>Causes respiratory infections in newborns according to route of acquisition</th>
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<tbody>
<tr>
<td>Transplacental</td>
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<td>Infections</td>
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<td>Birth asphyxia</td>
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<td>Respiratory distress syndrome</td>
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Radiological Evidence of Pneumonia

- Consolidation
- Infiltrates
- Mediastinal widening
- Pleural effusion
- Pleural line
- Lung collapse
- Increased intercostal spaces
- Prominent aorta
- Diaphragmatic elevation
- Mediastinal shift
- Rounded heart edges
**Treatment**

- Treat the symptoms:
  - Blood cultures and other diagnostic tests:
  - Tracheal aspirates obtained within 8 hours of birth which show both bacteria and WBCs on Wright's stain are highly predictive of pneumonia.
  - Treatment is usually begun with broad-spectrum antibiotics.
  - Follow course and cultures.

**Respiratory Distress Syndrome**

**Pathophysiology**

- Surfactant deficiency is primary etiology.
- Overly compliant chest wall.
- Progressive atelectasis.
- Failure to establish FRC.

**Surfactant Deficiency**

- Surface-active lipoprotein (phospholipid - 75%, protein - 10%) whose function is to stabilize the walls of the alveoli.
- Synthesized and secreted by type II epithelial cells (pneumocytes) in the alveoli.
- This cell line differentiates and begins surfactant production between 24 and 28 weeks gestation.
**Surfactant protein B deficiency**

- A genetic disorder of surfactant production; causes congenital alveolar proteinosis that in its early stages can resemble RDS.
- This is usually lethal although much work is currently being done in the realm of genetic research.
- Usually seen in term infants who present with the classic 5&5 of RDS.

**Prevention of RDS**

- Prevent prematurity
- Antenatal steroids

**Factors Increasing Risk**

- Prematurity
- Male sex (Caucasian?)
- Familial predisposition
- C/S without labor
- Perinatal asphyxia
- Chorioamnionitis
- Hydrops
- Maternal diabetes

**Factors Decreasing Risk**

- Chronic intrauterine stress
- PROM
- Maternal HTN
- Narcotic/cocaine use
- IUGR or SGA
- Corticosteroids
- Thyroid hormone
- Tocolytic agents
**Diagnosis**

- The DDx for a premature infant with Respiratory Distress includes:
  - RDS
  - Air Leak
  - Pneumonia
  - TTNB
  - Sepsis
  - CHD
  - Hypoglycemia
  - Cold Stress

**Evaluation**

- History
- Physical exam
- Chest x-Ray
- ABG
- CBC/diff

**Laboratory**

- Arterial Blood Gas – typically see a mild to moderate respiratory acidosis.
- Sepsis work-up – early onset sepsis can mimic RDS and GBS pneumonia is often indistinguishable from RDS on chest x-ray.
- Serum glucose
- Serum electrolytes – want to wait 8 to 12 hours to avoid obtaining maternal values.

**Radiographic picture**
Treatment

- Surfactant Replacement Therapy
- Mechanical ventilation/ respiratory support as needed
- Supplemental Oxygen
- Thermoregulation
- Euglycemia

Respiratory Support

- Endotracheal intubation and mechanical ventilation.
- CPAP and nasal synchronized intermittent mandatory ventilation.
- HFNC with supplemental oxygen
- NC with supplemental oxygen

Medications

- Theophylline - Caffeine vs. Aminophylline
- Sedation - evidence that sedation of infants with fluctuating CBF may decrease risk of IVH.
  - Phenebarbital
  - Lorazepam
  - Versed
  *Morphine vs. Fentanyl if pain suspected
- Paralysis - Pancuronium - controversial

Prognosis

- Use of surfactant replacement has not significantly decreased the over-all incidence of RDS.
- The survival has improved greatly.
- Major morbidity (BPD, NEC and IVH) is highly dependent on birth weight.
Air Leak Syndrome

- Pulmonary air leaks comprise a spectrum of processes that includes:
  - Pneumothorax
  - Pneumomediastinum
  - PIE
  - Pneumopericardium

Pneumothorax is the most frequent.
- Spontaneous
- Vigorous resuscitation
- RDS
- MAS
- Pulmonary hypoplasia

Pathophysiology

- Rupture of alveolus in over-distended lung.
- Air from the ruptured alveoli move up the vascular sheath into the mediastinum and from there into the pleural cavity.

