### From “A” to “Wheeze”

**Acetaminophen’s Role in the Asthma Epidemic**

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**A 7-year-old child on controller therapy for asthma has a temperature of 100.1°F and a new prescription for an antibiotic. Her mother tells you that the pediatrician recommended that she should also get “something OTC for the fever”**.

Do you recommend:

A. Acetaminophen?  
B. Ibuprofen?

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### Learning Objectives

- Discuss the role of acetaminophen (APAP) in the asthma epidemic in children
- Evaluate safety of other alternatives
- Provide appropriate analgesic/antipyretic recommendations for children with asthma
Background
Asthma

Asthma Statistics

- 10.5 million physician office visits
- 1.8 million ED visits
- $50+ billion spent per year
- 49% of children with asthma missed >1 day of school

Current Asthma Prevalence Percents by Age, Sex, and Race/Ethnicity, United States, 2014

Data, Statistics, and Surveillance, Center for Disease Control and Prevention (2016)
What causes asthma?

- Environmental triggers
- Airway infections
- Genetics
- "Hygiene Hypothesis"
What is asthma?

Cell mediated immunity & Delayed hypersensitivity

Pathophysiology

APAP and Asthma
Three Main Questions

1. Does frequent APAP use lead to asthma in children?
2. Does frequent APAP use worsen symptoms in children who already have asthma?
3. Are the alternatives (i.e. ibuprofen) any safer?

Noted in 1980s:
- Pediatric aspirin (ASA) use decreased
- Childhood asthma prevalence increased

 Decreased use of ASA may be a factor in facilitating allergic sensitization and asthma.

Cell mediated immunity & Delayed hypersensitivity
Allergic inflammation
The First Hypothesis:
Varner, et al. (1998)

- Conclusion:
  - Elimination of pediatric ASA may be an important contributor
  - Relationship between APAP and asthma is unproven, further investigation is needed

Epidemiological Evidence:
Shaheen, et al. (2000)

- Background:
  - Animal studies showed that APAP depletes glutathione (GSH) in lungs
  - GSH is an antioxidant that may defend against oxidative stress of asthma inflammation
  - Increased GSH levels in airways of adults with asthma

Frequent APAP use is associated with asthma.
**Epidemiological Evidence:**
Shaheen, et al. (2000)

**Design**
- Population based case-control
- Survey on frequency of ASA/APAP use in people with asthma vs. without
- Controlled for confounding risk factors

**Participants**
- Aged 16-49y
- Defined “asthmatic” or “non-asthmatic” based on screening questions
- N = 1574 (664 cases vs. 910 controls)

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**Epidemiological Evidence:**
Shaheen, et al. (2000)

**Table 2** Association between asthma and frequency of analgesic use

<table>
<thead>
<tr>
<th>Drug</th>
<th>Case N (%)</th>
<th>Control N (%)</th>
<th>Odds OR (95% CI)</th>
<th>OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>537 (90)</td>
<td>504 (91)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>&lt;Monthly</td>
<td>254 (29)</td>
<td>250 (27)</td>
<td>0.87 (0.69 to 1.08)</td>
<td>1.04 (0.81 to 1.35)</td>
</tr>
<tr>
<td>Monthly</td>
<td>46 (7)</td>
<td>36 (5)</td>
<td>0.99 (0.67 to 1.48)</td>
<td>0.97 (0.54 to 1.75)</td>
</tr>
<tr>
<td>Weekly</td>
<td>39 (6)</td>
<td>31 (5)</td>
<td>1.13 (0.70 to 1.82)</td>
<td>1.01 (0.60 to 1.70)</td>
</tr>
<tr>
<td>Daily</td>
<td>14 (2)</td>
<td>7 (1)</td>
<td>1.24 (0.98 to 1.59)</td>
<td>0.95 (0.47 to 1.90)</td>
</tr>
<tr>
<td>Paracetamol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>153 (17)</td>
<td>142 (16)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>&lt;Monthly</td>
<td>42 (5)</td>
<td>38 (4)</td>
<td>0.95 (0.71 to 1.28)</td>
<td>1.06 (0.77 to 1.45)</td>
</tr>
<tr>
<td>Monthly</td>
<td>219 (24)</td>
<td>205 (23)</td>
<td>1.23 (0.99 to 1.54)</td>
<td>1.23 (0.97 to 1.57)</td>
</tr>
<tr>
<td>Weekly</td>
<td>97 (11)</td>
<td>82 (9)</td>
<td>1.69 (1.16 to 2.44)</td>
<td>1.79 (1.21 to 2.65)</td>
</tr>
<tr>
<td>Daily</td>
<td>17 (2)</td>
<td>12 (1)</td>
<td>2.76 (1.44 to 5.35)</td>
<td>2.84 (1.35 to 5.99)</td>
</tr>
</tbody>
</table>

*p (trend) = 0.017

*Controlling the other analgesic and factors listed in table 1.

