Ventilator-Associated Pneumonia in Neonatal Patients: An Update

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Key Words

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Abstract

Ventilator-associated pneumonia (VAP) is a serious complication related to mechanical ventilation in the neonatal period. However, lack of a specific definition and difficulties obtaining noncontaminated samples of the lower respiratory airway render microbiological diagnosis and etiological treatment extremely difficult. Thus far, only few studies have approached VAP using accepted Centers for Disease Control and Prevention criteria and reliable sampling techniques. In recent years, however, the blind-protected bronchoalveolar lavage technique with protected specimen brush and the development of validated biomarkers have attempted to overcome the diagnostic difficulties and assess the response to therapy. This updated review on neonatal VAP aims to stimulate neonatologists' interest in this subtle but serious complication of mechanical ventilation.

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Introduction

The survival rate of extremely preterm infants in the last decades has substantially improved [1, 2]. Interventions that have helped to achieve this include: regionaliza-

tion of perinatal care, generalization of antenatal steroids, and postnatal supplementation with exogenous surfactant. In addition, changes introduced in the NICU, including new modalities of mechanical ventilation (MV), more efficient antibiotics, enhanced nutrition, and non-invasive point-of-care ultrasound diagnosis, have altogether contributed to lowering mortality especially among extremely-low-birth-weight infants [3].

Advances in MV have enabled the provision of respiratory support to extremely preterm infants within the limits of viability. However, baro- and volutrauma derived from MV cause cytoarchitectural changes and abnormal remodeling of the lung structure contributing to the development of chronic pulmonary disease. Additional complications secondary to MV include air leaks, interstitial emphysema, subglottic stenosis, and ventilator-associated pneumonia (VAP) [4]. Conspicuously, the most effective strategy proven to minimize ventilator-associated lung injury consists of reducing the duration of MV [5]. However, in spite of these recommendations, the rates of endotracheal intubation reported by the National Nosocomial Infection Surveillance System (NNIS) from January 2002 to June 2004 were still 43% in neonates with a birth weight of less than 1,000 g and 16% in newborns with a birth weight between 1,000 and 1,499 g [6].

This review aims to update the scientific literature related to neonatal VAP and thereby draw attention to this severe and frequent complication of MV.

Table 1. Diagnostic criteria for VAP in infants younger than 1 year

Radiological signs	Patient with one or more (in patients with underlying diseases two or more) chest X-rays with one of the following findings: <ul style="list-style-type: none">– new or progressive and persistent infiltrate– consolidation– cavitation– pneumatoceles
Clinical signs and symptoms	Worsening of gas exchange [e.g. oxygen desaturations (e.g. pulse oximetry <94%), increased oxygen requirements, or increased ventilation demand] and three of the following: <ul style="list-style-type: none">– temperature instability with no other recognized cause– leukopenia (<4,000 WBC/mm³) or leukocytosis (>15,000 WBC/mm³) and left shift (>10% band forms)– new onset of purulent sputum, or change in the character of sputum, or increase in respiratory secretions, or increased suctioning requirements– apnea, tachypnea, nasal flaring with retraction of chest wall or grunting– wheezing, rales, or rhonchi– cough– bradycardia (<100 beats/min) or tachycardia (>170 beats/min)
Microbiological findings	At least one of the following: <ul style="list-style-type: none">– positive growth in blood culture not related to another source of infection– positive growth pleural fluid culture– positive quantitative culture from a minimally contaminated LRT specimen [e.g. BAL (≥10⁴ CFU/ml) or protected specimen brushing (≥10³ CFU/ml)]– ≥5% BAL-obtained cells contain intracellular bacteria on direct microscopic examination (e.g. Gram stain)– histopathological exam shows at least one of the following criteria for pneumonia:<ul style="list-style-type: none">abscess formation or foci of consolidation with intense PMN accumulation in bronchioles and alveoli,positive quantitative culture of lung parenchyma (≥10⁴ CFU/g tissue), or evidence of lung parenchyma invasion by fungal hyphae or pseudohyphae

WBC = White blood cells; LRT = lower respiratory tract; CFU = colony-forming units.

