BEYOND THE BLUE:

What Fellows Are Reading in Other Journals

Risk Factors Associated with Asthma Development and Control in Children

Mouse Infestation, Antipyretics, Respiratory Viruses, and Allergic Sensitization

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Recommended Reading from Vanderbilt University Pediatric Pulmonary Fellows; Andrew G. Sokolow, M.D., Paul E. Moore, M.D., Program Directors

Matsui EC, et al. Effect of an Integrated Pest Management Intervention on Asthma Symptoms among Mouse-sensitized Children and Adolescents with Asthma: A Randomized Clinical Trial. *JAMA* (1)

Reviewed by Mark Wurth

Mouse infestation is common in many low-income, urban environments in the United States (2). The Mouse Allergen and Asthma Intervention study was a randomized controlled trial (RCT) conducted by Matsui and colleagues evaluating the benefit of an intensive, professionally delivered, integrated pest management home intervention (IPM) with pest management education (PME) against PME alone in reducing asthma morbidity in children (1).

Three hundred and sixty-one children aged 5–17 years with persistent asthma and at least one exacerbation in the previous year, evidence of mouse sensitization, and evidence of mouse allergen exposure in the home (defined as presence of mouse allergen [Mus m 1] concentration ≥ 0.5 $\mu\text{g/g}$ in bedroom floor dust or ≥ 0.4 $\mu\text{g/g}$ of dust from bed) were recruited from two metropolitan areas in the United States. Participants were randomized 1:1 to one of the two treatment arms (IPM/PME vs. PME). For the IPM/PME group, a home reinfestation assessment was conducted every 3 months with repeat IPM treatment if indicated. The primary outcome was defined as the highest number of days with asthma symptoms in the prior 2 weeks among three different domains (number of days of slowed activity due to asthma; number of nights of waking up due to asthma; and number of days with cough, wheeze, or chest tightness),

and assessed across the 6-, 9-, and 12-month time points. Secondary outcomes included individual symptoms, rescue medication use, healthcare use, mouse allergen exposure, serum mouse-specific IgE, and spirometry measures.

The population was largely low income, minority, and sensitized to other common indoor allergens. Of the 361 randomized children, 334 were included in primary analyses (166 in the IPM/PME group and 168 in the PME group). There were no significant differences in the primary or secondary outcomes between the treatment arms. In exploratory analyses, substantial reductions in floor mouse allergen levels were seen across the study population (IPM/PME group: from 6.1 to 2.0 $\mu\text{g/g}$; PME group: from 6.6 to 2.5 $\mu\text{g/g}$), which correlated with reductions in frequency of asthma symptoms, short-acting β -agonist usage, and healthcare use for asthma in both treatment arms.

Despite the reductions in floor mouse allergen levels, only 47% of homes in the IPM/PME group and 40% of the homes in the PME group fell below 0.5 $\mu\text{g/g}$, a threshold previously reported to be clinically relevant (3). The PME group also had much greater decreases in floor mouse allergen levels than expected based on previous studies. For instance, whereas the decrease in floor mouse allergen level was $\sim 65\%$ in the study by Matsui and colleagues, it was only $\sim 27\%$ in another RCT using a more complex intervention (4). The latter raises the possibility of a Hawthorne effect, in which participants in the PME group may have been more agreeable to implementing the suggested practices because of the frequent interactions with the research team. In addition, the study by Matsui and colleagues is limited by the failure to address other exposures both inside and outside the home. Several other

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studies examining interventions against a single indoor allergen, such as house dust mites, have found a lack of an important clinical effect of such measures (5), but it is certainly possible that comprehensive, multifaceted interventions against multiple indoor allergens and other environmental exposures (such as tobacco smoke) could have a beneficial effect (6).

The study by Matsui and colleagues concludes that IPM/PME is not superior to PME alone in reducing floor mouse allergen levels and asthma morbidity in mouse-sensitized and -exposed children. However, in view of the results of the exploratory analyses, it reinforces the role of mouse allergen exposure as an important driver of certain outcomes in this population. Based on this, as well as on the many other detrimental health outcomes associated with mouse infestations, PME should be considered in all children (with and without asthma) with evidence of mouse sensitization and/or exposure. ■

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Sheehan WJ, *et al.*; NIH/NHLBI AsthmaNet. Acetaminophen versus Ibuprofen in Young Children with Mild Persistent Asthma. *N Engl J Med* (7)

Reviewed by Christina M. Papantonakis

Previous observational studies and a *post hoc* analysis of an RCT have shown an association between the use of acetaminophen and poor asthma control in both children and adults (8–10), which has led some healthcare providers to recommend complete avoidance of this medication in children with asthma (11).

The study by Sheehan and colleagues was a multicenter, prospective, double-blind, parallel-group RCT of 300 preschool-aged children with mild persistent asthma assigned to receive either acetaminophen or ibuprofen as an antipyretic or analgesic over the course of 48 weeks (7). Children ages 12 to 59 months were enrolled from 18 sites across the United States between 2013 and 2015. Mild persistent asthma was diagnosed using national

guidelines (12). The participants' caregivers recorded each use of the study medications and asthma outcomes throughout the study period. The primary outcome was the number of asthma exacerbations per participant that led to the use of systemic steroids. Prespecified secondary outcomes included the percentage of asthma-control days, average use of albuterol, and frequency of unscheduled healthcare visits for asthma.

