Pediatric RESEARCH

www.nature.com/pr

EDITORIAL

Ventilator-associated pneumonia in the NICU: time to boost diagnostics?

Pediatric Research (2020) 87:1143–1144; https://doi.org/10.1038/s41390-019-0672-5

Extremely low birth weight (ELBW) infants frequently require endotracheal intubation and invasive mechanical ventilation (MV) after birth due to surfactant deficiency and respiratory failure. While every effort is made to extubate these infants to non-invasive modes of MV, some ELBW infants fail extubation attempts and need to remain on invasive MV for several days to weeks. Invasive MV is associated with an increased risk of ventilator-associated pneumonia (VAP), which adversely impacts the severity of bronchopulmonary dysplasia (BPD) and prolongs the duration of assisted ventilation and overall hospitalization.[1]

Prompt diagnosis and treatment of VAP with antibiotics helps to minimize the risk of additional lung injury and dissemination of infection in ELBW infants.[2] However, unnecessary and prolonged antibiotic use should also be avoided in keeping with antibiotic stewardship efforts. Unfortunately, establishing an accurate diagnosis of VAP in intubated preterm infants is highly challenging due to the lack of a gold-standard case definition and diagnostic test for VAP in intubated newborns. The current Centers for Disease Control and Prevention (CDC) guidelines employ the same VAP definition for all infants <1 year of age and include clinical criteria, such as tachypnea, wheezing, cough, and bradycardia, which are neither specific nor relevant in intubated neonatal intensive care unit (NICU) patients (available on line at https://www.cdc.gov/nhsn/pdfs/pscmanual/6pscvapcurrent.pdf). As a result, the CDC definition of VAP is not routinely endorsed by clinicians in the NICU setting. Instead, they often rely on semi-quantitative neutrophil (polymorphonuclear leukocyte (PMN)) counts and quantitative bacterial culture results from tracheal aspirate fluids (TAFs) in conjunction with clinical and radiographic signs to diagnose VAP. An evaluation for VAP may be prompted by a change in the quality of endotracheal secretions or concerning changes on chest radiographs, such as a new area of consolidation, in intubated infants with clinical or respiratory deterioration. These indications that prompt an evaluation for VAP are problematic for several reasons. For example, assessment of the quality of airway secretions is subjective. Furthermore, radiographic changes in autopsy-proven neonatal pneumonia is known to include a broad spectrum of non-specific abnormalities, which can mimic other lung diseases, such as respiratory distress syndrome due to surfactant deficiency.[3] Another challenging area that lacks standardization is the method by which TAFs are obtained and processed. For example, clinicians who interpret the results of the TAF tests and make treatment decisions may not be aware of the amount of sterile saline instilled in the endotracheal tube during suctioning. It is also not clear whether or how the dilution of TAF sample should be taken into account when interpreting the results of PMN counts, which are usually reported semi-quantitatively in the 1+ to 4+ range. Interpretation of the PMN counts in TAF is further complicated by virtue of the fact that both invasive MV and evolving BPD are associated with significant PMN accumulation in the airways, even in the absence of a pulmonary infection.[4] Similarly, TAF culture results may be difficult to interpret as invasive MV per se leads to bacterial colonization in the airways of preterm infants and there is an important knowledge gap and lack of consensus on how to distinguish colonization from infection.[5,6]

Interestingly, one of the CDC diagnostic criteria for VAP in older patients, ≥5% of cells with intracellular bacteria on bronchoalveolar lavage samples, is not included in the current guidelines for VAP diagnosis for patients <1 year of age. Furthermore, to our knowledge, this is not a routinely assessed parameter on neonatal TAF samples sent to clinical laboratories although it has the potential to add valuable information to the TAF PMN counts or bacterial culture results when a diagnosis of VAP is being considered. An example of this is shown in Fig. 1, where a TAF cytospin sample from a patient with severe BPD and VAP demonstrates abundant intraepithelial bacteria, which are no longer detectable after a course of intravenous antibiotics, whereas TAF cultures grew the same microorganisms before and after treatment.

Despite all the shortcomings surrounding the diagnosis of VAP in intubated preterm infants, the incidence of VAP, as a healthcare-associated infection, is used as a key quality metric in the NICUs. This is an unfortunate practice as it incorrectly assumes that VAP can be accurately and reliably diagnosed in NICU patients, thereby potentially discouraging new research in an area with much needed improvement. It could also serve as a disincentive for neonatologists to consider a diagnosis of VAP even in patients with a critical respiratory status who could benefit from a course of antibiotics. Finally, using VAP as a quality measure has led to a body of quality improvement studies to prevent VAPs, the results of which are difficult to interpret or adapt without a consensus on how to diagnose VAP.

