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

Stokholm J, Chawes BL, Vissing NH, Bjarnadóttir E, Pedersen TM, Vinding RK, Schoos AM, Wolsk HM, Thorsteinsdóttir S, Hallas HW, Arianto L, Schjørring S, Krogfelt KA, Fischer TK, Pipper CB, Bønnelykke K, Bisgaard H.

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

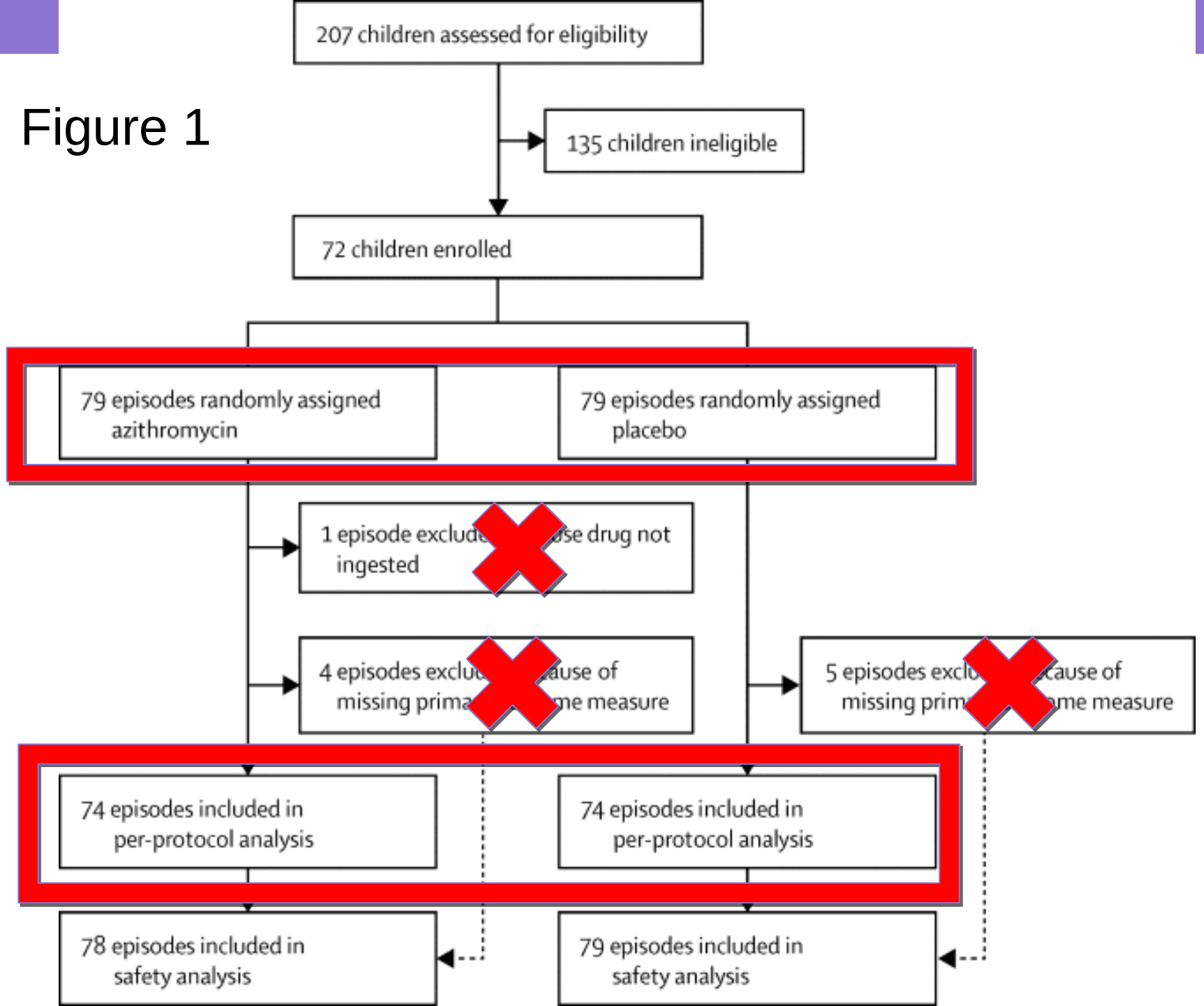
Results

