Nonsteroidal Anti-Inflammatory Drug without Antibiotics for Acute Viral Infection Increases the Empyema Risk in Children: A Matched Case-Control Study

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Objective To investigate the risk factors of empyema after acute viral infection and to clarify the hypothesized association(s) between empyema and some viruses and/or the use of nonsteroidal anti-inflammatory drugs (NSAIDs).

Study design A case-control study was conducted in 15 centers. Cases and controls were enrolled for a source population of children 3-15 years of age with acute viral infections between 2006 and 2009.

Results Among 215 empyemas, 83 cases (children with empyema and acute viral infection within the 15 preceding days) were included, and 83 controls (children with acute viral infection) were matched to cases. Considering the intake of any drug within 72 hours after acute viral infection onset and at least 6 consecutive days of antibiotic use and at least 1 day of NSAIDs exposure, the multivariable analysis retained an increased risk of empyema associated with NSAIDs exposure (aOR 2.79, 95% CI 1.4-5.58, $P = .004$), and a decreased risk associated with antibiotic use (aOR 0.32, 95% CI 0.11-0.97, $P = .04$). The risk of empyema associated with NSAIDs exposure was greater for children not prescribed an antibiotic and antibiotic intake diminished that risk for children given NSAIDs.

Conclusions NSAIDs use during acute viral infection is associated with an increased risk of empyema in children, and antibiotics are associated with a decreased risk. The presence of antibiotic-NSAIDs interaction with this risk is suggested. These findings suggest that NSAIDs should not be recommended as a first-line antipyretic treatment during acute viral infections in children. *(J Pediatr 2016;175:47-53)*.

Although relatively infrequent, empyema is a serious bacterial infection of the pleural space that remains a cause of substantial morbidity, with an in-hospital case-fatality ratio of 0.4% for children.[1] Late diagnosis and onset of appropriate therapy contribute to increased morbidity. In addition, the in-hospital management of patients with empyema is associated with substantial economic costs.[2]

In the 2000s, the incidence rate of empyema in children increased worldwide as in France without clear explanations.[1,3-6] This trend was not modified by 7-valent pneumococcal conjugate vaccine (PCV-7) programs,[1,3-7] but hospitalizations for uncomplicated pneumonia clearly declined thereafter.[8] Previous retrospective studies suggested that the use of nonsteroidal anti-inflammatory drugs (NSAIDs) during community-acquired pneumonia may be associated with an increased risk of empyema,[3,9-13] but a protopathic bias could not be excluded. This case-control study was undertaken to investigate children's risk factors for empyema after acute viral infection and determine whether some viruses,[14,15] use of NSAIDs, or both were associated.

Methods

The study was approved by the Institutional Review Board of University Hospital Necker-Enfants Malades (CCP06-03-09). All participating parents and case and control children older than 7 years of age were given oral and written information and provided written consent.

LRTVI	Lower respiratory tract viral infection
NRCP	National Reference Center for Pneumococci
NSAID	Nonsteroidal anti-inflammatory drug
PCR	Polymerase chain reaction
PCV-7	7-valent pneumococcal conjugate vaccine

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This matched case-control study included cases and controls from a source population of children with acute viral infections and was conducted in 15 French pediatric respiratory clinical departments from September 2006 to June 2009.

Acute viral infection was diagnosed by clinical symptoms by the provider. The following acute viral infections were as follows: herpes virus infection; varicella; gastroenteritis, defined as acute diarrhea, with at least 3 loose stools per day; nasopharyngitis, defined as runny nose, nasal congestion, and cough; bronchiolitis, defined as cough, shortness of breath, and wheeze at auscultation; flu-like syndrome, defined as cough with fever and myalgia; bronchitis, defined as cough and bronchial congestion; and viral pharyngitis documented by a negative test for rapid diagnosis of group A streptococcal infection. Acute viral infections were divided into 3 groups: upper respiratory tract viral infections, lower respiratory tract viral infections (LRTVIs) (bronchiolitis, bronchitis, and flu), and others. All acute viral infections were not severe and did not require hospitalization.

