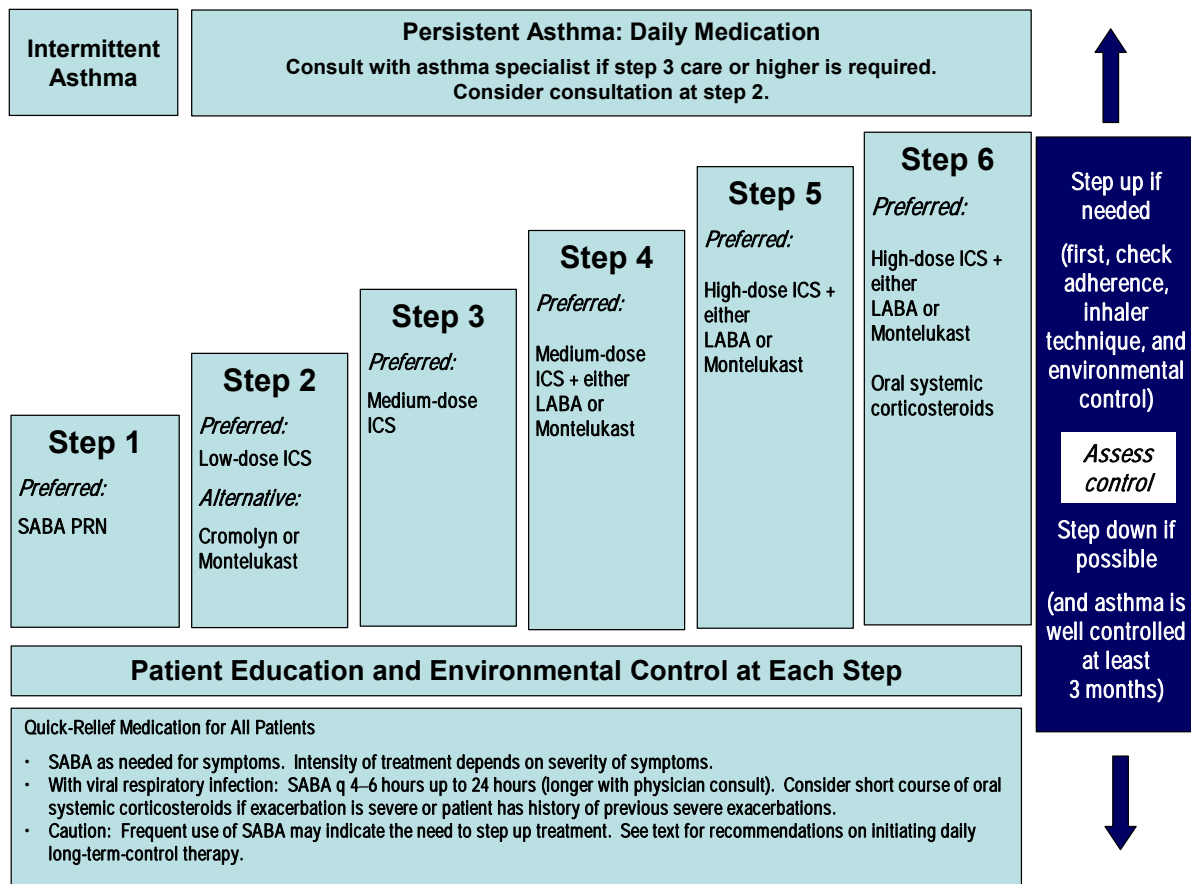


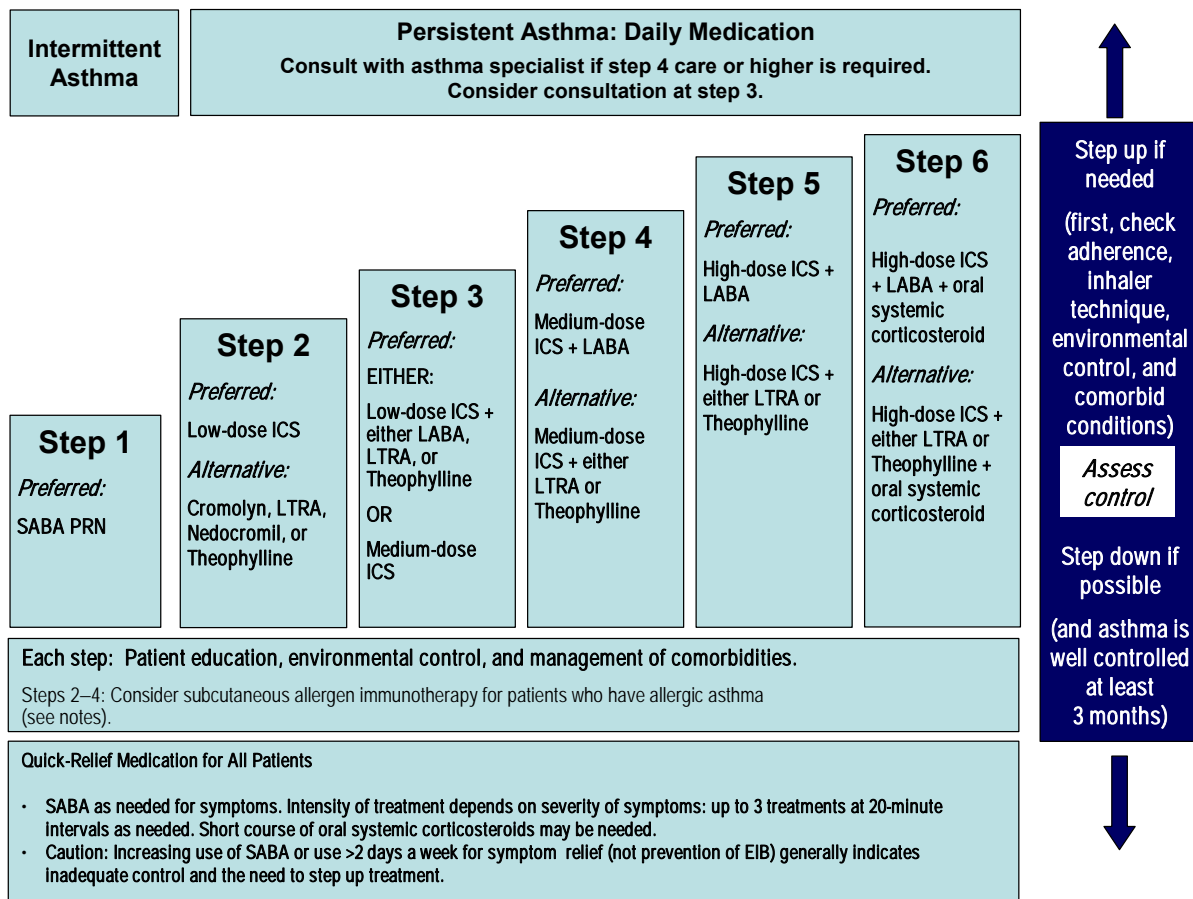
**FIGURE 4–1a. STEPWISE APPROACH FOR MANAGING ASTHMA IN CHILDREN 0–4 YEARS OF AGE**



**Key:** Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy. ICS, inhaled corticosteroid; LABA, inhaled long-acting beta<sub>2</sub>-agonist; SABA, inhaled short-acting beta<sub>2</sub>-agonist

**Notes:**

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- If clear benefit is not observed within 4–6 weeks and patient/family medication technique and adherence are satisfactory, consider adjusting therapy or alternative diagnosis.
- Studies on children 0–4 years of age are limited. Step 2 preferred therapy is based on Evidence A. All other recommendations are based on expert opinion and extrapolation from studies in older children.

**FIGURE 4–1b. STEPWISE APPROACH FOR MANAGING ASTHMA IN CHILDREN 5–11 YEARS OF AGE**

**Key:** **Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy.** ICS, inhaled corticosteroid; LABA, inhaled long-acting beta<sub>2</sub>-agonist, LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta<sub>2</sub>-agonist

**Notes:**

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- Theophylline is a less desirable alternative due to the need to monitor serum concentration levels.
- Step 1 and step 2 medications are based on Evidence A. Step 3 ICS + adjunctive therapy and ICS are based on Evidence B for efficacy of each treatment and extrapolation from comparator trials in older children and adults—comparator trials are not available for this age group; steps 4–6 are based on expert opinion and extrapolation from studies in older children and adults.
- Immunotherapy for steps 2–4 is based on Evidence B for house-dust mites, animal danders, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is greater in children than in adults. Clinicians who administer immunotherapy should be prepared and equipped to identify and treat anaphylaxis that may occur.

**FIGURE 4–2a. CLASSIFYING ASTHMA SEVERITY AND INITIATING TREATMENT IN CHILDREN 0–4 YEARS OF AGE**

Assessing severity and initiating therapy in children who are not currently taking long-term control medication

Components of Severity		Classification of Asthma Severity (0–4 years of age)			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	0	1–2x/month	3–4x/month	>1x/week
	Short-acting beta <sub>2</sub> -agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2 exacerbations in 6 months requiring oral systemic corticosteroids, or ≥4 wheezing episodes/1 year lasting >1 day AND risk factors for persistent asthma		
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time. → Exacerbations of any severity may occur in patients in any severity category.			
Recommended Step for Initiating Therapy		Step 1	Step 2	Step 3 and consider short course of oral systemic corticosteroids	
(See figure 4–1a for treatment steps.)		In 2–6 weeks, depending on severity, evaluate level of asthma control that is achieved. If no clear benefit is observed in 4–6 weeks, consider adjusting therapy or alternative diagnoses.			


