

Association of Acetaminophen and Ibuprofen Use With Wheezing in Children With Acute Febrile Illness

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Abstract

Background: Many infants and children receive acetaminophen and/or ibuprofen during febrile illness. Previously, some studies have linked acetaminophen and ibuprofen use to wheezing and exacerbation of asthma symptoms in infants and children. **Objective:** To assess whether acetaminophen or ibuprofen use are associated with wheezing in children presenting to the emergency department (ED) with febrile illness. **Methods:** This was a cross-sectional study of children who presented with fever to the pediatric ED between 2009 and 2013. The data were collected from questionnaires and from the children's medical files. Patients with wheezing in the ED were compared with nonwheezing patients. Associations between medication use and wheezing were assessed using univariate and multivariate analyses. The multivariate analysis adjusted for potential confounding variables (ie, age, atopic dermatitis, allergies, smoking, antibiotics use, etc) via propensity scores. **Results:** During the study period, 534 children admitted to the ED met our inclusion criteria, of whom 347 (65%) were included in the study. The use of acetaminophen was similar in children diagnosed with wheezing compared with those without wheezing ($n = 39$, 81.3%, vs $n = 229$, 82.7%, respectively). Ibuprofen use was significantly lower in children diagnosed with wheezing ($n = 22$, 52.4%, vs $n = 168$, 69.4%, respectively). In multivariate analysis, acetaminophen was not associated with a higher rate of wheezing during acute febrile illness (adjusted odds ratio [OR] = 0.76, 95% CI = 0.24–2.39), whereas ibuprofen was associated with a lower risk of wheezing (adjusted OR = 0.36, 95% CI = 0.13–0.96). **Conclusions:** Our study suggests that acetaminophen and ibuprofen are not associated with increased risk for wheezing during acute febrile illness.

Keywords

asthma, pediatrics, acetaminophen, nonsteroidal anti-inflammatory drugs, antipyretics

Introduction

Wheezing and asthma are common in children. Almost 50% of children will experience at least 1 episode of wheezing by the age of 3 years.^{1,2} Whereas wheezing can be precipitated by several factors, such as respiratory tract infections, foreign body aspiration, and congenital or acquired lung diseases, one of the most common causes of wheezing is asthma.^{3,4}

The incidence of asthma is increasing worldwide; however, the reasons for this increase are not clear.^{1,2} Acetaminophen use in children has also increased in recent decades. The increased use of acetaminophen was likely the result of a decrease in the use of other antipyretics and analgesics, such as the decline in phenacetin use in the 1950s as a result of concerns for nephrotoxicity and the decline in aspirin use in the 1980s as a result of concerns for Reye's syndrome.⁵ The increased incidence of asthma is positively correlated with the increase in acetaminophen use.^{2,5} Recent

studies reported that an increased exposure to acetaminophen is associated with an increased risk of asthma, both in children and in adults,^{6–12} and some studies reported that exposure to acetaminophen during pregnancy was associated with childhood asthma.^{11,13} In addition, some studies have linked acetaminophen use to wheezing and exacerbation of asthma symptoms in infants and children,¹⁴ whereas others have not.¹⁵ It has been suggested that the possible link between acetaminophen use and wheezing could be a

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result of depletion of airway mucosal glutathione that could subsequently modulate inflammatory response and contribute to vulnerability to oxidant stress.^{16,17}

Whereas in the past the use of NSAIDs was generally avoided in children,¹⁸ recent decades saw a dramatic increase in the use of these agents in children, particularly in the use of ibuprofen.¹⁹⁻²¹ This increase was likely driven by the approval of over-the-counter pediatric ibuprofen products in the 1990s and the accumulation of evidence indicating ibuprofen's safety in children.^{19,22} Ibuprofen, like all NSAIDs, has also previously been linked to asthma exacerbations, especially among patients with aspirin-sensitive asthma.^{23,24} This has been attributed to inhibition of the Cox-1 enzyme and the subsequent upregulation of leukotrienes.²⁵ In fact, in children with asthma and self-reported aspirin allergy, 2 days of treatment with ibuprofen was associated with a decrease in FEV1 (forced expiratory volume in 1 s) and an increase in FeNO levels.²⁶ However, there have also been reports linking ibuprofen with a decreased risk of wheezing and asthma.²⁷

In this study, we aimed to determine whether acetaminophen or ibuprofen use is associated with wheezing in children presenting to the ED with febrile illness.