Pneumothorax

- A pneumothorax may be asymptomatic or may present with significant respiratory distress.
- Transillumination of the chest may be revealing but the chest x-ray is the definitive diagnostic tool.
- Symptomatic pneumothorax will likely require needle aspiration followed by thoracostomy tube placement.
- Nitrogen "wash-out" may be successful in less severe cases.
Nitrogen Wash-Out Procedure

- The administration of 100% oxygen to term infants is said to potentially resolve a non-life-threatening pneumothorax more rapidly than observation alone.
- The theory is that nitrogen in the air contained in the pleural space passively diffuses across the lung into the alveoli full of 100% oxygen changing the pressure gradient.
- The difference in gas tension between the loculated gas in the pneumothorax encourages resolution of the intrapleural air leak.

Pneumomediastinum

- Some refer to the elevated thymus as the "angel wing sign" or "spinnaker sail sign".
- Resolves spontaneous in all but rare cases.
- Careful observation is essential.

Pulmonary Interstitial Emphysema: (PIE)

- Single or multiple circular radiolucencies with well-demarcated walls.
- May be localized or diffuse.

PIE Management

- Prevent! Prevent! Prevent!
- Minimize PIP, shorten Inspiratory Time, Reduce MAP.
- Positional therapy with affected side down if unilateral.
- HFJV or HFOV
**Tension Pneumothorax**

- Always symptomatic with sudden deterioration, especially if on PPV.
- May become hypotensive with bradycardia as the high intrathoracic pressure impedes cardiac output.
- Prompt relief by thoracentesis or thoracostomy tube placement is indicated.

**Pneumopericardium**

- Usually occurs in association with one or more other air leaks.
- Rare in the non-ventilated infant.
- Muffled heart sounds.
- Halo completely surrounds the heart - including the inferior surface.
- Symptoms mostly based on degree of tamponade.

**Management**

- Must acutely manage symptoms.
- May resolve spontaneously with support of the infant’s symptoms.
- Treat with pericardiocentesis or pericardial tube placement - 79% survival.
- Conservative management - 32% survival.
- 53% incidence of re-accumulation with pericardial taps alone.

**BPD vs. CLD**

- Late Respiratory Distress in the neonate.
- "Many experts now believe the term, Bronchopulmonary Dysplasia (BPD), is more accurate in describing the pathogenesis and that Chronic Lung Disease (CLD) is not a specific diagnosis or description." (Dr. Namasivayam Ambalavanan, UAB Division of Neonatology).

**Definitions**

- Use of supplemental oxygen for greater than 28 days after birth.
- Use of supplemental oxygen at 36 weeks post conceptional age (predictor of more severe pulmonary dysfunction in early childhood).
- Classic BPD follows a course of primary pulmonary failure.
- The "New BPD" is described in ELBW infants who may have had minimal or no lung disease (?interference with separation).

**Risk Factors**

- Same risk factors as for RDS
- Chorioamnionitis
- Tracheal colonization with ureaplasma
- Extremely low birth weight
- Symptomatic PDA

**DDx for similar x-ray changes**

- Stranding with lymphatic engorgement or atelectasis.
- Cardiomegaly if large PDA or fluid overload.
- Chronic changes are early and severe if from infection. (R/O myco/ureaplasma pneumonia)
Laboratory Findings

- **ABG**: CO2 retention. If chronic, pH is usually >7.25.
- **Electrolytes**: Elevated serum bicarbonate from chronic CO2 retention; hyponatremia, hypokalemia or hypochloremia if chronic diuretics; elevated BUN or creatinine if fluid restricted.
- **Urinalysis**: RBCs from possible nephrocalcinosis from prolonged diuretics.

