

22. NEONATALOGISTS AT WORK I

PERSISTENT PULMONARY HYPERTENTION (PPH) IN THE NEONATE

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OVERVIEW:

Persistent pulmonary hypertension (abnormally high pulmonary artery pressure) in the neonate, also known as persistent fetal circulation, was first described at Columbia University by Welton Gersony, M.D. in 1969. At that time, the disorder was thought to be a single disease entity; as time has progressed, we now know pulmonary hypertension in the neonate is the end pathway common to multiple disease processes, all of which share similar pathophysiology and all of which present with a similar clinical picture, hypoxia with dyspnea.

LEARNING OBJECTIVES:

At the conclusion of the lecture, you should be able to:

- 1) Describe the normal and complex cardiopulmonary changes that occur at birth.
- 2) Briefly discuss the pathophysiology associated with neonatal persistent pulmonary hypertension
- 3) Discuss treatment modalities currently utilized to support neonatal cardiopulmonary function until pulmonary hypertension resolves.

GLOSSARY:

Dyspnea: difficult or labored breathing

Hypocarbica: deficiency of carbon dioxide in the blood

Hypoxia: low oxygen content or tension; deficiency of oxygen in inspired air

Meconium: green mucilaginous material in the intestine of the normal full term fetus

LECTURE NOTES:

Epidemiology:

The prevalence of this disorder is approximately 2 per 1000 live births with a range in incidence from 0.43-6.82 per 1000 live births. Multiple risk factors are usually implicated in the pathophysiology of the disease process. An abnormal fetal heart rate tracing occurs in approximately 50% of affected neonates, meconium staining of the amniotic fluid occurs in approximately 50% of affected neonates, and approximately 60% of affected neonates have low Apgar scores (**see Figure 22-1**). For the majority of affected neonates, a “hostile intra-uterine environment” has been present either as an acute or subacute complication of pregnancy, labor, or delivery.

COMPONENTS OF THE APGAR SCORE			
Sign	Score		
	0	1	2
Heart rate	Absent	<100 beats/minute	>100 beats/minute
Respiratory effort	Absent	Slow, irregular	Good cry
Color	Cyanotic, pallid	Acrocyanotic	Pink
Muscle tone	Limp	Minimal	Active
Reflex response	Absent	Minimal	Active

Fig. 22-1

Pathophysiology:

Birth is an astonishing process. Within hours, a series of incredibly complex events is initiated and completed that transform a fetus, totally dependent upon his/her mother for various physiologic functions prior to birth, to a neonate with total independence shortly after birth. Prior to birth, the fetus is totally dependent upon the mother for regulation of body temperature, glucose and electrolyte homeostasis, accretion of nutritional elements, elimination of bodily wastes, and respiratory gas exchange to name but a few. After birth, the end result with regard to respiratory gas exchange is a shift from placental circulation to the lungs for CO₂ and O₂ exchange. For a successful transition to occur, both gas and blood must enter into the lungs, establishing gaseous lung volumes and pulmonary blood flow. Matching of ventilation and perfusion within lung units is necessary for survival.

During fetal life pulmonary alveoli are filled with fluid. The first few breaths are crucial in the process of successfully filling alveoli with gas (air). In order to affect this change, a neonate must overcome the natural forces which tend to collapse alveoli and which include but are not limited to: alveolar surface active forces and both tissue elastic and resistive forces. Those first few inspirations help establish functional residual capacity (FRC) which in and of itself decreases both pulmonary vascular resistance and the inspiratory pressure generated for subsequent breaths. FRC is important in tethering open alveolar capillaries adjacent to the expanding alveoli with resultant decreasing of pulmonary vascular resistance. The increase in PAO₂ and decrease in PACO₂ associated with the transition from fetal to neonatal circulation further decreases pulmonary vascular resistance. Establishment of adequate pulmonary blood flow is dependent therefore upon establishment of adequate ventilation of the lungs in the immediate peripartum period (see Figures 22-2, 22-3 and 22-4).

