



## EDITORIAL

# Can biomarkers be used to predict bronchopulmonary dysplasia? ☆



Vineet Bhandari <sup>a,\*</sup>, Mitali Sahni <sup>b,c</sup>

<sup>a</sup> Neonatology Research Laboratory (Room #206), Education and Research Building, Cooper University Hospital, Camden, USA

<sup>b</sup> Pediatrix Medical Group, Sunrise Children's Hospital, Las Vegas, USA

<sup>c</sup> University of Nevada, Las Vegas, USA

Bronchopulmonary dysplasia (BPD) is the most common chronic lung disease of infancy that occurs secondary to a complex interaction of genetic and environmental factors in premature infants.<sup>1</sup> Among the environmental factors, the duration of invasive mechanical ventilation and supplemental oxygen use are two of the critical factors contributing to the pathogenesis of BPD.<sup>2</sup> Despite its heavy disease burden, our ability to predict BPD in premature infants and diagnose it appropriately is limited. The pathogenesis of BPD involves an inflammatory cascade that leads to impaired alveolarization and dysregulated angiogenesis during lung development.<sup>3</sup> This has led to researchers investigating the use of biochemical biomarkers that are integral to the pathogenesis of BPD, in effectively predicting the risk of this disease. Many studies have evaluated a variety of biomarkers in serum, tracheal aspirate and urine to identify infants predisposed to BPD.<sup>4</sup> Some studies have also evaluated multivariate models that combine cytokine levels with clinical predictors of the disease to predict the risk of development of BPD.<sup>5,6</sup>

In the study by Nascimento et al.,<sup>7</sup> the authors investigated relevant clinical variables and the ability of specific biomarkers associated with the use of invasive mechanical ventilation in the first few days of life to predict the risk of development of BPD in premature infants.

In their study, it was noted that the type and duration of the respiratory support were significantly associated with the development of BPD. Specifically, the duration of continuous invasive ventilator support was the sole predictor variable for the development of BPD. This is an important observation, and well worth reiterating as efforts made to avoid invasive ventilation at the outset or extubation to non-invasive (commonly, nasal continuous positive airway pressure or NCPAP and nasal intermittent positive pressure ventilation or NIPPV) modes of respiratory support in the first three days of life have been shown to decrease the risk of BPD.<sup>8,9</sup> We,<sup>9,10</sup> and others,<sup>11,12</sup> have shown that even if an infant requires re-intubation after the first few days of life i.e. at a more mature stage of lung development, this does not significantly increase the risk of developing BPD. Hence, the fear of non-invasive respiratory support failure, i.e. the need to re-intubate, should not be a reason to attempt to extubate an infant from invasive mechanical ventilation in the first few days of postnatal life. A study has noted that systemic inflammation occurs in the early phase of BPD development,<sup>13</sup> and hence an effort to avoid/diminish this initiation of persistent inflammation<sup>14</sup> can potentially decrease the incidence and/or severity of BPD.

In addition, Nascimento et al.<sup>7</sup> analyzed serum samples collected between 36–48 h of life from 40 very low birth weight (VLBW) infants born at <34 weeks gestational age. Twenty-one infants from this prospective cohort developed BPD and 19 did not. They report that when compared to infants that did not develop BPD, infants with BPD have higher levels of granulocyte and macrophage colony stimulating factor (GM-CSF) ( $p=0.002$ ), lower levels of eotaxin ( $p=0.02$ ), and an increased ratio of GM-CSF to eotaxin

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\* Corresponding author.

E-mail: [bhandari-vineet@cooperhealth.edu](mailto:bhandari-vineet@cooperhealth.edu) (V. Bhandari).

