Review Article :

Update on Ventilator Associated Pneumonia in Neonates and Children

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Abstract:

Ventilator-associated pneumonia (VAP) is relatively common in mechanically-ventilated children, but there is a wide variation in reported VAP rates, depending on settings and geographical regions. Surveillance definitions in children are challenging. Although these are provided by the German nosocomial infection surveillance system and an independent Dutch group, the combination of clinical and radiologic signs leaves room for interpretation. Of note, the United States Centers for Disease Prevention and Control guidelines do not offer algorithms for neonates. Despite the fact that most experts agree on the low sensitivity and specificity of existing definitions, little has changed over the past years. However, the number of studies reporting on VAP prevention programs has increased in recent years. Single interventions, such as chlorhexidine mouth wash or stress ulcer prophylaxis, were not effective. Successful prevention programs combined multiple interventions, such as hand hygiene, glove and gown use for endotracheal tube manipulation, backrest elevation, oral care with chlorhexidine, stress ulcer prophylaxis, cuff pressure maintenance where appropriate, use of orogastric tubes, avoidance of gastric distension, and elimination of non-essential tracheal suction. These multimodal strategies have proved to be successful among neonates, infants, and children. Importantly, they are applicable in high- as well as in low- and middle-income countries. This review provides an update of VAP incidence rates and summarizes current knowledge on its epidemiology, risk factors, surveillance definitions, and prevention programs in the pediatric setting.

Introduction:

Healthcare-associated infections (HAIs) are associated with morbidity, mortality, and prolonged hospitalization, and represent a serious threat to patient safety, cost and hospital and healthcare reputation. Hospitalized children and neonate being immunologically fragile are a particularly vulnerable population[1]. The incidence of HAI in adult and pediatric intensive care units (PICUs) is high. This is due to the many invasive procedures and frequent antibiotic use, which put the patients at risk for infection and promote the emergence of multidrug-resistant organisms[2]. The use of invasive devices in NICUs, such as central vascular lines and mechanical ventilation(MV), is similar to adult intensive care and thus the burden of ventilator-associated pneumonia (VAP) and other HAIs are also similar[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].

In this review, we have tried to describe the epidemiology of VAP, risk factors study, and discuss effective prevention measures and neonatal ICUs (NICUs).

Definitions:

A uniform definition of VAP needs to have the capacity to be relevant for clinical trials, while balancing the risks of experimental therapy and sampling procedures with potential benefits for study patients[4]. If the definition of VAP is already controversial for adults, it is even more challenging for children, in particular for ventilated neonates. The starting point of the recent United States (US) Centers for Disease Prevention and Control (CDC) definitions for adults is a ventilator-associated complications (VAC), which is further narrowed towards infectious VAC and then towards possible or probable VAP, according to additional diagnostic. However, it is not clear whether this algorithm can be applied to children in different age groups and, thus, the conventional CDC definitions of hospital-acquired pneumonia for children and neonates remain valid for the time being [7]. These definitions do not specify between "ventilated" or "non-ventilated" and the use of the term "VAP" depends on the time on ventilation (48 h or longer). The German national nosocomial infection surveillance system (Krankenhaus Infektions Surveillance System [KISS]) offers a definition for very low birth weight infants in their "Neo-KISS" module [8]. A Dutch study group established their own definition for VAP in neonates, which are more inclusive than the CDC definitions[9,10].

Table 1 summarizes the definitions of hospital-acquired pneumonia by stratifying age groups into neonates, infants (≤1 year), and children (>1 year to≤16 years). All definitions combine clinical and radiologic signs. In addition, the CDC and the European Centre for Disease Prevention and Control (ECDC) definitions further distinguish between definite, probable, and possible healthcare-associated pneumonia, based on microbiologic findings (Table 2). Clinical and radiologic findings lack sensitivity and specificity. However, tracheal aspirate cultures have also low sensitivity (31-69%) and specificity (55-100%). A positive tracheal culture alone does not discriminate between bacterial colonization and respiratory infection. Bronchoalveolar lavage (BAL) provides better results, but the range of sensitivity (11-90%) and specificity (43-100%) is large.