Methods

We conducted a cross-sectional study at the pediatric emergency department (ED) at Assaf-Harofeh Medical Center between September 2009 and March 2013. The study recruited children aged 6 months to 6 years who were admitted to the ED with fever ($>38^{\circ}\text{C}$ [100.4°F]) on admission, or during the day prior to admission, and who could provide data on antipyretic treatment during the current febrile illness, specifically with acetaminophen or ibuprofen. Exclusion criteria for the study were as follows: children with cystic fibrosis or chronic lung disease, children who were ventilated on admission, children whose parents did not speak Hebrew or Arabic, and children whose parents or legal guardians did not consent to participate in this study. Wheezing was diagnosed at the ED based on the physician's physical examination according to a predetermined protocol.

We retrieved data on demographics, gender, and the gestational week of delivery for each of the children included in the study. The parents of the included children were interviewed to retrieve data on the antipyretic drug that the child was treated with (ie, acetaminophen and ibuprofen) as well as the child's and family's medical history. Medical history recorded included previous history of wheezing and asthma, atopic dermatitis, any previous use of systemic steroids (such as prednisolone and betamethasone), any previous inhaled corticosteroid controller treatment, previous admissions to the ED or the pediatric intensive care unit (ICU) for wheezing, and exposure of the child to maternal smoking during pregnancy and childhood. Data on the presence of

allergies in the child's and the family's medical history were collected as well. These included any known environmental (eg, house dust mites), food, or drug allergies.

Data on the present illness were also collected. This included the number of days with fever, other symptoms (eg, diarrhea, nausea, vomiting, etc), use of inhaled β_2 agonists and inhaled corticosteroids, use of antitussive medication, diagnosis and medications used in the ED, and whether the child was hospitalized. The study was approved by the internal research ethics board of Assaf-Harofeh medical center.

Statistical Analysis

We calculated that 182 children would need to be enrolled in the study to detect a 33% increase in the risk for wheezing with acetaminophen ($\alpha = 0.05$; power = 80%). In practice, we aimed to enroll 300 to 400 patients to allow for more flexibility in our assumptions because we were unsure what the actual prevalence of acetaminophen and ibuprofen use would be.

Descriptive statistics were used to summarize the characteristics of children with wheezing and without wheezing. Categorical variables were described using counts and percentages from the available data. Continuous variables were expressed as the mean and SD if they were normally distributed or as median and range for nonnormally distributed data (tested using the Kolmogorov-Smirnov test). Differences in the descriptive characteristics of children with and without wheezing were evaluated using univariate statistical tests (*t*-test, Mann-Whitney, χ^2 , and Fisher's exact test, as appropriate).

The significance of differences in the prevalence of antipyretic use between children with and without wheezing was assessed using the χ^2 statistic. The association between antipyretic use and wheezing was further evaluated using logistic regression adjusted for potential confounders using propensity scores. Propensity scores for antipyretic use (ie, scores predicting the probability of a child to receive acetaminophen, ibuprofen, or both) were calculated using a multivariate logistic regression. The covariates used in the propensity score models included the following: age, sex, gestational week at birth, use of inhalers, atopic dermatitis, previous episodes of wheezing, previous hospitalizations resulting from wheezing, previous ICU hospitalizations resulting from wheezing, known allergy, known allergy in the family, exposure to smoking, maternal smoking during pregnancy, asthma in the family, number of days with fever, and antibiotics use. A *P* value <0.05 was considered statistically significant. All analyses were performed with SPSS version 21 (IBM SPSS, Chicago, IL).

Results

During the study period, 534 children admitted to the ED met our inclusion criteria. Of these, 358 (67%) agreed to

Table 1. Demographic Characteristics of Children With Wheezing Compared With Children Without Wheezing (Total n = 347).

