Episodic vs. Continuous Use of Inhaled Steroids in Preschool Wheezing Children

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Disclosures

- **Employment**
  - Washington University

- **Financial Interests**
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  - Research Support: Vectura, Sanofi/Regeneron

- **Research Interests**
  - NIH – NHLBI, NIAID

- **Organizational Interests**
  - AAAAI Annual Meeting Planning Committee
  - ABAI – Director
  - JACI – Associate Editor
  - GINA – Science Committee

- **Gifts**
  - Nothing to Disclose

- **Other Interests**
  - Nothing to Disclose
Learning Objective

Examine the potential roles of continuous and intermittent ICS therapy in the management of recurrent wheezing in preschool children.
Stepwise Approach – Pharmacotherapy (children ≤5 years)

**CONSIDER THIS STEP FOR CHILDREN WITH:**

**RELIEVER**
- As-needed short-acting beta₂-agonist (all children)

**PREFERRED CONTROLLER CHOICE**
- Other controller options

**STEP 1**
- Daily low dose ICS

**STEP 2**
- Leukotriene receptor antagonist (LTRA)
- Intermittent ICS

**STEP 3**
- Double 'low dose' ICS
- Low dose ICS + LTRA

**STEP 4**
- Continue controller & refer for specialist assessment
- Add LTRA
- Inc. ICS frequency
- Add intermittent ICS

**Other controller options**
- Intermittent ICS
- Daily low dose ICS
- Double 'low dose'

Infrequent viral wheezing and no or few interval symptoms

Symptom pattern consistent with asthma and asthma symptoms not well-controlled, or ≥3 exacerbations per year

Symptom pattern not consistent with asthma but wheezing episodes occur frequently, e.g. every 6–8 weeks.

Give diagnostic trial for 3 months.

Asthma diagnosis, and not well-controlled on low dose ICS

Not well-controlled on double ICS

First check diagnosis, inhaler skills, adherence, exposures
Case

- 3 yr old with atopic dermatitis and 4 episodes/yr of wheezing, 2-3 severe enough to require oral corticosteroids
- Episodes separated by long periods without any asthma-related symptoms
- At high risk for persistent asthma (positive asthma predictive index) – recurrent wheeze and atopic dermatitis
Modified Asthma Predictive Index (mAPI)

Identifies High Risk Children Ages 2-3 Years

≥ 4 wheezing episodes in the past year (at least one must be MD diagnosed)

PLUS

One major criterion
- Parent with MD asthma
- MD atopic dermatitis
- Aeroallergen sensitivity

OR

Two minor criteria
- Food sensitivity
- Peripheral eosinophilia (≥4%)
- Wheezing not related to infection

Daily ICS Therapy

- NAEPP/EPR3 and GINA Recommended First Line Therapy
  - Efficacy
  - Heterogeneity in response
  - Growth effects
PEAK – Outcomes

Screening/Eligibility → Run-in 1 month → Treatment Phase – FP 88mcg BID or Placebo → Observation Phase

Treatment Phase:
↓ Exacerbations (57.4/100 child-yrs vs 89.4/100 child-yrs)
↓ Supplemental medications (ICS and LTRA)
= bronchodilator use and unscheduled visits

Observation Phase:
= Exacerbations
= Supplemental medications (ICS and LTRA)
= Bronchodilator use and unscheduled visits

EFD: No cough or wheeze, unscheduled clinic, urgent care, ED or hospital visits; no use of asthma medications

Guilbert, NEJM 2006
Meta-analysis of 23 studies (3592 subjects) 1-23mo with wheezing or asthma for ≥6mo

ICS therapy associated with **significantly fewer exacerbations** requiring oral corticosteroids (18 vs 32.1%, RR 0.59, 0.52-0.67, p=0.0001)), **NNT=7 (95% CI 6-9)**

- Effect greater in those with “asthma” rather than “wheezing” (RR 0.65 (0.55-0.80) for wheeze vs 0.50 (0.41-0.61) for asthma; Interactive test RR 0.76 (0.58-0.99), p=0.04

