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REVIEW

Respiratory inflammation and infections in high-performance athletes

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Upper respiratory illness is the most common reason for non-injury-related presentation to a sports medicine clinic, accounting for 35–65% of illness presentations. Recurrent or persistent respiratory illness can have a negative impact on health and performance of athletes undertaking high levels of strenuous exercise. The cause of upper respiratory symptoms (URS) in athletes can be uncertain but the majority of cases are related to common respiratory viruses, viral reactivation, allergic responses to aeroallergens and exercise-related trauma to the integrity of respiratory epithelial membranes. Bacterial respiratory infections are uncommon in athletes. Undiagnosed or inappropriately treated asthma and/or allergy are common findings in clinical assessments of elite athletes experiencing recurrent URS. High-performance athletes with recurrent episodes of URS should undergo a thorough clinical assessment to exclude underlying treatable conditions of respiratory inflammation. Identifying athletes at risk of recurrent URS is important in order to prescribe preventative clinical, training and lifestyle strategies. Monitoring secretion rates and falling concentrations of salivary IgA can identify athletes at risk of URS. Therapeutic interventions are limited by the uncertainty of the underlying cause of inflammation. Topical anti-inflammatory sprays can be beneficial for some athletes. Dietary supplementation with bovine colostrum, probiotics and selected antioxidants can reduce the incidence or severity of URS in some athletes. Preliminary studies on athletes prone to URS indicate a genetic predisposition to a pro-inflammatory response and a dysregulated anti-inflammatory cytokine response to intense exercise as a possible mechanism of respiratory inflammation. This review focuses on respiratory infections and inflammation in elite/professional athletes.
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Common, recurrent and/or persistent respiratory illness can have a negative impact on health and performance of athletes undertaking high levels of strenuous exercise. Upper respiratory illness is the most common reason for non-injury-related presentations to sports medicine clinics, accounting for 35–65% of illness presentations.[1–7] In Olympic[5–8] and international competitions[3,4] upper respiratory illness interfered with training and ability to compete in up to 10% of athletes. These occurrences have led to the perception that respiratory tract infections are common in elite athletes, however, evidence to support this assertion is inconclusive and appears sport specific.[9,10] Nonetheless, athletes presenting with an illness may experience decrements in performance, sometimes after many years of hard training. Although transient exercise-induced immune suppression can increase susceptibility to infection,[11] not all episodes have an infective aetiology[12–14] and susceptibility is influenced by other lifestyle and environmental factors.[10,15,16] The impact of the intensity of exercise on upper respiratory symptoms (URS) varies between sports[10,11,15–17] with evidence that URS can impair swimming performance.[18] High training volumes necessary to compete successfully at international levels can only be achieved if the athlete experiences few days of sickness.[19] Gender differences have also been reported in athletes with women experiencing more URS episodes.[10,20,21]

Common symptoms of an upper respiratory illness include a sore throat, headache, fatigue, runny nose and/or watery eyes. The underlying aetiology of a sore throat is complex and often management is left to symptomatic relief rather than therapeutic intervention. The major reasons for investigating a sore throat in an athlete are to exclude a serious viral infection, treat bacterial and fungal infections, and identify and treat other non-infectious causes of the symptoms. Pathology investigations to identify upper respiratory tract infections (URTI) associated with exercise in athletes are limited (Table 1)[8,12–14] and debate on whether sore throats are actually caused by infections, or simply a reflection of other inflammatory stimuli, remains unclear.[12,14,22,23]

Non-infective inflammatory causes of URS include allergic responses to aeroallergens, asthma and trauma to respiratory epithelial membranes, particularly in athletes who experience drying of the

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Table 1 Pathogens identified in studies of athletes presenting with symptoms of upper respiratory infections and the number of cases identified

Pathogen identified by microbial and viral investigations	*Tri-athletes undertaking routine training and competitions*[13] *(n = 63)*	*Elite athletes presenting to a sports clinic*[14] *(n = 70)*	*Elite athletes with persistent fatigue and poor performance*[12] *(n = 41)*	*Olympic athletes presenting with persistent fatigue and poor performance*[8] *(n = 19)*
Rhinovirus	7	6	—	?
Influenzae (A and B)	7	1	—	?
Parainfluenzae (1, 2 and 3)	4	3	—	—
Adenovirus	0	2	—	1
Coronavirus	2	0	—	?
Metapneumovirus	1	0	—	?
EBV (primary infection)	1	1	3	5
EBV reactivation	—	1	8	—
CMV	0	0	5	?
HSV types 1 and 2	0	—	0	?
Ross River virus	—	—	1	?
Toxoplasmosis	—	—	1	0
Mycoplasma pneumoniae	0	1	1	1
Streptococcus pneumonia	2	1	—	2
Staphylococcus pyogenes	0	1	—	?
Haemophilus influenzae	0	0	—	?
Moraxella catarrhalis	0	0	—	?
Enterococcus spp	0	0	—	1
Parvovirus	—	—	—	1
Coxsackie B1-5	—	—	—	0