Table 1

Case definitions of hospital-acquired pneumonia in children stratified by different age groups

Neonates	Onset >72 h after birth and one of the following radiologic criteria: -new or progressive infiltrates -consolidations -adhesions or fluid in lobar fissures/pleura **And** Worsening gas exchange (SaO2 ?; O2 requirement ?; Ventilation parameters ?) **And** Four of the following signs and symptoms: -fever (>38.0°C), hypothermia (<36.5°C), or temperature instability -new onset or increasing bradycardia (<80/min) or tachycardia (>200/min) -new onset or increasing tachypnoea (>60/min) or apnoea (>20 seconds) -new onset or increasing signs of dyspnoea (retractions, nasal flaring, grunting) -increasing production of respiratory secretions and need for suctioning -purulent tracheal secretion -isolation of a pathogen in respiratory secretions -elevated C-reactive protein (>20 mg/L) I/T-ratio >0.2
Infants: 2–11 months	One of the following radiologic criteria: -new or progressive infiltrate -consolidations -cavitations -pneumatoceles **And** Worsening gas exchange (SaO2 ?; O2 requirement ?; Ventilation parameters ?) **And** Three of the following signs and symptoms: -fever (>38.0°C), hypothermia (<36.5°C), or temperature instability

	-leucopenia (<4000 WBC/mm3) or leucocytosis (?15,000 WBC/mm3) with left shift (?10% band forms)
	-new onset of purulent sputum, or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements
	-apnoea or dyspnoea (tachypnoea, nasal flaring, retraction of chest wall, grunting)
	-wheezing, rales, or rhonchi
	-cough
	-bradycardia (<100/min) or tachycardia (>170/min)
Children: 1–16 years	One of the following radiologic criteria:
	-new or progressive and persistent infiltrate
	-consolidation
	-cavitation
	And
	Three of the following signs and symptoms:
	-fever (>38.4°C) or hypothermia (<36.5°C)
	-leukopenia (<4000 WBC/mm3) or leucocytosis (?15,000 WBC/mm3)
	-new onset of purulent sputum or change in character of sputum or increased respiratory secretions or increased suctioning requirements
	-new onset or worsening cough or dyspnoea, apnoea, or tachyponea
	-rales or bronchial breath sounds
	-worsening gas exchange (SaO2 ?; O2 requirement ?; Ventilation parameters ?)

SaO2: Oxygen saturation; I/T-ratio: immature to total neutrophil ratio; WBC: white blood cell count; ↑: increase; ↓: decrease.

Table 2

Classification of hospital-acquired pneumonia in children based on microbiological results

Definite VAP	A child who fulfils the case definitions for hospital-acquired pneumonia (Table 1) and has one of the following: -same pathogen isolated from bronchial secretions/BAL and blood -pathogen or virus isolated from lung biopsy, or positive growth in culture of pleural fluid, or histopathologic examination with evidence of pneumonia manifested as abscess formation, positive culture of lung parenchyma, or fungal hyphae -Pathogen or virus isolated from BAL (bacteria ?104 CFU/ml), or ?5% of BAL-obtained cells contain intracellular bacteria on direct microscopic exam, or protected brush with a threshold of ?104 CFU/ml, or distal protected aspirate with a threshold of ?104 CFU/ml, or positive exams for particular microorganisms (Legionella, Aspergillus, mycobacteria, Mycoplasma, Pneumocystis jirovecii)
Probable VAP	A child who fulfils the case definitions for hospital-acquired pneumonia (Table 1) and has one of the following: -pathogen isolated from BAL (bacteria <104 CFU/ml) -pathogen or virus isolated from bronchial secretions, or quantitative culture of lower respiratory tract specimen (endotracheal aspirate) with a threshold of bacteria ?106 CFU/ml
Possible VAP	A child who fulfils the case definitions for hospital-acquired pneumonia (Table 1) with non-quantitative lower respiratory tract specimen culture or no positive microbiology, but has been treated for hospital-acquired pneumonia

BAL: bronchoalveolar lavage;
CFU: colony-forming units.

