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EDITORIAL

When more can lose more: Comments to the long-term use of prophylactic antibiotics for very low birth weight infant resulting in the adverse outcomes

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The population of size in Taiwan has been continuously decreased in the recent years, resulting in an absolutely negative balance of population in 2021.[1] Although many causes contributing to the decreased population size have been reported in Taiwan, one definite cause is the result of death rate exceeding birth rate.[1] Therefore, the policy to encourage couples to get pregnancy and subsequently offering a better care for maternal-fetal wellbeing before, during, and after pregnancy is of paramount importance.[2–6] Many efforts have been conducted, but the morbidity and mortality of women during pregnancy and perinatal morbidity and mortality are still high in Taiwan.[1] Among these, premature preterm birth (PPB) has been one of the critical causes resulting in the high morbidity and mortality of both mothers and infants. Additionally, PPB has been increased in recent years dramatically, and it becomes a biggest challenge not only for obstetricians but also pediatricians.[7–9] An early identification of risk factors associated with PPB and an offering the prompt and effective treatment may decrease the PPB-related morbidity and mortality.[10] However, none of them can totally avoid the incidence and prevalence of PPB and the outcomes of very low–birth weight (VLBW) newborns are still disappointing based on their immature organogenesis and physiological malfunction, even though advances of current medical care have improved the survival of these infants.[11] These VLBW infants are vulnerable to insults-related injuries either from internal or external sources.[11] Attacks by microorganisms may be one of the most common etiologies compromising the wellbeing of these PPB infants, contributing to a main cause of infant morbidity and mortality in modern medicine. This catastrophic event is particularly apparent in the VLBW preterm infant population.[12]

A recent publication from the *Journal of the Chinese Medical Association* entitled "Increased antibiotics exposure in early life is associated with adverse outcomes in very low birth weight infants" has focused on the worse outcomes about the use of antibiotics in these VLBW infants.[13] The authors found that increased antibiotic exposure to the VLBW infants was associated with increased risks of necrotizing enterocolitis (NEC) and bronchopulmonary dysplasia (BPD), and the longer duration of antibiotics exposure further augmented the existed risk of NEC and BPD with adjusted odds ratio (aOR) of 1.278 and 1.630, respectively, in antibiotic exposure per day.[13] Although their findings may be informative, some uncertainties are worthy of further discussion, since it may significantly influence our decision in the management of VLBW infants in the future.

First, it should clarify the indications or needs of using antibiotics for these VLBW infants. Since Dr. Chen's study focused on the management of early-onset sepsis (EOS within 3 days from birth) in VLBW infants, the information about the indication of using antibiotics should be offered and further analyzed.[13] EOS pathogenesis predominantly involves colonization and invasion of the fetus or newborn by maternal genitourinary flora, which is typically presented as a vertically transmitted infection from mother to neonate (in utero, intrapartum, and postpartum),[12,14,15] and therefore, rupture of membrane and vaginal delivery may be a risk associated with EOS.[15] As expected, *Escherichia coli* (*E. coli*) is the most common pathogen associated with EOS in PPB infants and also a leading cause of morbidity and mortality in these PPB infants.[12] VLBW infants are also vulnerable to bacterial infection based on their internal and external potential risks, including immature immune defense systems, need for prolonged hospitalizations, delays in enteral feeding, requirements for invasive monitoring, testing, and treatments, which bypass or destroy the normal skin or respiratory barrier defense systems,[14] contributing to the rationale or assumptions of routinely application of antibiotics to these VLBW infants (predictable and manageable in risk associated with antibiotic use and significant benefits even for those without known organisms or antibiotic susceptibility data).[15] In the literature review, most studies showed more than 75% of VLBW infants will be treated with antibiotics for the risk of EOS.[13] Based on Dr. Chen's study

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showing the day of antibiotic exposure was ranged from 0 to 14 days, and the median number of days of antibiotic exposure was 8, it is believed that majority of VLBW infants in Dr. Chen's study were treated with antibiotics, and additionally, the antibiotic use was based on for "rule-out sepsis" targeting not only EOS, but also late-onset sepsis (LOS, infection occurring >72 hours of age).

Second, based on the literature review, culture-confirmed EOS occurs only in near 1% of VLBW infants, but in 20% of extremely low birth weight (ELBW) infants, resulting in the need of antibiotic use based on the above-mentioned assumptions, such as life-saving for infected infants.[15] However, Dr. Chen's study had already excluded the culture-proven sepsis.[13] Additionally, the strategy for the management of these PPB has followed the recent guideline recommendations, such as the choice of cesarean section (CS) without labor and with rupture of membrane at delivery.[15] In fact, the majority of VLBW infants (88%) were delivered by cesarean section and only a few newborns (20%) had rupture of membrane >24 hours in Dr. Chen's study.[13] All suggest that the enrolled subjects (VLBW infants) in Dr. Chen's study belonging to the "low-risk" of EOS may be not a good candidate for long-term use of antibiotics. Therefore, it is rationale to suppose that the indications of using antibiotics for these low-risk VLBW infants in Dr. Chen's study were prophylactic. If this assumption is real, the following questions are worthy of further discussion.

We are uncertain why two different types of antibiotics for those low-risk VLBW infants were applied in Dr. Chen's study if antibiotic use is prophylactic. The authors have explained their choice of treatment, which was dependent on the clinical presentations, such as the teicoplanin and meropenem regimen for ill-appearing infants and ampicillin and cefotaxime for infants with EOS.[13] We understand that it is not easy to distinguish clinical symptoms or signs from prematurity to neonatal sepsis,[12] contributing to dilemma to decide whether the prophylactic empiric antibiotics should be administered or which regimen should be provided with sympathy, but we are still wondering to know whether the guideline addressing the therapeutic plan for those VLBW preterm infants was available or not in their institute. Did nearly all VLBW infants have received antibiotic treatments in routine? In fact, there are many consensuses available in the societies or experts' comments to recommend the prophylactic use of antibiotics for these VLBW infants, including a traditional 48 and 72 hours' "rule out" period or a new recommendation of 36 hours of incubation to discontinue antibiotic.[15]

Finally, we should recognize that Dr. Chen's study provides very useful information to us that the potential risk of overtreatment by antibiotics for those low-risk VLBW infants is really present in our daily clinical routine practice, although it is retrospective in nature. There is no doubt that antibiotic use is associated with a cumulative risk that is neither entirely predictable nor immediately manageable, Dr. Mukhopadhyay said.[15] We indeed appreciate Dr. Chen's effort to provide their experience to remind us that overtreatment may not always get the better outcome, and by contrast, it may be associated with an increased risk of unwanted immediate and delayed adverse events, similar to our comments about the treatment for many troublesome diseases.[16,17] To do more may not be ended by getting more and "to do one" may not have a result of "to get more,"[18] since all treatments should be based on evidence and by contrast, we should abandon the therapy based on only "tradition" or "routine" or "assumption" reasons.[19]

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