

REVIEW ARTICLE

Jeffrey M. Drazen, M.D., *Editor*

Asthma and Exercise-Induced Bronchoconstriction in Athletes

Louis-Philippe Boulet, M.D., and Paul M. O'Byrne, M.B.

REGULAR EXERCISE IS ONE OF THE MOST EFFECTIVE MEANS TO MAINTAIN good health. A substantial proportion of the general population engages in competitive sports, including many people with asthma; when controlled, asthma does not restrict exercise performance. Indeed, exercise training can improve asthma symptoms, quality of life, exercise capacity, and pulmonary function, as well as reduce airway responsiveness.¹

Intense exercise imposes demands on the cardiorespiratory system. Cardiac output increases, as does minute ventilation, which can reach 200 liters per minute in high-level athletes.² At high minute ventilations, the airways are the site of intense respiratory heat and water exchange as they condition inspired air to body temperature and humidity levels. Furthermore, because mouth breathing is common during exercise, there is an increased penetration of allergens and pollutants — such as chloramines from chlorinated pools, ozone, and particulate matter from ambient air — into the lower airways. Therefore, it is not surprising that as compared with nonathletes, high-level endurance athletes have an increased prevalence of various respiratory ailments, such as asthma and rhinitis, and related coexisting conditions.³⁻⁵

The term exercise-induced bronchoconstriction describes the transient narrowing of the airways after exercise, a phenomenon that occurs frequently among athletes who may not have a diagnosis of asthma or even have any respiratory symptoms.⁵⁻⁸ Exercise-induced bronchoconstriction is a distinct form of airway hyperresponsiveness, which is defined as the tendency of airways to constrict more easily and more forcefully than normal airways in response to a wide variety of bronchoconstrictor stimuli. Airway hyperresponsiveness, which is a cardinal feature of asthma, is more common among endurance athletes — particularly winter-sports athletes and swimmers — than in the general population.^{7,8}

The mechanism of exercise-induced bronchoconstriction has not been established with certainty; both airway cooling resulting from conditioning of inspired air and postexercise rewarming of airways have been proposed as mechanisms. However, the key stimulus is probably airway dehydration as a result of increased ventilation, resulting in augmented osmolarity of the airway-lining fluid.⁹ This is thought to trigger the release of mediators — such as histamine, cysteinyl leukotrienes, and prostaglandins — from airway inflammatory cells, which leads to airway smooth-muscle contraction and airway edema. However, uncontrolled airway inflammation can exacerbate this process and increase exercise-induced bronchoconstriction.¹⁰ Furthermore, not only can osmotic and mechanical stress to the airways play a role in the acute response to exercise, but they may also be involved in the development of airway remodeling in athletes, probably through their effects on airway epithelial cells.^{4,8,9} Finally, transient immunosuppression may also develop in athletes during periods of intense training, with increased susceptibility to respiratory infections, particularly viral infections¹¹; this may increase airway response to exercise acutely and affect overall asthma control.

From the Quebec Heart and Lung Institute, Laval University, Quebec City, QC (L.-P.B.), and the Firestone Institute of Respiratory Health, Department of Medicine, McMaster University, Hamilton, ON (P.M.O.) — both in Canada. Address reprint requests to Dr. Boulet at the Institut Universitaire de Cardiologie et de Pneumologie de Québec, 2725 Chemin Sainte-Foy, Québec, QC G1V 4G5, Canada, or at lpboulet@med.ulaval.ca.

N Engl J Med 2015;372:641-8.

DOI: 10.1056/NEJMra1407552

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High-intensity training may therefore contribute to the development of asthma, exercise-induced bronchoconstriction, and airway hyperresponsiveness.^{12,13} For example, swimmers training in chlorinated pools and cross-country skiers exposed to cold, dry air can have airway epithelial damage, inflammation, and remodeling similar to that seen in asthmatic airways.^{8,14,15} This observation has led to the inference that preventive strategies to protect airways, as recommended for persons with other types of relevant occupational exposures, may be a useful therapeutic option for high-level athletes. This reasoning is supported by the fact that airway hyperresponsiveness can improve or even normalize in swimmers after they refrain from competitive swimming for a sustained period (the duration differs among athletes but is usually weeks to years).¹⁶

In this article, we review the current management of asthma and exercise-induced bronchoconstriction in athletes. We focus particularly on athletes who engage in endurance sports, and we provide specific recommendations for high-level athletes.