# PEAK - Heterogeneity of ICS Response Within the mAPI+ Population

<table>
<thead>
<tr>
<th>Stratifying Variable</th>
<th>Percentage of Episode-Free Days</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ICS Mean (95% CI)</td>
<td>Placebo Mean (95% CI)</td>
<td>Difference (95% CI)</td>
<td>P-value (ICS vs Placebo)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>93 (92, 95)</td>
<td>86 (83, 89)</td>
<td>7.3 (3.9, 11.1)</td>
<td>0.0005</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>92 (89, 94)</td>
<td>92 (89, 94)</td>
<td>0.1 (-3.4, 3.5)</td>
<td>0.9</td>
<td></td>
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<tr>
<td>Caucasian</td>
<td>93 (91, 95)</td>
<td>84 (80, 88)</td>
<td>9.1 (4.8, 13.9)</td>
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<tr>
<td>Non-Caucasian</td>
<td>92 (89, 94)</td>
<td>93 (91, 94)</td>
<td>-1.0 (-3.9, 1.7)</td>
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<tr>
<td>Run-In EFD &lt;80%</td>
<td>92 (90, 94)</td>
<td>84 (79, 87)</td>
<td>8.6 (4.2, 13.2)</td>
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<td>Run-In EFD ≥80%</td>
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<td>93 (91, 95)</td>
<td>0.0 (-2.5, 2.5)</td>
<td>0.9</td>
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<tr>
<td>ED/Hospitalization History</td>
<td>95 (93, 96)</td>
<td>87 (83, 90)</td>
<td>7.7 (3.9, 11.6)</td>
<td>0.0004</td>
<td></td>
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<tr>
<td>No ED/Hospitalization History</td>
<td>90 (87, 92)</td>
<td>91 (89, 93)</td>
<td>-1.1 (-4.4, 2.1)</td>
<td>0.6</td>
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<tr>
<td>≥1 Positive Aeroallergen Skin Test</td>
<td>93 (91, 94)</td>
<td>86 (83, 89)</td>
<td>6.5 (3.2, 10.0)</td>
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<td>Negative Aeroallergen Skin Test</td>
<td>93 (90, 95)</td>
<td>92 (89, 94)</td>
<td>0.9 (-2.5, 4.4)</td>
<td>0.6</td>
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# PEAK - Heterogeneity of ICS Response Within the mAPI+ Population

<table>
<thead>
<tr>
<th>Stratifying Variable</th>
<th>Number of Prednisolone Bursts</th>
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<tr>
<td></td>
<td>ICS Mean (95% CI)</td>
<td>Placebo Mean (95% CI)</td>
<td>Relative Rate (95% CI)</td>
<td>P-value (ICS vs Placebo)</td>
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<tr>
<td>Male</td>
<td>1.1 (0.9, 1.4)</td>
<td>1.8 (1.5, 2.2)</td>
<td>0.6 (0.5, 0.8)</td>
<td>0.0009</td>
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</tr>
<tr>
<td>Female</td>
<td>1.6 (1.2, 1.9)</td>
<td>1.4 (1.1, 1.7)</td>
<td>1.2 (0.8, 1.6)</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>1.4 (1.1, 1.7)</td>
<td>2.2 (1.9, 2.7)</td>
<td>0.6 (0.5, 0.8)</td>
<td>0.0004</td>
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<tr>
<td>Non-Caucasian</td>
<td>1.3 (1.0, 1.6)</td>
<td>1.1 (0.9, 1.4)</td>
<td>1.2 (0.8, 1.7)</td>
<td>0.3</td>
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<tr>
<td>ED/Hospitalization History</td>
<td>1.2 (0.98, 1.6)</td>
<td>2.3 (1.9, 2.8)</td>
<td>0.5 (0.4, 0.7)</td>
<td>&lt;0.0001</td>
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<tr>
<td>No ED/Hospitalization History</td>
<td>1.4 (1.1, 1.8)</td>
<td>1.1 (0.8, 1.3)</td>
<td>1.3 (0.97, 1.8)</td>
<td>0.08</td>
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<tr>
<td>≥1 Positive Aeroallergen Skin Test</td>
<td>1.3 (1.0, 1.5)</td>
<td>2.1 (1.7, 2.4)</td>
<td>0.6 (0.5, 0.8)</td>
<td>0.0003</td>
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</tr>
<tr>
<td>Negative Aeroallergen Skin Test</td>
<td>1.4 (1.1, 1.8)</td>
<td>1.2 (0.9, 1.5)</td>
<td>1.2 (0.8, 1.7)</td>
<td>0.4</td>
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</tr>
</tbody>
</table>

Linear Growth Not Different Two Years After Treatment Discontinuation

Guilbert, J Allergy Clin Immunol 128(5): 956-963
Linear Growth Different in Younger And Lighter Children

Guilbert, J Allergy Clin Immunol 128(5): 956-963
Linear Growth Not Different in Older Children

Guilbert, J Allergy Clin Immunol 128(5): 956-963
Conundrum with Daily ICS Use

- **Most effective and guideline preferred controller for persistent pediatric asthma** as it improves day-to-day asthma control and prevents exacerbations.

