Changes in recommended treatments for mild and moderate asthma

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Practice recommendations

- Every patient with persistent asthma, regardless of disease severity, should use a daily controller medication.
- Consider an inhaled corticosteroid (ICS) first when choosing controller medications for long-term treatment of mild, moderate, and severe persistent asthma in adults and children.
- Leukotriene modifiers, cromolyn, and nedocromil may be considered as alternative, not preferred, controller medications for patients with persistent asthma.
- Long-acting β_2-adrenergic agonists should not be used as monotherapy.
- Long-term use of ICSs within labeled doses is safe for children in terms of growth, bone mineral density, and adrenal function; nonetheless, asthma should be monitored and ICS therapy stepped down to the lowest effective dose.
- Low- to medium-dose ICSs are not associated with the development of cataracts or glaucoma in children, but high cumulative lifetime doses may slightly increase the prevalence of cataracts in adults and elderly patients.
- ICSs are recommended for use in pregnant women with asthma; budesonide is the only ICS rated Pregnancy Category B.

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Consider an adult with the following characteristics. To which disease severity would you assign this patient's asthma?

- Forced expiratory volume in 1 second (FEV_1) or peak expiratory flow (PEF) ≥80%
- PEF variability 20%–30%
- Daytime symptoms less than once a day
- Nighttime symptoms more than 1 night a week.

This patient is said to have *moderate persistent* asthma based on nighttime symptoms. An accurate classification of a patient's asthma is the foundation for selecting an appropriate treatment strategy.

In 2002 the National Asthma Education and Prevention Program (NAEPP) updated select topics[1] from its 1997 Guidelines for the Diagnosis and Management of Asthma.[2] These evidence-based revisions to the stepwise approach to asthma management were made following a systematic review of the literature (see **Search function**).

This article reviews the 2002 NAEPP recommendations for the use of controller medications for asthma, including:

- Relative effectiveness of inhaled corticosteroids (ICSs) versus other controller medications
- Safety of long-term ICS use in children
- Potential benefits of early ICS treatment.

We emphasize mild and moderate persistent asthma because the recommended treatments for these levels of severity have been most affected by the recent guideline changes.

We also discuss a recent change by the US Food and Drug Administration (FDA) in its pregnancy category rating for an ICS.

2002 STEPWISE APPROACH TO ASTHMA MANAGEMENT

New criteria for classifying asthma severity

The NAEPP classifies asthma severity according to symptoms and lung function in adults and children older than 5 years, and symptoms in children 5 years and younger.[1] Persistent asthma is classified as mild, moderate, or severe according to the feature of greatest severity.

Asthma severity should be assigned according to symptoms before treatment.[1] Because it is difficult to predict which infants and young children who wheeze with acute viral upper respiratory infection will go on to develop persistent asthma, new criteria have been detailed to help distinguish these children from those with transient wheeze (**Table 1**).[1,4]

Choosing pharmacologic treatment according to asthma classification

Quick-relief medications, which include the short-acting β_2-agonists (SABAs), are taken as needed to promptly reverse acute airflow obstruction and relieve accompanying symptoms.[2]

Asthma controller medications (ie, ICSs, cromolyn sodium, long-acting β_2-adrenergic-agonists [LABAs], leukotriene modifiers, nedocromil, and theophylline) are used daily to achieve and maintain long-term control of persistent asthma. All patients with persistent asthma, regardless of disease severity, should use a daily controller. Criteria for determining asthma severity and updated recommendations for the use of controller treatment in mild and moderate persistent asthma are presented in the **Figure**.[3,5] Levels of evidence justifying NAEPP treatment recommendations are shown in **Table 2**.

