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>> Hi! This is Aaron Carroll, and I'm the digital media editor for JAMA Pediatrics. In this podcast, I talk about interesting articles featured in the Journal and what they might mean to you. This week I'm focusing on acid-suppressive medications and antibiotics during infancy are associated with allergic diseases in early childhood by Edward Mitre and colleagues.

For the past several decades the prevalence of both allergies and atopic diseases have been on the rise. Food allergies, especially, have been getting more and more common. Why? There are any number of theories. Relatively new one has to do with the microbiome. What's the microbiome? It refers to the very tiny bacteria, fungi, and archaea that live in us.

Although they're small individually, all together they're not! It's thought today that every person has as many independent microbial cells living in them as human cells. The microbiome, as it's collectively called, performs a number of useful functions. It can help with digestion, vitamin synthesis, and even immunological responses.

That's where allergies come in. It's possible that medications that affect the microbiome might affect whether or not we have allergies. Acid-suppressing medications and antibiotics are two classes of drugs that could conceivably affect the microbes that live in our gut in unpredictable ways. It's also possible that acid-suppression drugs might change the ways in which we respond to orally ingested antigens. At least that's what's been seen in some animal studies.

This study wanted to explore whether infants exposed to acid-suppressing medications or antibiotics in infancy were more likely to develop allergic diseases in childhood. The researchers used the TRICARE management activity MHS database, which contains data on healthcare utilization for U.S. uniformed service members and their dependents. A cohort was built of all kids born into the system between 2001 and 2013 and followed continuously for at least a year after that. Kids who developed an allergy in the first six months of life were excluded, as were kids who stayed in the hospital for longer than a week at birth. The main exposure of interest was being prescribed an H2 antagonist, a proton-pump inhibitor, or an antibiotic.

The main outcome of interest was a diagnosis of a food allergy, anaphylaxis, asthma, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, urticaria, contact dermatitis, medication allergy, or other allergy. Analyses were adjusted for prematurity, whether a child was born by C-section, gender, the other drug classes, and any significant first order interaction terms.

This was a big study. More than 790,000 children were in the cohort and more than 60,000, or 7.6%, received an H2 antagonist. Most than 13,000, 1.7%, received a PPI. And more than 131,000, about 16, 17%, received an antibiotic in the first six months of life.

Many kids got more than one of these, of course. Ranitidine was by far the most commonly prescribed H2 antagonist. Lansoprazole counted for about three-quarters of PPI prescriptions. For antibiotics, the most common classes were penicillins, about two-thirds; cephalosporins, 14%; and macrolides about 10%. All right, of the 792,000 kids, about 24,000 developed a food allergy. Peanut was the most common followed by cow's milk and egg. Much more common were allergic rhinitis and contact dermatitis and a host of atopic disorders.

All of the covariates showed a statistically significant association with allergic disease, which isn't totally surprising given the massive size of this cohort. Males, for instance, did more commonly than females at 59.5% versus 56.6%. Children prescribed antacids had an adjusted hazard ratio of more than two for food allergy and more than 1.4 for medication allergy, anaphylaxis, allergic rhinitis, and asthma. Children prescribed an antibiotic in the first six months of life had an adjusted hazard ratio of 2.09 for asthma, 1.75 for allergic rhinitis, 1.51 for anaphylaxis, and 1.42 for allergic conjunctivitis. All of these were statistically significant.

In terms of actual incidents, let's take food allergies, for instance, because the numbers are a bit smaller. Those with no drug exposure had an incidence of 73.7 cases per 100,000 person years. This rose to 101.3 for those prescribed an antibiotic, 118.8 for those prescribed an H2 antagonist, and 153 for those prescribed a PPI. Those are still pretty rare. The cohort is so big, though, that statistical significance is going to be achieved even with small differences.

These results are somewhat in line with prior research, which has shown that early prescriptions for antibiotics are associated with an odds ratio of about 1.5 for developing an allergy. I don't want to minimize the strengths of this study. It's a huge cohort, and the analysis was very well done. It does, however, have some limitations that certainly warrant consideration. Reverse causality could be one. Some of these drugs could have been prescribed because symptoms of allergies were mistreated with antacids or an antibiotic. There were also a limited number of covariates. It's possible that something else unmeasured is the real predictor here, and it's associated with both increased drug use and increased rates of allergies. It's also possible that there's not causality here at all. Maybe kids who got prescribed drugs for some reason are also more likely to get allergies. In that case, it's a predictor but not causal.

But here's the thing. Why are we prescribing antacids for kids less than six months of age? Studies have shown that the risk of harm from a PPI may be higher than the chance of a benefit for a kid with gastroesophageal reflux. We should be avoiding antibiotic use unless it's necessary. It's very likely that these drugs are being overused in the very young. If the tail of this study is that we should be even more thoughtful about using antacids or antibiotics in infants less than six months of age, then I'm totally onboard. But if for some reason your child needs to have one of these drugs for real illness, it's not time to panic. This shouldn't be taken

as evidence that you're consigning your child to a later allergy. The article is free this week, so please do go read it online at JAMANetwork.com/journals/JAMApediatrics.

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