DIAGNOSING ASTHMA
AND BRONCHOCONSTRICTION
IN ATHLETES

An early diagnosis of asthma or exercise-induced bronchoconstriction in an athlete may prevent the impaired performance that can ensue if preventive measures are not taken.¹⁷ In athletes, the diagnosis of asthma can be made on the basis of a history of characteristic symptom patterns and documentation of variable airflow limitation, by means of bronchodilator reversibility testing or other means, such as bronchoprovocation tests. However, respiratory symptoms alone have poor predictive value for making a diagnosis of asthma and exercise-induced bronchoconstriction in athletes.^{4,18} The documentation of variable airway obstruction is a requirement for a diagnosis of these conditions in all patients. Furthermore, expiratory flows can be supranormal (e.g., >120% of the predicted value) in some athletes, such as swimmers, and therefore maximal achievable expiratory flows should always be documented. In this regard, the demonstration of more than 10% diurnal variability in peak expiratory flows measured twice daily over a period of 2 weeks, or more than 12% (and >200 ml) variability in forced expiratory volume in 1 second (FEV₁) over time or

after 4 weeks of treatment, is consistent with a diagnosis of asthma or exercise-induced bronchoconstriction (Fig. 1).

The likelihood of airways to narrow can also be demonstrated, if airflow limitation is present, by a more than 12% (and >200 ml) change in the FEV₁ after inhalation of an aerosolized β_2 -agonist; if the baseline airway caliber is normal, this likelihood can be assessed as the presence of airway hyperresponsiveness documented with the use of bronchoprovocation testing. These tests include direct challenges (e.g., with inhaled methacholine), which act on airway smooth muscle to cause bronchoconstriction, and indirect challenges, such as eucapnic voluntary hyperpnea (particularly recommended for athletes¹⁹), hyperosmolar tests with saline or mannitol, and laboratory or field exercise tests.²⁰⁻²² However, athletes may have a positive response to only one of these types of tests, and airway responsiveness can normalize a few weeks after they stop intense training.¹⁶ Therefore, more than one type of test may be needed, and ideally the testing should be performed during a period of intense training. There is a lack of data on the value of noninvasive measurements of airway inflammation, such as induced sputum analysis or measures of fractional exhaled nitric oxide (FE_{NO}), in the diagnosis of asthma and exercise-induced bronchoconstriction and assessment of treatment needs in athletes.

Particular attention has to be devoted to identifying asthma confounders and coexisting conditions, which can mimic or be associated with asthma in athletes (Fig. 1). One of the most common is exercise-induced glottic or supraglottic laryngeal obstruction, including vocal-cord dysfunction, a paradoxical closure of vocal cords during inspiration. Other conditions, such as rhinitis, gastroesophageal reflux, and hyperventilation syndrome, are common among athletes and should be considered if the tests described above are inconclusive or if the response to a therapeutic trial (see below) is poor.²³

MANAGEMENT OF ASTHMA
AND BRONCHOCONSTRICTION
IN ATHLETES

The goals of asthma treatment are to achieve and maintain asthma control, optimize pulmonary function, and prevent risk factors for acute events, such as exacerbations.²⁴ The management of asthma in athletes, however, requires some specific