Search function

A comprehensive search of Medline and EMBASE databases was performed to identify controlled clinical studies relevant to each topic that were published (in English or foreign languages with English abstracts) from 1980 through August 2000. The search included studies published before 1980 if referenced in the post-1980 literature. Studies that did not include control groups were excluded, except for those reporting adverse effects of ICSs. Studies that met the study selection criteria established for each topic were included in a systematic review of the evidence. An expert panel reviewed the evidence, along with additional literature published since August 2000, and reached a consensus on whether the evidence supported 1997 guideline recommendations or indicated a need for revision. Writing committees were then assigned to developed position statements for each topic. The level of evidence for included studies was rated based on the system of Jadad and colleagues,[3] where **A** = randomized controlled trials, rich body of data; **B** = randomized controlled trials, limited data; **C** = nonrandomized trials and observational studies; **D** = panel consensus judgment.

For use in children. Asthma controller medications approved for use in children younger than 5 years include the fluticasone dry-powder inhalers (Flovent, Rotadisk, and Flovent Diskus), which are approved for children as young as 4 years (Flovent Diskus is not yet commercially available), and nebulized budesonide inhalation suspension (Pulmicort Respules), which is approved for children as young as 12 months.

The LABAs formoterol (Foradil) and salmeterol (Serevent Diskus) are approved for children as young as 5 and 4 years, respectively. Cromolyn sodium nebulizer solution is approved for children

TABLE 1

Criteria for children with intermittent wheeze

Infants and young children meeting these criteria should receive controller therapy for asthma:

- Significant exacerbations that occur <6 weeks apart
- ≥4 episodes of wheeze in the past year lasting >1 day and affecting sleep,

AND presence of risk factors for development of persistent asthma:

- Atopic dermatitis or parental asthma,
- OR 2 of the following:
  - Diagnosis of allergic rhinitis
  - >4% peripheral blood eosinophilia
  - Wheezing apart from colds

as young as 2 years, and theophylline is available for use at any age.

Based on safety and extrapolation of efficacy data in older patients, the oral granule formulation of the leukotriene receptor antagonist (LTRA) montelukast (Singulair) is approved for children as young as 1 year, and the chewable tablets are approved for children 2 to 5 years of age. Zafirlukast (Accolate) is approved for use in children 5 years and older.

New recommendations for *mild* persistent asthma. Recommendations for the treatment of mild and moderate persistent asthma have changed considerably from the 1997 guidelines. ICSs are now the preferred controller medications, based on greater efficacy. The updated guidelines no longer recommend an initial trial of cromolyn or nedocromil for the treatment of mild persistent asthma; these agents, along with the leukotriene modifiers and slow-release theophylline, are now considered alternatives to low-dose ICSs for *adults and children older than 5 years* with mild persistent disease (**Figure**).

According to the NAEPP update, daily low-dose ICS treatment also is preferred for the control of mild persistent asthma in *preschool children*. As in older children, cromolyn and nedocromil are no longer considered appropriate initial treatments for infants and children 5 years and younger. Cromolyn is considered an alternative controller, whereas nedocromil is no longer recommended for use.

New recommendations for *moderate* persistent asthma. For *adults and children older than 5 years* with moderate persistent asthma, revision to the guidelines involved recommendation of a low- to medium-dose ICS plus a LABA as the preferred controller treatment (**Figure**). Comparative low, medium, and high daily doses for ICSs are shown in **Table 3**.[1]

For *preschool children,* preferred controller treatments for moderate persistent asthma include low-dose ICSs plus a LABA, or increasing ICSs within the medium-dose range (**Figure**). Recommendations for the use of LABAs as add-on therapy in this age group are based on extrapolation of data from older patients, since therapy with an ICS/LABA combination has not been adequately studied in children younger than 5 years. Four studies included in the NAEPP evaluation showed clear benefit of medium-dose ICSs in this age group, supporting the use of medium-dose ICSs as a preferred option.[6–9] LABAs are not recommended for use without an ICS, and the only ICS/LABA combination product currently available has been FDA approved only for patients aged 12 years and older.

