AAIFNC JOURNAL CLUB

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Azithromycin for episodes with asthma-like symptoms in young children aged 1–3 years: a randomised, double-blind, placebo-controlled trial

How should we treat this?
Introduction

• Bacteria and viruses equally likely to trigger asthma-like Sx in the first 3 yrs of life (COPSAC 2000)
  • Challenge to previously held notions
• Potential role for bacterial infections ➔ antibiotics as treatment?
• Antibiotics not part of current treatment guidelines… but commonly prescribed
  • Previous RCTs: no beneficial effect of beta-lactam antibiotics for asthma exacerbations
  • Current study: 1st RCT of azithromycin as treatment for acute episodes of asthma-like Sx in young children
Methods

- Randomized, double-blind, placebo-controlled trial conducted Nov 2010-Jan 2014
- Subject Population: Children aged 1-3 from the COPSAC2010 cohort
- Inclusion criteria: Recurrent troublesome/asthma-like Sx (cough, wheeze or dyspnea) lasting at least 3 days
- Exclusion criteria:
  - Macrolide allergy
  - Heart, liver, neurological and kidney disease
  - 1 or more clinical signs of PNA: RR>50, fever 39C or higher, CRP 50mg/L or higher
Methods

- Random allocation to oral solution of azithromycin vs placebo
  - Subjects eligible for repeated randomization, independent of previous treatment
- N = total # of episodes, not subjects
  - 158 asthma like episodes in 72 subjects
- 1:1 randomization of 158 episodes
  - 79 in azithromycin group
  - 79 in placebo group
- Investigators and families were blinded until youngest child turned 3 and until data analysis for primary outcome was complete
- Good Clinical Practice guidelines
Procedures

- Daily recording of respiratory Sx from birth
- For Sx lasting ≥3 consecutive days, child brought in for acute visit
- Acute visit
  - Sx diary reviewed and validated with composite scoring system
  - Physical exam
  - Labs: CRP
  - Hypopharyngeal aspirate sent for bacterial culture
  - Nasopharyngeal aspirate sent for viral PCR analysis
  - Treatment: beta 2 agonist salbutamol and:
    - Montelukast x2 weeks for children who had previously benefited
    - Prednisolone 1-2 mg/kg daily x 3 days for severe episodes
Procedures

- Recurrent “troublesome lung Sx” defined as:
  - 5 episodes of Sx within 6 months or
  - 4 weeks of continuous Sx or
  - severe acute episode requiring prednisolone or hospitalization

- When recurrence criteria met, 3-month course of fluticasone 2x50 mcg BID
  - If rebound in Sx after cessation of ICS ➔ 6-month course
  - For subsequent acute episodes, randomization to azithromycin 10mg/kg x3 days or placebo
Data Analysis Plan

• **Primary** outcome:
  • 1) Duration of asthma like Sx after initiation of treatment (based on symptom diary)
    • Analysis excluded those without a primary outcome or who did not receive treatment

• **Secondary** outcomes:
  • 1) Time from current treatment to the next episode
  • 2) Number of severe exacerbations (i.e. those needing oral steroids or hospitalization)
  • 3) Duration of beta2 agonist use after treatment

• Safety analysis using daily symptom diary and hospital records
  • Included all those who received treatment, even those without primary outcome
Data Analysis Plan

- Poisson regression to assess duration of Sx and beta2 agonist use after treatment

- Included a random effect of child to account for heterogeneity between children

- Assessed potential modifiers of the treatment effect
Results

- Of the 700 children enrolled in the COPSAC2010 cohort, 207 (30%) were diagnosed with recurrent troublesome lung symptoms during first 3 years of life.

- Of the 207 eligible for enrollment, 72 (35%) were enrolled in the study.