Management

- Prevent prematurity!
- Reduce exposure to risk factors: minimize oxygen toxicity, minimize excessive tidal volume, judicious fluid administration, timely PDA closure, adequate nutrition.
- CPAP shortly after birth with avoidance of intubation and mechanical ventilation.
- Vitamin A prophylaxis?

Treatment

Treatment is directed toward the major presenting pathophysiology.

- Pulmonary edema - diuretics
- Optimize airway - bronchodilators
- Airway inflammation - steroids?
- Chronic injury and repair - antioxidants, nutrition, infection prevention.
- Cor pulmonale - Vasodilators

Respiratory Support

- Supplemental Oxygen: Friend or Foe?
- It is important to maintain adequate oxygenation to prevent PPHN, bronchospasm, cor pulmonale and growth failure.
- It is also important to minimize the risk of oxygen toxicity as this is a risk factor for damage to the lungs.
- Monitor SpO2 during various activities such as sleep and feeding.
Respiratory Support

- PPV: Friend or Foe?
  - Mechanical ventilation: If necessary, limit use of Tidal Volume greater than 4 – 6 mL/kg.
  - Permissive hypercapnia (PCO2 in excess of 50 – 60 mm Hg?) Try to avoid acidosis although lower pH may be acceptable.
  - Nasal CPAP (? Nasal IMV).

Optimize Lung Function – Fluid management

- Fluid restriction - no specific intake can be stated as the actual target. Evaluate individually. Can increase calories in order to accomplish desired intake.

Optimize Lung Function – Diuretics

- Chlorothiazide & spironolactone – for chronic management. Fewer side effects - monitor potassium.
- Furosemide - more potent and useful for rapid diuresis. Many side effects - electrolyte abnormalities, interference with bilirubin-binding, calcium with bone demineralization, nephrocalcinosis, ototoxicity.
- Bumetanide - similar to Lasix - less ototoxicity and less interference with bilirubin-binding.

Optimize Lung Function – Bronchodilators

- B2-Agonists - Use for management of acute exacerbations due to time-limited effects. Side effects - tachycardia, hypertension, hyperglycemia, and possible arrhythmias. Albuterol - racemic - nebulized. Xopenex (levalbuterol) non-racemic form - lower doses lead to fewer side effects.
- Theophylline - dilate smooth airway muscles, increase diaphragmatic contractions, central respiratory stimulation, and mild diuretic effect. Side effects include CNS irritability, GER, GI irritability.
- Anticholinergic agents - nebulized Atrovent.
Meconium Aspiration Syndrome

- MAS is the most common aspiration syndrome that causes respiratory distress in the neonate.
- Infants most commonly post-mature.
- Can be seen in late term or term infants who have passed meconium in utero.

Risk Factors

- Postterm pregnancy
- Preeclampsia-eclampsia
- Maternal hypertension, chronic respiratory or cardiovascular disease
- Maternal diabetes mellitus
- Abnormal fetal heart pattern
- IUGR
- Abnormal biophysical profile
- Oligohydramnios
- Maternal smoking

Prevention

- Prenatal management
  - Identification of high risk pregnancies
  - Fetal monitoring
  - Amnioinfusion
  - Delivery room management

Delivery Room Management

- The goal of management of the infant is to decrease the severity of aspiration.
- The sickest of these infants usually aspirated in utero and present with reactive pulmonary vasoconstriction.
- Endotracheal intubation and suctioning of the airway is necessary in any infant with meconium stained fluid if the infant is not vigorous at birth.
Delivery Room Management

- Clinical judgment is required in deciding on the number of intubation/suctioning efforts.
- Prolonged suctioning is not recommended as it will exacerbate the preexisting asphyxial insult.
- Further resuscitative measures such as ventilation and oxygenation will take priority in order to avoid or lessen pulmonary hypertension.

Classic Sequence

- Airway obstruction - the thick material can result in simple acute upper airway obstruction.
- The material progresses distally creating total or partial airway occlusion.
- Atelectasis follows distal to the obstruction.
- With partial airway obstruction, air can enter but cannot be exhaled (ball-valve phenomenon).
- Results in air trapping and alveolar hyperexpansion. Great risk for air leak!
- Chemical irritant leading to bronchial edema and narrowing of the airways.

