EXERCISE

Mechanisms and Management of Exercise-Induced Asthma in Elite Athletes

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Objective and methods. Asthma is often reported by elite athletes, especially endurance athletes. The aim of this article is to review current knowledge of mechanisms and management of exercise-induced asthma (EIA) in adult elite athletes. Results. The mechanisms underlying EIA is incompletely understood, but the two prevailing hypotheses are the hyper-osmolarity and the thermal hypothesis. Both hypotheses consider inflammation and activation of mast cells as being crucial for the development of EIA, although the assumed mechanisms triggering the inflammatory response differ. Objective testing is of utmost importance in the diagnosis of EIA in elite athletes. Management of EIA can be divided into pharmacologic and non-pharmacologic treatment. The basic principles for the treatment of EIA in elite athletes should be as for any asthmatic individual, including use of inhaled corticosteroids (ICS), β2-agonists, and leukotriene antagonists. However, evidence suggests that daily use of β2-agonists might lead to the development of tolerance. ICS therapy is, due to its anti-inflammatory effects, the recommended primary therapy for EIA also in elite athletes. All doctors treating individuals with asthma, especially elite athletes, should remain updated on doping aspects of asthma therapy. Non-pharmacologic management of EIA in elite athletes includes physical warm-up, which takes advantage of the refractory period following an attack of EIA, whereas high intake of antioxidants may reduce airway inflammation. Wearing heat masks, specially designed for outdoor winter athletes, might protect against bronchoconstriction triggered by inhalation of cold and dry air. Conclusion. EIA in elite athletes should be managed as in any individual with asthma, but the risk of developing tolerance to bronchodilators as well as doping aspects should always be taken into account.

Keywords asthma, doping, elite athletes, management, mechanisms

INTRODUCTION

Elite athletes often report respiratory symptoms and use of asthma medication (1–5). Asthma is a chronic inflammatory disease of the airways characterized by respiratory symptoms both at rest and triggered by a number of factors, including exercise, allergen exposure, and viral infections (6). Exercise-induced asthma (EIA) is an acute transient airway narrowing that occurs during and most often after exercise in elite athletes, as well as in other individuals with asthma. EIA is objectively defined as a greater than 10% fall in forced expiratory volume in the first second (FEV1) from baseline that may be measured up to 30 minutes following exercise (6–10). EIA is, in some scientific papers, also referred to as exercise-induced bronchoconstriction (EIB); however, we will use the term EIA in the present review. Higher prevalence of asthma has been reported among elite athletes, especially athletes in endurance sports like swimming, rowing, and cross-country skiing, compared to the general population (4, 11–14). In the general population, large regional differences have been observed in the prevalence of asthma with estimates from 4% to more than 20% (6, 15). In contrast, studies among elite athletes have observed prevalence rates of EIA from 11% up to 50% (16–20). Not only does high-intensity exercise probably contribute to the development of asthma, but the complex interplay between high physical demands and respiratory symptoms may also have important implications for management of elite athletes diagnosed with asthma.

The aim of this review is to present and discuss the current knowledge of the mechanisms underlying EIA and management of EIA in elite athletes.

METHODS

We carried out a series of searches, last updated December 2011, using the database PubMed. The strategy was intended to be broad in order to maximize the capture of citations for peer-reviewed publications relevant to asthma in elite athletes. The PubMed searches were carried out using the following algorithm of MeSH terms: asthma or EIA or EIB or bronchoconstriction or bronchospasm or hyperresponsiveness AND exercise or athlete or activity. The searches were repeated with these terms in combination with pathogenesis, treatment, prevention, and epidemiology. The citation pool was further supplemented from manual assessment of the reference lists accompanying other systematic reviews of aspects related to asthma in elite athletes and from other publications identified as being relevant for further review.