TRANSITION FROM FETAL TO NEONATAL CIRCULATION		
Event	Physiological Consequence	Effect on Cardiovascular System
Alveolar ventilation	Decreased PVR (increased PO ₂ , prostacyclin, nitric oxide) Increased pulmonary blood flow Increased pulmonary venous return	Increased LA pressure
Placental separation	Decreased IVC return Closure of ductus venosus	Decreased RA pressure Increased SVR Closure of foramen ovale
Decreased RA pressure and increased LA pressure	Reversal of ductal flow Increased PO ₂ in ductus	Closure of ductus arteriosus

IVC, inferior vena cava; LA, left atrium; PVR, pulmonary vascular resistance; RA, right atrium; SVR, systemic vascular resistance.

Fig. 22-2

Fig. 22-3 Factors that modulate pulmonary vascular resistance in the fetus and newborn infant. Persistent pulmonary hypertension may arise from an imbalance in the factors modulating pulmonary vascular resistance, favoring vasoconstrictive over vasodilatory mediators (Indiana University Medical Illustrations, 1998)

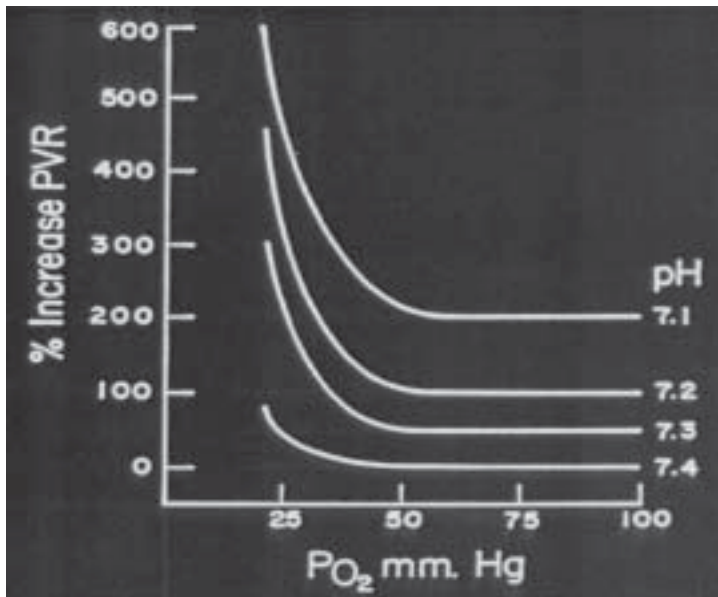
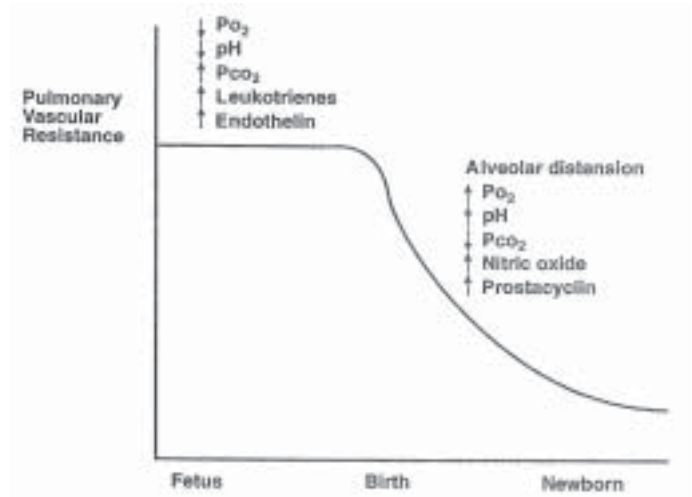


Fig. 22-4

Categorization of persistent pulmonary hypertension (PPHN): Etiologies (see Figure 22-5)

One approach to the differential diagnosis of persistent pulmonary hypertension utilizes an algorithm based upon both numbers and caliber of pulmonary arteries. Pulmonary arteries may be normal or decreased in number. If normal in number, the pulmonary arteries may be of a normal caliber or, may have a decreased caliber related to increased musculature within the media of the pulmonary vessels. Pulmonary vascular resistance is inversely related to intraluminal caliber; the smaller the lumen, the higher the pulmonary vascular resistance and resultant pulmonary artery pressure. Pulmonary hypertension may also occur with obstruction to pulmonary blood flow secondary to abnormal pulmonary venous drainage. The latter is seen in complex congenital heart disease with obstruction to pulmonary venous flow, such as that seen in total anomalous pulmonary venous return or cor triatriatum.

