

TITLE PAGE

Treating Asthma Exacerbations in Athletes - TUE or not TUE?

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It is undoubtedly true that the prevalence of asthma or at least exercise-induced bronchoconstriction is far greater in the elite athletic than in the general population (1). Although the pathogenesis of exercise related symptoms is not always clear (2), potentially relevant airway hyperresponsiveness can be detected in as many as two-thirds of certain groups of internationally-competitive athletes (3). Accordingly, it is not surprising that asthma is now the most common chronic medical condition in Olympians and respiratory illness the most common non-injury related reason for medical intervention at major athletic events (4,5).

But with these high prevalence rates comes heightened suspicion. The use of asthma medication by elite athletes has attracted significant media attention over the past two years and there has been a degree of hysteria regarding the potential exploitation of asthma treatment for performance gain. Indeed some eminent athletes have argued that their contemporaries (or adversaries) with asthma should not be permitted to compete in 'able-bodied' sport (6).

In contrast to this belief, there is actually no clear evidence of performance enhancement for the most commonly prescribed asthma therapies, at least when treatment is prescribed at standardly prescribed inhaled doses. A great number of studies have now evaluated this issue and this conclusion is quite clear (7). Accordingly, whilst the most commonly prescribed class of asthma medication (i.e. beta-2 agonist) is prohibited in-competition, the use of the most common

inhaled form of this class (i.e. salbutamol) is permitted with a simple 'declaration of use' from the athlete.

There is, of course, the need to differentiate systemic from inhaled use and thus urine drug 'threshold levels' have been established to help differentiate route of administration. An athlete returning a level above an accepted drug threshold is reported as having an adverse analytical finding (AAF), regardless of whether there is prior dispensation to use this medication. The lack of an established detection level for some novel inhaled asthma therapies (e.g. vilanterol) however mandates application for a Therapeutic Use Exemption (TUE); a specifically awarded dispensation, requiring proof of diagnosis and a clear explanation for the necessity of this treatment over 'non-prohibited' alternatives.

The majority of recent attention on TUEs in asthmatic athletes however concerns their utilization for treatment of acute respiratory illness or for exacerbations of asthma. The latter is typically defined as an 'a progressive increase in shortness of breath, cough, wheezing, or chest tightness, or some combination of these symptoms, accompanied by a decrease in expiratory airflow, that can be quantified by measurement of lung function', i.e. either peak flow or spirometric indices (8). In such cases, there is clear and widely accepted and utilized international guidance indicating that an asthma exacerbation should be treated with an escalation in therapy to the maximum 'step' of the treatment cascade and this most commonly mandates the need for a short-course of oral corticosteroid (OCS) (GINA 2014, BTS, ERS/ATS).

Thus the use of OCS to treat an exacerbation of asthma is a standard approach employed for many thousands of asthmatics worldwide and is underpinned by the sound biological rationale that, generally speaking, exacerbations are associated with heightened airway inflammation (ref). i.e. OCS treatment is employed with the aim of attenuating inflammation and to shorten time to recovery. The presence of heightened airway inflammation (e.g. airway eosinophilia) in athletes with 'sport' asthma, suffering an exacerbation has not yet been established and indeed some prior cross-sectional studies indicate some key differences in the airway inflammatory profile of elite athletes (9). Regardless, at this point in time, the early initiation of OCS has been and still is the bedrock of outpatient acute asthma exacerbation management and is a key component of most asthma self-management plans. Indeed, in the UK's National Review of Asthma Deaths (NRAD), delay and lack of ability to promptly initiate anti-inflammatory therapy was identified as a key factor underpinning mortality in young asthmatics (10). Moreover, it is a long held supposition that escalating use of 'unopposed' bronchodilator therapy (i.e. without appropriate use of anti-inflammatory therapy) is associated with increased asthma mortality, particularly in the young (11).