RESULTS

Characteristics of Asthma in Elite Athletes

Exercise has been implicated as the most common trigger of an acute asthma attack among elite athletes who have
been clinically diagnosed with asthma, and it has been estimated that up to 90% of all individuals with asthma are hyperresponsive to exercise (16). EIB, defined as a postexercise fall in FEV₁ of 10%, also occurs in up to 10% of subjects who are classified as being non-atopic and non-asthmatic (21), and in up to 50% among specified groups of elite athletes without known asthma (4, 11, 17, 22–25). Exercise-related respiratory symptoms are frequent in elite athletes (5, 17, 26), but some of them probably do not have asthma (27). In a recent study, Knopfli et al. (26) studied seven athletes from the Swiss national triathlon team, who at baseline were characterized as non-asthmatic, not treated with anti-asthmatic medication, and who had performed at international level for at least three consecutive years. Running tests were conducted on a 400 m track-and-field facility for 8 minutes at intensities equal to the anaerobic threshold; and the study revealed a five times greater prevalence of EIA, defined as a postexercise fall in FEV₁ of more than 10%, in elite athletes compared to the prevalence of asthma in the general population. After extrapolation of the decrease in FEV₁ in all seven athletes, the limit of 10% was determined to occur within 1.77–4.81 years, resulting in 21–57% of athletes with newly developed bronchial hyper-reactivity per year. That EIA is common in athletes who are otherwise healthy, including having no symptoms of asthma, has also been shown in a Finnish study (28).

However, most elite athletes, who are diagnosed with EIA, have neither a history of childhood asthma nor a family history of asthma (29–31), suggesting that environmental factors are more important than genetic inheritance. At rest, they seldom experience asthma symptoms (32), but symptoms occur during high-intensity exercise. In an excellent follow-up study, Helenius et al. (33) have shown that EIA in elite athletes is most likely a disease that develops during an active sports career and in many cases seems to go slowly into remission after retiring from the elite career. However, our current knowledge of the natural history of asthma in elite athletes is incomplete, and further studies are clearly needed.

Several studies have shown that the prevalence of EIA among elite winter athletes is higher than the prevalence of EIA among elite summer athletes (4, 5, 18). Wilber et al. (17) found that 18–26% of Olympic winter athletes had EIA, with the highest prevalence, defined as a postexercise decline in FEV₁ of at least 10%, being 50% in cross-country skiers. During the Winter Olympics in 1998, the overall prevalence of EIA across all sports and genders was 22% (18). More than 20% of the American athletes who participated in the 1996 Olympic Games were reported to have EIA based on symptoms and use of asthma medication (5). In keeping with this, data reported by Dickinson et al. (34) suggest a prevalence of EIA of 21% among British summer Olympic sports athletes. The US Olympic Committee reported an 11% prevalence of EIA in all athletes who competed in the 1984 summer Olympics (35). The available studies, therefore, suggest an increased prevalence of EIA among elite athletes, compared to the background population.

Pathogenesis of Exercise-Induced Asthma

The pathogenesis of EIA has been debated for years and is not fully understood. For many years the two prevailing hypotheses of the relationship between physical activity and EIA have been the hyper-osmolarity and thermal hypothesis, respectively. Both hypotheses include environmental stress, such as air temperature and humidity, as precipitating factors for development of EIA. A study by Evans et al. (36) has demonstrated that water content of the air is the main contributor to EIA severity and not air temperature.

The nose protects the lower airways by filtering, moistening, and heating the inhaled air. However, breathing through the nose alone cannot cover the oxygen demand, when elite athletes exercise, as ventilation through the nose cannot exceed 30 L/min. Therefore, when ventilation exceeds this level through the nose, concomitant ventilation through the mouth automatically appears. The combined breathing can be harmful to the lower airways because they are now exposed to air with allergens, other small particles, and unheated air (37).

Anderson et al. (38) proposed that water loss in the airways triggers EIA through the development of hypertonicity of the liquid at the surface of the airways. As cool and/or dry air is inhaled, heat is transferred away from the airway mucosa to air passing through the bronchial tree. When the inhaled cold air is heated, the saturation with water vapor consequently drops, which results in the evaporation of water from the mucosa, thus cooling of the respiratory tract. The evaporation of water results in transient dehydration of the mucosal liquid, leading to an increase in Na⁺, Cl⁻, Ca²⁺, and K⁺ ion concentrations, and thereby an increase in surface liquid hypertonicity. This osmotic gradient stimulates mast cells to release inflammatory mediators such as histamines, leukotrienes, and prostaglandins (39). These mediators, especially leukotrienes, activate specific receptors and cause airway smooth muscle contraction and mucus secretion (40, 41). This triggers airway narrowing and the clinical manifestations of EIA appear. This hypothesis proposed by Anderson and coworkers (38, 42) is known as the hyper-osmolarity hypothesis. The effectiveness of inhaled mannitol as the challenge test to diagnose airway hyperresponsiveness further supports this hypothesis (43).

