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Pneumonia

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A B S T R A C T

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 postnatal 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 selection of empiric therapy, and the response to treatment must be closely monitored.

1. Introduction

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 [1]. Although these numbers represent a decline from earlier estimates [2,3], neonatal pneumonia remains a considerable global health burden that falls disproportionately on developing countries [1,4,5].

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 [6]. Even when pneumonia is suspected, the technical barriers to lower airway sampling in small infants may render conclusive identification of an etiologic organism impossible [7], necessitating careful reasoning about empiric therapy [8].

This review covers the risk factors, pathophysiology, 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 microorganisms. These subtypes are:

- Congenital pneumonia: infection established during fetal life may result from an ascending infection across the chorioamniotic membranes or a hematogenous transplacental route.
- Early-onset pneumonia: develops within the first week of life and results from perinatal pathogen exposure, either intrauterine or during passage through the birth canal.
- Late-onset pneumonia (including ventilator-associated pneumonia; VAP): develops after the first week of life from environmental, often nosocomial, pathogen exposure.

2. Neonatal pneumonia risk factors

2.1. Immature innate and adaptive immunity increases neonatal susceptibility to pneumonia

Compared to children and adults, newborns have a limited capacity to defend against pulmonary infection. Immature innate immunity – both systemic [9,10] and localized to the respiratory mucosae and lung parenchyma [11,12] – is a fundamental risk factor for neonatal pneumonia [13], and is more significant in premature and growth-restricted patients [14]. Adaptive immunity – mostly in the form of maternally derived IgG – is rudimentary in the immediate newborn period [15]. Adaptive immunity requires antigenic exposure and molecular refinement during infancy and childhood in order to establish strong protection [11].

Structurally, the newborn lung has key deficiencies in important barrier functions that provide a first line of defense against

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infection. A relative paucity of resident alveolar macrophages, coupled with impaired mucociliary clearance of debris, permits establishment of early colonization by potential pathogens [12]. Surfactant deficiency due to prematurity has been linked to enhanced growth of group B streptococcus (GBS) and deterioration in an animal model of *Escherichia coli* pneumonia. There is also evidence that pulmonary infection inactivates existing surfactant and damages type II pneumocytes, preventing replenishment [16]. Surfactant replacement therapy has been shown to improve oxygenation in patients with GBS pneumonia [17].

Phagocytosis by neutrophils recruited to the lungs is an essential first step in clearing pulmonary bacterial infection, but neonates show multiple forms of neutrophil dysfunction. Based on a dataset of >30,000 measurements from healthy subjects, ~2% of term and 5% of preterm newborns have neutropenia (absolute neutrophil count: <1000/μL) at baseline [18]. Newborns also exhibit blunted neutrophil recruitment from the bone marrow in response to infection [19] and defects in neutrophil chemotaxis to sites of inflammation [20]. Neutrophils derived from preterm infants are especially affected.

The efficiency of pathogen clearance by recruited neutrophils and resident phagocytes – such as macrophages and monocytes – is dependent on opsonization with complement, antibodies, and other non-specific binding proteins, including fibronectin, C-reactive protein (CRP), and mannose-binding lectin [21]. In addition to facilitating effective phagocytosis, complement also has important direct microbicidal activities through formation of the membrane attack complex [21] and promotes recognition of host cells harboring intracellular pathogens (bacterial or viral) [22]. Unfortunately, the neonate has lower levels of many complement components, and lacks specific antibodies and accessory opsonins, limiting the capability of the innate immune system to mount an effective response to pneumonia [23].

2.2. Maternal risk factors for congenital pneumonia

Congenital pneumonia results from maternal infection during pregnancy, and typically presents as one component of a systemic illness.

Congenital toxoplasmosis is due to primary maternal infection by the intracellular protozoa *Toxoplasma gondii*. The main maternal risk factors are eating undercooked meat or exposure to cat feces during pregnancy. The risk of transmission to the fetus increases with gestational age, but severity of congenital illness – including pneumonia – decreases as pregnancy progresses [24].