The use of OCS is prohibited in-competition and there is certainly some, albeit limited, evidence that OCS use may enhance performance and provide metabolic benefits (12-14). It is thus a clear requirement that a TUE is issued for use of OCS for an asthma exacerbation occurring in the competition phase (i.e. within x days of competing). How OCS impacts performance in athletes suffering an exacerbation of asthma, has never been and will likely never be studied. Studying

performance outcome measures in individuals who are acutely unwell poses clear ethical dilemmas, let alone difficulties reconciling the multitude of potential confounding factors.

Several recent internet-based 'leaks' or exposes have focused scrutiny on the use of TUEs for asthma exacerbations (15). This has both intended and unintended consequences. Firstly, this exposure has served to highlight the widespread nature and impact of airways disease in elite athletes. The importance of respiratory care in athlete health often appears to be relegated below that of cardiac assessment (16) and yet the sheer prevalence and impact of this problem should act to re-energise an effort to better understand the reasons for the high prevalence of airway dysfunction and the best way to assess acute respiratory illness, in this population. Secondly, with this increased transparency, comes the risk that an athlete and their clinical team may opt to avoid OCS during an exacerbation. i.e. to avoid the potential accusation of use simply for performance gain. This is likely to be occurring already and many anti-doping bodies have noticed a worrying trend in the increased use of nebulized bronchodilator therapy to help worsening asthma symptoms in athletes.

So where does this leave the clinician assessing an athlete with an exacerbation of respiratory symptoms? Firstly, there is a significant body of evidence that now firmly establishes the fact that that a diagnosis of asthma in an elite athlete should not be based on 'clinical' assessment alone (17). Respiratory symptoms (i.e. cough and wheeze) are poorly predictive in this context (18) and the presence of conditions such as exercise-induced laryngeal obstruction (EILO)

can act to confound diagnostic accuracy (19). It is therefore important that a diagnosis of 'asthma' in an elite athlete is made on the basis of robust objective supporting data. i.e. allied measures showing a reduction in airflow on exercise or following provocation (20).

Secondly, it is likely that the same is true in the context of an exacerbation of respiratory symptoms. Thus, again it is important to utilize objective testing (i.e. measures of airflow impairment) alongside a thorough clinical assessment; in order to robustly characterize the nature of a deterioration or exacerbation. This is central in demonstrating objective corollary information for a TUE and indeed a recent randomized controlled study revealed that OCS was of no benefit in improving respiratory recovery, when prescribed for 'non-asthma' respiratory ailments in the general population (21). The injudicious use of OCS for non-asthma respiratory illness in athletes could thus, at best, be based on a lack of evidence and at worst intended with alterative consequences.

It could be argued that a measure of inflammation (e.g. blood or sputum eosinophil level or measure of exhaled nitric oxide) should be used in assessing the place of OCS treatment in this context (22,23). However these studies have never been performed in an elite athletic population and thus at the current time it would seem medically negligent to deviate from currently accepted international guidance for the treatment of exacerbations. i.e. to prescribe prednisolone at 0.5 mg/kg for 5-10 days, for those already prescribed inhaled corticosteroid. Remarkably, the best OCS or optimal duration of treatment is not firmly established (24) however there is no place for intra-muscular steroid

administration in this context, i.e. this approach is not mandated in any of the major international treatment guidelines. Prompt detection and treatment of infection and allied measures (i.e. checking inhaler technique and treatment of co-morbid nasal and reflux disease) are also important to optimize treatment and recovery.

Finally, there is the ultimate and vexing question of whether an athlete with an exacerbation of asthma should be competing *at all*. Some would argue that the severity and physiological implications of this type of illness must mandate rest from strenuous athletic activity. For many athletes their clinician will deem this to be the correct and logical choice of action, however some will take a different standpoint, based of course, on both internal and external motivators and pressures. Indeed, whilst an argument could be used to preclude athletes from competing in this scenario ultimately the provision of this type of mandate runs the risk of coaxing an asthmatic athlete to deliberately avoid treatment; in order to continue competing and worse still may motivate them to increase their bronchodilator use to 'keep going'. The NRAD outlines the risk in this scenario and for clinicians caring for athletes with asthma, above everything we must act at all times to protect their health, TUE or no TUE.

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