Inhaled steroids in the treatment of mild to moderate persistent asthma in children: once or twice daily administration?

Scenario
A 6 year old girl comes to your outpatient paediatric clinic with a two month history of cough and shortness of breath, requiring, nearly three times a week administration of beta-2 agonists by jet nebulizer. She has often been noticed to wheeze at school during the gymnastic class and when she’s laughing or crying; almost once a week she awakes during the night complaining of cough and respiratory difficulties.

Your diagnosis is persistent asthma (1) and after a short course of nebulized salbutamol (albuterol) and oral steroids you decide to start, twice a day, prophylaxis with inhaled steroids via a spacer device. As her mother is working outside the home until late afternoon, she asks you if a once-daily administration would have the same efficacy.

Structured clinical question
In [children with mild to moderate persistent asthma] does [once daily and twice daily administration of inhaled steroids] have [the same efficacy]?

Search
The search was conducted independently by two reviewers (the authors). Medline 1966-12/01 using OVID interface, Cochrane Library (2001), PubMed clinical queries using “Inhaled steroids” OR glucocorticoids OR glucocorticosteroids OR budesonide OR mometasone OR flunisolide OR fluticasone propionate OR beclomethasone dipropionate AND (once versus twice OR once with twice daily OR OD OR BID administration) AND asthma. Limits: All children:0-18 years, randomised controlled trial.