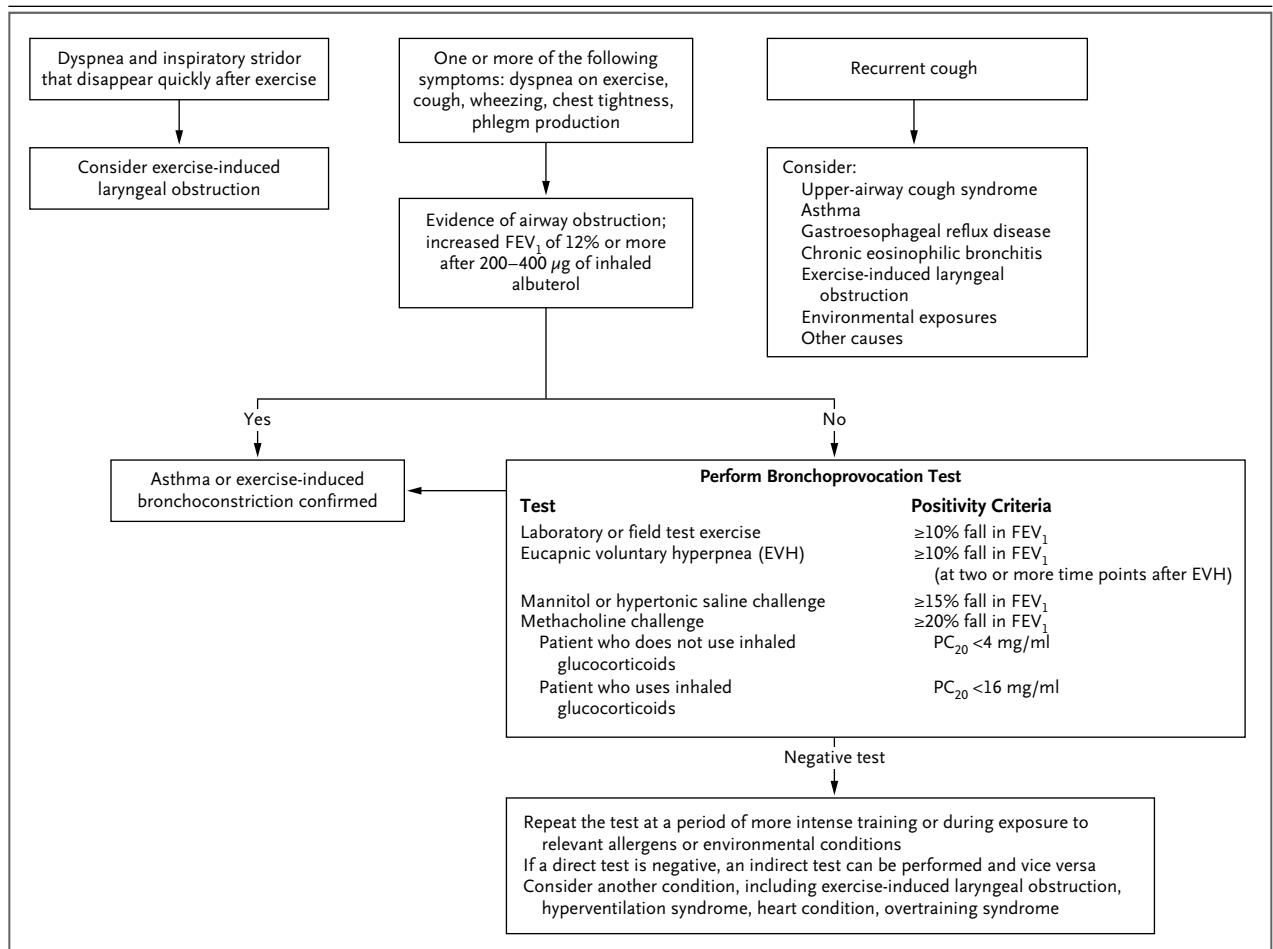


Figure 1. Diagnosis of Asthma and Exercise-Induced Bronchoconstriction in Athletes.

Shown is the suggested algorithm for the evaluation of respiratory symptoms suggestive of asthma and airway hyperresponsiveness in athletes. Note that in the presence of airway obstruction, the forced expiratory volume in 1 second (FEV_1) is usually less than 80% of the predicted value, and the FEV_1 :forced vital capacity ratio is usually reduced to less than 0.75 in adults; however, the FEV_1 may look normal in some high-level athletes with airway obstruction, as a result of supranormal baseline values. Furthermore, demonstration of more than 10% diurnal variability in peak expiratory flow over a period of 2 weeks or of more than 12% (and >200 ml) variability in FEV_1 is consistent with a diagnosis of asthma or exercise-induced bronchoconstriction. The International Olympic Committee Medical Commission has recommended the EVH test to identify exercise-induced bronchoconstriction among Olympic athletes because of its high sensitivity.¹⁹ In the methacholine challenge, for patients who have not used inhaled glucocorticoids, a provocative concentration of methacholine inducing a 20% decrease in FEV_1 (PC_{20}) of 4 to 16 mg per milliliter suggests borderline airway hyperresponsiveness.

considerations (Table 1). In high-level athletes, minimizing the possible deleterious effects of exercise on airway function is mandatory to allow optimal performance. Unfortunately, athletes are often unaware of, or do not report, respiratory symptoms.

