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Seminars in Fetal & Neonatal Medicine 22 (2017) 206–213

Contents lists available at ScienceDirect

Seminars in Fetal & Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

# Pneumonia

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*Keywords:*
Pulmonary
Immunity
Infection
Ventilator-associated pneumonia
TORCH infection
Multidrug resistance

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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http://dx.doi.org/10.1016/j.siny.2017.03.002
1744-165X/

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 |

respiratory mucosae [41,42]. In addition to demonstrating the causative micro-organism, pathological examination of lungs from stillborns or newborns who died of early-onset pneumonia routinely identifies leukocytes of maternal origin and aspirated amniotic debris, supporting the concept that congenital or early-onset pneumonia may arise from direct mucosal seeding from infected amniotic fluid [43]. Meconium aspiration increases the risk of pneumonia by decreasing the antimicrobial properties of amniotic fluid and by serving as a vector for bacterial entry and postnatal persistence in the lungs [44–46].

Another opportunity for pathogens to enter the neonatal respiratory tract occurs during passage through the birth canal. Maternal vaginal colonization with GBS is a key risk factor for developing early-onset GBS sepsis, which often includes pneumonia. In the absence of prophylactic antibiotics, ~50% of infants born to GBS-colonized mothers will become colonized intrapartum [47]. Aspiration of respiratory secretions containing GBS will—in a small subset—progress to pulmonary infection that quickly leads to hematogenous spread and evolution to full-blown sepsis [47,48]. The same progression from intrapartum mucosal colonization to early-onset pneumonia has been identified for *Escherichia coli*, *Chlamydia trachomatis*, *Pneumococcus pneumoniae*, and *Haemophilus influenza* [49–52].

The major pathogens responsible for congenital and early-onset pneumonia are listed in Box 2.

### 3.2. Pathogenesis of late-onset pneumonia and VAP

Late-onset pneumonia results from colonization of the oropharyngeal mucosa by a potential pathogen, which then seeds the lower respiratory tract where inadequate immune defense permits dissemination. Late-onset pneumonia that develops in the hospital may be termed healthcare-associated pneumonia (previously nosocomial pneumonia), which has distinct epidemiology from late-onset pneumonia occurring after discharge. Multiply drug-resistant bacteria are a more frequent cause of healthcare-associated pneumonia, whereas community-acquired viral infections such as respiratory synctitial virus (RSV), parainfluenza, and adenovirus are more frequent causes of late-onset pneumonia in the home setting [53]. Box 3 lists frequently occurring late-onset pneumonia pathogens.

The source of initial oropharyngeal colonization leading to pneumonia can be exogenous or endogenous. Common exogenous sources include caretaker skin (usually the hands of a medical professional), contaminated equipment, or environmental surfaces. There is strong evidence that inadequate hand hygiene is a major contributor to healthcare-associated neonatal pneumonia. Two large observational studies comparing nosocomial infection rates before and after introduction of intensive handwashing improvement initiatives showed significant decreases in neonatal VAP rates [54,55].

The main endogenous sources of micro-organisms responsible for late-onset pneumonia are the nasal and oropharyngeal mucosae. Pooled oral secretions in the posterior oropharynx can foster local overgrowth of pathogenic species, whose subsequent aspiration sets the stage for pneumonia. An intubated – perhaps sedated – newborn with an uncuffed endotracheal tube (ETT) is at high risk for passage of infected secretions into the lower airways [56,57], necessitating careful attention to head-of-bed elevation and adequate tracheal suctioning.

Reflux and aspiration of contaminated gastric secretions represents another potential route of pulmonary infection, but the exact role of gastric bacteria in pneumonia pathogenesis remains controversial. Tracheal fluid from intubated infants has been shown to contain gastric pepsin, the concentration of which varies inversely with the degree of head elevation [58]. A study of intubated adults who underwent technetium labeling of gastric contents followed by scintigraphy of endotracheal suctioning samples also demonstrated migration of gastric fluids to the airway, and again found that supine positioning exacerbated aspiration [59].

However, other studies on adults have suggested that gastric bacteria may not contribute significantly to healthcare-associated pneumonia. Two research groups performed serial microbiological sampling from the trachea, pharynx, and stomach on intubated adults. In one of these studies, 19 subjects who developed VAP also underwent bronchoalveolar lavage (BAL). Examination of culture results from the different sites allowed a temporal reconstruction of bacterial population dynamics, and did not support the theory that frequent migration of gastric bacteria to the airway occurs. Furthermore, none of the patients who developed VAP grew bacteria of gastric origin from BAL samples [56,60].

