methods such as the propensity score, considering variables available at the decision time to initiate or not early antibiotic treatment.

The authors state that a clinical trial using early and short antibiotic treatment to prevent NEC could be considered. We want to emphasize that other studies found an increased risk of NEC, but also late-onset sepsis and death associated with early antibiotic use,[2,3] and that antibiotic treatment has short- and long-term consequences,[4,5] as mentioned by the authors. Thus, additional evidence and caution are required before concluding causality for the association between early antibiotic exposure and reduced rate of NEC.

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Reply

To the Editor:

We agree with Letouchzey et al that no one should jump to the conclusion that a short course of antibiotics after birth in infants with very low birth weight will be protective against necrotizing enterocolitis (NEC). We also agree that fetal growth restriction (FGR) is likely to increase the risk of NEC and lead to physician-induced delivery via cesarean and abstaining from prescribing antibiotics to the infant right after birth. This is why we took care in the attempts to adjust for size for age at birth. We agree that FGR is different from small for gestational age. We may, however, wish to discuss the likely significance of that difference in terms of risk of bias. Most often the diagnosis of FGR is made by antenatal ultrasound shortly before delivery and therefore correlates well with birth weight for gestational age (or small for gestational age status), although, conceptually, it should be diagnosed by monitoring of fetal growth.[1] Unfortunately, body proportions at birth ("asymmetric growth restriction") do not correlate well with growth velocity in the months before birth.[2] Therefore, we think it is unlikely that the use of the clinical diagnoses of FGR in 13 hospitals across the world could substantially change our results, but we do not have data to test it.

Other maternal factors may contribute to a physician-induced preterm delivery, such as maternal hypertension and preeclampsia. However, a high-quality case–control study failed to demonstrate a strong association between NEC and any of a long list of maternal and pregnancy complications.[3]

Propensity scores appear to be better than logistic regression when the number of events is low.[4] Our dataset, however, was relatively large, so we doubt that another statistical analysis would have yielded a substantially different result.

We agree that more studies are needed. We need to be restrictive with prophylactic antibiotics. In contrast, infants with very low birth weight constitute a high-risk group of patients, and they need the best of care. We hope that our report will encourage precisely predefined analyses of other infant datasets to confirm or refute the present associations. Together with mechanistic, experimental studies this could provide a better basis for rational use of antibiotics in newborns with low birth weight.

Finally, the ongoing efforts in antibiotic stewardship will likely increase the number of infants with very low birth weight

who are not given "pre-emptive" antibiotics after birth. The association between early empiric antibiotic treatment and lower incidence of NEC has now been reported in several studies.[5-7] Randomized trials of the effects and consequences of antibiotics are likely to be planned.[8] It would be relevant to consider design and power to address the effect on NEC.

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Risk of bias in study on early antibiotics and necrotizing enterocolitis

To the Editor:

Li et al present data on the association between antibiotic use and necrotizing enterocolitis (NEC) in 2831 very low birth weight (VLBW) infants from 13 neonatal intensive care units (NICU) in 5 continents.[1] Their main result is that early administration of antibiotics is associated with less NEC compared with no early exposure to antibiotics. These results are in line with some studies[2,3] but challenge the concept that early antibiotic exposure disturbs the intestinal microbiota and increases the subsequent risk for NEC in preterm infants.[4,5]

This report is based on a secondary analysis from a retrospective-prospective observational cohort study primarily assessing feeding practices and short-term clinical outcomes.[6] Entry of patient data started in September 2013 with the aim of enrolling "at least 100 VLBW infants born consecutively" from each NICU between January 2011 and September 2014. Other than "consecutive enrollment," there is no information on whether the included infants are representative of all VLBW infants in the participating NICUs, and no data on overall eligible number of infants. This introduces a risk for selection bias, exemplified by the fact that large NICUs in Perth and Amsterdam contributed only 152 and 174 infants, respectively. Moreover, the long time to full feeds, predominantly with formula, and the massive antibiotic exposure among 1366 infants in the 5 Chinese NICUs was "apparently" not associated with more NEC or higher mortality, but the authors speculated about differences in Bell scoring.[6] Only 8 (0.6%) of the included infants from China had undergone surgery for NEC. The overall rates of NEC and survival for VLBW infants admitted to all these NICUs were not presented. The no-early antibiotic group had a mean gestational age of 31 weeks and the NEC incidence of 9% in this population was surprisingly high.

The results from this mainly retrospective study may be true, but a high risk of selection bias questions its validity.

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