NONPHARMACOLOGIC MEASURES

As for all patients with asthma, education about asthma self-management is essential; this should include advice about environmental measures, in-

haler-use technique, and the use of an asthma action plan for the management of exacerbations, in addition to regular follow-up.²⁴ Mechanical barriers such as face masks, although they are not always well tolerated, can help reduce the effects of cold air exposure in winter-sports athletes²⁵ or the inhalation of particulate air pollutants. A pre-exercise warm-up (i.e., low-intensity or variable-intensity precompetitive exercise) can result in a reduction in exercise bronchoconstriction in more than half of persons.²⁶ This is attributed to a “re-

Table 1. Specific Issues in the Management of Asthma in Athletes.

Issue	Examples and Suggestions
Poor recognition of or difficulties in assessing asthma symptoms	Symptoms may be denied, not recognized, or considered insufficient to be treated.
Unrecognized alterations in lung function	Despite bronchoconstriction, expiratory flows may look normal as a result of a high baseline value.
Possible need for more than one type of bronchoprovocation test to confirm the diagnosis	If negative, the tests may need to be repeated during a high-intensity training period or in an environment where a suspected trigger is present (e.g., allergens or pollutants). If a direct test (e.g., methacholine) is negative, an indirect test (e.g., eucapnic voluntary hyperpnea or mannitol challenge) may be needed for the diagnosis.
Increased prevalence of coexisting conditions	Examples include exercise-induced laryngeal obstruction, rhinitis, gastroesophageal reflux, and hyperventilation syndrome.
Undertreatment, overtreatment, or poor control with current therapy	β_2 -Agonists are sometimes overused, and inhaled glucocorticoids have been used insufficiently (including poor adherence).
Need to avoid the development of tolerance to β_2 -agonists	Regular or frequent use of short-acting β_2 -agonists should be avoided.
Difficulties in reducing exposure to sensitizers and irritants	All athletes should avoid exercising while exposed to large amounts of allergens or pollutants. Winter-sports athletes should avoid exercising in very low temperatures and should consider the use of face masks. Protective measures for swimmers should include ensuring the hygiene of athletes and checking that chlorine levels are as low as safely possible to reduce chloramine formation in pools.
Antidoping regulations	Athletes should check the requirements for Therapeutic Exemption Use.

fractory period” induced by the release of protective prostaglandins and by airway smooth-muscle tachyphylaxis to mediators of bronchoconstriction,^{26,27} during which time (about 2 hours) airways are less likely to constrict after exercise. Treatment should be offered for coexisting conditions associated with asthma, such as gastroesophageal reflux, rhinitis, or exercise-induced laryngeal obstruction; in the case of exercise-induced laryngeal obstruction, treatment should mainly involve the use of specific breathing exercises and removal of laryngeal irritants.

Although it is preferable for athletes not to train in conditions of very cold, dry air or during times of high levels of exposure to allergens or atmospheric pollutants, this is often difficult to avoid. However, whenever possible, it is preferable to avoid exercise close to busy roads or, for sensitized athletes, to avoid exercise activities and timing that would result in high allergen exposure, such as running through a ragweed field in the autumn.^{13,28} Improved ventilation of pool environments, measures to reduce chloramine formation in chlorinated pools, and reduction of exposure to other indoor and outdoor pollutants, including ozone, particulate matter, and nitrogen oxides, should also be promoted.^{13,29} There are insufficient data to recommend fish oil (n-3 fatty acids),³⁰ vitamins,³¹ or antioxidants as treatment.

PHARMACOTHERAPY

Recommendations for the treatment of asthma and exercise-induced bronchoconstriction in athletes are shown in Table 2.^{3,4,21,24} These are largely based on expert opinion, because there have been few adequately powered randomized clinical trials on asthma management in elite athletes.

Inhaled glucocorticoids are the mainstay of asthma therapy in athletes, as they are in non-athletes^{4,24}; these agents are allowed by sports authorities. Inhaled glucocorticoids have been underused in the treatment of athletes, and β_2 -agonists have been overused.³² Apart from helping to control asthma and improve pulmonary function, an additional benefit of treatment with inhaled glucocorticoids is a progressive reduction, with regular use, in airway responses to various stimuli, including exercise.³³ In our opinion, inhaled glucocorticoids, usually at a low daily dose, should be considered if an athlete needs to use a rescue β_2 -agonist more than twice per week — including doses required to prevent exercise-induced bronchoconstriction — or if asthma is limiting exercise tolerance (i.e., the ability to exercise without troublesome symptoms). However, recent recommendations suggest that for some patients, inhaled glucocorticoids can be considered even earlier (e.g., if asthma symptoms occur or rescue medication is needed more than twice per month,

