Pulmonary Hemorrhage, Transient Tachypnea, and Neonatal Pneumonia

55

Mary Elaine Patrinos and Richard J. Martin

Contents

Abstract

The intent of this chapter is to address three other common pulmonary causes of respiratory distress in the high-risk infant. These other forms of parenchymal lung disease range in severity from mild, as seen in transient tachypnea, to severe as is often the case in pulmonary hemorrhage. It is worth noting that on occasion, one or more of these conditions may coexist in the same patient. The treatment for all conditions is largely supportive or involves the use of targeted antimicrobial therapy.

M. E. Patrinos
Case Western Reserve University School of Medicine, Cleveland, OH, USA
e-mail: maryelaine.patrinos@uhhospitals.org

R. J. Martin (✉)
Rainbow Babies and Children's Hospital, Division of Neonatology, Case Western Reserve University School of Medicine, Cleveland, OH, USA
e-mail: rxm6@case.edu

55.1 Salient Points

- Pulmonary hemorrhage occurs as a result of extreme pulmonary vascular congestion where blood-tinged secretions suctioned from the endotracheal tube may quickly evolve into frank blood. The volume of blood loss can be life-threatening, resulting in hypovolemic shock.
- The management of pulmonary hemorrhage is largely supportive with the goals of correcting hypoxic and hypercapnic respiratory failure, maintaining cardiac output, replacing blood and volume loss, and correcting abnormalities in clotting studies.
- Transient tachypnea of the newborn (TTN) is a transient early-onset respiratory distress with radiographic findings of lung hyperinflation increased pulmonary vascular markings and cardiomegaly.
- Risk factors for developing TTN include elective cesarean section without labor, prematu-

G. Buonocore et al. (eds.), *Neonatology*,
https://doi.org/10.1007/978-3-319-29489-6_203

rity, multiple gestation, male gender, maternal diabetes, macrosomia, prolonged maternal administration of hypotonic fluid, and maternal asthma.

- Neonatal pneumonia may be acquired pre- or post-natally and may be of bacterial, viral, fungal, or protozoal origin.
- The incidence of neonatal pneumonia is ten times higher for preterm infants then term infants.
- The onset of neonatal pneumonia can be congenital, early onset, and late onset. Congenital or intrauterine pneumonia is usually caused by organisms ascending from the maternal urogenital tract before or during labor or via the transplacental route. Early-onset pneumonia is usually acquired in the perinatal period. Late-onset pneumonia is diagnosed when symptoms arise after 48 h of life and the pathogens are typically acquired from the infant's environment.
- It is difficult to diagnose pneumonia, especially when it coincides with RDS. If the index of suspicion for infection is high, the accepted treatment is antibiotics for 48 h while awaiting culture results and following other clinical and laboratory parameters.

55.2 Pulmonary Hemorrhage

Pulmonary hemorrhage (PH) occurs as a result of extreme pulmonary congestion where blood-tinged secretions suctioned from the endotracheal tube may quickly evolve into frank blood. The volume of blood loss can be life-threatening, resulting in hypovolemic shock. PH usually presents in the second to fourth day of life and may be associated with lung tissue damage from respiratory distress syndrome, infection, mechanical ventilation, and oxygen-induced lung injury. Patients at highest risk for a PH include extremely preterm infants (<28 weeks' gestation) and multiples. Other predisposing factors include hypoxia, acidosis, hypervolemia, hypoproteinemia, congestive heart failure, and coagulation abnormalities. Kluckow confirmed an association between pulmonary hemorrhage and a large patent ductus arteriosus (PDA) with high pulmonary blood flow (references Kluckow and Evans 2000).

Pulmonary hemorrhage occurs when a buildup of filtrate containing plasma and whole blood produces hemorrhagic edema fluid leading to an increase in capillary pressure and subsequent rupture (Cole et al. 1973). The presence of blood in the sputum of an otherwise stable intubated infant should raise the possibility of erosion or ulceration of the carina/upper airway by an endotracheal tube or trauma from a suction catheter.