TOPICS IN THE MANAGEMENT OF ASTHMA IN CHILDREN

Recognizing the need for continual appraisal of the benefits and risks of asthma medications in children, the NAEPP Expert Panel considered new studies comparing the effectiveness of ICS monotherapy with that of as-needed SABAs and other controllers used as monotherapy in

TABLE 2

Levels of evidence for NAEPP assessments*

Medication	NAEPP assessment	SOR*
ICS	Preferred treatment for children of all ages with persistent asthma	A (A)
SABA	ICSs improve asthma control compared with as-needed SABAs	A (A)
Cromolyn/ nedocromil	For use as alternative, not preferred, treatment of mild persistent asthma in children of all ages (cromolyn) or children >5 years of age (nedocromil)	A (A)
LABA	For use with ICSs as the preferred combination treatment for moderate and severe persistent asthma in children >5 years of age	A (A)
	For use as a preferred option for combination treatment in children ≤5 years of age	B (B)
Leukotriene modifier	For use as alternative, not preferred, treatment of mild persistent asthma and as ICS adjunct in moderate persistent asthma	B (B)
Theophylline	For use as an alternative ICS add-on in moderate or severe persistent asthma if serum concentrations are monitored	D (D)
	Not considered an alternative controller for young children with mild persistent asthma due to potential adverse effects in infants with frequent febrile illnesses	

*Highest level of evidence available is reported. Strengths of recommendation are based on the method of Jadad et al.[3] Strength of evidence based on the Oxford Center for Evidence-Based Medicine[5] is in parentheses.
SOR, strength of recommendation; NAEPP, National Asthma Education and Prevention Program; ICS, inhaled corticosteroid; SABA, short-acting β_2-adrenergic agonist; LABA, long-acting β_2-adrenergic agonist.

children with mild or moderate persistent asthma. In addition, the safety of long-term ICS use in children was evaluated based on vertical growth, bone mineral density, ocular toxicity, and adrenal suppression.

Effectiveness of ICSs compared with other asthma medications

Short-acting β_2-adrenergic agonists. Eight studies met the eligibility criteria for evaluating the effectiveness of ICSs versus as-needed SABAs.[6,10–16] Six studies (4 involving budesonide) in children 5 years and older showed that ICSs improve lung function and symptoms and reduce the need for emergency intervention compared with as-needed SABAs.[1] Among all studies included in the NAEPP update, the Childhood Asthma Management Program (CAMP) Research Group Study,[9] a placebo-controlled study of inhaled budesonide and nedocromil, contributed the most evidence. Studies with children 5 years and younger are limited to 2 small studies enrolling a total of 69 children.[6,15] Consistent with studies of older children, these studies indicate that ICSs improve asthma control compared with as-needed SABAs.[1]

Cromolyn and nedocromil. Despite well-established safety profiles, cromolyn and nedocromil are no longer recommended as first-line therapy for children, even those with mild disease. New recommendations reflect the greater effectiveness of inhaled budesonide

FIGURE

Updated National Asthma Education and Prevention Program recommendations for long-term controller treatment in mild and moderate persistent asthma

