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Pulmonary Hemorrhage, Transient Tachypnea and Neonatal Pneumonia

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63.1 Pulmonary Hemorrhage

In newborn infants, pulmonary hemorrhage, often a manifestation of pulmonary edema can range in severity from blood-tinged secretions in the endotracheal tube to life threatening blood loss with hypovolemic shock. It usually presents in the second to fourth day of life and may be associated with lung tissue damage (RDS, infection, and mechanical ventilation with high-inspired oxygen), hypoxia, hypervolemia, hypoproteinemia, congestive heart failure, and coagulation abnormalities. Klukow confirmed an association between pulmonary hemorrhage and a large patent ductus arteriosus with high pulmonary blood flow [1].

Pulmonary hemorrhage occurs when a build up of filtrate containing plasma and whole blood produces hemorrhagic edema fluid and results in an increased capillary pressure [2]. When the pressure cannot be contained, the resultant injury leads to an acute hemorrhagic picture. Erosion or ulceration following an injury to the upper airway is another mechanism by which bleeding into the lung can occur.

Pulmonary hemorrhage was present in the lungs of up to 68% of infants who died in the first week of life and associated with the need for cardiopulmonary resuscitation in the neonatal intensive care unit [3]. In 9% of neonatal autopsies, pulmonary hemorrhage was the principal cause of death and a major risk of mortality associated with meconium aspiration syndrome. Of the total population of VLBW infants, 5.7% had pulmonary hemorrhage with a high associated mortality, possibly related to gasping during labor [4].

The clinical picture of pulmonary hemorrhage is quite distinct. The infant may present with signs of hypovolemic shock, cyanosis, and apnea. Red or pink tinged secretions are suctioned from the oropharynx or endotracheal tube and, at any time, secretions may turn into massive bleeding. The radiographic picture constitutes patchy infiltrates as seen in Fig. 63.1.

The management of pulmonary hemorrhage comprises maintaining cardiac output, transfusion of blood products as necessary and correction of acidosis. The initiation of mechanical ventilation with increase in PEEP or PIP may potentially tamponade small pulmonary vessels. In some instances, high frequency ventilation may also be helpful, possibly by maintaining a high mean airway pressure. Furthermore, several studies have suggested that closure of the patent ductus arteriosus with early medical intervention may reduce the risk of pulmonary hemorrhage. It is widely believed that pulmonary hemorrhage in the preterm infant is secondary to a patent ductus arteriosus and resultant pulmonary edema in the majority of cases.

While surfactant therapy has been implicated as one of the possible etiologies for pulmonary hemorrhage, it also has

Fig. 63.1 Diffuse, patchy infiltrates and right-sided atelectasis caused by pulmonary hemorrhage
a therapeutic role in the management of the same phenomenon [5–10]. This is due to the possible inactivation of surfactant production by the hemorrhagic fluid.

In a recent small study, the introduction of hemoagglutinase via the endotracheal tube every 4–6 hours in addition to mechanical ventilation increased survival, decreased the length of pulmonary hemorrhage and decreased the need for prolonged mechanical ventilation due to the pulmonary hemorrhage [11]. The outcome of pulmonary hemorrhage depends on the underlying etiology and the severity of the infant’s underlying cardiopulmonary status.

63.2 Transient Tachypnea of the Newborn

Transient tachypnea of the newborn (TTN) was originally described by Avery et al. in 1966 as the clinical manifestation of delayed clearance of fetal lung fluid [12]. In her work, Avery characterized early onset of respiratory distress in eight late premature infants with radiographic findings of lung hyperinflation, increased pulmonary vascular markings and cardiomegaly. Symptoms were mild and transient with infants improving in a 2–5 day period. Until recently, it was believed that once TTN resolves, there is no added respiratory morbidity or long-term effect on the infant [12–14]. However, a recent large retrospective study of term infants suggested that TTN might be significantly associated with childhood asthma with increased propensity in males. This study also suggested TTN as a marker of diminished pulmonary function, which may reflect an inherited susceptibility to asthma [15].

