REVIEW ARTICLE

The Impact of Neonatal Pneumonia on Infant Health; A Review

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Abstract

Neonatal pneumonia may occur in isolation or as one component of a larger infectious process. Bacteria, viruses, fungi, and parasites are all potential causes of neonatal pneumonia and may be transmitted vertically from the mother or acquired from the post-natal environment. The patient's age at the time of disease onset may help narrow the differential diagnosis, as different pathogens are associated with congenital, early-onset, and late-onset pneumonia. Supportive care and rationally selected antimicrobial therapy are the mainstays of treatment for neonatal pneumonia. The challenges involved in microbiological testing of the lower airways may prevent definitive identification of a causative organism. In this case, secondary data must guide the selection of empiric therapy, and the response to treatment must be closely monitored.

Key words: Immunity, infection, multidrug resistance, pulmonary, TORCH infection, ventilator-associated pneumonia

INTRODUCTION

Neonatal pneumonia is a serious respiratory infectious disease caused by a variety of microorganisms, mainly bacteria, with the potential of high mortality and morbidity.[1] Worldwide neonatal pneumonia is estimated to account for up to 10% of childhood mortality, with the highest case fatality rates reported in developing countries.[2] It is impact may be increased in the case of early onset, prematurity, or an underlying pulmonary condition such as respiratory distress syndrome (RDS), meconium aspiration, or chronic lung disease/bronchopulmonary dysplasia (BPD), when the pulmonary capacity is already limited. Urea plasma pneumonia and ventilator-associated pneumonia (VAP) have also been associated with the development of BPD and poor pulmonary outcome.[3] In this chapter, we will review different aspects of neonatal pneumonia and will present case reports from our level III neonatal unit in Graz.

The newborn lung is susceptible to bacterial and viral infections, and neonatal pneumonia is a major cause of morbidity and mortality worldwide. Between 152,000 and 490,000 infants aged <1 year die of pneumonia annually.[4] Although these numbers represent a decline from earlier estimates,[2] neonatal pneumonia remains a considerable global health burden that falls disproportionately on developing countries.[5]

Diagnosing pneumonia in the newborn period can be challenging. Compared to older children, neonates show fewer localizing signs of pulmonary infection; pneumonia frequently manifests as a systemic deterioration involving multiple organ systems. Common, non-infectious respiratory complications of prematurity often coexist with and exacerbate pneumonia, and may cloud the clinical impression.[2] Even when pneumonia is suspected, the technical barriers to lower airway sampling in small infants may render conclusive identification of an etiologic organism impossible, necessitating careful reasoning about empiric therapy.[6]

This review covers the risk factors, path physiology, diagnosis, and treatment of neonatal pneumonia. The discussion is organized around three disease subtypes, which are distinguished by age at presentation, route of acquisition, and major causative micro-organisms. These subtypes are:

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1. Congenital pneumonia: Infection established during fetal life may result from an ascending infection across the chorioamniotic membranes or a hematogenous transplacental route.
2. Early-onset pneumonia: Develops within the 1st week of life and results from perinatal pathogen exposure, either intrauterine or during passage through the birth canal.
3. Late-onset pneumonia (including VAP): Develops after the 1st week of life from environmental, often nosocomial, pathogen exposure. Figure 1 shows the chest radiograph of a neonate with neonatal pneumonia.[5]

EPIDEMIOLOGY

Reported frequencies of neonatal pneumonia range from 1% to 35%, the most commonly quoted figures being 1% for term infants and 10% for preterm infants. The incidence varies according to gestational age, intubation status, diagnostic criteria or case definition, the level and standard of neonatal care, race, and socioeconomic status. In a retrospective analysis of a cohort of almost 6000 neonates admitted to our neonatal intensive care unit (NICU), pneumonia was diagnosed in all gestational age classes. The incidence of bacterial pneumonia including urea plasma urealyticum pneumonia was 1.4% with a median patient gestational age of 35 weeks (range 23–42 weeks) and a mortality of 2.5%. There was only one case of viral pneumonia, due to respiratory syncytial virus -infection and no case of fungal pneumonia. The mortality rate associated with pneumonia is in general inversely related to gestational age and birth weight, being higher in cases of early-onset compared to late onset, and especially high in low socioeconomic groups and developing countries.[1] Group B *Streptococcus* accounts for most cases of early onset pneumonia, the most common bacteria causing late-onset pneumonia are Gram-negative bacilli such as *Escherichia coli* or *Klebsiella* spp. The bacterial pathogens found in the early infection and late onset sepsis/pneumonia.

