Key points

- Intermittent doses of inhaled β_2-agonists are the treatment of choice to block exercise-induced asthma/exercise-induced bronchoconstriction (EIA/EIB) if taken immediately before exercising.
- Regular use of inhaled β_2-agonists has been found to increase the underlying severity of EIA/EIB.
- Inhaled β_2-agonists become less effective at blocking EIA/EIB and less effective bronchodilators if taken regularly or frequently.
- The rules governing the use of inhaled β_2-agonists at the Olympic Games and other elite sporting events have changed several times, but many successful athletes continue to use them.
- Athletes requiring frequent or regular doses of inhaled β_2-agonists should consider preventative measures and anti-inflammatory treatments to reduce the need for inhaled β-agonists.

Exercise and asthma: β_2-agonists and the competitive athlete

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Provenance
Commissioned article, peer reviewed.

Competing interests
See end of article

Educational aims

- Discuss the role of inhaled β-agonists in the management of exercise-induced asthma and exercise-induced bronchoconstriction.
- Review the beneficial *versus* untoward effects of inhaled β-agonists on asthma, exercise-induced asthma and exercise-induced bronchoconstriction.
- Report on current and past usage of these drugs by Olympic athletes.

Summary

Inhaled β-agonists effectively block exercise-induced asthma/exercise-induced bronchoconstriction (EIA/EIB). They are the treatment of choice for this condition and are used by many elite and Olympic athletes. However, regular or frequent use of inhaled β-agonists leads to an increase in the underlying severity of EIA/EIB and a reduction in their bronchoprotective and bronchodilator effects, which means that they become less effective at preventing and treating EIA/EIB. Emphasis should be placed on preventative measures and anti-inflammatory treatments such as inhaled corticosteroids in order to minimise the need for inhaled β-agonists to prevent EIA/EIB.

Asthma is characterised by an increased response of the airways to various triggers, among which exercise is one of the most frequently reported. The term "exercise-induced asthma (EIA)" usually describes the occurrence of a transient narrowing of the airways after exercise that is reversible by inhalation of a bronchodilator in an individual with asthma. "Exercise-induced bronchoconstriction (EIB)", describes such narrowing of the airways only with exercise [1] and may simply represent a very mild form of asthma (fig. 1).

Inhaled β_2-adrenoceptor agonists (IBA) are currently used to prevent EIA/EIB and as rescue medication for intercurrent asthma symptoms. Current guidelines recommend that the use of IBA as rescue medications should be kept to a minimum while priority should be given to anti-inflammatory treatment. In the last decade, the use of IBA by high-level athletes has been regulated by sports authorities to ensure proper usage of these drugs.

β_2-agonists in the global management of asthma and prevention of EIA/EIB

The main goal of asthma management is to achieve control of the disease, defined as minimal symptoms and need for rescue bronchodilator therapy, in addition to optimal pulmonary function [3]. The reader can refer to current guidelines, such as the Global Initiative on Asthma, GINA Guidelines, to check specific asthma control criteria [4].

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HERMES syllabus link: module B.1.1

