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CONFERENCES IN EXERCISE IMMUNOLOGY

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Preface

Exercise immunology is a relatively recent new area of research world wide, with an exponential growth in published papers after 1975. In Portugal, this research area was almost ignored and, until recently, been confined to the Medical Departments of Immunology. Only now have the Sport and Exercise Scientist in Portugal started to take notice of the research questions associated with exercise immunology. Reports from athletes, coaches and team doctors that athletes seemed to have a high incidence of infections (mainly from the upper respiratory tract) have sparkled the interest in this area. Since then some epidemiological studies appear to have confirmed that during heavy training and following competitive prolonged exercise events, endurance athletes seem to be more susceptible to infections of the upper respiratory tract (URTI). Several studies indicate that prolonged exercise may result in a temporary depression of the immune system and that chronic impairment of immune function can occur during periods of intensified training. On the other hand, moderate regular exercise seems to be associated with an improved immune function and a reduced incidence of URTI when compared to sedentary lifestyle.

The researchers are now looking at the possible mechanisms by which exercise improves or impairs immune function. In this book authors report on intervention studies aimed at investigating the effects of diet and nutritional supplements on immune responses to exercise, looked at environmental factors like altitude, and provided helpful information that can be used by the coaches and team doctors in the management of athletes.

This book is a compilation of the first conferences organized in Portugal by a sport sciences research group (Centro de Estudos Biocinéticos) from the Faculty of Sports Science and Physical Education, University of Coimbra, and represents a first step for the development and introduction of this area of research as an area of study in sport and exercise science degree programs in Portugal.

I would like to thank all the authors of this book for their valuable contributions and wiliness to make time in their recognized carriers to visit Coimbra, do the conferences and write the articles that we can now all enjoy.

The relevance of salivary IgA for the immunological management of athletes

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Abstract

This review examines the relevance of salivary IgA (Sal-IgA) to immunological health and successful sports performance in athletes. The consequences of alterations in Sal-IgA for infection risk, and the effects of acute exercise and exercise training on Sal-IgA secretion in this context are examined, as well as issues relating to the practicality of Sal-IgA measurement and monitoring. Routine Sal-IgA monitoring in asymptomatic athletes may be neither feasible nor justified, but monitoring athletes with ongoing or recurrent symptoms of illness may be beneficial. The current status of a number of strategies that may be useful in increasing Sal-IgA levels are provided.

Keywords

URTI, immunity, exercise, training, monitoring

Introduction

Successful athletic performance requires appropriate training and optimal performance in competition. Illness that restricts training or compromises competitive sports performance has long been of concern to athletes, coaches and sports medicine professionals. Athletes vary in their susceptibility to illness, and one aspect of this variation is the competence and resilience of the immune system. One of the most common types of infectious illness experienced by athletes is upper respiratory tract infection (URTI) [7]. Strategies to prevent or limit URTI in athletes have led investigators to explore the impact of exercise on changes in mucosal immune function, measured by salivary immunoglobulin A (Sal-IgA).

This review will examine the role of Sal-IgA in the health and performance of athletes. The consequences of variations in Sal-IgA are presented, followed by a summary of the effects of exercise on Sal-IgA levels; the practicalities of routine measurement of Sal-IgA in athletes; the role of Sal-IgA monitoring; and the potential for interventions to enhance Sal-IgA status.

What is secretory IgA (SIgA) and what does it do?

IgA is the major antibody class in the Common Mucosal Immune System (CMIS), which is a component of the acquired (specific) immune system and the CMIS is the largest immune organ in the body. The CMIS consists of a network of immune structures at mucosal surfaces throughout the body including the respiratory, gastrointestinal and uro-genital tracts, salivary, lacrimal and lactating mammary glands, as well as bronchus-associated, gut-associated and nasal-associated lymphoid tissues. The SIgA antibodies are secreted onto mucosal surfaces in a dimeric form as Secretory IgA (SIgA) and provide specific local immunity for protection against pathogens including bacteria, viruses, allergens and antigens presented at mucosal surfaces.

What happens if levels of SIgA at mucosal surfaces are low?

SIgA is important in both exercising and non-exercising populations. Measuring changes in mucosal immunity has been monitored most often by measuring IgA concentrations in saliva (Sal-IgA). Studies indicate that there is a critical level of SIgA required at mucosal surfaces to prevent infections and subsequent detrimental health outcomes. Individuals with reduced SIgA levels are at greater risk of developing infections, especially URTI and gastrointestinal tract (GIT) infections.

Some people have a SIgA deficiency. Fortunately, the immune system has some built in redundancy, and those with a SIgA deficiency are more dependent on the secretory immunoglobulin M (SIgM) class of antibodies; however, individuals with an IgA deficiency still experience a higher incidence of infections, especially URTI and GIT infections.

What infections are common in athletes?

The two most common groups of infections in athletes are URTI and GIT infections [7]. These infections can have substantial negative effects on an

athlete's capacity to train and/or compete with optimal performance. Therefore it is desirable for athletes to reduce their risk of such infections. One strategy is to reduce the risk of exposure to pathogens, but it is also desirable to maintain mucosal immune protection through appropriate levels of SIgA. Athletes are not only at risk of exposure to new pathogens, as reactivation of viruses such as Epstein-Barr virus (EBV) to which an athlete has previously been exposed may also be a consequence of reduced levels of SIgA [14].

Why is SIgA measured in saliva?

Measurement of the concentration of SIgA in saliva (Sal-IgA) is a common means of assessing mucosal immune status due to the ease of collecting saliva samples. Unfortunately there is considerable variability in Sal-IgA concentrations [6], due to both analytical and biological factors, which have been reviewed previously [16]. This means that great care must be taken in the interpretation of changes in Sal-IgA measurements.

Does exercise influence the levels of Sal-IgA in athletes?

The impact of exercise on Sal-IgA depends on the characteristics of the exercise and the training status of the athlete [15]. Both acute bouts of exercise and long-term exercise training have been shown to alter Sal-IgA levels. From an immunological protection perspective, exercise can be potentially beneficial by increasing Sal-IgA, neutral by having little effect on Sal-IgA, or detrimental by decreasing Sal-IgA secretion. Different intensities of exercise have been shown to have each of these effects on Sal-IgA [5, 21]. A single bout of aerobic exercise usually has a short-term effect on Sal-IgA concentration, altering both IgA secretion rate and saliva flow rate.

What are the effects of exercise intensity on Sal-IgA?

Both the direction and magnitude of Sal-IgA responses to exercise appear to be intensity dependent. High intensity exercise can lead to a decrease in Sal-IgA secretion, which may be observed immediately following exercise and may be sustained for some hours after the exercise [13]. Conversely, moderate intensity exercise, for example at 50-60% of VO_{2max}, may increase Sal-IgA secretion. The magnitude of changes observed may depend on the relative intensity, the duration of the exercise, the training status of the subjects, and whether the change in Sal-IgA is reported as a concentration, concentration

relative to salivary composition changes such as albumin concentration or osmolality, or as a secretion rate, and have been reviewed previously [15, 16].

Few studies have compared the effect of exercise intensity on the response to exercise in the same subjects. Williams *et al.* [21] found that a short bout of cycling exercise at a moderate intensity (50% VO_{2max}) increased Sal-IgA in young adults whereas cycling exercise at 70% VO_{2max} and performing a VO_{2max} test led to progressively greater decreases in Sal-IgA immediately post-exercise. Dorrington *et al.* [5] found similar patterns of Sal-IgA in response to cycling at different intensities in children.

What are the effects of aerobic fitness level on Sal-IgA?

Dorrington *et al.* [5] compared the Sal-IgA responses to cycling in children with lower and higher aerobic fitness levels. There were no differences between fitness groups in the Sal-IgA responses to high intensity exercise, but the children with higher aerobic fitness levels had greater increases in Sal-IgA in response to moderate intensity exercise at 50% VO_{2peak}. The difference in responses was considerable with the less fit children exhibiting a 25% increase in Sal-IgA compared to a 65% increase in children with greater aerobic fitness. This suggests that the possible benefits of stimulating increases in Sal-IgA with moderate intensity exercise are fitness level dependent. It is also possible that the relative intensity that optimally stimulates IgA may differ with aerobic fitness level.

One explanation for the observed variation in the pattern of Sal-IgA responses to exercise of similar relative intensity among studies is differences in training status (EIR), and aerobic fitness level may be one characteristic that differs among these populations [16].

What are the effects of exercise training on Sal-IgA?

Many studies have reported Sal-IgA responses to training periods of varying durations, and in many of these studies the training loads were well tolerated and Sal-IgA levels were well maintained or even increased. Repeated days or weeks of high intensity exercise training sessions, particularly if the training volume is large or combined with intense competition appear to increase an athlete's vulnerability to reductions in Sal-IgA. This pattern of

training is much more likely in high performance or elite athletes than in recreational exercisers. Therefore, vulnerability to adverse immune consequences of exercise training has largely been explored in this context. Decreases in IgA over a training season have been observed in elite swimmers [11]. Changes in IgA have been reported to vary with training load in sprinters and jumpers with decreases in IgA during a high intensity training cycle followed by an increase in IgA during a recovery phase.

We recently observed a gradual decline in pre-game IgA levels across a season in elite Rugby League players (unpublished data). The lowest pre-game levels were observed mid-season and preceded a marked increase in reports of URTI. The lower IgA levels may have increased the risk of developing these illnesses. Rugby League players are frequently exposed to pathogens by visitors to the locker room after games when they may be particularly vulnerable to infections due to reduced post-game levels of IgA.

Multiple intense training sessions in a day have been shown to impair Sal-IgA recovery such that an athlete commences a subsequent session with reduced Sal-IgA levels [13]. The immunosuppression is compounded if this training pattern is repeated on subsequent days, as was demonstrated in the case study of an elite kayaker performing 2-4 exercise session per day.

Are Sal-IgA measurements and responses to exercise reliable?

Common observations in studies of Sal-IgA and exercise are the variability in the response patterns and values obtained. This has raised questions about the sources of variability and repeatability of Sal-IgA measurements. Francis *et al.* [6] found substantial biological variability in Sal-IgA levels between individuals and within an individual, which has important implications for monitoring Sal-IgA in athletes and for the design of research studies. To observe statistically significant differences, the subject numbers may need to be higher in studies of elite athletes than non-elite exercisers, and non-elite exercisers or sedentary populations may not necessarily form appropriate control subjects for studies of immune function in elite athletes due to differences in variance between populations. However, Sal-IgA responses to exercise do appear repeatable under controlled laboratory conditions [2] in healthy athletes. This is good news for studies of Sal-IgA responses to exercise in groups of athletes as it provides confidence in the results obtained and the

conclusions drawn.

Do we know when a change in Sal-IgA is relevant?

Reductions in Sal-IgA *alter the risk* of infections such as URTI, but exposure to a pathogen is also necessary before there is a consequence of reduced Sal-IgA secretion. Vulnerability to URTI increases with the level of Sal-IgA concentration decreases, and chronically low Sal-IgA levels increase the risk of URTI substantially. Gleeson *et al.* [11] observed this increasing vulnerability in elite swimmers. A progressive increase in infection risk was directly proportional to the decrease in Sal-IgA level.

Is there an established critical level of Sal-IgA?

Defining a precise concentration of Sal-IgA below which risk clearly increases for all individuals has not yet been established. This is extremely difficult due to the substantial biological variability in Sal-IgA levels observed in some individuals. The daily variability in the values obtained from an individual varies between athletic populations, and may be greater in more elite athletes [6]. These findings mean that regular monitoring is required to establish the normal and vulnerable Sal-IgA ranges for an individual athlete, and that more extensive monitoring may be required to establish these ranges in elite athletes than less highly trained individuals. Consequently Sal-IgA monitoring may not be logistically or financially feasible with currently available methodologies.

What do we know that is useful about Sal-IgA?

We know that athletes are more likely to experience decreases in Sal-IgA levels following high training loads and that exposure to a pathogen while vulnerable increases the risk of developing an illness. The consequence of these two factors is observed in illness clusters such as has been reported in swimmers at competitions [19]. As mentioned earlier, team athletes with decreasing Sal-IgA levels as the season progresses combined with increased exposure to pathogens during travel or in the locker room after games may result in a cluster of illness reports. Consequently, monitoring training loads at key times or in individuals susceptible to recurrent infections, combined with strategies to minimize exposure to pathogens, may be the most cost-effective strategies to prevent frequent or untimely bouts of URTI or other infectious illnesses in athletes.

Does it affect performance?

Performance is not necessarily compromised in athletes who report upper respiratory symptoms [18, 19]. Training volume and intensity may be reduced when athletes are experiencing symptoms as observed in runners reporting upper respiratory illness [18], but minimal differences in performance measures such as maximal oxygen uptake, running economy, and time to exhaustion were observed in this cohort. Pyne *et al.* [18] found the impact of mild upper respiratory illness on international performance in swimmers to be variable, with trivial effect on performance in some swimmers, substantial detrimental effects in some, and surprisingly, beneficial effects in a small number of swimmers.

When is monitoring Salivary IgA relevant to individual athletes?

The athletes who are most likely to benefit from Sal-IgA monitoring are those who suffer from recurrent URTI, regularly present with URT symptoms, or report unresolved fatigue. Repetitive high intensity training has been shown to decrease Sal-IgA levels and contribute to the recurrent bouts of URTI in a swimmer over a season [10] whereas appropriate rest allowed an increase in Sal-IgA and a reduction in bouts of URTI. Reductions in Sal-IgA have been shown to precede reactivation of EBV associated with upper respiratory symptoms [14]. Athletes who suffer recurrent fatigue should be investigated for Herpes group viral reactivation, and Sal-IgA monitoring may be useful in establishing appropriate training loads on resumption of training.

It takes time to develop an effective monitoring program for an athlete. It requires sufficient monitoring to establish a personal critical Sal-IgA level for the individual athlete, ongoing monitoring of pre-training Sal-IgA, and monitoring Sal-IgA responses to normal training sessions. Periods of increased risk of URTI need to be identified and a willingness to modify training accordingly is essential. Also it requires timely assaying of the saliva samples collected such that modifications to training to can be introduced before the health of the athlete is further compromised.

Can Salivary IgA levels be increased in at-risk athletes?

A number of interventions have been proposed to increase (restore) Sal-

IgA levels to a low risk level. A typical recommendation is to first reduce or eliminate sources of both physical and psychological stressors [17]. This may include modifying training by decreasing intensity, eliminating sessions or increasing rest days. Psychological issues that have an impact of Sal-IgA suppression, whether related to training or not, need to be addressed. Financial or work-related stress as well as problems in personal relationships may be important but more difficult to address than training. Dietary interventions may have a role [9, 12]. Whether the athlete's regular diet is appropriate in terms of both energy and other nutrients [8] or whether specific dietary interventions such as increased carbohydrate intake [12], caffeine [1], and possibly probiotics [3] are beneficial are not yet clear but promising possibilities. Pharmacological interventions such as antivirals are only justified with a confirmed diagnosis against which the therapeutic agent is known to be effective [4].

What medical conditions are associated with long-term fatigue and poor performance in athletes?

Reid et al. [20] investigated long-term fatigue in athletes and found that this fatigue and the associated poor performance were a consequence of undiagnosed or poorly controlled disease states. A number of the athletes investigated suffered recurrent infections, which were primarily due to CMV and EBV; 47% of those with recurrent infections had IgG3 suppression. The other most common conditions were asthma (37%) and allergy (32%). Early studies suggest there may be a role for probiotics in athletes experiencing recurrent fatigue and poor performance[3].