ETIOLOGY

Organisms are acquired from the maternal genital tract or the nursery. This organ is in includes Gram-positive cocci (e.g., groups A and B streptococci, both methicillin-sensitive and methicillin-resistant *Staphylococcus aureus*) and Gram-negative bacilli (eg, *E. coli*, *Klebsiella* species, *Proteus* species). In infants who have received broad-spectrum antibiotics, many other pathogens may be found, including *Pseudomonas*, *Citrobacter*, *Bacillus*, and *Serratia*. Viruses or fungi cause some cases. Pneumonia may be acquired by intrauterine (e.g. transplacental hematogenous, ascending from birth canal), intrapartum (e.g., aspiration), or post-natal routes (e.g., hematogenous, environmental). The pathogens include mainly bacteria, followed by viruses and fungi which include an inflammatory pulmonary condition.[7]

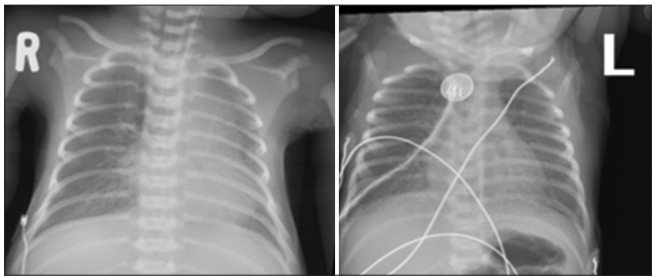

Figure 1: Chest radiograph of a neonate with neonatal pneumonia

SYMPTOMS

The signs and symptoms of pneumonia vary from mild to severe, depending on factors such as the type of germ causing the infection, and your age and overall health. Mild signs and symptoms often are similar to those of a cold or flu, but they last longer, shown in figure 2.

Signs and symptoms of neonatal pneumonia may include:

- Chest pain when you breathe or cough
- Confusion or changes in mental awareness (in adults age 65 and older)
- Cough, which may produce phlegm
- Fatigue
- Fever, sweating and shaking chills
- Lower than normal body temperature (in adults age 65 and people with weak immune systems)
- Nausea, vomiting or diarrhea.

Shortness of breath Newborns and infants may not show any sign of the infection.[8] Or they may vomit, have a fever and

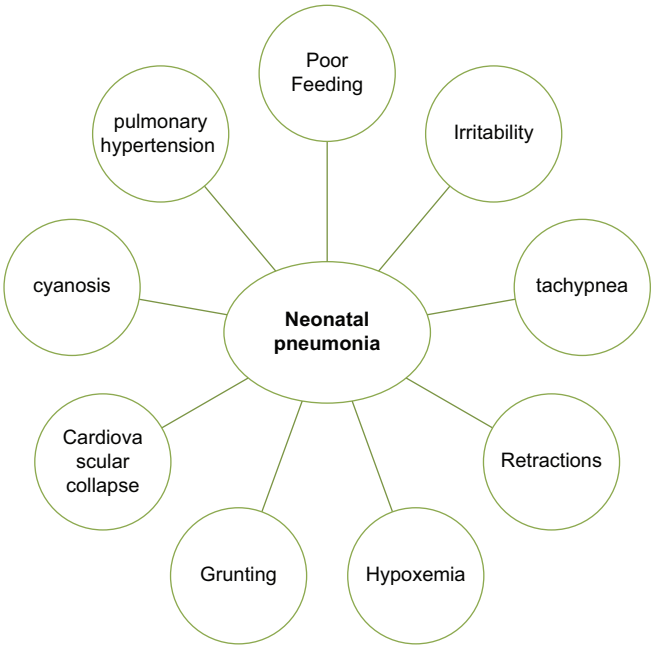

Figure 2: Symptoms of neonatal pneumonia

cough, appear restless or tired and without energy, or have difficulty breathing and eating.[9]

PATHOPHYSIOLOGY

Bacterial or viral growth in the distal airways and the resultant inflammatory response lead to cellular injury that impairs gas exchange alters pulmonary circulation and interferes with normal respiratory mechanics.