Variable	Children With Wheezing (n = 50)	Children Without Wheezing (n = 297)	P Value ^a
Age in years, mean (SD)	1.4 (0.8)	1.9 (1.3)	0.003 ^b
Birth week, median (IQR)	38 (37-40)	39 (38-40)	0.004 ^c
Female gender, n (%)	19 (38.8)	145 (49.0)	0.241 ^d
Wheezing prophylaxis, ^e n (%)	7 (14.6)	21 (7.9)	0.165 ^f
Atopic dermatitis, n (%)	4 (9.1)	24 (8.8)	1 ^f
Known allergy, n (%)	5 (10.0)	30 (10.3)	1 ^d
Known allergy in the family, n (%)	8 (16.3)	60 (20.9)	0.586 ^d
Asthma in the family, n (%)	10 (20.4)	42 (14.7)	0.419 ^d
Exposure to smoking, n (%)	21 (46.9)	103 (40.1)	0.506 ^d
Maternal smoking during pregnancy, n (%)	5 (11.6)	24 (9.7)	0.853 ^d
Former episodes of wheezing, n (%)	32 (64.0)	77 (31.8)	<0.001 ^d
Previous hospitalizations for wheezing, n (%)	14 (28.6)	22 (8.0)	<0.001 ^d
ICU hospitalizations for wheezing, n (%)	1 (2.1)	4 (1.4)	0.553 ^f
Number of days with fever, median (range)	2 (1-7)	3 (1-14)	0.052 ^c
Antibiotics, n (%)	11 (22.9)	59 (21.1)	0.932 ^d

Abbreviations: ICU, intensive care unit; IQR, interquartile range.

^aDifferences in the descriptive characteristics of children with and without wheezing were evaluated using univariate statistical tests, as appropriate.

^bt-Test.

^cMann-Whitney U test.

^d χ^2 Test.

^eWheezing prophylaxis was defined as use of inhaled steroids or leukotriene inhibitors.

^fFisher's exact test.

participate in the study, and 11 were excluded because of inappropriate age, leaving 347 (65%) children for inclusion in the study.

The most common primary diagnosis in the children included in the study was fever without a source (n = 169, 49%). Acute otitis media was diagnosed in 48 (14%) of the children, and wheezing was diagnosed in 50 (14.4%). Other diagnoses included pneumonia, tonsillitis/pharyngitis, and upper-respiratory-tract infection. The mean age (in years) of the children diagnosed with wheezing was 1.4 ± 0.8 , compared with 1.9 ± 1.3 in children without wheezing ($P = 0.003$). The median number of days of fever before admission to the ED was 2 for children with wheezing (range = 1-7 days), compared with a median of 3 days (range = 1-14 days) in children without wheezing ($P = 0.052$). Additional characteristics of the children included in this study are detailed in Table 1.

In a crude comparison of the prevalence of acetaminophen use among children with and without wheezing, we found that the use of acetaminophen was similar in the children diagnosed with wheezing compared with children without wheezing (n = 39, 81.3%, vs n = 229, 82.7%, respectively; Table 2). In contrast, the use of ibuprofen was significantly lower in the children diagnosed with wheezing compared with those without wheezing (n = 22, 52.4%, vs n = 168, 69.4%, respectively). Of the children diagnosed with wheezing, 14 (35%) were treated with both acetaminophen and ibuprofen, whereas 112 (50%) children without wheezing were treated with both drugs.

Table 2. Use of Antipyretics in Children With and Without Wheezing (n = 347).

	Wheezing (n = 50)	No Wheezing (n = 297)
Acetaminophen, n (%)	39 (81.3)	229 (82.7)
Ibuprofen, n (%)	22 (52.4)	168 (69.4)
Double therapy, n (%)	14 (35.0)	112 (50.0)

In multivariate analyses adjusting for propensity score, acetaminophen was not associated with wheezing (adjusted odds ratio [OR] = 0.76; 95% CI = 0.24-2.39; Table 3), whereas ibuprofen was negatively associated with wheezing (OR = 0.36; 95% CI = 0.13-0.96; Table 3).

