Clinical Features, Virus Identification, and Sinusitis as a Complication of Upper Respiratory Tract Illness in Children Ages 4-7 Years

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Objective To determine the rate of sinusitis complicating upper respiratory tract illnesses (URIs) in children. We prospectively identified the clinical, virologic, and epidemiologic characteristics of URIs in a population of 4- to 7-year-old children followed for 1 year.

Study design This was an observational cohort study in 2 primary care pediatric practices in Madison, Wisconsin. Nasal samples were obtained during 4 asymptomatic surveillance visits and during symptomatic URIs. A polymerase chain reaction-based assay for 9 respiratory viruses was performed on nasal samples. A diagnosis of sinusitis was based on published criteria.

Results Two hundred thirty-six children ages 48-96 months were enrolled. A total of 327 URIs were characterized. The mean number of URIs per child was 1.3 (range 0-9) per year. Viruses were detected in 81% of URIs; rhinovirus (RV) was most common. Seventy-two percent of URIs were resolved clinically by the 10th day. RV-A and RV-C were detected more frequently at URI visits; RV-B was detected at the same rate for both asymptomatic surveillance visits and URI visits. Sinusitis was diagnosed in 8.8% of symptomatic URIs. Viruses were detected frequently (33%) in samples from asymptomatic children.

Conclusions Sinusitis occurred in 8.8% of symptomatic URIs in our study. The virus most frequently detected with URIs in children was RV; RV-A and RV-C detection but not RV-B detection were associated with illness. Viruses, especially RV, are detected frequently in asymptomatic children. Most URIs have improved or resolved by the 10th day after onset. Children experienced a mean of 1.3 URIs per year, which was lower than expected. *(J Pediatr 2016;171:133-9)*.

Upper respiratory tract illness (URI) is the most common infectious disease of childhood and one of the most frequent reasons that parents seek medical care.[1] The first characterization of URI symptoms using modern virologic techniques was in the 1960s in young adults.[2] The frequency of URI in children and the nature and duration of respiratory symptoms has received increasing attention in the current era of molecular virology.[3-15] Historically, children have been reported to experience an average of 6-8 acute respiratory illnesses per year.[16] However, the number of URIs and the particular viruses involved vary with age, season, geography, and attendance at out-of-home childcare. Previous studies have evaluated URIs in: (1) birth cohorts of children at high risk for atopy[11,12,17,18]; or (2) cross-sectional studies during a single respiratory season.[4,5,7,15,17] Only a few studies have prospectively followed substantial numbers of young children longitudinally, both when well and during symptomatic URI.[18-20]

Although the frequency of acute otitis media as a complication of viral URI has been reported, there has been relatively little systematic investigation of the rate of sinusitis as a complication of URI. The single recent study investigating this question was performed in children 6-36 months of age.[9] In this age group, acute otitis media is a frequent early complication of URI (30%-37%) that leads to antimicrobial treatment that, in turn, may prevent the subsequent development of acute bacterial sinusitis.[9,19] To determine the rate of sinusitis complicating

ADV	Adenovirus
CoV	Coronavirus
EV	Enterovirus
FLU	Influenza virus
GEE	Generalized estimating equation
hBoV	Human bocavirus
hMPV	Human metapneumovirus
PIV	Parainfluenza virus
RSV	Respiratory syncytial virus
RV	Rhinovirus
URI	Upper respiratory tract illness

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URI in children less susceptible to the confounding effects of otitis media, we prospectively studied the clinical, virologic, and epidemiologic characteristics of URIs in a population of 4- to 7-year-old children in an observational cohort study.

Methods

Healthy children ages 48-96 months were recruited in a rolling fashion from 2 primary care pediatric practices in Madison, Wisconsin and followed for 1 year. Families of eligible children received information about the study by mail approximately 2 weeks before their next scheduled well-child visit. Parental interest in the study was queried by the office nurse. If interest was expressed, the study coordinator provided additional information and invited the parent to participate in the study. Children were excluded from the study if they had an underlying condition reported by the parent or noted in the medical record, likely to alter the natural history of URI, including congenital or acquired immunodeficiency, craniofacial abnormalities, cystic fibrosis, allergic rhinitis, or a previous episode of chronic sinusitis. Written, informed consent was obtained and assent also was obtained from older children (≥7 years of age). Subjects received a small stipend for participation. The study was approved by the University of Wisconsin Institutional Review Board. Demographic information was obtained by the study nurse. Responses to race/ethnicity questions were self-reported by the subject's parent.