Pulmonary hemorrhage was present in the lungs of up to 68% of infants who died in the first week of life and was associated with the need for cardiopulmonary resuscitation in the neonatal intensive care unit (Kostelanetz and Dhanireddy 2004). Blood aspiration syndrome is a distinct and separate entity associated with maternal hemorrhage and early-onset respiratory distress (Gordon et al. 2003).

The clinical picture of pulmonary hemorrhage is quite dramatic and warrants immediate attention. The infant may present with signs of hypovolemic shock, cyanosis, bradycardia, and apnea. Red or pink-tinged secretions suctioned from the oropharynx or endotracheal tube may, at any time, progress to massive bleeding. The radiographic picture demonstrates patchy infiltrates, as seen in Fig. 1, or a complete white out.

The management of pulmonary hemorrhage is largely supportive with the goals of correcting hypoxic and hypercapnic respiratory failure, maintaining cardiac output, replacing blood and volume loss, and correcting abnormalities in clotting studies. The initiation of mechanical ventilation with settings adjusted to achieve high mean airway pressures may tamponade small pulmonary vessels. High-frequency oscillatory ventilation is often helpful. There is increasing evidence that closure of the patent ductus arteriosus with early medical therapy may reduce the risk of pulmonary hemorrhage. It is widely accepted that pulmonary hemorrhage in the preterm infant is secondary to a patent ductus arteriosus coupled with an acute change in pulmonary compliance and fall in pulmonary vascular resistance, resulting in pulmonary over circulation and edema. Recent data indicate

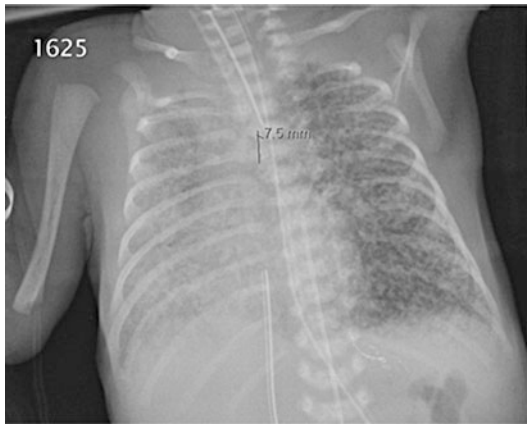

Fig. 1 Diffuse, patchy infiltrates, and right-sided atelectasis caused by pulmonary hemorrhage

that small-for-gestational-age preterm infants with a moderate to large PDA are at greatest risk (Scholl and Yanowitz 2015).

While surfactant therapy has been implicated in the pathogenesis of pulmonary hemorrhage, it also has a therapeutic role in its management (Findlay et al. 1995; Long et al. 1992; Pandit et al. 1995; Pappin et al. 1994; Raju and Langenberg 1993; Amizuka et al. 2003). This is due to the deactivation of surfactant by the hemorrhagic fluid.

In a small study, the introduction of hemocoagulase via the endotracheal tube every 4–6 h 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 (Shi et al. 2005). The outcome of pulmonary hemorrhage depends on the severity of the infant's underlying cardiorespiratory status. Mortality rates as high as 50% occur in ELBW infants. Morbidities include periventricular leukomalacia, intraventricular hemorrhage, cerebral palsy, and cognitive delays.

55.3 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 (Avery et al. 1966). In her work, Avery characterized early-onset 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 are no long-term consequences for the infant (Avery et al. 1966; Martin et al. 2015; Miller et al. 1980). However, a large retrospective study of term infants suggests that TTN might be significantly associated with childhood asthma with increased propensity in males. This study also suggests that TTN is a marker of diminished pulmonary function, which may reflect an inherited susceptibility to develop asthma (Liem et al. 2007).