Conclusions

Sal-IgA monitoring can be a valuable tool in the management of athletes experiencing ongoing fatigue and/or recurrent infections, particularly URTI. Routine measurement of Sal-IgA in asymptomatic athletes may not be practical either logistically or financially. Sal-IgA measurement can be an effective tool for evaluating the impact of different types of exercise and exercise training on URTI risk in different exercising populations, but care should be taken in the determination of participant numbers and the choice of control groups for such studies as Sal-IgA concentrations vary substantially within and among individuals and different sporting populations. A number of interventions have been proposed to increase Sal-IgA secretion, but their effectiveness at reducing URTI risk remains to be established.

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Prevention and Management of Respiratory Tract Infections in Athletes.

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Abstract

Exercise-induced suppression of certain immune functions during strenuous training periods, increased exposure to foreign pathogens while travelling, as well as sharing the same training- and living facilities within a team may put athletes at increased risk of infections. Preventive measures are the first and foremost tasks to implement, to avoid disruption of crucial training and competition schedules. However, when signs of respiratory tract infections (RTI) appear in individual athletes or among members of athletic teams, fast and proper management is paramount to limit the disruption of training and performance capacity. A short review of clinical manifestations, diagnosis and proper management of both upper and lower respiratory tract infections is given in the first section. Mononucleosis among athletes is briefly discussed and some general guidelines for management of the return to regular training during the convalescence phase of this particular infection are given. This is most pertinent to health professionals dealing with athletes with infections. The second section outlines guidelines with respect to prevention of RTI as well as management strategies when athletes are suffering from RTI. At the end, practical guidelines for safe return to normal a training schedule are summarized, aiming primarily at coaches and athletes.

Introduction

Athletes performing at high levels in their sports are most often members of a selected group of people that are able to withstand the stress imposed from strenuous training and competition schedules without major illnesses and prolonged periods of fatigue (Gleeson, 2000;Nieman, 2000;Ronsen et al., 2001). Nevertheless several studies suggest that athletes are at increased risk of respiratory tract infections (RTI)(Gleeson, 2000;Nieman et al., 1989;Nieman et al., 1990;Peters, 1997). Exercise-induced suppression of certain immune

functions during strenuous training periods, increased exposure to foreign pathogens (microbes) while travelling, as well as sharing the same training- and living facilities within a team may contribute to this increased frequency or duration of RTI (Gleeson, 2000). Obviously, some sort of microbe (virus, bacteria, fungus, etc.) must be transmitted to the body at a certain time point and have the ability to invade the respiratory tract for an RTI to occur. However, several environmental and physiological circumstances such as heat and cold exposure, psychological stress, nutritional status, and training load are known to modulate the body's response to such pathogens and thus increase or decrease the course of the infection(Pedersen et al., 1994).

A recent survey among 74 Norwegian athletes participating in the 2002 Olympic Winter Games and the 2004 Olympic Summer Games showed that more than 90% of the athletes reported one ore more infectious episodes during a year (data presented at ISEI congress 2005). Respiratory tract infections and gastroenteritis were the most common diseases reported and the duration of symptoms was mostly within 1 week. However, since many suffered several infectious episodes through a year, the average number of lost training days was 15 per year. Frequent absence from vital training sessions is highly undesirable for both athletes and coaches and will most likely have a negative impact on the performance level during parts of the season. The study also showed that on the average one important competition per year was lost due to illness. Finally, there was a large degree of variability in the frequency and duration of infectious diseases reported by the athletes, with some never being sick while others missed more than 30 days/year of scheduled training due to illness. This of course sets the stage for important preventive measures among the most illness susceptible athletes.

Prevention is always preferable and superior to treatment, even the best sports medicine based treatment. Therefore, all means and methods to avoid unnecessary and unprotected exposure to virus, bacteria should be practiced in athletic settings in order to avoid loss of training and competitions to episodes of infections (Ronsen, 2003). Consequently, athletes and coaches need to be educated and guided with regard to important preventive measures on how to avoid infectious diseases. However, all contact with unknown sources of microbes is unavoidable in a normal life style of an athlete. This makes the correct management of infectious illnesses of paramount importance in order to limit the negative consequences of the infection. Management of RTI from a

physician standpoint should always be based on a thorough medical history, an evaluation of clinical signs and symptoms, a skilled physical examination and a specific microbial diagnosis. The first section in this chapter outlines the basics in detection and management of RTI, aiming at the medical personnel dealing with athletes. This part contains mostly text-book material as well as review articles and is thus not specifically referenced (Dasaraju P.V and Lui C., 1996;Gleeson et al., 2004;Nieman, 1998;Nieman, 2000;Weidner, 1994). The second section outlines practical guidelines with respect to the management and prevention of RTI, aiming primarily at coaches and athletes. The information here is based on a mixture of personal clinical experience from 12 years of providing medical care to Olympic athletes as well as well established knowledge in the field of infectious medicine.

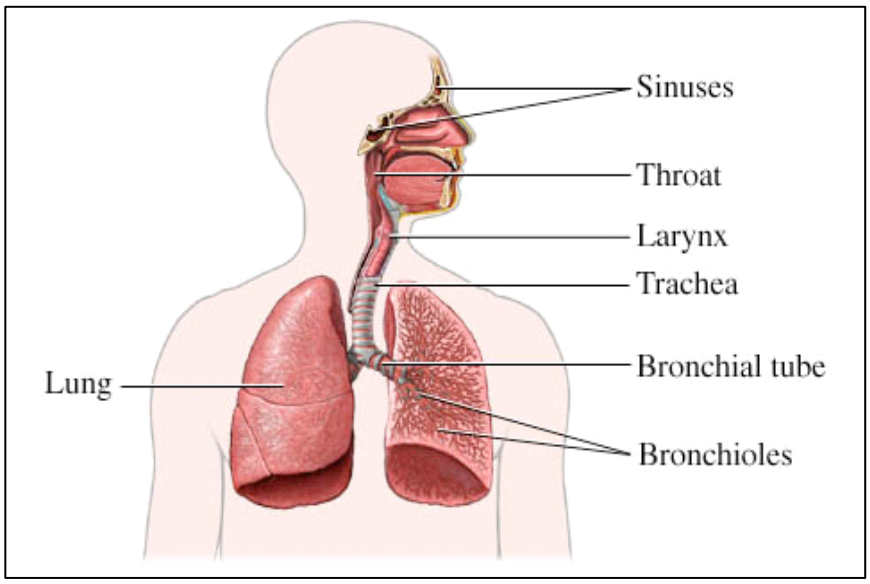

Figure 1. Location of upper and lower respiratory tract infections.

Physician-based management of RTI

Upper Respiratory Infections: Common Cold, Otitis, Sinusitis, Pharyngitis, Epiglottitis and Laryngotracheitis.

Etiology and Pathogenesis: Most upper respiratory infections are caused by virus. In some cases, bacteria like Haemophilus influenzae type b and Streptococcus pyogenes may be the primary cause of infection (sinusitis, tonsillitis, epiglottitis and laryngotracheitis/croup). An episode of viral infection may also progress into a bacterial infection in certain locations of the respiratory

system. The micro-organisms enter the respiratory tract by inhalation of droplets and invade the mucosa, resulting in epithelial destruction with redness, edema and exudate.

Clinical manifestations and Diagnosis: Initial symptoms of a common cold are runny, congested nose, sneezing, and/or a soar throat. Fever and general feeling of malaise may or may not acompany these initial symptoms. Common colds typically have mild to moderate symptoms with duration of approximately 4-7 days. Sinusitis is usually characterized by pressure pain in the forhead or maxillary bone(s) in addition to the symptoms mentioned above. Infections in the middle ear (otitis media) usually presents with pressure-pain in/around the ear(s) in addition to fever and stuffy nose and are mostly seen in children. Bacterial pharyngitis/tonsillitis most often starts with high fever, glandular hypertrophy and a painfull throat. Upon inspection the tonsils are enlarged, inflamed and often covered with purulent secretion. Epiglottitis and laryngotracheitis (croup) may also cause difficulties with breathing, but are most common in children. Different strains of influenza virus appears during seasonal epidemics and is usually diagnosed on the basis of clinical manifestations such as high fever, severe feeling of malaise, myalgia and headache.

Bacterial and viral cultures of throat swab specimens or nasal discharge are used for diagnosing pharyngitis, sinusitis, epiglottitis and laryngotracheitis. Specific quick-tests (Enzyme-linked immunoassay methods) for diagnosing infections by Streptococcus type A are commercially available. A rise in the C-reactive protein (CRP) to values between 10-50 mg/L may indicate a viral infection, while bacterial infections most often result in CRP values above 50 mg/L. However, these are general guidelines and must be evaluated along with clinical manifestations of an infection. Blood cultures or serological antibody titres may be helpful in obtained a microbiological diagnosis in cases of severe or longstanding infections. A CT or MRI scan of the paranasal/cranial sinuses may be helpful in the diagnosis of recurrent or chronic sinusitis.

It is wise to remember that several of the clinical manifestations characteristic for bacterial tonsillitis and pharyngitis are similar to the debut of mononucleosis, an infection caused by the Epstein Bar virus. However, mononucleosis is a systemic infection that affects lymphatic glands in most of the body, the liver and spleen, and often causes prolonged high fever, lethargy, swelling of the lymphatic nodes and organs, in addition to the symptoms of throat infection. When it coincides with a bacterial tonsillitis/pharyngitis, proper antibacterial therapy should be administered even though antibiotics do

not affect the EB viral infection. If strenuous physical exercise is performed during the initial or convalescence phase of mononucleosis, this may lead to increased morbidity (worsening of the clinical manifestations) and/or relapse with a more prolonged recovery period(Sevier, 1994). Therefore, it is essential to recognize this infection at an early stage with specific Enzyme-linked immunoassay tests and/or serologic detections of specific antigens and/or antibodies to the Epstein Bar virus. The clinical manifestation of mononucleosis may be mild in childhood and thus not specifically recognized and diagnosed. However, when it appears in adolescence or adults, the symptoms are usually much more severe and long standing with higher risks of relapses during the convalescence period.

With respect to return to exercise and sports participation, it is important that the physician and the athlete use an individual approach based on the improvement of symptoms, clinical sign and lab results (Dommerby et al., 1986;Sevier, 1994). However, some general guidelines may be helpful to the physician and athlete in this process.

Guidelines for return to exercise after mononucleosis

1. Before starting light exercise (brisk walking, easy cycling, light resistance training etc), have 5-7 days without febrile episodes and lethargy or other systemic symptoms.
2. Ensure a substantial decrease in EB antibody titre and liver enzymes (ALAT, ASAT)
3. Limit the exercise sessions to 20-30 min every other day for the first week with a low intensity (puls rate<120 bpm)
4. Avoid exercises modes may cause increased pressure or pounding to the abdomen
5. Observe the tolerance to each exercise session and during the recovery day thereafter.
6. Discontinue the exercise if relapse or worsening of earlier symptoms
7. Consult with your physician before commencing exercise again
8. If acceptable tolerance to first week of exercise, continue the next week with 30-45 min sessions every other day with a moderate intensity (puls rate<140 bpm).
9. Have your physician perform a clinical exam and lab assessment before progressing towards further normalization of your training schedule.
10. Exclude the possibility of hepatosplenomegalia (enlarged liver and

spleen) in those athletes returning to contact sport by an ultrasound or CT scan of the upper abdomen.

11. Always respect signs and symptoms of relapse and/or intolerance to a progressing exercise load and consult with your physician about continuing exercise or not.

Treatment: Common viral infections of the upper respiratory tract are treated symptomatically and include such measures as nasal washings with sodium cloride, nasal decongestions (beware of possible banned substances for athletes), non-steroidal anti-inflammatory drugs, paracetamol, acetaminophen, or other analgesics. The main strategy is to facilitate drainage of excessive exudate from the mucosa of the upper airways and prevent stagnation of infected exudate in sinuses, nasopharynx and ear. A purulent sinusitis will in most cases be successfully treated with a beta-lactamase resistant antibiotic such as amoxicillin or a cephalosporin for 10-14 days and pharyngitis/tonsillitis with *beta-hemolytic streptococci* should be treated with Penicillin G for the same amount of days. Other bacterial infections should be treated with proper antibiotics, in accordance with the results of a good clinical evaluation and microbiological diagnosis. Epiglottitis and laryngotracheitis (croup) that results in major breathing problems (stridor and cyanosis) must be treated immediately with proper medication facilitating airway expansion, preferably in hospitals. Epiglottitis caused by *Hemophilus influenzae* bacteria needs to be treated with antibiotics. Surgical treatment should be considered in cases of recurrent bacterial tonsillitis and chronic sinusitis.

Vaccine against *Haemophilus influenzae* type b infections and specific seasonal influenza viruses are commercially available. The influenza vaccine is altered each year according to the change in seasonal epidemics around the world, and thus needs to be taken each year to acquire specific immunization. The need for such vaccines is questionable for healthy people but may be considered in athletes prone to recurrent or prolonged infections during a season with multiple competitions.

Lower Respiratory Infections: Bronchitis, Bronchiolitis and Pneumonia.

Etiology and Pathogenesis Lower respiratory infections may be viral or bacterial. Viruses cause most cases of bronchitis and bronchiolitis. In community-acquired pneumonias, the most common bacterial agent is

Streptococcus pneumoniae. Atypical pneumonias are cause by such agents as *Mycoplasma pneumoniae, Chlamydia pneumoniae* and viruses. Organisms enter the distal airway by inhalation, aspiration of gastric content or by hematogenous seeding. The pathogen multiplies in or on the epithelium, causing inflammation, increased mucus secretion, impaired mucociliary function which may lead to airway obstruction.

Clinical Manifestations and Diagnosis: Lower respiratory infections are usually characterized by cough, sputum production, shortness of breath and/or tachypnea, fever, generalized malaise, and/or chest pain. Patients with pneumonia and bronchopneumonia may also exhibit non-respiratory symptoms such as, headache, myalgia, nausea and abdominal pain.

Auscultation of the lungs often reveal a characteristic crepitating sound or reduced ventilation in localized (lobar pneumonia) or more generalized (bronchopneumonia) areas. A two-way chest X-ray may be helpful in differentiating between pneumonia, bronchopneumonia and other causes of persistent cough and lower airway symptoms. A differential count of white blood cells and measurement of CRP may be helpful in the initial assessment of respiratory infections. However a specific microbial diagnosis requires a specimen from sputum or nasal discharge to be cultured for bacteria, fungi and viruses. Blood cultures and/or serologic detections of antigens and antibodies can also be used to identify several micro-organisms. Enzyme-linked immunoassay methods and detection of nucleotide fragments specific for the microbial antigen in question by DNA probe or polymerase chain reaction can offer a rapid diagnosis.

Treatment: Symptomatic treatment is used for most viral infections of the lower respiratory tract. Couch-reducing medications should for the most part be restricted to conditions of dry, non-productive coughing, and athletes must be careful not to use medications with banned substances. The inflammatory reaction during an acute episode of bronchitis may lead to temporary constriction of the bronchial airways and ventilatory obstruction (asthma). Such conditions need to be properly diagnosed and treated with bronchio-dilatory medications and inhalation steroids. Bacterial bronchitis and pneumonias are treated with antibiotics, according to the identification of a specific micro-organism and its sensitivity/resistance pattern to selected antibiotics.