Neonatal pneumonia may be one manifestation of congenital cytomegalovirus (CMV) infection, which affects up to 2% of pregnancies [25]. Seronegative mothers who develop primary CMV infection during pregnancy are at the highest risk of delivering an affected newborn, with transplacental transmission rates up to 40%; the risk of vertical transmission is highest if maternal infection occurs during the first half of pregnancy. Whereas 10–30% of seropositive mothers experience CMV reactivation during pregnancy, the risk of vertical transmission among this group is only 1–3% [26].

A severe, often hemorrhagic, viral pneumonitis may be one manifestation of disseminated herpes simplex virus (HSV) infection. Pulmonary symptoms are uncommon in skin–eye–mouth or central nervous system disease, the two other forms of neonatal HSV disease [27]. Respiratory distress is a presenting feature in approximately half of disseminated HSV cases, and typically begins during the first two weeks of life [27]. Neonatal disseminated HSV infection usually results from ascending intrauterine infection or intrapartum exposure to the infected genital tract. The major risk factors for neonatal HSV are vaginal delivery in the setting of a primary maternal infection with either HSV-1 or HSV-2 [28]. Cesarean section or prior maternal exposure to either HSV subtype reduces the risk of transmission considerably [29]. Demographic risk factors for maternal HSV infection include African- or Mexican-American ethnicity, past history of other sexually transmitted infections, and poverty. Risk correlates directly with age and number of lifetime sexual partners, and inversely with degree of education [30].

2.3. Perinatal risk factors for early-onset bacterial pneumonia

The risk factors for early-onset bacterial pneumonia overlap with those for early-onset bacteremia and meningitis (Box 1), reflecting shared pathogenic mechanisms (discussed in Section 3.1). Chorioamnionitis is a key risk factor for early-onset infection, including pneumonia. Inflammation of the decidua and chorioamniotic membranes often signals microbial invasion of the fetoplacental unit, and can be accompanied by a powerful fetal inflammatory response syndrome (FIRS) that induces structural remodeling of the lungs—leading to simplification of the cellular architecture and increasing the odds of later pneumonia or chronic lung disease [31,32]. Chorioamnionitis and FIRS may also trigger preterm rupture of the membranes and preterm labor and delivery, further compounding the infectious risk [33].

2.4. Risk factors for late-onset neonatal pneumonia

The major risk factors for late-onset pneumonia – including VAP – are prematurity, low birth weight, and duration of mechanical ventilation [34,35]. Since these risks are often correlated, it is difficult to conclusively establish the independent contributions from each, and different studies have reached varying conclusions. A 41-month longitudinal study of neonatal nosocomial infections identified a significantly increased risk of pneumonia among patients with birth weight <1500 g [36]. However, a prospective study of VAP in almost 200 neonates intubated for at least 48 h identified duration of mechanical ventilation as the sole independent risk factor for pneumonia [37]. Other risk factors for VAP include prior bloodstream infection, low nurse:patient ratios, inadequate environmental air filtration, frequent suctioning (more than eight times per day), and sedation while intubated [6,38,39].

3. Pathophysiology

3.1. Pathogenesis of congenital and early-onset pneumonia

Amniotic fluid is moderately but incompletely microbicidal and has modest levels of antiviral cytokines [40]. During acute intrauterine infection bacterial or viral growth occurs in amniotic fluid, allowing direct contact between the pathogen and the fetal

Box 1
Risk factors for early-onset pneumonia.

Prematurity and low birth weight
Low socio-economic status
Male gender
Colonization with a known pathogen (e.g. group B streptococcus)
Prolonged rupture of membranes >18 h
Galactosemia (increased susceptibility to infections with Gram-negative organisms)
Premature rupture of membranes
Chorioamnionitis