DOI: 10.1183/18106838.0701.064

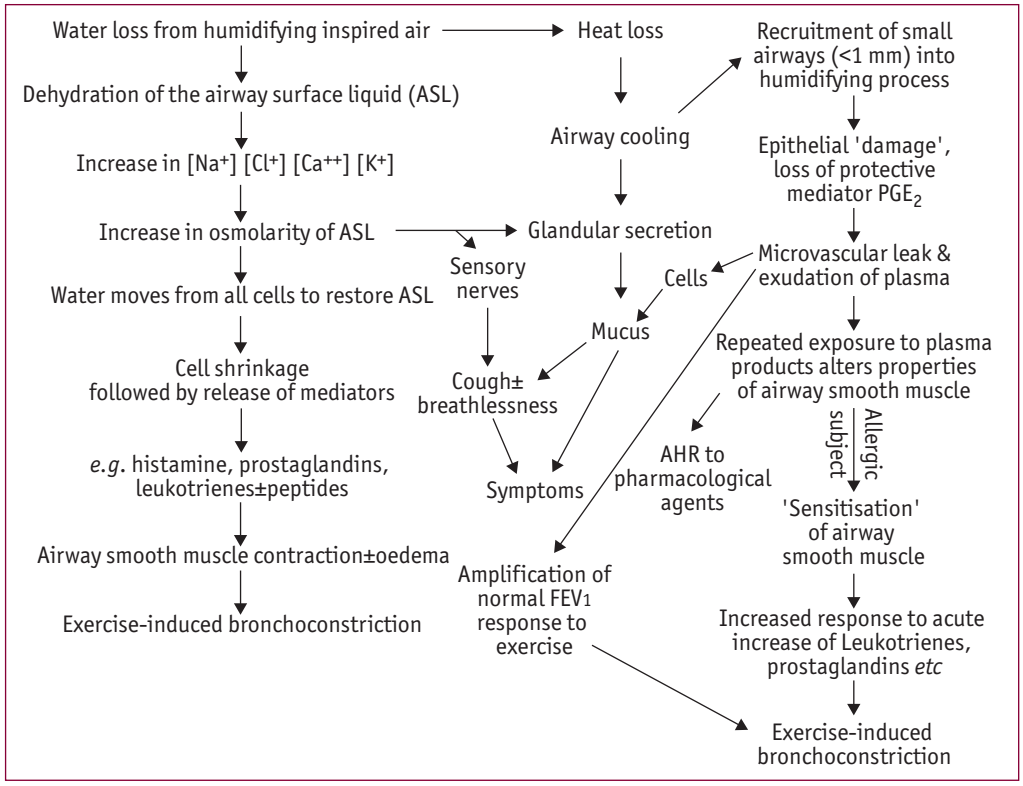

Figure 1
Acute events leading to EIB in the subject with classic asthma (left) and the events leading to the development of EIB in the athlete (right). Reproduced from Anderson and Kippelen [2] with permission from the publisher. AHR: airway hyperresponsiveness; FEV1: forced expiratory volume in 1s.; PGE_2: prostaglandin E_2.

Good control of asthma is essential to minimise EIA/EIB. In this regard, it has been shown that obtaining such control of asthma, for example with an inhaled corticosteroid (ICS), results in a better tolerance to exercise, with a reduced tendency to develop EIA/EIB [5].

As there are no specific guidelines on asthma treatment in the athlete, it is currently recommended to treat them in the same way as non-athletes (fig. 2). The therapeutic plan consists of: 1) patient education, including self-assessment and self-management skills, optimal inhaler technique and a written action plan for exacerbations; 2) environmental control; 3) individualised pharmacotherapy; 4) treatment of co-morbidities, such as frequent rhinitis in athletes; and 5) regular follow-ups [4, 6].

In the athlete, particular care should be given to the prevention of EIA/EIB. Environmental factors, such as allergens, pollutants, particulate matter, ozone, and extreme weather conditions, in association with the high ventilation required for intense exercise in endurance sports, promote the development of airway narrowing in athletes with airway hyperresponsiveness (AHR), and measures to reduce such exposures should be considered [7]. Allergens in sensitised athletes, chlorine derivatives, indoor and outdoor pollutants and cold air can particularly affect the athlete's airways, induce symptoms and possibly contribute to the development of AHR [1].

In regard to the pharmacotherapy of asthma, fast-acting IBAs are commonly used in the athlete for the treatment and prevention of intercurrent symptoms and EIA/EIB (table 1).

When IBAs are used every week, ICS should be introduced because these usually reduce the tendency to develop EIA/EIB, in addition to reducing the risk of asthma exacerbations [8]. If a low dose of ICS is insufficient to control asthma, a long-acting IBA may be added for the maintenance treatment of asthma but should only be used in association with an ICS.

Although usually less potent than ICS [9], leukotriene receptor antagonists (LTRAs) are an alternative anti-inflammatory treatment and are the second choice as an add-on medication in adults. If formoterol is the long-acting IBA used in association with an ICS, it can also be used as a rescue medication for this specific purpose. Long-acting IBAs should not be used alone as monotherapy of asthma.