The incidence of TTN is approximately 1% of live births. Risks for developing TTN include elective cesarean section without labor, prematurity, multiple gestation, male gender, maternal diabetes, and macrosomia (Gross et al. 1983; Rawlings and Smith 1984). Prolonged maternal administration of hypotonic fluid and maternal asthma have also been suggested as a cause for TTN (Martin et al. 2015; Hook et al. 1997; Demissie et al. 1998) (Fig. 2).

Most of the published work related to the pathophysiology of TTN is consistent with Avery's original conclusions that TTN is the result of delayed fetal lung fluid clearance (Jain and Dudell 2006; Birnkrant et al. 2006). 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 body compartments are controlled by a chloride active pump (Liem et al. 2007; Adams et al. 1963; Barker and Olver 2002; Bland 1988; Cummings et al. 1993). Two to three days prior to delivery, the fetus begins to clear lung fluid in anticipation of transition to extrauterine life. This process begins with a decrease in 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 via the epithelial

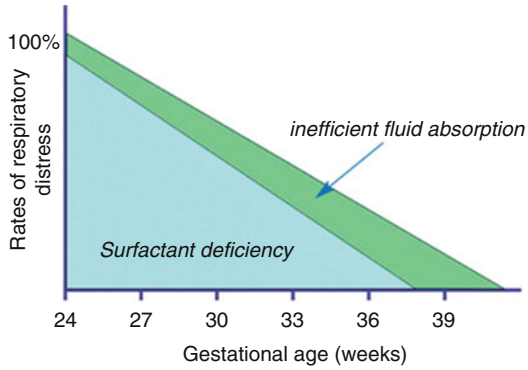

Fig. 2 Relative contribution of surfactant deficiency and insufficient fluid absorption [TTN] to neonatal respiratory distress (Adapted from Helve et al. (2009))

sodium channel (ENaC). The importance of endogenous steroids in this process is demonstrated by the relationship between low expression of serum and glucocorticoid-inducible kinase, ENaC, and poor lung liquid clearance (Janér et al. 2015). The expression of these epithelial ion transport channels is also directly related to gestational age so that TTN, like RDS, is largely a developmental condition with decreasing incidence as gestation progresses. 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 plays a relatively minor role in lung fluid clearance. Milner et al. (1978) 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 in functional residual capacity (FRC) in vaginally delivered infants (Jain and Dudell 2006; Hägnevik et al. 1991). Results by Birnkrant and a retrospective study by Liem et al. (2007; Birnkrant et al. 2006) found an association between TTN and the development of wheezing syndromes. These data support the hypothesis of fetal lung fluid clearance at the cell pump level and not the mechanical compression theory as the pathophysiologic basis for TTN.

TTN commonly presents soon after birth with tachypnea, grunting, nasal flaring, subcostal retractions, and possible cyanosis. An arterial blood gas is likely to show mild respiratory acidosis with hypoxemia. Chest radiographs demonstrate perihilar streaking due to periarterial lymphatic engorgement. TTN may also present in premature infants in association with respiratory distress syndrome. TTN is transient in nature with resolution of symptoms often within 8–12 h, but tachypnea may persist for up to 5 days. Infants may require oxygen support but rarely over 40% inspired oxygen. In the case of rare respiratory acidosis, CPAP may be instituted. 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 h (Martin et al. 2015). Lung ultrasound has been used for early diagnosis of TTN and may allow a less-invasive approach to respiratory support in infants exhibiting early signs of respiratory distress (Copetti and Cattarossi 2006; Raimondi et al. 2014).