Athlete-based prevention and management of RTI

There is no single method or measure that completely eliminates the risk of contracting a RTI, but there are several effective ways of reducing the number of infectious episodes incurred over a period. Some of these measures are scientifically founded while others are supported mostly by clinical and personal experience. In essence, it is all about avoiding transmission of microbes from one person to another! It is important to underline that virus and bacteria causing RTI may be both *received* by and *passed on* from the same individual. This means that one should pay as much attention to preventing transmission of potentially contagious material *from oneself to others* as the opposite way, *from others to oneself*. Therefore, the overall "golden rule" of practicing the same standard of hygiene when you are in contact with others as you expect others to practice towards you, should be the general objective of RTI prevention. A list of the most common preventive measures and practical guidelines against RTI infections, but also against any contagious disease, is given in the following guidelines.

Guidelines for prevention of infections among athletes

1. Make sure that you are updated on all vaccines needed at home and for travels
2. Minimize contacts with infected/sick people, animals and contagious objects
3. Keep at distance to people who are coughing, sneezing or having a "runny nose"
4. Wash hands regularly, before meals, and after direct contact with potentially contagious people, animals, blood, secretions, public places, bathrooms, etc.
5. Use disposable paper towels and limit hand to mouth/nose contact when suffering from RTI symptoms
6. Quickly isolate a team member with RTI symptoms and move out his/her roommate
7. Check air condition/ventilation systems for potential contagious material
8. Do not use other peoples drinking bottle, cups, silverware, etc
9. Wear proper out-door clothing and avoid getting cold and wet after exercise

10. Protect upper and lower airways from being directly exposed to cold and dry air during strenuous exercise, by using facial mask etc. at temperatures below -15°C
11. Practice good recovery routines, including proper nutrition and re-hydration

Even if meticulously practicing all the important preventive measures that athletes, coaches and medical support staff can put up against respiratory tract infections, it is everybody's experience that RTI, nevertheless, takes its toll, both on individual athletes and in teams. Therefore, it is crucial that all episodes of RTI including the initial symptomatic phase are well managed and that the spread of microbes between members of a team of family is limited. For athletes on a training schedule the obvious question when initial symptoms of RTI appears is about continuing, decreasing or stopping their regular exercise training.

The athletes themselves must make the first assessment on these matters and then consult with a physician to make clinically based decision for each individual athlete. Nevertheless, some general "rules of thumb" may be offered to guide the athlete and his support team to make the best choices on *if* and *how* exercise should be continued through an infectious episode. The guidelines are summarized bellow.

Guidelines regarding exercise during episodes of RTI in athletes

First day of illness:

- Drop strenuous exercise or competitions when experiencing RTI symptoms like
  - Sore throat or coughing
  - Runny or congested nose
- Drop all exercise when experiencing additional RTI symptoms like
  - Muscle/joint pain and headache
  - Fever and generalized feeling of malaise

- Drink plenty of fluids, keep from getting wet and cold, and

minimize life-stress

- Consider use of topical therapy with nasal drainage, decongestants and analgesics if fever
- Report illness to a team physician or health care personnel and keep away from other athletes if you are part of a team training or travelling together

Second day:

- If you have fever (temp >37,5-38^{o}C) or increased coughing : No training !!
- If no fever or malaise and no worsening of "above the collar"-symptoms: Light exercise (pulse < 120bpm) for 30-45 min, indoor during winter and by yourself

Third day

- If still fever and RTI symptoms: Consult your (team) physician by phone or at office
- If no fever or malaise and no worsening of initial symptoms: Moderate exercise (pulse < 150bpm) for 45-60 min, preferably indoor and by yourself

Forth day:

- If no symptom relief: Do not try to exercise but make an office visit to your doctor
- If first day of improved condition: Follow the guidelines of "return to exercise" below :

In a similar fashion, and with the same constraint of not substituting these guidelines for physician based individual advises, further strategies for safe and healthy return to regular a training schedule is given bellow. It must be emphasized that the author is not responsible for the individual medical outcome of adhering to these guidelines.

Guidelines for return to normal training after respiratory tract infections

1. Make sure that you have one day without fever and with improvement of RTI symptoms before returning to exercise.
2. Observe the body's reaction to your first exercise session before starting on a new session.
3. Stop physical exercise and consult you physician if
   - New episode with fever or worsening of initial symptoms
   - Persistent coughing and exercise-induced breathing problem
4. Use the same number of days to step up to normal training as spent off regular training because of illness.
5. Observe closely your tolerance to increased exercise intensity and take an extra day off if you do not recovering satisfactory.
6. Use proper outdoor clothing and specific cold air protection for airways when exercising in temperature below –10^{o}C the first week after RTI

Summary

Although regular exercise seems to have a stimulatory effect on the immune system and thus may decrease the risk of respiratory tract infections, both personal experience as well as some scientific evidence support the contention that athletes may be at increased risk of RTI during periods of intense training and competition schedules. Several factors may explain this phenomenon, including training-induced immune suppression, increased exposure to foreign microbes while travelling, as well as sharing of training- and living facilities which increases the exposure as well as the transmission of pathogens. Most of the common microbes that cause RTI are relatively harmless for healthy people perhaps with exception of the Epstein Bar virus that causes mononucleosis. Nevertheless, if extreme environmental factors, stress and strenuous training schedules are imposed on a person that have contracted a respiratory infection, this may result in significant aggravation and protraction of the symptoms and physiological disturbances in the body. Thus, immediate diagnostic assessment and patient management is imperative to reduce the negative consequences on the health as well as on the performance

level of the athlete. However, the most effective way of fighting respiratory tract infection for an athlete may be to apply common-sense preventive measures against transmission of contagious material in his/her environment and life style.

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Asthma and sports.

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I. General aspects of asthma

Asthma is currently defined as a "chronic inflammatory disease of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment".

The prevalence of asthma has been increasing over the past 30 years, as can be seen in TableI.

Table I - Rising prevalence of allergic asthma

Country	Ages	Years of study	Prevalence
Austrália	8 - 10	1982 and 1992	7 → 11%
Escócia	8 - 13	1964 and 1989	4 → 10%
Gales	12	1973 and 1988	4 → 9%
Austrália	Adults	1981 and 1990	9 → 16%

Asthmatic patients can have varying degrees of asthma severity. Pre-treatment asthma severity is classified according to clinical criteria and lung function testing into intermittent or persistent. The latter is subdivided into mild, moderate and severe (Global Initiative for Asthma Guidelines).

Most people with asthma have symptoms when exposed to various factors (namely physical exercise). However, some asthmatic patients only have symptoms when they perform physical exercise. This is known as Exercise-

Induced Asthma (EIA).

Currently, exercise-induced asthma is regarded as a form of intermittent asthma.

Types of asthma

Depending on triggers, asthma can be subdivided into: a) intrinsic or non-allergic asthma, and b) extrinsic or allergic asthma. Extrinsic asthma is the more common form and is more frequently observed in younger patients. In contrast, intrinsic asthma is more frequent in older patients. Environmental allergens are the triggers for allergic asthma and various non-allergic factors may be the triggers for non-allergic asthma. In both cases, non-specific factors such as colds, inhalation of cold air, etc, may also act as inducers of asthma symptoms.

Immunopathophysiology of bronchial asthma

When an allergen a person is sensitised to (allergic to) reaches the bronchi, it binds IgE molecules that are specific for it and which are bound to high affinity receptors (FcεRI) on the cellular membrane of cells such as mast cells which are located in the mucosa. Cross-linking of FcεRI-bound IgE molecules by the allergen activates mast cells and induces an extensive degranulation of cytoplasmic granules. These granules are rich in various substances (e.g. histamine, tryptase, etc.) that are crucial for the development of acute-onset asthma symptoms. In addition, this process also initiates the synthesis of arachidonic acid-derived molecules (leucotrienes, prostaglandins) in the mast cells. These lipid mediators contribute towards several deleterious aspects of bronchial asthma such as bronchoconstriction, bronchial vasodilatation, increased mucus production, etc.

However, apart from these mechanisms related to the immediate effects of exposure to allergens, one must also take into consideration that an allergen is a protein. In fact, as an external protein, allergens are endocytosed by cells that are resident in the bronchi, particularly dendritic cells (or B lymphocytes). Dendritic cells process the ingested allergen and present the allergen-derived peptides to T lymphocytes, in the context of MHC class II molecules. In case such antigen presentation is correct, T cells become activated, proliferate and start producing high levels of cytokines. In allergic patients, allergen-specific T cells are biased towards producing an unbalanced pattern of cytokine

production known as a Th2-type pattern. This pattern involves the production of high levels of interleukin (IL)-4, IL-5, and IL-IL-13 as well as low levels of IFN-γ. Such cytokine pattern contributes towards the development and maintenance of allergic responses because IL-4 and IL-13 induce isotype switching to IgE in B lymphocytes, and IL-5 stimulates the influx, activation and resistance to apoptosis in eosinophils. It should be remembered that high IgE levels and eosinophilia are the hallmarks of allergic disease. IgE synthesised by B cells will then be free to bind FcεRI on mast cells, thereby being ready for further interaction with the relevant allergen. The aspects related to the allergen as a protein are associated with the maintenance of chronic, ongoing, allergic inflammation in the bronchi (Figure 1).

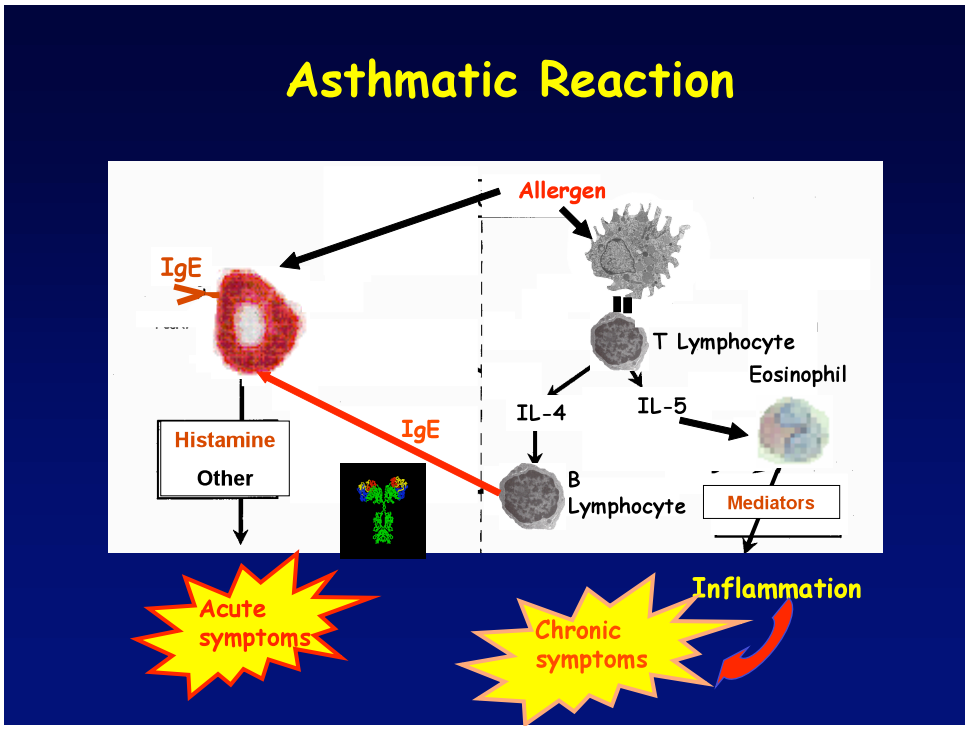

Figure 1. Immunopathology of early and late-phase (chronic) inflammation in asthma.

Clinical symptoms of bronchial asthma

The most frequent asthma symptoms observed in asthmatic symptoms are:

- persistent dry cough
- shortness of breath (dyspnoea)
- wheezing

- chest tightness

These symptoms generally occur in association. However, they may also arise independently. In fact, some asthmatic patients only have chronic dry cough, particularly at night.

Lung function in bronchial asthma

Due to the presence of bronchial obstruction, which may be more or less generalized, asthma modifies respiratory physiology in mainly two ways:

a) an increase in expiratory pressure;
b) an increase in air trapped in the bronchi.

Treatment of bronchial asthma

Asthma treatment involves basically two types of inhaled drugs (although oral medication may also be necessary):

a) those that inhibit or reverse bronchial constriction; and
b) anti-inflammatory drugs.

β2-agonists (salbutamol, terbutaline, formoterol, salmeterol) belong to the first type of drug. These drugs relieve acute symptoms and relax the bronchial muscle. On the other hand, anti-inflammatory drugs such as corticosteroids (such as beclomethasone, budesonide or fluticasone) act as preventive medicines, are crucial for inhibiting bronchial inflammation and are crucial for reducing chronic asthma symptoms.

Bronchial asthma and Physical Exercise

In asthmatic patients, physical exercise may help with respiratory physiology, although it may also trigger asthma symptoms. Exercise-induced asthma is frequent in patients with bronchial asthma (Table II).

Table II – Prevalence of exercise-induced asthma

Country (Year)	Sample	Methodology	Prevalence
Malaysia (2001)	Schoolchildren	Questionnaire	8% (NC) 50% (BA)
USA (1998)	Military recruits	Prova de esforço	7%
USA (2001)	Elite athletes	Questionnaire ("self-report") and LFT	29% (Q) 26% (LFT)
Kenya (1998)	Children and adolescents	Questionnaire (parents) and LFT	23% (city) 13% (rural)

II. Exercise-induced asthma

Asthma symptoms induced by physical exercise (EIA) are more frequent in cold and dry environments. EIA generally arises a few minutes (> 5 min) upon having stopped physical exercise, although, more rarely, it may also start during the exercise itself. Curiously, EIA-related symptoms are followed by a refractory period of several hours, during which asthmatic patients may potentially engage in physical activities without developing asthma symptoms. However, if symptoms were more severe, care should be taken in deciding how soon after an asthma attack can an athlete or PE student return to practising exercise.

Pathophysiology of Exercise-Induced Asthma

In general, non-asthmatic individuals appear to have maximally dilated airways at rest and, thus, have little change associated with exercise, at least during short duration exercise (< 15 minutes). Potent bronchodilating influences are in operation during physical exercise. In fact, physical exercise has been shown by various studies to improve airway calibre in asthmatic individuals when the exercise lasts less than 15 minutes. In contrast, there is generally a decline in pulmonary function over time during exercise in asthmatic individuals, after the initial bronchodilation. This may, at least in part, have to do with the fact that when performing physical exercise, breathing rate

increases. Apart from allowing a greater intake of eventually noxious, irritating environmental substances such as some types of pollutants or allergens, an increased breathing rate also implies that inhaled air has less time to be conditioned and warmed by the upper airways. It is therefore thought that two types of effects may contribute towards the development of asthma symptoms while exercising: a) a decrease in temperature in the bronchial mucosa, due to a lower degree of warming of inhaled air; b) an increased dehydration of the bronchial mucosa, due to a more rapid passage of air through the nose which is, therefore, less humidified. Whichever of these two mechanisms is the more relevant is debatable. Both may, in fact, be involved. Nevertheless, the most important fact is that either may lead to the stimulation of nervous endings in the bronchi and to the induction of a local cellular influx. These two events will be associated with bronchial constriction and inflammation.

Types of physical exercise and EIA

Although, potentially, all types of physical exercise may induce asthma, some are more "asthmogenic" than others. For example, in the context of anaerobic exercise, athletics more often induces EIA than swimming does. However, it must be borne in mind that the actual development of EIA symptoms depends on various types of factors such as:

a) difficulty and duration of physical exercise (e.g., free running > treadmill > cycloergometer);

b) environmental factors (temperature and humidity, cold air, rapid re-warming, pollutants such as SO2, NO2, particulate agents, tobacco smoke, or other, and aeroallergens);

c) patient's health and habits, namely the presence of respiratory infections (sinusitis, bronchitis) or the lack of pre-exercise warming up.