- However, despite daily ICS, **exacerbations occur** yearly in about 30% of children with mild and 40% of children with mild-moderate asthma in trials.

- **Suboptimal real-world adherence**: Long-term adherence with daily ICS is consistently low: 30-50% in general pediatric practice.

- **Fear/anxiety of using too much medication**

- **Growth effects small but may be permanent**
Alternative Regimens to Daily ICS Use

- Intermittent ICS: Administering ICS whenever specific events occur & for prespecified duration

- Rescue ICS: Administering ICS whenever asthma symptoms appear as needed (prn) with beta-agonists till symptoms resolve
Alternative Regimens to Daily ICS Use

- Intermittent ICS: Administering ICS whenever specific events occur & for pre-specified duration

- Rescue ICS: Administering ICS whenever asthma symptoms appear as needed (prn) with beta-agonists till symptoms resolve
Is Intermittent ICS an Alternative Strategy in Preschool-aged Children?
Episodic Use of an ICS or LTRA in Preschool Children with Moderate-to-Severe Intermittent Wheezing

- Randomized, double-blind placebo-controlled trial
- 238 children 12-59 months old with recurrent moderate-severe wheezing in the context of a URI
- Primary outcome: proportion of episode free days over 1 year

Randomization

Run in → Randomization

At first sign of RTI symptoms x 7 days

- Budesonide 1 mg bid + Placebo LTRA + β-agonist
- Montelukast 4 mg daily + Placebo ICS + β-agonist
- Placebo LTRA + Placebo ICS + β-agonist

Episodic Use of an ICS or LTRA in Preschool Children with Moderate-to-Severe Intermittent Wheezing

- No difference in proportion of episode free days (EFDs) or in oral corticosteroid use

<table>
<thead>
<tr>
<th></th>
<th>% of EFDs (95% CI)</th>
<th># OCS courses (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budesonide</td>
<td>76% (70% to 81%)</td>
<td>0.7 (0.5-1.0)</td>
</tr>
<tr>
<td>Montelukast</td>
<td>73% (66% to 79%)</td>
<td>1.0 (0.7-1.3)</td>
</tr>
<tr>
<td>Conventional</td>
<td>74% (65% to 81%)</td>
<td>0.9 (0.6-1.4)</td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- No growth effects of intermittent ICS

**POSITIVE Asthma Predictive Index**

- Montelukast
- Budesonide

* P<0.05 vs Conv Therapy, ** P<0.01 vs Conv Therapy

**Negative Asthma Predictive Index:** No significant effect of treatment on any symptom measure

Preemptive Use of High-Dose Fluticasone for Virus-Induced Wheezing in Young Children

- 129 children 1-6 yrs of age with ≥3 wheezing episodes (lifetime) “seemingly triggered by URIs”
  - No intercurrent symptoms
  - ≥1 course of oral corticosteroids in past 6 months (or 2 in past 12 mo)
  - Exclusion of children with suspected allergic rhinitis or allergic sensitization to aeroallergen(s)
- Triple-blind placebo-controlled trial
- At 1st sign of URI, parents began study drug (fluticasone 750mcg BID or placebo) until 48 hrs with no symptoms of cough or wheeze + albuterol as needed
- Primary outcome: group rate of oral corticosteroid use

Ducharme FM et al. NEJM 2009;360:339-53
Preemptive Use of High-Dose Fluticasone for Virus-Induced Wheezing in Young Children

<table>
<thead>
<tr>
<th>Outcome</th>
<th>FP Group</th>
<th>Placebo Group</th>
<th>OR for FP Group</th>
</tr>
</thead>
<tbody>
<tr>
<td># URTI</td>
<td>521</td>
<td>526</td>
<td></td>
</tr>
<tr>
<td>URTI requiring oral steroids</td>
<td>43 (8%)</td>
<td>93 (18%)</td>
<td>0.49 (0.3, 0.83)</td>
</tr>
</tbody>
</table>

- No difference in proportion of URTI associated with wheezing, cough, dyspnea, or hospitalization
- FP associated with shorter duration of albuterol use
- FP group had significantly smaller increases in height (6.23cm vs 6.56 cm) and weight (1.53kg vs 2.17kg)
- No differences in basal cortisol level, bone mineral density, or adverse events

Ducharme FM et al.  NEJM 2009;360:339-53
Which is Superior?