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( $p < 0.0001$ ). They also reported that infants who developed BPD were of lower gestational age, lower birth weight and were exposed to longer periods of invasive mechanical ventilation, as also discussed above. The authors further conclude that use of mechanical ventilation was associated with the cytokine profile seen in their cohort, suggesting increased lung injury and a higher risk of progression to BPD. This study is well designed, includes appropriately matched subjects in the case/control groups and has the additional advantage of being a prospective study. However, the results of the study are limited by the small number of infants evaluated. Information about chorioamnionitis is lacking, which has been reported to impact GM-CSF levels.<sup>15</sup> The group with BPD also has a statistically significant higher use of antibiotics ( $p = 0.04$ ), suggesting a higher risk for infection that could affect the cytokine profile of the infants included in this group. Furthermore, the study only included measurement of serum cytokines; a concurrent measurement of tracheal aspirate (TA) or bronchoalveolar lavage (BAL) would have added further value to the results since it would have better represented the chemokine-associated inflammation seen in the pathogenesis of BPD. Lastly, the study is effectively an observational study by design and can only show association with the disease and not causation.

T helper cells (Th1 and Th2) help regulate inflammatory responses and maintain inflammatory homeostasis in the lungs.<sup>16</sup> There is limited evidence regarding the role of Th1 and Th2 responses in the neonatal period and its effect on BPD. GM-CSF is preferentially associated with Th1 responses while eotaxin plays a role in Th2 responses. GM-CSF is also known to play a role in surfactant homeostasis and has previously been reported to be elevated in the first week of life in BAL samples of infants who progress to develop BPD when compared to infants that do not.<sup>17</sup> In animal models of hyperoxia-induced acute lung injury (HALI), transgenic mice with overexpressed GM-CSF had increased survival and this was thought to be beneficial in HALI.<sup>18,19</sup> In a fetal sheep model, lung stretch injury induced by large volume ventilation was associated with an increase in GM-CSF at one hour and was also thought to help with lung maturation due to its role in surfactant homeostasis.<sup>20</sup> In another study, D'Angio et al. reported altered levels of GM-CSF in blood spot samples of premature infants who developed BPD as compared to infants with no lung pathology.<sup>5</sup> In their study, Nascimento et al.<sup>7</sup> also found an increase in serum levels of GM-CSF in infants exposed to invasive mechanical ventilation that can cause stretch lung injury and may lead to increase in secretion of GM-CSF. In this study, the authors also looked at eotaxin levels, since eosinophilic activation has been linked to BPD<sup>21</sup> and the main role of eotaxin is in eosinophil chemotaxis and activation. However, they found a decrease in eotaxin levels in infants that progressed to develop BPD compared to infants that did not develop BPD. On the other hand, Zhou et al. reported a significant increase in eotaxin levels in serum samples at day 1, 7 and 14 of life, in VLBW infants born at <32 weeks GA, that progressed to develop BPD.<sup>22</sup> In the study by Kandasamy et al., multiple cytokines were analyzed in blood samples from 152 extremely LBW (ELBW) infants and combined with clinical variables to develop predictive models for BPD/death soon after birth. In their study, they also reported increased levels of eotaxin-1 in infants who developed BPD compared to

those who survived without BPD ( $p = 0.002$ ). This increase in levels of eotaxin-1 also correlated with levels of GM-CSF.<sup>23</sup>

Most studies evaluate biomarkers in VLBW infants in the first week of life to help predict the risk of BPD, but there is limited data available on the use of biomarkers to diagnose and stratify the severity of BPD once the disease is established. Our group recently reported higher levels of intercellular adhesion molecule (ICAM)-1 in infants with established BPD when compared to preterm and term infants of comparable postmenstrual age with no lung pathology. The level of ICAM-1 also correlated with the severity of the disease.<sup>24</sup>

Alteration in levels of cytokines and proteins in the serum of preterm infants can be used to identify the infants at risk for BPD and help with confirmation of the diagnosis. Validation of these specific patterns of biomarkers in prospective cohorts of premature infants is needed to reproduce these results and demonstrate their role in improving the diagnosis and management of BPD. An increase in GM-CSF and alteration in eotaxin early in the course of lung injury in VLBW infants may be useful in identifying infants at risk of BPD; however, there are conflicting reports in the literature regarding the directionality of change in eotaxin levels. In addition, concurrent measurements of their level in serum and TA/BAL specimens may be more accurate in assessing the risk of lung injury. Further investigation is needed to determine if eotaxin and GM-CSF are involved in lung injury and pathogenesis of BPD.

## Conflicts of interest

The authors declare no conflicts of interest.

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