Clinical aspects of EIA

Exercise-induced asthma manifests itself just like any other form of asthma. In fact, it may involve shortness of breath and wheezing, although it may simply manifest as dry cough. As mentioned in terms of the pathophysiology, EIA-related symptoms may start during exercise although, more often, they only become apparent a few minutes after having stopped the exercise. Curiously enough, as mentioned before, once the symptoms resolve, a refractory period

ensues, during which the patient may again engage in physical exercise without developing any symptoms.

In general, there are some clinical features that may alert towards the presence of a situation of exercise-induced asthma in a student or athlete:

- Feeling of chest tightness;
- Dry cough (after physical exercise or at night)
- Prolonged shortness of breath (dyspnoea)
- Difficulty falling asleep
- Post-exercise wheezing
- Well trained athlete demonstrating lower than expected performances
- Family history of bronchial asthma
- Personal history of allergies and allergic rhinitis

Diagnosis of EIA

There are various parameters that help to reach a diagnosis of exercise-induced asthma. These include:

a) Relevant clinical aspects (environmental triggers, types of symptoms, personal and/or family history, etc);
b) Altered lung function tests (showing bronchial obstruction);
c) Altered forced exercise test (spirometry; oximetry)
    a. Performed outdoors, in usual training conditions (field challenge);
    b. Performed indoors, at a specific laboratory environment (treadmill; eucapneic hyperventilation).

Forced exercise testing may be crucial for the diagnosis of EIA in that it may be the only way to reproduce and quantify the symptoms.

Approach to EIA

Various measures may be taken with a view to improving the situation of exercise-induced asthma. These include aspects related to:

a) Appropriate selection of physical exercise;
b) Correct medical advice;
c) The role of schools and sports clubs.

a) Appropriate selection of physical exercise

The general idea will be to choose the type of physical exercise that is less "asthmogenic", provided it is appealing to the person performing it. This will depend on the existence or not of previous allergic diseases in the patient as well as on environmental conditions. It should also be remembered that, in some cases, the same type of physical exercise may be practised either indoors or outdoors. In this context, whenever outdoor conditions are more critical for patients with EIA (e.g., strong wind, cold air, high pollen counts, high pollutant levels), it is possible for the exercise to carried out indoors.

b) Correct medical advice

It is very important to seek medical help whenever EIA is suspected. In this regard a specialist doctor (Allergist) will be able to assess the situation and give appropriate advice. This will involve recommendations regarding the best type of physical exercise but also preventive measures and therapeutic approaches (what to do when EIA occurs).

c) The role of schools and sports clubs

Schools and sports clubs are very important for dealing with children and adults with EIA. In this regard, the coach and physical education (PE) teacher have a crucial role.

Coaches, PE teachers and EIA

Both coaches and PE teachers must be aware of "cloakroom" cough in an athlete or PE student. It will be more apparent after a game or a session of physical exercise. In addition, well trained athletes with EIA may be detected because of an otherwise unexplained lack of mid-season form. Coaches should also be aware that athletes are trained to withstand pain and discomfort and may therefore be less prone to acknowledge the presence of any symptoms. In addition, athletes are also afraid of having to take medication and thereby be accused of doping.

Both coaches and PE teachers should be prepared to take appropriate

action with EIA patients. This will imply appropriate training and information. These measures are as follows:

a) To have an asthma emergency action plan (preferably discussed with an Allergist);
b) To know how to measure lung function using a mini-Wright peak flow meter;
c) To ensure that all asthmatic athletes or students involved in physical exercise bring their rescue inhalers to training sessions;
d) To make sure that the school or club has a spare inhaler device and a spacer for using it (Figure …);
e) To know how to use a spacer for the inhalers;
f) To have alternative training places and plans for asthmatic athletes or students, in case they are necessary;
g) To adapt pre-warming periods to asthmatic patients;
h) To ensure that asthmatic patients are regularly seen by an Allergist;
i) To know the basics of asthma therapy, particularly in terms of rescue medication (inhaled bronchodilators)

Figure 2. Metered-dose inhaler (in green) coupled to a large spacer device.

Athletes and EIA

It is important to note that, apart from coaches or PE teachers, the principal person that should actively be engaged in dealing with EIA is the asthmatic athlete himself. In this regard, people performing physical exercise, namely athletes, should thoroughly know what asthma and EIA are. In addition, the athlete should be knowledgeable about the different types of clinical manifestations of EIA and should also rigorously follow the rules of medication prescribed by the Allergist. It is useful for the professional athlete to be aware of medication that is allowed and not allowed for doping reasons. This can be

looked up at **http://www.wada-ama.org/en/**. It is also important to know how to take the medication and to be familiar with spacers for inhalers. Finally, it is crucial to know how to avoid exposure to pollutants and aeroallergens.

Practical aspects for dealing with EIA

a) Pre-medication

Patients with EIA may significantly reduce or totally abrogate symptoms if they take their rescue medication preventively. This implies inhaling a short- (terbutaline or salbutamol) or long- (formoterol or salmeterol) acting β2-agonist, 5 to 10 minutes before starting physical exercise. This approach will reduce underlying, unapparent bronchial constriction and prevent exercise-induced bronchoconstriction. This type of medication is permitted in asthmatic athletes since they only act as anabolizers and stimulator drugs in high doses.

b) Medical control of baseline asthma

It is important to remember that bronchial asthma (and EIA) involve the presence of bronchial inflammation. In this context, prolonged use of anti-inflammatory inhalers (corticosteroids such as fluticasone or budesonide) may very significantly reduce the probability of development of bronchial constriction, by inhibiting local inflammation which may be crucial in the pathophysiology of EIA. These drugs are only permitted in an inhaled form in asthmatic athletes. In addition, they may also be applied topically on the skin.

c) Correct training session (and pre-warming)

It is crucial for a correct pre-warming phase to be included in training sessions. Training sessions should be performed on a regular basis because this may contribute towards reducing the development of EIA in an athlete. Training sessions should be adapted to the asthmatic athlete / student and triggers should be avoided (cold air, etc).

d) Medical and psychological support

Medical support is crucial for the correct preventive and therapeutic approach to asthma and EIA. In addition, psychological support may also be crucial in terms of motivating for performing physical exercise in spite of EIA and also for dealing with this type of illness.

e) Other measures

Other measures may be taken in order to reduce the probability of developing EIA, although some of them are not totally proven. These include reducing salt intake, poly-unsaturated fatty acid supplementation, and avoidance of aspirin.

In Summary

Exercise-induced asthma is a situation which is more frequent than generally thought. It is crucial that an asthmatic athlete or student does not give up physical exercise or hide his illness from his coach or PE teacher. Both coach / PE teacher and asthmatic athlete / student should be aware of preventive and therapeutic measures for EIA. Training sessions should be adapted to EIA athletes / students. A number of these studies have reported some reductions in hospitalisations, wheeze frequency, school absenteeism, doctor consultations and medication usage in asthmatic children that perform physical exercise on a regular basis. It is, therefore, recommended that children and adolescents with asthma should participate in regular physical activity. Generally speaking, it is crucial that a stable, controlled situation is attained, so that people involved in physical exercise carry on enjoying their activities in spite of EIA and may achieve the same goals as those the people that do not have EIA.

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Nutrition interventions to limit exercise-induced immunodepression.

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Abstract

Prolonged exercise and heavy training are associated with depressed immune cell function. To maintain immune function, athletes should eat a well balanced diet sufficient to meet their energy, carbohydrate, protein and micronutrient requirements. Consuming carbohydrate during prolonged strenuous exercise attenuates rises in stress hormones and appears to limit the degree of exercise-induced immune depression. Recent evidence suggests that antioxidant vitamin supplementation may also reduce exercise stress and impairment of leukocyte functions. Further research is needed to evaluate the effects of other antioxidants and dietary immunostimulants such as probiotics and echinacea on exercise-induced immune impairment.

Immune function and the nutrition of elite athletes

The immune system protects against, recognises, attacks and destroys elements that are foreign to the body. The immune system can be divided into two broad functions: innate (natural and non-specific) and acquired (adaptive and specific) immunity which work together synergistically. The attempt of an infectious agent to enter the body immediately activates the innate system. This so-called 'first-line of defence' comprises three general mechanisms with the common goal of restricting micro-organism entry into the body: (1) physical/structural barriers, (skin, epithelial linings, mucosal secretions); (2) chemical barriers, (pH of bodily fluids and soluble factors such as lysozymes and complement proteins); and (3) phagocytic cells (e.g. neutrophils and monocytes/macrophages) and cytotoxic cells (natural killer cells). Failure of the innate system and the resulting infection activates the acquired system, which aids recovery from infection. Monocytes or macrophages ingest, process and present foreign material (antigens) to lymphocytes. This is followed by clonal proliferation of T- and B-lymphocytes that possess receptors that recognise the antigen, engendering specificity and 'memory' that enable the immune system to mount an augmented cell-mediated and humoral (antibody) response when the

host is reinfected by the same pathogen.

Critical to the activation and regulation of immune function is the production of cytokines including interferons,interleukins and colony stimulating factors. A fundamental characteristic of the immune system is that it involves multiple functionally different cell types which permits a large variety of defence mechanisms. Assessing immune function status therefore requires a thorough methodological approach targeting a large spectrum of immune system parameters. However, currently no instruments are available to predict the cumulative effects of several small changes in immune cell functions determined *in vitro* on host resistance to infection (1).

A heavy schedule of training and competition can lead to immune impairment in athletes and this is associated with an increased susceptibility to infections, particularly upper respiratory tract infections (URTI) (2,3). This exerciseinduced immune dysfunction seems to be mostly due to the immunosuppressive actions of stress hormones such as adrenaline and cortisol. Since many of the immunological changes to acute exercise appear to arise in response to stress hormones, factors such as exercise intensity, duration and subject fitness, which influence stress hormone secretion, will affect the immune response. Both circulating leukocyte numbers and functions are affected by catecholamines (4), which are elevated by acute exercise in an intensity dependent manner. Subject fitness has a bearing on the relative intensity of a bout and will, therefore, alter the immunological outcome to an acute exercise bout (5). Furthermore, exercise-induced elevations in cortisol affect the leukocyte count and function, and the secretion of this hormone is affected by the intensity and duration of exercise (6). Mild to moderate exercise (<50% VO2max) seems to reduce cortisol concentrations due to an enhanced elimination and a suppressed secretion, whereas more intense exercise (>60% VO2max) increases cortisol (6). However, if the bout is sufficiently prolonged, even relatively moderate intensities can elicit increases in cortisol because it is released to increase gluconeogenesis and maintain blood glucose concentrations (7). Exercise intensity and duration both contribute to the metabolic stress of the bout and thus influence fuel depletion. Since recent evidence suggests skeletal muscle can release IL-6 when fuel provision becomes challenged8 and this cytokine is known to have immunological actions (9) factors such as intensity, duration and subject fitness that can influence metabolic demand will affect the immunological outcome.

Acute exercise appears to modify T cell function and as for many other aspects of immune function, such effects are proportional to exercise intensity

and duration. There is evidence that prolonged acute exercise is associated with a decrease in T cell IL-2 and IFN-□ production immediately after exercise, and a decline in the number of circulating T cells that secrete IFN-□ (10). There are numerous reports in the literature of decreased mitogen-stimulated T cell proliferation following acute exercise (11,12) but interpretation of these findings may be confounded by the presence of NK cells and B cells in the cell cultures. Furthermore, it should be remembered that *in vitro* stimulation with 2 mitogen does not necessarily reflect the more subtle responses of cells following a specific antigen encounter within the body. Moreover, exercise may alter T cell function *in vitro* through an increase in the rate of apoptosis in cell culture rather than a decrease in T cell proliferation (13).

The effect of exercise on humoral immune function has been assessed through measurements of serum and mucosal Ig concentration *in vivo* and lymphocyte Ig synthesis following *in vitro* mitogen-stimulation. Serum Ig concentration appears to remain either unchanged, or slightly increased, in response to either brief or prolonged exercise (14). Mucosal Ig production has been chiefly assessed by measurement of IgA in saliva, with intensive exercise frequently associated with a decline in s-IgA concentration and/or secretion rate (15).

In general post-exercise immune function depression is most pronounced when the exercise is continuous, prolonged (>1.5 hours), of moderate to high intensity (55-75% VO2max) and performed without food intake. Periods of intensified training (overreaching) lasting one week or more result in chronically depressed immune function (16). Although elite athletes are not clinically immune deficient, it is possible that the combined effects of small changes in several immune parameters may compromise resistance to common minor illnesses such as URTI.

Protracted immune depression linked with prolonged training may determine susceptibility to infection, particularly at times of major competitions (15). Hundreds of studies have now been conducted that confirm both acute and chronic effects of exercise on the immune system, yet there are still very few studies that have been able to show a link between exercise-induced immune depression and increased incidence of illness in athletes. This is an important issue that needs to be addressed in future studies, though it must be recognised that this is a difficult task. Even among the general population we do not know the impact of small changes in specific immune parameters on risk of infection (1). Most clinical studies have only been concerned with the risk of life-threatening illness in immunodeficient patients, not with the risks of picking

up common infections such as colds and flu.

Nutritional deficiencies can also impair immune function and there is a vast body of evidence that many infections are increased in prevalence or severity by specific nutritional deficiencies (17). However, it is also true that excessive intakes of individual micronutrients (e.g. n-3 polyunsaturated fatty acids, iron, zinc, vitamins A and E) can impair immune function and some (particularly excess iron) can increase the risk of infection (17). As most athletes will be aware, even medically harmless infections can result in a decrement in athletic performance. This review will consider the various components of the diet that can potentially influence the degree of exercise-induced immunodepression.

Undoubtedly, a key to maintaining an effective immune system is to avoid deficiencies of the nutrients that play an essential role in immune cell triggering, interaction, differentiation or functional expression. Malnutrition decreases immune defences against invading pathogens and makes the individual more susceptible to infection (17,18). Infections with certain pathogens can also affect nutritional status by causing appetite suppression, malabsorption, increased nutrient requirements and increased losses of endogenous nutrients (18).

Macronutrients

Protein and energy

It is well accepted that an inadequate intake of protein impairs host immunity with particularly detrimental effects on the T-cell system, resulting in increased incidence of opportunistic infections (17,18). It is not surprising that protein deficiency impairs immunity because immune defences are dependent on rapid cell replication and the production of proteins with important biological activities such as immunoglobulins, acute phase proteins and cytokines. In humans, protein-energy malnutrition (PEM) has been found to depress the number of mature, fully differentiated T lymphocytes and the in vitro proliferative response to mitogens, although the latter is reversible with nutritional repletion (19). Additionally, in PEM the T-lymphocyte CD4+/CD8+ (helper/suppressor cell) ratio is markedly decreased and phagocytic cell function, cytokine production, and complement formation are all impaired.

Essentially all forms of immunity have been shown to be affected by PEM in humans, depending on the severity of the protein deficiency relative to energy intake. While it is unlikely that athletes would ever reach a state of such

extreme malnutrition unless dieting very severely, some impairment of host defence mechanisms is observed even in moderate protein deficiency (19). Among the athletic population, individuals at most risk from protein deficiency are those undertaking a programme of food restriction in order to lose weight, vegetarians and athletes consuming unbalanced diets (e.g. with an excessive amount of carbohydrate at the expense of protein). Often, deficiencies in protein and energy will be accompanied by deficiencies in micronutrients. Energy-restricted diets are common in sports where leanness or low body mass is thought to confer a performance or aesthetic advantage (e.g. gymnastics, figure skating, endurance running) or is required to meet certain body weight categories (e.g. boxing, martial arts, weight lifting, rowing). Indeed, this has lead to the identification of a new subclinical eating disorder 'anorexia athletica' which has been associated with an increased susceptibility to infection (20). Even short-term dieting can influence immune function in athletes. For example, it has been shown that a loss of 2 kg body mass over a 2-week period adversely affects macrophage phagocytic function (21).