Daily Low Dose ICS Therapy OR Episodic High Dose ICS Therapy

in Preschool Children with Recurrent Severe Episodes of Wheezing and Positive APIs
Maintenance vs. Intermittent Inhaled Steroids in Wheezing Toddlers (MIST)

Daily or Intermittent Budesonide in Preschool Children with Recurrent Wheezing


NEJM 2011;365:1990-2001
MIST - Inclusion Criteria (N=278)

- 12-53 months
- Number of wheezing episodes in the prior year: ≥4 or ≥3 with at least 3 months of asthma controller therapy
- Positive modified Asthma Predictive Index
- ≥1 severe exacerbation requiring systemic corticosteroids, urgent unscheduled, emergent visit or hospitalization in prior year

Zeiger RS et al. NEJM 2011;365:1990-2001
MIST - Exclusion Criteria

- History in the prior year:
  - >6 courses of oral corticosteroids or
  - >2 hospitalizations for wheezing
- Course during 2-week run-in on placebo respule nightly and albuterol prn
  - Persistent symptomatic asthma
    - Albuterol use on average ≥3 days per week or
    - ≥2 nights with awakenings due to symptoms
  - Inadequate adherence
    - <75% of days adherent to diary completion and placebo nebulization

Zeiger RS et al. NEJM 2011;365:1990-2001
# MIST Protocol - Overview

<table>
<thead>
<tr>
<th>Run-in: 2 wks</th>
<th>Treatment Phase: 52 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo respule nightly + albuterol PRN</td>
<td><strong>Randomized Treatment Group</strong></td>
</tr>
<tr>
<td><strong>Nightly EXCEPT</strong> During Respiratory Tract Illnesses</td>
<td><strong>During Respiratory Tract Illnesses ONLY for 7 days</strong></td>
</tr>
<tr>
<td>Daily low-dose budesonide</td>
<td>0.5 mg PM</td>
</tr>
<tr>
<td>Intermittent high-dose budesonide</td>
<td>Placebo PM</td>
</tr>
</tbody>
</table>

Zeiger RS et al. NEJM 2011;365:1990-2001
Primary Outcome - Frequency of Exacerbations

- Intermittent (Rate 0.95/person yr)
- Daily (Rate 0.97/person yr)

p-value = 0.6

Zeiger RS et al. NEJM 2011;365:1990-2001
MIST – Secondary Outcomes

- No difference in:
  - Time to 1st exacerbation
  - # of RTIs
  - % of RTIs requiring oral steroids (25%)
  - Severity of symptoms during RTI
  - Symptom free days (78%)
  - Health care utilization
  - Growth

- Intermittent group used less budesonide during trial (150mg vs 46mg)

Zeiger RS et al. NEJM 2011;365:1990-2001
MIST Conclusions

**Recommend** for +mAPI children 12-53 mo with an exacerbation in the past year, ≤3 days/week of albuterol and <2 nights with awakenings/2 weeks

- Intermittent 7-day treatment with high-dose budesonide started early during predefined respiratory-tract illnesses since this regimen may be preferable to daily low-dose budesonide given its
  - similar efficacy
  - less frequent use
  - lower ICS exposure

Zeiger RS et al. NEJM 2011;365:1990-2001
Alternative Regimens to Daily ICS Use

- Intermittent ICS: Administering ICS whenever specific events occur & for pre-specified duration

- Rescue ICS: Administering ICS whenever asthma symptoms appear as needed (prn) with beta-agonists till symptoms resolve
Regular vs PRN ICS Treatment in Children with Persistent Symptoms

- Double-blind placebo controlled trial (N=276)
- 1-4yrs with ≥3 episode of wheeze in past 6 months
- Cough, wheeze &/or shortness of breath on ≥7 days of 14 day run-in period
- Stratified by asthma risk factors (eczema, 1st degree relative with asthma, eosinophilia >4%)
- 12 week placebo-controlled treatment period
  - Regular BDP – BDP 400mcg BID + albuterol 2.5mg PRN
  - PRN Combination Group – BDP 800mcg + albuterol 2.5mg PRN
  - PRN Albuterol Group – Albuterol 2.5mg PRN
- Outcome measures
  - Primary: Percentage of symptom-free days (not including reliever use)
  - Secondary: Symptom scores, nocturnal symptoms, medication use, exacerbations (number and time to 1st exacerbation)