Abbreviations: CMV, cytomegalovirus; EBV, Epstein Barr virus; HSV, Herpes simplex virus.
The symbol (—) in table indicates where the pathogen was not assessed in the study and (?) indicates where the study did not specify if the pathogen was included in the testing regime.

airways because of increased expired ventilation or cold-air exposure. Another source of inflammation is viral reactivation. Regardless of the underlying cause of the URS, a major concern for the athlete is the accompanying fatigue that can limit or prevent training[8,12] and impair performance.[18] Identifying athletes at risk of recurrent URS is important in order to adopt preventative clinical, training and lifestyle strategies.

Studies have examined the effectiveness of various biomarkers to identify athletes at risk of URS, based on the premise that transient immune alterations after exercise provide a window of opportunity for infections. The only consistent biomarker for identifying and monitoring athletes at risk of URS is measurement of the concentration or excretion rates of salivary IgA.[11] Secretory IgA is an important component of protection against infections at mucosal surfaces, together with integrity of the epithelial barrier and regulatory T-lymphoid cells. Low levels of salivary IgA and a decline over a training period have identified athletes at risk of URS. Until recently, the use of salivary IgA as a biomarker has been limited because of time-consuming laboratory assays and delays in obtaining timely results. The availability of point-of-care detection systems for salivary IgA[24] pave the way for more systematic monitoring of immune status in athletes.

RESPIRATORY ILLNESS IN ATHLETES

Although athletes have a similar distribution of URTI episodes to the general population,[9] the association with seasonal variation does not always hold true for the competitive athlete, with the influence of training and competition schedules masking seasonal differences. However, a recent 4-year prospective study identified a higher incidence of URS in elite swimmers during winter.[16] A small proportion (5–7%) of athletes experience recurrent episodes of URS at significantly higher rates than the incidence in the general population.[9,25] In these athletes the URS can be associated with fatigue and poor performance.[12,26,27] Increased risk of URS is more likely during periods of intense training[10,16] and competition,[3] in swimmers,[16,25] whereas in other sports such as distance runners they appear more frequently after a competition.[28] Studies of illness-prone athletes indicate higher susceptibility to URS following increases in training load.[10,16,23,27] However, a study of distance runners showed no clear association of training mileage, intensity or load with the incidence of respiratory illness.[17] Although fitter adults are less likely to experience URS than sedentary individuals,[29] this paradigm does not hold true for elite athletes who experience recurrent URS.[26,27] There appears to be a threshold of training load that puts athletes at increased risk of URS. Longitudinal studies have identified the impacts of intense training over both short (months)[30–33] and long (years)[16] periods (Table 2).

RESPIRATORY INFLAMMATION

The known causes of inflammation in the respiratory tract in athletes include immune activation in response to local infections, allergic responses to inhaled allergens, asthma and trauma to the respiratory epithelium predominantly disruption of mucosal membrane integrity. An athlete typically presents with common symptomology, and the associated inflammation may be difficult to differentiate without physician assessment and supportive pathology evidence or other clinical investigations.[12,14] Despite a combination of clinical and laboratory investigations a substantial proportion of presentations are classified as 'unidentified' aetiology.

There is good evidence for the impact of inhaled allergens in susceptible athletes.[34–36] Several clinical studies have identified a prevalence of 20–40% for aeroallergen sensitivity in athletes[12,14] resulting in allergic rhinoconjunctivitis. Two studies of Olympic athletes[35,36] identified a 40–50% prevalence of allergic rhinoconjunctivitis confirmed by a positive skin-prick test to at least one aeroallergen, with 29–34% positive for seasonal aeroallergens (mainly

pollens). A study of French commandos undertaking intense training identified that 40% of illnesses were associated with rhinopharyngitis[23]. Allergy as a cause for URS is often overlooked and was under-diagnosed in 39% of athletes with confirmed IgE antibodies to areoallergens.[14] Treatment of airway allergic conditions with topical medications can benefit athletes with a history of URS (Table 2).[37,38]