Key: EIB, exercise-induced bronchospasm

**Notes**

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- Level of severity is determined by both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2–4 weeks. Symptom assessment for longer periods should reflect a global assessment such as inquiring whether the patient's asthma is better or worse since the last visit. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past 6 months, or ≥4 wheezing episodes in the past year, and who have risk factors for persistent asthma may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

**FIGURE 4–2b. CLASSIFYING ASTHMA SEVERITY AND INITIATING TREATMENT IN CHILDREN 5–11 YEARS OF AGE**

Assessing severity and initiating therapy in children who are not currently taking long-term control medication

Components of Severity		Classification of Asthma Severity (5–11 years of age)			
		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting beta <sub>2</sub> -agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	<ul style="list-style-type: none"> <li>• Normal FEV<sub>1</sub> between exacerbations</li> <li>• FEV<sub>1</sub> &gt;80% predicted</li> <li>• FEV<sub>1</sub>/FVC &gt;85%</li> </ul>	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub> = &gt;80% predicted</li> <li>• FEV<sub>1</sub>/FVC &gt;80%</li> </ul>	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub> = 60–80% predicted</li> <li>• FEV<sub>1</sub>/FVC = 75–80%</li> </ul>	<ul style="list-style-type: none"> <li>• FEV<sub>1</sub> &lt;60% predicted</li> <li>• FEV<sub>1</sub>/FVC &lt;75%</li> </ul>
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note) 		
		← Consider severity and interval since last exacerbation. → Frequency and severity may fluctuate over time for patients in any severity category.			
		Relative annual risk of exacerbations may be related to FEV <sub>1</sub> .			
Recommended Step for Initiating Therapy (See figure 4–1b for treatment steps.)		Step 1	Step 2	Step 3, medium-dose ICS option	Step 3, medium-dose ICS option, or step 4 and consider short course of oral systemic corticosteroids
		In 2–6 weeks, evaluate level of asthma control that is achieved, and adjust therapy accordingly.			

Key: EIB, exercise-induced bronchospasm; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids

#### Notes

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- Level of severity is determined by both impairment and risk. Assess impairment domain by patient's/caregiver's recall of the previous 2–4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

**FIGURE 4–3a. ASSESSING ASTHMA CONTROL AND ADJUSTING THERAPY IN CHILDREN 0–4 YEARS OF AGE**

Components of Control		Classification of Asthma Control (0–4 years of age)		
		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakenings	≤1x/month	>1x/month	>1x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting beta <sub>2</sub> -agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	2–3/year	>3/year
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
<b>Recommended Action for Treatment</b>  (See figure 4–1a for treatment steps.)		<ul style="list-style-type: none"> <li>Maintain current treatment.</li> <li>Regular followup every 1–6 months.</li> <li>Consider step down if well controlled for at least 3 months.</li> </ul>	<ul style="list-style-type: none"> <li>Step up (1 step) and Reevaluate in 2–6 weeks.</li> <li>If no clear benefit in 4–6 weeks, consider alternative diagnoses or adjusting therapy.</li> <li>For side effects, consider alternative treatment options.</li> </ul>	<ul style="list-style-type: none"> <li>Consider short course of oral systemic corticosteroids.</li> <li>Step up (1–2 steps), and Reevaluate in 2 weeks.</li> <li>If no clear benefit in 4–6 weeks, consider alternative diagnoses or adjusting therapy.</li> <li>For side effects, consider alternative treatment options.</li> </ul>

Key: EIB, exercise-induced bronchospasm

**Notes:**

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- The level of control is based on the most severe impairment or risk category. Assess impairment domain by caregiver’s recall of previous 2–4 weeks. Symptom assessment for longer periods should reflect a global assessment such as inquiring whether the patient’s asthma is better or worse since the last visit.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not-well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma.
- Before step up in therapy:
  - Review adherence to medications, inhaler technique, and environmental control.
  - If alternative treatment option was used in a step, discontinue it and use preferred treatment for that step.

**FIGURE 4–3b. ASSESSING ASTHMA CONTROL AND ADJUSTING THERAPY IN CHILDREN 5–11 YEARS OF AGE**

Components of Control		Classification of Asthma Control (5–11 years of age)		
		Well Controlled	Not Well Controlled	Very Poorly Controlled
<b>Impairment</b>	Symptoms	≤2 days/week but not more than once on each day	>2 days/week or multiple times on ≤2 days/week	Throughout the day
	Nighttime awakenings	≤1x/month	≥2x/month	≥2x/week
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting beta <sub>2</sub> -agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week	Several times per day
	Lung function • FEV <sub>1</sub> or peak flow • FEV <sub>1</sub> /FVC	>80% predicted/ personal best >80%	60–80% predicted/ personal best 75–80%	<60% predicted/ personal best <75%
<b>Risk</b>	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2/year (see note) Consider severity and interval since last exacerbation	
	Reduction in lung growth	Evaluation requires long-term followup.		
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
<b>Recommended Action for Treatment</b>  (See figure 4–1b for treatment steps.)		<ul style="list-style-type: none"> <li>Maintain current step.</li> <li>Regular followup every 1–6 months.</li> <li>Consider step down if well controlled for at least 3 months.</li> </ul>	<ul style="list-style-type: none"> <li>Step up at least 1 step and</li> <li>Reevaluate in 2–6 weeks.</li> <li>For side effects: consider alternative treatment options.</li> </ul>	<ul style="list-style-type: none"> <li>Consider short course of oral systemic corticosteroids,</li> <li>Step up 1–2 steps, and</li> <li>Reevaluate in 2 weeks.</li> <li>For side effects, consider alternative treatment options.</li> </ul>