McFadden and colleagues (44–46) have proposed that rewarming of the airways following exercise contributes to the pathogenesis of EIA, known as the thermal hypothesis. According to this hypothesis, the hyperventilation during exercise cools the surface epithelium of the airways. During and, primarily, postexercise a rewarming process begins, which is a physiological consequence of the previous cooling of the airways. The rewarming process causes secondary hyperemia, and by that increases the permeability in capillaries, which contributes to a leakage of fluid from the capillaries to the submucosa. This results in airway edema whereby mast cells are stimulated to release inflammatory mediators, leading to airway inflammation and bronchoconstriction (47, 48).
Anderson et al. (49) have more recently suggested that the pathogenesis of EIA in elite athletes relates to the epithelial injury arising from breathing poorly conditioned air at high flows for long periods of time or high volumes of irritant particles or gases. The evidence to support this proposal comes from markers of injury. The restorative process after injury involves plasma exudation and movement of cells into the airways, a process repeated many times during a season of training. This process has the potential to expose smooth muscle to a wide variety of plasma- and cell-derived substances. The exposure to these substances over time can lead to an alteration in the contractile properties of the smooth muscle, making it more sensitive to mediators of bronchoconstriction (39).

All hypotheses entail airway inflammation as being crucial for the development of EIA and assume that mast cells play an important role in triggering EIA. However, the mechanisms assumed to trigger the stimulation of mast cells differ. Direct evidence for airway inflammation in EIA has been demonstrated (50–52), as leukotriene E4 or the metabolite of prostaglandin D2 (9α, 11β-PGF2α), a marker of mast cell mediator release, has been measured in urine (51, 52) and sputum after exercise challenge test in asthmatics (50). This indicates that mast cell mediators are released into the airways during EIA, supporting an inflammatory basis for EIA.

As expected, there is an ongoing discussion about the validity of the hypotheses. A combination of several factors most likely orchestrates the development of EIA and, as expected, it has been suggested that the truth may be a combination of the hypotheses (48). Inflammation is, based on the available evidence, crucial for the pathogenesis of EIA (53), but further studies are needed in order to reveal the molecular mechanisms underlying EIA.

Objective Assessment of EIA among Elite Athletes

Diagnosing EIA and asthma in elite athletes requires objective testing, primarily bronchial challenge testing, not least because so many elite athletes report asthma-like symptoms and also use of asthma medication (1–5). Different methods have been used to diagnose EIA in elite athletes (6–11, 27, 32), but although the choice of test is very important, it is also important to carefully select the cut-off point used to discriminate between AHR, that is, a positive test, and normal responsiveness. The prevalence of EIA, defined as AHR, varies greatly between different types of sport, and there may also be important differences between athletes within the same sport living under different climates (1, 4, 9, 11, 17). The test of choice for assessment of airway responsiveness in elite athletes may therefore differ between different types of sport, but in general it seems that indirect challenges, like the use of mannitol and eucapnic voluntary hyperventilation, seem to offer the highest sensitivity (34). The International Olympic Committee-Medical Commission considers, in spite of the fact the stimulus is a surrogate for exercise, the eucapnic voluntary hyperpnoea (EVH) test to be the optimal laboratory-based challenge to confirm EIA in elite athletes.

Management of Exercise-Induced Asthma in Elite Athletes

The high prevalence of EIA among elite athletes has led to a great demand for effective prevention and treatment (54). Management of asthma in elite athletes can be divided into pharmacological and non-pharmacological treatments. The pharmacological treatments use medications to reduce the inflammation or contraction of the airways. Some non-pharmacological treatments focus on the reduction of airway inflammation and others on reduction of environmental stress such as air temperature and air humidity and thereby reducing the contraction induced by inflammation in airways.

Pharmacological Treatment

The primary goals of pharmacotherapy for asthma are control of asthma symptoms, reduction in airway inflammation and airway hyperresponsiveness, maintenance of normal lung function, and prevention of exacerbations—together with minimal medication-related adverse effects (55). At present, the recommendations regarding the pharmacological treatment of asthma in elite athletes follow the international guidelines for treatment of any individual with asthma (6), although elite athletes are likely to have a demand above average for the degree of asthma control.