- Power calculation based on duration of troublesome lung symptoms seen in COPSAC2000:
  - 86 independent episodes needed to detect a difference of 1 day of \( Sx \) duration.
Figure 1

207 children assessed for eligibility

135 children ineligible

72 children enrolled

79 episodes randomly assigned azithromycin
79 episodes randomly assigned placebo

1 episode excluded because drug not ingested

4 episodes excluded because of missing primary outcome measure

5 episodes excluded because of missing primary outcome measure

74 episodes included in per-protocol analysis
74 episodes included in per-protocol analysis

78 episodes included in safety analysis
79 episodes included in safety analysis
Results

• Mean age at randomization: 2.0 years

• Mean number of randomizations: 2.2

• Concurrent medications
  • ICS treatment in 82% of the 148 episodes (84% in the A group, 80% in the P group)
  • Montelukast in 60% of the 148 episodes (64% in the A group, 57% in the P group)
Results

• Good (97%) adherence to treatment
  • 1 treatment never given (A group)
  • 3 treatments discontinued before completion (1 in A group, 2 in P group)

• Excellent follow-up from enrollment in the study until age 3 in 71 of 72 children!

• Baseline characteristics of participants and non-participants did not differ significantly
  • Except for maternal history of asthma (p=0.03)
  • Table 1
## Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>RCT participants (n=72)</th>
<th>Non-RCT participants (n=135)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participant History:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>47 (65%)</td>
<td>74 (55%)</td>
</tr>
<tr>
<td>White</td>
<td>70 (97%)</td>
<td>130 (96%)</td>
</tr>
<tr>
<td>Older children in the home at birth</td>
<td>39 (54%)</td>
<td>70 (52%)</td>
</tr>
<tr>
<td>Sensitization (SPT or specific IgE)</td>
<td>8 (11%)</td>
<td>20 (15%)</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>21 (30%)</td>
<td>39 (30%)</td>
</tr>
<tr>
<td>17q21 risk variant (RS2305480)</td>
<td>26 (41%)</td>
<td>46 (39%)</td>
</tr>
<tr>
<td>Smoking in pregnancy</td>
<td>9 (13%)</td>
<td>16 (12%)</td>
</tr>
<tr>
<td>Cat or dog at birth</td>
<td>26 (36%)</td>
<td>48 (36%)</td>
</tr>
<tr>
<td>Antibiotics in pregnancy</td>
<td>31 (43%)</td>
<td>50 (37%)</td>
</tr>
<tr>
<td>Term birth &gt;37 weeks</td>
<td>67 (93%)</td>
<td>127 (94%)</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>18 (25%)</td>
<td>31 (23%)</td>
</tr>
<tr>
<td>Season of birth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Winter</td>
<td>25 (35%)</td>
<td>38 (28%)</td>
</tr>
<tr>
<td>Spring</td>
<td>17 (24%)</td>
<td>37 (27%)</td>
</tr>
<tr>
<td>Summer</td>
<td>12 (17%)</td>
<td>29 (21%)</td>
</tr>
<tr>
<td>Autumn</td>
<td>18 (25%)</td>
<td>31 (23%)</td>
</tr>
</tbody>
</table>
## Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>RCT participants (n=72)</th>
<th>Non-RCT participants (n=135)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal History:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal age at birth (years)</td>
<td>31.9 (4.7)</td>
<td>32.2 (4.5)</td>
</tr>
<tr>
<td>Maternal asthma</td>
<td>31 (44%)</td>
<td>38 (28%)</td>
</tr>
<tr>
<td><strong>Maternal educational level</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>9 (13%)</td>
<td>15 (11%)</td>
</tr>
<tr>
<td>Medium</td>
<td>53 (74%)</td>
<td>83 (61%)</td>
</tr>
<tr>
<td>High</td>
<td>10 (14%)</td>
<td>37 (27%)</td>
</tr>
<tr>
<td><strong>Household annual income</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>4 (6%)</td>
<td>17 (13%)</td>
</tr>
<tr>
<td>Medium</td>
<td>45 (63%)</td>
<td>73 (54%)</td>
</tr>
<tr>
<td>High</td>
<td>23 (32%)</td>
<td>45 (33%)</td>
</tr>
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</table>
Results-