Key: EIB, exercise-induced bronchospasm; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity

**Notes:**

- The stepwise approach is meant to assist, not replace, the clinical decisionmaking required to meet individual patient needs.
- The level of control is based on the most severe impairment or risk category. Assess impairment domain by patient's/caregiver's recall of previous 2–4 weeks and by spirometry/or peak flow measures. Symptom assessment for longer periods should reflect a global assessment such as inquiring whether the patient's asthma is better or worse since the last visit.
- At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.
- Before step up in therapy:
  - Review adherence to medications, inhaler technique, environmental control, and comorbid conditions.
  - If alternative treatment option was used in a step, discontinue it and use preferred treatment for that step.

**FIGURE 4–4a. USUAL DOSAGES FOR LONG-TERM CONTROL MEDICATIONS IN CHILDREN\***

Medication	Dosage Form	0–4 years	5–11 years	Comments
<b>Inhaled Corticosteroids (ICSs)</b> (See figure 4–4b, <i>Estimated Comparative Daily Dosages for ICSs in Children.</i> )				
<b>Systemic Corticosteroids</b>				<b>(Applies to all three corticosteroids)</b>
Methylprednisolone	2, 4, 8, 16, 32 mg tablets	0.25–2 mg/kg daily in single dose in a.m. or qod as needed for control	0.25–2 mg/kg daily in single dose in a.m. or qod as needed for control	<ul style="list-style-type: none"> <li>■ For long-term treatment of severe persistent asthma, administer single dose in a.m. either daily or on alternate days (alternate-day therapy may produce less adrenal suppression).</li> <li>■ Short courses or “bursts” are effective for establishing control when initiating therapy or during a period of gradual deterioration.</li> <li>■ There is no evidence that tapering the dose following improvement in symptom control and pulmonary function prevents relapse.</li> <li>■ Patients receiving the lower dose (1 mg/kg/day) experience fewer behavioral side effects (Kayani and Shannon 2002), and it appears to be equally efficacious (Rachelefsky 2003).</li> <li>■ For patients unable to tolerate the liquid preparations, dexamethasone syrup at 0.4 mg/kg/day may be an alternative. Studies are limited, however, and the longer duration of activity increases the risk of adrenal suppression (Hendeles 2003).</li> </ul>
Prednisolone	5 mg tablets, 5 mg/5 cc, 15 mg/5 cc	Short-course “burst”: 1–2 mg/kg/day, maximum 30 mg/day for 3–10 days	Short-course “burst”: 1–2 mg/kg/day, maximum 60 mg/day for 3–10 days	
Prednisone	1, 2.5, 5, 10, 20, 50 mg tablets; 5 mg/cc, 5 mg/5 cc			
<b>Long-Acting Beta<sub>2</sub>-Agonists (LABAs)</b>				<ul style="list-style-type: none"> <li>■ <b>Should not be used for symptom relief or exacerbations. Use only with ICSs.</b></li> <li>■ Decreased duration of protection against EIB may occur with regular use.</li> <li>■ Most children &lt;4 years of age cannot provide sufficient inspiratory flow for adequate lung delivery.</li> <li>■ Do not blow into inhaler after dose is activated.</li> <li>■ Most children &lt;4 years of age cannot provide sufficient inspiratory flow for adequate lung delivery.</li> <li>■ Each capsule is for single use only; additional doses should not be administered for at least 12 hours.</li> <li>■ Capsules should be used only with the inhaler and should not be taken orally.</li> </ul>
Salmeterol	DPI 50 mcg/blister	Safety and efficacy not established in children <4 years	1 blister q 12 hours	
Formoterol	DPI 12 mcg/single-use capsule	Safety and efficacy not established in children <5 years	1 capsule q 12 hours	
*Dosages are provided for those products that have been approved by the U.S. Food and Drug Administration or have sufficient clinical trial safety and efficacy data in the appropriate age ranges to support their use.				

