Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Sheehan WJ, Mauger DT, Paul IM, et al. Acetaminophen versus ibuprofen in young children with mild persistent asthma. N Engl J Med 2016;375:619-30. DOI: 10.1056/NEJMoa1515990

Supplementary Appendix:

Supplement to:

Acetaminophen versus Ibuprofen in Children with Mild Persistent Asthma

Sheehan WJ, Mauger DT, Paul IM, et al.

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CRITERIA FOR INITIATING RESCUE THERAPY (PREDNISOLONE)

The criteria for the initiating prednisolone are outlined below. These assume that the subject is already receiving treatment with short-acting beta agonist (SABA) as needed.

Criteria for initiating prednisolone. There are four scenarios for which prednisolone may be administered. The specific criteria for initiating prednisolone include the following:

1. Symptoms:

A. Symptoms do not improve after 3 ICS/SABA treatments administered every 20 minutes,

-OR-

B. >6 rescue treatments are needed for >24 hours (*Note: 1 rescue treatment equals 1 nebulized albuterol treatment or 2 inhalations of albuterol by a metered dose inhaler. Nebulized albuterol is NOT encouraged for use in this study, but is listed here in the event that subjects ignore study advice concerning rescue treatment),

-OR-

C. Moderate-severe cough or wheeze occurs for at least 5 of the preceding 7 days,

-OR-

D. Specified thresholds of rescue ICS/SABA use are reached (see below):

I. **Short-term use**: a 2-day average of 528 mcg or more of fluticasone per day. This is equivalent to 12 or more inhalations of fluticasone (44 mcg/inhalation) for symptom relief for 2 consecutive days (1056 mcg or more in total over those two days).

II. **Medium-term use**: a 5-day average of 352 mcg or more of fluticasone per day. This is equivalent to 8 or more inhalations of fluticasone (44 mcg/inhalation) for symptom relief for 5 consecutive days (1760 mcg or
more in total over those 5 days).

III. **Long-term use:** a 30-day average of 132 mcg or more of fluticasone per day. This is equivalent to 3 or more inhalations of fluticasone (44 mcg/inhalation) for symptom relief for 30 consecutive days (3960 mcg or more in total over those 30 days).

-OR-

2. There is an unscheduled visit for acute asthma care requiring repeated doses of SABA
(physician office, urgent care, emergency department),

-OR-

3. Hospitalization is needed for asthma,

-OR-

4. Physician discretion.

If physician discretion is utilized, a specific reason for initiation of prednisolone will be recorded. As outlined above, specific criteria were established for initiating systemic corticosteroid therapy with prednisolone for increasing asthma symptoms. Since initiation of systemic corticosteroid treatment is the primary outcome, specific measures will be implemented to optimize consistency of its initiation, including: 1) re-emphasis of these guidelines to all investigators, 2) inclusion of multiple questions of this process in the investigator's certification examination to document their understanding of the process, 3) completion of a reporting form when systemic corticosteroids are initiated that includes the reason(s) for its initiation, and 4) Data Coordinating Center monitoring for potential disparities of prednisolone use and deviations from the process by center.

Supplemental Table S1:

Sensitivity Analyses on Primary Outcome

Analysis		Exacerbation Rate (95% CI)		Relative Rate (95% CI)
		Acetaminophen	**Ibuprofen**	
Primary: use actual follow-up time and observed number of exacerbations		0.81 (0.65, 1.02)	0.87 (0.69, 1.10)	**0.94 (0.69, 1.28)**
Sensitivity: impute full follow-up time for all dropouts	Impute additional exacerbations beyond those observed to bring the total to 4	1.51 (1.24, 1.82)	1.58 (1.30, 1.91)	**0.95 (0.73, 1.25)**
	Impute no additional exacerbations beyond those observed prior to dropout	0.74 (0.59, 0.93)	0.75 (0.59, 0.94)	**1.00 (0.73, 1.35)**
	Impute random number of exacerbations, with maximum being 4 and minimum being the observed number of exacerbations prior to dropout	1.13 (0.93, 1.37)	1.16 (0.96, 1.41)	**0.97 (0.74, 1.26)**