In subgroup analysis, we stratified patients into 2 groups: above and below 1.5 years of age. We found no significant association between acetaminophen use and wheezing in infants younger or older than 1.5 years (<1.5 years: OR = 1.5, 95% CI = 0.32-7.64; ≥ 1.5 years: OR = 0.26, 95% CI = 0.043-1.51). Likewise, we found no significant association between ibuprofen and wheezing in both age groups (<1.5 years: OR = 0.51, 95% CI = 0.17-1.47; ≥ 1.5 years: OR = 0.42, 95% CI = 0.09-1.98).

Discussion

Among children attending ED with fever, we found a negative association between ibuprofen use and wheezing and

Table 3. The Risk for Wheezing Following Exposure to Acetaminophen and Ibuprofen.

	Crude OR (95% CI)	Adjusted ^a OR (95% CI)
Acetaminophen	0.91 (0.41-2.00)	0.76 (0.24-2.39)
Ibuprofen	0.49 (0.25-0.94)	0.36 (0.13-0.96)

Abbreviation: OR, odds ratio.

^aAdjusted for propensity score (propensity score for each drug was calculated separately). Covariates used to calculate propensity score: age, sex, gestational week at birth, use of inhalers, atopic dermatitis, previous episodes of wheezing, previous hospitalizations for wheezing, previous intensive care unit hospitalizations for wheezing, known allergy, known allergy in the family, exposure to smoking, maternal smoking during pregnancy, asthma in the family, number of days with fever, and antibiotics use.

no association between acetaminophen use and wheezing. Children who were diagnosed with wheezing were on average younger, and born at an earlier gestational week. In analyses stratifying participants by age, we found no significant association between acetaminophen or ibuprofen use and wheezing.

Wheezing is a very common respiratory symptom among children, especially in the first years of life. The prevalence of wheezing with lower-respiratory-tract illness among children has been reported to be as high as 32.0% in the first year of life, after which it declined to 17% and 12.0% in the second and third years, respectively.²⁸ Epidemiological studies have identified several factors that are associated with an increased risk for wheezing in childhood. These include factors such as preterm birth (<37 weeks of gestation), family history of asthma, and allergic disposition.^{29,30} In the Avon Longitudinal Study of Parents and Children, preterm birth was associated with as much as a 70% to 80% increase in the risk for persistent and late-onset wheeze.²⁹

Wheezing has also been linked to a number of environmental factors, such as exposure to cigarette smoke.^{4,29,30} Exposure to some medications has also been reportedly associated with an increased risk for wheezing, most notably exposure to antibiotics and acetaminophen. Several studies have reported on an increased risk for developing wheezing and asthma after early life exposure to antibiotics,³¹⁻³³ and it has been suggested that this could be attributed to immunological effects as a result of changes in the microbiota.^{31,34} However, a meta-analysis examining the association between infant antibiotic use and wheeze and asthma risk found that the reported increased risk was not observed when the analysis was restricted to studies with low risk of confounding.²⁸

Similarly, a number of previous studies have reported that exposure to acetaminophen is positively associated with wheezing and asthma in children.^{6,7,35} Beasley et al⁶ reported that exposure to acetaminophen in childhood is associated with an increased risk for asthma (OR = 1.46; 95% CI = 1.36-1.56). Del-Rio-Navarro et al⁷ reported the association between exposure to acetaminophen in the first year of life,

and wheezing and asthma in 3 cities in Mexico (OR = 6.10, 95% CI = 3.30-8.81 for the risk of asthma in Mexico City). Similarly, a study by Amberbir et al,³⁶ in a cohort of infants in Ethiopia, linked acetaminophen use in the first 3 years of life with increased incidence of wheeze and eczema between ages 3 and 5 years. In contrast, a recent cross-sectional study of Canadian infants, by Batool et al,³⁷ found that acetaminophen exposure was inversely associated with allergic disease (defined as parental report of any of the following: wheezing, eczema, allergic rhinitis, or food allergy).

