

Clinical & Experimental Allergy

Antibiotics and risk of asthma: a debate that is set to continue

This editorial discusses the findings of the paper in this issue by J. Metsala et al. [14], pp. 137–145.

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Despite the epidemic in allergic disease in developed countries over the last several decades, explanations for the rise remain elusive. Intense interest in the role of antibiotics in the development of childhood allergic disease has been sustained because of the increasing biological plausibility for the association, the ongoing lack of conclusive evidence and because of the emergence of widespread antibiotic resistance that calls for curtailing their inappropriate use.

The initial suggestion of a role for antibiotics in the aetiology of asthma was based on ecological and retrospective data demonstrating that the epidemic of asthma paralleled the increase in antibiotic use. Subsequently, the link between antibiotics and asthma was supported by three potential biological mechanisms. Firstly, antibiotics modify the course of infection, by reducing the severity and length of infections and may lead the immune system towards an allergic pathway. Secondly, experimental studies have shown antibiotics themselves to induce a Th2-skewed response, which may act as a step in the aetiology of allergies [1]. Furthermore, animal studies have shown that perinatal antibiotic exposure impacts on the gut microbiome and increases the susceptibility to the Th2 model of allergic asthma [2]. Despite these biologically plausible casual links between antibiotic use and asthma, the current

epidemiological evidence on this potential association is contradictory and controversial.

The initial epidemiological findings on the link between exposure to antibiotics and increased risk of asthma were consistent and arose from cross-sectional studies in which parents recalled the *in utero* and early-life antibiotic exposure for their infants and subsequent development of asthma symptoms [3]. However, the findings of subsequent longitudinal studies that used prospectively collected data have produced conflicting results [4–7]. Some have reported a strong dose–response relationship between the number of courses of antibiotics and increased risk of asthma, providing an argument for causality [8]. However, systematic reviews [9, 10] conducted to date have concluded there is insufficient evidence to support the impact of exposure to antibiotics and asthma and allergy risk because most of the studies have not been able to tease out inherent alternative explanations of this association. Three alternative explanations have been put forward for the observed associations between antibiotic use and asthma and allergies—all relating to study design flaws. These include recall bias, reverse causation and confounding by indication.

Inconsistency in the findings between cross-sectional and longitudinal studies can be partially explained by the recall bias where parents' recall of prior antibiotic use is worse in parents of non-asthmatic children compared to asthmatic children. Such differences can create a spurious association in cross-sectional studies and highlight the importance of using prospectively collected data to investigate the antibiotic and asthma link.

Reverse causation may occur if children who have early-onset symptoms of asthma have these symptoms treated with antibiotics. Given the diagnostic uncertainty in the nature of wheeze in young children, this is

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a plausible explanation. Reverse causation is further supported by asthma being associated with propensity for subsequent infections [11], which in turn will be treated with antibiotics. Prospective studies, including our work, have shown that frequent use of antibiotics is associated with increased risk of childhood asthma, but this association is attenuated when children with a diagnosis or symptoms of asthma within the first 2 years of life are excluded [5, 12]. These findings highlight that reverse causation can exaggerate the strength of the antibiotic/asthma association. However, some have shown the association to be present even after adjusting for reverse causation by either adjusting for early-life wheeze or excluding those children with wheeze prior to the administration of antibiotics [6].

Confounding by indication is the final explanation for an association between early-life antibiotic exposure and asthma. Antibiotics are most commonly given to infants for respiratory infections. Respiratory tract infections, particularly those caused by rhinovirus and RSV, are very strongly associated with increased risk of childhood asthma [13]. These infections may be the true reason for the subsequent increase in the risk of asthma rather than the antibiotics that are used to treat them. This alternative explanation for the antibiotic/asthma association has been the hardest to refute as only a few studies have information on the type of antibiotics used and reasons for using antibiotics [6, 7]. This is the debate to which the newly published study by Meltsala et al. [14] has been able to contribute with the detailed information on the type of antibiotics used by the participants.

Meltsala et al. [14] conducted a nested-matched case-control study using linked data of Finnish population-based registries with the aim of investigating the impact of both prenatal and post-natal exposure to antibiotics on early-childhood asthma. To avoid potential reverse causation, children who were diagnosed with asthma before the age of 3 years were excluded from the study. Both prenatal and post-natal antibiotics were grouped into specific antibiotics and categorised as overall use of most common specific antibiotics. To investigate confounding by indication mothers/children were categorised into groups of: 'only antibiotics for gram-positive bacterial infections' (included those who had used only antibiotics commonly used to treat respiratory infections); 'only antibiotics for urinary tract infections' (included those who had used only antibiotics commonly used to treat urinary tract and other infections) and; 'both antibiotics for gram-positive bacteria and urinary tract infections' (included those who had used antibiotics for both indications). The study showed that the increased risk of asthma related to early-life exposure to only antibiotics for gram-positive infections was similar to early-life exposure to only

antibiotics for urinary tract infections. However, the evidence on the latter was modest, which is probably related to the power. These findings support the antibiotic asthma link as the association between early-childhood exposure to antibiotics used only to treat urinary tract infections and asthma and should not be subject to confounding by indication. No association was seen between prenatal antibiotic use for urinary tract infections and childhood asthma. Interestingly, the risk estimates were highest when both types of antibiotics have been used. This may be related to either frequency of exposure or a wider range of antibiotics having a higher impact, which has not been teased out in the study. It should be noted that a registry-based study in a younger age group [4-7] analysed antibiotics data in a similar manner to the current study but did not find a link between antibiotics used only to treat urinary tract infections and asthma. Given identifying asthma in children under the age of 5 years is challenging and misclassification of asthma can bias the results towards null, the difference in the age at outcome assessment between the studies may have contributed to the discrepant results. On the other hand, findings by Meltsala et al. are not conclusive because they were not able to fully control for confounding by indication as the study did not have information on the exact indication for use of antibiotics.

As evidence mounts concerning antibiotics and their potential role in allergy promotion through disturbance of the gut microbiome and subsequent impairment of immune programming in young children, there is increasing interest in the potential role of pre- and probiotics for treatment and prevention of allergic diseases. While antibiotics are known to reduce the stimulation of the immune system by altering the natural course of infections and to disturb the normal microflora of the intestine, pre/probiotics are hypothesised to stimulate gut microbial environment and thought to protect against allergic diseases. However, the results of clinical trials to date have not been as promising as expected [15, 16].

In summary, while suggestive, the findings to date do not provide evidence for a causal link between antibiotic exposure (or use of pre/probiotics) and asthma and allergies. While the discovery and use of antibiotics was a major breakthrough in medicine, the use of unnecessary antibiotics and non-compliance with the prescribed antibiotic doses and regime leads to antibiotic resistance, which is now identified by World Health Organization as a major threat to human health. Therefore, clinicians should continue to adhere to the current guidelines concerning appropriate antibiotic prescribing and educate patients about the importance of adhering to the prescribed regime. The link between antibiotics and asthma and allergies requires further investigation either to confirm or refute. If this link is

established, including understanding which specific classes of antibiotics are implicated, it provides a plausible mechanism concerning the aetiology of asthma and the allergy epidemic and will inform clinical guidelines on prescription of antibiotics. To date, researchers have either analysed the existing data within longitudinal studies or used registry-based data. Both these approaches suffer from a lack of comprehensive information with which to tease out

confounding by indication. As it is not feasible to conduct randomised controlled trials, population-based longitudinal studies that have been specifically designed to answer this particular question are needed to resolve this debate.

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