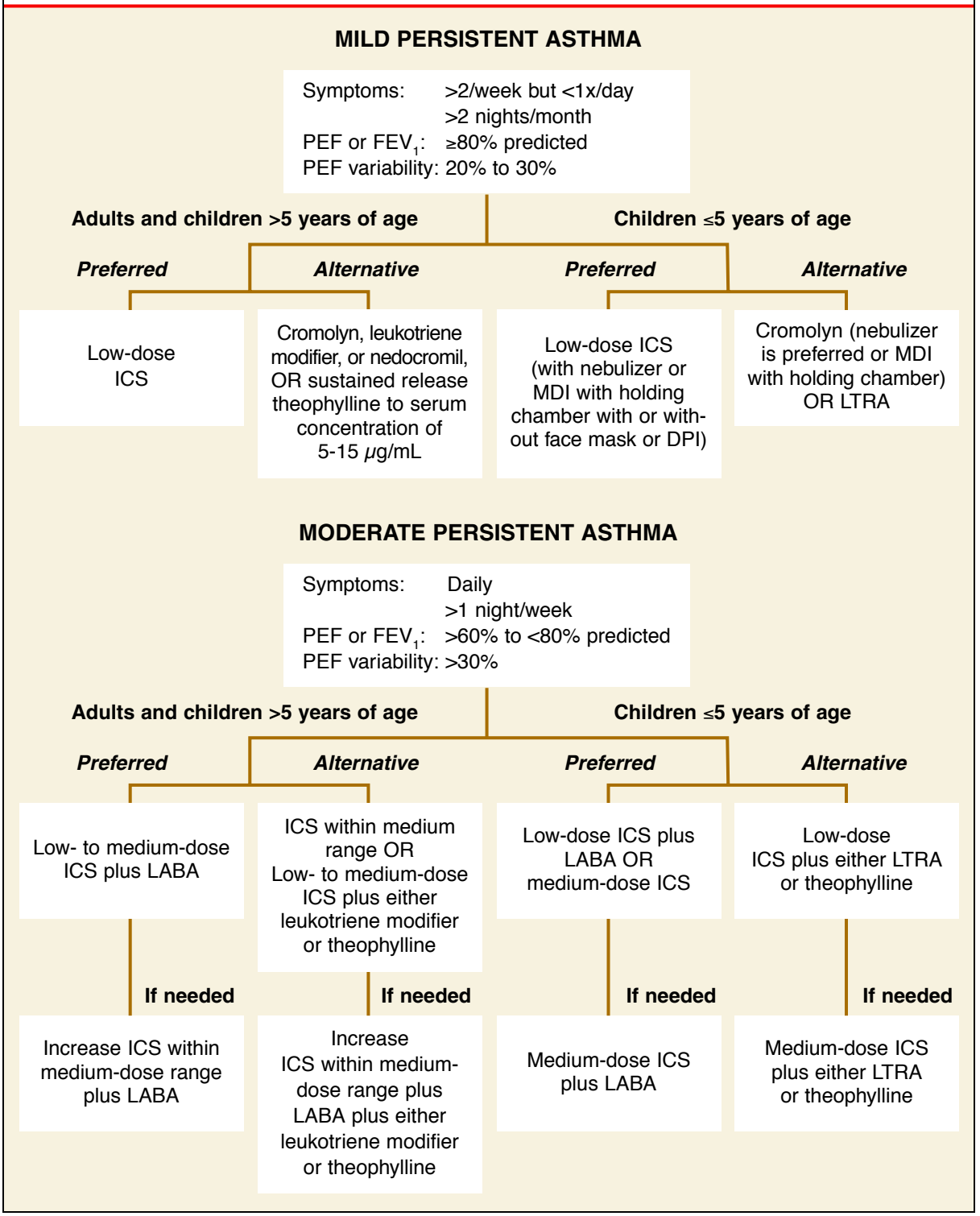

TABLE 3

Estimated comparative daily doses for inhaled corticosteroids*

Drug	Low daily dose		Medium daily dose		High daily dose	
	Adult	Child†	Adult	Child†	Adult	Child†
Beclomethasone CFC 42 or 84 μg/puff	168–504 μg	84–336 μg	504–840 μg	336–672 μg	>840 μg	>672 μg
Beclomethasone HFA 40 or 80 μg/puff	80–240 μg	80–160 μg	240–480 μg	160–320 μg	>480 μg	>320 μg
Budesonide DPI 200 μg/inhalation	200–600 μg	200–400 μg	600–1200 μg	400–800 μg	>1200 μg	>800 μg
Budesonide inhalation suspension for nebulization (child dose)		0.5 mg		1.0 mg		2.0 mg
Fluticasone MDI 44, 110, or 220 μg/puff	88–264 μg	88–176 μg	264–660 μg	176–440 μg	>660 μg	>440 μg
Fluticasone DPI 50, 100, or 250 μg/inhalation	100–300 μg	100–200 μg	300–600 μg	200–400 μg	>600 μg	>400 μg
Triamcinolone acetonide 100 μg/puff	400–1000 μg	400–800 μg	1000–2000 μg	800–1200 μg	>2000 μg	>1200 μg

*The most important determinant of appropriate dosing is the clinician's judgment of the patient's response to therapy. This updated comparative dose chart is based on review of recently published clinical trials involving more than 5000 patients and published reviews. Some doses may be outside package labeling, especially in the high-dose range.

