Editors' choice article

Increased risk of serious pneumococcal disease in patients with asthma

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Background: Individuals with asthma have been reported to be at increased risk of invasive pneumococcal disease (IPD). These findings need to be confirmed in a different population-based study setting.

Objective: We assessed whether serious pneumococcal disease (SPD), defined as an IPD, pneumococcal pneumonia, or both, was associated with asthma status.

Methods: This is a retrospective case-control study using criteria-based methods for ascertaining SPD, as well as asthma. Subjects were residents of Rochester, Minnesota, who had SPD between 1964 and 1983 (the primarily pre–pneumococcal vaccine era) and their age- and sex-matched control subjects using 1:2 matching. Potential cases and control subjects were identified by using the Rochester Epidemiology project database and confirmed by medical record reviews. All cases and control subjects were merged with the database comprising the entire pool of Rochester residents with and without asthma between 1964 and 1983.

Results: A total of 3941 records of potential patients with SPD were reviewed, and we identified 174 cases of SPD (51% male subjects and 94% white subjects). SPD was associated with a history of asthma among all ages (odds ratio, 2.4; 95% CI, 0.9-6.6; $P = .09$) and among adults (odds ratio, 6.7; 95% CI, 1.6-27.3; $P = .01$), controlling for high-risk conditions for IPD and smoking exposure. The population-attributable risk percentage was 17% in the adult population.

Conclusion: Adults with asthma might be at increased risk of SPD. (J Allergy Clin Immunol 2008;122:719-23.)

Key words: *Asthma, invasive pneumococcal disease, epidemiology, risk, microbial infection, pneumococcal pneumonia, adults, Rochester Epidemiology Project*

Asthma affects almost 30 million Americans and 300 million persons worldwide.[1-3] The prevalence of asthma has increased over the past 2 decades in both children and adults.[4,5] Indeed, these same trends have been seen in Rochester, Minnesota. The annual age- and sex-adjusted incidence of asthma increased from 183 per 100,000 in 1964 to 284 per 100,000 in 1983.[6] In this study we assessed whether asthma is associated with an increased risk of serious pneumococcal disease (SPD), which was defined as invasive pneumococcal disease (IPD), pneumococcal pneumonia, or both.

Before the introduction of heptavalent pneumococcal conjugate vaccine, patients aged 2 to 64 years who had IPDs (n = 3469) were assessed for underlying conditions. Of these patients, only 50.6% (n = 1755) had at least 1 condition that was a known indication for either the pneumococcal polysaccharide or conjugate vaccine.[7] At present, asthma is not a pneumococcal vaccine–eligible condition, and to what extent asthmatic patients contribute to the burden of SPD at a population level has not been known. To address this question, recently, Talbot et al[8] reported that having a diagnosis of asthma is associated with an increased risk of IPD (odds ratio [OR], 2.4; 95% CI, 1.9-3.1). The study population included only those receiving Medicaid insurance, and the relationship between asthma and SPD needs to be confirmed in another study population.

We conducted a population-based case-control study using a cohort in whom those with asthma status have been previously defined and that uses information from the primarily pre–pneumococcal vaccine era (ie, 1964-1983).

METHODS

The study was approved by the Institutional Review Boards of both Mayo Clinic and Olmsted Medical Center. This is a population-based, retrospective case-control study of 3941 records from a Rochester, Minnesota, population from 1964 through 1983 designed to assess whether there is a higher incidence of SPD among persons with asthma. Among the 3941 study participants, the diagnosis of asthma had been previously determined as part of another study by using a structured algorithm and predetermined criteria for asthma.

Study population and setting

All study subjects are residents of Rochester, Minnesota, which is located in southeast Minnesota. The Olmsted County and Rochester populations are

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Abbreviations used
ICD: International Classification of Diseases
IPD: Invasive pneumococcal disease
OR: Odds ratio
PAR%: Population attributable risk percentage
SPD: Serious pneumococcal disease

similar to the US white population, with the exception of a higher proportion of the working population employed in the health care industry.[9-11] In 1980, the Rochester population was 60,541 (97% white). Rochester, Minnesota, is an excellent setting to conduct a retrospective case-control study because medical care is virtually self-contained within the community, and the Rochester Epidemiology Projects provides information on persons attending medical care in all health care sites in Rochester. The medical records for each site contain all inpatient and outpatient data. All diagnostic information has been indexed since 1935 by using Berkson codes, even before International Classification of Diseases (ICD) codes were available.[12] The incidence rate of asthma in Rochester was 238 per 100,000, which is comparable with rates in other communities, such as Tecumseh, Michigan (250/100,000).[13]

Study subjects: Case ascertainment (SPD)

Because all cases of SPD were confirmed by means of medical record review, we used very broad criteria to identify potential subjects. This allowed us to increase both the sensitivity and specificity in identifying cases of SPD. Our broad criteria for potential cases of SPD included the diagnostic categories of sepsis, bacteremia, meningitis, leptomeningitis, pneumococcal infections, diplococcal infections, lobar pneumonia, acute pneumonia, pneumococcal pneumonia, pneumococcal bacteremia, diplococcal pneumonia, osteomyelitis, pleuritis, pleurisy, pleural effusion, empyema, peritonitis, septic arthritis, shock (bacteremic), septic shock, streptococcal septicemia, and streptococcal bacteremia. A total of 85 different medical index search codes (Berkson codes and ICD codes) were used to identify potential cases of SPD. Each potential case was then confirmed by means of medical records review. Case definition of SPD included isolation of *Streptococcus pneumoniae* from a normally sterile site (eg, blood or cerebrospinal fluid) or pneumococcal pneumonia requiring all 3 of the following criteria: (1) a physician's diagnosis of pneumonia, (2) the isolation of pneumococcus from sputum Gram stain or culture, and (3) pneumonia documented by means of chest radiography. We defined the index date of onset of SPD as the date of documented isolation of *S pneumoniae*.