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**Epidemiological Evidence:**
Shaheen, et al. (2000)

**Table 4** Indications for analgesic use among individuals who reported continuing frequent (daily/monthly) use when re-surveyed

<table>
<thead>
<tr>
<th>Condition</th>
<th>Paracetamol</th>
<th>Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case</strong> (n = 71)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>61 (86%)</td>
<td>15 (60%)</td>
</tr>
<tr>
<td>Migraine</td>
<td>14 (19%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Backache/Back pain</td>
<td>22 (31%)</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>General headache</td>
<td>26 (37%)</td>
<td>8 (33%)</td>
</tr>
<tr>
<td>Asthma/asthma/bronchitis</td>
<td>3 (4%)</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>Hayfever/rash allergy/blocked nose</td>
<td>10 (14%)</td>
<td>5 (12%)</td>
</tr>
<tr>
<td><strong>Control</strong> (n = 23)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Epidemiological Evidence:**
Shaheen, et al. (2000)

- **Conclusion:**
  - Frequent (daily/weekly) APAP use, possibly overuse, positively associated with asthma
  - Dose-related response - causal?
  - Unlikely that relationship is attributable to higher prevalence of co-morbidity
  - ASA avoidance can only explain part of the association, not all

**An Ecological Look:**
Newson, et al. (2000)

So far:
- **Varner:** \(\downarrow\) ASA \(\rightarrow\) \(\uparrow\) APAP \(\rightarrow\) \(\uparrow\) asthma?
- **Shaheen:** frequent APAP \(\leftrightarrow\) asthma?

**Hypothesis**
Countries with higher national APAP sales are associated with higher asthma symptom prevalence.

**Design**
- Linear regression analysis:
  - International symptom-prevalence data
  - National per-capita APAP sales

**Participants**
- Aged 6-7y, 13-14y
- \(N = ?\) (22 countries)
An Ecological Look:
Newson, et al. (2000)

Table 1. - International Study of Asthma and Allergies in Childhood-Regression coefficients (b) of symptom prevalences with respect to national per capita personal disposable income

<table>
<thead>
<tr>
<th>Treatment</th>
<th>b (95% CI)</th>
<th>p-value</th>
<th>b (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.49 (0.46-0.52)</td>
<td>&lt;0.0001</td>
<td>0.52 (0.49-0.55)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Wheeze</td>
<td>0.30 (0.27-0.33)</td>
<td>&lt;0.0001</td>
<td>0.30 (0.27-0.33)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Asthma scores</td>
<td>0.32 (0.29-0.35)</td>
<td>&lt;0.0001</td>
<td>0.32 (0.29-0.35)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Renal function</td>
<td>0.30 (0.27-0.33)</td>
<td>&lt;0.0001</td>
<td>0.30 (0.27-0.33)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

n = 111 countries (119 for symptoms in 10 national studies); * = 94 countries (95 for symptoms in 28 studies for symptoms). ** GDP = gross domestic product; CI = confidence interval.

"Anglophone effect"
English-speaking Western countries tend to have:
- Highest prevalence of asthma symptoms
- Highest APAP sales

Post hoc analysis:
- All associations between APAP and asthma symptoms → abolished or non-significant
**An Ecological Look:**
Newson, et al. (2000)

- **Conclusion:**
  - National APAP sales positively associated with prevalence of asthma symptoms
  - “Anglophone effect”
  - Likely due to confounder strongly associated with English-speaking countries
  - Warrants further investigation

**Limitations to Observational Studies**

- Weak strength of evidence
- Confounding by indication
  - Causal association is difficult to determine
- Exposure data not linked to individuals

**Putting It All Together**

- Meta-Analysis
**Meta-Analysis:**
Garcia-Marcos, et al. (2011)

- 41 sub-studies
- Infants, children, adults, pregnant women
- Longitudinal, cross-sectional
- Pooled OR = 1.48

"... no matter what type of study, age, or time of exposure, there is always a positive association between exposure and respiratory symptoms"
**First Randomized Controlled Trial:**
Lesko, et al. (2002)