**FIGURE 4–4a. USUAL DOSAGES FOR LONG-TERM CONTROL MEDICATIONS IN CHILDREN\* (CONTINUED)**

Medication	Dosage Form	0–4 years	5–11 years	Comments
<b>Combined Medication</b>				
Fluticasone/ Salmeterol	DPI 100 mcg/ 50 mcg	Safety and efficacy not established in children <4 years	1 inhalation bid	<ul style="list-style-type: none"> <li>There have been no clinical trials in children &lt;4 years of age.</li> <li>Most children &lt;4 years of age cannot provide sufficient inspiratory flow for adequate lung delivery.</li> <li>Do not blow into inhaler after dose is activated.</li> </ul>
Budesonide/ Formoterol	HFA MDI 80 mcg/4.5 mcg	Safety and efficacy not established	2 puffs bid	<ul style="list-style-type: none"> <li>There have been no clinical trials in children &lt;4 years of age.</li> <li>Currently approved for use in youths ≥12. Dose for children 5–12 years of age based on clinical trials using DPI with slightly different delivery characteristics (Pohunek et al. 2006; Tal et al. 2002; Zimmerman et al. 2004).</li> </ul>
<b>Cromolyn/Nedocromil</b>				
Cromolyn	MDI 0.8 mg/puff	Safety and efficacy not established	2 puffs qid	<ul style="list-style-type: none"> <li>4–6 week trial may be needed to determine maximum benefit.</li> <li>Dose by MDI may be inadequate to affect hyperresponsiveness.</li> </ul>
	Nebulizer 20 mg/ampule	1 ampule qid Safety and efficacy not established <2 years	1 ampule qid	<ul style="list-style-type: none"> <li>One dose before exercise or allergen exposure provides effective prophylaxis for 1–2 hours. Not as effective as inhaled beta<sub>2</sub>-agonists for EIB.</li> </ul>
Nedocromil	MDI 1.75 mg/puff	Safety and efficacy not established <6 years	2 puffs qid	<ul style="list-style-type: none"> <li>Once control is achieved, the frequency of dosing may be reduced.</li> </ul>
<b>Leukotriene Receptor Antagonists (LTRAs)</b>				
Montelukast	4 mg or 5 mg chewable tablet 4 mg granule packets	4 mg qhs (1–5 years of age)	5 mg qhs (6–14 years of age)	<ul style="list-style-type: none"> <li>Montelukast exhibits a flat dose-response curve.</li> <li>No more efficacious than placebo in infants 6–24 months (van Adelsberg et al. 2005).</li> </ul>
Zafirlukast	10 mg tablet	Safety and efficacy not established	10 mg bid (7–11 years of age)	<ul style="list-style-type: none"> <li>For zafirlukast, administration with meals decreases bioavailability; take at least 1 hour before or 2 hours after meals.</li> <li>Monitor for signs and symptoms of hepatic dysfunction.</li> </ul>
<b>Methylxanthines</b>				
Theophylline	Liquids, sustained-release tablets, and capsules	Starting dose 10 mg/kg/day; usual maximum: <ul style="list-style-type: none"> <li>&lt;1 year of age: 0.2 (age in weeks) + 5 = mg/kg/day</li> <li>≥1 year of age: 16 mg/kg/day</li> </ul>	Starting dose 10 mg/kg/day; usual maximum: 16 mg/kg/day	<ul style="list-style-type: none"> <li>Adjust dosage to achieve serum concentration of 5–15 mcg/mL at steady-state (at least 48 hours on same dosage).</li> <li>Due to wide interpatient variability in theophylline metabolic clearance, routine serum theophylline level monitoring is essential.</li> <li>See next page for factors that can affect theophylline levels.</li> </ul>
Key: DPI, dry powder inhaler; EIB, exercise-induced bronchospasm; HFA, hydrofluoroalkane (inhaler propellant); MDI, metered dose inhaler				

**FIGURE 4–4a. USUAL DOSAGES FOR LONG-TERM CONTROL MEDICATIONS IN CHILDREN\* (CONTINUED)****Factors Affecting Serum Theophylline Concentrations<sup>†</sup>**

<b>Factor</b>	<b>Decreases Theophylline Concentrations</b>	<b>Increases Theophylline Concentrations</b>	<b>Recommended Action</b>
Food	↓ or delays absorption of some sustained-release theophylline (SRT) products	↑ rate of absorption (fatty foods)	Select theophylline preparation that is not affected by food.
Diet	↑ metabolism (high protein)	↓ metabolism (high carbohydrate)	Inform patients that major changes in diet are not recommended while taking theophylline.
Systemic, febrile viral illness (e.g., influenza)		↓ metabolism	Decrease theophylline dose according to serum concentration. Decrease dose by 50 percent if serum concentration measurement is not available.
Hypoxia, cor pulmonale, and decompensated congestive heart failure, cirrhosis		↓ metabolism	Decrease dose according to serum concentration.
Age	↑ metabolism (1–9 years)	↓ metabolism (<6 months, elderly)	Adjust dose according to serum concentration.
Phenobarbital, phenytoin, carbamazepine	↑ metabolism		Increase dose according to serum concentration.
Cimetidine		↓ metabolism	Use alternative H <sub>2</sub> blocker (e.g., famotidine or ranitidine).
Macrolides: erythromycin, clarithromycin, troleandomycin		↓ metabolism	Use alternative macrolide antibiotic, azithromycin, or alternative antibiotic or adjust theophylline dose.
Quinolones: ciprofloxacin, enoxacin, perfloxacin		↓ metabolism	Use alternative antibiotic or adjust theophylline dose. Circumvent with ofloxacin if quinolone therapy is required.
Rifampin	↑ metabolism		Increase dose according to serum concentration.
Ticlopidine		↓ metabolism	Decrease dose according to serum concentration.
Smoking	↑ metabolism		Advise patient to stop smoking; increase dose according to serum concentration.

<sup>†</sup>This list is not all inclusive; for discussion of other factors, see package inserts.