In case of allergy to aeroallergens, where allergen avoidance is not effective or not possible, and the elite athlete present with concomitant symptoms of allergic rhino-conjunctivitis, treatment with nasal steroid, oral antihistamines, and leukotriene antagonists should be considered.

Inhaled Corticosteroids. The most effective therapy for EIA symptoms is inhaled corticosteroids (ICS), just as ICS are the most effective controller therapy for asthma (6). ICS reduce symptoms of asthma, including nighttime symptoms, improve lung function and quality of life, suppress airway inflammation, reduce airway hyperresponsiveness, and by that improve outcome of the disease also with regard to severity of exacerbations and mortality (6, 56). ICS are, therefore, also recommended as first-line controller therapy for elite athletes with EIA, when asthma control is not achieved by reliever therapy alone (57). Regular use of ICS is effective, but although some effect is seen within 4 weeks (58, 59), best possible effect is not expected until after at least 8 weeks of treatment (59). A systematic review included in the Cochrane Database has combined results from two parallel studies, which have shown that a duration of at least 4 weeks of ICS significantly attenuated the percent postexercise fall index in FEV1 (14.07%; 95% CI: 11.62–16.52%) (59). Sue-Chu et al. (60) in a randomized double-blind placebo-controlled parallel-group bronchial biopsy and bronchoalveolar lavage (BAL) study of 25 competitive cross-country skiers (mean age 18 (16–20) years for a mean (range) treatment period of 22 (10–32) weeks) were unable to show any clear beneficial effect of budesonide in ‘ski asthma’ and suggest that more attention should be directed at reducing environmental stress to the airways than at attempting pharmacological modulation of induced inflammatory changes. ICS
in the doses we usually prescribe for asthma, that is, a daily dose equivalent to a maximum of 800 μg of beclometasone, do not have systemic side effects, but high-dose therapy, which is only recommended for a maximum of 6 months unless it is clearly documented that high-dose therapy leads to improved asthma control (6), may have long-term side effects due to systemic effects such as muscle wasting and demineralization of bones (osteoporosis) (61, 62).

ICS are not on The World Anti-Doping Agency 2012 list of banned substances (63).

β2-Agonists. Short-acting β2-agonists (SABA) have a beneficial effect on EIA if taken 15 minutes before exercise. Anderson and colleagues (64) have in a randomized double-blind study showed that SABA significantly reduced the % fall in FEV1 after exercise in asthmatic subjects with EIA. The mean ± SD% fall in FEV1 was 39.4 ±17.6% in subjects on placebo and 13.4 ±13.2% in subjects on SABA. Inhaled β2-agonists relax smooth muscles, dilate the bronchial airways, increase air flow, and reduce vascular permeability. Regular use of β-agonist drugs can lead to the development of tolerance (tachyphylaxis) (65, 66). Tolerance is caused by the downregulation of the β2-receptor gene expression that gives rise to a decreased receptor density and a decreased binding affinity of the receptors to β2-agonists. The protective effect of the drug wears off as β2-receptors are downgraded (67, 68). Hancox et al. (69) have shown that regular use of β2-agonists leads to increased EIB and a suboptimal bronchodilator response to β2-agonists. Theoretically, regular therapy with SABA might be associated with failure to respond to emergency treatment for asthma exacerbations, but fortunately there is little evidence to suggest that this is a problem of clinical importance. However, our current knowledge supports the use of SABA only as rescue medication, also in elite athletes.

Inhaled long-acting β2-agonists (LABA) are used as add-on therapy for individuals not achieving acceptable asthma control on ICS alone (6). LABA are not recommended for treatment of asthma in individuals not on ICS because of risk for serious asthma-related events (70). In a review, Reynolds et al. (71) reported that the combination of salmeterol and fluticasone was superior to fluticasone alone for the prevention of EIA; and, likewise, it has been shown by Pauwels et al. (72) that the combination of formoterol and budesonide is more effective than budesonide alone with regard to symptoms and asthma control. Development of tolerance after regular use of LABA for asthma has been reported in several studies (73, 74) and appears to include tolerance to the bronchodilating effect, after a few days of regular treatment, and to the bronchoprotective effect, after weeks of treatment.