Fat

Relatively little is known about the potential contribution of dietary fatty acids (FA) to the regulation of exercise induced modification of immune function. Two groups of polyunsaturated fatty acids (PUFA) are essential to the body: the omega-6 (n-6) series, derived from linoleic acid and the omega-3 (n-3) series, derived from linolenic acid. These FA cannot be synthesised in the body and therefore must be derived from the diet. There are reports that diets rich in n-3 PUFA improve the conditions of patients suffering from diseases characterised by an over-active immune system, such as rheumatoid arthritis; that is to say they have anti-inflammatory effects (18). It has been suggested that high intakes of n-6 PUFA such as arachidonic acid relative to intakes of FA of the n-3 group may exert an undesirable influence on inflammation and immune function during and after exercise (22), though direct evidence of this is currently lacking. However, a recent study showed that n-3 PUFA supplementation did not influence the exercise-induced elevation of pro- or anti-inflammatory cytokines (23). More research is needed on the effects of altering essential FA intake on immune function after exercise and during periods of heavy training.

Carbohydrate

Since many aspects of exercise-induced immune function impairment seem

to be caused by elevated levels of stress hormones, nutritional strategies that effectively reduce the stress hormone response to exercise would be expected to limit the degree of exercise-induced immune dysfunction (24). There is certainly some considerable experimental evidence that supports a beneficial effect of carbohydrate (CHO) feeding during exercise (25,26), although it is not clear if the magnitude of such effects is sufficient to affect infection risk.

Consumption of CHO during exercise attenuates (i.e. reduces the magnitude of) rises in plasma catecholamines, growth hormone, adrenocorticotrophic hormone, cortisol (Figure 1) and cytokines (25).

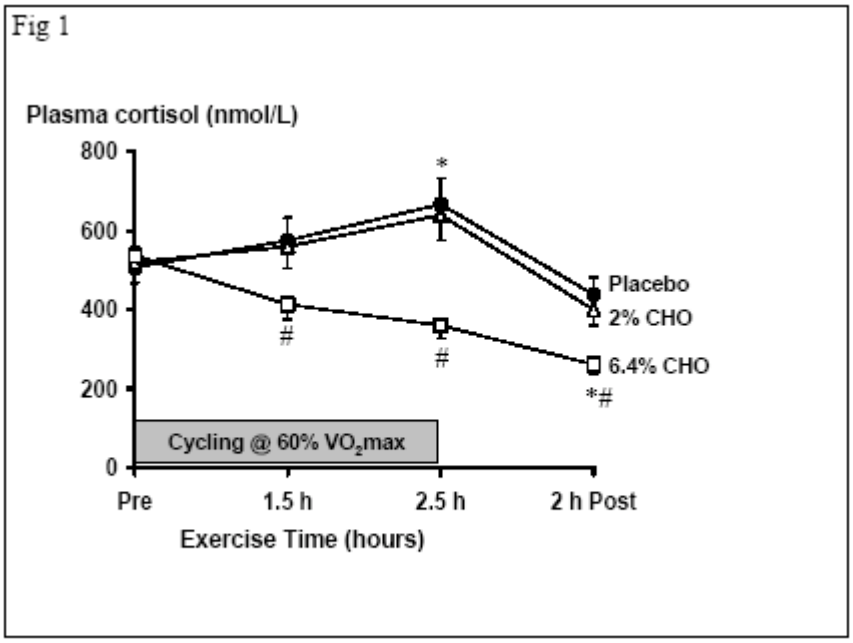

Figure 1. Consumption of 30-60 g carbohydrate per hour as a 6.4% w/v beverage during 2.5 h strenuous cycling exercise attenuates rises in plasma cortisol observed on the placebo trial.

* significantly different to pre-exercise, P<0.05; # significantly lower than PLA, P<0.05. Note that ingesting a small amount of carbohydrate as a 2% w/v beverage has no significant effect on the plasma cortisol response to exercise. The volume of drinks consumed was 500 ml immediately preexercise and 200 ml every 20 min during exercise. Data from Lancaster et al.(15).

CHO intake during exercise also attenuates the trafficking of most leukocyte and lymphocyte subsets, including the rise in the

neutrophil:lymphocyte ratio (25), prevents the exercise-induced fall in neutrophil function (27) and reduces the extent of the diminution of mitogen-stimulated T-lymphocyte proliferation (28) following prolonged exercise (Figure 2).

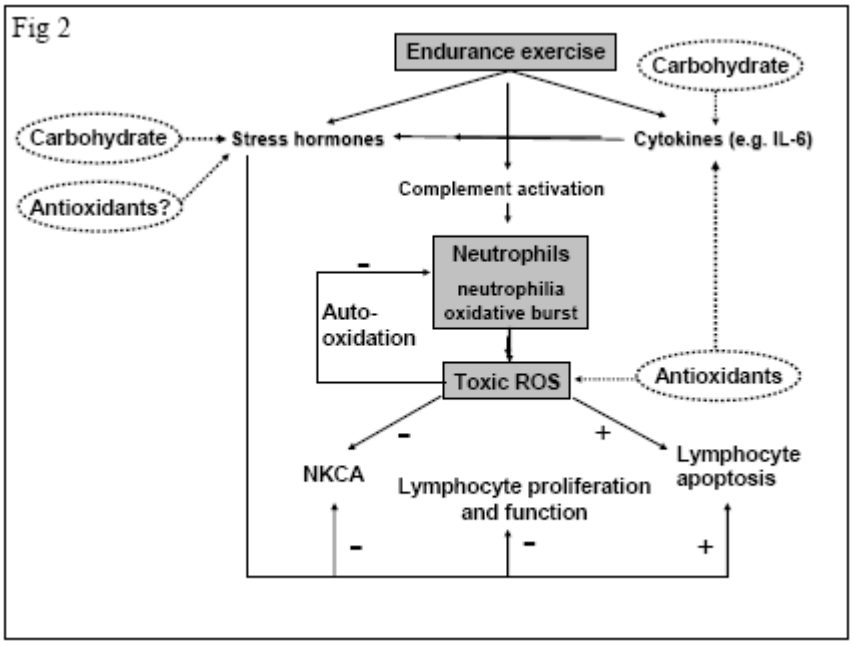

Figure 2. Mode of action of carbohydrate and antioxidant supplements in limiting exercise-induced immune function depression. Carbohydrate ingestion during prolonged exercise maintains plasma glucose availability and limits rises in circulating IL-6, cortisol and adrenaline. Antioxidant supplementation for several weeks also attenuates rises in circulating IL-6 and cortisol during exercise, elevates the plasma antioxidant capacity and scavenges reactive oxygen species (ROS) generated by active muscle and activated neutrophils.

Very recently, it was shown that consuming 30-60 g of CHO per hour during 2.5 h of strenuous cycling prevented both the decrease in the number and percentage of interferon (IFN)-□ positive T lymphocytes and the suppression of IFN-□ production from stimulated T lymphocytes (Figure 3) observed on the placebo control trial.10 IFN-□ production is critical to antiviral defence and it has been suggested that the suppression of IFN-□ production may be an important mechanism leading to an increased risk of infection after prolonged exercise bouts (29).

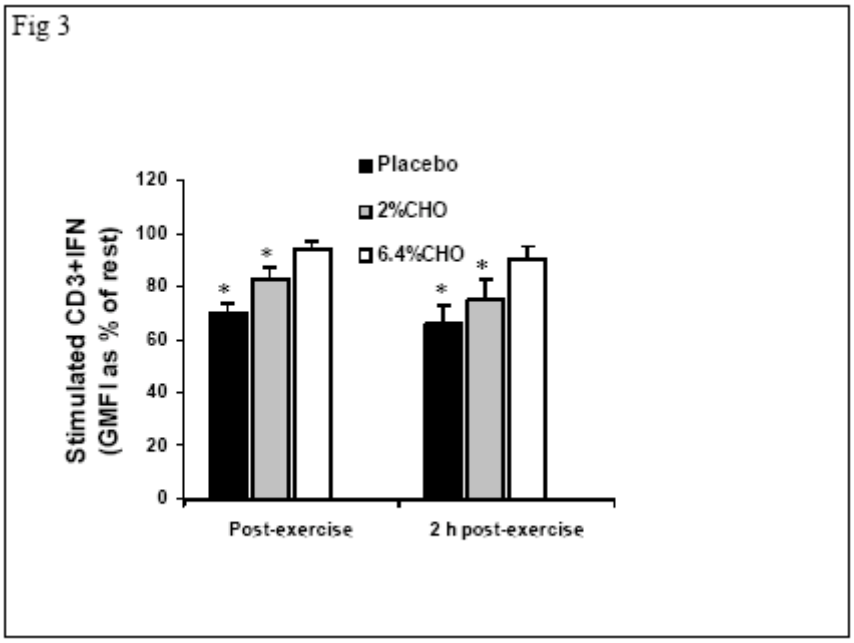

Figure 3 Consumption of 30-60 g carbohydrate per hour as a 6.4% w/v beverage during 2.5 h strenuous cycling exercise prevents the suppression of interferon (IFN)-□ production from stimulated T lymphocytes observed on the placebo control trial. * significantly lower than pre-exercise, P<0.05. Note that ingesting a small amount of carbohydrate as a 2% w/v beverage is not so effective. The volume of drinks consumed was 500 ml immediately pre-exercise and 200 ml every 20 min during exercise. Data from Lancaster et al. (15).

In a randomised, counterbalanced, crossover study carbohydrate beverage compared with placebo beverage ingestion during a 3-h treadmill run at 70%VO2max attenuated plasma levels of interleukin (IL)-6, and IL-10 and muscle gene expression for IL-6 and IL-8.30 The 3-h treadmill run in both the CHO and placebo trials induced gene expression within the muscle for two primary proinflammatory cytokines IL-1□ and tumour necrosis factor-□. IL-6 and IL-8, which are often considered to be components of the secondary inflammatory cascade, were also expressed, but to a smaller degree in the CHO trial. Anti-inflammatory indicators, including plasma IL-1-receptor antagonist, IL-10, and cortisol, were also decreased with CHO feeding. These data suggest that CHO ingestion attenuates the secondary but not the primary pro-

inflammatory cascade, decreasing the need for immune responses related to anti-inflammation (30).

When CHO is ingested during prolonged exercise, the release of IL-6 from working muscles can be totally inhibited (31) and the exercise-induced expression of a number of metabolic genes are blunted compared with exercise in the fasted state (32). Infusion of IL-6 in humans stimulates cortisol secretion (with plasma cortisol levels reaching similar values to those observed during exercise and with a similar timecourse) and induces lipolysis as well as eliciting a strong anti-inflammatory response (33). Thus, although CHO ingestion during exercise attenuates the IL-6 response and so reduces the magnitude of the cortisol-induced lymphocytopenia, it will, at the same time, inhibit lipolysis, reduce the anti-inflammatory cytokine response to exercise and attenuate the expression of a number of metabolic genes in the exercised muscle. In other words, it is possible that CHO ingestion during exercise sessions could limit metabolic adaptation of skeletal muscle to training. However, it can also be argued that CHO intake during training allows the athlete to work harder and longer and as yet there is no evidence that physiological and performance adaptations are impaired by CHO intake during training sessions. Indeed, recent studies indicate that appropriate CHO intake is necessary for improvements in endurance performance following periods of intensified training that temporarily induce overreaching (34, 35).

While CHO feeding during exercise appears to be effective in minimising some of the immune perturbations associated with prolonged continuous strenuous exercise, it seems less effective for less demanding exercise of an intermittent nature, for example football (36) or rowing (37) training. It is also apparent that CHO feeding is not as effective in reducing immune cell trafficking and functional depression when continuous prolonged exercise is performed to the point of fatigue (38). Pre-exercise feeding of CHO does not seem to be very effective in limiting exercise-induced leukocytosis or depression of neutrophil function.39 It must also be said that evidence that the beneficial effect of feeding CHO on immune responses to exercise actually translates into a reduced incidence of URTI following prolonged exercise such as marathon races is currently lacking. Although a trend for a beneficial effect of CHO ingestion on post-race URTI was reported in a study of 98 marathon runners, 40 this did not achieve statistical significance and larger scale studies are needed to investigate this possibility.

The size of the glycogen stores in muscle and liver at the onset of exercise

will also influence the hormonal and immune response to exercise. The amount of glycogen stored in the body is rather limited (usually less than 500 g) and is affected by recent physical activity and the amount of dietary carbohydrate intake. When individuals perform prolonged exercise following several days on very low CHO diets (typically <10% of dietary energy intake from CHO), the magnitude of the stress hormone (e.g. adrenaline and cortisol) and cytokine (e.g. IL-6, IL-1ra and IL-10) response is markedly higher than on normal or high CHO diets.41,42 It has been speculated that athletes deficient in CHO are placing themselves at risk from the known immunosuppressive effects of cortisol, including the suppression of antibody production, lymphocyte proliferation and NK cell cytotoxic activity. In the study by Mitchell et al.(42) it was observed that exercising (1 h at 75% VO2max) in a glycogen depleted state (induced by prior exercise and 2 days on a low CHO diet) resulted in a greater fall in circulating lymphocyte numbers at 2 h postexercise compared with the same exercise performed after 2 days on a high CHO diet. In this study the manipulation of CHO status did not affect the decrease in mitogen-stimulated lymphocyte proliferation that occurred after exercise. However, a more recent study by Bishop et al.(43) showed that lymphocyte proliferation responses to mitogen and influenza were lower 24 h following a 90-minute intermittent high intensity exercise bout when subjects consumed a placebo beverage compared with a carbohydrate beverage before, during and following the exercise bout (Figure 4). Interestingly, these differences were independent of changes in the plasma cortisol

concentration, implying that these CHO effects were mediated via a different mechanism.

Fluid intake during exercise

The consumption of beverages during exercise not only helps prevent dehydration (which is associated with an increased stress hormone response) but also helps to maintain saliva flow rate during exercise. Saliva contains several proteins with antimicrobial properties including IgA, lysozyme and □-amylase. Saliva secretion usually falls during exercise. Regular fluid intake during exercise is reported to prevent this effect and a recent study has confirmed that regular consumption of lemon-flavoured CHO-containing drinks helps to maintain saliva flow rate and hence saliva IgA secretion rate during prolonged exercise compared with a restricted fluid intake regimen (44).