**FIGURE 4–4b. ESTIMATED COMPARATIVE DAILY DOSAGES FOR INHALED CORTICOSTEROIDS IN CHILDREN**

Drug	Low Daily Dose		Medium Daily Dose		High Daily Dose	
	Child 0–4	Child 5–11	Child 0–4	Child 5–11	Child 0–4	Child 5–11
<b>Beclomethasone HFA</b> 40 or 80 mcg/puff	NA	80–160 mcg	NA	>160–320 mcg	NA	>320 mcg
<b>Budesonide DPI</b> 90, 180, or 200 mcg/inhalation	NA	180–400 mcg	NA	>400–800 mcg	NA	>800 mcg
<b>Budesonide inhaled</b> Inhalation suspension for nebulization (child dose)	0.25–0.5 mg	0.5 mg	>0.5–1.0 mg	1.0 mg	>1.0 mg	2.0 mg
<b>Flunisolide</b> 250 mcg/puff	NA	500–750 mcg	NA	1,000–1,250 mcg	NA	>1,250 mcg
<b>Flunisolide HFA</b> 80 mcg/puff	NA	160 mcg	NA	320 mcg	NA	≥640 mcg
<b>Fluticasone HFA/MDI:</b> 44, 110, or 220 mcg/puff	176 mcg	88–176 mcg	>176–352 mcg	>176–352 mcg	>352 mcg	>352 mcg
<b>DPI:</b> 50, 100, or 250 mcg/inhalation	NA	100–200 mcg	NA	>200–400 mcg	NA	>400 mcg
<b>Mometasone DPI</b> 200 mcg/inhalation	NA	NA	NA	NA	NA	NA
<b>Triamcinolone acetonide</b> 75 mcg/puff	NA	300–600 mcg	NA	>600–900 mcg	NA	>900 mcg

Key: HFA, hydrofluoroalkane; NA, not approved and no data available for this age group

**Notes:**

- **The most important determinant of appropriate dosing is the clinician's judgment of the patient's response to therapy.** The clinician must monitor the patient's response on several clinical parameters and adjust the dose accordingly. The stepwise approach to therapy emphasizes that once control of asthma is achieved, the dose of medication should be carefully titrated to the minimum dose required to maintain control, thus reducing the potential for adverse effect.
- Some doses may be outside package labeling, especially in the high-dose range. Budesonide nebulizer suspension is the only ICS with FDA approved labeling for children <4 years of age.
- Metered-dose inhaler (MDI) dosages are expressed as the actuator dose (the amount of the drug leaving the actuator and delivered to the patient), which is the labeling required in the United States. This is different from the dosage expressed as the valve dose (the amount of drug leaving the valve, not all of which is available to the patient), which is used in many European countries and in some scientific literature. Dry powder inhaler (DPI) doses are expressed as the amount of drug in the inhaler following activation.
- For children <4 years of age: The safety and efficacy of ICSs in children <1 year has not been established. Children <4 years of age generally require delivery of ICS (budesonide and fluticasone HFA) through a face mask that should fit snugly over nose and mouth and avoid nebulizing in the eyes. Wash face after each treatment to prevent local corticosteroid side effects. For budesonide, the dose may be administered 1–3 times daily. Budesonide suspension is compatible with albuterol, ipratropium, and levalbuterol nebulizer solutions in the same nebulizer. Use only jet nebulizers, as ultrasonic nebulizers are ineffective for suspensions.
- For fluticasone HFA, the dose should be divided 2 times daily; the low dose for children <4 years is higher than for children 5–11 years of age due to lower dosedelivered with face mask and data on efficacy in young children.

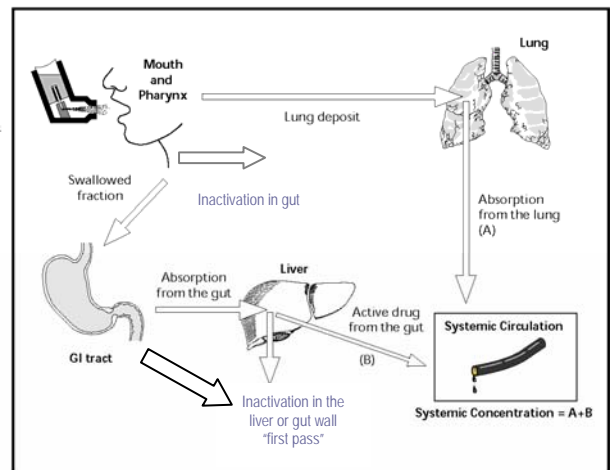
## FIGURE 4–4b. ESTIMATED COMPARATIVE DAILY DOSAGES FOR INHALED CORTICOSTEROIDS IN CHILDREN (CONTINUED)