(1) Disorders associated with diminished numbers of pulmonary arteries: In this subset of patients, persistent pulmonary hypertension occurs as a consequence of hypoplasia of the pulmonary vascular bed. The number of pulmonary vessels is decreased related to inability of the developing fetal lung to grow and expand within the fetal thorax.

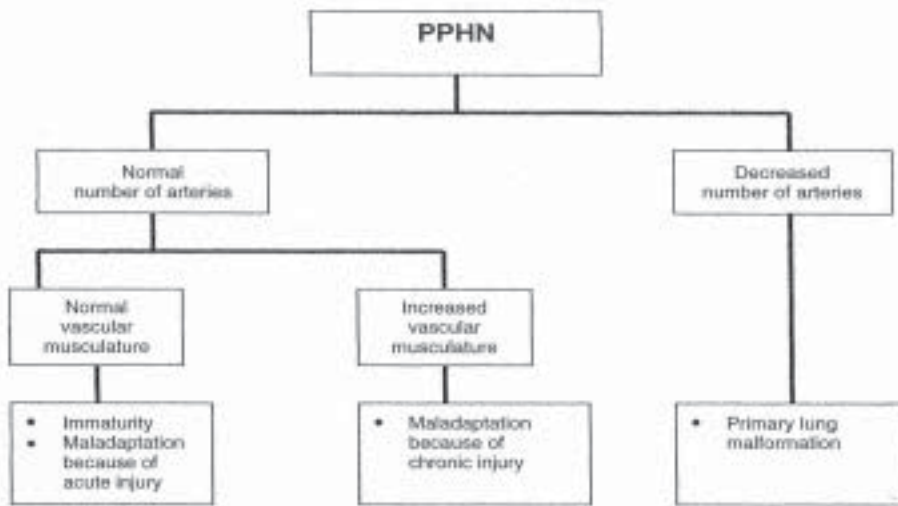


Fig. 22-5 Classification of persistent pulmonary hypertension of the newborn. (From Geggel R, Reid L: The structural basis of PPHN. Clin Perinatol 11:525-549, 1984; with permission.)

(2) Disorders associated with normal numbers of pulmonary arteries and normal vascularization. In this subset of patients, persistent pulmonary hypertension is present despite normal numbers of pulmonary arteries and normal vascularization because the usual decrease in pulmonary vascular resistance which occurs immediately post birth is delayed by acute hypoxia with or without lung injury; it is usually reversible. This subgroup of patients represents the greatest number of neonates with persistent pulmonary hypertension. The abnormally high pulmonary vascular resistance may be caused by high concentrations of leukotrienes and other vasoconstrictive substances released by or into pulmonary vessels. Subacute or chronic in utero hypoxia, as opposed to acute peripartum (following birth) hypoxic events, may produce hypertrophy of the media of the pulmonary arterial bed and increased pulmonary vascular resistance by decreasing the luminal diameter of pulmonary vessels. Additionally, muscularization of the intraacinar arteries may occur with either subacute or chronic in utero hypoxia further reducing luminal diameter; these vessels should not be muscularized (see **Figure 22-6**).