Definition of VAP

The Centers for Disease Control and Prevention (CDC; Atlanta, Ga., USA) defines VAP as ‘a nosocomial infection diagnosed in patients undergoing MV for at least 48 h’ [7]. It is noteworthy that diagnosis of a VAP episode requires a combination of radiological, clinical, and laboratory criteria (table 1) [7]. However, CDC/NNIS criteria refer to infants younger than 1 year and do not define specific criteria for the newborn period in term or preterm infants. In spite of this lack of specificity, most studies of VAP performed in NICUs are based on these criteria [8].

Moreover, etiological diagnosis is hindered by the difficulty in obtaining noncontaminated samples from the infants’ airways.

The CDC permits the diagnosis of ‘clinically defined pneumonia’, based only on clinical and radiological findings, without any isolated pathogen. Nevertheless, some authors have emphasized the importance of microbiolog-

ical diagnosis in the adult population to avoid VAP over-diagnosing [9]. On the other hand, isolation of pathogens without clinical and radiological signs is not diagnostic of VAP and could just represent colonization of the airways. Hence, microbiological criteria for neonatal VAP diagnosis has been a prerequisite only in some studies [10–12], while in others only clinical and/or microbiological criteria have been required [13–15].

Incidence

According to data published by the NNIS program sponsored by the CDC, VAP is the second most frequent cause of nosocomial infection (20% of nosocomial infections) in pediatric intensive care units (PICU), with rates that oscillate from 1.4 to 7 episodes per 1,000 ventilator days [6, 16, 17]. In developing countries the reported rates are significantly higher, ranging from 16.1 to 89 episodes per 1,000 ventilator days [12, 18, 19].

Table 2. Description of the most relevant features of studies published in relation to VAP in the neonatal period

	Afjeh et al. [12]	Apisarnthanarak et al. [13]	Cernada et al. [10]	Deng et al. [18]	Geffers et al. [14]	Tripathi et al. [11]	Yuan et al. [15]
Study design	Prospective cohort	Prospective cohort	Prospective cohort	Retrospective case-control	Prospective surveillance	Prospective cohort	Retrospective cohort
Population	Newborn; MV >48 h	BW <2,000 g; MV >48 h	Newborn; MV >48 h	Newborn; MV >48 h	BW <1,500 g; MV >48 h	Newborn; MV >48 h	Newborn; MV >48 h
Diagnostic criteria	Radiographic Clinical	Radiographic Need for antibiotics	Radiographic Clinical Microbiologic (BAL)	CDC criteria for infants aged <1 year [7]	Radiographic Clinical Analytical	CDC criteria for infants aged <1 year [7]	Radiographic Clinical Purulent secretions
Incidence ¹	11.6 episodes	<28 weeks: 6.5 episodes >28 weeks: 4 episodes	10.9 episodes	Prevalence: 33.5%	2.7 episodes	37.2 episodes	Prevalence: 20.1%
Sampling method	ET aspirate	ET aspirate	Blind-protected BAL	ET aspirate	Not provided	ET aspirate	ET aspirate
Most common pathogen (mono-polymicrobial)	<i>E. coli</i> <i>K. pneumoniae</i>	<i>Pseudomonas</i> spp. <i>Enterobacter</i> spp. Polymicrobial 58%	<i>P. aeruginosa</i> <i>S. aureus</i> Polymicrobial 16.7%	<i>Klebsiella</i> spp. <i>A. baumannii</i> Polymicrobial 24.8%	CONS <i>S. aureus</i>	<i>K. pneumoniae</i> <i>E. coli</i> Polymicrobial 6%	<i>K. pneumoniae</i> <i>P. aeruginosa</i>
Outcome	Not provided	Increased mortality Increased LOF	Increased LOF	Not provided	Not provided	Increased mortality Increased LOF	Increased LOF

¹ Expressed as episodes per 1,000 ventilator days. BW = Birth weight; ET = endotracheal; LOF = length of stay; CONS = coagulase-negative staphylococci.

Focusing exclusively on the neonatal population accounted for, the incidence is highly influenced by gestational age and regional economic development. Hence, while in developed countries the incidence oscillates between 2.7 to 10.9 episodes per 1,000 ventilator days, in developing countries it may reach up to 37.2 cases per 1,000 ventilator days [6, 10, 11, 13, 14, 20]. This variability could also be explained by the use of different criteria to define VAP (table 2).