Nasal samples were obtained at entry and during 4 surveillance visits (February, April, September, and December) when children were asymptomatic as verified by the study nurses. Parents were instructed to call the study nurse at the first sign of a URI, which was defined as at least 48 hours of respiratory symptoms including nasal congestion, nasal discharge, or cough. Nasal samples were obtained on day 3-4 of illness by the study nurse, and a recovery sample was obtained on day 15. A clinical assessment at the time of the visit assured that symptoms reflected illness confined to the upper respiratory tract. A symptom survey was filled out on day 3-4 and subsequently by telephone on days 7, 10, and 15.[21] The survey inquired about fever, nasal symptoms, cough, headache, irritability, facial pain, facial swelling, activity, sleep, and impaired appetite. If a symptom was present initially, a score of 2 was assigned. If it was absent the score was 0. If a symptom became more severe, less severe, or stayed the same, +1, −1 or 0, respectively, was added to the previous score for each symptom. The URI was considered resolved if the score was ≤2. In addition, parents were asked to record any missed days of childcare, school, or work because of respiratory illness in their child on a calendar provided for that purpose.

Each URI was classified as either an uncomplicated viral URI or sinusitis. The diagnosis of sinusitis was based on one of the following clinical criteria: (1) persistent symptoms—respiratory symptoms, including nasal discharge or cough or both, that lasted more than 10 days and were not improving (symptom score at 10 days ≥50% of highest score); (2) severe symptoms—a combination of purulent (thick, colored, and opaque) nasal discharge plus temperature >39°C for at least 72 hours; or (3) worsening symptoms—sudden onset of respiratory symptoms or fever after apparent improvement, usually beyond the sixth day of illness.[22]

Samples of nasal mucus were obtained using an established nose blowing technique.[18,23] Saline was sprayed into each nostril and then blown into a plastic "baggie." Two milliliters of a solution containing buffered saline (pH 7.4) along with 0.5% gelatin was added to the baggie; the contents were transferred to a sterile tube, processed, and frozen.

Virus Identification

Diagnostic virology was performed on nasal samples by multiplex polymerase chain reaction (Respiratory Multicode Assay; EraGen Biosciences, Madison, Wisconsin; or Respiratory Viral Panel; Luminex Co, Austin, Texas) to test for the following viruses: respiratory syncytial virus (RSV, groups A and B), rhinovirus (RV ~160 known types), parainfluenza virus (PIV; 1, 2, 3, 4a, and 4b), influenza virus (FLU; A, B, and C), adenovirus (ADV; B, C, and E), coronavirus (CoV; 229E, NL63, OC43, HK, and SARS), enterovirus (EV), human bocavirus (hBoV), and human metapneumovirus (hMPV; A and B). Nasal specimens also were analyzed by partial sequencing to determine which RV types were present, and to differentiate closely related EVs from RVs.[24]

Statistical Analyses

The number of URIs per subject was transformed to the log(x+1) scale to obtain a more symmetric distribution for estimating the mean. The result was transformed back to the original scale. Percentages of URI and surveillance visits with virus (or RV species) present were calculated using the generalized estimating equation (GEE) approach to logistic regression for clustered binomial data where the clusters are subjects. GEE also was used to estimate the proportion of visits each calendar month in which each virus was present. Models with a term for visit type were used to compare percentages between surveillance and URI visits. *P* values and CIs were calculated using a normal approximation.

GEE analysis with a random effect for subject was used on data from the URI visits to estimate the percentage of URIs with various symptoms, complications, and symptom recovery rates. The same approach was used to estimate the proportion of URIs that resulted in missed school and work days and the effect of the presence of viruses on the proportion of URIs with fever. Mean days missed from work and school and mean duration of fever were estimated using a linear mixed effects model with a random effect for patient. Mean symptom scores were estimated for URIs with only RV present and without RV present using a mixed effects model with random effects for subject and for URI within subject and fixed effects for day and RV. The interaction term between RV and day was not significant. Symptom scores were transformed to the log(x+2) before analysis to