et al found that IVMg was not an effective treatment in children with acute episodic viral wheezing and also did not result in a reduction of hospital admission.[2] This inequality may be explained by different pathophysiology between acute episodic viral wheezing and acute asthma. Endobronchial biopsies showed, for example, that the thickening of the epithelial reticular basement membrane and the eosinophilic inflammation characteristics was present in children and adults with acute asthma, but not seen in symptomatic infants with reversible airflow obstruction.[7] It would be interesting to know if differences in IVMg use were also observed in the study of Johnson and if so, were due to lower expectations of efficacy in the younger age group.

We agree that a large randomized controlled trial is necessary to determine the efficacy and safety of early IVMg administration thereby taking into account these 2 age groups. Because administration of IVMg is used as treatment in children with asthma exacerbations, the need for intravenous salbutamol administration and transfer to a pediatric intensive care unit may also be included as outcome measures.

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Reply

To the Editor:

As van Weelden et al recognize, there is ongoing debate and investigation to understand how best to treat children with wheezing, and whether young children with wheezing benefit from the same asthma treatment as older children. Although we did not subdivide our published analysis by age, analyzing children 2-5 years separately from those older than 5 years, our unpublished data include 7737 visits for asthma treatment in children younger than 2 years of age. In 407 of these visits, children received IVMg, and the use of IVMg varied by site, similar to the published dataset. Variation in use of IVMg in children under 2 years of age and in children 2-17 years of age would suggest similar variability is expected in children 2-5 years of age. We agree that only in a prospective clinical trial can we expect to learn whether intravenous magnesium is effective in these children.

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Neonatal antibiotics and infantile colic in term-born infants

To the Editor:

Salvatore et al[1] assessed the prevalence of functional gastrointestinal disorders (FGIDs) in the first year of life and the influence of different neonatal factors on the development of FGIDs. In 42% of term-born infants, infantile colic was diagnosed by the Rome III criteria through standardized interviews at 1, 3, 6, and 12 months. A high percentage of full-term infants received antibiotics at birth (22%), although severe acute infection was an exclusion criterion for the study. An important finding was that antibiotic use in the first week of life was associated with an increased risk of infantile colic in (pre)term-born infants (aRR, 1.24; 95% CI, 1.06-1.45). Unfortunately, no data on the duration of antibiotic exposure were available.

The authors state that this was the first study to find an association between neonatal antibiotics and infantile colic in newborn infants. However, in 2018, we published our findings of the INCA study,[2] in which we prospectively followed 151 term-born infants exposed to antibiotics at birth and 285 controls by daily questionnaires throughout the first year of life for clinical symptoms, including crying for >3 hours/day. We found a lower incidence of parent-reported infantile colic in the whole cohort (74 of 436; 17.0%), but with an aOR of 1.66 (95% CI, 1.00-2.77) for infantile colic after exposure to neonatal antibiotics. Only antibiotic exposure for 7 days, and not exposure for 2 days, was significantly associated with increased risk of infantile colic.

Currently, we are analyzing the fecal microbiome to further elucidate the association between neonatal antibiotics and infantile colic, along with conducting follow-up studies at 4-6 years to evaluate whether neonatal antibiotics are associated with FGIDs later in life. We agree with Salvatore et al regarding the need for careful consideration of antibiotic use at birth and that early cessation, if possible, may limit the occurrence of infantile colic in term-born infants.

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Reply

To the Editor:

We thank van Elburg et al for their interest and comment on our report. The authors pointed out that the INCA study reported an increased risk of infantile colic in term infants treated with a 7-day course of antibiotics compared with infants treated for a 2-days course and to healthy controls. We acknowledged that at the time of writing our article that we could not retrieve their paper from Medline search.[1] Moreover, we stated that our study was the first to assess the effect of both neonatal antibiotics and preterm delivery on all functional gastrointestinal disorders (FGIDs). We could not fully analyze the determinant duration of antibiotic treatment that seems critical in the INCA study to the development of colic. Unfortunately, these data were not recorded in all of our participating centers, although in most neonates broad spectrum antibiotics were administered for <7 days for prolonged rupture of membranes or suspected chorioamnionitis (maternal fever >38°C or leukocytosis >10 000/mmc, foul-smelling amniotic fluid) or for preventing neonatal group B streptococcal infection.

Different from previous studies, in our report one-third of participants were preterm babies, who seemed to be a significantly vulnerable population for FGIDs and particularly for infantile colic. We could limit the drop-out rate throughout all the follow-up period below the threshold of 20% (lower than in INCA study) that is considered critical for a reliable result. We agree with the authors that fecal microbiome analysis and well-designed long-term follow-up in large population of both preterm and term infants are needed to confirm the association between neonatal antibiotics and FGIDs. We also noticed that, in INCA study, there was a striking discrepancy between parental and clinician rate of colic in the antibiotic treated group, with ≤21.9% of parental-based report vs only 4% of cases (6 infants) diagnosed by a doctor. One possible hypothesis could be that excessive crying reported in some infants could have been related to cow's milk allergy, because eczema was identified in 11.9% and allergic sensitization was documented in 16.9% of their population treated with antibiotics. Thus, the interconnection between neonatal antibiotics, microbiota, allergy, and FGIDs still need to be further elucidated to identify all risk factors and to provide a tailored approach for all term and preterm infants.

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