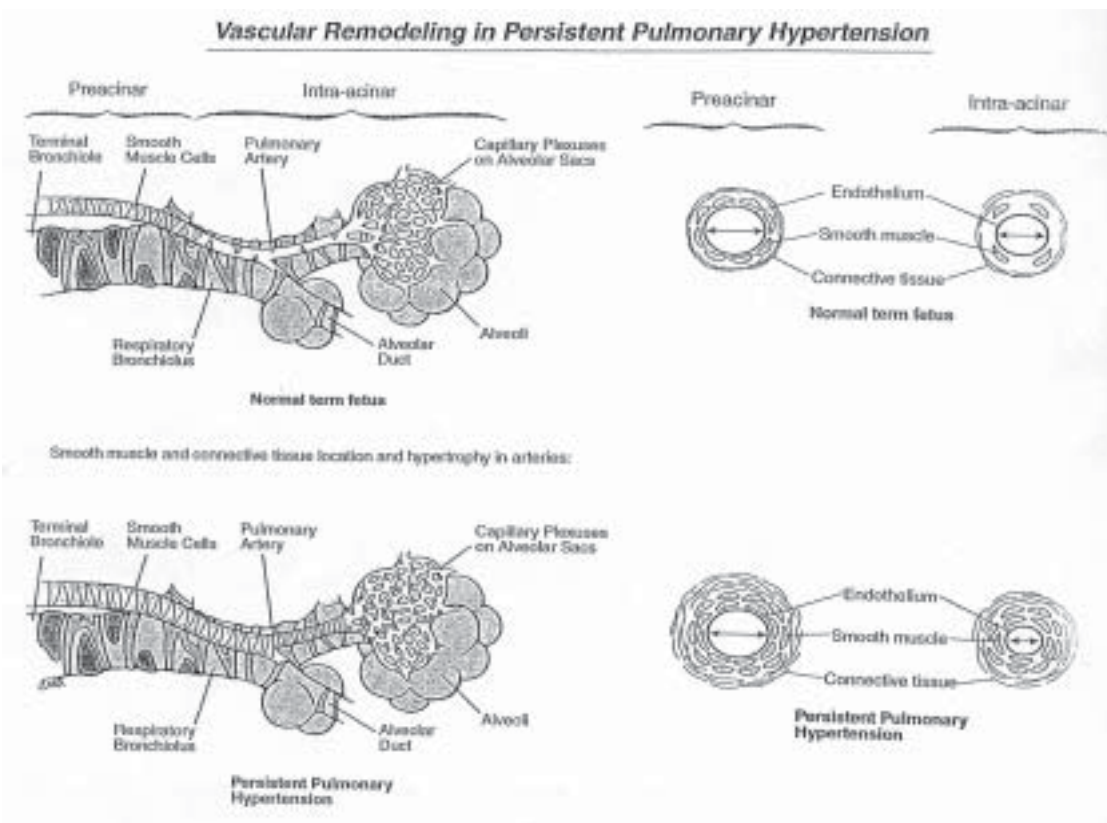


Fig. 22-6

Diagnosis:

The diagnosis of persistent pulmonary hypertension is suspected by the clinical presentation of hypoxia with dyspnea, and confirmed by diagnosing high pulmonary vascular resistance and high pulmonary arterial pressure in the absence of congenital heart disease. The current “gold standard” for diagnosis is echocardiography, a non-invasive method to assess cardiac anatomy and heart function. Important for the diagnosis are: increased right ventricular pressure, abnormal blood flow from the right to the left side of the heart at atrial and/or ventricular level (intracardiac shunt), blood flow through a patent ductus arteriosus from the pulmonary artery to the aorta (extracardiac shunt), and abnormally high pulmonary arterial pressures. Tricuspid insufficiency is frequently present in babies with persistent pulmonary hypertension; when present, some right ventricular output may, during ventricular systole, be ejected into the right atrium, thereby increasing right atrial pressures, and allowing blood to flow from the right to the left atrium along a pressure gradient. Since this blood bypasses the lungs, it has no chance to become oxygenated; systemic hypoxia is produced by this intracardiac shunt.

Prior to the widespread use of echocardiogram for confirmation of the diagnosis, invasive cardiac catheterization, which allows direct measurement of pulmonary artery pressures and direct visualization of intra and extracardiac shunts, was performed.

Therapy:

Although persistent pulmonary hypertension in the neonate has been an entity known to pediatricians and neonatologists for over three decades, there have been few if any prospective randomized trials to evaluate the various therapies utilized in its treatment.

Therapeutic Modalities:

(1) Intermittent positive pressure ventilation (mechanical ventilation). Clinicians vigorously ventilated neonates with persistent pulmonary hypertension in an effort to produce hypocarbia with the hope of decreasing pulmonary vascular resistance. We now know the detrimental effects of this excessive ventilation technique. The incidence of chronic lung disease in survivors of persistent pulmonary hypertension who were hyperventilated was significantly increased because of the barotrauma and volutrauma associated with this ventilation strategy. Additionally, significant neurologic sequela were present in survivors related to the detrimental effects of hypocarbia upon the central nervous system; hypocarbia produces cerebral brain injury.

(2) Surfactant and High Frequency ventilation. In a small number of babies, administration of exogenous surfactant has been shown to decrease the need for extracorporeal membrane oxygenation (ECMO, see below). Although these preliminary data suggest surfactant replacement therapy may decrease the need for ECMO therapy in these neonates, the FDA has stated that not enough data yet exists to approve surfactant use in persistent pulmonary hypertension of the newborn. High frequency ventilation (HFV) has been utilized in neonates with persistent pulmonary hypertension secondary to meconium aspiration syndrome. No randomized trial has ever proven significantly better survival utilizing HFV compared to conventional ventilation nor has HFV been shown to decrease the need for ECMO therapy.