Diagram depicting progress and treatment protocol for VAP
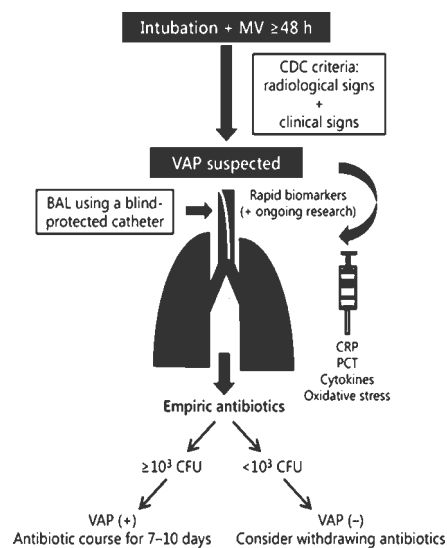
The Centers for Disease Control and Prevention (CDC; Atlanta, Ga., USA) defines VAP as 'a nosocomial infection diagnosed in patients undergoing MV for at least 48 h'[7]. It is noteworthy that diagnosis of a VAP episode requires a combination of radiological, clinical, and laboratory criteria (table 1)[7]. 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.

Clinical Criteria

Clinical criteria for healthcare-associated pneumonia include fever, leukocytosis or leucopoenia, purulent secretions, new or worsening cough, dyspnoea, tachypnoea, crackles or bronchial breath sounds, and worsening gas exchange. These criteria are nonspecific and their sensitivity and specificity relative to the underlying pathology is poor[2]. Clinical findings must be combined with radiologic and microbiologic findings. In a study of 70 children with VAP, the modified clinical pulmonary infection score (mCPIS) of six or higher had a sensitivity of 94%, a specificity of 50%, a positive predictive value of 64%, a negative predictive value of 90%, and positive and likelihood ratios of 1.9 and 0.1, respectively[11].

Radiologic Criteria

Radiologic criteria include the presence of new or progressive pulmonary infiltrates, adhesions or fluid in lobar fissures/pleura, cavitations, air bronchograms, or pneumatoceles on chest x-rays. The presence of air bronchograms has a higher sensitivity (58-83%) than "evolving infiltrates" (50-78%) [2]. Sequential chest x-rays (days -3, 0, 2, 7) help to confirm healthcare-associated pneumonia in complex cases, such as children with underlying cardiac or pulmonary disease. It should be noted that onset and progression of pneumonia in imaging is fast, but improvement takes time.

Microbiologic Criteria

Respiratory cultures are obtained by tracheal aspirates, bronchoalveolar lavage (BAL), non-bronchoscopic BAL, or protected brush specimens (PBS) [10]. Thresholds are summarized in Table 2.

Epidemiology:

Healthcare-associated pneumonia was the most common HAI in five studies[12, 13, 14, 15,16], and second only to bacteremia in another two reports [17, 18]. The range of VAP incidence density rates in both children and neonates is large. Rates as low as 1/1000 ventilator-days and as high as 63/1000 ventilator-days have been reported (Table 3). The incidence follows a geographical distribution and depends on the type of hospital and the country income level. A surveillance study from the International Nosocomial Infection Control Consortium (INICC) identified higher VAP rates in academic compared to non-academic hospitals [19]. The same study reported higher rates in lower-middle-income compared to upper-middle-income countries. Extreme PICU rates have been reported from India (36.2%)[20] and Egypt (31.8/1000 ventilator-days)[21]. Surveys in the USA and Germany found consistently lower rates (Table 3) [22, 23, 24]. However, high rates were reported also by high-income countries. A European multicenter study found that 23.6% of children admitted to a PICU developed VAP[25]. An Italian study identified 6.6% children with VAP among 451 on mechanical ventilation[26], and a mixed PICU in Australia identified 6.7% children with VAP among 269 on mechanical ventilation [27].