- Comparative dosages are based on published comparative clinical trials (Adams et al. 2005; Barnes et al. 1998; Kelly 1998; Lasserson et al. 2005; Pedersen and O'Byrne 1997). The rationale for some key comparisons is summarized as follows:
  - The high dose is the dose that appears likely to be the threshold beyond which significant hypothalamic-pituitary-adrenal (HPA) axis suppression is produced, and, by extrapolation, the risk is increased for other clinically significant systemic effects if used for prolonged periods of time (Martin et al. 2002; Szeffler et al. 2002).
  - The low- to medium-doses reflect findings from dose-ranging studies in which incremental efficacy within the low- to medium dose ranges was established without increased systemic effect as measured by overnight cortisol excretion. The studies demonstrated a relatively flat dose-response curve for efficacy at the medium-dose range; that is, increasing the dose of high-dose range did not significantly increase efficacy but did increase systemic effect (Adams et al. 2001; Martin et al. 2002; Szeffler et al. 2002).
  - The dose for budesonide DPI is based on recently available comparative data with other medications. These new data, including meta-analyses, show that budesonide DPI is comparable to approximately twice the microgram dose of fluticasone MDI or DPI (Adams et al. 2005; Barnes et al. 1998; Nielsen and Dahl 2000).
  - The dose for beclomethasone in HFA inhaler should be approximately one-half the dose for beclomethasone chlorofluorocarbon (CFC) inhaler for adults and children, based on studies demonstrating that the different pharmaceutical properties of the medications result in enhanced lung delivery for the HFA (a less forceful spray from the HFA propellant and a reengineered nozzle that allows a smaller particle size) and clinical trials demonstrating similar potency to fluticasone at 1:1 dose ratio (Boulet et al. 2004; Busse et al. 1999; Gross et al. 1999; Lasserson et al. 2005; Leach et al. 1998; Pedersen et al. 2002; Szeffler et al. 2002; Thompson et al. 1998).
  - The dose for budesonide nebulizer suspension is based on efficacy and safety studies (Baker et al. 1999; Kemp et al. 1999; Shapiro et al. 1998). It is noted that the efficacy studies did not demonstrate a clear or consistent dose-response, although the high dose of 2.0 mg was effective in a placebo-controlled study in 40 infants who had severe asthma (de Blic et al. 1996). In a small, open-label, long-term safety study, the ACTH-stimulated cortisols appeared lower in the 13 infants receiving a high dose of 2.0 mg budesonide compared to infants receiving lower doses, but this result was not statistically significant, perhaps due to the small study size (Scott and Skoner 1999).
  - The dose for flunisolide HFA is based on product information and current literature (Corren et al. 2001; Gillman et al. 2002; Richards et al. 2001).
  - The dose of budesonide/formoterol in children is based on product information and current literature (Pohunek et al. 2006; Tal et al. 2002; Zimmerman et al. 2004).
  - The dose for fluticasone HFA in children <5 years of age is based on clinical studies demonstrating efficacy at this dose of 176 mcg/day (Bisgaard et al. 2004; Guilbert et al. 2006).

### ■ Bioavailability

Both the relative potency and the relative bioavailability (systemic availability) determine the potential for systemic activity of an ICS preparation. As illustrated here, the bioavailability of an ICS is dependent on the absorption of the dose delivered to the lungs and the oral bioavailability of the swallowed portion of the dose received.

- Absorption of the dose delivered to the lungs:
  - ◆ Approximately 10–50 percent of the dose from the MDI is delivered to the lungs. This amount varies among preparations and delivery devices.
  - ◆ Nearly all of the amount delivered to the lungs is bioavailable.



Adapted with permission from Barnes 1995.

**FIGURE 4–4b. ESTIMATED COMPARATIVE DAILY DOSAGES FOR INHALED CORTICOSTEROIDS IN CHILDREN (CONTINUED)**

— Oral bioavailability of the swallowed portion of the dose received:

- ◆ Approximately 50–80 percent of the dose from the MDI without a spacer or valved holding chamber is swallowed.
- ◆ The oral bioavailability of this amount varies:

Either a high first-pass metabolism or the use of a spacer/holding chamber with an MDI can decrease oral bioavailability, thus enhancing safety (Lipworth 1995).

The approximate oral bioavailability of ICS has been reported as: beclomethasone dipropionate, 20 percent; flunisolide, 21 percent; triamcinolone acetonide, 10.6 percent; budesonide, 11 percent; fluticasone propionate, 1 percent; mometasone, <1 percent (Affrime et al. 2000; Chaplin et al. 1980; Check and Kaliner 1990; Clissold and Heel 1984; Davies 1993; Harding 1990; Heald et al. 1995; Martin et al. 1974; Mollmann et al. 1985; Szeffler 1991; Wurthwein and Rohdewald 1990).

**Potential drug interactions**

- A number of the ICSs, including fluticasone, budesonide, and mometasone, are metabolized in the gastrointestinal tract and liver by CYP 3A4 isoenzymes. Potent inhibitors of CYP 3A4, such as ritonavir and ketoconazole, have the potential for increasing systemic concentrations of these ICSs by increasing oral availability and decreasing systemic clearance. Some cases of clinically significant Cushing syndrome and secondary adrenal insufficiency have been reported (Johnson et al. 2006; Samaras et al. 2005).