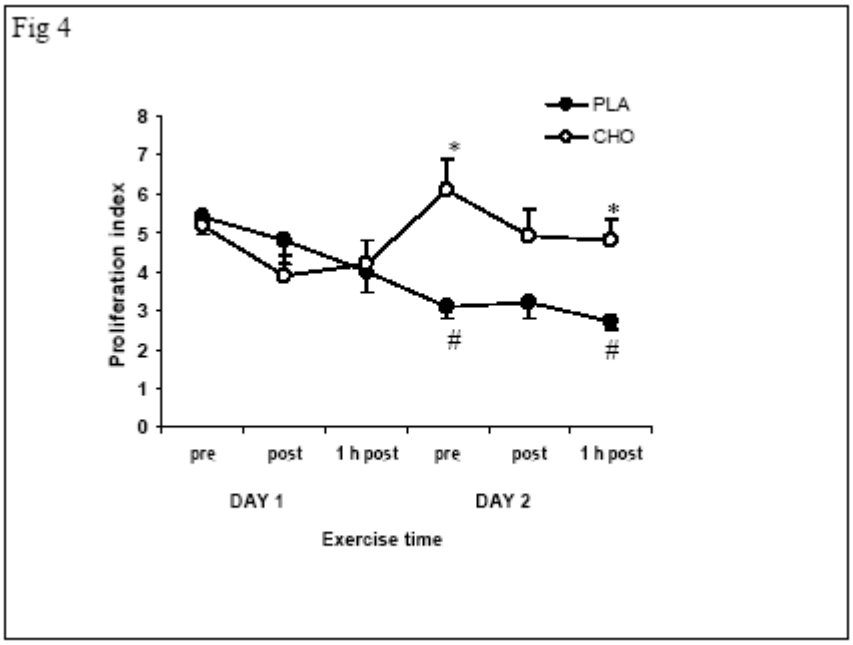

Figure 4. Mitogen (phytohemagglutinin)-stimulated T lymphocyte proliferative response (fold increase relative to unstimulated cells) before and after two bouts of high intensity intermittent exercise performed on consecutive days with either carbohydrate (6.4% w/v) or placebo beverage ingestion before, during and after exercise bout. * significantly higher than PLA, $P<0.05$. # significantly lower than pre-exercise on Day 1 (PLA only), $P<0.05$. Data from Bishop et al.(30).

Micronutrients

Minerals

Several minerals are known to exert modulatory effects on immune function, including zinc, iron, magnesium, manganese, selenium and copper, yet with the exception of zinc and iron, isolated deficiencies are rare. Field studies consistently associate iron deficiency with increased morbidity from infectious disease.17,18 Furthermore, exercise has a pronounced effect on both zinc and iron metabolism.45 Requirements for these minerals are certainly higher in athletes compared with sedentary people because of increased losses in sweat and urine. However, excess intakes of some minerals (particularly iron and zinc) can impair immune function and, at least for iron, have been shown to increase

susceptibility to infection.17,18,45 Hence, supplements should be taken only as required and regular monitoring of iron status (serum ferritin and blood haemoglobin) and zinc status (erythrocyte or leukocyte zinc content) is probably a good idea.

The efficacy of zinc supplementation as a treatment for the common cold has been investigated in at least 11 studies that have been published since 1984. The findings have been equivocal and recent reviews of this topic have concluded that further research is necessary before the use of zinc supplements to treat the common cold can be recommended (46,47). Although there is only limited evidence that taking zinc supplements reduces the incidence of

URTI (48) in the studies that have reported a beneficial effect of zinc in treating the common cold (i.e. reduction of symptom duration and/or severity) it has been emphasised that zinc must be taken within 24 h of the onset of symptoms to be of any benefit. Potential problems with zinc supplements include nausea, bad taste reactions, lowering of HDL-cholesterol, depression of some immune cell functions (e.g. neutrophil oxidative burst) and interference with the absorption of copper (45).

Vitamins

Several vitamins are essential for normal immune function. Deficiencies of fat-soluble vitamins A and E and watersoluble vitamins folic acid, B6, B12 and C impair immune function and decrease the body's resistance to infection (17,18). Correcting existing deficiencies with specific vitamin supplements can be effective in restoring immune function to normal levels and moderately increasing the intake of some vitamins (notably vitamins A andE) above the levels normally recommended may enhance immune function, particularly in the very young and the elderly (17). Consuming megadoses of individual vitamins, which appears to be a common practice in athletes, can actually impair immune function and have other toxic effects (18). In a recent exercise study, supplementation of athletes with 600 mg.day-1 vitamin E for two months prior to an Ironman triathlon event resulted in elevated oxidative stress and inflammatory cytokine responses during the triathlon compared with placebo (49). In a study on elderly people (n=652) a daily 200 mg vitamin E supplement increased the severity of infections, including total illness duration, duration of fever and restriction of physical activity (59). However, in that study, health assessment was by self-evaluation which could be a limiting factor, particularly in an elderly population whose cognitive function was not described. In a recent large placebocontrolled trial (n=617 elderly nursing home residents) by Meydani

et al. (51) which used weekly documentation by nurses and physicians to assess health status, fewer participants receiving daily supplementation with 200 IU vitamin E aquired one or more respiratory tract infections and the vitamin E group had a lower incidence of colds than the placebo group. Recently, vitamin E supplementation (600 mg.day-1) in patients with ischaemic heart disease has been demonstrated to have either no effect on all cause mortality (52) or to increase the number of cases who died compared with placebo (53). In contrast in a large cohort of women (n=22,000) , there was a 24% reduction in risk for cardiovascular death for those who took a supplement of 600 IU/day vitamin E every other day for 10 years and no effect on overall mortality (54). Meydani et al.(55) concluded that 200 mg of vitamin E daily represents the optimal level for the immune response. Intakes in excess of 300 mg/day of vitamin E in the human diet have been associated with decreases in phagocytic cell functions (56,57). Megadoses of vitamin A may impair the inflammatory response and complement formation as well as having other pathological effects, including causing an increased risk of foetal abnormalities when consumed by pregnant women (5).

Vitamins with antioxidant properties including vitamins A, C, E and □-carotene (provitamin A) may be required in increased quantities in athletes in order to inactivate the products of exercise-induced reactive oxygen species (ROS) generation (58). However, there are no convincing data demonstrating an effect of nutritional antioxidants on exercise performance. Increased oxygen free-radical formation that accompanies the dramatic rise in oxidative metabolism during exercise could potentially inhibit immune responses (18,59) and contribute to exercise-induced lymphocytopenia by activating apoptosis (an internal program that allows cells to commit suicide) (60) ROS inhibit locomotory and bactericidal activity of neutrophils, inhibit natural killer (NK) cell cytotoxic activity, reduce the proliferation of T- and B-lymphocytes and promote lymphocyte apoptosis (Figure 2) (60). Sustained endurance training appears to be associated with an adaptive up-regulation of the antioxidant defence system (61) though this may be insufficient to protect athletes who train extensively (58) Vitamin C (ascorbic acid) is found in high concentration in leukocytes and has been implicated in a variety of antiinfective functions including promotion of T-lymphocyte proliferation, prevention of corticosteroid-induced suppression of neutrophil activity, and inhibition of virus replication.62 It is also a major water-soluble antioxidant that is effective as a scavenger of ROS in both intracellular and extracellular fluids. Vitamin C is also required for the regeneration of the reduced form of the lipid-soluble

antioxidant, vitamin E.

In a study by Peters et al. (63) using a double blind placebo research design, it was determined that daily supplementation of 600 mg (15 times the RNI) of vitamin C for 3 weeks prior to a 90-km ultramarathon reduced the incidence of symptoms of URTI (68% compared with 33% in age- and sex-matched control runners) in the 2 week post-race period. In a follow-up study, Peters et al.64 randomly divided participants in a 90-km ultramarathon (n=178), and their matched controls (n=162) into four treatment groups receiving either 500 mg vitamin C alone, 500 mg vitamin C plus 400 IU vitamin E (1IU is equivalent to 0.67 mg), 300 mg vitamin C plus 300 IU vitamin E plus 18 mg □-carotene, or placebo. As runners were requested to continue with their usual habits in terms of dietary intake and the use of nutritional supplements, total vitamin C intake of the 4 groups was 1004, 893, 665, and 585 mg daily, respectively. The study confirmed previous findings of a lower incidence of symptoms of URTI in those runners with the highest mean daily intake of vitamin C and also indicated that the combination of water-soluble and fat-soluble antioxidants was not more successful in attenuating the post-exercise infection risk than vitamin C alone (Figure 5). This

study certainly provides some support for the notion that megadoses of vitamin C reduce URTI risk in endurance athletes, though a limitation is that infection symptoms were self-reported and not clinically confirmed in these studies. However, some similar studies have not been able to replicate these findings: for example, Himmelstein et al.(65) reported no difference in URTI incidence among 44 marathon runners and 48 sedentary subjects randomly assigned to a 2-month regimen of 1000 mg.day-1 vitamin C or placebo. Furthermore, a subsequent double-blind, placebo controlled study found no effect of vitamin C supplementation (1000 mg.day-1 for 8 days) on the immune response to 2.5 h running (66), though a larger dose of vitamin C supplementation (1500 mg.day-1 for 7 days prior to the race and on race day) did reduce the cortisol and cytokine response to a 90-km ultramarathon race.67 However, in the latter study, no difference in URTI incidence was found between subjects on vitamin C and placebo treatments. Again, URTI was self-evaluated and a confounding factor in this study was that subjects consumed carbohydrate during the race ad libitum and this was retrospectively estimated.

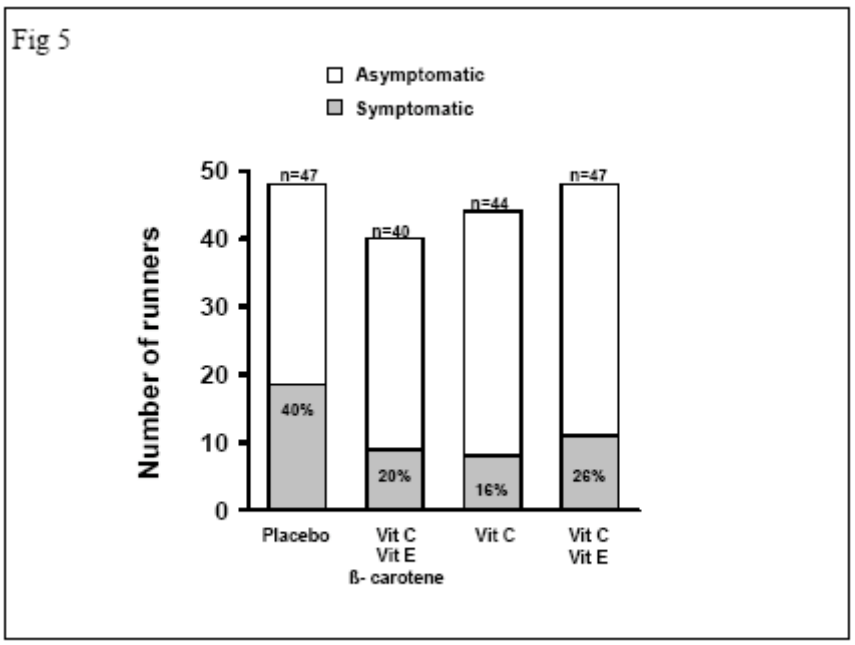

Figure 5. The incidence of upper respiratory tract infection (URTI) in the week following the 1993 Comrades Marathon (90 km) in South Africa. Different groups of runners received different combinations of antioxidant supplements or placebo for 3 weeks prior to the ultramarathon. The incidence of URTI in a control group of 45 non-runners receiving placebo was 20%. Data from Peters et al.(46).

In a more recent randomised, double blinded, placebo-controlled study, 1500 mg.day-1 vitamin C for 7 days before an ultramarathon race with consumption of vitamin C in a carbohydrate beverage during the race (subjects in the placebo group consumed the same carbohydrate beverage without added vitamin C) did not affect oxidative stress, cytokine or immune function measures during and after the race (68). In contrast, it has recently been reported that 4 weeks combined supplementation with vitamin C (500 mg.day-1) and vitamin E (400 IU.day-1) prior to a 3-h knee extension exercise protocol reduced muscle IL-6 release and reduced the systemic rise in both circulating IL-6 and cortisol (Figure 6) (69). Furthermore, administration of the antioxidant N-acetyl-L-cysteine (a precursor of glutathione) to mice prevented the exercise-induced reduction in intracellular glutathione concentration and markedly reduced post-exercise apoptosis in intestinal lymphocytes.60 Thus, although there are some inconsistencies in the literature regarding antioxidant

supplementation and immune responses to exercise, there is some basis for believing that such supplementation could have beneficial effects in alleviating exercise-induced immunodepression.

Dietary immunostimulants

Glutamine

Glutamine is the most abundant free amino acid in human muscle and plasma and is utilised at very high rates by leukocytes to provide energy and optimal conditions for nucleotide biosynthesis. Indeed, glutamine availability is considered important to lymphocytes and other rapidly dividing cells including the gut mucosa and bone marrow stem cells. Prolonged exercise is associated with a fall in the plasma concentration of glutamine and it has been hypothesised that such a decrease could impair immune function (70,71). It has been suggested that exogenous provision of glutamine supplements may be beneficial by maintaining the plasma glutamine concentration and hence preventing the impairment of immune function following prolonged exercise.

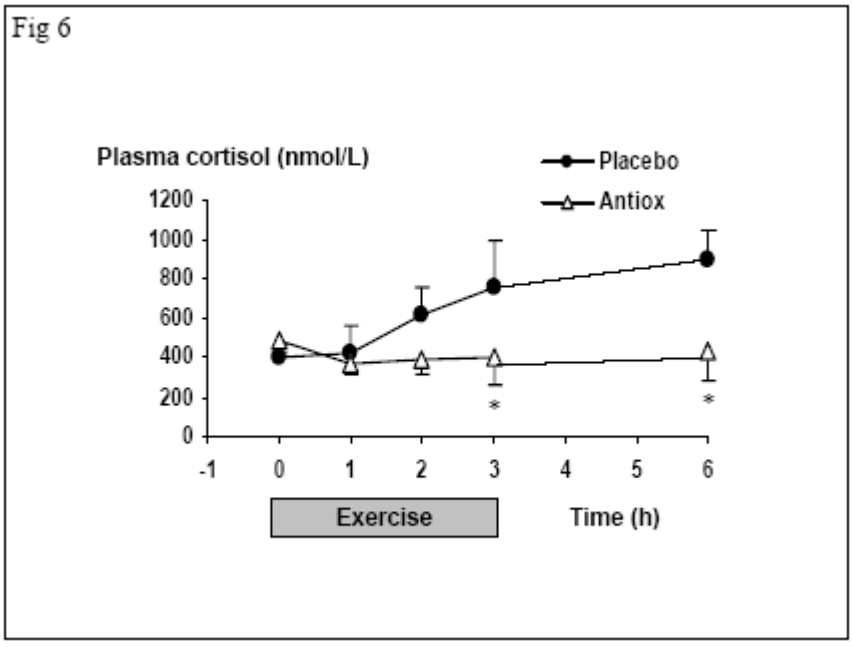

Figure 6. The effect of 4 weeks of antioxidant supplementation (500 mg.day-1 vitamin C and 400 IU.day-1 vitamin E) compared with placebo on plasma cortisol responses to 3 h of dynamic knee extensor exercise. Data from Fischer et al.(51).

Castell et al. (72) have provided the only prophylactic evidence that an oral glutamine supplement (5 g in 330ml water) consumed immediately after and 2 h after a marathon reduces the incidence of URTI (in the 7 days following the race). However, it is unlikely that this amount of glutamine supplementation could actually have prevented the post-exercise fall in the plasma glutamine concentration. Provision of glutamine has been shown tohave a beneficial effect on gut function, morbidity and mortality and on some aspects of immune cell function in clinical studies of diseased or traumatised patients. However, several recent studies that have investigated the effect of large amounts of glutamine supplementation during and after exercise on the exercise-induced fall in lymphokine-activated killer cell activity, neutrophil function and mitogen-stimulated lymphocyte proliferation have failed to find any beneficial effect (73,74).

Branched chain amino acids

Very recently, Bassit et al.75 reported that supplementation of branched chain amino acids (6 g.day-1 for 15 days) prior to a triathlon or 30-km run in experienced male triathletes and marathoners, respectively, prevented the ~40% decline in mitogen-stimulated lymphocyte proliferation observed in the placebo control group after exercise. Branched chain amino ingestion was associated with increased lymphocyte IL-2 and IFN-□ production. The postexercise fall in plasma glutamine concentration was prevented by the branched chain amino acid ingestion, but it is not clear if this was the mechanism of action or if there was a direct effect of the branched amino acids themselves.