Airway inflammation associated with asthma might also be a cause of URS in athletes. Clinical investigation of athletes with recurrent URS and fatigue identified newly diagnosed or poorly controlled asthma in 13% of athletes and upper airway dysfunction in another 5%.[12] Poor application of medications to control allergy was also reported in 50% of endurance athletes with clinically confirmed allergic rhinitis.[39] The correct clinical diagnosis of the underlying cause of inflammation in the airways, and appropriate management of medical conditions, is important to assist athletes avoid recurrent episodes that interfere with training and competitive performance.[12,36]

Changes in the integrity of epithelial membranes can occur in a variety of sports[34] in response to environmental irritants, climatic conditions and hyperventilation causing airway drying.[40,41] An increase in inflammatory cells (neutrophilia) in the airways is not always associated with markers of neutrophil activation, symptoms of asthma or increased airway hyperresponsiveness.[42] A study comparing airway hyper-reactivity and eosinophilia revealed that despite increased airway responsiveness in swimmers this was not associated with increased eosinophila.[43] Although eosinophilic airway inflammation was present in both pool- and land-based athletes it was accompanied by increased numbers of epithelial cells in the sputum suggesting damage to the airway lining. It is clear that immune and epithelial cell distribution can be altered during exercise-induced airway inflammation.

Changes in membrane integrity and migration of inflammatory cells into the airways may explain the higher prevalence of URS in endurance sports.[10,15] Similarly, the highly strenuous nature of football,[44] hockey and basketball might also exacerbate airway disturbance. It is possible that the attenuated immune response following exercise is a stress response in preparation for immune defence. In the absence of an infection or allergen an adaptive response may explain the substantial proportion of episodes of URS in athletes with an unknown aetiology.[14]

The underlying mechanism of inflammation in the airways is most likely a local immune response rather than the effect of muscle-derived inflammatory cytokines associated with the metabolic stress of intense exercise.[45] There is currently no evidence for systemic circulation of pro-inflammatory cytokines to distant mucosal sites. An evaluation of IL-6, a commonly used marker of inflammation following intense exercise, showed no correlation between IL-6 in plasma and saliva in distance runners in response to intense exercise,[46] indicating non-systemic mechanisms for control of inflammation in the respiratory tract. The rapid (within minutes) changes in salivary IgA and other innate and adaptive immune parameters in the respiratory tract in response to exercise support a local control mechanism.

RESPIRATORY INFECTIONS

Until recently, physician confirmation of an infective cause of upper respiratory illness, based on clinical signs and symptoms, was the 'gold standard' for clinical practice and exercise immunology studies. However, physicians are rarely involved in assessments in research settings particularly large sample field-based events such as a marathon race. Physician-verified diagnosis of URTI has limitations, with one study showing only 57% of the suspected viral URTI episodes confirmed by pathogen identification (30%) or other laboratory investigations suggestive of infection (27%).[14] In addition, the physicians in this study failed to identify allergic rhinoconjunctivitis, confirmed by aeroallergen serology, as a cause of the symptoms in 39% of athletes. In assessment of elite athletes, URS should not be assumed to be infective unless confirmed and all other potential differential clinical conditions excluded.

Various factors influence inflammation and infections in the respiratory tract in high-performance athletes (Figure 1). Approximately one-third of sore throats are attributable to an identifiable pathogen.[13] The distribution of pathogens is similar to those identified for respiratory infections in the general population, with common respiratory viruses accounting for the majority (30–55%) of cases (Table 1). Bacterial infections are rare in athletes accounting for $<5\%$

