2014 AAAAI Annual Meeting

**5313 Course:** Mechanisms and Treatment of Exacerbations of Asthma

**Talk Title:** Etiology of Exacerbations in Different Populations

This talk will provide a review of current knowledge of the etiology of exacerbations documented in different age groups (infants, children, adults and the elderly), racial groups (especially African-American), and geographic areas (urban vs. rural) and will discuss possible differential effects of sex and genetics underlying exacerbations.

**Attachment:** Sears MR, Johnston NW. *Understanding the September asthma epidemic*. J Allergy Clin Immunol 2007;120:526-529
Understanding the September asthma epidemic

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The highly predictable increase in emergency department visits, hospital admissions, and unscheduled physician consultations for childhood asthma in North America every September is uniquely related to school return. Rhinovirus infection is likely the major trigger, initially affecting asthma in school-age children, followed by similar but lesser increases in asthma morbidity in younger children and in adults. Low use of asthma medications during summer may fuel the epidemic, which may be attenuated by the short-term addition of an effective controller therapy. (J Allergy Clin Immunol 2007;120:526-9.)

Hospital admissions, emergency department (ED) visits, and physician consultations for childhood asthma increase with predictable regularity every September in many Northern Hemisphere countries. Epidemics have been reported in the United States, the United Kingdom, Mexico, Israel, Finland, Trinidad, and Canada, where 20% to 25% of all childhood asthma exacerbations requiring hospitalization have occurred in September.1 Fig 1 shows cycles of asthma hospitalization from 1990 to 2004 in school-age children in Canada. The stability of the pattern in timing and the amplitude of the peak in relation to the rest of the yearly cycle suggests that factors underlying the epidemic are constant.

DATA SOURCES

Over the last several years we have, after ethical approval, collected data from multiple sources to study patterns of respiratory disease. Data for all inpatient respiratory disease hospitalizations were obtained from the Canadian Institute for Health Information (1990-2004; also all ED presentations in Ontario, Canada, 2001-2004), the Center for Epidemiology at the (Swedish) National Board of Health and Welfare (1992-2002), and the Small Area Health Statistics Unit (Imperial College, London, United Kingdom, 1990-2002).

RELATION OF THE EPIDEMIC TO LABOR DAY AND SCHOOL RETURN

The peak of the epidemic of asthma hospitalization in school-age children in Canada is synchronized with school return after the summer vacation, which occurs the day after Labor Day. Every year between 1990 and 2004, the peak occurred during week 38 (September 17-23) except in 1992 (week 39) and 1997 and 2003 (week 37). In 1992, Labor Day was at its latest possible date (September 7) and in 1997 and 2003 at its earliest (September 1).

We applied mathematical modeling to estimate the exact timing and magnitude of these September peaks in Canada.2 In school-age children, the asthma hospitalization peak occurred on average 17.7 days after Labor Day (95% CI, 16.8-18.5; range, 15.5-20.3). Epidemics of lesser magnitude were observed in preschool children peaking 1.7 days later (95% CI, 0.9-2.5; P < .001), and in adults 6.3 days later (95% CI, 4.7-7.9; P < .001) than in school-age children. The peaks are thus 17.7, 19.4, and 24.0 days after Labor Day in school-age children, preschool children, and adults, respectively. The timing of the peak of the epidemic each year was highly correlated to the timing of Labor Day in school-age children (r = .77; P < .001) and preschool children (r = .65; P < .01).

School-age children show not only the earliest peak but also the greatest amplitude of the peak, suggesting that they are primarily affected and subsequently transmit the agents causing asthma exacerbations to both older and younger family members. The average amplitudes of the epidemic peaks of asthma hospitalization, expressed as a multiple of the height of the background distribution in each respective age group, were 2.2 (95% CI, 1.9-2.6) for school-age children and 1.6 (95% CI, 1.3-1.9) for preschool children versus 1.0 (95% CI, 0.3-1.7) for adults. Hence morbidity...
was greater among school-age children than among preschool children ($P<.001$) and adults ($P<.01$).