VAP is also common in the NICU and proportions between 6.8% and 57.0% of HAIs have been reported. A Spanish study identified VAP in 9.1% of 198 neonates on mechanical ventilation. In a Taiwanese NICU, 11.4% of 528 neonates had one or more HAIs, with VAP contributing to 18.6%. An INICC survey summarizing results from 30 NICUs in 15 countries reported significantly higher VAP rates in academic compared to non-academic institutions [. VAP incidence densities in an Iranian and Turkish NICU were 13.8/1000 and 11.6/1000

ventilator-days, respectively. A higher incidence was reported in another Iranian study with 42% of 38 neonates on mechanical ventilation.[28-33] Table 3 summarizes birth weight-dependent numbers from different studies.

Several studies from the USA, Italy, and Iran found that VAP prolonged mechanical ventilation by approximately 8-12 days, and this may even be as high as 56 days in extremely preterm neonates. Prolonged length of stay was the main driver of attributable costs of up to US$ 1040 in Iran and US$ 51,157 in the USA[35, 34 36]. There are no data on the attributable mortality of VAP. The mortality of HAI in the PICU is estimated to range between 5-14%, to which VAP may significantly contribute [37].

Pathogenesis and Pathogens:

It is presumed that microorganisms invading the respiratory airways and infecting the lung parenchyma may cause VAP. In his excellent review article, Garland[37] 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. On the contrary, blood-borne seeding of the lung constitutes a rare cause of VAP. Sometimes, 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). [38]

Technical difficulty in obtaining nonconta-

minated samples is main hinderence for the assessment of VAP etiology difficult. Apisarnt-hanarak et al.[39] reported isolation of multiple organisms from tracheal aspirates (TA) in 58% of episodes of VAP in extremely preterm neonates. In addition, Deng et al.[40] (in neonates) and Srinvasan et al.[41] (in pediatric patients) found a polymicrobial etiology in 25-40% of VAP episodes. However it should be noted that in these studies, samples were taken 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 [42].

The most common pathogens isolated in the neonatal population are Pseudomonas aeruginosa and Staphylococcus aureus[37-41]. However, isolation of other microorganisms such as Klebsiella pneumoniae and Escherichia coli has also been reported[37-41] (table 3).

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 [43]. 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.

TABLE 3: Description of the most relevant features of studies published in relation to VAP in the neonatal period

	Afjeh (38)	Apisarnthanarak (39)	Cernada (42)	Deng (40)	Geffers (22)	Tripathi (44)	Yuan (45)
Study design	Prospective cohort	Prospective cohort	Prospective cohort	Retrospective case-control	Prospective surveillance	Prospective cohort	Retrospective cohort
population	Newborn MV>48 hr	BW<2000 gm MV>48 hr	Newborn MV>48 hr	Newborn MV>48 hr	BW<1500 gm MV>48 hr	Newborn MV>48 hr	Newborn MV>48 hr
Diagnostic criteria	Radiographic clinical	Radiographic Need for antibiotics	Radiographic Clinical Microbiologic (BAL)	CDC criteria for infant aged< 1 yr	Radiographic clinical	CDC criteria for infant aged< 1 y	Radiographic clinical
incidence	11.5 episodes	<28 weeks: 6.5 episodes >28 weeks: 4 episodes	10.9 episodes	Prevalence: 33.5%	2.7 episodes	2.7 episodes	37.2 episodes
Sampling method	ET aspirate	ET aspirate	Blind-protected BAL	ET aspirate	Not provided	ET aspirate	ET aspirate
Most common pathogen	E.coli K.pneumoniae	Pesudomonas spp. Enterobacter spp. Polymicrobial 58%	P. airigenosa S. aureus polymicrobial	Klebsiella spp. a.baumanii polymicrobial	CONS S.aureus	K. pneumonia E.coli polymicrobial	K. pneumonia P.auriginosa
Outcome	Not provided	Increased mortality Increased LOF	Increased LOF	Not provided	Not provided	Increased mortality Increased LOF	Increased LOF

Expressed as episodes per 1000ventilator day,BW-Birth weight ,ET-endotracheal ,LOF-length of stay.

Sample Collection Methods:

The diagnostic techniques which have high false-positive rates can increase antibiotic prescription and results in selection pressure for multidrug-resistant bacteria and increased costs. 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[46].