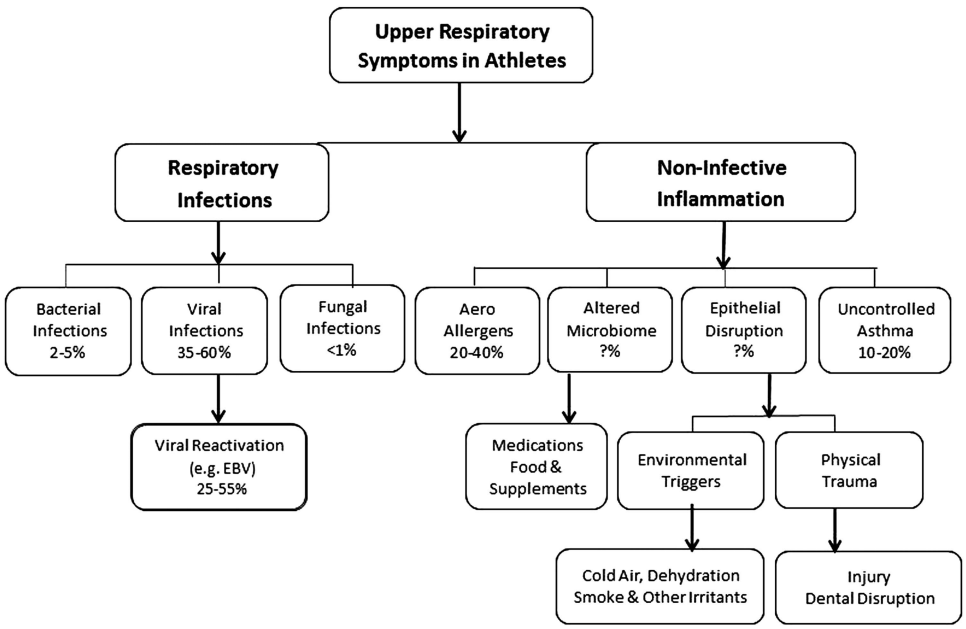

Figure 1 Factors influencing infections and inflammation in the respiratory tract in high-performance athletes.

of URTI cases and can usually be identified by differential clinical symptoms. A study of throat swabs collected monthly from elite swimmers over a 9-month period indicated there was no difference in the quantitative carriage rates for common respiratory pathogens, or any significant changes during infective periods.[47]

Another cause of a sore throat is infection with the Epstein Barr virus (EBV) as infectious mononucleosis is a common presentation in elite athletes (Table 1). Viral reactivation of EBV is also a common finding (22–50%) in athletes experiencing recurrent URS and associated fatigue.[48–50] Transient reactivation may account for the relatively short duration of the symptoms (2–4 days) elicited via viral reactivation rather than primary infection *per se*. However, in a study of antiviral treatment in runners, not all episodes of URS were associated with EBV expression,[49] and the frequency of EBV expression differs substantially between sports. Although an anti-herpes virus treatment was effective in reducing EBV expression in the long-distance runners it did not reduce the frequency of episodes of URS, indicating other causes for the URS. In studies of swimmers[48] and footballers[50] expression of EBV DNA in saliva was associated with a prior reduction in salivary IgA levels and increased detection of URS. Saliva samples from swimmers were also examined for expression of other herpes group viruses but did not exhibit viral DNA for Cytomegalovirus or HSV1 or HSV2.[48] IgA has a major role in controlling viral reactivation and low levels before the appearance of EBV viral DNA indicates that salivary IgA could be used as a surrogate marker for increased risk of viral reactivation. Considering EBV viral reactivation as a cause of URS is important as it can be controlled either therapeutically or by altering training loads to prevent IgA suppression and reactivation.

MUCOSAL IMMUNE PROTECTION

The mucosal immune system at external body surfaces has a key role as a first line of defence, employing both innate and acquired mechanisms for protection and modulation against adverse responses. A recent review of the mucosal immune system structure, development and control,[51] highlighted the complex interactions at external surfaces for protection while avoiding overstimulation to maintain integrity of the mucosal barrier.[52] Effective protection against pathogens relies on functional interactions between epithelial cells, lymphocytes and dendritic cells. Maintenance of the mucosal epithelium is critical to these interactions as well as acting as an exclusion barrier. The immune response at mucosal surfaces is predominantly anti-inflammatory to prevent local tissue damage. The epithelial cells produce cytokines that direct the B cells towards synthesis of IgA antibodies, which unlike IgG antibodies, has non-inflammatory interactions with antigens. However, mucosal immune lymphoid tissue in the bronchial tracts and nasal passages can induce IgG antibody responses promoting B-cell migration to the bone marrow and interferon (IFN)-γ-producing T cells in response to infections, as well as IgE isotype switching in response to allergens in the presence of Th2-inducing conditions.