In the case of bacterial pneumonia, initial cellular injury results from direct exposure to bacteria-secreted and surface-associated toxins.[10] Cytomegalovirus or disseminated herpes simplex virus triggers lytic or apoptotic loss of pneumocytes, which serve as viral host cells during pulmonary infection.[11] Denudation of the alveolar surfaces interferes with surfactant function, allows transudation of pulmonary edema, and culminates with alveolar collapse.

The inflammatory response triggered by pulmonary infection may also cause significant injury and dysfunction. Neutrophils recruited to the lungs serve primarily as antimicrobial phagocytes but also secrete reactive oxygen species and other tissue-damaging molecules such as elastase and urokinase.[12] This is particularly true of senescent neutrophils, and there is evidence that defects in neonatal neutrophil apoptosis may render them more dangerous to host tissues than neutrophils from adults.[13] Airway obstruction from bacterial and inflammatory debris – combined with smooth muscle contraction due to inflammatory mediators such as C3a and C5a – impairs effective ventilation and promotes atelectasis, air trapping, and subsequent ventilation-perfusion mismatch.[14] Inflammatory procoagulants and vasoconstrictors released by activated endothelial cells and platelets increase pulmonary vascular resistance, potentially triggering pulmonary hypertensive crisis.[15] Already limited surfactant pools fail further. The clinical manifestation of these spiraling infectious and immune processes is a severely ill patient with failing respiratory and circulatory systems Figure 3 shows path physiology of neonatal pneumonia.[16]

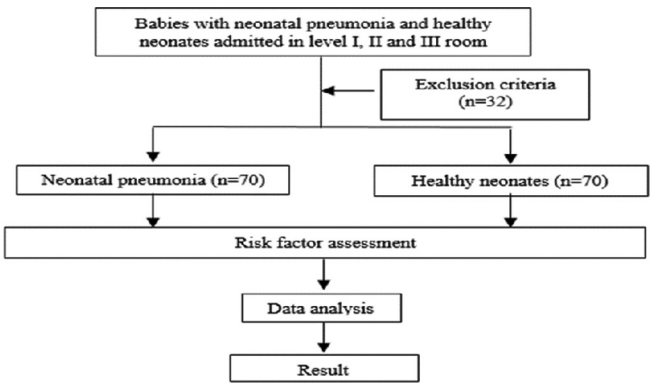

Figure 3: Study of statistical data on neonatal pneumonia

DIAGNOSIS

The diagnosis of neonatal pneumonia is based on a combination of physical examination findings, radiographic evidence, and supporting laboratory data. The centers for disease control and prevention (CDC) criteria for diagnosing pneumonia in patients aged <1 year are radiographic evidence of a persistent consolidation, cavitation, or pleural effusion and evidence of worsening gas exchange plus at least three additional clinical and/or laboratory findings.[17] VAP may be diagnosed in patients who have been intubated for at least 48 h and meet the criteria for pneumonia. Recently, an international working group developed case definitions for significant neonatal infections, including pneumonia. Their diagnostic criteria for pneumonia align with the CDC's, but they also provide guidelines for diagnosis in resource-limited environments.[18] and it was shown in figure 4 and table 1.

CDC/National Nosocomial Infections Surveillance (NNIS) definition of pneumonia; must meet criteria in all three categories.[19]

1. Radiographic

If there is underlying pulmonary or cardiac disease, two serial X-rays demonstrating at least one of the following:
- New or progressive infiltrate
- Consolidation
- Cavitation
- Pneumatocele

If there is no underlying pulmonary or cardiac disease, one definitive imaging test result is acceptable.

