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Pets and Childhood Asthma—How Should the Pediatrician Respond to New Information That Pets May Prevent Asthma?

ABBREVIATIONS. IgE, immunoglobulin E; CAMP, Childhood Asthma Management Program; IgG, immunoglobulin G.

Childhood asthma is intimately connected to inhalant allergen sensitization. Although not every child with asthma is allergic, most are.¹ The longitudinal study of Melbourne schoolchildren initiated in the 1960s by Williams and McNicol has clearly demonstrated the importance of allergic sensitization in not only the presence of asthma, but also its severity.² Sears and colleagues came to the same conclusion in follow-up of the Dunedin birth cohort, in that prevalence of asthma was highly correlated with level of total serum immunoglobulin E (IgE)³ as well as sensitization to cat allergen.⁴ A classic study by Sporik and colleagues⁵ demonstrated that exposure to high levels of dust mite ($>10 \mu\text{g Der p1/g}$ of dust) during the first 2 years of life increased the risk of developing asthma 4.8-fold in a cohort of children at risk due to having at least 1 parent with asthma or hay fever.

Numerous studies have demonstrated the effects of inhalant allergen exposure on asthma severity. Exposure and allergic sensitization to cockroach was associated with significantly greater risk of asthma hospitalization and greater health care utilization among 476 children aged 4 to 9 years who participated in the National Cooperative Inner-City Asthma Study.⁶ Allergic sensitization to the mold *Alternaria* has been identified associated with increasing airway hyperresponsiveness among schoolchildren,⁷ as well as with a nearly 200-fold increased risk of respiratory arrest attributable to asthma.⁸ The Childhood Asthma Management Program (CAMP), comprised of 1041 children aged 5 to 12 with mild to moderate asthma, found that allergic sensitization to tree pollen, weed pollen, *Alternaria*, cat dander, dog dander, or indoor molds was associated with greater airway hyperresponsiveness to methacholine.¹ In CAMP patients, nocturnal awakening was strongly associated with allergy to environmental allergens.⁹

Pet allergy is particularly important in asthma control. There is a clear association between sensitization to pets and current wheezing and bronchial hyperresponsiveness.^{10–12} Dharmage and co-workers¹¹ found that a high level of cat allergen in floor dust was associated both with an increased risk of being sensitized to cat and the presence of current asthma in adults. A large prospective population study in

Finland found that keeping pets at home for more than the previous year increased the risk of developing asthma in adulthood.¹³ There is also a clear relationship between the combination of cat exposure and sensitization to asthma morbidity. Women with asthma sensitized to cat and living in houses with concentrations of $8 \mu\text{g/g}$ or greater of cat allergen in dust were more likely to have used steroids and wheezed without a cold during a 4-year follow-up.¹⁴ In the CAMP population, children sensitized to dog and exposed to high levels of dog allergen or sensitized to cat and exposed to high levels of cat allergen had significantly increased risk of nocturnal awakenings attributable to asthma.⁹

Given the clear evidence that asthma is worsened by exposure to pets, how are pediatricians to interpret the recent studies showing a possible protective effect of having lived with a pet early in life or currently living with a pet? Three cohort studies provide evidence of a lower risk of asthma among children exposed to pets in early life compared with unexposed children.^{15,16} Children exposed to cat in the home during the first year of life had a lower frequency of asthma at age 12 to 13 years compared with those not exposed to cat during the first year of life.¹⁵ A longitudinal birth cohort study in Norway demonstrated a reduction in the odds of asthma at 4 years of age among children who were exposed to pets in the home when the child was born.¹⁶ In a prospective birth cohort study, living in a household with at least 1 indoor dog at birth was associated with a lower cumulative incidence of frequent wheezing during the first 13 years of life.¹⁷ A recently published prospective study followed 835 children in suburban Detroit from birth until the age of 6 to 7 years.¹⁸ The overwhelming majority of the children were white. Children exposed to 2 or more dogs and cats in the home during the first year of life were significantly less likely to have developed allergic sensitization to cat or dog at age 6 to 7 years. In addition to decreasing the likelihood of sensitization to cat and dog, exposure to 2 or more dogs or cats also reduced the likelihood of the development of allergy to other environmental allergens including house dust mite and pollens. Exposure to 2 or more dogs or cats during the first year of life was associated with lower serum IgE levels, less methacholine responsiveness, and higher level of lung function, but these findings were only seen in boys. Perzanowski and colleagues¹⁹ recently reported that 7- to 8-year-old children who lived with a cat in the home had a significantly lower risk of having a positive skin test to cat and physician-diagnosed asthma. This effect on asthma was most pronounced among children with a positive family history of asthma. Other studies have also found that individuals living with a pet have significantly less asthma or less severe bronchial hyperresponsiveness.^{10,20} Previous studies showing protection from pet ownership are potentially confounded by the likelihood that subjects with less severe asthma can keep the pets, whereas subjects with more severe disease are unable to hold pets. However, in the report by Ownby et al,¹⁸ there

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was no difference in the rate of pet ownership based on parental history of asthma, allergy, or hay fever, suggesting that, at least in this study, there was no effect of the presence of parental allergic disease on the rate of pet ownership.