(3) Inhaled nitric oxide. Nitric oxide (NO), formerly known as endothelial derived relaxation factor (EDRF) is a gas produced endogenously in the pulmonary endothelial cell by nitric oxide synthetase, an enzyme which synthesizes nitric oxide from arginine and oxygen (see **Figure 22-7**). NO has the

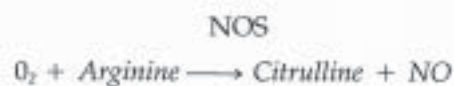


Fig. 22-7

unique property of relaxation of the pulmonary capillary bed through up-regulation of cyclic GMP production. It has a very short half life: it may a) be excreted through the lungs, b) degrade in the presence of oxygen to higher oxides of nitrogen without bioactivity, or c) bind to hemoglobin forming Hb-NO without bioactivity. Because it is rapidly metabolized, there is virtually no nitric oxide present in the pulmonary venous blood. It has virtually no effect upon systemic vascular resistance. Nitric oxide synthetase activity is present within the neonatal lung and may actually be important in the immediate pulmonary vasodilatation post birth. Inhaled nitric oxide rapidly diffuses across the alveolar membrane to affect relaxation of the pulmonary bed. Use of inhaled nitric oxide in patients with persistent pulmonary hypertension has significantly decreased the need for ECMO therapy by greater than 50%.

(4) ECMO: This is the treatment “of last resort” for patients with persistent pulmonary hypertension who have failed to respond to conventional therapies including inhaled nitric oxide. Not only is ECMO quite labor intensive, but there are significant risks associated with ECMO therapy. At time of institution of ECMO, cannulas are placed into the right atrium through the jugular vein and into the arch of the aorta through the internal carotid artery (see **Figure 22-8**). Blood drains by gravity from the right atrial cannula into a small reservoir from which a roller pump propels it into and through a membrane oxygenator. It is through this semi-permeable membrane that carbon dioxide is removed from the blood and oxygen diffuses into the blood. The O₂ rich, CO₂ poor blood passes through a re-heating circuit after which it is returned to the body via the cannula in the arch of the aorta. During ECMO therapy, the lungs are minimally ventilated, if at all, to allow healing of any ventilator induced lung damage. Hypoxia and hypercarbia are relieved, thus promoting pulmonary vascular relaxation. Complications include but are not limited to: bleeding,, consumption of white blood cells and platelets by the ECMO circuit and membrane, infection, embolic infarctions, and/or rupture/clotting of various components of the ECMO circuit. Despite these potential complications, ECMO may be lifesaving to a baby with pulmonary hypertension. In order to be considered a candidate for this therapy, neonates with reversible pulmonary hypertension must have an expected mortality greater than 90%; ECMO therapy changes the 90% mortality to at least an 85% survival.

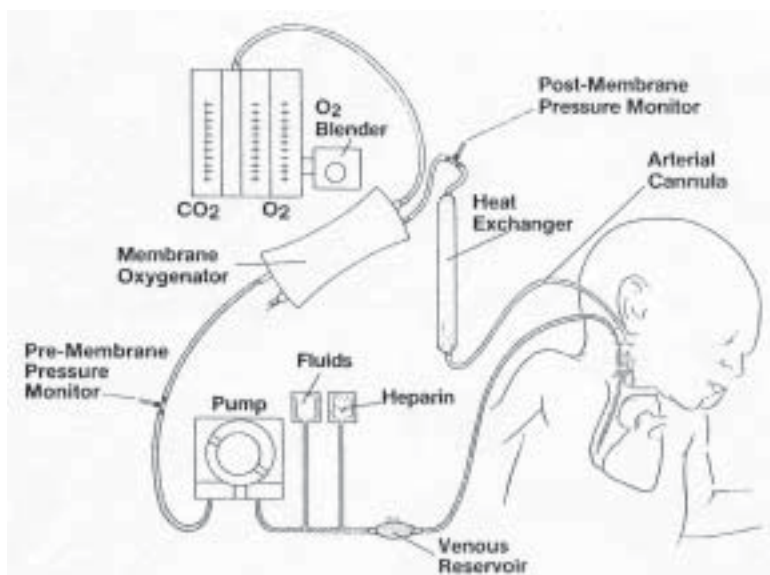


Fig. 22-8 Venoarterial extracorporeal membrane oxygenation (ECMO) circuit and its components.