Papi A et al. Allergy 2009;64:1463-71
Regular vs PRN ICS Treatment in Children with Persistent Symptoms

Prolonged time to 1st exacerbation in regular BDP group compared to PRN albuterol group (p=0.03) and PRN combination group (p=0.03)

Time to 1st course of oral corticosteroids longer in regular BDP compared to PRN albuterol (p=0.01), but not different from PRN combination

Papi A et al. Allergy 2009;64:1463-71
Regular vs PRN ICS Treatment in Children with Persistent Symptoms

Conclusions

- Regular treatment with ICS is the most effective therapy (regardless of the presence or absence of asthma risk factors)
- Rescue use of a fixed combination of a SABA and ICS could be an alternative to PRN SABA use alone

Papi A et al. Allergy 2009;64:1463-71
**Individualized Therapy For Asthma in Toddlers (INFANT)**

- **Run-In (2-8 weeks)**
  - Placebo or Active Therapy

- **16 weeks**
  - Daily ICS
  - Placebo LTRA
  - As needed placebo ICS

- **16 weeks**
  - Placebo ICS
  - Daily LTRA
  - As needed placebo ICS

- **16 weeks**
  - Placebo ICS
  - Placebo LTRA
  - As needed active ICS

300 children 12-59 mo necessitating treatment with Step 2 controller

Blood and urine sample collection for predictor analyses

- Inhaled fluticasone (44 mcg/actuation) 2 inhalations twice daily
- Oral montelukast (4 mg) once daily HS
- As-needed albuterol plus inhaled fluticasone (44 mcg/actuation) 2 inhalations for every 2 inhalations albuterol

**AsthmaNet**

AsthmaNetResearch.org

Which Step 2 Asthma Therapy is **BEST** for the Greatest Number of Children?

Hierarchical composite variable of time to exacerbations and number of asthma control days

Differential response between at least two treatments was observed in **74% (170 of 230)** of children who provided usable data for analysis

- Probability of best response highest for daily ICS
- Non-differential responders had indicators of less disease severity

Are there baseline characteristics that predict which treatment will produce the best response (for the greatest number of children)?

A.

Non-differential responders (N = 60)

Not aeroallergen sensitized (N = 91)

Aeroallergen sensitized (N = 79)

Cumulative exacerbation probability

Days from Start of Treatment

Daily ICS  As-needed ICS  Daily LTRA

B.

Non-differential responders (N = 60)

Blood eosinophils <300/μL (N = 82)

Blood eosinophils ≥300/μL (N = 71)

Cumulative exacerbation probability

Days from Start of Treatment

Daily ICS  As-needed ICS  Daily LTRA

C.

Non-differential responders (N = 60)

Not sensitized and eosinophils <300/μL (N = 61)

Not sensitized and eosinophils ≥300/μL (N = 19)

Sensitized and eosinophils <300/μL (N = 21)

Sensitized and eosinophils ≥300/μL (N = 52)

Cumulative exacerbation probability

Days from Start of Treatment

Daily ICS  As-needed ICS  Daily LTRA

Intermittent ICS in Preschool Children Reduces Risk of Severe Exacerbation

We searched MEDLINE (1946-2/25/15), EMBASE (1947-2/25/15), and CENTRAL

Studies were included based on

- Design (randomized controlled trials)
- Population (children <6 years with asthma or recurrent wheeze)
- Intervention/comparison (daily ICS/placebo, intermittent ICS/placebo, daily ICS/intermittent ICS, ICS/montelukast)
- Outcome (wheezing exacerbations requiring systemic steroids)

Kaiser SV et al. Pediatr 2016;137(6);e20154496
Records identified through database searching (n = 4,285)

Records after duplicates removed (n = 3,982)

Records screened (n = 3,982)

Records excluded (n = 3,859)

Full-text articles assessed for eligibility (n = 123)

Full-text articles excluded, (reasons for exclusion in Appendix 3) (n = 101)

Studies included in qualitative synthesis (n = 22)

Studies included in quantitative synthesis (meta-analysis) (n = 22)