**Hypothesis**
- Short-term use of ibuprofen increases asthma morbidity in children

**Design**
- Randomized, double-blind, APAP-controlled
- Measured hospitalization and outpatient visits for asthma

**Participants**
- Aged 6m-12y with asthma and fever
- N = 1879

**Intervention**
- APAP 12 mg/kg, ibuprofen 5 mg/kg, ibuprofen 10 mg/kg
- Followed x 4 weeks

**Results**
- No difference in hospitalization rates
- Outpatient visits significantly lower in ibuprofen group

**TABLE 1.** Distribution of Outpatient Visits for Asthma During Follow-up According to Antipyretic Assignment Among Children With Asthma

<table>
<thead>
<tr>
<th>Antipyretic</th>
<th>Number of Visits</th>
<th>Total Number</th>
<th>Unadjusted Relative Risk Estimate (99% CI)</th>
<th>Adjusted Relative Risk Estimate (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>37</td>
<td>692</td>
<td>1.09 (0.97-1.23)</td>
<td>1.09 (0.97-1.23)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>37</td>
<td>1207</td>
<td>0.59 (0.37-0.95)</td>
<td>0.56 (0.34-0.95)</td>
</tr>
</tbody>
</table>
First Randomized Controlled Trial: Lesko, et al. (2002)

- **Conclusion:**
  - Compared to APAP, ibuprofen has lower risk of asthma morbidity
  - Due to no placebo-control, cannot determine whether difference is due to APAP increasing risk or ibuprofen decreasing risk

AVICA Trial
Sheehan, et al. (2016)

- **Hypothesis**
  - Asthma morbidity is higher in APAP vs. ibuprofen in children with mild persistent asthma

- **Design**
  - Multicenter, prospective, double-blind, parallel-group
  - 48 weeks, measured exacerbation frequencies
AVICA Trial
Sheehan, et al. (2016)

Participants
- Aged 1-5y with mild persistent asthma
- N = 300

Intervention
- APAP 15 mg/kg q6h prn
- Ibuprofen 9.4 mg/kg q6h prn

AVICA Trial
Sheehan, et al. (2016)

Results
- No significant difference in exacerbation rates between groups

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Aminophylline (N=238)</th>
<th>Ibuprofen (N=239)</th>
<th>Relative Rate (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Among 298 trial participants</td>
<td>0.91 (0.66 to 1.23)</td>
<td>0.97 (0.69 to 1.39)</td>
<td>0.54 (0.36 to 0.84)</td>
<td>0.67</td>
</tr>
<tr>
<td>Among 238 participants who completed the trial</td>
<td>0.91 (0.68 to 1.23)</td>
<td>0.74 (0.51 to 1.09)</td>
<td>1.01 (0.71 to 1.43)</td>
<td>0.79</td>
</tr>
<tr>
<td>Among 238 participants who completed the trial and used at least one dose of trial medication</td>
<td>0.74 (0.51 to 1.09)</td>
<td>0.74 (0.51 to 1.09)</td>
<td>1.01 (0.71 to 1.43)</td>
<td>0.79</td>
</tr>
</tbody>
</table>

AVICA Trial
Sheehan, et al. (2016)

Conclusion:
- No significant difference does not necessarily mean that they are equal (RR CI = 0.69-1.28)
- Results may not be generalizable to:
  - Higher severity of asthma
  - Non-adherent children
  - Due to no placebo-control, cannot exclude possibility that both ibuprofen and APAP may be associated
What Do You Think?
Revisiting the Patient Case

A 7-year-old child on controller therapy for asthma has a temperature of 100.1°F and a new prescription for an antibiotic. Her mother tells you that the pediatrician recommended that she should also get “something OTC for the fever”.

Do you recommend:
A. Acetaminophen?
B. Ibuprofen?

Reviewer’s Thoughts
+ **Evidence Checklist**

- Exposure precedes onset of disease
- Plausible biological mechanism
- Consistency across different study settings
- Temporal relationship to exposure
- Identification of dose-response effect
- Specificity to causative agent with no convincing alternative explanation
- Reversibility of the causal effect


+ **Conclusion**

- Multiple observational studies suggest:
  - Dose-related relationship between APAP use (possibly APAP overuse) and asthma
  - Plausible mechanism(s)
- Existing RCTs suggest:
  - Ibuprofen is not necessarily a better alternative
  - More RCTs needed to strengthen evidence
  - Lacking data on reversibility of effect

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+ Bibliography


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