The incidence of TTN is approximately 1% of live births. The risk for developing TTN seems to increase with prolonged labor with failure to progress, cesarean section, prematurity, birth of a male infant, and macrosomia [16, 17]. Prolonged maternal administration of hypotonic fluid such as during prolonged labor, decreased resorption of lung fluid in the neonate, and maternal asthma have all been suggested as a cause for TTN [13, 18, 19].

Most of the published work related to the pathophysiology of TTN has sided with Avery’s conclusions that TTN is the result of delayed fetal lung fluid clearance [20, 21]. The lung’s functional residual capacity comprises a potential air space of 20–30 mL/kg body weight. This space is filled in utero with fetal lung fluid containing high potassium and chloride, and low bicarbonate and protein. Shifts between the body compartments are controlled by a chloride active pump [15, 22–25]. Two to three days prior to delivery, the fetus begins its lung fluid clearance in anticipation of transition to extrauterine life. This process begins with a decreased rate of fetal lung fluid secretion. The major clearance takes place with the onset of labor. At this time, the lung epithelium becomes a sodium absorbing membrane and lung fluid flow is directed from the air space to the interstitium. In addition, low protein containing lung fluid exhibits low oncotic pressure, which is another driving force for lung fluid to enter the vascular system.

Mechanical compression via vaginal delivery may also play a role in lung fluid clearance. Milner et al. [26] showed that when infants were not delivered through the vaginal canal and were not exposed to vaginal compression they had higher interstitial and alveolar fluid volume. Furthermore, these infants also had a decrease in their lung gas volume. This hypothesis is not supported by later animal and human studies that showed no increase of functional residual capacity (FRC) in vaginally delivered infants [20, 27]. Results by Birnkrant and a retrospective study by Liem [15, 21], that found an association between TTN and the development of wheezing syndromes, support the pathophysiologic hypothesis of fetal lung fluid clearance at the cell pump level and not the mechanical compression theory.

The common clinical picture is of a term or a late premature infant with possible mild birth depression, who shortly after birth presents with respiratory distress including tachypnea, grunting, nasal flaring, subcostal retractions, and possibly cyanosis. The maternal history is often positive for maternal anesthesia, maternal diabetes, or cesarean section. Arterial blood gas is likely to show mild respiratory acidosis with potential hypoxemia. Chest radiographs typically demonstrates peripheral streaking which may be due to periartricular lymphatic engorgement. TTN may also present in premature infants. In this group of infants, TTN and pulmonary edema may further complicate surfactant deficiency and increase the likelihood of requiring exogenous surfactant and ventilator support. With advancing gestation and in the late preterm infant, TTN increasingly contributes to the pathophysiology of respiratory distress when compared to surfactant deficiency [28].

TTN is transient in nature and the resolution of symptoms is usually within 8–12 hours but may take up to 5 days. Infants may require oxygen support but, rarely over 40% inspired oxygen. In the case of respiratory acidosis, CPAP will support ventilation. Due to difficulty in distinguishing TTN from pneumonia, infants may receive a course of antibiotics. The radiographic findings of TTN should spontaneously resolve by 48 hours [13]. In the past, furosemide was thought

![Fig. 63.2](image_url) Relative contribution of surfactant deficiency and insufficient fluid absorption [TTN] to neonatal respiratory distress. Adapted from [28]
to help in the fluid clearance, however in a randomized control trial of oral furosemide there was no significant difference between treated and control TTN groups.

63.3 Neonatal Pneumonia

Lungs are a major site of origin and location for sepsis in the newborn. Pneumonia may be acquired pre- or postnatally and be of bacterial, viral, fungal or protozoan origin. Morbidity is high which should lead to high alertness when facing an infant with signs of respiratory distress. An immature immune system and poor mechanical defense mechanisms may increase susceptibility to invasion of pathogens into the lungs. Furthermore, when an infant has added morbidity such as respiratory distress syndrome (RDS), meconium aspiration syndrome or chronic lung disease (CLD), both vulnerability to and consequences of pneumonia may be enhanced.

