more frequently compared with other patients and healthy volunteers. This was most notable in association with corneal ulceration, suggesting a role for SE.

**REVIEWER COMMENTS.** This study suggests that SE has a pathogenic role in the development of ulcers in AKC. SE could produce tissue damage to the cornea by initiating an immune response or possible secondary to direct toxic effects, although SE is not a protease. The study supports the concept of prompt targeted immunomodulatory therapy to reduce morbidity from AKC, and additional studies are needed.

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### Asthma

#### PATHOPHYSIOLOGY

**The Significance of Early Recurrent Wheeze for Asthma Outcomes in Late Childhood**


**PURPOSE OF THE STUDY.** To assess the prognosis of early-life recurrent bronchial obstruction (rBO) through adolescence.

**STUDY POPULATION.** Five hundred and fifty of the 3754 healthy newborns enrolled in the Environment and Childhood Asthma prospective population-based birth cohort study in Oslo, Norway, and attended the 16-year follow-up study visit.

**METHODS.** rBO was determined between 0 and 2 years of age as ≥2 episodes of ≥3 respiratory symptoms (tachypnoea, wheezing, expiratory stridor, respiratory chest retractions, and sibilations/whistles) or if such an episode lasted ≥4 weeks. Subjects were assessed again at age 10 and 16 years of age for diagnosis of asthma, bronchial hyperresponsiveness (BHR) by methacholine challenge, and asthma symptoms (heavy breathing, wheezing, chest tightness, or dry nighttime cough without current cold or lower airway infection). Asthma was defined as ≥2 of the following: doctor-diagnosed asthma, asthma symptoms, and the use of antiasthmatic medication.

**RESULTS.** Of the 143 subjects with rBO at 2 years of age, 71% were classified as asthma between 2 and 10 years and 34% between 10 and 16 years of age, including 10% of those who were in remission in the 2- to 10-year time period and relapsed in adolescence. Forty-eight percent of the adolescents in the rBO-remission group had ≥1 of the reported asthma symptoms, asthma medication use, or BHR compared with 26.7% of those with no rBO/never asthma (P = .001). Lung function was significantly reduced in the rBO-remission group and rBO-asthma group compared with the no rBO group and similar to each other.

**CONCLUSIONS.** The prognosis of early rBO in this cohort demonstrated that only one-third had persistent asthma throughout childhood and adolescence. However, those with rBO at age 2 in remission at age 16 had reduced lung function as well as more frequent BHR and use of asthma medications, possibly indicating increased risk of subsequent respiratory disease in adulthood.

**REVIEWER COMMENTS.** This study reaffirms the overall good prognosis for infants and toddlers with a recurrent wheezy phenotype. However, half of the children with rBO and subsequent remission still suffered from asthma symptoms, used asthma medications, or had BHR in adolescence, indicating that the prevalence of asthma may be an underestimate of subsequent respiratory morbidity associated with early-life rBO.

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### Childhood Infections and the Risk of Asthma: A Longitudinal Study Over 37 Years


**PURPOSE OF THE STUDY.** To determine if past common childhood illnesses and infectious diseases including pneumonia, pertussis, measles, mumps, rubella, chickenpox, and diphtheria are associated with an increased risk of asthma persisting at various ages.

**POPULATION.** In the Tasmanian Longitudinal Health Study, 8583 Tasmanian schoolchildren were surveyed in 1968 at age 7 years and again at age 13 years.

**METHODS.** In 2004, a detailed respiratory questionnaire was completed by 5729 of the original participants. Each child’s history was cross-referenced for a history of measles, mumps, rubella, chickenpox, diphtheria, and pertussis and immunizations against diphtheria, pertussis, tetanus poliomyelitis, and smallpox. Associations with current, persisting, or incident asthma were examined by using regression techniques.

**RESULTS.** There was no association between any childhood infectious disease and current asthma at ages 7, 13, 32, and 44 years. Pertussis was associated with reduced odds of asthma persisting at age 13, whereas chickenpox and rubella indicated reduced odds of asthma persisting to age 32. The incidence of asthma was associated with pertussis in preadolescence and with measles in adolescence. As infection load increased, there was a decrease in the incidence of asthma risk in adult life. Childhood pneumonia was associated with current asthma at ages 7 and 13 after adjustments for other factors including eczema but did not reveal an association between childhood pneumonia and asthma persisting from childhood to ages 13, 32, and 44 years.
CONCLUSION. Overall, childhood infectious diseases protected against asthma persisting in later life. Pertussis and measles, however, were associated with an increased risk of incident asthma in preadolescence and adolescence, which does not support the original hypothesis. History of pneumonia was the most relevant which does not support the original hypothesis. History of incident asthma in preadolescence and adolescence, measles, however, were associated with an increased risk of incident asthma in preadolescence and adolescence. Pertussis and measles may be predisposing factors for asthma is important to understanding asthma. Many parents wonder if their child’s previous infections may be possible causes for their asthma, especially with no family history. We look forward to additional research comparing infectious disease to asthma risk.