It has been suggested that asthma medications are less effective in reducing airway inflammation and improving respiratory symptoms in the athlete than in the non-athlete [10, 11]. Pharmacological treatment should therefore be carefully selected in athletes and the benefits of each introduced treatment properly evaluated. Difficult-to-control asthma or unresponsive EIA/EIB may be due to an incorrect diagnosis; for example, glottic dysfunction and hyperventilation

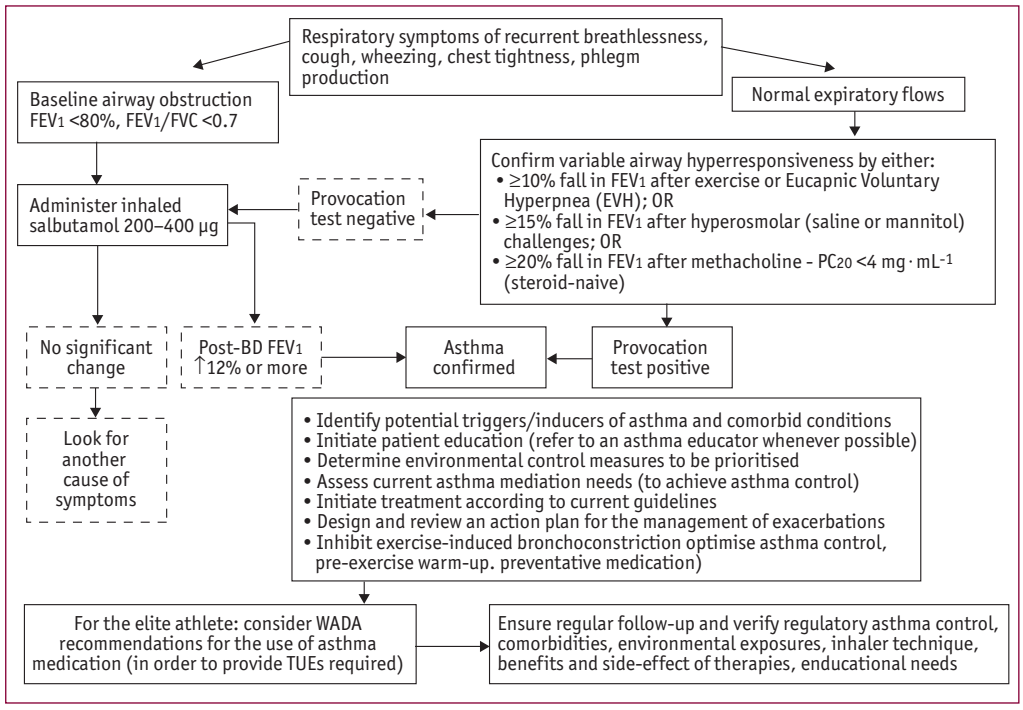

Figure 2
Asthma management in the athlete. FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; BD bronchodilation; TUE: therapeutic use exemption; WADA: World Anti-Doping Agency. Reproduced from Fitch et al. [1] with permission from the publisher.

Table 1 Prevention of exercise-induced asthma /bronchoconstriction

Ensure good control of asthma
Warm-up before exercise
Mechanical barriers (*e.g.* masks for cold air exposure during training?)
Pharmacological agents before the exertion
Inhaled β_2-adrenoceptor agonists
Leukotriene receptor antagonists
Anticholinergics - chromones (more rarely)

syndrome may mimic asthma and EIA/EIB. The diagnosis of asthma should always be confirmed, as for non-athletes, by objective means.

Finally, in regard to EIA/EIB, warming-up before exercise, and in the case of cold air sports using physical barriers (*e.g.* masks, although often not well tolerated by the athlete) may help minimise EIB (table 1).

Beneficial, adverse effects and tolerance to β_2-agonists in exercise-induced asthma

Single doses of inhaled (but not oral) β-agonists taken shortly before exercise are highly effective at preventing EIA/EIB and are widely used for this purpose [4, 12–13]. Unfortunately this bronchoprotective effect diminishes with chronic β-agonist treatment. A reduction in the bronchoprotective effect against EIA/EIB has been observed after as little as one week of regular treatment with short or long-acting IBAs [14–19]. Although these studies usually indicate only a partial loss of bronchoprotection immediately after inhalation of β-agonist, several studies of the long-acting IBA salmeterol have found that the bronchoprotective effect against EIA/EIB is no better than a placebo 6–9 h after inhalation in subjects who had received 4 weeks of regular treatment [15, 17, 18]. These findings indicate that there is almost complete loss of bronchoprotection within the usual 12-h dosing interval of a long-acting IBA if the drug is taken regularly. This loss in bronchoprotection does not appear to be influenced by ICS treatment [17].