2. Worsening gas exchange

Any of the following:
- O_2 desaturation
- Increased oxygen requirement
- Increased ventilator demand

3. Clinical/laboratory evidence

Must have at least three of the following:
- Temperature instability
- Leucopenia (≤4000 white blood cells [WBC]/mm_3) or leukocytosis (≥15,000 WBC/mm_3) and left shift (≥10% band forms);
- New onset of purulent sputum or change in character of sputum, or increased respiratory secretions or increased suctioning requirements;
- Apnea, tachypnea, nasal flaring with retractions of the chest wall, or nasal flaring with grunting;
- Wheezing, rales, or rhonchi;
- Cough;
- Bradycardia (<100 beats/min) or tachycardia (>170 beats/min)

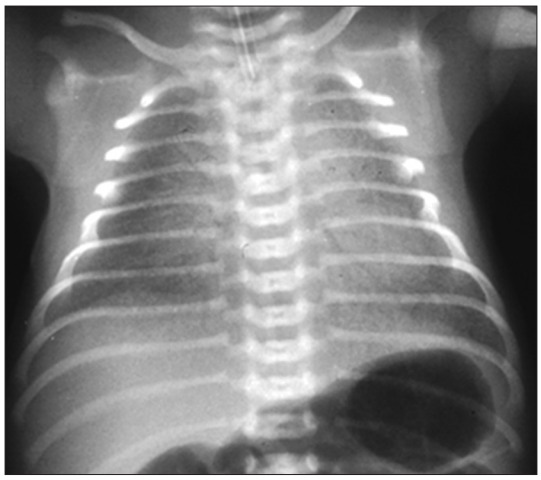

Figure 4: chest radiograph after medication used in neonatal pneumonia

Table 1: Treatment

Potential pathogens	Combination antibiotic therapy
Multidrug-resistant *Pseudomonas aeruginosa* *Klebsiella* spp. *Acinetobacter* spp. Methicillin-resistant *Staphylococcus aureus*	Anti-pseudomonal cephalosporin (cefepime, ceftazidime) or Anti-pseudomonal carbapenem (imipenem or meropenem) or β-Lactam/β-lactamase inhibitor (piperacillin–tazobactam) plus Anti-pseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or Aminoglycoside (amikacin, gentamicin, or tobramycin) plus Linezolid or vancomycin

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- CDC; NNIS system; WBC.
- VAP is defined as meeting the above criteria and receiving mechanical ventilation through an endotracheal tube for at least 48 h.

TREATMENT

Initial empiric therapy for ventilator-associated pneumonia (VAP) in patients with significant risk factors for multidrug-resistant (MDR) pathogens should be broad and aggressive, targeting common MDR pathogens.[20]

COMPLICATIONS

Complications of neonatal pneumonia include the following:

- Empyema
- Pleural effusion
- Lung abscess
- Necrotizing pneumonia
- Sepsis
- Restrictive pleural effusion
- Infected pleural effusion
- Systemic infection with metastatic foci
- Persistent pulmonary hypertension of the newborn.

CLINICAL PRESENTATION, CLASSIFICATION

Depending on the time of manifestation of infection neonatal pneumonia may be classified as early onset pneumonia (within the first 3 or 7 days of life, mostly within 48 h), or late onset pneumonia (within 4 and 28 days of life). Congenital or intrauterine pneumonia can be considered a variant of early onset pneumonia. Other classifications refer to the underlying pathogen, like bacterial or viral pneumonia or the pattern of lung infiltrates (e.g., interstitial pneumonia) on chest radiographs. Clinical signs are unspecific and present as respiratory distress of various degree, suspicious appearing tracheal aspirates, cough, apnea, high or low temperature, poor feeding, abdominal distension, and lethargy. Tachypnea is a predominant clinical sign, present in 60–89% of cases. Persistent fever is rather unusual but has been reported in neonates with viral pneumonia. The radiographical appearance may also vary, showing reticulogranular-nodular infiltrates, and bilateral streaky or hazy lungs. As small bronchioli tend to collapse there may be compensatory hyperaeration in areas free of pneumonia infiltration. In addition, there may be pleural effusions and/or pneumatocele formation in more complicated cases. Alveolar patterns with coarse, patchy parenchyma infiltrates, consolidation, and diffuse granularity are more typical for bacterial infections while parahilar streakiness, diffuse hazy lungs, or reticulo-nodularity are more common in viral disease. The differential diagnoses to be considered on initial presentation are mainly surfactant deficiency syndrome and transient tachypnoe of the newborn, in addition meconium aspiration syndrome, pulmonary hemorrhage, pulmonary edema, primary pulmonary lymphangiectasis or pulmonary lymphangiomatosis, congestive heart failure, and Wilson-Mikity syndrome.[21] Additional investigations such as echocardiography, high-resolution computed tomography, further laboratory studies, and in rare cases, lung biopsy are helpful in the diagnostic workup.

