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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References

1. Petersen S, Larsen T, Greisen G. Judging fetal growth from body proportions at birth. Early Hum Dev 1992;30:139-46.
2. Larsen T, Petersen S, Greisen G, Larsen JF. Normal fetal growth evaluated by longitudinal ultrasound examinations. Early Hum Dev 1990;24:37-45.
3. March MI, Gupta M, Modest AM, Wu L, Hacker MR, Martin CR, et al. Maternal risk factors for neonatal necrotizing enterocolitis. J Matern Fetal Neonatal Med 2015;28:1285-90.
4. Cepeda MS, Boston R, Farrar JT, Strom BL. Comparison of logistic regression versus propensity score when the number of events is low and there are multiple confounders. Am J Epidemiol 2003;158:280-7.
5. Krediet TG, van Lelyveld N, Vijlbrief DC, Brouwers HAA, Kramer WLM, Fleer A, et al. Microbiological factors associated with neonatal necrotizing enterocolitis: protective effect of early antibiotic treatment. Acta Paediatr 2003;92:1180-2.
6. Berkhout DJC, Klaassen P, Niemarkt HJ, De Boode WP, Cossey V, Van Goudoever JB, et al. Risk factors for necrotizing enterocolitis: a prospective multicenter case-control study. Neonatology 2018;114:277-84.
7. Ting JY, Roberts A, Sherlock R, Ojah C, Cieslak Z, Dunn M, et al. Duration of initial empirical antibiotic therapy and outcomes in very low birth weight infants. Pediatrics 2019;143.
8. Ruoss JL, Bazacliu C, Russell JT, de la Cruz D, Li N, Gurka MJ, et al. Routine Early Antibiotic use in SymptOmatic preterm Neonates (REASON): a prospective randomized controlled trial. MedRxiv 2020.

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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References

1. Li Y, Shen RL, Ayede AI, Berrington J, Bloomfield FH, Busari OO, et al. Early use of antibiotics is associated with a lower incidence of necrotizing enterocolitis in preterm, very low birth weight infants: Neomune-NeoNutriNet Cohort Study. J Pediatr 2020.
2. Berkhout DJC, Klaassen P, Niemarkt HJ, De Boode WP, Cossey V, Van Goudoever JB, et al. Risk factors for necrotizing enterocolitis: a prospective multicenter case-control study. Neonatology 2018;114:277-84.
3. Ting JY, Roberts A, Sherlock R, Ojah C, Cieslak Z, Dunn M, et al. Duration of initial empirical antibiotic therapy and outcomes in very low birth weight infants. Pediatrics 2019;143:e20182286.
4. Cotten CM, Taylor S, Stoll B, Goldberg RN, Hansen NI, Sánchez PJ, et al. Prolonged duration of initial empirical antibiotic treatment is associated

with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants. Pediatrics 2009;123:58-66.
5. Esaiassen E, Fjalstad JW, Juvet LK, van den Anker JN, Klingenberg C. Antibiotic exposure in neonates and early adverse outcomes: a systematic review and meta-analysis. J Antimicrob Chemother 2017;72:1858-70.
6. de Waard M, Li Y, Zhu Y, Ayede AI, Berrington J, Bloomfield FH, et al. Time to full enteral feeding for very low-birth-weight infants varies markedly among hospitals worldwide but may not be associated with incidence of necrotizing enterocolitis: the NEOMUNE-NeoNutriNet cohort study. JPEN J Parenter Enteral Nutr 2019;43:658-67.

Reply

To the Editor:

We agree with Dr Klingenberg that our study is open to potential bias due to missing data. We appreciate the chance to discuss this further.

The infants contributed from the 13 NICUs represent a variable proportion of the total number of admissions during the 3.5-year study period from each NICU. Nonetheless, they were included consecutively in one or several shorter periods. Because we were unable to obtain information on the number and basic characteristics of the missing infants within these periods, we refrained from analyzing or reporting this. Therefore, we acknowledge that some infants are missing in the dataset. The study was carried out by medical file review without central funding. The data extraction and goals for enrollment were developed prospectively. Part of the enrollment was done retrospectively, and we were not able to search long for missing files. However, the missing infants are unlikely to be missing at random; they are more likely to represent infants who were admitted for a shorter time, were transferred to other departments or hospitals, or were the subjects of people reviewing files—for example, infants who died early or who were transferred for surgery for necrotizing enterocolitis (NEC) elsewhere. For this to lead to systematic bias to occur (regardless of cause), it would have had to be associated with the administration (or recording) of early antibiotics as well as with NEC. We cannot posit good reasons why this should occur very often or in a biased fashion. Our data came from infants who were admitted to the NICU. Infants with birth weight >1500 g, considered too healthy for intensive care, and considered too immature for life support are not represented. Both groups likely did not receive antibiotics and did not get NEC.

We were also surprised by the 9% risk of NEC in the relatively mature group of infants who were admitted to the NICU and did not receive early antibiotics. However, this number is the value that we have the least reason to doubt. Although NEC is not always a purely objective diagnosis, it is unlikely that the diagnosis was biased by a lack of early antibiotic use.

We are concerned with the overuse of antibiotics, so the motivation for the study was to look for clinically relevant complications to help clinicians. This was an unexpected finding–although we realize that others had data pointing in the same direction.

Finally, we want to emphasize that we do not believe that this question has been answered definitely. Rather, the question has been (re)opened, and many neonatal network datasets exist that can be used to test it again. We hope these data will become available. Furthermore, we hope that our results will motivate a search for potential mechanisms of preventing NEC. NEC remains a significant problem in neonatology and even appears to be increasing in extremely preterm infants in our own country.[1]

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Reference

1. Juhl SM, Gregersen R, Lange T, Greisen G. Incidence and risk of necrotizing enterocolitis in Denmark from 1994-2014. PLoS One 2019;14:e0219268.