There is also evidence that regular IBA treatment actually increases the underlying severity of EIA/EIB [16, 20]. In one study, the exercise-induced fall in forced expiratory volume in 1 s (FEV_1) was nearly twice as great after a week of regular salbutamol than after placebo treatment (fig. 3). In that study, salbutamol was withheld for several hours before the exercise challenge, so the extent to which an IBA given immediately before exercise would have "masked" the underlying worsening of bronchoconstriction is unknown. However, the possibility that IBA treatment may contribute to EIA/EIB in real life was recently confirmed in a recent study of children with exercise–induced asthma [21]. This study demonstrated significant improvements in exercise-induced bronchoconstriction after withdrawal of long-acting β-agonist treatment.

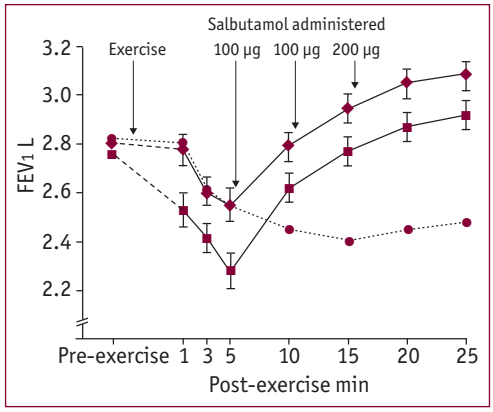

Figure 3
The effect of regular β_2-agonist on exercise-induced asthma. Reprinted from the publisher from HANCOX et al, [20] with permission. Forced expiratory volume in 1 s (FEV_1) changes before and after exercise and after salbutamol following 1 week of regular salbutamol (Square) or placebo (Diamond) treatment. Error bars represent 95% confidence intervals. For comparison the FEV_1 changes from the pre-randomisation screening challenge (Circle) are shown to illustrate the spontaneous changes in FEV_1 following exercise.

To add to these concerns, the bronchodilator response to IBAs following bronchoconstriction induced by exercise is also impaired in people treated with regular short- or long-acting IBAs [20, 22]. Hence the ability of inhaled β-agonists to reverse EIA/EIB will be suboptimal in athletes using IBAs regularly (fig. 3). Tolerance (or tachyphylaxis) to bronchodilation can also be demonstrated after methacholine and hypertonic saline challenges and the extent to which the bronchodilator response is impaired appears to depend on the severity of the bronchoconstriction [23, 24, 25]. Hence athletes with more severe EIB may experience a greater reduction in bronchodilator response to their IBAs than those with mild EIB.

The loss of bronchoprotection, reduction in bronchodilation, and worsening in bronchoconstriction induced by exercise are considered to be due to down-regulation of airway β_2-receptors, resulting in a reduced ability of β-agonists to stabilise airway mast cells and functionally antagonise airway smooth muscle contraction in response to an increase in bronchoconstricting mediators [26]. Tolerance to the bronchodilator and bronchoprotective effects of IBAs develops within a few days of treatment [27]. It occurs with both short- and long-acting IBAs and is not prevented by ICS [17, 22, 23, 26].

These findings present a dilemma for athletes who train every day. Long-acting IBAs are routinely used to improve asthma control in patients who have frequent symptoms despite adequate ICS treatment, but even once a day use of a long-acting IBA will result in tolerance to their bronchoprotective effects [28]. There is little evidence to guide management for athletes in this situation. The trade-off between improving asthma control by adding a long-acting IBA to ICS treatment and avoiding regular IBAs to maintain their bronchoprotective effects and prevent worsening of EIB should be considered on an individual basis. Even if a regular IBA is used, short-acting IBAs remain the medication of choice for pre-treatment of EIA/EIB in current guidelines, because tolerance to their effects is only partial and they are likely to remain more effective than alternative drugs immediately after dosing [4, 12, 13]. However, the severity of EIB may increase between doses and we believe that the treating clinician needs to be aware of the potential for these adverse effects when prescribing IBA treatment.

Preventer therapy with ICS should be routine in athletes who use more than occasional IBA treatment. Although this will not stop athletes from developing tolerance to IBAs, it will reduce the severity of EIA/EIB and reduce their need for IBAs. Unfortunately, IBAs taken solely to prevent EIA/EIB are often disregarded when assessing the severity of asthma from the frequency of β-agonist use [13] so athletes could be regarded as having mild intermittent ("step 1") asthma and not requiring regular preventer therapy despite using several doses of IBA a day before training sessions.