Supplemental Table S2:

Adverse Events (those with at least 5%) during the Treatment Phase

Adverse Event Description	Ibuprofen	Acetaminophen
Acute nasopharyngitis	15 (10%)	9 (6%)
Acute pain NEC	41 (27%)	59 (39%)
Acute uri NOS	6 (4%)	10 (7%)
Allergic rhinitis NOS	35 (23%)	43 (29%)
Allergy, unspecified	28 (19%)	28 (19%)
Asthma NOS w (ac) exac	11 (7%)	12 (8%)
Cough	55 (37%)	54 (36%)
Diarrhea	30 (20%)	32 (21%)
Fever NOS	7 (5%)	10 (7%)
Headache	75 (50%)	92 (61%)
Nonspecif skin erupt NEC	15 (10%)	13 (9%)
Otalgia NOS	8 (5%)	12 (8%)
Otitis media NOS	7 (5%)	10 (7%)
Strep sore throat	28 (19%)	29 (19%)
Teething syndrome	13 (9%)	16 (11%)
Throat pain	3 (2%)	9 (6%)
Vomiting alone	4 (3%)	9 (6%)
Wheezing	17 (11%)	17 (11%)

Supplemental Table S3:

Serious Adverse Events (SAE) during the Treatment Phase

SAE #	Reason for SAE	Follow-up Treatment	Treatment Arm
1	Influenza	Hospitalization	Ibuprofen
2	Pneumonia due to RSV	Hospitalization	Acetaminophen
3	Asthma Exacerbation	Hospitalization	Acetaminophen
4	Asthma Exacerbation	Hospitalization	Ibuprofen
5	Asthma Exacerbation	Hospitalization	Ibuprofen
6	Wheezing/Hypoxia	Hospitalization	Ibuprofen
7	Constipation	Hospitalization	Ibuprofen
8	Bronchitis	Hospitalization	Ibuprofen
9	Chronic Tonsillitis and Adenoiditis	Hospitalization	Ibuprofen
10	Asthma Exacerbation	Hospitalization	Acetaminophen
11	Asthma Exacerbation	Hospitalization	Ibuprofen
12	Simple laceration of simple mucosa	Hospitalization	Acetaminophen
13	Cough	Hospitalization	Ibuprofen
14	Asthma Exacerbation	Hospitalization	Ibuprofen
15	Asthma Exacerbation	Hospitalization	Ibuprofen
16	Status Asthmaticus	Hospitalization	Acetaminophen
17	Asthma Exacerbation	Medication	Acetaminophen
18	Asthma Exacerbation	Hospitalization	Iburprofen

Supplemental Table S4:

Comparison of the frequency of usage of acetaminophen in this trial with other previous studies

	Other Study	AVICA Study Usage
Wickens et al. CEA 2010 - Ages 5-6 - One year - New Zealand	**ONE YEAR OF DATA:** ● 37% given acetaminophen >10 times ● 48% given acetaminophen 3-10 times ● 16% given acetaminophen 0-2 times	● 46.7% given acetaminophen >10 times per year ● 29.3% given acetaminophen 3-10 times per year ● 24.0% given acetaminophen 0-2 times per year
Sordillo et al. JACI 2015 - Birth to 1 year - One year - USA	**ONE YEAR OF DATA:** ● 42% given acetaminophen >10 times ● 24% given acetaminophen 6-10 times ● 29% given acetaminophen 1-5 times	● 46.7% given acetaminophen >10 times per year ● 16.0% given acetaminophen 6-10 times per year ● 20.7% given acetaminophen 1-5 times per year
Lowe et al. BMJ 2010 - Birth to 2 years - Two years - Australia	**TWO YEARS OF DATA:** ● Cumulative "Days" of Exposure = 17 (10-27) Median (IQR)	● 16.7 (4.2, 36.5) doses of exposure per 2 years Median (IQR)