- 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

Results-Table 1

Baseline characteristics

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

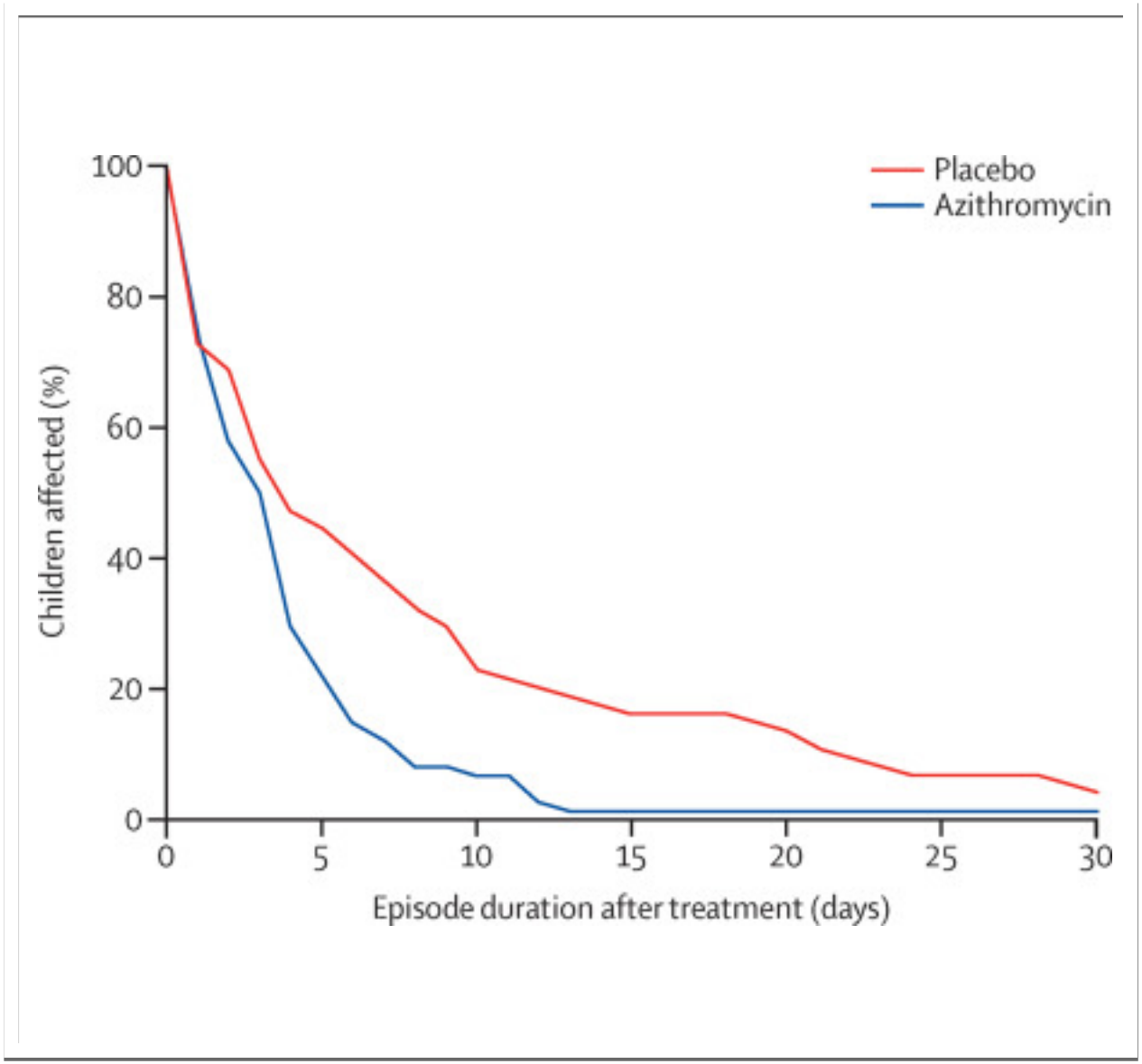
Results-Table 1, con't

Baseline characteristics

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

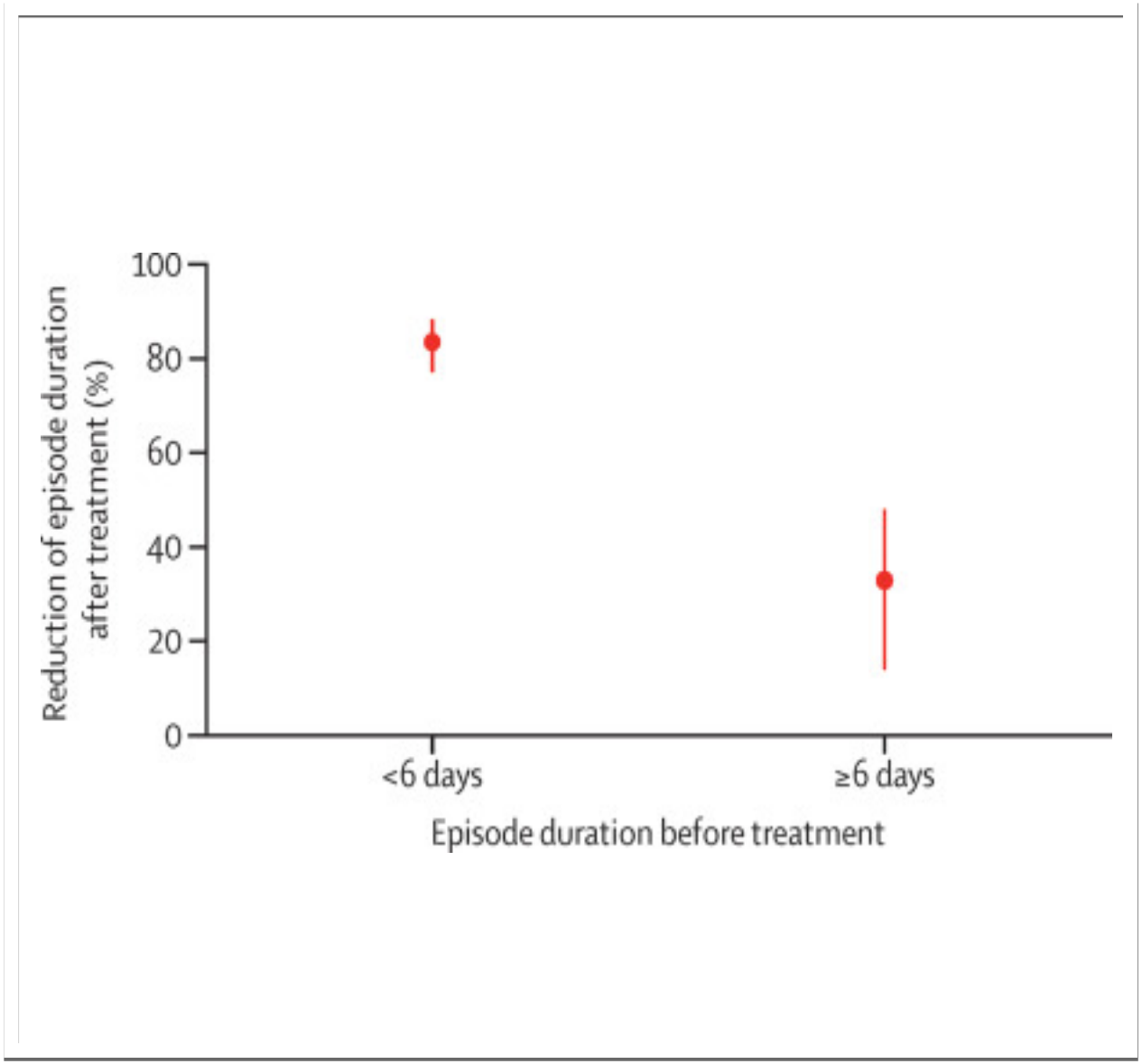
Results- Figure 2

- 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 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

JAMA- AsthmaNet

- United States
- Diverse
- Age 12-71 months
- Prevention
- More exclusion criteria
- Concurrent meds restricted

Lancet- COPSAC

- Europe
- Homogenous
- Age 1-3 years
- Treatment
- Less exclusion criteria
- Concurrent meds allowed

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