



# Strategies to improve outcomes of bronchopulmonary dysplasia

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In this issue of *Korean Journal of Pediatrics*, Sung<sup>1)</sup> reviewed potential therapeutic strategies to improve outcomes of bronchopulmonary dysplasia (BPD). In this review, various risk factors of BPD were described, including inflammatory responses, chorioamnionitis, *Ureaplasma* infection, environment, genetic susceptibility, resuscitation in the delivery room, mechanical ventilation, and fetal growth restriction. She also suggested potentially beneficial therapeutic strategies from the antenatal care to postnatal corticosteroids. Conventional medications such as diuretics, caffeine, vitamin A, and novel drugs that are under investigation were described in this review. She concluded that the preventive or therapeutic strategies for BPD are inadequate and further studies are needed to identify optimal and effective preventive or therapeutic strategies to decrease the incidence and severity of BPD.

As Sung<sup>1)</sup> mentioned, BPD is a heterogeneous disease. Since it was first described in 1967 by Northway et al.,<sup>2)</sup> BPD has evolved fundamentally as increasing numbers of premature infants are surviving due to advances in neonatal medicine. The classic form of BPD that prevailed in the presurfactant era is now rarely observed, probably because preterm infants born in this era of modern sophisticated neonatal care are much less commonly exposed to high concentrations of oxygen and mechanical ventilation. The most remarkable pathologic finding of modern BPD is a lack of alveolar and pulmonary vascular development, while that of classic BPD is emphysema, fibrosis, and airway remodeling.<sup>3,4)</sup> In this regard, BPD is a heterogeneous disease whose phenotype changes over time.

Many new perspectives have been suggested regarding the pathogenesis of BPD, but extreme prematurity, oxidative stress, and mechanical ventilation play a major role. However, much preclinical and clinical evidence has shown that intrauterine infection and/or inflammation, fetal growth restriction, and pregnancy-induced hypertension are involved in the development of BPD.<sup>5-7)</sup> Although controversy persists regarding the role of these prenatal conditions in the pathogenesis of BPD, the associations between these prenatal factors and BPD have been demonstrated in many studies. In a recent study of a very low birth weight infant cohort by the authors, fetal lengthwise growth restriction was associated with an increased risk of BPD.<sup>8)</sup> The mechanism by which fetal growth restriction is involved in the development of BPD might be quite different from the mechanism by which chorioamnionitis is involved. Fetal growth restriction might impede growth of the fetal lungs with its global adverse impact on the overall fetal growth, while chorioamnionitis might do so by implementing inflammatory responses. In this regard, BPD is a heterogeneous disease with different pathogeneses.

Furthermore, genetic susceptibility may also be crucial in the pathogenesis of BPD and a reason why extremely preterm infants show different outcomes in response to common injuries.<sup>9,10)</sup> This era of precision medicine enables the tailoring of therapies to individuals with different genetic susceptibilities. This is also the case for BPD. Why some preterm infants develop greater inflammatory responses that lead to organ or tissue damage and some have more emphysematous changes or airway problems in response to conventional neo-

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natal respiratory care is not yet understood. The answers to these questions could be obtained from increasing knowledge of genetic susceptibilities.

There are currently no specific preventive or therapeutic measures for BPD. Many novel therapies and drugs are under investigation. Mesenchymal stem cells, inhaled corticosteroid with or without surfactant, zinc, L-citrulline, inhaled furosemide, volume-targeted ventilation in the delivery room, early hydrocortisone therapy, and other treatments are under clinical trial investigation.<sup>11)</sup> However, the target populations of these clinical trials are primarily extremely preterm infants. As the authors mentioned above, BPD is a heterogeneous disease that changes over time and has different pathogeneses. Therefore, it may be reasonable to target the study population according to the mechanisms of action of these therapies or drugs. For example, for clinical trials of anti-inflammatory agents like corticosteroids, preterm infants who were exposed to chorioamnionitis would be the optimal target population, while for clinical trials of growth factors or aggressive nutritional strategies, preterm infants who are small for gestational age would be the optimal target population. The genetic susceptibility of the preterm infants should be also considered. To enable optimization of the target population for clinical trials of novel therapies or drugs, we must subtype BPD according to pathogenesis and genetic susceptibility and delineate the detailed mechanisms of action of these novel therapies or drugs for BPD.

In conclusion, BPD remains a great threat to the survival and long-term outcomes of extremely preterm infants. Because BPD is not a homogenous disease, tailored preventive or therapeutic strategies should be identified based on its pathogenesis and genetic susceptibility. Further studies are required to delineate the detailed pathogeneses of BPD, identify the genetic susceptibilities for BPD, and subtype BPD according to the different pathogeneses and genetic susceptibilities.

## Conflicts of interest

No potential conflict of interest relevant to this article was reported.

## References

1. Sung TJ. Bronchopulmonary dysplasia; what should we do to improve its outcomes? *Korean J Pediatr* 2019;62:367-73.
2. Northway WH Jr, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. *N Engl J Med* 1967;276:357-68.
3. Jobe AH. The new bronchopulmonary dysplasia. *Curr Opin Pediatr* 2011;23:167-72.
4. Baker CD, Abman SH. Impaired pulmonary vascular development in bronchopulmonary dysplasia. *Neonatology* 2015;107:344-51.
5. Hartling L, Liang Y, Lacaze-MasmonTEIL T. Chorioamnionitis as a risk factor for bronchopulmonary dysplasia: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed* 2012;97:F8-17.
6. Bose C, Van Marter LJ, Laughon M, O'Shea TM, Allred EN, Karna P, et al. Fetal growth restriction and chronic lung disease among infants born before the 28th week of gestation. *Pediatrics* 2009;124:e450-8.
7. Hansen AR, Barnés CM, Folkman J, McElrath TF. Maternal pre-eclampsia predicts the development of bronchopulmonary dysplasia. *J Pediatr* 2010;156:532-6.
8. Jung YH, Park Y, Kim BI, Choi CW. Length at birth z-score is inversely associated with an increased risk of bronchopulmonary dysplasia or death in preterm infants born before 32 gestational weeks: a nationwide cohort study. *PLoS One* 2019;14:e0217739.
9. Bhandari V, Bizzarro MJ, Shetty A, Zhong X, Page GP, Zhang H, et al. Familial and genetic susceptibility to major neonatal morbidities in preterm twins. *Pediatrics* 2006;117:1901-6.
10. Walsh MC, Szeffler S, Davis J, Allen M, Van Marter L, Abman S, et al. Summary proceedings from the bronchopulmonary dysplasia group. *Pediatrics* 2006;117(3 Pt 2):S52-6.
11. Baud O, Watterberg KL. Prophylactic postnatal corticosteroid: early hydrocortisone. *Semin Fetal Neonatal Med* 2019;24:202-6.