The epithelium has important roles in assembly of secretory IgA (S-IgA) and transport to the mucosal surface, elimination of infections bound to S-IgA that have crossed the mucosal barrier, and processing and presentation of antigens to the adjacent T cells. The subset of T helper (Th) cells at mucosal surfaces, known as Th17, produce cytokines (IL-17 and IL-22) that facilitate transport of S-IgA by enhancing production of the polymeric immunoglobulin receptor (pIgR) in epithelial cells. Th17 cells upregulate innate antimicrobial proteins and peptides, recruit neutrophils through chemokine activation, and promote epithelial repair. Virus-specific cytotoxic T cells can be rapidly reactivated to provide immediate responses against infections, especially EBV-infected epithelial cells. EBV establishes latency in B cells of the bronchus-associated lymphoid tissue and viral reactivation can be stimulated in a bystander manner by environmental antigens inducing bronchus-associated lymphoid tissue reactivity.[53]

The majority of studies in exercise science use salivary IgA concentration or its excretion rate to monitor the impact of exercise on mucosal protection and associations with URS. The consensus[11] of studies of elite athletes in different sports is that low levels of salivary IgA and/or secretion rates,[25,28] low pre-season salivary IgA levels[54,55] and declining levels over a training period[25,56] are associated with an increased risk of URS. However, several studies have reported no clear association between salivary IgA levels and URS.[57,58] Divergent outcomes may relate to variations in methodology, as more recent studies[32,33,56,59] reported a decline in salivary IgA levels and/or secretion rates before the appearance of symptoms, and lower levels of IgA associated with an increased risk of URS. Low concentrations of both IgA1 and IgA2 subclasses[54] in saliva have been associated with an increased incidence of URS in swimmers.

Recovery of IgA levels to pre-training resting levels between training sessions or training days is also important. Where the post-training level of salivary IgA fails to recover to the pre-training level there can be an increased risk of URS in the following days.[27,60] A similar pattern was reported in sailors, where a decline in IgA secretion rate over several weeks increased the risk of URS.[32] However, substantial within- and between-subject variability of salivary IgA limits its utilisation for group comparisons.[61] The best predictive use of salivary IgA is monitoring immune status in individual athletes over time, particularly those with a history of URS.[26,27] The recent development of a point-of-care device for quantifying salivary IgA[24] has improved the ability to undertake research in field environments[44] and provide timely results for monitoring and management of athletes.

Collection protocols for saliva, assay methodologies for IgA, and confounding issues such as prior exercise, and dehydration or food/drink contamination, all add to the variability in salivary IgA levels between studies.[11] The magnitude of change in salivary IgA in response to exercise is influenced by the intensity, duration and overall workload of exercise bouts or training sessions, length of the training season, and number of competitions and years competing at an elite/professional level.[62] There is an inverse relationship between exercise intensity and change in salivary IgA concentration characterised by a reduction in salivary IgA during and after high-intensity exercise, but an increase in response to moderate exercise.[63] Increases in salivary IgA observed after moderate exercise training may contribute to reduced susceptibility to URS.[29,64]

CYTOKINE RESPONSES TO EXERCISE

Intense exercise induces a well-characterised systemic cytokine response, particularly in association with micro-trauma of muscle tissue and the metabolic stress responses to exercise.[11] The systemic response is rapid with an initial pro-inflammatory response (IL-6, IL-8) followed by an anti-inflammatory response (IL-10, IL-1ra) that usually resolves within 6–24 h. The rapid cytokine responses to intense exercise have the potential to be involved in expression of URS that mimic URTI, however, there is little supporting research to indicate a direct influence in the respiratory tract. Only a few studies have assessed the relationship of cytokine responses to exercise in association with URS in athletes.[30,65]

A study comparing cytokine responses in illness-prone distance runners demonstrated impaired inflammatory cytokine regulation

compared with runners who did not suffer frequent episodes of URS.[65] Pre-exercise concentrations of IL-8, IL-10 and IL-1ra were significantly lower in the illness-prone runners, as were the post-exercise concentrations of IL-10 and IL-1ra. In contrast, the illness-prone runners had higher concentrations of IL-6 in response to treadmill running. Moreover, C-reactive protein response to treadmill running did not distinguish between healthy and illness-prone runners.[66] In contrast to low IL-10 concentrations,[65] high levels of production of IL-10 in antigen-stimulated whole-blood culture were evident in illness-prone endurance athletes, compared with healthy athletes.[30] The high IL-10 secretion rates were correlated with higher training loads and lower salivary IgA secretions rates. The illness-prone athletes also had high IL-4 production and trends for higher IL-2 and IFN-ɣ, but only IL-10 production was associated with illness.