Kaiser SV et al. Pediatr 2016;137(6);e20154496
# Daily ICS Reduce Exacerbations

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Daily ICS</th>
<th>Placebo</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
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<td>Bisgaard et al 1999</td>
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<td>20</td>
<td>2</td>
<td>21</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

| Total events | 2067 | 1211 | 100.0% | 0.70 [0.61, 0.79] |

**Heterogeneity:** Chi² = 24.30, df = 14 (P = 0.04); I² = 42%

**Test for overall effect:** Z = 5.33 (P < 0.00001)

Kaiser SV et al. Pediatr 2016;137(6);e20154496
### Daily ICS versus Intermittent ICS

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Daily ICS</th>
<th>Intermittent ICS</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Papi et al 2009</td>
<td>2</td>
<td>110</td>
<td>6</td>
<td>110</td>
</tr>
<tr>
<td>Zeiger et al 2011</td>
<td>62</td>
<td>139</td>
<td>64</td>
<td>139</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>249</strong></td>
<td><strong>249</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

Total events: 64
Total events: 70

Heterogeneity: Chi² = 1.76, df = 1 (P = 0.18); I² = 43%

Test for overall effect: Z = 0.68 (P = 0.49)

Kaiser SV et al. Pediatr 2016;137(6);e20154496
### Daily ICS versus Daily Montelukast

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Daily ICS</th>
<th></th>
<th>Daily Montelukast</th>
<th></th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>Szeffler et al 2013</td>
<td>23</td>
<td>105</td>
<td>36</td>
<td>97</td>
<td>100.0%</td>
<td>0.59 [0.38, 0.92]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>105</td>
<td>97</td>
<td></td>
<td>100.0%</td>
<td>0.59 [0.38, 0.92]</td>
</tr>
<tr>
<td>Total events</td>
<td>23</td>
<td>36</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: $Z = 2.33$ ($P = 0.02$)

### Intermittent ICS versus Intermittent Montelukast

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Intermittent ICS</th>
<th></th>
<th>Montelukast</th>
<th></th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>Bacharier et al 2008</td>
<td>37</td>
<td>96</td>
<td>44</td>
<td>94</td>
<td>100.0%</td>
<td>0.82 [0.59, 1.15]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>96</td>
<td>94</td>
<td></td>
<td>100.0%</td>
<td>0.82 [0.59, 1.15]</td>
</tr>
<tr>
<td>Total events</td>
<td>37</td>
<td>44</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: $Z = 1.15$ ($P = 0.25$)

Kaiser SV et al. Pediatr 2016;137(6);e20154496
Results: Subgroup Analyses

Most studies of daily ICS focused on children with persistent asthma (8 of 15), and most studies of intermittent ICS focused on children with intermittent or viral-triggered wheezing (5 of 6).

Subgroup analysis of children with **persistent asthma** showed reduced exacerbations with daily ICS compared to placebo (8 studies, N=2505, RR 0.56, 95% CI 0.46-0.70, NNT=11) and daily ICS compared to montelukast (1 study, N=202, RR 0.59, 95% CI 0.38-0.92).

Kaiser SV et al. Pediatr 2016;137(6);e20154496
Subgroup analysis of children with intermittent asthma or viral-triggered wheezing showed reduced exacerbations with preemptive high-dose intermittent ICS compared to placebo (5 studies, N=422, RR 0.65, 95% CI 0.51-0.81, NNT=6)

Kaiser SV et al. Pediatr 2016;137(6);e20154496
Conclusions

- There is strong evidence to support daily ICS for preventing severe exacerbations in preschool children with recurrent wheeze, specifically in children with persistent asthma.

- For preschool children with intermittent asthma or viral-triggered wheezing, there is strong evidence to support intermittent ICS for preventing severe exacerbations.

- With either treatment strategy, we recommend frequent reassessment of wheezing symptoms/pattern, close monitoring of growth, and active titration to the lowest ICS dose that is effective.

- More studies are needed that directly compare these strategies.

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Caveats to Alternative Non-Daily ICS Use

- Remember the efficacy and preferred position of daily ICS is based on a multitude of well-designed randomized trials over the entire asthma spectrum.

- Alternative strategies of ICS use are based on a growing number of studies over the past few years.

- However, consistent demonstration of populations with preschool children with mild asthma who do not appear to benefit with daily ICS over intermittent ICS.
Summary for Non-Daily ICS Use in Preschool Children

- Phenotype to consider use:
  - Preschoolers with frequent wheeze, prior year exacerbation, and positive asthma predictive index
  - Parents willing and capable of following Action Plan

- Phenotypes to **not** consider use:
  - Persistent uncontrolled asthma
  - More moderate to severe disease