22. NEONATALOGISTS AT WORK II

PATHOGENESIS, TREATMENT and PREVENTION OF NECROTIZING ENTEROCOLITIS (NEC)

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SUGGESTED READING: For those interested in knowing more about NEC and ways of treating it, the following review by Doctors Jane S. Lee and Richard A. Polin is available in the SBPMD reserve section of the library: Treatment and Prevention of Necrotizing Enterocolitis (2003). Seminars in Neonatology, vol 8, pp. 449-459.

LEARNING OBJECTIVES:

At the end of this lecture you should be able to:

- 1) Describe the risk factors and pathogenesis of NEC
- 2) Describe how you would evaluate and treat an infant with suspected NEC
- 3) Discuss strategies for prevention of NEC

SUMMARY:

Necrotizing enterocolitis (NEC) is the most common serious, acquired gastrointestinal disease in the newborn infant affecting 1 to 3% of neonatal intensive care unit admissions. Although many variables associated with the onset and diagnosis of NEC will be discussed, only prematurity has been consistently identified in case-controlled studies and prevention of NEC still remains elusive. Avoidance of preterm birth, use of antenatal steroids and breast milk feedings are practices that offer the greatest potential benefits.

GLOSSARY:

Diving seal reflex: blood flow is selectively shunted away from the intestine

Intestinal ischemia: deficiency of blood in the intestine

Necrosis: death of tissue, usually of cells, groups of cells or in localized areas

Perinatal: period shortly before and after birth

Ascitis: serous fluid in the peritoneal cavity

Antenatal: the period before birth

Apgar score: a numerical assessment of the condition of a newborn infant at 60 seconds after birth

LECTURE NOTES:

- ◆ Prematurity is the only consistent determinant of NEC; incidence varies inversely with birthweight and gestational age.
- ◆ Timing of presentation also varies inversely with gestational age.
- ◆ Intestinal ischaemia appears to be the final pathway and not the primary initiator of NEC.
- ◆ NEC likely represents an elaborate interaction of factors predisposing to mucosal injury, including the release of vasoconstricting substances and inflammatory mediators.
- ◆ A regimen consisting of bowel rest, gastric compression, systemic broad-spectrum antibiotics, and parenteral nutrition is the mainstay of treatment. Intestinal perforation remains the only absolute indication for laparotomy.
- ◆ Primary peritoneal drainage may be an alternative to laparotomy in cases of perforated NEC in very-low birthweight infants.
- ◆ Avoidance of preterm birth, judicious use of antenatal steroids in preterm deliveries, breast-milk feedings and trophic feedings may be reasonable strategies in reducing the incidence of NEC.
- ◆ Prevention of NEC still remains elusive.

RESEARCH DIRECTIONS:

- ◇ A better understanding of the risk factors and the underlying pathway leading to NEC.
- ◇ Determination of the role of feeding practices in the pathogenesis of NEC.
- ◇ Clarification of the efficacy and safety of probiotic supplementation.
- ◇ Development of a prediction model for the risk of NEC.

LECTURE SLIDES BEGIN ON THE NEXT PAGE ----

- ✓ *Epidemiology*
- ✓ *Pathophysiology*
- ✓ *Diagnosis*
- ✓ *Management*
- ✓ *Prevention*

The Case Begins

- ✓ Baby “M” was a *1150 male infant* (27 wk gestation), born to a 26 year old woman. Mrs. “M” admitted to recreational use of *cocaine*. At 31 weeks gestation (3 days prior to delivery) she was given *indomethacin* because of preterm labor.

The Case Continued -1

- ✓ The baby was delivered by emergency cesarean section because of late decelerations. *Apgar scores were 1 & 3* & baby “M” required endotracheal intubation. At ten minutes of life he was extubated and placed on CPAP (45% O₂).