Selection of control subjects

This study was designed as a cumulative-incidence case-control study in which cases were selected at the end of the study period and control subjects were selected from among individuals who at the end of the study period did not have SPD. Therefore control subjects were not at risk of becoming cases in the study. Control subjects were randomly selected from sex- and birthday-matched individuals who did not have SPD by the end of the study period. Additional criteria for control subjects were as follows: (1) must be residents of Rochester, Minnesota, between 1964 and 1983; (2) must have research authorization for medical record review; and (3) had the same (ie, within 1 year) clinic registration year as their matched case. Two control subjects were matched for each case with regard to sex and birthday (within 2 months for those <18 years of age and within 1 year for those ≥18 years of age). A list of potential control subjects was generated from the Rochester Epidemiology computerized database, and the index date for control subjects was defined as the index date of SPD for the corresponding matched case. Therefore because subjects with SPD and their matched control subjects had similar clinic registration date (starting point) and the same index date (end point), by selecting control subjects at the end of the study period, we ensured that cases and control subjects had a similar length of follow-up with regard to disease and exposure status.

Exposure ascertainment (asthma status)

Once we identified cases and their control subjects, we used the previously collected data on asthma to ascertain the asthma status among the subjects with confirmed cases of SPD and control subjects. Data abstractors of this study were not blinded to asthma status, but they were not aware of the study hypothesis at the time of data abstraction. The asthma status of all children and adults in Rochester, Minnesota, had been determined for a previous study during the period 1964 to 1983 (n = 2499).[6] Briefly, all potential cases of asthma were identified by using the medical diagnostic list within the Rochester Epidemiology Project, and then each person's medical records were reviewed to confirm asthma by using the prespecified criteria. Diagnostic categories have been linked across the many updates of the diagnostic indices, including revisions of the ICD (eg, ICD-7, ICD-8, and ICD-9). From the 18,000 potential asthma cases, 2499 patients met the criteria for asthma.

To determine the relationship between SPD and asthma status, we merged SPD case and control data with the previously confirmed database for asthma by using unique identifiers, such as clinic registration numbers, names, and birthdays. We were also able to address the temporal relationship between asthma and SPD because the previous study included the incidence dates for asthma in all confirmed cases of asthma.[14]

Other variables

During medical record abstraction, we collected information, including sociodemographic variables (age, sex, ethnicity, and educational status), high-risk conditions for IPD (based on Advisory Committee on Immunization Practices–recommended pneumococcal vaccine–eligible conditions) before and after the index date, smoking status at the time of the index date (either active or passive smoking exposure to any number of cigarettes, cigars, or pipes a day by patient or household members within 1 month of index date; if smoking exposure was documented in medical records both before and after the index date, we included it as smoking exposure), pneumococcal vaccination status based on medical records during the study period, and antibiotic use within 7 days before the index date of SPD.

Data analysis

We calculated the age- and sex-adjusted annual incidence of IPD and SPD per 100,000 by using the year 2000 US population for adjustment for age and sex. A conditional logistic regression for matched analysis was used to determine whether the risk of SPD was associated with asthma status. We conducted data analysis by using the entire group of subjects and stratified analysis by age, focusing on adult subjects because of the small sample size of pediatric subjects. We also assessed the relationship between other variables and the risk of SPD. For any potential interaction between asthma and other variables in relation to the risk of SPD, we used stratified analysis and tested the statistical significance of the interaction term by using a regression model. The full model included variables associated with risk of SPD that meet an entry criterion ($P < .2$) based on univariate analysis.[15] The OR for a history of asthma was calculated with the 95% CI and tested for significance by using a 2-sided test ($\alpha = .05$). In addition to these primary analyses, we calculated the population-attributable risk percentage (PAR%) of asthma on SPD. PAR% was calculated by using the following formula: $P(OR-1)/[1+P(OR-1)]$, where P is the prevalence of asthma in the population and OR is the matched OR.[16]

RESULTS

Study subjects

The characteristics of the subjects and the relationship between individual risk factors and SPD are summarized in Table I. We identified 174 confirmed SPD cases, of which 16% (n = 28), 22% (n = 38), and 62% (n = 108) had IPD, IPD with pneumococcal pneumonia, and pneumococcal pneumonia, respectively. Of the 174 subjects with SPD, 51% were male, and 94% were white. The median and mean ages at the index date of SPD were 65 and 57 years, respectively. Only 21 (12%) cases were younger than 18

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