Chest X-Ray Findings

[Image of chest x-ray]

Laboratory

Arterial Blood Gas
- Characteristically reveals hypoxemia and respiratory acidosis.
- May see metabolic acidosis in cases of perinatal asphyxia.
- Infants with pulmonary hypertension and right-to-left shunting may have a gradient in oxygenation between pre-ductal and post-ductal samples.

Cardiac

Cardiac 2D Echo
- Typically reveals right to left atrial and ductal shunting as a result of pulmonary hypertension and hypoxemia.
- The shunting further exacerbates the hypoxemia leading to increase in pulmonary hypertension.

Management

Management of the apparently "well infant" born through meconium-stained amniotic fluid
- Any infant with meconium-stained amniotic fluid should be monitored for respiratory distress.
- Most infants who develop symptoms will do so in the first 12 hours of life.

Management of the Sick Infant

The goals of management revolve around increasing oxygenation while reducing the risks of barotrauma.
- Relatively rapid rate (40 - 60)
- Minimum effective PIP for chest rise
- Low to moderate PEEP (3 - 5 cm H2O)
- Adequate expiratory time (0.5 - 0.7)
- May need expiratory time 0.7 - 1.0 with PEEP 3 - 5 cm H2O if gas trapping present.
Medications

- Antibiotics
- Surfactant replacement
- Sedation

Sedation

- May maximize the efficiency of mechanical ventilation.
- Minimizes oxygen consumption.
- Same as for RDS
  - Phenobarbital
  - Lorazepam
  - Versed
* Morphine vs. Fentanyl for pain management

Prognosis

- Prognosis is related to severity of complications.
- Complicated by development of PPHN.
- May result in BPD or CLD from prolonged mechanical ventilation.
- May be complicated by neurologic sequelae if associated with significant asphyxial insult.

PPHN

- Persistent Pulmonary Hypertension of the Newborn (PPHN) was referred to as Persistent Fetal Circulation (PFC) in the past.
- Idiopathic or Sequela/consequence of another disorder.
- Combination of pulmonary hypertension (high pressure in the pulmonary artery) and R to L shunting (away from the lungs) through the foramen ovale or ductus arteriosus.
- Structurally normal heart.
**Pathophysiology of PPHN**

- Syndrome that results from primary failure of the pulmonary vascular resistance to decrease after birth.
- Pulmonary vascular resistance remains equal to or greater than systemic vascular resistance.
- Foramen ovale and ductus arteriosus remain patent allowing shunting of blood away from the pulmonary system.
- With the loss of the placental gas exchange unit, the PaO2 will fall to extremely low levels.

**Etiology of PPHN**

- Type I: Abnormally constricted pulmonary vasculature due to lung parenchyma disease
- Type II: Idiopathic PPHN with normal parenchymal and remodeled pulmonary vasculature
- Type III: Hypoplastic vasculature

**Associated Factors**

- Primary lung disease:
  - MAS
  - RDS
  - pulmonary hypoplasia
  - pneumonia
  - cystic lung disease
  - congenital cystic adenomatoid malformation
  - congenital lobar emphysema
  - CDH
  - congenital alveolar capillary dysplasia

- Systemic disorders
  - polycythemia
  - hypoglycemia
  - hypoxia
  - acidosis
  - hypocalcemia
  - hypothermia
  - sepsis
**Associated Factors**

- Congenital Heart Disease
  - total anomalous venous return
  - hypoplastic left heart
  - transient tricuspid insufficiency
  - transient myocardial ischemia
  - coarctation of the aorta

- Critical aortic stenosis
- Endocardial cushion defect
- Ebstein's anomaly
- Transposition of the great arteries
- Endocardial fibroelastosis
- Cerebrovenous malformations

**Associated Factors**

- Perinatal factors
  - asphyxia
  - perinatal hypoxia
  - Maternal ingestion of NSAIDs (3rd trimester)
  - Maternal ingestion of SSRIs (second trimester)

**Associated Factors**

- Miscellaneous
  - Central nervous system disorders
  - Neuromuscular disease
  - Upper airway obstruction

**Clinical Presentation**

- Cyanosis
- Tachypnea
- Respiratory distress
- Loud single S2
- Possible harsh systolic murmur secondary to TR
- Poor perfusion
Laboratory Studies

- **ABG:** Initially see hypoxemia. Prolonged hypoxemia can lead to metabolic acidosis due to the presence of anaerobic metabolism. No longer recommended to treat with hyperventilation.