There is some evidence that alternate day use of an IBA is less likely to result in tolerance [29]. Avoiding daily use of IBAs for training sessions and using short-acting rather than long-acting IBAs might reduce the development of tolerance and allow them to be reserved for exercise most likely to cause bronchoconstriction and in competition. Non-pharmacological measures such as warm-up before exercise and face masks (for cold-air athletes) may help. Alternative drugs such as LTRA and chromones may also be useful. If IBAs are used specifically to prevent EIA/EIB, short-acting β-agonists may cause less down-regulation of β-receptors than long-acting IBAs, although there is little empirical evidence that this is the case.

β_2-adrenoceptor agonists in elite athletes: past and present usage

The availability of IBAs to elite athletes with asthma or AHR has fluctuated widely since these agents were released prior to the 1972 Olympic Games. At that time, their use for athletes was prohibited by the International Olympic Committee (IOC). In 1975, the IOC, who had global responsibility for deciding whether drugs were permitted or prohibited in sport, allowed salbutamol and terbutaline only by inhalation, on

condition that intended use was notified prior to the Games. Other IBAs were added in 1985 and later removed, and for 7 years, 1986–1993, IBAs were permitted without restriction by the IOC. Salmeterol in 1996 and formoterol in 2000 were added to salbutamol and terbutaline, all being permitted subject to prior notification [30].

Concerned at the rapid increase in use of IBAs by athletes, in 2001 the IOC required athletes to demonstrate current asthma and/or AHR to justify the use of IBAs at the Olympic Games. This was tantamount to demanding a therapeutic use exemption (TUE). The TUE procedure had been started by the IOC in 1992 to allow athletes to use prohibited medications for medical reasons, and the only TUEs approved for asthmatics had been for systemic corticosteroids.

To use an IBA, athletes and their doctors had to submit applications including recent bronchodilator or bronchial provocation tests, which were assessed by an Independent Expert Panel. Unless the IOC criteria were met [31], the athlete could not use an IBA at the Games. One or two sports including track and field athletics (IAAF) followed the IOC's lead but most continued the notification process. The IOC's asthma panel published the outcome of their responsibilities after Salt Lake City 2002 [31] and Athens 2004 [32].

In 2004, the World Anti-Doping Agency (WADA) replaced the IOC as the body that decides which substances and methods are prohibited in sport. WADA continued the notification of IBAs to which most sports had adhered since 1993. In 2008, the IOC reviewed its policy and the recommendation of the resultant conference was that athletes must continue to justify their use of IBAs *via* a TUE [1].

In 2009, WADA ceased the notification process and followed the IOC's example by introducing a TUE, with athletes having to demonstrate current asthma and/or AHR to use IBAs with the same criteria as the IOC. However, a year later, WADA permitted salbutamol and salmeterol with the only mandatory requirement being that athletes must declare their use on the doping control form should he/she be tested. All other IBAs could be inhaled only after the athlete sought and was granted a TUE. Surprisingly, WADA demanded that athletes wishing to commence treatment with prohibited IBAs must justify why salbutamol and/or salmeterol were ineffective [33]. The 2010 Olympic Winter Games in Vancouver were staged shortly after this change was implemented and although the IOC's Asthma Panel was prevented from demanding a TUE for all IBAs, it was observed that 181 of the 186 athletes had a TUE, including the 46% of athletes who were inhaling only permitted IBAs (salbutamol and salmeterol). Only five declared use of permitted IBAs; almost all because their TUE had just expired. This situation may be explained by the duration of approval of a TUE for an IBA, which is four years. It is however likely that WADA will make further changes to its IBA policy in 2011.

The IOC's experience has disclosed that the prevalence of IBA approvals differs greatly between countries but generally reflects the known prevalence of asthma globally. IBA approvals vary significantly between sports with the highest approvals in endurance sports, including cycling, triathlon, swimming and cross country skiing. The proportion of Olympic athletes whose asthma/AHR commenced in adult life exceeds the usual proportion, suggesting that years of endurance training may be inducing AHR. However, athletes approved for IBAs have consistently outperformed their peers in winning Olympic medals and this discrepancy has been much greater in Winter than Summer Games [1]. The proportion of athletes combining ICS with IBAs increased steadily from 46.1% in 1996, 65.7% in 2004, 77.2% in 2006 to a gratifying 87.2% in 2008, only to decline to

Educational questions

1. Non-endurance athletes have a higher prevalence of asthma than endurance athletes: True/False?
2. Regular use of inhaled β_2-agonist leads to tolerance to bronchoprotection, but their bronchodilator effects are preserved: True/False?
3. Patients on long-acting inhaled β_2-agonists may find that the protection against EIA/EIB is not sustained for the usual 12 h dosing interval: True/False?
4. Over time, the regular use of inhaled corticosteroids is effective in reducing EIA/EIB: True/False?