It has been previously noted that many of the studies that report an association of acetaminophen with wheezing may have been subject to methodological issues.^{35,38,39} Reports of positive associations between acetaminophen use and asthma or wheezing could have been the result of confounding by indication because children and adults with asthma have an increased risk for viral illness and fever, thus increasing their exposure to acetaminophen.^{35,38-40} Indeed, in our study, more than 80% of children with fever were treated with acetaminophen, indicating that the reported association between exposure to acetaminophen and asthma could have resulted from exposure to a viral pathogen and not the drug itself.^{41,42} Additionally, some have proposed that asthma itself can cause pain or fever and, thus, increase the exposure to acetaminophen.^{35,38,39}

The association between acetaminophen use and wheezing has also been evaluated in a post hoc analysis of a randomized controlled trial,¹⁴ which reported a positive association. Most recently, a randomized controlled trial, published by Sheehan et al,¹⁵ was performed to evaluate whether acetaminophen use increases the risk for asthma exacerbation. This trial demonstrated that acetaminophen use did not increase the risk of asthma exacerbation among children (aged 27-53 months) with mild persistent asthma. The authors of this important study note that their results might not extrapolate well outside of the clinical trial setting. Our results can, therefore, provide additional support for this trial's findings because they provide data regarding the risk for wheezing with acetaminophen in the general pediatric population presenting at the ED, in real-world settings. Because we had few and limited exclusion criteria, we believe that our study population is relatively representative of pediatric patients presenting to the ED with febrile illness.

Our results linking ibuprofen use with reduced risk of wheezing could theoretically indicate a protective effect of this agent, as has previously been reported.¹⁴ This effect has been attributed to the anti-inflammatory effects of ibuprofen¹⁴ and has some plausibility because ibuprofen has been found to preserve pulmonary function in children with cystic fibrosis.^{43,44} However, because this possibility is quite novel and inconsistent with other studies (including the recent randomized controlled trial by Sheehan et al¹⁵), we believe that a more likely explanation is that our results

arise from a propensity to avoid ibuprofen use among children with wheezing. Ibuprofen product labels include warnings regarding the use of ibuprofen in patients with asthma and state that ibuprofen may cause wheezing. We believe that it is likely that this deters some parents from using ibuprofen in children with wheezing.

Our results extend prior studies in several additional ways. First, our study population included a large number of participants <2 years of age, thus providing important data suggesting no association between acetaminophen and wheezing in this age group. Second, we found that there was likely a propensity to avoid ibuprofen use among children with wheezing. Third, our propensity score-adjusted analyses indicated that our findings with acetaminophen and ibuprofen were independent of several potentially confounding factors. Finally, when stratifying participants by age, we found no association between acetaminophen or ibuprofen use and wheezing; however, this may have been a result of the reduction in sample size inherent to stratification.

This study has several strengths and limitations. The study included a relatively large number of children, thus, powering it to detect associations between medication use and symptoms. The study design, by which only children with acute febrile illness were included for analysis, minimized the chance of confounding by indication. Additionally, the cross-sectional study design, by which the population was recruited at a single center under similar circumstances, reduced the chance of selection bias common to studies with case-control designs. Finally, the diagnosis of wheezing was made by a pediatrician, thus decreasing the probability of misclassification in diagnosis.

However, because this was a cross-sectional study, we were unable to assess whether the wheezing started before or after exposure to either acetaminophen or ibuprofen. We also did not have data on dose and duration of antipyretic use and were, therefore, unable to conduct a dose-response analysis and evaluate whether dose or duration might be linked with wheezing or with patient outcome. Additionally, because this was an observational study, and though our analyses and study design controlled for several potential confounding factors, the results could still suffer from residual confounding. And finally, as is wont in studies of this sort, not all eligible patients were recruited.

In conclusion, we report that acetaminophen was not associated with wheezing in the general pediatric population presenting to the ED. Our findings provide additional data negating earlier reports linking acetaminophen to wheezing and asthma exacerbations and could help inform clinicians and parents regarding the safety of acetaminophen use in children.

Authors' Note

The first 2 authors contributed equally to this article.

Declaration of Conflicting Interests

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