Pathogenesis and Pathogens

Microorganisms invading the respiratory airways and infecting the lung parenchyma may cause VAP. In his excellent review article, Garland [21] describes the possible sources of microorganisms and the pathogenic mechanisms by which they may cause VAP. Endogenous sources of microorganisms comprise colonization of the naso-/oropharynx, gastric fluid pool, or tracheal secretions. Aspiration of these contaminated fluids into the lung can result in pneumonia. Contrarily, blood-borne seeding of the lung constitutes a rare cause of VAP. Moreover, pathogens can also reach the lung from exogenous sources

such as the hands of healthcare workers, ventilator circuits, and the biofilm of endotracheal tubes (ETT) [21].

The difficulty in obtaining noncontaminated samples renders the assessment of VAP etiology difficult. Apisarnthanarak et al. [13] reported isolation of multiple organisms from tracheal aspirates (TA) in 58% of episodes of VAP in extremely preterm neonates. In addition, Deng et al. [18] (in neonates) and Srinivasan et al. [22] (in pediatric patients) informed of a polymicrobial etiology in 25–40% of VAP episodes. Of note, in these studies, samples were retrieved from ETT instead of using invasive sampling techniques of the lower respiratory tract, and therefore they might represent colonization instead of true infection. Conspicuously, when focusing on studies that used invasive techniques for sample collection, polymicrobial etiology represented only 16.7% of the VAP episodes [10].

The most common pathogens isolated in the neonatal population are *Pseudomonas aeruginosa* and *Staphylococcus aureus* [10, 13, 15]. However, isolation of other microorganisms such as *Klebsiella pneumoniae* and *Escherichia coli* has also been reported [11, 12, 23] (table 2).

There is evidence that *Ureaplasma urealyticum*-derived inflammation in different compartments (intrauterine,

lung, blood, or brain) during a common developmental window of vulnerability contributes to preterm labor and lung and brain injury [24]. Although no mention of this agent has been made in the literature as a causative agent of VAP, it could be a confounding factor overlapping with VAP diagnosis. Therefore, *Ureaplasma* should be looked for in cultured samples and if present it should be taken into consideration when prescribing antibiotic therapy.

Sample Collection Methods

The use of diagnostic techniques with high false-positive rates increases antibiotic prescription and results in selection pressure for multidrug-resistant bacteria and increased costs [25]. Currently, both noninvasive and invasive (bronchoscopic) techniques are equally employed for sample collection. Bronchoalveolar lavage (BAL) is highly specific but invasive and only effective in experienced hands. Contrarily, noninvasive techniques such as TA are more accessible and easy to use, but they tend to overdiagnose VAP and, as a result, increase the use of antibiotics [9].

Bronchoscopic BAL and protected specimen brush (PSB) have been increasingly adopted for sample collection in VAP-suspected adults. These techniques are highly reliable as they avoid sample contamination and constitute at present the standard for microbiological sampling in the respiratory airways [26]. Gauvin et al. [27] performed a prospective cohort study in PICU patients with suspicion of VAP and concluded that blind BAL with a bacterial index (sum of the log of all species obtained from BAL) ≥ 5 was the most reliable method for diagnosing VAP. Labenne et al. [28] tested the sensitivity and specificity of BAL and PSB in children and neonates with suspected VAP. As reference standards they used positive pleural fluid, positive lung biopsy, histopathological evidence, pulmonary abscesses in computed tomography scans, isolation of identical bacteria in blood and TA cultures or clinical diagnosis using CDC guidelines evaluated by two independent investigators blinded for BAL/PSB. They reported 72% sensitivity and 88% specificity for BAL culture, which increased to 79 and 88%, respectively, when combined with an intracellular bacteria count. A combination of these techniques with PSB reached a sensitivity of 90% and a specificity of 88%. Furthermore, both techniques seemed to be safe and only minor complications such as minimal bronchial hemorrhage, a moderate increase in oxygen or ventilator requirement, and transient fever were reported [28].

Unfortunately, bronchoscopic BAL and PSB are not applicable in neonatology because of the small diameter of the ETT. Under these circumstances, blind-protected BAL appears to be the most reliable sampling method in the neonatal patient [10]. Thus, in a recent prospective observational study including 198 neonates intubated for more than 48 h who fulfilled CDC criteria for VAP, lower airway secretions were collected using the BAL technique with a blind-protected catheter under sterile conditions. A total of 18 episodes of VAP were diagnosed. Among the causative agents there was a predominance of Gram-negative bacteria representing 61.9% of the total isolated bacteria, with *P. aeruginosa* being the most frequently isolated microorganism (19%). Other relevant pathogens were coagulase-negative staphylococci and *S. aureus*, while 16.7% of the cultures were polymicrobial [10].