GENETIC PREDISPOSITION TO INFLAMMATION

An individual's immune response is determined by their genetic makeup for cytokines and other key immune control factors. Polymorphisms in cytokine genes have been associated with an underlying genetic predisposition to high expression of the pro-inflammatory IL-6 in athletes prone to frequent URS, and a decreased likelihood associated with the genotype for high expression of IL-2.[67] This study of 170 highly trained athletes from various sports failed to identify significant differences in the gene polymorphisms for other pro-inflammatory cytokines IL-4, IL-8 or IFN-ɣ or the anti-inflammatory cytokines IL-10 or IL-1ra between the healthy athletes and those prone to URS. A recent study of elite male athletes in endurance sports has identified genetic variation in the distribution of IL-10 polymorphisms, with athletes prone to URS having the high-expression genotype (GG) more frequently than the other two genotypes (AG+AA) and an increased likelihood of frequent URS.[68] A study unrelated to exercise indicated that differences in IFN-ɣ and IL-10 polymorphisms affect illness severity, cytokine protein levels and duration of illness in response to various viruses,[69] suggesting genetically determined variation in inflammatory responses are associated with the severity of the response and recovery time from viral infections.

NUTRITIONAL INTERVENTIONS

Nutritional interventions have been extensively studied in elite athletes based on the assumption that improving immune protection and/or reducing inflammation will reduce the incidence and impact of URS.[15] The investigations have evaluated ways to boost immunity, prevent inflammatory symptoms, prevent overtraining and improve performance, but not all have examined the impact on reducing airway inflammation or infections in the study design. The impact of diets enriched with carbohydrates and/or fats on immune parameters and performance have not evaluated direct associations with URS. Elite athletes can be at risk of micronutrient deficiencies resulting from the high demands of training and in the case of vitamin D from reduced UV exposure. Lowered levels of essential vitamins and minerals contribute to immune dysfunction that has the potential to place an athlete at higher risk of infection or inflammation. Only a few studies have established clear evidence for a link between URS and either baseline micronutrient status, or a positive impact of dietary supplementation in athletes (Table 2).[70]

Vitamin A (β-carotene) is essential for T-cell development and deficiencies have been associated with increased adherence of bacteria to respiratory tract epithelium and reduced IgA production. Supplementation for 3 weeks in conjunction with vitamin A in ultramarathon runners showed a small reduction in post-race URTI but was less effective than supplementation with vitamin C alone.[70] The anti-infective properties of vitamin C are thought to be mediated via induction of T lymphocyte responses, suppression of neutrophil activity and interference in viral replication through enhanced production of IFN-ɣ. Vitamin C showed no impact on the incidence of URTI in one study of marathon runners[21] but in most studies small reductions in the incidence of URS have been reported for ultramarathon runners, skiers and military recruits undertaking intensive training.[70] A consistent finding has been a reduction in severity of the symptoms when supplemented with vitamin C alone or in conjunction with other vitamins.[70]

Vitamin D status is critical to effective immune modulation and antimicrobial activity. Vitamin D deficiency in endurance athletes was associated with a higher number of days with symptoms of URS and lower salivary IgA secretion rates.[71] Cytokine production from antigen-stimulated whole-blood culture was lower for TNF-α, IL-1β, IL-6 and IFN-ɣ in vitamin D-deficient athletes, with a trend for lower IL-4 production but no associations for IL-2 or IL-10 production. Vitamin E prevents free-radical damage at membrane surfaces and is thought to stimulate both T- and B-cell proliferation. Caution is required with vitamin E supplementation in athletes, as the beneficial cell membrane protective effects were reversed in cyclists during exhaustive training.[70] Zinc inhibits lipopolysaccharide and IL-1β-induced nitric oxide formation, and promotes repair of respiratory epithelium via upregulation of zinc-dependent metalloproteinases.[72] Zinc supplementation can reduce cold symptoms, cough and nasal discharge.[73] Excessive zinc however can impair T-cell proliferation and antibody formation.