55.4 Neonatal Pneumonia

The lungs are often a portal of entry for early onset sepsis/pneumonia in the neonatal period. Pneumonia may be acquired pre- or postnatally and be of bacterial, viral, fungal, or protozoal origin. Morbidity is high, prompting a high index of suspicion 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 comorbidities 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 ten times higher for preterm infants then term infants. Barnett and Klein (Barnett and Klein 2001) reported intrauterine 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 et al. (2003) showed 28% of ventilated infants developed ventilator-associated pneumonia (VAP), and, in 1986, Halliday et al. (1984) 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 no gold standard for diagnosing VAP in the neonatal period. For infants <1 year of age, the CDC has published clinical, radiographic, and laboratory criteria for VAP (Buonocore Chap. 55, "Pulmonary Hemorrhage, Transient Tachypnea, and Neonatal Pneumonia"). The incidence in developed countries ranges from 2.7 to 10.9 episodes per 1000 ventilator days. In developing countries, the incidence has been reported as high as 37.2 cases per 1000 ventilator days (Cernada et al. 2014). Over the last decade, VAP prevention bundles have been largely successful in reducing the incidence of hospital-acquired pneumonias.

The etiology of neonatal pneumonia can be divided into three categories: congenital, early onset, and late onset. Congenital or intrauterine pneumonia is usually caused by ascending organisms from the maternal urogenital tract before or during labor or via the transplacental route. 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 congenital pneumonia. Early-onset pneumonia is usually due to introduction of bacteria from the birth canal during the delivery process, especially in a situation of prolonged membrane rupture (Levine 1991; Airede 1992). Gasping due to asphyxia and/or meconium aspiration may introduce organisms into the respiratory system. 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] remains the primary cause of pneumonia in the term neonate (Apisarnthanarak et al. 2003). Overt GBS sepsis was seen in 1% of colonized infants or 1–4/1000 live births if no intrapartum antibiotic prophylaxis was given. In the USA, guidelines for intrapartum chemoprophylaxis have proven successful with a significant decrease in GBS sepsis to 0.41 per 1000 births (Stoll et al. 2011). Algorithms provide for the management of GBS-positive mothers 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 [E.coli]*, *Klebsiella* spp., *Proteus mirabilis*, *H. influenzae*, group D *Streptococci*, *Listeria monocytogenes*, and pneumococci. In very low birth weight infants, rates of *E. coli* sepsis (5/1000) exceed that of GBS (2/1000). In addition, nonbacterial pneumonia may be seen in the early postnatal period such as caused by *Candida* (Gerberding et al. 1989; Aldana-Valenzuela et al. 2005), viruses (Takahashi et al. 2007; Barker et al. 1990; Faden et al. 2005), and *Chlamydia* (Numazaki et al. 2003).

Late-onset pneumonia is diagnosed when symptoms arise after 48 h of life. The pathogens are commonly acquired from the environment or nosocomial. Late-onset pneumonia is more common in premature infants or infants on prolonged ventilatory support (Yuan et al. 2007). Gram-negative bacteria (*E. coli*, *Serratia marcescens*, *Proteus* spp., *Klebsiella* spp., *Pseudomonas* spp.), coagulase-negative *Staphylococci* (Philip 1994; Chartrand and McCracken 1982), and *Staphylococcus aureus* along with GBS are among the most common bacterial organisms isolated in late-onset pneumonia. Viral organisms such as CMV (Takahashi et al. 2007; Bradshaw and Moore 2003), VZV, RSV, parainfluenza, influenzas A and B (Yusuf et al. 2007), *Rhinovirus* (Calvo et al. 2007), *Enterovirus* (Abzug 2004), and *Coronavirus* are also seen in this type of pneumonia. Recent data indicate that with increased testing, 6% of all NICU sepsis

evaluations may detect a respiratory virus via multiplex polymerase chain reaction (Ronchi et al. 2014). In addition, fungal etiologies have been implicated. Infections are acquired mainly through skin colonization and breakdown, through 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) (Frakking et al. 2007; Gupta 2002; Webber et al. 1990; Garland et al. 1992).