Table 2. Treatment of Asthma and Exercise-Induced Bronchoconstriction in Athletes.**Main goals of treatment**

- Achieve and maintain asthma control
- Inhibit or minimize exercise-induced bronchoconstriction to avoid affecting performance
- Prevent risk factors for acute events (e.g., exacerbations)
- Reduce the risk of reduction of lung function
- Ensure compliance with sports-authorities' regulations (www.wada-ama.org)

General measures for management

- Identify possible triggers and inducers and suggest environmental control measures
 - For swimmers: reduce chloramine formation and exposure in the pool environment
 - For winter-sports athletes: avoid exercising in extreme cold, wear protective masks
 - For all athletes: avoid high levels of exposure to pollutants and relevant allergens during training
- Identify and treat coexisting conditions: for example, rhinitis, gastroesophageal reflux disease, exercise-induced laryngeal obstruction (including vocal-cord [glottic] dysfunction), and hyperventilation syndrome
- Provide asthma education and guided self-management abilities
 - Refer to an asthma educator whenever available
 - Explain how to monitor asthma control and provide an action plan for exacerbations
 - Check inhaler technique
 - Assess and promote medication adherence

Prevention of exercise-induced bronchoconstriction

- Ensure effective asthma control
- Engage in pre-exercise warm-up
- Use a short-acting β_2 -agonist before exercising (should not always be needed); cromones are a second choice

Pharmacologic treatment

- Follow current general guidelines to assess medication needs
- Provide rescue therapy (e.g., short-acting β_2 -agonist on demand at the minimum dose and frequency)
- Provide maintenance therapy (first choice, inhaled glucocorticoid; second choice, leukotriene-receptor antagonist)
- If uncontrolled with a low dose of an inhaled glucocorticoid, prescribe a combined inhaled glucocorticoid and inhaled long-acting β_2 -agonist or add a leukotriene-receptor antagonist to inhaled glucocorticoid after checking general measures and contribution of coexisting conditions

particularly if there are risk factors for exacerbations).²⁴ If low doses of inhaled glucocorticoids do not achieve asthma control, the addition of another controller drug should be considered, preferably a long-acting inhaled β_2 -agonist.

Leukotriene modifiers also reduce exercise-induced bronchoconstriction^{34,35} and have protective effects against the bronchoconstriction caused by exposure to pollutants.³⁶ Cromolyn sodium and nedocromil sodium also protect against exercise-induced bronchoconstriction, but inhaled β_2 -agonists are more effective. As is the case with nasal inhaled glucocorticoids and nasal ipratropium, antihistamines may help to control associated rhinitis but are not considered effective against exercise-induced bronchoconstriction. Immunotherapy has limited efficacy in the treat-

ment of asthma and has not been formally studied in athletes.²⁴

Currently used inhaled β_2 -agonists have no performance-enhancing effect in athletes, with or without asthma. Short-acting inhaled β_2 -agonists are the most effective drugs for the relief of bronchoconstriction and are also effective in preventing exercise-induced bronchoconstriction when used 5 to 10 minutes before exercise. However, the regular or frequent use of inhaled β_2 -agonists may increase airway responsiveness to bronchoconstrictor stimuli and lead to tolerance to β_2 -agonists and to a decrease in their bronchoprotective effects during exercise,³⁷ possibly as a result of downregulation of the β_2 receptor. This effect may be particularly detrimental in athletes with asthma or exercise-induced bronchoconstriction, because

Table 3. Current Antidoping Status of Asthma Medications.*

Drug	Status
Inhaled β_2 -agonists	
Albuterol†	Permitted
Formoterol†	Permitted
Salmeterol†	Permitted
Terbutaline‡	Prohibited
Inhaled anticholinergics	Permitted
Inhaled glucocorticoids	Permitted
Leukotriene antagonists	Permitted
Cromolyn or nedocromil	Permitted
Omalizumab§	Permitted
Oral glucocorticoids¶	Prohibited

* Prohibited substances can be used by athletes only if a Therapeutic Use Exemption is granted in accordance with the International Standards on Therapeutic Use Exemptions. The athlete should, however, list all medications used on the doping control form.