†Children ≤12 years of age.

CFC, chlorofluorocarbon; HFA, hydrofluoroalkane; DPI, dry-powder inhaler; MDI, metered-dose inhaler.

compared with nedocromil demonstrated in the CAMP study,[10] and the lack of apparent benefit of cromolyn as maintenance treatment in childhood asthma reported by Tasche and colleagues in a systematic review of the literature.[17]

In the CAMP study, children 5 to 12 years of age receiving inhaled budesonide showed greater reductions in symptoms and albuterol use, lower rates of hospitalization and urgent care visits, and less need for additional asthma therapy and oral prednisone compared with placebo over 4 to 6 years of treatment.[10] The marginal effectiveness of nedocromil demonstrated in the CAMP study mirrored that of cromolyn reported in the review of 24 randomized placebo-controlled studies by Tasche and colleagues.[1,17]

For children 5 years and younger, the NAEPP Expert Panel took into account 1 randomized placebo-controlled study conducted with children 2 to 5 years of age; it showed improvements in lung function, symptoms, and bronchial hyperreactivity with inhaled budesonide.[9] Support for the new NAEPP recommendations preferring ICSs for preschool children is found in a more recent open-label study[18] that showed greater symptom improvement and significantly lower rates of asthma exacerbations, urgent care visits, and oral prednisone use with budesonide inhalation suspension, compared with cromolyn sodium nebulizer solution (Intal Nebulizer Solution) in children 2 to 6 years of age with persistent asthma.

Leukotriene modifiers. The LTRAs zafirlukast and montelukast are approved for use in children. According to the NAEPP Expert Panel, studies have shown only modest improvements in lung function and other asthma control outcomes with LTRA monotherapy in children as young as 6 and 2 years, respectively.[1] Because studies

comparing ICSs with LTRAs in children are lacking, findings of greater overall efficacy of ICSs in adults with persistent asthma have been extrapolated for use with children; clear superiority of ICSs versus LTRAs in most outcomes has resulted in the recommendation for ICSs as the preferred treatment for mild persistent asthma in children.

Long-acting β_2-adrenergic agonists. There is no role for LABAs as monotherapy in asthma. No studies have compared the effectiveness of ICS versus LABA monotherapy in children younger than 5 years, and studies in older children have shown greater effectiveness of inhaled beclomethasone versus salmeterol.[14,19] In the study by Verberne and colleagues, salmeterol monotherapy was associated with deterioration in FEV_1.[19] In a more recent study that included patients as young as 16 years, a switch from ICS to LABA treatment was associated with a significant increase in treatment failures and exacerbations.[20]

Theophylline. Only 1 study has compared outcomes with low-dose ICSs versus theophylline in adults and children.[21] Although limited, the data support greater effectiveness of ICSs based on symptoms, bronchial hyperresponsiveness, and the need for β_2-adrenergic agonists and oral corticosteroids.[1]

Safety of long-term ICS use in children

Systemic corticosteroids have the potential to suppress growth over the long term.[2] Short-term growth studies with ICSs show an average reduction in growth velocity of 1 cm per year during the first year of treatment, but the CAMP study showed that initial reductions in growth velocity with inhaled budesonide were not maintained over a 4- to 6-year treatment period.[1,10]

Although catch-up growth was not observed in the CAMP study, Agertoft and Pedersen reported no effect of long-term treatment with inhaled budesonide (mean 9.2 years) on final adult height.[22] Based on these long-term prospective studies of budesonide, showing only a transient reduction in growth velocity and attainment of expected final adult height, and retrospective studies including inhaled beclomethasone, the Expert Panel concluded that the ICS class is safe regarding growth effects.