In summary, the diagnosis and management of VAP in the NICU setting have not progressed over the past several decades despite advances in other aspects of NICU care that have significantly improved the survival of ELBW infants. Thus there is an urgent need to improve the diagnosis of VAP in this patient population through research that focuses on developing more sensitive and specific diagnostic tools and biomarkers rather than "looking for the keys under the lamppost". In this regard, advancement of knowledge on parameters that are informative about host–bacteria interactions, such as the relative numbers of neutrophils or epithelial cells with intracellular bacteria or abundance of bacteria trapped by neutrophil extracellular traps,[7] in BPD and VAP could be a good starting point. While any research to improve diagnosis of VAP in the NICU setting will have the inherent weakness of lacking a gold-standard test for validation purposes, this should not be a factor to dissuade investigators from pursuing translational research in this long-neglected area with significant knowledge gaps.

Received: 16 October 2019 Revised: 22 October 2019 Accepted: 27 October 2019
Published online: 11 November 2019

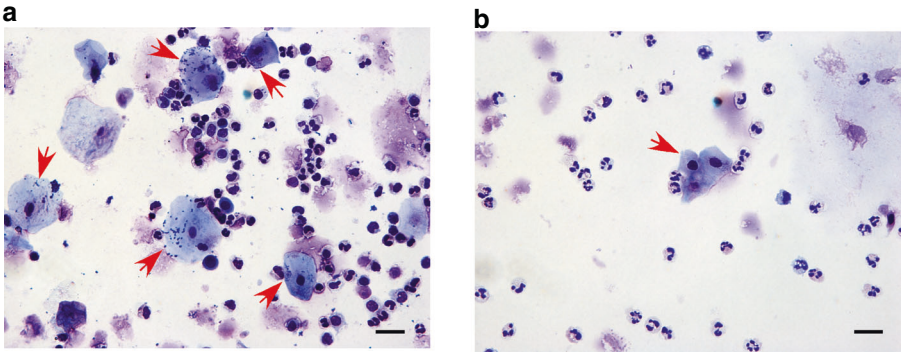

Fig. 1 Distinguishing VAP from colonization—the presence of intraepithelial bacteria. Discarded tracheal aspirate fluid (TAF) samples were used to prepare cytospins from a patient with severe BPD when VAP was diagnosed (**a**) and after the completion of a 7-day course of intravenous antibiotics (**b**). TAF cytospins stained with a modified Giemsa stain demonstrate intracellular bacteria in epithelial cells (red arrows) in the pretreatment (**a**) but not the posttreatment sample (**b**). Epithelial cells demonstrate squamous cell morphology, which is characteristic of squamous cell metaplasia seen in severe BPD. Both TAF samples grew *Acinetobacter baumannii* and *Staphylococcus aureus*. The first sample was treated as an infection and the second was regarded as colonization. Notably intracellular bacteria are absent from neutrophils in both samples. Scale bar, 25 µm

ACKNOWLEDGEMENTS

We thank Dr. Dara Brodsky, Dr. Daniel Irimia, Dr. Xiao Wang, Dr. Linda Van Marter, Dr. Gerald Pier, and members of the Çataltepe Laboratory and Brigham and Women's Hospital Neonatal Respiratory Therapy Department for helpful discussions on this topic. This work was financially supported by grant number 5R21HD092934 (to S.C.).

AUTHOR CONTRIBUTIONS

E.E. and S.C. developed the concept, reviewed the literature, drafted, and finalized the manuscript. S.C. provided the patient data.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ebru Ergenekon[1] and Sule Çataltepe[2]
[1]Division of Newborn Medicine, Department of Pediatrics, Gazi University Hospital, Ankara, Turkey and [2]Department of Pediatric Newborn Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
Correspondence: Sule Çataltepe (scataltepe@bwh.harvard.edu)

REFERENCES

1. Cernada, M., Brugada, M., Golombek, S. & Vento, M. Ventilator-associated pneumonia in neonatal patients: an update. *Neonatology* **105**, 98–107 (2014).
2. Wu, I. H. et al. Incidence, clinical features, and implications on outcomes of neonatal late-onset sepsis with concurrent infectious focus. *BMC Infect. Dis.* **17**, 465 (2017).
3. Haney, P. J., Bohlman, M. & Sun, C. C. Radiographic findings in neonatal pneumonia. *AJR Am. J. Roentgenol.* **143**, 23–26 (1984).
4. Dell'Orto, V. et al. Cell count analysis from nonbronchoscopic bronchoalveolar lavage in preterm infants. *J. Pediatr.* **200**, 30.e2–37.e2 (2018).
5. Mourani, P. M., Harris, J. K., Sontag, M. K., Robertson, C. E. & Abman, S. H. Molecular identification of bacteria in tracheal aspirate fluid from mechanically ventilated preterm infants. *PLoS ONE* **6**, e25959 (2011).
6. Cordero, L., Ayers, L. W., Miller, R. R., Seguin, J. H. & Coley, B. D. Surveillance of ventilator-associated pneumonia in very-low-birth-weight infants. *Am. J. Infect. Control* **30**, 32–39 (2002).
7. Brinkmann, V. et al. Neutrophil extracellular traps kill bacteria. *Science* **303**, 1532–1535 (2004).