Clinical Signs and Risk Factors

According to CDC criteria, VAP diagnosis should only be considered after 48 h of MV.

However, it should be underscored that different studies have reported a wide range of days of MV before the VAP diagnosis was made. Hence, while some authors have reported VAP diagnoses in the range of 21–39 days after the initiation of MV [10, 12, 13, 29], others have reported diagnoses as early as 4–10 days after the start of MV [11, 15, 30].

The most prevalent clinical sign associated with VAP refers to changes in the characteristics and volume of respiratory secretions and the appearance of purulent mucus in TA. Other signs include hypo- or hyperthermia and worsening of the respiratory distress [10, 12, 13, 15].

There are a series of risk factors that predispose to VAP (table 3). Among them, perhaps prematurity and days of MV are the most relevant ones. Prematurity is characterized by an anatomic and functional immaturity of the lung and respiratory airways together with immature antioxidant defense and immune systems. These peculiarities prompt the need for respiratory support and the tendency towards inflammation and infection, all of which favor the appearance of VAP [3]. Very low birth weight (VLBW), described by Afjei et al. [12] and Tripathi et al. [11] as an additional independent risk factor for developing VAP, should be considered a possible confounder since extremely-low-birth-weight infants need MV for prolonged periods of time compared to term infants [1].

Duration of ventilation has been acknowledged in studies performed with different sampling methods. Hence, Cernada et al. [10], Afjeh et al. [12], and Tripathi et al. [11] identified duration of MV as the most common risk factor. Of note, Cernada et al. [10] employed a novel invasive bronchoalveolar technique to avoid sample contamination for the first time in neonates.

Diagnostic Biomarkers

In 2001, a panel of the NIH put forth a broad definition of biomarker, describing it as a ‘characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention’ [29]. Specific biomarkers of VAP allowing differentiation of pneumonia from colonization have been extensively studied in the adult population, albeit with unreliable results probably due to inconsistencies in the design of most of the studies [30]. Therefore, studies targeting the role of biomarkers in predicting/diagnosing VAP should employ validated sampling techniques to obtain BAL fluid and secretions, disregard patients under antibiotic or corticosteroid therapy prior to sampling, apply similar sensitivity and specificity cutoff values as reported in the literature, and include a homogeneous patient population [31].

Procalcitonin

Procalcitonin (PCT) is a prohormone secreted into serum as part of the systemic inflammatory response to endotoxin or mediators released in response to bacterial infections [interleukin (IL)-1 β , IL-6, or TNF- α]. Interestingly, upregulation of PCT is inhibited by interferon (IFN)- γ , a cytokine released in response to viral infections rendering PCT more suitable to identify bacterial infections [32]. The PCT kinetic profile is extremely favorable for use as a clinical marker. Hence, after only 6–12 h of stimulation PCT blood levels will increase and once the infection is controlled these values will descend rapidly [33]. PCT has been widely used for VAP diagnosis and follow-up in the adult population. However, the results provided by these studies have been very inconsistent, reporting great variability in the cutoff values and broad ranges of sensitivity and specificity [34–36], or even informing of a lack of association between PCT concentration and adequacy of therapy, etiology of VAP, or outcome [37].

Table 3. Risk factors for the development of VAP in the newborn period

Risk factor	Specific reference	General reference
Prematurity and/or low birth weight	11, 12, 30	
Reintubation	15	
Primary blood stream infection	13	
Prior antibiotic use		27, 33, 34, 35
Sedation		27, 33, 34, 35
Enteral feeds		27, 33, 34, 35
Parenteral nutrition	19	
Endotracheal suctioning	15	
Days of MV	10, 11, 12, 15, 19	
Transfusion of any blood product		27, 33, 34, 35
Genetic syndrome		27, 33, 34, 35
Steroids	19	
Histamine type 2 receptor blockers		27, 33, 34, 35