- **CBC:** Polycythemia and hyperviscosity may be a predisposing factor in some cases. Thrombocytopenia has been reported in as many as 60% of cases - unknown etiology. R/O sepsis.

- **Basic metabolic profile:** PPHN is sometimes associated with hypoglycemia or hypocalcemia. Calcium is a critical cofactor for nitric oxide synthesis activity.

Radiography

- **Chest x-ray appearance** will be related to the etiology of the PPHN (for example, MAS, CDH, pneumonia).

- Without associated pulmonary disease, there will be decreased pulmonary vascularity due to diminished pulmonary blood flow.

- **Cardiac shadow** will reflect degree of cardiac involvement (Congenital heart disease?)

- **Clear lung fields** in the presence of severe hypoxemia is highly suggestive of PPHN if cyanotic CHD has been ruled out.

Echocardiogram

- Normal cardiac anatomy
- R to L shunting through ductus arteriosus or across the foramen ovale

Differential Blood Gas Results

- In the presence of R to L shunting via the PDA, the PaO2 will be higher in a pre-ductal site than from a post-ductal site.

- Pre-ductal = right radial artery (right arm and head)

- Post-ductal = left radial artery, umbilical artery, posterior tibial arteries (left arm, umbilical artery and lower extremities)

- A difference > 10 mm Hg between pre and post-ductal PaO2 suggestive of R to L shunt.
**Differential Pulse Oximetry**

- Simultaneous monitoring of oxygen saturation via pulse oximeter (SpO2) is a useful indicator of R to L shunting at the ductal level.
- SpO2 difference > 5% is suggestive of R to L shunt via the PDA.
- No difference will not rule out PPHN however.

**Management**

- Treat the underlying condition if known.
  - Minimal handling.
  - Avoid hypovolemia.
  - Monitor serum glucose and calcium.
  - Mechanical ventilation.
  - Medications
    - ECMO

**Basic Strategies**

- Avoid hyperventilation: Hypocarbia leads to decreased cerebral blood flow and has been associated with poor neurologic outcome and sensorineural hearing loss.
- Correct acidosis with buffer: NaHCO3 or Tham (tromethamine)

**Medications**

- Sedation and analgesia with opioids is often necessary.
  - Fentanyl: (85 - 200 X more potent than morphine.) Causes little CV compromise used alone. Side effects - acute muscle rigidity or chest-wall syndrome if administered too rapidly. Reversible with Naloxone.
  - Midazolam (Versed Tolerance may develop with withdrawal if weaned rapidly. Watch for hypotension if used concurrently with opioids.)
Medications

- Paralytic agents: Controversial therapy but may be indicated if infant does not respond to sedation and analgesia (labile and “fighting ventilator”).
- Pancuronium (Pavulon) is commonly used drug. Start with 0.05 - 0.1 mg/kg (0.04 - 0.15 mg/kg) IV push. May give every 1 - 2 hours.
- Vecuronium has also been used (0.1 mg/kg). *May increase PVR by under-ventilation of dependent alveoli worsening V/Q mismatch.

Vasopressors

- Dopamine (Intropin): Thought to increase BP by stimulating alpha-adrenergic receptors. Continuous infusion of 2 - 20 mcg/kg/min IV.
- Dobutamine (Dobutrex): Increases BP by stimulating beta-1 adrenergic receptors. Continuous infusion of 2 - 25 mcg/kg/min IV. Has less of a pressor effect than Dopamine.
- Milrinone (Primacor): Bipyridine inotropic/vasodilator agent with phosphodiesterase inhibitor activity. Increases BP primarily by increasing cardiac cAMP. Continuous infusion of 0.2 - 0.5 mcg/kg/min IV.