A diet rich in antioxidants can reduce airway inflammation in asthmatics,[74] but there are no investigations examining the impact of supplementation with natural dietary antioxidants (fruit and vegetables) on URS in athletes. A non-alcoholic beer that has strong antioxidant and anti-inflammatory properties was examined in runners who consumed the beverage for 3 weeks before and 2 weeks after a marathon.[75] There was a three-fold lower incidence of post-race URS and reduced systemic inflammatory responses compared with the control group who did not consume the beverage. Reductions in URS post intense exercise have been observed following supplementation with high doses of quercetin, either alone or in conjunction with other flavonoids.[76]

Studies investigating dietary supplementation with bovine colostrum have reported reduced URS in athletes.[77–79] Bovine colostrum contains bioactive cell growth factors (TGF-β, insulin-like growth factors) that promote intestinal repair/growth and muscle strength in humans and antimicrobial/immunomodulatory components that modulate cytokines.[80] Bovine colostrum given to swimmers over 10 weeks had little impact on salivary IgA, plasma C-reactive protein or immunoglobulin levels but reduced the incidence of URS.[77] Athletes who received bovine colostrum for 12 weeks during winter had a lower incidence of URS and reduced bacterial load in saliva, but little effect on neutrophil oxidative burst,[79] suggesting an inflammatory rather than infective cause of the symptoms. Antioxidants and bovine colostrum have not been shown to inhibit respiratory infections and the reduction in URS following supplementation is most likely due to the positive effect on inhibiting mucosal membrane disruption and reduced inflammation.

Supplementation with various stains of *Lactobacillus* has been examined in athletes. Eight weeks of supplementation with *Lactobacillus casei* Shirota strain reduced the frequency of URS episodes, the severity and duration of symptoms; and increased salivary IgA levels.[81]

Table 2 Evidence-based interventions, modifiable lifestyle and environmental factors that have a positive impact on reducing URS in high-performance athletes

Author and reference	*Study design*	*Intervention*	*Impact on URS*
Training modifications			
Konig *et al.*[10]	Epidemiological questionnaire of 852 athletes attending for a medical check-up	None	Lower training intensity was associated with reduced URS. Endurance training increases the risk
Tiollier *et al.*[23]	21 military cadets undertaking 3 weeks of intensive training and 5-day combat course	Reduced training load during the recovery period post intensive combat course	Lower incidence of URS in recovery period
Hellard *et al.*[16]	Prospective study of 28 national swimmers over 4 years	Changes in intensity and type of training	Incidence of URS increased with training load and resistance training
Putlur *et al.*[55]	Prospective study of 14 college soccer players over 9-week season	None	Incidence of URS increased with training load
Fricker *et al.*[26]	Case study of elite swimmer with recurrent URS and immune suppression	Reduced training and stopped international competitions	Decreased incidence of URS at 1- and 3-year follow-ups
Therapeutic interventions			
Schwellnus *et al.*[37]	96 elite runners in a DBPCT assessed pre- and post 56 km marathon	Daily topical anti-inflammatory nasal spray (fusafungine) intervention period not specified	Decreased incidence of URS
Cox *et al.*[38]	45 well-trained half-marathon runners in a DBPCT	Daily topical anti-inflammatory nasal spray (Difflam) for 1 week prior and 2 weeks post the race	Decreased severity of symptoms but not incidence of URS
Cox *et al.*[49]	28 elite runners in a DBPCT with crossover arms	Anti-herpes viral therapy (Valtrex) for 1 month in active arm	Eliminated EBV but did not reduce incidence of URS
Nutritional supplements			
Kingsbury *et al.*[8]	19 Olympic athletes with fatigue, inability to train and URTI and low glutamine levels	Increased protein intake for 3 weeks, resulting in increased glutamine levels	URS abated within 2 months, but fatigue persisted and reduced ability to undertake high-intensity training
Scherr *et al.*[75]	277 marathon runners in a DBPCT over 5 weeks	Non-alcoholic beer containing polyphenols (anti-oxidant, anti-microbial and anti-inflammatory properties) intake daily for 3 weeks prior and 2 weeks post a marathon	Reduced incidence of URS post marathon
Nieman *et al.*[76]	20 trained male cyclists and 20 controls in DBPCT over 5 weeks of training and a 3-day intense cycling period	Quercetin daily high dose for 3 weeks before, during and 2 weeks after a 3-day period of intense cycling	Reduced incidence of URS in 2 weeks post the intensive training
Shing *et al.*[78]	29 elite road cyclists in a DBPCT over 5 weeks of routine training followed by 5 days of intensive training	Bovine colostrum daily	Trend for reduced incidence of URS ($P=0.08$)
Crooks *et al.*[77]	25 elite swimmers in a DBPCT over 10 weeks of routine training period before a national competition	Bovine colostrum daily	Trend for reduced incidence of URS ($P=0.055$)
Jones *et al.*[79]	53 active males (not elite) in a DBPCT over 12 weeks	Bovine colostrum daily	Reduced incidence of URS and reduced salivary bacterial load
Clancy *et al.*[82]	25 athletes in a DBPCT over 4 weeks	Probiotic (*Lactobacillus acidophilus* LAFT1-L10 strain) daily	Reversal of defect in IFN-γ secretion from T cells (viral control mechanism)
Cox *et al.*[83]	20 male distance runners in a DBPCT over 16 weeks	Probiotic (*Lactobacillus fermentum* VRI-003 strain) daily	Reduced incidence of URS and reduced severity of symptoms and trend for higher IFN-γ secretion from T cells ($P=0.07$)
Gleeson *et al.*[81]	84 endurance athletes in a DBPCT over 16 weeks	Probiotic (*Lactobacillus casei* Shirota strain) daily	Reduced incidence of URS
Lifestyle and environmental impacts			
Konig *et al.*[10]	Retrospective questionnaire of 852 athletes attending for a medical check-up	None	Coping with daily stress reduces incidence of URS Sleep deprivation increased the risk of URS
Hellard *et al.*[16]	Prospective study of 28 national swimmers over 4 years	None	URS incidence was higher in winter months
He *et al.*[71]	Prospective study of 225 endurance athletes over 16 weeks	None	URS incidence was higher in athletes with vitamin D deficiency