Clinical evidence
No systematic reviews. 31 studies found, 9 were relevant. (Papers available in abstracts only and studies including both adults and children aged > 12 were excluded).
<table>
<thead>
<tr>
<th>Citation</th>
<th>Study group</th>
<th>Study type (level of evidence from the Oxford CEBM)</th>
<th>Outcome</th>
<th>Key Result</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Campbell et al. *</td>
<td>167 children, age 5-12 yrs with symptomatic asthma, multicenter study</td>
<td>OD vs BID</td>
<td>PEF, FEV1, FVC, well-being and symptom score, albuterol use, adverse events</td>
<td>OD &gt; BID for evening PEF: +19.7 l/min vs +8.3 l/min (p=0.013), no other significant differences (morning PEF: +24.6 l/min vs +15.2 l/min, p=0.059).</td>
<td>Ten patients excluded from the all-patients-treated population. A greater number of patients randomised to the BID arm: 90 vs 77. Patient compliance not assessed.</td>
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<tr>
<td>Jonasson et al. *</td>
<td>163 children, age 7-16 yrs, with mild asthma, outpatient clinic</td>
<td>OD vs BID</td>
<td>PEF, FEV1, FVC, symptom score, beta agonist use, markers of collagen turnover</td>
<td>No significant differences between OD and BID: FEV1% -0.05 (95% CI –3.3 to +3); PEF 2.9 l/min (95% CI –10.8 to +16.6)</td>
<td>Patients with near-normal lung function: FEV1 at baseline &gt;100%, reversibility of 3%.</td>
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<td>Heuck et al. *</td>
<td>24 children, age 5.6-12.5 yrs, with mild asthma, multicenter study</td>
<td>OD vs BID</td>
<td>Lower leg growth, PEF, symptom score, albuterol use, markers of collagen turnover</td>
<td>Significant reduction of lower leg growth rate (p=0.04) and markers of collagen turnover with BID. No other significant differences between OD and BID: Morning PEF (95% CI –4 to +15 L/min). Evening PEF (95% CI –3 to +16 L/min)</td>
<td>Small study. The trial did not include a placebo period.</td>
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<tr>
<td>Moller et al. *</td>
<td>206 children, age 5-15 yrs, with stable asthma, multicentre study</td>
<td>OD vs BID</td>
<td>FEV1, FVC, FEF25-75, PEF, symptom score, albuterol use, adverse events</td>
<td>No significant differences between OD and BID: Morning PEF –2.8 L/min (90% CI –10.4 to +4.5); FEV1% -0.08 (95% CI –3.4 to +0.9)</td>
<td>Difference in patients demographic characteristics (duration of asthma in months) between OD e BID.</td>
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<tr>
<td>Baker et al. *</td>
<td>480 children, age 6 mo-8 yrs, with moderate persistent asthma, multicenter study</td>
<td>Budesonide inhalation suspension by jet nebulizer: 0.25 mg OD vs. 0.25 mg BID vs. 0.50 mg BID vs.1 mg OD vs. Placebo X 12 wks</td>
<td>Improvement in FEV1 significant between Budesonide 0.50 mg BID and placebo (0.17 / 0.04 L/min). but not significant between Budesonide 0.1 mg OD and placebo(0.11/0.04 L/min). For the other outcomes: 0.50 mg BID &gt; 1 mg OD, but not significant.</td>
<td>Difference in patients demographic characteristics (duration of asthma in months) between OD e BID.</td>
<td></td>
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<tr>
<td>Jonasson et al. *</td>
<td>122 children, age 7-16 yrs, with mild asthma, outpatient clinic</td>
<td>OD vs BID</td>
<td>FEV1, FVC, 25-75, PEF, symptom score, albuterol use, adverse events and in a subgroup cortisol testing</td>
<td>Improvement in FEV1 significant between Budesonide 0.50 mg BID and placebo (0.17 / 0.04 L/min). but not significant between Budesonide 0.1 mg OD and placebo(0.11/0.04 L/min). For the other outcomes: 0.50 mg BID &gt; 1 mg OD, but not significant.</td>
<td>Difference in patients demographic characteristics (duration of asthma in months) between OD e BID.</td>
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<td>LaForce et al. *</td>
<td>242 children, age 4-11 yrs, with persistent stable asthma, multicenter study</td>
<td>OD vs BID</td>
<td>FEV1, PEF symptom score, night time awakening, albuterol use, adverse events</td>
<td>BID &gt; OD for FEV1 change in % (95% CI –11.28 to –0.124); not other significant differences: for Morning PEF (95% CI –27.26 to +9.26)</td>
<td>Asthma had to remain stable for all the study period; high rate of discontinuation in the placebo group.</td>
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<td>Purucker et al. *</td>
<td>262 children, age 4-11 yrs, with persistent stable asthma, single study</td>
<td>Fluticasone propionate by dry powder</td>
<td>FEV1, PEF symptom score, nighttime awakening, albuterol use.</td>
<td>Change in FEV1 in L/min from baseline: OD Fluticasone 0.08 (NS), BID Fluticasone 0.13 (NS) and placebo 0.05 (NS). BID &gt; OD for PEFR change;</td>
<td>Lost to follow-up: 27% Differences in % patients using inhaled steroids before entering into the study between OD and BID groups.</td>
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<td>Study FLTA 2008 USA</td>
<td>242 children, age 4-11 yrs, with persistent (more severe than that of Study FLTA 2007) stable asthma, single study. Fluticasone propionate by dry powder. 100 µgr OD vs 200 µgr BID vs placebo X 12 wks</td>
<td>Double blind RCT (level 1b)</td>
<td>FEV1, PEF symptom score, nighttime awakening, albuterol use</td>
<td>BID = OD for FEV1 change: 50 µgr BID Fluticasone vs. Placebo: Absolute Reduction for FEV1 in L/min 0.27 (p&lt;.001). 100 µgr OD Fluticasone vs. Placebo: Absolute Reduction for FEV1 in L/min 0.16 (p&lt;.001). No significant difference between the two FP arms.</td>
<td>Lost to follow-up: 45%. No details about how randomisation was performed and about demographic characteristics of the three groups</td>
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**Abbreviation used:**
- OD: once-daily dose
- BID: twice-daily dose
- RCT: Randomised Controlled Trials
- PEF: Peak Expiratory Flow
- FEV1: Forced expired volume in 1 second
- FEF 25-75: Forced expiratory flow between 25 and 75% of Forced Vital Capacity
- FVC: Forced Vital Capacity
- yrs: years
- mo: months
- MDI: Metered-Dose-Inhaler
- mg: milligrams
COMMENTARY
As Baker’s study evaluate the efficacy of different doses of Budesonide (4 Groups) compared to placebo, 8 studies were found that specifically compare the once-daily vs twice-daily administration of inhaled steroids.

Overall the methodological quality of the included studies was not always satisfactory: even if the majority of the references mentioned the number of patients excluded from the study, withdrawals and drop-outs were described and commented only in Heuck’s and in Moller’s articles; in Baker’s and in both Purucker’s studies “lost to follow-up” was > 20%. Intention to treat analysis was reported to be used by Jonasson, by LaForce and by Purucker; allocation concealment was unclear in most of the cases and often details of methods used to generate the random allocation sequence were lacking.

This overview found a heterogenous group of trials with different results; although the majority of studies reported not significant difference between the two regimens the overall findings of the seven studies are not sufficient to support the evidence that administering inhaled steroids once-daily and twice–daily has the same efficacy.

CLINICAL BOTTOM LINES
• In mild to moderate persistent asthma, in children, inhaled steroids should continue to be given twice-daily.
• The once-daily administration might have a similar efficacy at least in some subgroups of patients with more stable asthma, but further well conducted randomized controlled studies are needed.

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References