Based on long-term studies, the panel concluded that the ICS class is safe regarding growth effects

According to the NAEPP Expert Panel, clinical study data for children monitored for up to 6 years strongly suggest that ICSs are safe when used at recommended doses (strength of recommendation: **A**).[1] The panel could not rule out a potential cumulative effect of ICS use on some conditions, (eg, osteoporosis, cataracts, glaucoma) in adulthood, as sufficient long-term data are not available.

The panel did conclude that low- to medium-dose ICSs (**Table 3**) appear to have no serious adverse effects on bone mineral density in children.

Likewise, low- to medium-dose ICS use was not associated with the development of cataracts or glaucoma in children, although the potential for high cumulative lifetime doses of ICSs to slightly increase the prevalence of cataracts in adults and elderly patients was noted.

Strong evidence also indicates that ICS effects on adrenal function are usually clinically insignificant at low to medium doses; however, certain individuals may be at higher risk for hypothalamic pituitary adrenal axis effects while using conventional ICS doses.[1]

Although ICSs are safe when used within labeled dosing, it is still preferable to maintain doses at the lowest effective dose. In general, treatment should be reviewed every 1 to 6 months and doses reduced in a stepwise fashion when possible.[1] For children showing a favorable response to treatment, a step down in dose should be considered, but not more frequently than every 3 months. If children show no clear response to treatment within 4 to 6 weeks, consider an alternative treatment or diagnosis.[1]

Safety of long-term ICS use in pregnant women

Uncontrolled asthma during pregnancy is associated with an increased risk of perinatal complications.[23] Since the consequences of not using asthma controllers during pregnancy can be worse than those with using them, daily controller treatment is recommended for all pregnant women with persistent asthma.[23]

The American College of Obstetricians and Gynecologists and the American College of Allergy, Asthma and Immunology previously recommended cromolyn as the treatment of choice for pregnant women with mild persistent asthma. ICSs were recommended for patients whose asthma was inadequately controlled with cromolyn.[24] Beclomethasone and budesonide were the ICSs of choice for pregnant women and those who might become pregnant, with a preference for budesonide when high-dose therapy was indicated.[24]

These recommendations predate the 2002 NAEPP recommendations for ICSs as preferred therapy in mild persistent asthma and the 2004 NAEPP recommendations for ICSs as the first-choice controller therapy for mild persistent asthma during pregnancy.[25] Among ICSs, one (inhaled budesonide) has an FDA Pregnancy Category B rating based on studies showing no risk in pregnant women.[26,27] All other ICSs are rated Pregnancy Category C.

Based on current evidence, it seems reasonable to consider whether budesonide should now be the preferred therapy for mild persistent asthma during pregnancy.

Effects of early treatment on asthma progression

The potential for early ICS intervention to prevent progression of mild or moderate persistent asthma was evaluated solely with data from children enrolled in the CAMP study.[10] The NAEPP Expert Panel concluded that CAMP study data do not support a progressive decline in lung function in children aged 5 to 12 years with mild or moderate persistent asthma, but do suggest that lung function decline is influenced by age of asthma onset.

According to the panel, CAMP data suggest that most deficits in lung function growth due to childhood asthma occur during the first 3 years of life. Preliminary results of the recent START study (Inhaled Steroid Treatment As Regular Therapy in Early Asthma),[28] conducted with 7165 corticosteroid-naïve patients 5 to 66 years of age with recent onset mild persistent asthma, did show a decline in lung function in patients with mild persistent disease.

Although improvements in prebronchodilator and postbronchodilator FEV_1 were significant after 3 years of treatment with inhaled budesonide, differences from placebo in both outcomes were greatest after the first year. When patients with mild persistent disease inhaled budesonide once daily in addition to normal treatment within 2 years of asthma onset,[28] they enjoyed considerable protection from severe and life-threatening asthma exacerbations and overall greater asthma control.

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DRUG BRAND NAMES

Budesonide • Pulmicort, Rhinocort
Cromolyn • Intal
Fluticasone • Flovent
Formoterol • Foradil
Montelukast • Singulair
Nedocromil • Tilade
Salmeterol • Servent
Triamcinolone acetonide • Azmacort
Zafirlukast • Accolate