More research is needed to resolve these conflicting findings of branched chain amino acids and glutamine supplementation on immune responses to exercise.

□ -carotene

□ -carotene (pro-vitamin A) acts both as an antioxidant and an immunostimulant, increasing the number of T-helper cells in healthy humans and stimulating NK cell activity when added *in vitro* to human lymphatic

cultures (76,77). Furthermore, elderly men who had been taking □-carotene supplements (50 mg on alternate days) for 10-12 years were reported to have significantly higher NK cell activity than elderly men on placebo (78). However, supplementing runners with □-carotene or vitamin A was found to have an insignificant effect on the incidence of URTI following a 90-km ultramarathon (64,79).

Echinacea purpurea

Several herbal preparations are reputed to have immunostimulatory effects and consumption of products containing *Echinacea purpurea* is widespread among athletes. However, few controlled studies have examined the effects of dietary immunostimulants on exercise-induced changes in immune function. In one recent double-blinded and placebo-controlled study, the effect of a daily oral pretreatment for 28 days with pressed juice of *Echinacea purpurea* was investigated in 42 triathletes before and after a sprint triathlon (80). Another subgroup of athletes was treated with a magnesium supplement. The most important finding was that during the 28-day pretreatment period, none of the athletes in the Echinacea group fell ill, compared with 3 subjects in the magnesium group and 4 subjects in the placebo group who became ill.

Numerous experiments have demonstrated that *Echinacea purpurea* extracts do indeed demonstrate significant immunomodulatory activities. Among the many pharmacological properties reported, macrophage activation has been demonstrated most convincingly (81, 82). Phagocytotic indices and macrophage-derived cytokine concentrations have been shown to be Echinacea-responsive in a variety of assays and activation of polymorphonuclear leukocytes and NK cells has also been demonstrated.83 Changes in the numbers and activities of T- and B lymphocytes have been reported, but are less certain. Despite this cellular evidence of immunostimulation, pathways leading to enhanced resistance to infectious disease have not been described adequately. Several dozen human experiments, including a number of blind randomized trials, have reported health benefits. The most robust data come from trials testing *Echinacea purpurea* extracts in the treatment for acute URTI. Although suggestive of modest benefit, these trials are limited both in size and in methodological quality. In a recent randomised, double-blind placebo-controlled trial, administering unrefined Echinacea at the onset of symptoms of URTI in 148 college students did not provide any

detectable benefit or harm compared with placebo (84). Hence, while there is a great deal of moderately goodquality scientific data regarding the *in vitro* effects of Echinacea on selected immune cell functions, its effectiveness in treating illness or in enhancing human health is still debated and it is not yet known if Echinacea is effective in modifying exercise-induced immunodepression.

Probiotics

Probiotics are food supplements that contain "friendly" gut bacteria. There is now a reasonable body of evidence that regular consumption of probiotics can modify the population of the gut microflora and influence immune function (85,86). Some studies have shown that probiotic intake can improve ratesofrecovery from rotavirus diarrhoea, increase resistance to enteric pathogens and promote anti-tumour activity; there is even some evidence that probiotics may be effective in alleviating some allergic and respiratory disorders in young children (see Kopp-Hoolihan (87) for a review). However, to date, there are no published studies of the effectiveness of probiotic use in athletes.

Alcohol and caffeine

Although there are some established health benefits of regular light-to-moderate alcohol consumption including reduced risk of myocardial infarction, ischaemic stroke, diabetes and osteoporosis,88 it is well established that excessive intake of alcohol has negative effects on immune function.89 For other obvious reasons alcohol should not form a significant part of an athlete's diet. Although red wine is contains flavonoids which are polyphenol compounds with potent antioxidant properties, these can be obtained, if desired, from the juice of black grapes. Polyphenols are also found in abundance in berries, green tea, dark chocolate and other foods. Caffeine is the most commonly consumed drug in the world, and athletes frequently use it as an ergogenic aid (90). It improves performance and endurance during prolonged exhaustive exercise.90,91 At present, there is little information of the effects of caffeine ingestion on immune function at rest or during exercise. Addition of pharmacological doses of caffeine to cell culture media is associated with a dose-dependent suppression of *in vitro* mitogen-stimulated lymphocyte proliferative responses and cytokine production in humans (92). In rats the *in vivo* administration of 6 mg kg-1 day-1 of caffeine caused NK cell cytotoxicity

and pokeweed mitogen-stimulated B cell proliferative response to be significantly decreased,93 though in the same study administration of three times this dose of caffeine was associated with a significant increase in phytohemagglutinin-stimulated T cell proliferation. In vitro, a broad range of caffeine concentration (1-1000 mg/l) exhibited dose-dependent inhibition of both B and T cell proliferative responses (93). Recent exercise studies have demonstrated that caffeine compared with placebo ingestion 1 h before a bout of intensive endurance exercise was associated with greater perturbations in numbers of circulating lymphocytes, CD4+ and CD8+ cells and an increased percentage of CD4+ and CD8+ cells expressing the early activation marker CD69 *in vivo* both before and after exercise (94). Furthermore, the post-exercise fall in neutrophil oxidative burst activity was attenuated by caffeine ingestion.95 It is thought that these effects may be largely mediated through the caffeine's action as an adenosine receptor antagonist and the inhibition of cyclic AMPspecific phosphodiesterase activity (92,94).

Conclusions

Dietary deficiencies of energy, protein and specific micronutrients are associated with depressed immune function and increased susceptibility to infection. An adequate intake of iron, zinc, and vitamins A, E, B6 and B12 is particularly important for the maintenance of immune function. Athletes need to avoid micronutrient deficiencies.

To maintain immune function, athletes should eat a well balanced diet sufficient to meet their energy requirements. This should ensure an adequate intake of protein and micronutrients. For athletes on energy-restricted diets, vitamin supplements are desirable.

An athlete exercising in a carbohydrate-depleted state experiences larger increases in circulating stress hormones and a greater perturbation of several immune function indices. Thus, sufficient carbohydrate intake to restore glycogen stores on a daily basis is desirable. Consumption of carbohydrate (30-60 g.h-1) in drinks during prolonged exercise is recommended as this practice appears to attenuate some of the immunodepressive effects of prolonged exercise. However, the clinical significance of this is yet to be determined.

Routine consumption of megadoses of vitamins and minerals is not advised. Excess intakes of some micronutrients (e.g. iron, zinc, vitamin A) can impair immune function. Convincing evidence that so-called "immune-boosting" supplements including glutamine, echinacea, and probiotics prevent

exercise-induced immune impairment is currently lacking. Current evidence regarding the efficacy of such supplements in preventing or treating common infections is limited (particularly in athletes) and there is insufficient evidence to recommend these supplements at this time. It is still debatable as to whether antioxidant supplements are required or are desirable for athletes. There is conflicting evidence of the effects of high dose vitamin C in reducing post-exercise incidence of URTI and this practice has not yet been shown to prevent exercise-induced immune impairment. Elevations of vitamin E intake up to about 200 mg/day seem to be effective in reducing URTI incidence in the general population and several recent studies indicate that several weeks of antioxidant vitamin (C and E) supplementation can attenuate stress hormone and cytokine responses to prolonged exercise.

In summary, it appears that appropriate nutrition can go some way to limiting exercise-induced immunodepression and this remains a fertile area of future research.

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Further Textbook Reading:

Immune Function in Sport and Exercise. Gleeson M (Editor). Elsevier, November 2005. ISBN 0-443-10118-3

Altitude, Stress and Exercise

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Introduction

Ascent to high altitude is a known stressor with physiologic and metabolic consequences. These adjustments to high altitude are further complicated by the added stress of physical activity. Such disruptions in homeostasis elicit sympathoadrenal responses designed to help an individual adapt to the stress imposed by high-altitude exposure. Specifically, over the past two decades, our group has examined the sympathoadrenal responses to both acute and chronic high-altitude exposure at the summit of Pikes Peak, CO (4,300 m) in sea level residents. Utilizing a variety of techniques and measurements (arterial blood sampling, 24-hr urinary excretion rates, and net uptake/release of catecholamines from the leg), we have documented the sympathoadrenal responses over time while at high altitude both at rest and during submaximal exercise. Via interaction with their specific adrenergic receptors (Table 1), the catecholamines play an important regulatory role in adjusting to a variety of stressors. We have examined the physiologic and metabolic implications of these responses during altitude exposure under a variety of conditions (rest, exercise), subjects (men, women) and treatments (α- or β-adrenergic blockade). Finally, the potential mechanisms responsible for the dissociation of the adrenal medullary response from that of the sympathetic nervous system will be addressed in this review. Taken together, the results clearly indicate that the sympathoadrenal pathways play an essential role in the adaptations necessary to adjust to the stress imposed during high-altitude exposure.

Acute High-Altitude Exposure

Rest: Upon acute exposure to 4,300 m, homeostasis is immediately disrupted due to the reduction in P_IO_2 resulting in P_aO_2 levels well below normal (S_aO_2 ~ 80% and P_aO_2 ~ 40 torr). In an attempt to preserve O_2 delivery to essential tissues, a number of physiological adjustments are made initially in response to the stress of acute hypoxia. The sympathoadrenal

pathways play a critical role in adjusting to this perturbation in homeostasis. Specifically, we have demonstrated that upon acute exposure (within 4 hrs of arrival) arterial concentrations of epinephrine are significantly elevated at rest when compared to sea level values (~80-100%). Hypoxia has been shown to directly stimulate adrenal medullary epinephrine release resulting in increased arterial concentrations. The extent of this response is dependent upon the degree and severity of hypoxia with the decline in arterial oxygen content acting as the primary stimulus. This immediate adrenal medullary response is further supported when examining the 24-hr urinary excretion rates for epinephrine. This marker of daily adrenal activity indicates that urinary epinephrine excretion increases dramatically upon acute exposure to high altitude reaching a peak on days 2-4, then returns to sea level values after the first week of acclimatization . Arterial oxygen saturation falls to a nadir on arrival at high altitude and improves with subsequent ventilatory acclimatization (S_aO_2 ~ 88% and P_aO_2 ~ 50 torr after 1 week). As the degree of hypoxia lessens during acclimatization epinephrine levels fall. An inverse relationship between S_aO_2 and arterial epinephrine concentration becomes apparent (r= 0.73, 21 days at 4,300 m).

The epinephrine response to acute high-altitude exposure is primarily mediated via the β-adrenergic receptors and contributes immediately to improve oxygen delivery. Resulting are increases in heart rate, stroke volume (thus, increasing cardiac output), tissue vasodilation and bronchodilation) all promoting increased O_2 delivery to tissues. Further, epinephrine is well known to activate both muscle and liver glycogenolysis thereby enhancing carbohydrate utilization as well as lactate production. A greater utilization of carbohydrates is a more economical use of O_2 as more energy is derived per liter of O_2 consumed from carbohydrates (5.05 kcal/l) vs. that from fat (4.68 kcal/l). Thus, optimizing the energy yield per unit of O_2 would be beneficial during times of limited O_2 availability such as hypoxia. Additionally, the increase in β-adrenergic stimulation contributes to the elevation in metabolic rate associated with acute high-altitude exposure.

The norepinephrine response to hypoxia is somewhat different than that observed for epinephrine. Most studies indicate that when compared to sea level values, resting plasma norepinephrine levels do not change significantly with acute hypoxia. However, while resting plasma norepinephrine remain unchanged, muscle sympathetic nerve activity has been shown to increase while breathing 8-12% O_2 as well as during acute hypobaric hypoxia simulating 4,000-6000 m. In support of this, we have been able to demonstrate that within 4 hours after arrival to 4,300 m, there was a significant increase in norepinephrine

release from the resting legs compared to values measured at sea level. This occurred despite the fact that plasma norepinephrine levels remained unchanged. Thus, increases in SNS activity likely occurs to a variety of vascular beds during acute hypoxia, however, such activity cannot generally be detected by measurement of plasma norepinephrine content alone.

Plasma levels of norepinephrine are a function of the rate of spillover into the circulation (approximately 10-20% of the norepinephrine released by sympathetic nerves under resting conditions), a small amount secreted by the adrenal medulla and, the rate of its removal or clearance from the plasma pool. There appears to be no direct effects of hypoxia on enhancing the prejunctional release of neuronal norepinephrine nor on intraneuronal metabolism and uptake of the neurotransmitter in muscle suggesting that the enhanced spillover observed in our studies is directly related to an increase in sympathetic activity. No change or an increase in clearance of plasma norepinephrine has been reported during acute hypoxia. An increase in clearance would actually tend to lower plasma levels and therefore would not explain the increases associated with altitude. However, no studies exist which have examined the effect of chronic high-altitude exposure on plasma clearance of norepinephrine.

Exercise: The sympathoadrenal response to exercise generally follows the pattern described above for resting conditions. The added stress of exercise (in addition to hypoxia) results in accentuated catecholamine levels for a given submaximal workload. The magnitude of the epinephrine response is dependent upon both the exercise intensity as well as the degree of hypoxia. We have shown that exercise at altitude at the same absolute workload (100 watts), representing 50 and 65% VO_2max at sea level and 4,300 m, respectively, elicits significant increases in arterial epinephrine levels. Epinephrine values increase linearly over time during the 45-minute submaximal exercise with acute high altitude exposure while values for both sea level and chronic altitude exposure remained stable throughout the submaximal work bout. When the absolute workload is adjusted such that subjects are exercising at similar relative workloads (same % VO_2max) during both normoxic and hypoxic conditions, increased plasma epinephrine levels are still found to persist during acute hypoxia. Thus, it appears that an additive effect exists such that the stress imposed by hypoxia (directly effecting adrenal activity) and exercise (primarily an SNS stimulation of adrenal activity) yield greater epinephrine levels than that found for just each stressor alone.

During exercise, acute hypoxia results in elevated levels of plasma

norepinephrine compared to sea level. When individuals exercise at the same absolute workloads achieving steady-state VO_2, we have shown that norepinephrine levels are significantly elevated with acute hypoxia compared sea level. However, it appears that the norepinephrine response during acute hypoxia is primarily dependent upon the relative work intensity. Thus, if subjects work at a similar percentage of VO_2max under both conditions, the norepinephrine response is not significantly different between sea level and acute hypoxia.

Acclimatization to High-Altitude

Rest: During acclimatization, arterial epinephrine levels decline toward sea level values. As noted above, resting epinephrine concentrations fall as arterial oxygenation increases suggesting that concentrations are likely related to increases in oxygen carrying capacity and reduction in the severity of hypoxemia. This decline in circulating epinephrine levels, in conjunction with the documented down-regulation of β-receptors in the heart, contributes to the reduction in resting heart rate observed over time at altitude. The combination of a waning β-stimulation and decreased receptor sensitivity likely play a role in the decline in resting cardiac output over time at altitude to sea level values.

The norepinephrine response, however, as measured by both arterial and urinary levels, reacts in a very different manner than that observed for epinephrine. While plasma norepinephrine levels during acute exposure are similar to those found for sea level, concentrations rise significantly with time during the acclimatization period (70-100%). Furthermore, urinary norepinephrine gradually increases reaching a plateau on days 6-7 and staying elevated throughout the remaining 21 days at 4,300 m. This increase in SNS activity with chronic altitude exposure is further supported by measurements of net norepinephrine release across resting muscle. A dramatic reversal from net norepinephrine uptake by resting leg at sea level to that of net release after chronic exposure clearly reflects enhanced sympathetic nerve activity. This indicates that spillover from sympathetic nerves directed to skeletal muscle is a major contributor to the elevation observed in resting plasma norepinephrine with prolonged exposure to hypoxia. The Pikes Peak studies are the first to examine the effect of chronic hypoxia on skeletal muscle SNS activity, and to demonstrate a dissociation of sympathetic nerve activity (increasing) and adrenal medullary responses (decreasing) over time at high altitude.