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, but may instead, reflect colonization. Radiographic studies are difficult to interpret and cannot differentiate atelectasis or fluid from infiltrate secondary to pneumonia. The workup for suspected neonatal pneumonia includes blood and airway cultures (nasopharyngeal or tracheal if intubated). Sherman (Sherman et al. 1984) 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 (Ruderman et al. 1994; Brook et al. 1980). Although radiographic studies are frequently nonspecific, it is more common to find pleural effusions in bacterial and fungal infections. Other nonspecific 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 values of bacterial sepsis (Makhoul et al. 2006; Berger et al. 1995). Leslie et al. (1981) 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 h while awaiting culture results and following the above markers trends. It is also appropriate to treat every infant who deteriorates from a respiratory standpoint, especially if the infant was asymptomatic for the first 6 h 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 or vancomycin and an aminoglycoside. When cultures are definitive and sensitivities are known, antimicrobial therapy should be tailored for the specific organism. The prognosis of neonatal pneumonia depends on the underlying etiology and overall condition of the infant.

Acknowledgment We acknowledge the contribution of Amitai Kohn to this section in the prior addition.

References

Abzug MJ (2004) Presentation, diagnosis, and management of enterovirus infections in neonates. Paediatr Drugs 6:1–10

Adams FH, Fujiwara T, Rowshna G (1963) Surface properties and lipids from lungs of infants with hyaline membrane disease. J Pediatr 63:881–888

Airede AI (1992) Prolonged rupture of membranes and neonatal outcome in a developing country. Ann Trop Paediatr 12:283–288

Aldana-Valenzuela C, Morales-Marquec M, Castellanos-MartMart J, Deanda-Gda-G M (2005) Congenital candidiasis: a rare and unpredictable disease. J Perinatol 25:680–682

Amizuka T, Shimizu H, Niida Y, Ogawa Y (2003) Surfactant therapy in neonates with respiratory failure due to haemorrhagic pulmonary oedema. Eur J Pediatr 162: 697–702

Apisarnthanarak A, Holzmann-Pazgal G, Hamvas A et al (2003) Ventilator-associated pneumonia in extremely preterm neonates in a neonatal intensive care unit: characteristics, risk factors, and outcomes. Pediatrics 112(6 Part 1):1283–1289

Avery ME, Gatewood OB, Brumley G (1966) Transient tachypnea of newborn. Possible delayed resorption of fluid at birth. Am J Dis Child 111:380–385

Barker PM, Olver RE (2002) Invited review: clearance of lung liquid during the perinatal period. J Appl Physiol 93:1542–1548

Barker JA, McLean SD, Jordan GD et al (1990) Primary neonatal herpes simplex virus pneumonia. Pediatr Infect Dis J 9:285285J

Barnett ED, Klein JO (2001) Bacterial infections of the respiratory tract. In: Remington JS, Klein JO (eds) Infectious diseases of the fetus and newborn infant. WB Saunders, Pennsylvania, pp 1006–1018

Berger C, Uehlinger J, Ghelfi D et al (1995) Comparison of C-reactive protein and white blood cell count with differential in neonates at risk for septicaemia. Eur J Pediatr 154:138–144

Birnkrant DJ, Picone C, Markowitz W et al (2006) Association of transient tachypnea of the newborn and childhood asthma. Pediatr Pulmonol 41:978–984

Bland RD (1988) Lung liquid clearance before and after birth. Semin Perinatol 12:124

Bradshaw JH, Moore PP (2003) Perinatal cytomegalovirus infection associated with lung cysts. J Paediatr Child Health 39:563–566

Brook I, Martin WJ, Finegold SM (1980) Bacteriology of tracheal aspirates in intubated newborn. Chest 78: 875–877

Calvo C, García-García ML, Blanco C et al (2007) Role of rhinovirus in hospitalized infants with respiratory tract infections in Spain. Pediatr Infect Dis J 26:904–908

Cernada M, Brugada M, Golombek S et al (2014) Ventilator-associated pneumonia in neonatal patients: an update. Neonatology 105:98–107

Chartrand SA, McCracken GH Jr (1982) Staphylococcal pneumonia in infants and children. Pediatr Infect Dis 1:19–23