Although it appears as though pet exposure actually protects against the development of allergy, it has been strongly suggested that pet allergen exposure itself may not be the protective factor, but rather the endotoxin exposure that comes into the home by way of the pet that may provide the protective influence. Endotoxin is a component of Gram-negative bacterial cell walls and is found throughout nature, especially in feces of animals (especially farm animals such as cows and horses). In vitro studies have demonstrated that endotoxin is capable of modifying the type of immune response produced by T-helper cells. Endotoxin exposure results in production of Th-1 type cytokines (interferon- γ and interleukin-12) and decreases the increased production of Th-2 type cytokines (interleukins 4, 5 and 13),²¹ which are critical in the immunopathogenesis of allergic disease. Several studies have demonstrated that higher endotoxin exposure protects against the development of allergy.²¹⁻²³ A recently published study²⁴ compared the amount of endotoxin in mattresses of children 6 to 13 years of age living in rural Germany, Austria, and Switzerland. Children who were exposed to the highest levels of endotoxin had the lowest rates of allergy and asthma. Furthermore, greater endotoxin exposure was associated with lower levels of Th-1 cytokine production by leukocytes. Thus, endotoxin exposure is a potential explanation for the finding that 2 or more pets in the home during the first year of life protected children from developing allergy, whereas having 1 pet in the home did not. The amount of endotoxin necessary to protect against allergy may be below the amount produced by 1 furry house pet, but having >1 furry pet allows for greater endotoxin production.

Alternate immunologic mechanisms may contribute to the decreasing risk of allergic disease and asthma in the setting of allergen exposure. High levels of allergen may induce immunologic tolerance. Platts-Mills and colleagues noted that among children 12 to 13 years of age, those children with the highest exposure to cat allergen in the home demonstrated decreased allergic (IgE-mediated) sensitization but a higher prevalence of immunoglobulin G (IgG) antibodies (particularly IgG4) to the major cat allergen *Fel d1*. These results suggest that, while these children developed an immunologic response to cat allergen, it differs from the allergic (IgE-mediated) response, and may be considered a form of immunologic tolerance.^{25,26}

Studies such as those reviewed above have made the relationship between of pet exposure early in life on the development of allergic disease increasingly controversial. The clear dose-response relationship between early exposure to dust mite and the development of dust mite allergy and asthma, coupled with evidence that sensitization and exposure to animals worsened asthma, led to the recommendation of avoiding pets early in life of children at risk for

allergic disease and asthma. More recent studies now suggest that parents need not eliminate animals early in life, and in fact, having animals in the home may be beneficial.

How are pediatricians to deal with the apparent paradox that having a pet early may be good in the life of a child, but is clearly bad for a child with asthma, particularly when the child is allergic to the pet? Parents may look on the recent data as a reason not to remove a pet when the child develops asthma. Having a pet early in the life of a child makes removing the pet difficult.

Given the current data, a pediatrician cannot make a case for removing animals before a child comes into the home. On the other hand, it seems a poor choice to suggest that parents with asthma acquire cats or dogs before a child is born in an attempt to prevent future allergic disease, as siblings or the parents themselves may be sensitive and have more illness because of the pets. Although presence of animals was associated with less sensitization to dogs, cats, and other environmental allergens, it was not completely protective, as some children who were exposed to pets early in life did go on to develop allergic sensitization. Thus, bringing a pet into the home is not consistently and completely protective and should not be recommended in an attempt to decrease the likelihood of future sensitization. Furthermore, if the child does develop asthma and is sensitized, removal of the pet becomes difficult, causing trauma for all family members.

Pediatricians must be clear that presence of a pet in the house of a child who is allergic to the pet and has asthma causes worse disease. Recommendations about removal must be firm and clear. The protective effect of animals (probably attributable to the increased levels of endotoxin produced by the pets) and the IgE-mediated worsening of the disease must be clearly distinguished.

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Improved Outcomes Associated With Early Resuscitation in Septic Shock: Do We Need to Resuscitate the Patient or the Physician?

ABBREVIATIONS. ACCM, American College of Critical Care Medicine; PALS, Pediatric Advanced Life Support.

It is clear that early aggressive fluid resuscitation in children with septic shock results in improved survival. Children who receive larger volumes of intravenous isotonic fluid in the initial hour after presentation in septic shock have lower mortality, and children who receive >40 mL/kg of fluid do even better in terms of survival.¹ Furthermore, when groups receiving smaller versus larger volumes of intravenous fluids are compared, there is no increase in acute respiratory distress syndrome or noncardiogenic pulmonary edema, 2 significant potential complications of overly-aggressive volume expansion.¹ Similar findings are reported by investigators in London from their experiences with a specific type of septic shock, meningococemia. They also report improved survival when increased fluid resuscitation was instituted as part of early resuscitation therapy.²

In the study reported by Han et al³ in this month's issue of *Pediatrics*, investigators now turn their attention to evaluate how well community practitioners have adhered to recently published resuscitation guidelines for the treatment of septic shock in children.^{4,5} The American College of Critical Care Medicine (ACCM) recently published the *Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Patients in Septic Shock*,⁴ which have been incorporated into the most recent *Pediatric Advanced Life Support (PALS)* manual.⁵ The ACCM-PALS guidelines stress early aggressive fluid resuscitation for children with presenting evidence of hypotension, impaired organ perfusion, and shock. The present study makes a convincing argument that 1) utilization of the ACCM-PALS guidelines results in improved survival, and 2) the guidelines remain underutilized by most community practitioners when confronted with patients with septic shock resulting in significant, and potentially avoidable, mortality. Han et al go on to suggest that dissemination and adoption of current guidelines by a large segment of community physicians would directly result in improved outcomes.

The Han et al study utilizes a retrospective chart review of 91 patients who were transported by the children's hospital transport team with a diagnosis of septic shock. The authors reviewed the medical records with specific attention to the mechanism,

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