The incidence of neonatal pneumonia is clearly much higher for preterm infants than term infants. Barnett and Klein [29] reported intrapartum and early onset pneumonia in 10–38% of stillbirths and in 20–63% of autopsies from live births that died in the first 28 days of life. The difficulty of reporting incidence is in the inconsistency of defining pneumonia in infants less than 1 month of age. The majority of late onset pneumonias are diagnosed in premature infants and most were on ventilatory support at the time of diagnosis. A small single center study by Apisarnthanarak [30] showed 28% of ventilated infants developed ventilator associated pneumonia (VAP) and in 1986, Halliday [31] reported a 35% incidence of pneumonia in intubated patients with RDS. Despite efforts by the Center for Disease Control (CDC) and National Nosocomial Infection Surveillance System (NNIS) there is still not a gold standard for diagnosing VAP [32, 33]. This adds to the major discrepancies between studies that report rates between 10–35% [34–36].

The etiology of neonatal pneumonia can be divided into 3 categories: congenital, early onset and late onset. Congenital or intrapartum pneumonia is usually caused by ascending infecting organisms from the maternal urogenital tract before or during pregnancy, or via the transplacental route. Prolonged rupture of membrane increases the risk of bacterial acquisition by the newborn however; this is also seen with intact membranes. Microorganisms such as viruses (cytomegalovirus, rubella, herpes simplex virus, adenovirus, varicella zoster virus, enteroviruses and influenza A), bacteria (Listeria monocytogenes, Mycobacterium tuberculosis, Treponema pallidum), and protozoa (Toxoplasma gondii) are known causes of intrapartum pneumonia. However, these microorganisms cause multi-organ inflammation of which pneumonia represents a variable component.

Early onset pneumonia is usually due to introduction of bacteria from the mother’s vaginal tract during the delivery process especially in a situation of prolonged membrane rupture [37, 38]. Gasping due to asphyxia and/or meconium aspiration may introduce organisms into the respiratory system or be a consequence of infection in the fetus. Other factors such as prematurity and maternal urinary tract infection have a major role in increasing the risk of neonatal pneumonia. Group B streptococcus [GBS] is one the major causes of pneumonia in the neonate [34]. Overt GBS sepsis is seen in 1% of colonized infants or 1–4/1000 live births if no intrapartum prophylaxis with antibiotics is given. Premature infants comprise one third of all infants with GBS bacteremia [39]. In 1993, committees of the American Academy of Pediatrics published guidelines for intrapartum chemoprophylaxis of group B streptococcal positive mothers [40]. These guidelines were revised in 1997 and have proven successful to date with a significant decrease in GBS sepsis to 0.6 per 1000 births in 1998 [41]. In 2002 [42], the Centers for Disease Control and Prevention (CDC) in the USA revised the prevention of perinatal Group B streptococcal disease guidelines concentrating on prenatal screening, updated prophylaxis regimens, prenatal specimen collection, culture methods and susceptibility testing. In addition, the CDC argued against routine intrapartum antibiotic prophylaxis for GBS colonized women delivering by planned cesarean section prior to the onset of labor or rupture of membranes. They suggested algorithms for management of patients at risk for preterm delivery as well as infants exposed to prophylaxis treatment. Unfortunately, other microorganisms known to cause early onset pneumonia have increased in importance since the implementation of the GBS guidelines. The common pathogens that may influence the infant in the immediate postpartum period are Escherichia coli, Klebsiella spp, Proteus mirabilis, H. influenzae, Group D streptococci, Listeria monocytogenes and pneumococci. In addition, non-bacterial pneumonia may be seen in the early postnatal period such as caused by Candida [43, 44], viruses [45–47], and Chlamydia [48].