We analyzed the timing and magnitude of the epidemic peaks in relation to individual year of age. The peak occurred earliest in 6-year-old children and was progressively later with decreasing age down to 1 year and with increasing age up to 18 years with no change thereafter to age 50. The magnitude of the peak increased from ages 1 to 7 years and declined from ages 7 to 18 years, from which it remained stable until age 50 years. Thus, children about 6 to 7 years old appear to be both the earliest affected and the most seriously affected by the epidemics.

There was geographic variation in the timing of these epidemics; the peak occurred 4.2 days (95% CI, 1.2-7.1; $P<.001$) earlier in school-age children in northernmost compared with southernmost latitudes of Canada.

ETIOLOGY OF THE ASTHMA EPIDEMIC

Aeroallergens, air pollution, and their interactions with climate affect asthma exacerbations. However, we argued that the strong relation between the timing of exacerbations in children and Labor Day and the different timing in different age groups would be unlikely if aeroallergens were the primary cause, because all age groups would be exposed simultaneously. Rather, we concluded that the September peak has such highly predictable timing because it is related directly to the date of school return, and that the initial focus of the epidemic is in school-age children, most notably those at the beginning of their schooling. Viral infections, predominantly rhinovirus, have been shown to be associated with approximately 80% of asthma exacerbations in this age group.

Rhinovirus infections are most common in early fall, and school-age children introduce rhinovirus infections into their families 3 times more frequently than working adults. Our observation that the September peak in school-age children occurs earlier in northern areas of Canada suggests that opportunities for transmission of infection may be greater, possibly because of increased contact on school buses or in closed classrooms.

To test the hypothesis that viral infection was a dominant factor in the September epidemic, we studied children (cases) presenting to the ED for asthma in a major Canadian city during 3 weeks in September 2001. We concurrently studied community-recruited children (controls) with equally severe asthma but who did not require ED treatment during September. Assessments included questionnaires, skin prick allergen testing, and microbiological testing of nasal mucus using PCR techniques for picornaviruses with specific identification of human rhinoviruses, adenoviruses, influenza A and B, parainfluenza viruses 1 to 3, coronaviruses 229E and OC43, respiratory syncytial viruses A and B, Chlamydia pneumoniae, and Mycoplasma pneumoniae.

Among the cases, 62% had an identifiable respiratory virus infection at the time of ED presentation, mostly rhinovirus, as did 42% of controls. Because the timing of examination of control children was not selected according to any symptoms of infection (whereas the cases attended the ED at the time of an acute episode), the
prevalence of viral infection in the controls in that month may have been underestimated.

Despite comparable asthma severity by other criteria, the ED cases had experienced more frequent or severe exacerbations than controls. More than 90% of cases reported ED visits for asthma in the last year compared with 60% of controls. More than 3 ED visits in the previous year were reported by 47% of cases and 22% of controls. Inhaled corticosteroids and leukotriene receptor antagonists were prescribed only half as frequently for cases versus controls. We considered that the controls were spared ED visits because of better asthma treatment rather than because of fewer viral infections.

WHY DOES SCHOOL RETURN CONTRIBUTE TO THE EPIDEMIC?

Children returning to school after the summer vacation are re-exposed to respiratory viral infections, most commonly rhinovirus, at a time when they may not have been exposed to them for many weeks. The late summer is a period with high levels of environmental allergens, and sensitizing allergens are commonly present in the school environment.1 School return is also a period of high stress that can worsen asthma symptoms in children.8 Although a viral infection may be the immediate trigger for an asthma exacerbation, it is likely that these factors act together to bring about the September epidemic.

Given the seasonality of rhinovirus infection in late summer and early fall, some variability in the timing of the September epidemic of asthma would normally be expected. In contrast, our finding that the peaks of asthma hospitalization were in lock-step with the timing of Labor Day over a period of 13 years suggested that school return per se provides the conditions necessary to accelerate the transmission of rhinovirus infections to epidemic levels. This hypothesis is strengthened by data from countries with different school return dates.

