Is antibiotic exposure associated with an increased risk of developing necrotizing enterocolitis and bronchopulmonary dysplasia in very low birth weight infants?

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DEAR EDITOR,

We have read the article entitled "Increased antibiotics exposure in early life is associated with adverse outcomes in very low birth weight infants." published in the September issue of the *Journal of the Chinese Medical Association* with interest.[1] Chen et al[1] attempted to explore whether increased antibiotics exposure with the routine use of probiotics was associated with necrotizing enterocolitis (NEC) or bronchopulmonary dysplasia (BPD). The authors found that there was no significant difference of occurrence of NEC or BPD in very low birth weight (VLBW) infants, regardless probiotics were routinely used or not.[1] Additionally, they identified that increased antibiotic exposure of VLBW infants was associated with increased risks of NEC and BPD with an adjusted odd ratio of 1.278 (95% confidence interval [CI], 1.025-1.593) and 1.630 (95% CI, 1.233-2.156), respectively.[1] We appreciated the authors' excellent contribution to an improved care of these VLBW infants vulnerable to injuries due to prematurity,[2,3] but there are some questions that need clarification.

Based on the hypothesis the authors proposed, they attempted to explore the role of the duration of antibiotic exposure and probiotic use on the occurrence of NEC and BPD. We are wondering to know why the authors only separate the study subjects into two categories, 0 to 8 days of antibiotic exposure and 9 to 14 days of antibiotic exposure, since this separation did not answer their other aim to evaluate the effect of probiotic use on the development of NEC and BPD. If their strategy is correct, the "use of probiotics" and "no-use of probiotics" should be evaluated by another table.

There are many possible factors associated with the development of NEC and BPD, including antenatal factors, such as gestational age, birth weight, and Apgar score at the fifth minute; and infant information to day 14, such as score for neonatal acute physiology with perinatal Extension-II, use of surfactant, presence of hemodynamically significant patent ductus arteriosus (PDA), days of mechanical ventilation, days of oxygen supplementation more than fraction of inspired oxygen (FiO2) 40%, and days of steroid administration.[1] Although the authors adjusted the potential biases, such as Score for Neonatal Acute Physiology with Perinatal Extension-II, human milk feeding, use of probiotics, chorioamnionitis, days of mechanical ventilation, days of oxygen supplementation, days of steroid administration, and presence of hemodynamically significant PDA to identify two possible key factors associated with the development of NEC and BPD, including the duration of antibiotic exposure day as well as the longer antibiotic exposure period (>9 days), it is uncertain to know the reasons why the authors selected the aforementioned parameters to adjust their data. In our limited knowledge, at least two conventional key factors, such as gestational weeks and birth weight are reported to be a strongly independent risk factor associated with worse outcomes of newborns.[4,5] We are wondering to know why the authors did not include two factors for adjusting their targeted item (antibiotics exposure) in their study. Although we do not know the results if the authors would like to re-analyze their data, we supposed that both (gestational weeks and birth weight) may be an important and independent risk factor associated with the development of NEC and BPD.

Because of continuously decreasing birth rate in Taiwan from 1.218 per woman in 2019 to 1.07 per woman in 2021, resulting in a negative balance of population, any newborn should be considered a "hope" and an "angel".[6] However, these newborns may be complicated by premature preterm labor, which has been dramatically increased in recent years.[7] The challenge is not only exacerbated by shortage of obstetricians and pediatricians, but also associated with a dramatically increasing heavy economic and social burden.[6] To achieve this goal, we are looking forward to seeing the authors' kind response.

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