Vasodilating Agents

- Sildenafil: Produces pulmonary vasodilatation by selective inhibition of phosphodiesterase type 5 (which depletes cGMP), therefore reducing the breakdown of cGMP, which is the second messenger of endogenous NO. Is being currently studied in IV form, is available to give PO. In addition to the vasodilator effects, it may also increase cardiac contractility having a positive inotropic effect on the heart.

- iNO is the most commonly used and most specific agent for PPHN in the newborn. Has decreased the need for ECMO by > 35%. Leads to vasodilation by relaxation of vascular smooth muscle. Initiation of therapy frequently begins with 20 ppm with dosing adjustments as warranted. A common weaning protocol is to wean iNO if the infant can maintain PaO2 > 60 mm Hg in FiO2 < .60.
- Use in center with EMCO available or insure ability to transport on iNO.
**Mechanical Ventilation**

- The primary goal is to maintain normal FRC while avoiding over-expansion. Adequate and stable oxygenation is maintained using the lowest MAP.
- Over-expansion can elevate PVR and increase R to L shunting.
- Strategy is determined by underlying pathology.

**Conventional Mechanical Ventilation**

- Conventional ventilation has been successful in many institutions using guidelines for PaO2 50-70 and accepting PaCO2 up to 60. Aiming for higher PaO2 may require increased ventilator support and barotrauma.
- Avoid hyperventilation by correcting pH with buffers.
- Lowest possible MAP with lowest possible positive end-expiratory pressures.

**ECMO**

- Each ECMO center will establish specific inclusion criteria.
- Generally accepted: ANY of the following AND underlying disease process which is likely to be reversible.
  - Standard: OI > 40 on conventional ventilation or ≥ 50-60 on HFOV. (0.5 - 6 hours)
  - PaO2 < 40 mm Hg for >2 hours despite maximum ventilatory support.
  - Acidosis and Shock (pH < 7.25 due to metabolic acidosis, lactate build-up, intractable hypotension)

**OI Calculation**

- \[ OI = \frac{FiO2 \times MAP \times 100}{PaO2} \text{ (mm Hg)} \]
  - 1.0 $\times$ 18 $\times$ 100 / 40 = 45

- Oxygen Index calculators available online. One example:
Congenital Diaphragmatic Hernia: (CDH)

- Occurs at a frequency of 1 in 2500 live births.
- Most common on the left.
- Accompanied by ipsilateral pulmonary hypoplasia.
- Severe respiratory distress at birth.
- Usually has a scaphoid abdomen.

If prenatally diagnosed, endotracheal intubation and mechanical ventilation with rapid rate and low inflation pressures. Tolerate hypercapnia to a degree.

Most likely have or will develop PPHN.

Survival is poor in infants who are very symptomatic at birth. ECMO is often required to no avail.

Controversy among surgeons as to urgency of surgical repair.

Stabilization is by mechanical ventilation, vasopressors, correction of acidosis prior to surgery. Some perform surgical repair while the infant is under ECMO.

General Pathophysiology of Pulmonary Hypoplasia

- Pulmonary hypoplasia is a relatively common abnormality of lung development and has a variety of clinical associations and anatomic correlates.
- Most of you are familiar with Potter syndrome (primary renal agenesis associated with prolonged oligohydramnios.) This leads to a decrease in lung size and cell number.
- PPROM between 16 and 28 weeks gestation has the same effect.
- Magnitude of hypoplasia in general correlates with the severity and duration of the oligohydramnios.