Cytokines

The presence of bacterial pathogens will be sensed by specific cytosolic receptors such as Toll-like and Nod-like receptors triggering an inflammatory response. Proinflammatory cytokines such as IL-1, IL-6, IL-8, IL-10, and TNF- α have been evaluated in adults as markers of VAP, with discordant results. Conway Morris et al. [38] published an association between VAP and increased values of IL-1 β and IL-8 measured in BAL. Ramírez et al. [39] found that IL-6 was capable of accurately differentiating VAP from other causes of pulmonary infiltrates and therefore early IL-6 determination could be a reliable marker for patients at increased risk of VAP. Cytokines have also been rendered useful for monitoring the response to antibiotic treatment. Swanson et al. [40] reported that pulmonary concentrations of IL-8 and TNF- α decreased in microbiological responders with VAP; however, the sample size was relatively small and the results should be confirmed.

The Soluble Form of the Triggering Receptor Expressed on Myeloid Cells

The triggering receptor expressed on myeloid cells (TREM) is related to the natural killer cell receptors and is constitutively expressed on the surface of myeloid cells, neutrophils, monocytes, and macrophages. The expression of TREM-1 is upregulated after stimulation with bacterial and fungal products, and it is involved in mediating proinflammatory responses. The triggering soluble form of TREM (s-TREM) reflects an activation of phago-

cytes and has been proposed as a biomarker of VAP. Determann et al. [41] measured s-TREM in adult patients with VAP and controls and did not find differences in plasma levels; however, levels in BAL were higher in patients with VAP. These results differed from those published by Horoneko et al. [42], who did not find differences in s-TREM concentrations between patients with VAP and controls. Srinivasan et al. [43] evaluated the role of s-TREM and plasminogen activation inhibitor-1 (PLA-1) in the diagnosis of VAP in a PICU. They reported that elevated levels of PLA-1 had the strongest association with a clinical diagnosis of VAP and were the best biomarker to differentiate VAP from colonization.

Oxidative Stress

Following neutrophil activation through TREM-1, a burst of reactive oxygen species including hypochlorous acid (HOCl), the only source of which is the neutrophil enzyme myeloperoxidase, is generated. HOCl is too short-lived and cannot, therefore, be measured in biological materials. However, the effects of HOCl on other molecules such as tyrosine can be measured by mass spectrometry in biofluids in the form of 3-chloro-tyrosine [44]. Another relevant candidate reflecting the prooxidant action of HOCl is glutathione sulfonamide (GSA), a stable oxidation product of reduced glutathione (GSH). GSH is extremely abundant in the cells' cytoplasm but especially in the lung lining fluid. Therefore, GSA can be easily determined in BAL fluid. As infectious agents promote sequestration and activation of neutrophils at the inflammatory site, VAP should cause an increase in this specific biomarker in lung lavage fluid [45].

Few studies (and with disappointing results) on the use of biomarkers in neonatology have been reported. Hence, PCT has been extensively employed for the diagnosis of suspected sepsis and for guiding the duration of antibiotic treatment [46]. However, the presence of a normal, physiological surge in serum PCT 24 h after birth lasting up to 72 h has precluded its use in the early neonatal period, especially for the diagnosis of early-onset sepsis [47]. Of note, no study has yet established an association of PCT with neonatal VAP. Similarly, although cytokines and especially IL-6 have been successfully employed in the diagnosis of early-onset neonatal sepsis [48], no study correlating plasma interleukin levels and VAP has been published. Harwood et al. [49] detected GSA in 75% of TA of ventilated preterm infants. GSA median levels were significantly higher in culture-positive aspirates. In addition, GSA showed good sensitivity and specificity for detecting bacterial growth and has promise for detecting

lung infection. Further studies should confirm the validity of this new biomarker. Finally, Gram staining studies on TA have also shown promising results. Katayama et al. [23] recently reported a sensitivity of 82 and 100%, and a specificity of 100 and 82% for Gram-positive and Gram-negative VAP, respectively, in VLBW infants. Furthermore, Gram-stained TA-based initial antibiotic therapy was effective in 96% of the cases. These results should, however, be carefully interpreted for they did not fulfill CDC VAP diagnostic criteria [7].