REVIEWER COMMENTS. The authors suggest a few explanations for these results. (1) Pertussis and measles may be predisposing these individuals to pneumonia and thus increasing asthma incidence. (2) Measles virus may downregulate interleukin-12 and upregulate interleukin-4, shifting the immunity. (3) Increased incidence related to pertussis may be in part to failed pertussis immunity rather than pertussis itself; however, this was not consistent when comparing history of immunizations. This is a relevant and interesting study. The exploration of predisposing factors for asthma is important to understanding asthma. Many parents wonder if their child’s previous infections may be possible causes for their asthma, especially with no family history. We look forward to additional research comparing infectious disease to asthma risk.

Fungal Sensitization in Childhood Persistent Asthma Is Associated With Disease Severity


PURPOSE OF THE STUDY. To estimate the prevalence of fungal sensitization in moderate to severe persistent asthma and compare clinical characteristics between fungal-sensitized and non-fungal-sensitized patients.

STUDY POPULATION. Sixty-four children with moderate to severe persistent asthma were recruited from 2 academic pediatric pulmonary practices in the greater New York area between November 2010 and June 2012.

METHODS. Serum was analyzed for total and specific immunoglobulin E (IgE) for Aspergillus spp, Alternaria spp, Candida spp, Cladosporium spp, Setomelanomma spp, Mucor spp, and Penicillium spp. For purposes of the study, all IgE responses ≥0.35 kU/L (ie, class ≥1) were considered to be indicative of sensitization. Additional screening for allergic bronchopulmonary aspergillosis (ABPA) was performed for those sensitized to Aspergillus. Pulmonary function testing had been performed as part of routine care.

RESULTS. Twenty-five of the 64 children (39%) had evidence of fungal sensitization, most class ≥2. Twenty-five were sensitized to nonfungal allergens; 14 had no sensitization. Twelve sensitized to Aspergillus had IgE levels >1000 IU, but none met diagnostic criteria for ABPA. There was no gender differences between those fungal sensitized and the others. Fungal-sensitized children had a median age of 11 compared with 9 years for the others (P = .02). Their total IgE levels were higher (1049 IU/mL vs 78 IU/mL, P < .0001). Fungal-sensitized patients had worse pulmonary function testing than nonfungal sensitized, forced expiratory volume in 1 second 81.5% versus 95.5% predicted, respectively (P = .016) with similar differences when the fungal sensitized were compared with only those sensitized to nonfungal allergens. Similar magnitudes of differences were also present for forced expiratory volume in 1 second/forced vital capacity, and forced expiratory flow 25% to 75%. Aspergillus and Alternaria were the most common fungal allergens identified (84% and 72%, respectively). Severe persistence characterized 19 of the 25 (76%) fungal-sensitized patients, whereas only 13 of 39 (33%) had been so characterized among those without fungal sensitization for an odds ratio 6.33 (95% confidence interval 2.05–19.68, P = .0014).

CONCLUSION. Fungal sensitization in childhood asthma is associated with disease severity.

REVIEWER COMMENTS. This study is consistent with the observed association of Alternaria mold as a major cause of often severe seasonal allergic asthma in the Midwest, where it has even been associated with near-fatal episodes in a report from the Mayo Clinic (O’Hollaren MT, Yunginger JW, Offlord KP, et al. Exposure to an aeroallergen as a possible precipitating factor in respiratory arrest in young patients with asthma. N Engl J Med 1991;324:359–363). Although controlled clinical trials of immunotherapy for pollens provide strong support for the effective decrease in clinical sensitivity to those allergens, data for molds is much more limited despite their apparent greater importance for severe asthma.

Increased H1N1 Infection Rate in Children With Asthma


PURPOSE OF THE STUDY. In 2009, H1N1 influenza resulted in 87,000 hospitalizations among children. The most common comorbidity for patients hospitalized as a result of H1N1 infection was asthma. Were children with asthma more likely to be infected with H1N1 influenza?
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Jannelle M. Dupuis and Melinda Rathkopf
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