Late onset pneumonia is diagnosed when symptoms arise at or after 48 hours of life. The pathogens are commonly acquired from the environment and are nosocomial. Late onset pneumonia is more common in premature infants or infants on prolonged ventilatory support [30, 34, 49]. Gram-negative bacteria (E. coli, Serratia marcescens, Proteus spp, Klebsiella spp, Pseudomonas spp), coagulase-negative staphylococci [50, 51] and Staphylococcus aureus along with GBS are among the most common bacterial organisms isolated in late onset pneumonia. Viral organisms such as CMV [45, 52] VZV, RSV, para influenza, influenza A and B [53], rhinovirus [54], enterovirus [55], and coronavirus are also seen in this type of pneumonia. In addition, fungal etiologies have been implicated. Infections are acquired mainly through skin colonization and breakdown, gastrointestinal translocation of organisms, and from the respiratory tract of family and care providers. The colonization of an infant in the intensive care unit with common or unusual flora can be due to a weak immune system, health care provider exposure, and interventions (endotracheal tube, mechanical ventilation, and multiple courses of antibiotics) [56–59].
Ventilator associated pneumonia (VAP) is a nosocomial bacterial infection that has developed in patients who are receiving mechanical ventilation. VAP can occur at any time and is defined as early or late, based on the timing as mentioned earlier [60]. While similar to neonatal VAP in many aspects, most diagnostic criteria and work up guidelines are based on adult studies. In the neonatal population the clinical and laboratory signs of VAP are nonspecific [61].

It is difficult to diagnose pneumonia with great certainty. Isolation of bacteria or viruses from the trachea or the oropharynx does not necessarily correlate with invasive infection and may just reflect colonization. Radiographic studies may suggest a focal pneumonia, but this presentation is not common and atelectasis may be difficult to differentiate from infiltrate secondary to pneumonia. The work up for suspected neonatal pneumonia whether congenital, early or late is similar. Blood, and airway cultures (nasopharyngeal or tracheal if intubated) should be obtained and may be positive for the same microorganism in the case of respiratory infection [58]. Sherman [62], showed that tracheal secretions with a positive Gram stain in relation to neonatal bacteremia had a 74% sensitivity and 47% positive predictive value and concluded that gram stain of tracheal secretions may be of practical value in the diagnosis of congenital bacteremia. Positive airway culture alone may be more suggestive of early than late onset pneumonia, however in neither case is it sensitive [63, 64]. In the case of late, ventilator associated pneumonia (VAP), Mayhall [65] reviewed the diagnostic procedures for VAP based on the CDC (1997) Guidelines [66], although, these guidelines were intended for adult patients and are not specific for the neonatal population. Isolated positive tracheal culture did not distinguish between bacterial colonization and respiratory infection [61]. Radiographic studies are frequently non-specific, and it is more common to find pleural effusions in bacterial and fungal infections. Other non-specific laboratory values such as C-reactive protein (CRP) and WBC counts, especially immature to mature neutrophils ratio (I/T) may aid in the diagnosis of pneumonia.

The difficulty in diagnosing pneumonia especially when it coincides with RDS, presents the clinician with a therapeutic dilemma. Low absolute neutrophil count (ANC), high I/T ratio (>0.2) and CRP (>1) have shown to have positive predictive value of bacterial sepsis [66, 67]. Leslie et al [68] showed high I/T, low total neutrophil counts and positive gram stain to be more consistent with early onset bacterial pneumonia than RDS. However, diagnostic difficulty remains and if the index of suspicion for sepsis is high, the accepted treatment route is antibiotics for 48 hours while awaiting culture results and following the above markers trends. It is also accepted to treat every infant who deteriorates from a respiratory standpoint especially if the infant was asymptomatic for the first 6 hours of life.

The recommended empiric choice for early onset pneumonia is ampicillin in conjunction with an aminoglycoside (gentamicin). For late onset pneumonia, empiric therapy may constitute nafcillin and an aminoglycoside. Vancomycin is used empirically in extremely sick infants or infants deteriorating in spite of antibiotic treatment. When cultures are definitive and sensitivities are known appropriate antibiotics should be used. The prognosis of neonatal pneumonia depends on the underlying etiology and overall condition of the infant.

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