Figure 2

- Mean duration of symptomatic period was 3.4 days (A group) vs 7.7 days (P group), reflecting a reduction of 63.3%
- Highly statistically significant (p<0.0001)
- Difference observed even when analysis restricted to first randomized treatment
Results-Figure 3

- Increased effect size (83% vs 36%) with early introduction
Results

• No significant difference in treatment effect due to fever, elevated CRP, wheeze on exam, presence of pathogenic bacteria or viruses*, or use of ICS or montelukast
  • *Azithromycin was more effective when H. influenzae was cultured from participants (77% vs 33% reduction in episode duration, p=0.0323)

• Duration of respiratory episodes was not related to gender, maternal smoking status, sensitization to inhalant or food allergens (assessed at 6 and 18 months), atopic dermatitis, or 17q21 genetic variant
Results

• Secondary outcomes
  • 1) Azithromycin did not significantly change the time until the next episode
  • 2) No significant reduction in the duration of beta2 agonist use
    • 8.9 vs 10.1 days, reflecting a 22% reduction in A group (p=0.006)
  • 3) Too few episodes of severe exacerbations to assess the effect of azithromycin on this outcome

• Safety analysis
  • No differences between A and P groups with respect to serious (or any) adverse effects, GI Sx, or other infections
Summary of Results

• Azithromycin reduced the duration of respiratory symptoms in children aged 1-3 with prior history of recurrent episodes of asthma-like Sx by 63%

• Greater improvement if treatment with azithromycin was started early (before day 6 of Sx)

• No long-term effect on the risk of having subsequent episodes of asthma-like Sx

• Potential to have significant benefit to children, parents, and health care system


Discussion

Strengths

• Prospective
• Daily symptom diary before episodes
• Standardized, validated approach
• In-depth clinical assessment to collect objective data and to exclude PNA
• Excellent follow-up
• Potential for broad application

Limitations

• Not able to generalize to a less controlled setting, e.g. initiation at home by parents
• Resource intensive….but consider current use of health care resources
• Study population is relatively homogenous
  • Are results generalizable to less homogenous populations?
## Comparison of Studies

<table>
<thead>
<tr>
<th>JAMA- AsthmaNet</th>
<th>Lancet- COPSAC</th>
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<tbody>
<tr>
<td>United States</td>
<td>Europe</td>
</tr>
<tr>
<td>Diverse</td>
<td>Homogenous</td>
</tr>
<tr>
<td>Age 12-71 months</td>
<td>Age 1-3 years</td>
</tr>
<tr>
<td>Prevention</td>
<td>Treatment</td>
</tr>
<tr>
<td>More exclusion criteria</td>
<td>Less exclusion criteria</td>
</tr>
<tr>
<td>Concurrent meds restricted</td>
<td>Concurrent meds allowed</td>
</tr>
</tbody>
</table>
Discussion-Potential Mechanisms

• Antibacterial, anti-inflammatory, and possibly antiviral

• Decreased Sx duration even without bacterial pathogen suggests role other than antibacterial

• Likely acting on acute inflammatory or infectious process rather than on chronic underlying inflammation
  • Increased effect size with early initiation of treatment and no effect on time to next episode supports this

• Further research needed to distinguish inflammatory versus antibacterial versus antiviral aspects of the drug
Discussion

• Reduction of IL-8 in previous RCT of azithromycin in RSV-positive children suggests anti-inflammatory effect
  • Lack of benefit of antibiotics without anti-inflammatory effect in previous RCTs

• Neutrophilic inflammation is a common feature of recurrent asthma-like Sx in young children
  • May explain increased effect of azithromycin in the setting of H. influenzae that was observed in this RCT

• Some data to suggest that macrolides reduce exacerbations in adults with neutrophilic predominant inflammation
Conclusion

• Results are promising (potential treatment for a relatively common unmet medical need) but more research needed
  • Comparison to narrow-spectrum antibiotics
  • Long-term effects of azithromycin use
  • Emergence of bacterial resistance
  • Potential future use of biomarkers or identifying specific phenotypes to target therapy