**Box 2**
Causes of congenital and early-onset pneumonia.

| |
|---|
| Congenital pneumonia |
| *Toxoplasma gondii* |
| Herpes simplex virus |
| Cytomegalovirus |
| *Treponema pallidum* |
| Early-onset pneumonia (may also present at birth) |
| *Streptococcus agalactiae* |
| *Escherichia coli* |
| *Listeria monocytogenes* |
| *Staphylococcus aureus* |
| *Enterococcus* spp. |
| *Haemophilus* spp. |
| *Streptococcus viridans* |
| *Klebsiella* |
| *Enterobacter* spp. |
| Group A streptococcus |
| Coagulase-negative staphylococcus |

**Box 3**
Causes of late-onset pneumonia, including healthcare-associated pneumonia and ventilator-associated pneumonia (listed from most to least prevalent).

| |
|---|
| Bacterial |
| *Pseudomonas aeruginosa* |
| *Enterobacter* spp. |
| *Klebsiella* species |
| *Staphylococcus aureus* |
| *Escherichia coli* |
| *Enterococcus* spp. |
| *Acinetobacter* spp. |
| *Proteus* species |
| *Citrobacter* spp. |
| *Stenotrophomonas maltophilia* |
| *Streptococcus agalactiae* |
| Viral |
| Respiratory synctitial virus |
| Human rhinovirus |
| Human metapneumovirus |
| Adenovirus |
| Parainfluenza virus |
| Influenza A or B |
| Coronavirus |

Among intubated infants, the ETT itself represents an important reservoir for micro-organisms. Several studies have demonstrated early and progressive growth of bacterial biofilms on the outer and luminal surfaces of neonatal ETTs [61]. Of particular concern is the reliable finding that ETT biofilms tend to be enriched for potentially pathogenic species, such as *Staphylococcus aureus* and a variety of Gram-negative bacilli. Patients with VAP show a high correlation between micro-organisms colonizing the ETT and cultured tracheal secretions, suggesting that ETT biofilms are a probable source of infection [62]. Furthermore, the artificial surface of the ETT and the complex three-dimensional biofilm in which ETT colonizers subsist increase bacterial resistance to antibiotic therapy [62]. Finally, the ETT serves as a foreign body that impairs mucociliary transport and prevents effective coughing, further limiting debris clearance from the lower airways [63].

### 3.3. Pneumonia 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 [64,65]. CMV or disseminated HSV triggers lytic or apoptotic loss of pneumocytes, which serve as viral host cells during pulmonary infection [66–68]. 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 [69]. 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 [68,70].

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 [71]. Inflammatory pro-coagulants and vasoconstrictors released by activated endothelial cells and platelets increase pulmonary vascular resistance, potentially triggering pulmonary hypertensive crisis [69,72]. 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.

## 4. Diagnosis

The diagnosis of neonatal pneumonia is based on a combination of physical exam 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 (Box 4) [73]. 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 [74].

Unlike other frequently occurring neonatal infections, such as bacteremia or meningitis, microbiological identification of a single pathogen causing pneumonia is often not possible. Invasive lower airway culturing methods such as blind BAL or bronchoscopy with protected brush sampling are sometimes used in pediatric and adult ICUs. However, because of the technical challenges and increased risks associated with performing these techniques on neonates, invasive airway sampling is not considered a first-line diagnostic approach in the neonatal intensive care unit [73]. Pneumonia may lead to hematogenous seeding and bacteremia, but a positive blood culture is neither necessary nor sufficient to diagnose pneumonia.

Clinical and laboratory assessment of suctioned tracheal sputum samples from an intubated patient may be helpful for diagnosing neonatal pneumonia and for selecting an empiric antibiotic treatment regimen. Increased production of purulent sputum is an important diagnostic criterion and a frequent presenting sign of neonatal pneumonia [37]. Cultures of tracheal sputum rarely yield a single organism, indicating that tracheal secretions usually harbor a variety of colonizing species in addition to any pathogens that might be present [6]. However, a Gram stain of tracheal sputum that shows a leukocytic infiltrate and a predominance of a single bacterial morphotype (e.g. Gram-positive cocci in pairs and chains for GBS) suggests pneumonia caused by the dominant microbe, which may inform initial treatment. Furthermore, serial Gram stains of suctioned sputum during treatment may be used to track disease resolution or persistence of a single — potentially drug-resistant — organism.