MEDICATION USED IN NEONATAL PNEUMONIA

A male neonate was born at 42 weeks gestational age to a multiparous healthy mother following spontaneous labor in an external hospital. The membranes ruptured 3 h before delivery. There was no prenatal maternal screening for

Group B streptococci disease. After good primary transition, the infant developed clinical signs of respiratory distress with oxygen dependency and respiratory acidosis (6 h postpartum). After the initiation of our standard broad-spectrum antibiotic therapy, the infant was transferred to our NICU. A septic workup showed leucopenia of 2.70 G/L, a left shift in the white cell count (immature/total neutrophils (I/T) 0.33), markedly elevated procalcitonin (303 ng/mL) and interleukin-6 (IL-6 > 400 pg/L) levels, but normal C-reactive protein (CRP) values, and a positive urinary Group B *Streptococcus* testing. Blood cultures and tracheal aspirates were negative. Radio graphics showed bilateral reticulogranular patterns compatible with the diagnosis of RDS. The patient was first placed on nasal continuous positive airway pressure (CPAP) but had to be intubated and ventilated mechanically due to respiratory deterioration with an increasing oxygen demand up to a FiO_2 of 1.0 and persistent respiratory acidosis. Surfactant therapy showed no sufficient response. Inotropic support was necessary in case of arterial hypotension. Following inhaled nitric oxide therapy a decrease in oxygen requirement from 100 to 50% was achieved over the following 48 h, indicative of secondary pulmonary hypertension. On day 5 of life, the clinical course was complicated by the formation of a large left sided pneumatocele and a consecutive symptomatic tension pneumothorax, which was successfully treated by insertion of a chest drain. On day 11 of life, the patient was extubated, but the chest drain had to be left *in situ* for 3½ weeks due to recurrent air leaks. The laboratory parameters were normalized within a week using our standard antibiotic regimen. On day 37 of life, the neonate had recovered and was discharged home. A male neonate was born at 42 weeks gestational age to a multiparous healthy mother following spontaneous labor in an external hospital. The membranes ruptured 3 h before delivery. There was no prenatal maternal screening for Group B streptococci disease. After a good primary transition, the infant developed clinical signs of respiratory distress with oxygen dependency and respiratory acidosis (6 h postpartum). After initiation of our standard broad-spectrum antibiotic therapy, the infant was transferred to our NICU. A septic workup showed leucopenia of 2.70 G/L, a left shift in the white cell count (immature/total neutrophils [I/T] 0.33), markedly elevated procalcitonin (303 ng/mL) and interleukin-6 (IL-6 > 400 pg/L) levels, but normal CRP values, and a positive urinary group B *Streptococcus* testing. Blood cultures and tracheal aspirates were negative. Radiographics showed bilateral reticulogranular patterns compatible with the diagnosis of RDS. The patient was first placed on nasal CPAP but had to be intubated and ventilated mechanically due to respiratory deterioration with an increasing oxygen demand up to a FiO_2 of 1.0 and persistent respiratory acidosis. Surfactant therapy showed no sufficient response. Inotropic support was necessary in case of arterial hypotension. Following inhaled nitric oxide therapy a decrease in oxygen requirement from 100% to 50% was achieved over the following 48 h, indicative of secondary pulmonary hypertension. On day 5 of life, the clinical course was complicated by formation of a large left sided pneumatocele and a consecutive symptomatic tension pneumothorax, which was successfully treated by insertion of a chest drain. On day 11 of life, the patient was extubated, but the chest drain had to be left *in situ* for 3½ weeks due to recurrent air leaks. Laboratory parameters normalized within a week by our standard antibiotic regime. On day 37 of life, the neonate had recovered and was discharged home.[22]

CONCLUSION

Pneumonia is a frequent form of infection among hospitalized neonates and sporadically affects newborns without additional risk factors. Age of onset and surrounding circumstances, including maternal history, may provide important clues as to etiology and may help guide initial treatment decisions. Early intervention with broad-spectrum antibiotics is crucial for preventing systemic infection and the worst complications of pneumonia.

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