The mechanisms responsible for the increase in sympathetic activity that occur over time at altitude, however, remain to be determined. A direct effect of hypoxia on sympathetic nerve activity is not likely because sympathetic activity continues to increase with time at altitude while the degree of hypoxemia is decreasing. We have found a high correlation between the decline in plasma volume with the rise in norepinephrine over time at altitude ($r = -0.89$). A reduction in blood or plasma volume is known to activate the sympathetics (via baroreceptor activity) in an attempt to maintain arterial pressure. However, a baroreceptor-mediated increase in sympathetic activity is unlikely as blood pressure is significantly elevated during acclimatization. The declining plasma volume with rising norepinephrine levels is probably a result, rather than a cause, of the increase in sympathetic activity. End-tidal CO_2 pressure ($P_{ET}CO_2$) is inversely ($r=-0.90$, $p<0.001$) and minute ventilation (V_E) is positively correlated with norepinephrine excretion rates ($r=0.68$, $p<0.01$). This is compatible with the concept that ventilatory parameters are partially responsible for activating sympathetic nerve activity. Interactions between ventilatory drive and sympathetic nerve activity during acute stimulation (hypoxia) of both peripheral and central chemoreceptors has been documented. Furthermore, reticulospinal neurons, acting as central oxygen sensors, are directly excited by hypoxia resulting in an initiation of sympathetic activity and circulatory adjustments. Increasing drive from chemoreceptors, as well as altered sensitivity, over time at altitude is potentially responsible for both the ventilatory and sympathetic adaptations during acclimatization. These mechanisms likely act to protect the brain from sustained hypoxia.

Sympathetic neural release of norepinephrine is known to produce vasoconstriction via the α-adrenergic receptors resulting in an increase in vascular resistance. As a result, systemic vascular resistance is found to increase over time while at 4,300 m following a pattern very similar to that found for sympathetic nerve activity. This increase in vascular resistance translates into elevations in systemic arterial blood pressure over time at altitude, both of which appear to be directly related to the increase in sympathetic nerve activity. Additionally, our studies utilizing α-adrenergic blockade indicate that the changes in sympathetic nerve activity also play a role in the alterations in both substrate utilization as well as immune function during chronic altitude exposure. Our recent finding that the sympathetics via α-adrenergic mechanisms are responsible for the continued elevation in interluekin-6 while at altitude has implications for not only immune function but also the well-documented finding of cachexia associated with high-altitude exposure. Thus,

alterations in sympathetic nerve activity have significant implications to both the physiologic and metabolic adjustments associated with acclimatization.

Exercise: After acclimatization, the adrenal medullary responsiveness during exercise has a pattern similar to that found at rest. Compared to arrival, arterial epinephrine levels are dramatically reduced returning toward sea level values, despite exercising at similar absolute as well as relative workloads. Similar findings have been reported by others confirming this acclimatization in adrenal medullary function during exercise. As at rest, it would appear that the improved arterial oxygen saturation associated with acclimatization is responsible for this adaptation during exercise.

Compared to sea level and arrival at altitude, arterial norepinephrine levels and systemic vascular resistance are elevated throughout the duration of submaximal exercise, no matter whether the exercise was conducted at the same absolute or relative intensity. Similar increases are found for systemic vascular resistance during exercise. These findings are consistent with the chronic elevation in sympathetic nerve activity demonstrated under resting conditions.

Immune response to acute hypoxia

Regardless of the mechanism, it appears clear that acute exposure to altitude/hypoxia results in alterations of specific components of the immune system. Most prominent is the redistribution of T-lymphocytes with a notable reduction in $CD4^+$ T-cell numbers as well as an impairment in T-cell activation and proliferation. Further, acute exposure to hypoxia has been reported to result in significant lymphopenia and neutrophilia that is quite similar to that observed in response to a single bout of exercise. B-lymphocyte number and function appear to be unaltered by altitude. In total, these studies indicate the short-term hypoxic exposure results in physiological responses known to mediate immune cell trafficking and function.

Several studies have demonstrated that acute hypoxia results in increases in natural killer (NK) cell numbers and activity. This finding of enhanced NK cell number and activity appears to be transient as levels return to normal with more prolonged exposure to hypoxia. A potential mechanistic role involving the sympathoadrenal pathways was suggested. In support of this, epinephrine infusion can mimic the effect of hypoxia on NK cells while β-adrenergic blockade abolishes the increase in NK cell number.

Recently, more attention has been directed toward examining the influence

of hypoxia on inflammatory cytokines. Upregulation of circulating IL-6, IL-1ra and CRP have been observed during short-term high altitude exposure and a role for these inflammatory cytokines in the development of high-altitude pulmonary edema (HAPE) has been suggested.

It is now evident that the environmental stress of altitude/hypoxia exposure alone is sufficient to cause an elevation in circulating IL-6 even under resting conditions (independent of exercise stress). In cultured endothelial cells from mice acutely exposed to hypoxia, expression of IL-6 is dramatically increased. Similar results were reported in cultured rat neonatal cardiac myocytes after 4 hours of hypoxia. Klausen et al. examined the influence of acute hypoxia in humans and found serum IL-6 levels to be significantly increased while other proinflammatory cytokines remained unchanged. As indicated in, studies from the summit of Pikes Peak indicate that resting IL-6 levels increase immediately upon arrival to altitude and remain elevated for several weeks while residing at 4300 m. Thus, both acute and chronic altitude exposure results in elevated resting IL-6 levels in humans. These results are consistent with observation that the elevation in IL-6 persists while subjects are becoming acclimatized to high-altitude exposure.

It is known that the catecholamines can act as a potent stimulator for IL-6 production and release into plasma, however, this effect has generally been thought to result from activation of the β-adrenergic pathways. Infusion of epinephrine has been reported to induce a dose-dependent increase in plasma IL-6 concentrations in the rat. Importantly, this epinephrine-induced increase in plasma IL-6 was blocked by the beta-adrenergic receptor antagonist propranolol. A separate study in rats found similar results with propranolol but also demonstrated that isoprenalin, a beta-2 adrenergic agonist, also elicited very high levels of plasma IL-6, indicating that the release of IL-6 can be mediated via the beta-2 adrenergic receptors. β-adrenergic stimulation of IL-6 production upon initial exposure to high altitude is consistent with the rapid increase in both epinephrine and IL-6 levels associated with acute hypoxia.

However, the fact that resting IL-6 levels remain elevated over time at altitude while epinephrine levels return toward sea level values suggest that other mechanisms must be responsible to the sustained increase in IL-6. Recent evidence indicates that the SNS, via norepinephrine acting on the α-adrenergic receptors, is a primary factor responsible to the sustained elevation in IL-6 levels over time at altitude. In the presence of α-adrenergic blockade (prazosin), the sustained increase in resting IL-6 levels is completely abolished. Thus, while resting IL-6 levels remained elevated throughout the 12 days duration at altitude

for the group receiving the placebo, IL-6 levels returned to sea level values by day 3 and remained there throughout the remainder of stay at altitude in subjects receiving a-adrenergic blockade. Thus, the presence of α-adrenergic blockade clearly influenced the IL-6 response to the chronic stress of hypoxia. The sustained elevation in IL-6 throughout the duration at altitude followed a similar pattern to that found for the increase in urinary norepinephrine excretion. Urinary norepinephrine excretion (a marker of overall sympathetic nerve activity) continued to increase steadily during days at altitude peaking at days 4-6. As norepinephrine has a strong affinity for the α-adrenergic receptors, this is a potential mechanism likely to contribute to the continued elevation in plasma IL-6 levels over time at altitude, particularly in the face of declining β-adrenergic stimulation. This is supported by a significant correlation ($p=0.004$) between resting IL-6 and urinary norepinephrine excretion rates for subjects over the course of time while at altitude. Other studies have reported a similar relationship between peak plasma norepinephrine and IL-6 levels during high-intensity exercise in humans.

The physiological significance of the IL-6 response to hypoxia remains unknown, however, a number of possibilities have been suggested. It has been suggested that IL-6 can promote angiogenesis and may play a role via the induction of vascular endothelial growth factor (VEGF). Treatment of various cell lines with IL-6 for 6-48 h results in a significant induction of VEGF mRNA that is comparable to the documented induction of VEGF mRNA by hypoxia. Additionally, IL-6 can modulate production of erythropoietin (EPO) as the addition of IL-6 to hypoxic human hepatoma cells resulted in a dose-dependent stimulation of hypoxia-induced (EPO) production by as much as 81%. The associated increases in red blood cell number and oxygen carrying capacity are well-documented markers of adaptation to high altitude.

Exercise at altitude: an added stressor

There have been numerous studies documenting the effect of a single bout of exercise on immune function. Generally, depending upon the exercise intensity, duration and training status of the individual, exercise has been shown to be a physical stressor that can transiently affect immune function. However, there have been only a few studies that have examined the effect of exercise while at altitude on immune function. It is likely that, even when controlling for the relative exercise intensity (as VO_2max and maximal performance capacity declines with ascending altitude), hypoxia represents an added stressor to that

imposed by exercise alone. Klokker et al. have shown that the combined effect of exercise and hypoxia result in a more dramatic effect on the NK cell response when compared to exercise in normoxic conditions. It was suggested that hypoxic exercise induces a more pronounced immunological stress response than exercise under sea level conditions.

Recently, it has been demonstrated that when exercise is performed at the same relative metabolic stress (as indicated by similar blood lactate levels), exercise performed at altitude (1800 m) resulted in greater sympathetic activation compared to sea level. A greater exercise-induced increase in IL-6 levels were also reported which correlated with the increase in circulating epinephrine and norepinephrine. These findings are consistent with the concept of an exacerbated immunological stress response when exercise and hypoxia are combined. Several studies have identified skeletal muscle as a potential source of circulating IL-6 during exercise and this is also likely to be the case with exercise at altitude.

Similar findings were observed during submaximal exercise under conditions of both acute and chronic altitude exposure (4300 m). IL-6 levels were elevated during exercise with acute altitude exposure, likely due to the exaggerated epinephrine response associated with initial exposure to hypoxia. As described above, this appears to be mediated primarily via β-adrenergic stimulation as α-adrenergic blockade had no effect in reducing the exercise-induced increase in IL-6 during acute hypoxia. However, after these subjects had acclimatized for 12 days, α-adrenergic blockade significantly lowered IL-6 levels similar to those found at sea level. The group receiving the placebo still demonstrated elevated IL-6 levels during exercise suggesting a strong α-adrenergic component with more prolonged residence at high altitude.

Taken together, these studies suggest an additive effect of the physical stress imposed by exercise with that of hypoxic stress. This results in a more pronounced sympathoadrenal response which has implications for immune function.

Training at altitude

A number of studies have reported the benefits of altitude training for the endurance athlete with regard to improving sea level performance. Recently, it has been proposed that the ideal approach to maximize these benefits associated with acclimatization to altitude is the live high-train low model. This design calls for altitude exposure of at least 12-16 h/day for 3-4 weeks to elicit the desired adaptations (erythropoietin, red blood cell volume, etc) while

returning to a lower altitude for training. Training at altitude for sea level performance is not optimal as it impairs training quality (training velocity and absolute intensity) since VO_2max and maximal performance capacity are reduced at altitude.

Logistically, these studies are difficult to perform do to geographic limitations. Additionally, the use of hypobaric chambers is not ideal as it can lead to a disruption in sleep and eating patterns adversely affecting training, performance and immune function. Thus, to date, only one study has examined the effect of live high-train low on immune function. Tiollier et al. examined the effect of live high-train low on mucosal immunity. Highly trained cross-country skiers participated in an 18-day live high-train low training camp. The control group lived and trained at 1200 m while the live high-train low group trained at 1200 m but lived for 11 h/day in hypoxic rooms simulating an altitude of 2500, 3000 and 3500 m (six days at each altitude). Results indicated the salivary IgA concentrations decreased significantly over time in the live high-train low group but not in the control subjects. The findings suggested a cumulative adverse effect of exercise training and hypoxia on mucosal immunity over time at altitude.

When athletes live and train at altitude, the influence of hypoxia on altering immune function is evident. Pyne et al. found that when members of the Australian Olympic swimming team were exposed to a 21-day training camp at 2100 m, leukocyte numbers and ConA-induced blastogenesis was reduced 38 and 32%, respectively when compared to sea level values.

Finally, it is worth noting that some studies have provided support for training high while living at low altitude. When previously untrained individuals underwent 6 weeks of altitude training at 3850 m but lived at low altitude the remainder of the day, a significant upregulation of hypoxia inducible factor 1 (HIF-1alpha mRNA) was observed. No such training effect was found in subjects training under similar condition in normoxia. The combination of intense endurance training and hypoxia resulted in increases in VEGF mRNA and myoglobin mRNA suggesting hypoxic training improves various components associated with the transfer and utilization of oxygen. Impact of the train high-live low paradigm on immune function has not been investigated. Clearly, more studies need to be conducted to determine the extent to which these various training models involving altitude/hypoxia influence immune function and whether the actual susceptibility and incidence of illness is affected.

Conclusions

It is clear that hypoxia and exercise are two independent stressors that can influence immune function. Initial exposure to hypoxia is a sufficient stressor that can elicit a neuroendocrine response that may alter immune function. While many components of the immune system are likely affected, alterations in T cell-mediated immunity are found to be the most consistent and robust. An acute bout of exercise is an added stressor at altitude that can exacerbate immune suppression, most likely through sympathoadrenal mediated pathways. An increased risk of infection is more likely during initial exposure to high altitude. As such, it would be advisable to allow athletes approximately one week to begin the acclimatization process before engaging in intense exercise training. With acclimatization, the hypoxic stress is lessened as C_aO_2 levels increase over time and adrenal medullary release of epinephrine returns towards sea level values. Consequently, T cell function approaches sea level values and the risk of infection wanes. Thus, the LHTL paradigm can be beneficial for endurance athletes and, when approached properly, should have minimal effects on immune function and illness.

Future studies are warranted and should focus on elucidating the precise mechanisms responsible for alterations in immune function during hypoxic exposure. Additionally, there is a lack of information on the time course of these immunological changes as well as the extent to which the degree of hypoxia (or altitude elevation) influence these responses. Lastly, it is important to determine the clinical significance of these hypoxia-related changes in immune function and the extent to which the risk for infection is increased.

Considerations

Finally, a number of factors must be considered when discussing the interaction of altitude exposure and exercise on immune function. First, the altitude elevation or extent of the hypoxia is a primary factor that influences the degree of physiological stress, hormonal adjustments and immunological adaptations associated with exposure. Further, there is a minimum or threshold elevation that would be required to achieve the benefits associated with high altitude living while too high of an altitude could potentially have negative effects (sleep disruption, muscle loss) on not only immune function but performance as well. Second, the duration of stay and/or time spent at altitude will significantly impact both the extent and time course of key physiologic and

metabolic adaptations associated with the acclimatization process. Additionally, it is clear that, for a given altitude, there is inter-individual variability regarding the extent of these adaptations (e.g. - red cell volume, EPO, susceptibility to altitude sickness) as well as how the hypoxic stress is perceived by the body (differences in sympathoadrenal responses). Lastly, the potential benefits from the live high:train low paradigm are going to be event and training specific and will not necessarily result in improved performance.

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