Commentary: Paracetamol and asthma—lessons from the antibiotic hypothesis?

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The epidemic rise in asthma and atopic disease in the West is likely to have occurred, broadly speaking, for two reasons: either because we have lost protective exposures from our environment and lifestyle or because harmful exposures have increased.

Specific hypotheses related to both scenarios have been generated and tested by epidemiologists in recent decades. On the one hand, the ‘hygiene’ and ‘antioxidant’ hypotheses proposed that reduced exposure to microbes and falling intake of dietary antioxidants have been responsible; the jury is still out on both. On the other hand, the ‘antibiotic’ and ‘paracetamol’ hypotheses suggested that increased use of these drugs may have been to blame, by altering gut flora and oxidant/antioxidant balance, respectively. So how likely is it that asthma is an iatrogenic illness?
Systematic reviews and meta-analyses have summarized the evidence from observational studies linking infant antibiotic exposure to childhood asthma and paracetamol exposure across the life course to childhood and adult asthma. While on the face of it, the results of these meta-analyses might appear to have strengthened the evidence base, it should be remembered that, if the component studies are biased or confounded, then the pooled effect estimate will be too, albeit with tighter confidence intervals. Thus, such summaries may not have brought us closer to the ‘truth’ regarding causality. The weakest evidence regarding effects of antibiotic and paracetamol exposure in infancy on asthma in children comes from cross-sectional studies that have asked parents to report the use of these drugs in their infants some years later. In this issue of the IJE, Rusconi et al. report on associations between early paracetamol and antibiotic exposure and subsequent wheezing in the Italian arm of the International Study of Asthma and Allergies in Childhood. The main finding was that use of paracetamol and antibiotics in infancy was associated with wheezing in the first 2 years of life and wheezing that persisted to 6–7 years of age, but not with wheezing that began after 2 years of age. A limitation of this study is that information on the exposures of interest, and on infant wheeze illnesses (needed to define wheezing phenotypes), was based on retrospective parental recall 5 years later, which could potentially be unreliable and biased.

In contrast, prospective studies have not generally confirmed an association between infant antibiotic exposure and childhood asthma, and a more recent birth cohort study suggested that any apparent link is likely to reflect confounding by indication, where the indication is respiratory infections in early life. In other words, children who are already wheezing in infancy (and whose wheezing may persist) are more likely than non-wheezers to be given antibiotics to treat associated respiratory infections, even though these will usually be viral in origin. Some infants may even be given antibiotics for wheezing symptoms in the absence of infection. Despite the limitations of the cross-sectional design, and the absence of data on infections, Rusconi et al. reach similar conclusions regarding the associations between early paracetamol and antibiotic exposure and specific wheezing phenotypes. Indeed, their findings echo our recent observations in the Avon Longitudinal Study of Parents and Children (ALSPAC). In this prospective UK birth cohort, we found that the association between infant paracetamol use and childhood asthma was only seen in individuals who had wheezed in infancy. This also suggests confounding by indication, whereby paracetamol may have been used to treat febrile respiratory infections associated with early wheezing that subsequently persisted. This interpretation is supported by another birth cohort study involving children with a family history of atopy. After controlling for documented early respiratory infections, or restricting the analyses to paracetamol use for non-respiratory indications, no association was seen between early paracetamol use and later asthma.

What should we conclude from the epidemiological evidence to date, and where should we go from here? Regarding infant antibiotic exposure, it seems probable that confounding by indication explains associations with childhood asthma. This also seems the most likely explanation for apparent links between infant paracetamol use and asthma, although the possibility that paracetamol might promote persistence of wheezing, perhaps in synergy with early viral infection, cannot be ruled out. We should also perhaps not ignore clues which suggest that paracetamol exposure in infancy might affect the developing immune system. We have previously suggested plausible mechanisms by which paracetamol might, through glutathione depletion, promote Th2 responses, and we and others recently observed that infant paracetamol use is also associated with later atopy. Furthermore, a recent randomized controlled trial found that prophylactic use of paracetamol peri-vaccination was associated with impaired vaccine responses. However, I agree with others that a trial to determine if infant paracetamol exposure increases the risk of asthma and atopy would be logistically difficult, and perhaps hard to justify based on epidemiological evidence to date. In contrast, the association between prenatal paracetamol exposure and childhood asthma, replicated in a number of birth cohort studies, is less likely to be confounded by indication. Recently, causal inference was strengthened by our observation in ALSPAC that this association was modified by maternal antioxidant gene polymorphisms, whereas interactions between child gene variants and infant exposure on childhood asthma were not seen. There would, therefore, seem to be a stronger case for a primary prevention trial to be undertaken in pregnancy than in infancy, although such a study would still be ambitious and challenging, given that paracetamol is the analgesic of choice for pregnant women. Complementary prenatal interventions in animal models could also be informative.

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References