Outcomes

In a large European multicenter trial it was shown that nosocomial infections were associated with increased PICU/NICU and total hospital length of stay. In addition, the mortality of infected patients was also significantly increased. However, VAP patients' mortality was no different from that of patients with infections in other locations [50]. Other studies have confirmed that VAP is associated with increased morbidity, a longer duration of MV, and a longer hospital and/or ICU length of stay [17, 27, 51, 52]. Fischer et al. [53] reported an incidence of VAP of 9.6% in a neonatal and pediatric population after cardiac surgery and found a delay in extubation of 3.7 days attributable to VAP. Similarly, Srinivasan et al. [22], Elward et al. [54], and Gautam et al. [17] reported an increased length of stay and a longer duration of ventilation in pediatric and neonatal VAP patients with a tendency towards increased mortality that did not reach statistical significance [27, 51, 52].

Focusing on studies conducted exclusively in neonatal populations, Apistharnarak et al. [13] found VAP to be an independent predictor of mortality in VLBW infants; moreover, VAP significantly increased the NICU length of stay. Tripathi et al. [11], Yuan et al. [15], and Cernada et al. [10] reported significantly higher NICU and hospital lengths of stay in NICU patients, respectively. Although they reported higher mortality rates in VAP patients, the differences did not reach statistical significance (table 2).

Increased length of stay and morbidity causes VAP to increase hospital costs. In a 2-year study performed in PICU patients, VAP was independently associated with increased costs, after controlling for other predictors of cost including age, underlying disease, ventilator days, and severity of illness [55]. In addition, after implementation of the VAP prevention bundle, Brilli et al. [56] reported a decrease in VAP rates and therefore a significant reduction in hospital costs.

Treatment

Understanding the microbiology of VAP is critical for choosing empirical broad-spectrum antibiotic therapy followed by de-escalation to specific antimicrobial therapy once cultures are known or discontinuation of antibiotics if VAP is no longer suspected. However, there are no consensus guidelines for antibiotic treatment either in neonates or in children, and empirical treatment should be selected according to the nosocomial flora and resistance patterns of each individual unit. Interestingly, in extensive drug-resistant infections, aerosolized administration may be an appropriate route to deliver antibiotics and reduce systemic toxicity. Hence, Nakwan et al. [57] reported successful treatment of VAP due to *Acinetobacter baumannii* in a small series of preterm and term neonates with aerosolized colistin for 72 h associated with standard intravenous antibiotic therapy. No relevant side effects were noted and mortality was lower than in historical controls treated exclusively with intravenous antibiotics. Although these are promising data, more studies are needed to expand aerosolized antibiotic therapy in the newborn period, especially in drug-resistant pathogens.

The duration of antibiotic administration for VAP in the newborn period is still unknown. No published data in this regard are available in the literature. Therefore, until reliable information is accessible, the use of biomarkers of infection such as C-reactive protein or interleukins combined with the clinical course and radiological findings are the mainstay for deciding the duration of antibiotic therapy.

Prevention

Most studies of VAP in neonates focus on clinical signs, pathogens, risk factors, and outcomes. Surveillance strategies and evaluation of their effectiveness oriented toward preventing VAP in the neonatal period are scarce but of growing interest. No conclusive results have been reported on how to prevent VAP in the neonatal period; however, implementation of hygienic measures and early extubation are apparently the most efficient strategies to reduce VAP [58, 59].

ETT and Suction

To date, no specific recommendations related to types of ETT or airway suction have been addressed for newborn infants. However, for adults and pediatric patients the CDC and Healthcare Infection Control Practices Ad-

visory Committee suggest the use of ETT with dorsal lumens to allow drainage of respiratory secretions, orotracheal instead of nasotracheal intubation, and a change of ventilators' respiratory circuits only if they are visibly contaminated or do not work [60]. Interestingly, uncuffed ETT, commonly used in neonatal patients, could be a risk factor for increasing the incidence of VAP. Hence, in adults the use of polyurethane or taper-shaped cuffed ETT correlated with lower rates of VAP [51]. Intriguingly, the use of cuffed ETT in the pediatric population was associated with a reduced need for ETT changes and postextubation stridor but increased days of MV [61].

The use of ETT with nano-modified coatings apparently reduces the incidence of infections in the respiratory airways. Recently, Machado et al. [62], in a study performed in adults, reported that ETT with nano-modified coatings reduced the incidence of VAP by preventing biofilm formation and ETT colonization and providing free radical destruction of pathogens. Of note, published experiences in the neonatal period are lacking.