† The maximum daily doses of albuterol and formoterol permitted are 1600 and 54 μg per day, respectively. Inhaled salmeterol should be used in accordance with the manufacturer's recommended therapeutic regimen. A urinary concentration of albuterol greater than 1000 ng per milliliter or of formoterol greater than 40 ng per milliliter is considered by the World Anti-Doping Agency (WADA) to be an "adverse analytical finding," unless the athlete proves the drug was used therapeutically. There will be a presumption that the substance was not taken by inhalation therapeutically, and the athlete will have the burden of demonstrating by means of a controlled pharmacokinetic study that the level found in the athlete's urine sample was the result of therapeutic inhaled use.

‡ Terbutaline and all other β_2 -agonists not specifically mentioned above are always prohibited.

§ Omalizumab has been found useful in the rare cases of exercise-induced anaphylaxis⁴¹ but has not been formally studied in athletes with asthma. It is unlikely to be used in the treatment of high-level athletes because it is mostly indicated for severe allergic asthma.

¶ These agents are prohibited during competition only (see the WADA website).

they exercise frequently and need highly effective protection against exercise-induced bronchoconstriction. If asthma is well controlled, an athlete will only occasionally (less than daily) need these agents to prevent and treat exercise-induced bronchoconstriction. Long-acting inhaled β_2 -agonists are used, together with inhaled glucocorticoids, to better control asthma when low doses of inhaled glucocorticoids alone are insufficient²⁴; as in nonathletes, long-acting inhaled β_2 -agonists should never be used without an inhaled glucocorticoid.

The most common management strategy for athletes with asthma or exercise-induced bronchoconstriction who are exercising daily is daily treatment with inhaled glucocorticoids, with short-

acting inhaled β_2 -agonists used occasionally before exercise. Leukotriene-receptor antagonists are also an option for maintenance treatment, and the combination of inhaled glucocorticoids and leukotriene-receptor antagonists may provide additional protection.³⁵ However, current asthma drugs that are effective for many persons with asthma who are not athletes are often unable to provide excellent asthma control in athletes, possibly because of the supranormal stimuli to the airways, a wrong diagnosis of asthma, concomitant conditions, nonadherence to therapy, poor technique in using inhalers, or a more treatment-resistant phenotype of asthma.³⁸⁻⁴⁰

ANTIDOPING REGULATIONS

Athletes with documented asthma or exercise-induced bronchoconstriction should review and adhere to antidoping regulations. Inhaled glucocorticoids and leukotriene-receptor antagonists do not currently require a Therapeutic Use Exemption by sports authorities. All β_2 -agonists, including optical isomers, are prohibited, except inhaled albuterol, formoterol, and salmeterol, when used in accordance with the World Anti-Doping Agency (WADA) specifications (Table 3). Other inhaled β_2 -agonists and oral or systemic glucocorticoids require a Therapeutic Use Exemption. Athletes should check the WADA website (www.wada-ama.org/en) regularly to keep updated on these regulations.

CONCLUSIONS

The prevalence of asthma and exercise-induced bronchoconstriction among athletes is uncertain but has been estimated to be between 30% and 70% among elite athletes, depending on the type of sports performed; however, much remains to be learned about the reasons for this and how to reduce the risk.⁴² Asthma and exercise-induced bronchoconstriction can usually be well managed in athletes, most often with the use of maintenance inhaled glucocorticoids and occasional inhaled short-acting β_2 -agonists before exercise. Knowledge of and adherence to antidoping regulations regarding asthma drugs are important for developing an asthma-management plan for competitive athletes. The approach outlined here is based largely on expert opinion. We need better

data from controlled trials on ways to manage asthma and exercise-induced bronchoconstriction in athletes, who undertake frequent and intense efforts, often in challenging environmental conditions.

Dr. Boulet reports receiving consulting and lecture fees from Merck, GlaxoSmithKline, AstraZeneca, and Novartis and grant support from GlaxoSmithKline, AstraZeneca, Novartis, Genentech, Amgen, ONO, Boehringer Ingelheim, and AsthmaCure. Dr.

O'Byrne reports receiving consulting fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Forest, Verona, and Novartis, lecture fees from Chiesi and Takeda, and grant support from AstraZeneca, Novartis, Amgen, Genentech, ONO, and Axican. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Julie Turmel, Kenneth D. Fitch, Pascale Kippelen, and the reviewers, for their comments on an earlier version of the manuscript, and Sylvie Carette for assistance with manuscript preparation.

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