Clinical Associations of Pulmonary Hypoplasia

<table>
<thead>
<tr>
<th>Thoracic Compression</th>
<th>Body Position</th>
<th>Birth Trauma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diaphragmatic hernia</td>
<td>Head of fetus</td>
<td>Fetal distress</td>
</tr>
<tr>
<td>Abdominal distention limiting chest volume</td>
<td>Thoracic dystrophy</td>
<td>Intrathoracic masses</td>
</tr>
</tbody>
</table>

Decreased Intrathoracic Space

- Diaphragmatic hernia
- Fluid of fetus
- Abdominal distention limiting chest volume
- Thoracic dystrophy
- Intrathoracic masses

Decreased Fetal Breathing

- Intrathoracic CNS damage
- Fetal Wernicke-Korsakoff syndrome
- Other neuropathies and myopathies

Other Associations

- Primary pulmonary hypoplasia
- Trisomy 13
- Multiple congenital anomalies
- Erythroblastosis fetalis
**Cystic Adenomatoid (CCAM) Malformation**

- CCAM is an abnormal area of lung tissue that is usually unilateral and lobar.
- DDx: pulmonary sequestration, CDH, other congenital cystic malformations (e.g., bronchogenic, enteric, or neurogenic cysts).
- May enlarge significantly, leading to fetal hydrops; may remain unchanged; or may shrink and disappear prenatally.
- Hydrops is an ominous sign with almost 100% mortality.

**Associated Anomalies**

- Although a rare anomaly, there are cases of associated anomalies:
  - renal agenesis or dysgenesis
  - CDH
  - hydrocephalus
  - skeletal anomalies

**Pulmonary Hemorrhage**

- Risk Factors
  - RDS
  - Asphyxia
  - CHD
  - Aspiration syndromes
  - DIC and other bleeding disorders
  - Administration of pulmonary surfactant
  - PDA (L to R shunting with high pulmonary blood flow)

- Fetal surgery is a viable option when hydrops threatens survival of the fetus.
- Best performed between 21 and 27 weeks when lung growth continues.
- Type II cells are producing surfactant.
- There is still a possibility of pulmonary hypoplasia and the best results are obtained with delivery at a center where ECMO is available.
Radiograph

- Not that helpful.
- Appearance is variable and non-specific.
- May result in focal or diffuse ground-glass opacities.
- Looks a lot like pulmonary edema.

Presentation

- Usually detected by blood in ETT secretions.
- Sudden deterioration with hypotension, pallor, cyanosis, and bradycardia.
- If blood obtained from ETT shortly after intubation in a newborn, send specimen for APT to check for maternal blood aspiration.

Management

- Tracheal intubation with assisted ventilation.
- Increase is ventilator pressure including Peep.
- FFP and PRBC if necessary.
- Address underlying etiologies.
- Some evidence that instillation of low dose Epinephrine is helpful.
- Consider surfactant as hemorrhagic edema can inactivate endogenous surfactant production.

Whew!!

- In summary, I have reviewed the most common causes for Respiratory Distress in the Neonate. The presentation was not intended to be all inclusive as this would take a semester to accomplish.
- Go the the NCC web page [http://www.nccwebsite.org](http://www.nccwebsite.org) and open the certification tab. You will find a wealth of information concerning references and general topics to review.
- Good luck! My contact information is: bodinn@uab.edu if you have any questions.
Questions:

1. Which of the following measures are imperative for the infant with Choanal Atresia?
   a. Intubate and place on mechanical ventilation
   b. Place a #8 NG Tube into the stomach
   c. Place an oral airway

2. Radiograph findings of generalized ground-glass appearance may indicate all of the following except:
   a. GBS pneumonia
   b. MAS
   c. Pulmonary hemorrhage
   d. RDS

3. An Arterial Blood Gas from an infant with early RDS typically shows:
   a. Profound alkalosis
   b. Metabolic acidosis
   c. Mild to moderate Respiratory acidosis

4. Nitrogen wash-out treatment for neonatal pneumothorax is accomplished by:
   a. Placing the infant in 100% oxygen
   b. Placing the infant on iNO for 8 hours
   c. Lung lavage with nitrogen solution
Questions:

5. Permissive hypercapnia is indicated for all ventilated infants?
   a. True
   b. False

6. Side effects associated with long-term therapy with Lasix is:
   a. Excessive bone growth
   b. Nephrocalcinosis
   c. Speech impediments