The Case Continued -2

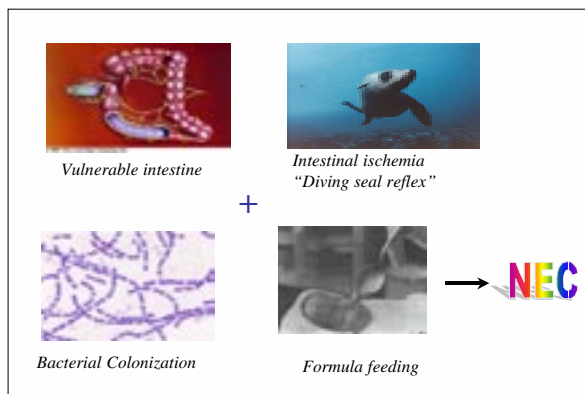
- ✓ A chest x-ray demonstrated findings consistent with mild RDS & an *umbilical arterial line* was placed at L4. A CBC obtained from the UA was remarkable for a *Hct = 71%*. On day one of life, the infant was placed on TPN.

The Case Continued -3

- ✓ Within 72 hours, *feedings* were begun. The baby was *advanced to full feedings over 3 days*. On day 4 of life a routine echocardiogram demonstrated a *patent ductus arteriosus*. Total fluid intake at that time was *185 ml/kg day*. The UA catheter was left in place.

The Case Continued -4

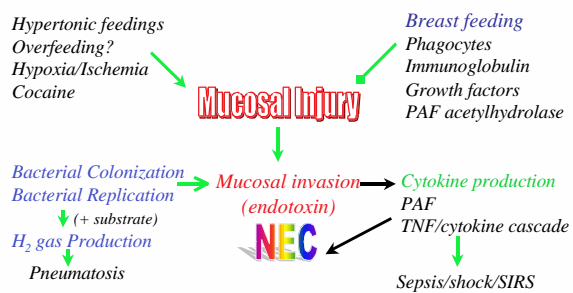
- ✓ On day 10 of life, he needed NaHCO₃ because of a mild metabolic acidosis. Gastric aspirates increased in volume and were blood tinged. A CBC was remarkable for leukopenia and thrombocytopenia. On day 11, he became distended & developed erythema of the abdominal wall.



Epidemiology of NEC

- ✓ Affects 6-8% of VLBW infants
- ✓ Widely varying incidence between centers
- ✓ Incidence inversely related to degree of prematurity
- ✓ No seasonal or sex predilection (? racial effect)

Pathophysiology of NEC



Diagnosis of NEC

- ✓ High index of suspicion based on history and physical findings
- ✓ Early appearances are subtle and easily confused with neonatal sepsis.
 - Apnea (pause in breathing)
 - Bradycardia (slowing of heart rate)
 - lethargy
 - temperature instability

Diagnosis and Staging of NEC

Early gastrointestinal findings may be non-specific

- ✓ Poor motility
- ✓ Blood in stool
- ✓ Vomiting
- ✓ Diarrhea
- ✓ Guarding
- ✓ Distension
- ✓ Feeding intolerance

Diagnosis and Staging of NEC

Later signs reflect progression of illness.

- ✓ Abdominal tenderness
- ✓ Abdominal wall erythema
- ✓ Peritonitis
- ✓ Ascites
- ✓ Palpable mass
- ✓ Hypotension
- ✓ Bleeding disorders
- ✓ Acidosis

How Do You Make the Diagnosis?

Think of the diagnosis!

- ✓ Serial physical examination
- ✓ Laboratory testing
- ✓ Abdominal x-rays

What is the Medical Treatment?

- ✓ Stop the feedings
- ✓ Parenteral antibiotics
- ✓ Nasogastric decompression
- ✓ Parenteral nutrition
- ✓ *Fluid* resuscitation

Firm Indications for Surgical Intervention

- ✓ Perforated viscus
- ✓ Abdominal mass
- ✓ Fixed, dilated loop
- ✓ Positive paracentesis



Necrotizing Enterocolitis
Intestinal gangrene and perforation

What is the outcome?

- ✓ Infants treated medically survival is > 95%
- ✓ Infants requiring surgery survival is 70-75%

How Can NEC be Prevented?

- ✓ Breast feeding
- ✓ Antenatal steroids
- ✓ Cautious advancement of feedings (perhaps)
- ✓ Cohorting during epidemics

Conclusion

- ✓ Prematurity is the single greatest risk factor for NEC & avoidance of premature birth is the best way to prevent NEC
- ✓ The role of feeding in the pathogenesis of NEC is uncertain, but it seems prudent to use breast milk (when available) and advance feedings slowly and cautiously