Consecutive patients 3 months to 15 years of age who were hospitalized for empyema in 1 of the 15 participating centers were eligible. Empyema was defined as the presence of a pleural effusion on chest radiograph and at least 1 of the following results of tests on pleural fluid: pH < 7.2, lactate dehydrogenase >1000 IU/L, glucose <2.2 mmol/L, protein >3000 mg/dL, white blood cell count >50 000 cells/μL,[16] and/or a positive bacterial culture or Gram stain. To be a case, the empyema had to follow doctor-diagnosed acute viral infection based on clinical symptoms and identified within a maximum of 15 days preceding the date of the first pleural puncture.

Controls were children 3 months to 15 years of age with acute viral infections from the same "source population" as case children, which was defined as children evaluated by the same private practitioner for acute viral infections. Controls were recruited as follows: upon case identification, the doctor who referred the child to the hospital was contacted to identify, among his/her patients, children matched for age (+/−1 year) who consulted for same viral symptoms during the 15 preceding days with the similar time window as the matched case (**Figure 1**; available at www.jpeds.com).

Exclusion criteria for cases and controls were chronic respiratory disease, acquired and/or congenital immunological disorders, malignancy, collagen vascular disease, sickle cell disease, congenital heart defects, neuromuscular disease, hemophilia, and/or heart failure; treatment with corticosteroids or immunosuppressive agents during the month preceding identification; and known intolerance of NSAIDs or acetaminophen.

Exclusion criteria for cases were absence of at least 24 hours of apyrexia between recovering from LRTVI symptoms and a diagnosis of empyema and time between onset of acute viral infection and a diagnosis of empyema <72 hours (to decrease the possibility that symptom onset was possible onset of the bacterial infection).

For each hospital case, after questioning the parents, a trained doctor or nurse completed a detailed and standardized form, recording symptoms, treatment concerning the period between onset of acute viral infection (first day of clinical symptom), and empyema diagnosis by pleural puncture, corresponding to the time of exposure. For the controls, the parents were contacted after the consultation with the treating physician and data recorded retrospectively exactly as done for the cases, with the same detailed and standardized form, recording clinical items concerning the same exposure window-timing from the acute viral infection onset as the matched case. Primary providers went at controls' home to obtain nasal swab specimen and record data (**Figure 1**). Symptoms, treatments (antibiotics, glucocorticoids, NSAIDs, acetaminophen) according to the doctors' prescriptions, and self-administered medications were recorded daily. The following information also was recorded for all enrolled children: demographics, immunization status, and type of acute viral infection as stated by the doctors. In addition, a nasal swab was obtained for respiratory virus screening.

For the cases, initial clinical findings, results of biochemistry and microbiology tests, radiograph findings, management, and length of stay were recorded. Two doctors reviewed the medical records of all identified patients and independently validated each case.

Microbiology

After identification in the laboratory of the hospital at which the case was admitted, bacterial strains from pleural fluids were sent for identity confirmation to the University Hospital Necker-Enfants Malades microbiology laboratory as, when feasible, a sample of pleural fluid was sent for pneumococcal antigen testing and polymerase chain reaction (PCR) testing for atypical bacteria (*Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*). When cultures were negative, pneumococcal and universal bacterial PCRs were performed. DNA was extracted from 100 μL of pleural fluid samples previously stored at −80°C with the automated MagNA Pure LC System (Roche Diagnostics, Meylan, France) and eluted in 100 μL of elution buffer using the DNA III Magna Pure DNA Isolation Kit (Roche Diagnostics). In-house *C pneumoniae* (OMP1 gene) and *M pneumoniae* (P1 cytadhesin gene) PCRs were performed as described previously.[17,18] *S pneumoniae* pneumolysin gene real-time PCR was performed according to Corless et al.[19] For negative pneumococcal PCR samples, real-time amplification of universal bacterial 16S rDNA was performed and the amplified product was sequenced, as previously reported.[20] Pneumococcal antigen was detected with the immunochromatographic test BinaxNOW for *Streptococcus pneumoniae* (Binax Inc, Portland, Maine), according to Le Monnier et al.[21] Pneumococcal strains were serotyped at the French National Reference Center for Pneumococci (NRCP) via the use of latex particles coated with a complete panel of antisera and factor serum (provided by the Statens Serum Institute, Copenhagen, Denmark), which is able to identify the 91 known serotypes. Pneumococcal strains of known serotypes from the Statens Serum Institute and from French NRCP were used as internal controls. When available, DNA from individual pleural fluid samples with