Cole VA, Normand IC, Reynolds EO, Rivers RP (1973) Pathogenesis of hemorrhagic pulmonary edema and massive pulmonary hemorrhage in the newborn. Pediatrics 51:175–187

Copetti R, Cattarossi L (2006) The 'double lung point': an ultrasound sign diagnostic of transient tachypnea of the newborn. Neonatology 91:203–209

Cummings JJ, Carlton DP, Poulain FR et al (1993) Hypoproteinemia slows lung liquid clearance in young lambs. J Appl Physiol 74:153–160

Demissie K, Marcella SW, Breckenridge MB, Rhoads GG (1998) Maternal asthma and transient tachypnea of the newborn. Pediatrics 102(1 Part 1):84–90

Faden H, Wynn RJ, Campagna L, Ryan RM (2005) Outbreak of adenovirus type 30 in a neonatal intensive care unit. J Pediatr 146:523–527

Findlay RD, Taeusch HW, David-Cu R, Walther FJ (1995) Lysis of red blood cells and alveolar epithelial toxicity by therapeutic pulmonary surfactants. Pediatr Res 37:26–30

Frakking FN, Brouwer N, van Eijkelenburg NK et al (2007) Low mannose-binding lectin (MBL) levels in neonates with pneumonia and sepsis. Clin Exp Immunol 150:255–262

Garland JS, Dunne WM Jr, Havens P et al (1992) Peripheral intravenous catheter complications in critically ill children: a prospective study. Pediatrics 89(6 Part 2):1145–1150

Gerberding KM, Eisenhut CC, Engle WA, Cohen MD (1989) Congenital candida pneumonia and sepsis: a case report and review of the literature. J Perinatol 9:159–161

Gordon E, South M, McDougall PN, Dargaville PA (2003) Blood aspiration syndrome as a cause of respiratory distress in the newborn infant. J Pediatr 142:200–202

Gross TL, Sokol RJ, Kwong MS et al (1983) Transient tachypnea of the newborn: the relationship to preterm delivery and significant neonatal morbidity. Am J Obstet Gynecol 146:236–241

Gupta A (2002) Hospital-acquired infections in the neonatal intensive care unit–*Klebsiella pneumoniae*. Semin Perinatol 26:340–345

Hägnevik K, Lagercrantz H, Sjöqvist BA (1991) Establishment of functional residual capacity in infants delivered vaginally and by elective cesarean section. Early Hum Dev 27:103–110

Halliday HL, McClure G, Reid MM et al (1984) Controlled trial of artificial surfactant to prevent respiratory distress syndrome. Lancet 1:476–478

Helve O, Pitkänen O, Janér C et al (2009) Pulmonary fluid balance in the human newborn infant. Neonatology 95:347–352

Hook B, Kiwi R, Amini SB et al (1997) Neonatal morbidity after elective repeat cesarean section and trial of labor. Pediatrics 100(3 Part 1):348–353

Jain L, Dudell GG (2006) Respiratory transition in infants delivered by cesarean section. Semin Perinatol 30:296–304

Janér C, Pitkänen OM, Süvari L et al (2015) Duration of gestation and mode of delivery affect the genes of transepithelial sodium transport in pulmonary adaptation. Neonatology 107:27–33

Kluckow M, Evans N (2000) Ductal shunting, high pulmonary blood flow, and pulmonary hemorrhage. J Pediatr 137:68–72

Kostelanetz AS, Dhanireddy R (2004) Survival of the very low birth infants after cardiopulmonary resuscitation in the neonatal intensive care unit. J Perinatol 24:279–283

Leslie GI, Scurr RD, Barr PA (1981) Early-onset bacterial pneumonia: a comparison with severe hyaline membrane disease. Aust Paediatr J 17:202–206

Levine CD (1991) Premature rupture of the membranes and sepsis in preterm neonates. Nurs Res 40:36–41

Liem JJ, Huq SI, Ekuma O et al (2007) Transient tachypnea of the newborn may be an early clinical manifestation of wheezing symptoms. J Pediatr 151:29–33