Abbreviations: DBPCT, double-blind placebo-controlled trial; EBV, Epstein Barr virus; URS, upper respiratory symptoms.

Supplementation with *Lactobacillus acidophilus* for 1 month in athletes presenting with fatigue associated with recurrent infections and impaired performance reversed a defect in IFN-ɣ secretion in whole blood cultures.[82] As IFN-ɣ is linked to control of virus shedding, a T-lymphocyte defect in IFN-ɣ secretion[82] may be important in control of EBV reactivation and appearance of URS. Restoration of the T-cell balance by the probiotic indicates a skewed T-cell response to dendritic cell signals as the subjects exhibited normal IL-4 secretion despite reduced IFN-ɣ secretion. *Lactobacillus fermentum* supplementation for 1 month in distance runners reduced the number of days with URS and severity of symptoms.[83]

PRACTICAL IMPLICATIONS FOR ATHLETES

Therapeutic interventions

Understanding the underlying causes of the URS is critical for providing targeted therapeutic interventions. Athletes suffering recurrent URS warrant a thorough clinical assessment and investigations of potentially treatable conditions. In general, treatment strategies for URTI in athletes follow the same guidelines as for the general community. Antibiotic preparations are effective although side effects can include fatigue, photosensitivity, cardiac disturbance, diarrhoea and increased risk of tendinopathy. Choice of narrow-spectrum antibiotics and avoiding extended courses around competitions is advised. In runners, topical respiratory anti-inflammatory medications may assist with reducing the severity of symptoms.[37,38] Anti-viral intervention may reduce the viral load of EBV but may not have an impact on the incidence of URS.[49] Expectorants to clear mucus production are usually well tolerated although exercise itself can have this effect. Use of antihistamines to dampen an inflammatory response is an option but can increase risk of heat illness and dehydration. Any adjunctive medications should be checked to avoid banned substances, highlighting the difficulty of prescribing clinical interventions when the aetiology of the symptoms is uncertain.

Monitoring salivary IgA

Predictors of increased risk of URS include low pre-season and low baseline pre-training salivary IgA concentrations and excretion rates, reduction in salivary IgA and excretion rates over a training period, and failure of salivary IgA concentration to recover adequately to pre-training levels after training. Adapting training regimes to maintain mucosal immune health assists with prevention of URS associated with a low salivary IgA level.

CONCLUSIONS

Studies of respiratory infections in athletes are limited by the lack of pathogen identification. Regardless of the underlying cause of inflammatory symptoms, the resulting cytokine cascade and associated fatigue can impair athlete performance. The cause of URS in athletes can be uncertain but the majority of cases are most likely related to common respiratory viruses, viral reactivation and/or aeroallergens. Inflammation from non-infective causes is common among athletes and many will have underlying treatable conditions. In research settings, differentiation between the inflammatory causes of the URS is often not feasible. Antioxidant, probiotic and bovine colostrum supplementations may be beneficial for some athletes. Identifying athletes with an underlying genetic predisposition to pro-inflammatory responses to exercise is a promising area of investigation. Further studies validating clinical and practical intervention strategies are needed to inform guidelines and recommendations for clinicians, coaches and athletes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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