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Reply

To the Editor:

We read with interest the well-founded observation made by Yung et al regarding no change in epidemiology or cases of Kawasaki disease in Singapore amid the current ongoing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. When it was initially recognized, there was uncertainty whether the SARS-CoV-2 associated multisystem inflammatory syndrome in children (MIS-C) represented Kawasaki disease. Evidence and evolving understanding suggest it to be a separate clinical entity.

A recent large multicenter case series from the US and Europe show that 22%-40% of MIS-C cases met either complete or incomplete Kawasaki disease criteria and were either classified as Kawasaki disease or Kawasaki disease shock syndrome.[1-3] The diagnostic criteria for Kawasaki disease and MIS-C are broad because both Kawasaki disease and MIS-C are inflammation-associated syndromes, and there is overlap.

Accumulating literature highlights the similarities and differences between MIS-C and Kawasaki disease.[4] Although a case definition for MIS-C was released by the US Centers for Disease Control and Prevention, vastly differing treatment modalities ranging from supportive care to immunomodulating agents and plasma infusion have been implemented with a lack of consensus on how to best treat this condition. Reassuringly, MIS-C thus far has been associated with low mortality.

Our study was designed to include critically ill children and adolescents who met criteria for SARS-CoV-2 associated MIS-C. Some patients in our series also may have met Kawasaki disease criteria. Whether "overlap" patients have Kawasaki disease, atypical Kawasaki disease, Kawasaki disease with macrophage activation syndrome, or represent a spectrum of MIS-C requires ongoing surveillance and longer term follow-up.

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Association of early antibiotic exposure and necrotizing enterocolitis: causality or confounding bias?

To the Editor:

We read with great interest the report by Li et al that compared the incidence of necrotizing enterocolitis (NEC) in infants with very low birth weight according to early antibiotic treatment.[1] We would like to raise the question: association of early antibiotic exposure and NEC: causality or confounding bias?

Antibiotic use was different from one neonatal intensive care unit to another, resulting in a small and highly selected nonexposed group. Indeed, the 2 groups displayed different baseline characteristics (gestational age, proportions of small for gestational age, and cesarean delivery), which suggest that the causes of preterm birth (not analyzed and potentially a confounding factor, ie, a pre-exposure covariate independently associated with both the exposure and the outcome) differ between the groups. Moreover, small for gestational age status is not equal to fetal growth restriction. Although a crude positive association between no early antibiotics and NEC was found, adjusting for relevant confounders such as fetal growth restriction or causes of preterm birth may decrease the OR and support the concept of confounding by indication. We suggest that indication bias would have been handled better using appropriate statistical

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