Table 2 IBAs at Olympic Games 1996-2010

Venue	Year	Method	IBA approved (rejected)	Athletes	Percentage %
Atlanta	1996	Notification	383	10,677	3.6
Nagano	1998	Notification	128	2,296	5.6
Sydney	2000	Notification	607	10,739	5.7
Salt Lake City	2002	TUE[#]	130 (29)	2,517	5.2
Athens	2004	TUE[#]	445 (45)	10,563	4.2
Torino	2006	TUE[#]	193 (15)	2,513	7.7
Beijing	2008	TUE[#]	781 (32)	10,810	7.2
Vancouver	2010	Declared or TUE[¶]	186	2,631	7.1

TUE: therapeutic use exemption. [#]: positive bronchodilator or bronchial provocation test required for approved use of IBA; [¶]: salbutamol and salmeterol declared only; all other IBAs had the same requirements as in 2002–2018.

75.3 % in 2010. Pleasingly, few athletes, nine in 2004, five in 2008 and five in 2010 used formoterol as monotherapy, but no athlete was approved for salmeterol without ICS (K.D. Fitch, unpublished data). Nevertheless, there does appear to be an ongoing need to educate team physicians about the optimal management of asthma in athletes especially because asthma (and AHR) is the commonest medical condition experienced by Olympic athletes (table 2).

Conclusion

Single doses of IBA effectively block EIA/EIB but their regular use is associated with an increase in the underlying severity of EIA/EIB and a reduction in their bronchoprotective and bronchodilator effects. Emphasis should be placed on preventative measures and anti-inflammatory treatment in order to minimise the need for IBA use to prevent EIA/EIB.

Glossary

EIA	Exercise-induced asthma
EIB	Exercise-induced broncoconstriction
AHR	Airway hyperresponsiveness
IBA	Inhaled β_2-agonists
ICS	Inhaled corticosteroid
Tolerance	A reduction in the effect of a medication following continued use. Also known as tachyphylaxis
TUE	Therapeutic use exemption for the use of a drug in competitive sport
Preventers	Anti-inflammatory asthma treatment such as inhaled corticosteroids
Rescue medication	Treatment taken to relieve bronchoconstriction and asthma symptoms, particularly inhaled β_2-agonists.

Competing interests

K.D. Fitch has acted as an expert witness on the subject of this study. L.P Boulet has served on advisory boards for AstraZeneca, Altana, GlaxoSmithKline, Merck Frosst and Novartis. He has received lecture fees from 3M, Altana, AstraZeneca, GlaxoSmithKline, Merck Frosst and Novartis. He has been given sponsorship from AstraZeneca, GSK, Merck Frosst and Schering for investigation generated research. He has participated in multicentre clinical trials for 3M, Altana, AsthmaTx, AstraZeneca, Boehringer-Ingelheim, Dynavex, Genentech, GSK, IVAX, Medimmune, Merck Frosst, Novartis, Roche, Schering, Topigen, and Wyeth for which he received research funding. He has had support for the production of educational materials from AstraZeneca, GSK, and Merck Frosst. He is an advisor for the Conseil du Medicament du Quebec Workmen Compensation Board Respiratory Committee. He is an organisational Chair of the Canadian Thoracic Society Guidelines Dissemination and Implementation Committee. He is co-leader of the Therapeutics Theme of the Canadian AllerGen Network of Centers of Excellence and holder of the Laval University Chair on knowledge transfer, Prevention and Education in Respiratory and Cardiovascular Health. He is also a member of the asthma committee of the World Allergy Organisation.

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Answers

1. False
2. False
3. True
4. True

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Further reading

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An excellent review of current knowledge of the causation of EIA/EIB. It also discusses the role of inflammatory mediators in EIA/EIB and reviews therapeutic approaches to management of EIA/EIB.