It should be noted that ICS and inhaled β2-agonists can potentially provide optimum treatment when used together. β2-Agonists can stimulate the glucocorticoid receptor and promote its translocation to the nucleus, resulting in increased corticosteroid-mediated gene transcription, and corticosteroids may also increase the transcription of the β2-agonists gene in the lung and the nasal mucosa (75).

The World Anti-Doping Agency has listed all β2-agonists (including both optical isomers where relevant) on its prohibited medication list except salbutamol (maximum 1600 μg over 24 hours), salmeterol when taken by inhalation in accordance with the manufacturers’ recommended therapeutic regime, and formoterol (maximum 36 μg taken over 24 hours) (63). Systemic use of β2-agonists is strictly prohibited in elite athletes, and athletes using inhaled β2-agonists should therefore be instructed only to use the drug in therapeutic doses, as the presence of salbutamol in the urine in excess of 1000 ng/mL in a doping test is regarded as not being due to therapeutic use and therefore classified as an adverse analytical finding (63).

Leukotriene Modifiers. Leukotriene modifiers have both anti-inflammatory and bronchodilating effects and are administered orally once daily for montelukast and twice daily for zafirlukast and zileuton. Montelukast is used as an alternative to LABA, as add-on to ICS when asthma control is not achieved on ICS alone (6). Montelukast can also be used to prevent EIA in elite athletes with asthma (76). Helenius et al. (77) have in a double-blind, randomized, cross-over, placebo-controlled study, including 4-week active treatment (10 mg oral montelukast, administered at bedtime), 1-week washout period, and 4-week placebo treatment, of 88 highly trained ice hockey players shown that montelukast was of no benefit in the treatment of asthma-like symptoms, increased bronchial hyperresponsiveness, or a mixed type of eosinophilic and neutrophilic airway inflammation in these highly trained ice hockey players. Neuropsychiatric adverse effects, including anxiety and depression, have been observed, although the drug does not pass the blood–brain barrier (17). Up to a 40% nonresponse rate on exercise-induced symptoms in asthmatics has been reported for leukotriene receptor antagonists, possibly the result of genetic polymorphisms of the thromboxane A2 and interleukin 13 gene sequences (57). So far no evidence has been reported for the development of tolerance with regular use of leukotriene modifiers. Treatment with leukotriene modifiers for asthma is permitted.

Non-pharmacological Treatment

Allergen Exposure. Both summer and winter sport athletes are exposed to allergens. Summer sport athletes are intensively exposed to airborne allergens during both training and competitions, whereas winter sport athletes are intensively exposed to cold air. In case of known allergy to aeroallergens or other known trigger factors, exposure to these factors should be reduced to a minimum, and eliminated if possible, in order to reduce symptoms and improve asthma control (6). Avoidance of potentially precipitating factors is of crucial importance, but unfortunately not always achievable. However, if possible, elite athletes with EIA triggered by extreme climate conditions should not perform outdoor training during very cold, hot, or humid weather and for those with seasonal allergy not
during the pollen season. Avoidance of triggers during competition, especially for outdoor sports, will in many cases be impossible, and preventive measures, primarily medication, will often be necessary.

Physical Warm-up. Physical warm-up has previously been shown to reduce EIA in asthmatic elite athletes (78). Warm-ups may reduce the bronchoconstrictor response to exercise and, by that, induce a significant protective effect against EIA (78, 79). Warm-up is believed to have the greatest protective effect, if short-acting $\beta_2$-agonist salbutamol is taken simultaneously (80). Mickleborough et al. (80) have shown that the mean maximum percent decline in postexercise FEV$_1$ significantly decreased ($p < .05$) to only $-9.1 \pm 0.6\%$ following the warm-ups, which is below the EIA diagnostic threshold of a 10% fall in post-exercise FEV$_1$. Warming up to 80–90% of the maximum work load before exercise can reduce the intensity of EIA. After an attack of EIA there is a refractory period where the risk of developing a second attack is reduced. The mechanisms underlying this refractory period are unclear, but it suggests that warm-ups promote the release of catecholamines, which prevent the release of inflammatory mediators from mast cells (81, 82). Inhibitory mediators are also released during warming-up (83), which partially protects the airways against repetitive muscle contractions. It should be mentioned, however, that refractory period does not occur in all individuals. Rundell et al. (84) have demonstrated that refractory period only occurs in 50% of winter athletes.