Long W, Corbet A, Allen A (1992) Retrospective search for bleeding diathesis among premature newborns with pulmonary hemorrhage after synthetic surfactant treatment. J Pediatr 120:S45–S48

Makhoul IR, Yacoub A, Smolkin T et al (2006) Values of C-reactive protein, procalcitonin, and Staphylococcus-specific PCR in neonatal late-onset sepsis. Acta Paediatr 95:1218–1223

Martin RJ, Fanaroff AA, Walsh MC (eds) (2015) Neonatal-perinatal medicine diseases of the fetus and infant, 10th edn. Mosby/Elsevier, New York

Miller LK, Calenoff L, Boehm JJ, Riedy MJ (1980) Respiratory distress in the newborn. JAMA 243: 1176–1179

Milner AD, Saunders RA, Hopkin IE (1978) Is air trapping important in the maintenance of the functional residual capacity in the hours after birth? Early Hum Dev 27: 103–110

Numazaki K, Asanuma H, Niida Y (2003) Chlamydia trachomatis infection in early neonatal period. BMC Infect Dis 3:2

Pandit PB, Dunn MS, Colucci EA (1995) Surfactant therapy in neonates with respiratory deterioration due to pulmonary hemorrhage. Pediatrics 95:32–36

Pappin A, Shenker N, Hack M, Redline RW (1994) Extensive intraalveolar pulmonary hemorrhage in infants dying after surfactant therapy. J Pediatr 124:621–626

Philip AG (1994) The changing face of neonatal infection: experience at a regional medical center. Pediatr Infect Dis J 13:1098–1102

Raimondi F, Migliaro F, Sodano A et al (2014) Use of neonatal chest ultrasound to predict noninvasive ventilation failure. Pediatrics 134:e1089–e1094

Raju TN, Langenberg P (1993) Pulmonary hemorrhage and exogenous surfactant therapy: a meta-analysis. J Pediatr 123:603–610

Rawlings JS, Smith FR (1984) Transient tachypnea of the newborn. An analysis of neonatal and obstetric risk factors. Am J Dis Child 138:869–871

Ronchi A, Michelow IC, Chapin KC et al (2014) Viral respiratory tract infections in the neonatal intensive care unit: the VIRIoN-I study. J Pediatr 165:690–696

Ruderman JW, Srugo I, Morgan MA et al (1994) Pneumonia in the neonatal intensive care unit. Diagnosis by quantitative bacterial tracheal aspirate cultures. J Perinatol 14:182–186

Scholl JE, Yanowitz TD (2015) Pulmonary hemorrhage in very low birth weight infants: a case-control analysis. J Pediatr 166:1083–1084

Sherman MP, Chance KH, Goetzman BW (1984) Gram's stains of tracheal secretions predict neonatal bacteremia. Am J Dis Child 138:848–850

Shi Y, Tang S, Li H et al (2005) New treatment of neonatal pulmonary hemorrhage with hemocoagulase in addition to mechanical ventilation. Biol Neonate 88:118–121

Stoll BJ, Hansen NI, Sánchez PJ et al (2011) Early onset neonatal sepsis: the burden of Group B Streptococcal and *E. coli* disease continues. Pediatrics 127:817–826

Takahashi R, Tagawa M, Sanjo M et al (2007) Severe postnatal cytomegalovirus infection in a very premature infant. Neonatology 92:236–236

Webber S, Wilkinson AR, Lindsell D et al (1990) Neonatal pneumonia. Arch Dis Child 65:207–211

Yuan TM, Chen LH, Yu HM (2007) Risk factors and outcomes for ventilator-associated pneumonia in neonatal intensive care unit patients. J Perinat Med 35: 334–338

Yusuf K, Soraisham AS, Fonseca K (2007) Fatal influenza B virus pneumonia in a preterm neonate: case report and review of the literature. J Perinatol 27:623–625