Of the 300 children randomized, 226 (~75%) completed the study (116 in the acetaminophen group and 110 in the ibuprofen group). The groups were similar in their baseline demographics, asthma and atopic measures, attrition rate, and median number of study medications received. The mean (SD) age at enrollment was 39.9 (13.2) months. In the primary intention-to-treat analysis, there was no significant difference between groups with regard to the primary outcome. The acetaminophen group had a mean of 0.81 exacerbations (95% confidence interval [CI], 0.65–1.02), and the ibuprofen group had a mean of 0.87 exacerbations (95% CI, 0.69–1.10). There were also no significant differences with respect to any of the secondary outcomes. Similar results were obtained in exploratory analyses of the primary outcome limited to participants who completed the study and in sensitivity analyses using several multiple imputation methods.

The median (interquartile range [IQR]) number of study medication doses was 7 (2–15) for the acetaminophen group and 4.5 (1–17) for the ibuprofen group ($P = 0.5$). There was a significant association between the number of doses and number of asthma exacerbations in each of these groups ($P < 0.001$). In the acetaminophen group, the median (IQR) number of doses was 5.5 (1–13.5), 6.5 (3–15), 7.0 (1.5–36.5), and 11.0 (4.5–26) in children with zero, one, two, and three asthma exacerbations, respectively. In the ibuprofen group, the median (IQR) number of doses was 2 (0–11), 5 (3–18), 16 (4–22), and 15 (5–24) in children with zero, one, two, and three asthma exacerbations, respectively. However, there was no difference between the acetaminophen and ibuprofen groups within each stratum of the number of asthma exacerbations.

The results of the study by Sheehan and colleagues suggest that acetaminophen may be safely used in young children with mild persistent asthma. However, this study does not address the different asthma phenotypes that may exist in preschool-aged children. For instance, acetaminophen could still be detrimental in certain subgroups (such as transient vs. persistent wheezers). Furthermore, the results do not apply to older children or those with more severe asthma. Participants were also concurrently enrolled in a separate RCT that closely monitored the use of asthma controller medications, potentially altering adherence. Thus, the results do not apply to children who have poor medication adherence. These limitations reduce the generalizability to other populations and represent an important area of further research. ■

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Rubner FJ, *et al.* Early Life Rhinovirus Wheezing, Allergic Sensitization, and Asthma Risk at Adolescence. *J Allergy Clin Immunol* (13)

Reviewed by Rebekah J. Nevel and Caroline S. Thomas

Early-life viral acute respiratory infections (ARIs) and allergic sensitization have been implicated in the development of childhood asthma; however, the link between these risk factors and the persistence of asthma into adolescence has not been well described (14–16).

The main objective of the study by Rubner and colleagues was to examine the association of common viral ARIs (such as those caused by human rhinovirus [HRV] and respiratory syncytial virus [RSV]) and allergic sensitization in preschool children with the risk of asthma in later childhood and early adolescence (13). The authors conducted a prospective birth cohort study of 289 children who had at least one atopic parent. Timing of ARIs in the first 3 years of life was recorded, and nasal washings were collected for identification of respiratory viruses by reverse transcription–polymerase chain reaction. Allergic sensitization was determined by serum allergen-specific IgE levels to common aeroallergens, which were obtained at ages 1, 3, and 5 years. The diagnosis of asthma was assessed at ages 6, 8, 11, and 13 years and defined as physician-diagnosed asthma or use of asthma-related medications.

Of the initial 289 children, 217 (~75%) children had available 13-year follow-up data. In multivariable analyses adjusting for other viral etiologies, early-life wheezing with RSV was not associated with asthma at any age, whereas early-life wheezing with HRV was associated with increased odds of asthma at each of the follow-up assessments (odds ratio for asthma at age 13 yr, 3.3;

95% CI, 1.5–7.1). Aeroallergen sensitization at age 1 year was also a risk factor for asthma at age 13 years (odds ratio, 6.1; 95% CI, 2.5–14.4). The timing of aeroallergen sensitization differentially affected asthma risk, with children sensitized by age 1 year having the highest rates of asthma (65%) when compared with those sensitized between ages 1 and 5 years (40%) or not sensitized by age 5 years (17%). In addition, there was an additive effect of early-life wheezing with HRV and aeroallergen sensitization on the odds of asthma at all ages.

The longitudinal design, comprehensive assessment of respiratory viruses, and high retention rates represent important strengths of the study; however, the authors' cohort only comprised high-risk children with mild viral ARIs from a nonminority, suburban setting, which limits the generalizability of the results. In prior studies, RSV ARI severity has also been shown to be an important determinant of asthma risk (15, 17). Furthermore, the sample size of children with RSV ARI was relatively small, and viral strains were not assessed. Thus, if certain viral ARIs cause asthma or if they identify a group predisposed to this disease remains unclear. In spite of these limitations, the study by Rubner and colleagues adds to the increasing literature exploring early-life risk factors of asthma development with the goal of identifying primary prevention strategies. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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