Diet. Several case–control studies and cross-sectional studies have examined how a change of diet may affect asthma attacks and EIA (85–90). The specific components of diet associated with reduced asthmatic symptoms are typically associated with the inflammatory response in the airways (86). Ascorbic acid is an antioxidant that reduces airway inflammation and by that, the narrowing of the airways. Tecklenburg et al. (91) have shown that an ascorbic acid diet significantly reduced ($p < .05$) the maximum fall in postexercise FEV$_1$ ($-6.4 \pm 2.4\%$) compared to usual ($-14.3 \pm 1.6\%$) and placebo diet ($-12.9 \pm 2.4\%$). An improvement in asthma symptom score was also observed ($p < .05$) on the ascorbic acid diet compared to the placebo and usual diet (91). Other studies have shown that supplementing the diet with fish oil may also reduce the amount of inflammatory mediators such as leukotrienes (92, 93). Mickleborough et al. (93) have shown a decrease in post-exercise (15 minutes) FEV$_1$ by 3 ± 2% on fish oil diet, 14.5 ± 5% on placebo diet, and 17.3 ± 6% on normal diet. Furthermore, VanHaitsma et al. (94) have in a randomized, double-blind, double-dummy cross-over study of 10 asthmatic subjects with EIA given each subject 1 hour before an exercise challenge 0, 3, 6, or 9 mg/kg of caffeine or placebo mixed in a flavored sugar drink. Pulmonary function tests were conducted pre- and postexercise. Caffeine at a dose of 6 and 9 mg/kg significantly reduced ($p < .05$) the mean maximum % fall in postexercise FEV$_1$ to $-9.0 \pm 9.2\%$ and $-6.8 \pm 6.5\%$. These data suggest that moderate (6 mg/kg) to high doses (9 mg/kg) of caffeine provide a significant protective effect against EIA. VanHaitsma et al. conclude that it is possible that the negative effects of daily use of SABA may be reduced simply by increasing caffeine consumption prior to exercise.

Breathing Filters. Athletes, who exercise outdoors in the winter (22), are more likely to develop EIA than athletes who exercise indoors because the cold and dry air increases the risk of EIA. Previous studies have shown that the severity of EIA can be reduced by increasing the temperature and humidity of inspired air (95, 96). A heat mask is intended to prevent athletes from inhaling cold and dry air and thereby developing EIA (54). The mask heats and moistens the air before the inspiration. This prevents the inhalation of cold air, protects against contraction of smooth muscles in the bronchial airway, and reduces the decline in FEV$_1$ but little controlled experience exists in elite athletes.

A single study (97) has shown that the use of heat mask with $\beta_2$-agonists may, at present, be the optimal treatment. $\beta_2$-Agonists protect against bronchoconstriction but cannot protect against edema. The heat mask protects against edema and bronchial contraction, so a combination therapy will be more effective.

DISCUSSION AND CONCLUSION

EIA is an acute transient airway narrowing that occurs during and most often after exercise in up to 50% among specified groups of elite athletes without known asthma. The mechanism triggering EIA is not fully understood, but it is believed that inflammation stimulated by mast cells starts a cascade of release of inflammatory mediators that cause airway smooth muscle contraction and mucus secretion and thereby triggers airway narrowing and the clinical manifestations of EIA.

There are many treatment opportunities for EIA: pharmacological and non-pharmacological. The most effective therapy is ICS. $\beta_2$-Agonists have a beneficial effect on EIA, but regular use as single therapy may lead to the development of tolerance. Among other therapy opportunities there are antileukotrienes, physical warm-up, heat mask, and a change in diet. However, the use of heat masks is probably for the very few athletes experiencing EIA, and the evidence for the effect of change in diet on symptomatic EIA is not very convincing.

Future studies should examine the possible dose–response relationship between the level of exercise-induced hyperventilation and respiratory changes and also investigate the threshold for intensity and duration of exercise related to the development of EIA. A detailed knowledge of remission, as assessed by objective testing, and natural course of the disease in former elite athletes is also missing and should be investigated.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.
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