Newborns with systemic disease and pneumonia should prompt consideration of congenital infection with CMV, HSV, or

**Box 4**
CDC/NNIS definition of pneumonia; must meet criteria in all three categories [73].

(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
    Pneumoatocele
  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
    Leukopenia ($\leq$4000 WBC/mm$^3$) or leukocytosis ($\geq$15,000 WBC/mm$^3$) and left shift ($\geq$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).

CDC, Centers for Disease Control and Prevention; NNIS, National Nosocomial Infections Surveillance system; WBC, white blood cells. Ventilator-associated pneumonia is defined as meeting the above criteria and receiving mechanical ventilation through an endotracheal tube for at least 48 h.

toxoplasma. Evaluation should include liver function tests including coagulation profiling, urine culture for CMV, surface cultures for HSV, lumbar puncture with CSF cell counts, differential, culture, and polymerase chain reaction (PCR) for HSV and toxoplasma. If the concern for toxoplasmosis or CMV is high, evaluation should include cranial imaging. Antibody titers from the infant and mother may confirm recent exposure [24,25,28].

Late-onset pneumonia caused by viral infection may be indistinguishable from bacterial disease. A recent prospective study found that, out of 137 infants with suspected late-onset sepsis, 7% had a viral infection [75]. A variety of high-sensitivity, high-specificity PCR- and enzyme-linked immunosorbent assay (ELISA)-based assays exist for specific viral testing, and many hospitals now run comprehensive, rapid multiplex testing from a single sample of suctioned pharyngeal sputum [76,77].

## 5. Treatment

Regardless of age at disease onset, treatment of suspected bacterial pneumonia should begin immediately with an empiric antibiotic regimen that is broad enough to cover the most likely etiologic organisms, including those that may be drug resistant. As more information becomes available, initial coverage should be narrowed, as much as possible, to limit the drawbacks of prolonged exposure to broad-spectrum antibiotics [8].

### 5.1. Empiric therapy for congenital or early-onset pneumonia

In the case of early-onset pneumonia, ampicillin and an aminoglycoside such as gentamicin is the appropriate starting regimen [78]. Cefotaxime may be substituted for gentamicin when there is a strong suspicion of concurrent bacterial meningitis. If there is significant concern for HSV, acyclovir should be started immediately. Standard treatment for congenital toxoplasmosis is pyrimethamine and sulfadiazine (plus folinic acid) through one year of age [79]. Recent recommendations for treatment of infants with congenital CMV suggest at least six months of treatment with valganciclovir, which limits the extent of neurologic sequelae in infants with symptomatic CMV infection [80,81].

### 5.2. Empiric therapy for late-onset pneumonia or VAP

Choosing empiric antibiotics for suspected late-onset bacterial pneumonia requires more nuance. Thought must be given to local patterns of bacterial antibiotic resistance and to the patient's history (if any) of previous infections, known colonizers, and antibiotic exposures that might have selected for drug-resistant organisms.

At a minimum, initial therapy should include two antibiotics with coverage of most drug-resistant Gram-positive and Gram-negative species. One of the antibiotics must have activity against meticillin-resistant *Staphylococcus aureus* (MRSA), a frequent cause of VAP that is associated with poor clinical outcomes [53]. Vancomycin or linezolid are acceptable anti-MRSA choices. Although the two antibiotics have never been compared in a head-to-head trial in treatment of neonatal VAP, evidence from pediatric and adult literature suggests that linezolid may have higher efficacy than vancomycin. Acceptable choices for the second antibiotic include piperacillin/tazobactam or gentamicin, although other possibilities may be valid depending on the situation [82,83]. Severely ill patients with late-onset pneumonia should be started on a three-drug regimen [84]. Potential combinations are suggested in Table 1.

