The role of LTs in patients with EIB is to sustain the bronchoconstrictive and inflammatory response, although their role appears to vary significantly among patients. Correspondingly, inhibitors of the LT pathway (LTRAs and lipoxygenase inhibitors) are effective in reducing the severity of the decrease in FEV_1, as well as enhancing recovery of airway narrowing. Furthermore, there is much variability in their effectiveness, from completely blocking EIB in some asthmatic patients to blocking EIB less so or not at all in others. There is a 30% to 80% attenuation of EIB, with approximately 50% of patients being responders.[E257,E318,E319] These percentages can vary, depending in part on the FEV_1 decrease required to make a diagnosis of EIB (>10%, >15%, or >20%) or used to define protection. Most patients do not experience complete protection.[E258] This is not surprising given that other mediators (eg, PGD_2 and histamine)[E48,E320] are involved in EIB.

Various LTRAs have been found to be effective in attenuating EIB.[E58,E321-E324] Most studies have examined specific LTD_4 receptor antagonists, particularly montelukast. Montelukast is approved by the FDA for treatment of EIB in adolescents and adults. Montelukast acts within 1 to 2 hours of oral administration[E62,E324-E326] and has a bronchoprotective activity of 24 hours (Table E1).[E58,E59,E257,E326-E329] Maximum protection might not be retained in some subjects toward the end of this period.[E329] LTRAs also accelerate the time to recovery from EIB.[E58,E299] Although LTRAs are not as effective overall in attenuating EIB as β-agonists,[E258] tolerance does not develop with long-term use.[E58,E286,E287,E330] The variability in effect on EIB suggests populations of responders and nonresponders similar to those shown for the LT effects on overall asthma control (Fig E1).[E331-E333]

A second group of agents that affects the LT pathway by inhibiting synthesis are the lipoxygenase inhibitors. Lipoxygenase inhibitors have been shown to attenuate EIB when given orally,[E60,E160,E334,E335] but the duration of inhibition of these compounds is relatively short,[E60,E160] and they are not currently recommended for this indication (Table E1). Early-stage studies have demonstrated that inhibition of the LT pathway by 5-lypoxygenase activating protein inhibitors can inhibit EIB.[E336]

Mast cell stabilizers

Summary Statement 22: Consider prescribing inhaled cromolyn sodium and nedocromil sodium (currently not available in the United States as a metered-dose inhaler or dry powder inhaler) shortly before exercise; this attenuates EIB but can have a short duration of action. There is no bronchodilator activity. They might be effective alone or as added therapy with other drugs for EIB. [Strength of Recommendation: Strong; Evidence: A][E2]

Cromolyn sodium and nedocromil sodium are 2 structurally unrelated compounds that have no bronchodilator activity but have similar bronchoprotective activity against EIB when inhaled.[E57,E259,E337,E338] Several mechanisms have been proposed for these agents, including interference with mast cell mediator release of PGD_2.[E57,E337,E339] The bronchoprotective effect is rapid[E340] but of short duration (1-2 hours; Fig E1 and Table E1).[E164,E341] These agents can be effective when taken alone or when inhaled shortly before, and perhaps simultaneously with, exercise and might increase overall inhibition of EIB when combined with other drugs used to diminish EIB.[E259,E275,E341,E342] Significant intersubject and between-study variability has been observed in the ability of these agents to attenuate EIB. Some studies found few or no subjects protected, whereas other studies showed complete protection.[E343,E344] The effectiveness of cromolyn might be dose related.[E344-E346] Long-term use of either drug is not accompanied by tolerance. For this reason and because of their excellent safety profiles and rapidity of action, these agents can be used repeatedly to attenuate EIB in responsive subjects.[E259,E347]

ICSs

Summary Statement 23: Consider prescribing ICSs in combination with other therapies because ICSs can decrease the frequency and severity of EIB but not necessarily eliminate it. [Strength of Recommendation: Strong; Evidence: A][E2]

EIB in otherwise symptomatic asthmatic patients is best controlled by maintenance anti-inflammatory treatment alone[E148,E348,E349] or in combination with other short-term preventive treatment.[E252,E318,E350] ICSs improve overall asthma control in most patients with chronic persistent asthma. Use of ICSs is associated with attenuation of hyperresponsiveness to direct and indirect stimuli, including exercise.[E351,E352] The dose-dependent effect of ICSs has been observed shortly after the initial (3-4) weeks of treatment[E148,E353]; however, the effects of ICSs are also time dependent with longer duration (12 weeks) of treatment, demonstrating no difference between different doses inhibiting EIB.[E349] The relationship between control of persistent asthma and bronchoprotection, however, is imperfect (Fig E5).[E89,E354] Nevertheless, the degree of EIB is considered a reflection of asthma control (or lack of control), and in particular, moderate-to-severe EIB strongly suggests the need for reassessment of therapy or another diagnosis.[E348]

Some bronchoprotective effect against EIB with high-dose ICSs has been recorded as early as 4 hours after the first dose in adults.[E56,E355,E356] However, it has also been demonstrated that lower doses consistent with the daily treatment of asthma can have a bronchoprotective effect on EIB in children.[E169] After 1 week of therapy, efficacy begins to plateau[E40,E148,E353]; however, bronchoprotection can increase further over weeks or even months until it reaches its final plateau.[E147,E348,E357] This final plateau can come in the form of complete inhibition of EIB.[E349] Bronchoprotection has been shown to occur in 30% to 60% of asthmatic patients with EIB, with marked individual variability ranging from “complete” protection to little or no evidence of protection.[E147] In the absence of definitive dose-ranging and repetitive studies in individual patients, it is not clear whether this reflects distinct subpopulations of responders and nonresponders (eg, a reflection of genetic differences) or whether this is related to EIB severity.

Allergic rhinitis is a common finding in atopic asthmatic patients, and there is some evidence that effective treatment of nasal congestion and obstruction by nasal ICSs is associated with at least mild reduction in EIB.[E357,E358,E359] To some extent, these findings validate the concept of the unified airway theory, which states that allergic rhinitis of the nose and atopic airway inflammation in asthmatic patients are manifestations of similar pathologic processes in the upper and lower respiratory airways, respectively.[E360] It is unclear whether treating EIB with both intranasal corticosteroids and ICSs leads to more effective treatment of EIB in allergic asthmatic patients compared with ICSs alone.