In relation to airway suctioning, Cordero et al. [63] compared the use of closed versus open endotracheal suction systems in ventilated neonates. No differences in the incidence of VAP or mortality between groups were found. Most nurses, however, found closed suction systems easier and faster to use and better tolerated by patients.

Hand Washing

Routine hand washing is one of the most important strategies to reduce nosocomial infections [64]. In a 2-year-long surveillance intervention with NICU patients, increased hand hygiene compliance (from 43 to 80%) significantly reduced the incidence of respiratory infections from 3.35 to 1.06 infections per 1,000 patient days [65]. In another study, systematic use of alcohol-based gels for hand hygiene by caregivers reduced the rate of VAP in VLBW infants by 38% [66].

Rapid Extubation

Since the duration of MV appears to be a major risk factor for the development of VAP in neonates, promptly weaning patients off the ventilator appears to be a desirable strategy to prevent VAP. Ng et al. [67], in a prospective study targeting reduction of the nosocomial infection rate in the NICU, implemented more aggressive strategies for the early weaning of patients off the ventilator during 3 months. When 1 year preintervention and 1 year postintervention were compared, the VAP rates decreased from 3.3/1,000 ventilator days to 1.0/1,000 ventilator days [67].

Fig. 1. Diagnostic algorithm for neonatal VAP in newborns. CRP = C-reactive protein; CFU = colony-forming units.

Use of Histamine 2 Receptor Antagonists or Antacids

The use of histamine 2 receptor antagonists or antacids is believed to increase the risk of VAP as acid gastric content may make colonization with pathogenic organisms difficult. However, no differences in the incidence of VAP were found when comparing patients using or not using histamine 2 receptor antagonists or antacids [68]. There is no published experience in the neonatal period.

Selective Decontamination

Selective decontamination consists of the establishment of a regimen of topical or intravenous antimicrobials in an attempt to reduce the burden of pathogenic bacteria in aspirated secretions. Randomized studies in pediatric patients have shown conflicting results [69, 70]. In a prospective cohort nonrandomized study, NICU patients received oral polymyxin E, tobramycin, and nystatin correctly (during the first 5 days) or incorrectly (after 5 days) or they did not receive any decolonization [71]. Results revealed that correct selective decolonization had a protective effect toward nosocomial infections of an intestinal origin. However, a separate analysis of the impact on respiratory infections alone was not performed [71]. Ac-

cordingly, no recommendation regarding selective decontamination in neonates is warranted.

Probiotics

The loss of gut commensals such as *Bifidobacterium* and *Lactobacilli* spp. is associated with prolonged antibiotic treatments, delayed enteral feeding, or nursing in incubators and translates into proliferation of pathogenic microflora and abnormal gut colonization. Seemingly, enhancement of the enteric microbiota composition with supplementation of probiotics seems to be a good strategy to prevent sepsis and could also be applied to prevent neonatal VAP [72]. Nevertheless, a recent meta-analysis of 7 randomized controlled trials conducted in adult populations concluded that probiotics showed no beneficial effect in patients who are mechanically ventilated, did not significantly decrease the incidence of VAP, and should not be recommended for routine clinical application [73]. To date, no information regarding the use of probiotics to prevent VAP is available.

Conclusions

VAP remains a serious and mainly unsolved problem among pediatric and neonatal intensive care units [59]. VAP increases respiratory morbidity and overall mortality and prolongs the hospital length of stay. VAP is especially associated with prematurity, low birth weight, chronic lung disease, and prolonged MV [58]. However, clinical and radiological diagnosis is extremely difficult given the unspecific signs and symptoms of VAP in the neonatal patient. In addition, retrieving noncontaminated biological samples from the lower respiratory airways for culture is still a major challenge. The use of BAL with blind-protected catheters seems to be a valid alternative. However, there is an urgent need for trials comparing BAL with traditional TA for culture as well as identifying reliable biomarkers of lung infection as the best way to diagnose VAP and improve the outcomes in ventilated neonates.

We propose a diagnostic approach to VAP in the flow diagram depicted in figure 1. It is important that caregivers treating ventilated preterm infants keep this diagnosis in mind when a sudden worsening of a patient with risk factors occurs and clinical signs suggest this entity. As a general rule, patients should be extubated as soon as possible as a main strategy to prevent VAP. This update aims to draw attention to this subtle but severe complication affecting preterm infants in the NICU.

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