**FIGURE 4–4c. USUAL DOSAGES FOR QUICK-RELIEF MEDICATIONS IN CHILDREN\***

Medication	Dosage Form	0–4 Years	5–11 Years	Comments
<b>Inhaled Short-Acting Beta<sub>2</sub>-Agonists</b>				
<i>MDI</i>				
Albuterol CFC	90 mcg/puff, 200 puffs/canister	1–2 puffs 5 minutes before exercise	2 puffs 5 minutes before exercise	<ul style="list-style-type: none"> <li>■ Differences in potencies exist, but all products are essentially comparable on a per puff basis.</li> <li>■ An increasing use or lack of expected effect indicates diminished control of asthma.</li> <li>■ Not recommended for long-term daily treatment. Regular use exceeding 2 days/week for symptom control (not prevention of EIB) indicates the need for additional long-term control therapy.</li> <li>■ May double usual dose for mild exacerbations.</li> <li>■ Should prime the inhaler by releasing 4 actuations prior to use.</li> <li>■ Periodically clean HFA actuator, as drug may plug orifice.</li> <li>■ Children &lt;4 years may not generate sufficient inspiratory flow to activate an auto-inhaler.</li> <li>■ Nonselective agents (i.e., epinephrine, isoproterenol, metaproterenol) are not recommended due to their potential for excessive cardiac stimulation, especially in high doses.</li> </ul>
Albuterol HFA	90 mcg/puff, 200 puffs/canister	2 puffs every 4–6 hours as needed	2 puffs every 4–6 hours as needed	
Levalbuterol HFA	45 mcg/puff, 200 puffs/canister	Safety and efficacy not established in children <4 years	2 puffs every 4–6 hours as needed	
Pirbuterol CFC Autohaler	200 mcg/puff, 400 puffs/canister	Safety and efficacy not established	Safety and efficacy not established	
<i>Nebulizer solution</i>				
Albuterol	0.63 mg/3 mL 1.25 mg/3 mL 2.5 mg/3 mL 5 mg/mL (0.5%)	0.63–2.5 mg in 3 cc of saline q 4–6 hours, as needed	1.25–5 mg in 3 cc of saline q 4–8 hours, as needed	<ul style="list-style-type: none"> <li>■ May mix with cromolyn solution, budesonide inhalant suspension, or ipratropium solution for nebulization. May double dose for severe exacerbations.</li> </ul>
Levalbuterol (R-albuterol)	0.31 mg/3 mL 0.63 mg/3 mL 1.25 mg/0.5 mL 1.25 mg/3 mL	0.31–1.25 mg in 3 cc q 4–6 hours, as needed	0.31–0.63 mg, q 8 hours, as needed	<ul style="list-style-type: none"> <li>■ Does not have FDA-approved labeling for children &lt;6 years of age.</li> <li>■ The product is a sterile-filled preservative-free unit dose vial.</li> <li>■ Compatible with budesonide inhalant suspension.</li> </ul>

**FIGURE 4–4c. USUAL DOSAGES FOR QUICK-RELIEF MEDICATIONS IN CHILDREN\* (CONTINUED)**

Medication	Dosage Form	0–4 Years	5–11 Years	Comments
<b>Anticholinergics</b>				
	<b>MDI</b>			
Ipratropium HFA	17 mcg/puff, 200 puffs/canister	Safety and efficacy not established	Safety and efficacy not established	<ul style="list-style-type: none"> <li>Evidence is lacking for anticholinergics producing added benefit to beta<sub>2</sub>-agonists in long-term control asthma therapy.</li> <li>See “Management of Acute Asthma” for dosing in ED.</li> </ul>
	<b>Nebulizer solution</b>			
	0.25 mg/mL (0.025%)	Safety and efficacy not established	Safety and efficacy not established	
<b>Systemic Corticosteroids</b>				
	<b>Applies to the first three corticosteroids</b>			
Methylprednisolone	2, 4, 6, 8, 16, 32 mg tablets	Short course “burst”: 1–2 mg/kg/day, maximum 60 mg/day, for 3–10 days	Short course “burst”: 40–60 mg/day as single or 2 divided doses for 3–10 days	<ul style="list-style-type: none"> <li>Short courses or “bursts” are effective for establishing control when initiating therapy or during a period of gradual deterioration.</li> <li>The burst should be continued until patient achieves 80% PEF personal best or symptoms resolve. This usually requires 3–10 days but may require longer. There is no evidence that tapering the dose following improvement prevents relapse.</li> </ul>
Prednisolone	5 mg tablets, 5 mg/5 cc, 15 mg/5 cc			
Prednisone	1, 2.5, 5, 10, 20, 50 mg tablets; 5 mg/cc, 5 mg/5 cc			
	<b>Repository injection</b>			
(Methylprednisolone acetate)	40 mg/mL 80 mg/mL	7.5 mg/kg IM once	240 mg IM once	<ul style="list-style-type: none"> <li>May be used in place of a short burst of oral steroids in patients who are vomiting or if adherence is a problem.</li> </ul>
Key: CFC, chlorofluorocarbon; ED, emergency department; EIB, exercise-induced bronchospasm; HFA, hydrofluoroalkane; IM, intramuscular; MDI, metered-dose inhaler; PEF, peak expiratory flow				
*Dosages are provided for those products that have been approved by the U.S. Food and Drug Administration or have sufficient clinical trial safety and efficacy data in the appropriate age ranges to support their use.				