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[48]. However in neonatology due to the small diameter of the ETT, bronchoscopic BAL and PSB are not applicable. Under these circumstances, blind-protected BAL appears to be the most reliable sampling method in the neonatal patient. 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[47].

Clinical Signs and Risk Factors:

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

However, 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, others have reported diagnoses as early as 4-10 days after the start of MV[47].

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[48].

There are a series of risk factors that predispose to VAP. Out of these, 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. Very low birth weight (VLBW), described by Afjeh et al.[38] and Tripathi et al.[44] 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 infant.

Duration of ventilation has been acknowledged in studies performed with different sampling methods. Hence, Cernada et al.[35], Afjeh et al.[38], and Tripathi et al.[44] identified duration of MV as the most common risk factor. Of note, Cernada et al.[35] employed a novel invasive bronchoalveolar technique to avoid sample contamination for the first time in neonates.

Diagnostic Biomarkers:

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. 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.

Procalcitonin, cytokines and chemicals related to oxidative stress have been studied extensively in adult population, but data in neonates and even in children is lacking.

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?, IL-6, or TNF-?]. Interestingly, upregulation of PCT is inhibited by interferon (IFN)-?, a cytokine released in response to viral infections rendering PCT more suitable to identify bacterial infections. 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. PCT has been widely used for VAP diagnosis and follow-up in the adult population.

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-? 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? and IL-8 measured in

BAL.

Srinivasan et al.[27] 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. 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[27].

Few studies (and with disappointing results) on the use of biomarkers in neonatology have been reported.

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 organs. 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. Fischer et al.[52] 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. [41],Elward[54],Gautam et al.[27] 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.

Focusing on studies conducted exclusively in neonatal populations, Apistharnarak et al.[39] found VAP to be an independent predictor of mortality in VLBW infants; moreover, VAP significantly increased the NICU length of stay. Tripathi et al.[44], Yuan et al.[45], and Cernada et al.[45] 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 .

Treatment:

Generally empiric antibiotics are started based on hospital data, and escalated or deescalated depending on cultures 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.[55] reported successful treatment of VAP due to Acinetobacter baumanii 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. (49)

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[49].

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 Advisory 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[57]. 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[57]. 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. [58], 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.[59] 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[60]. 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 [61]. In another study, systematic use of alcohol-based gels for hand hygiene by caregivers reduced the rate of VAP in VLBW infants by 38%[62].

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. Weiss M et al. [57], 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 [62].

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 [63]. 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 [64]. In a prospective cohort nonrandomized study, NICU patients received oral polymixin E, tobramycin, and nystatin correctly (during the first 5 days) or incorrectly (after 5 days) or they did not receive any decolonization. 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 [65, 66]. Accordingly, 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 [67]. 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 [67]. To date, no information regarding the use of probiotics to prevent VAP is available.

Conclusion:

VAP is common in mechanically-ventilated newborn with a wide variation of incidence and in most parts of world, be it developed or developing. Definitions are challenging in neonates since the combination of clinical and radiologic signs are difficult to interpret because of special physiology in newborn period. Gram-negative pathogens are the most common microorganisms, particularly A. baumannii and P. aeruginosa. However, there is a geographic variation with Gram-positive organisms more frequently observed in high-income compared to low- and middle-income countries. Similar to the evidence base of adult settings, a number of studies reported effective VAP prevention strategies. Multiple interventions, such as hand hygiene, glove and gown use for endotracheal tube manipulation, backrest elevation, oral care with chlorhexidine, stress ulcer prophylaxis, cuff pressure maintenance where appropriate, use of orogastric tubes, avoidance of gastric overdistension, and elimination of nonessential tracheal suction , are quite useful in prevention of VAP. These cost effective approaches can be programmed in NICU management even in resource limited set up in developing countries.

Conflict of interest: Nil
Competing interests: The authors declare that they have no competing interests.

Authors contributions:

Markanda K-reference work on definitions, **Vemula N**-studied epidemiology and pathogenesis, **Sherdiwalla F-** sample collection methods and microbiology search of references , **Vasaya T-** searched for preventive strategies, **Kamale V-** compilation and editing with final manuscript.

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