In England and Canada, school return for most children is in the first week of September, whereas in Scotland and Sweden it is in the third week of August. Large peaks in asthma hospitalization occur 2 to 3 weeks after school return in each of these 4 countries despite their different summer vacation schedules.1 However, the peaks in Scotland and Sweden are of lesser amplitude than those in Canada and England, suggesting that conditions in August for rhinovirus transmission and related asthma exacerbations may be less favorable than those in September.

UNDEARTREATMENT OF ASTHMA ON SCHOOL RETURN

Prescription data for Ontario, Canada, obtained from Brogan Consulting Inc, Ottawa, show fewer fillings of prescriptions for asthma medications, especially for children, in the summer months.6 Hence, use of asthma controller therapy may be at its lowest level of the year immediately before school return. There is a rapid acceleration in uptake of these prescriptions, again particularly in children, after school return. In addition, compliance with inhaled corticosteroids is generally poor and could be even lower in summer months when children are on vacation and out of routine.

CAN THE EPIDEMIC BE ATTENUATED?

Rhinovirus is ubiquitous, and return to school cannot be avoided. Specific rhinovirus vaccination may be a future possibility. Increasing adherence to prescribed inhaled asthma control medication before and during the school return period could be beneficial but is unlikely to be achieved through interventions easily and economically conducted in general practice. Leukotriene receptor antagonists can reduce exacerbations in children with persistent asthma9 and morbidity in children with intermittent apparent viral-induced wheezing.10 We considered that addition of leukotriene receptor antagonists to usual therapy over the time of the epidemic may offer advantages in that the therapeutic effects occur shortly after inception of treatment and oral medication can easily and safely be added to existing asthma therapy.

After a pilot study in September 2004,11 we undertook a larger study to test the hypothesis that montelukast, added to usual therapy of children with asthma during a 6-week period of high risk of asthma exacerbations, would decrease days with worse symptoms and unscheduled physician visits for asthma.12 Children with asthma (n = 194) age 2 to 14 years, stratified by age and sex, participated in this double-blind, randomized, placebo-controlled trial between September 1 and October 15, 2005. Children receiving montelukast experienced a 53% reduction in days with worse asthma symptoms compared with placebo (P < .02) and a 78% reduction in unscheduled physician visits for asthma (P = .011). The benefit of montelukast was seen both in those using and not using regular inhaled corticosteroids, and among those reporting and not reporting colds during the trial.

Although numerous studies have shown that montelukast is effective in reducing asthma symptoms compared with placebo, this study has demonstrated that the short-term addition of montelukast to usual asthma therapy for 6 weeks after school return could substantially reduce asthma morbidity and health service consumption during this predictably high-risk period when use of other controller medication is known to be at its lowest level, suggesting a possible strategy for attenuating the epidemic on a larger scale. Similar benefit may be obtainable through strategies to improve compliance with inhaled medications, but this study demonstrated a substantial benefit from an easily applied and highly acceptable short-term intervention.

In summary, the predictable increase in ED visits, hospital admissions, and physician visits for childhood asthma every September is closely related to school return. Rhinovirus infection is common and can be transmitted
easily, leading to an initial epidemic in school-age children with asthma followed by lesser and slightly delayed increases in asthma morbidity in younger children and in adults. Lack of adequate controller medication may fuel the epidemic. Short-term addition of effective controller therapy provides the opportunity to attenuate the epidemic.

Many people have contributed to our understanding of the September epidemic. We thank Drs Sebastian Johnston and Tatiana Kebadze, Imperial College, London, United Kingdom, for the virology assessments and general advice; Dr Geoff Norman for assistance with mathematical modeling; Jennifer Dai and Justina Greene for their statistical expertise and data management; Drs Piush Mandhane, Paul Keith, Madan Roy, Susan Waserman, and Lori Whitehead for their clinical support; Kim Lambert and Joanne Duncan, research coordinators, for their expert clinical trial management together with nurses Jan Falcone, Anne Merklinger, Sharon Smith, and Deborah Graham; and the McMaster University Faculty of Health Sciences School of Nursing class of 2002 for their participation in the ED study.

REFERENCES