### 5.3. Duration of antibiotic therapy

Antibiotic therapy should continue for a minimum of 7–14 days. Longer treatment may be warranted in cases of severe, persistent illness, or if there is concurrent infection beyond the lungs. Limited studies comparing different treatment durations have not yielded a clear consensus on the optimal course. An adult study comparing 8-day and 15-day treatment of VAP found no significant difference in mortality or relapse rates. However, the subset of patients with VAP caused by Gram-negative, non-fermenting bacilli who received the 8-day course had higher relapse rates [85]. A 10-day course of therapy is a reasonable starting point for uncomplicated pneumonia, which may be modified as circumstances require.

## 6. Prevention of VAP

The American Thoracic Society and the Infectious Diseases Society of America have published guidelines for reducing the incidence of hospital-acquired pneumonia, including VAP. The recommendations focus on limiting opportunities for cross-contamination between caregivers and patients, decreasing tissue damage from prolonged or recurrent intubation, avoiding unnecessary medication that may promote infection and/or antibiotic resistance, and maximizing oral hygiene and pulmonary toilet [84].

Many hospitals have adopted VAP “bundles,” consisting of multiple, simultaneous practices – applied universally to intubated patients – intended to minimize the risk of infection. There is currently no standard neonatal VAP bundle. Practices vary among units, as does the level of evidence for each bundle component. However, overall there is evidence to suggest that care bundles do reduce the risk of VAP [86,87]. Box 5 summarizes VAP bundle elements that have been implemented in neonatal populations.

**Table 1**
Initial empiric therapy for ventilator-associated pneumonia in patients with significant risk factors for multidrug-resistant pathogens [84].

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

**Box 5**
Possible components of a neonatal ventilator-associated pneumonia prevention bundle [86].

- Hand hygiene
  - Meticulous hand hygiene before and after patient contact and handling respiratory equipment.
  - Wear gloves when handling ventilator condensate and other respiratory/oral secretions.
- Intubation
  - Use a new, sterile ETT for each intubation attempt.
  - Ensure that the ETT does not contact environmental surfaces before insertion.
  - Use a sterilized laryngoscope.
  - Have at least two NICU staff members present for ETT re-taping or repositioning.
- Suctioning practices
  - Clear secretions from the posterior oropharynx prior to:
    - ETT manipulation;
    - patient repositioning;
    - extubation;
    - reintubation.
- Feeding
  - Prevent gastric distention.
  - Monitor gastric residuals.
  - Adjust feeding to prevent large residuals and/or distention.
- Positioning
  - Use side-lying position as tolerated.
  - Keep the head of bed elevated 15–30° as tolerated.
  - Use left lateral positioning after feedings, as tolerated.
- Oral care
  - Provide oral care:
    - within 24 h after intubation;
    - every 3–4 h;
    - prior to reintubation as time allows;
    - prior to orogastric tube insertion.
  - Use sterile water, mother's milk, or approved pharmaceutical oral care solution
- Respiratory equipment
  - Use a separate suction catheter, connection tubing, and canister for oral and tracheal suction.
  - Drain ventilator condensate away from the patient every 2–4 h and before repositioning.
  - Avoid unnecessary disconnection of the ventilator circuit.
  - Change ventilator equipment when visibly soiled or mechanically malfunctioning.
  - Use heated ventilator circuits.

ETT, endotracheal tube; NICU, neonatal intensive care unit.

## 7. 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.

## Practice points

- When considering the diagnosis of neonatal pneumonia, age at disease onset and maternal history can provide valuable clues about the potential pathogen.
- Neonatal pneumonia is diagnosed based on a combination of clinical, radiographic, and laboratory findings.
- Suctioned samples of tracheal sputum are usually contaminated with commensal organisms, which can prevent definitive microbiological identification of the pathogen(s). Sputum samples with a predominance of a single bacterial morphotype can help guide initial empiric therapy.
- Congenital pneumonia is frequently a component of certain TORCH infections, which should be considered, especially in the setting of systemic disease.
- Hand hygiene and VAP "bundles" are evidence-based approaches to limiting occurrence of late-onset pneumonia.

## Research directions

- Discovery of biomarkers to identify pneumonia, especially in the setting of prematurity or chronic lung disease, which can make pneumonia harder to identify.
- Establishing the role of the microbiome and dysbiosis in pneumonia pathogenesis.
- Characterizing the efficacy of different VAP "bundle" elements.
- Understanding the long-term morbidities of neonatal pneumonia.

## Conflict of interest statement

None.

## Funding sources

None.

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