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NUTRITION AND ATHLETE IMMUNE HEALTH: A NEW PERSPECTIVE

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- Sickness absence from training is incompatible with success in elite sport, which demands a consistently high training volume, i.e. the less sick, the more an athlete can train.
- Medal winners at major sporting events, including the Olympics and World Championships, suffer fewer and shorter-lasting respiratory infections than less successful, national level athletes.
- Nutrient availability influences immunity because macro and micronutrients are involved in a multitude of immune processes. Macronutrients are involved in immune cell metabolism and protein synthesis and micronutrients are involved in antioxidant defenses.
- A new paradigm for exercise immunology is presented that considers *resistance* (the strength of the immune weaponry) and *tolerance* (the ability to endure microbes and dampen defense activity).
- A contemporary view is that immune *resistance* is not suppressed in athletes under heavy training, so it is not surprising that nutritional supplements targeted toward improving immune *resistance* show limited benefits to reduce the infection burden in athletes — 'if it ain't broke, don't fix it!'
- This new paradigm of *resistance* and *tolerance* helps to explain why nutritional supplements with tolerogenic effects (e.g., probiotics, vitamin C and vitamin D) are the new targets, as these may reduce the infection burden in athletes.

INTRODUCTION

The aim of this sports science exchange article is to provide a new theoretical perspective to improve our understanding of how nutrition may influence athlete immune health. To set the scene, recent advancements in our understanding of the infection burden in athletes and the prominent infection risk factors will be discussed and scrutinized. As will be the overly simplistic and long-standing view held by many that nutritional supplements should be targeted toward countering the apparently weakened immune weaponry (termed resistance) in otherwise healthy elite athletes. A new paradigm for exercise immunology, recently adopted in human immunology from ecological immunology, will be offered that considers the beneficial tolerogenic interactions (tolerance refers to the ability to endure microbes) between pathogens and the immune system. Looking through this new lens provides a much clearer picture with regard to the rather conflicting and often disappointing findings of studies investigating nutritional supplements and athlete immune health. This new theoretical perspective provides a framework for research on targeted tolerogenic nutritional supplements to reduce the burden of infection in elite athletes.

INFECTIONS POSE A SERIOUS PROBLEM FOR ATHLETES

An upper respiratory infection (URI), such as a common cold, might only present an unwelcome nuisance for many of us. However, URI and other infections such as those that affect the gastrointestinal system may limit an elite athlete's availability to train and take part in a major competition. After injury, illness (primarily respiratory but also gastrointestinal) was the second most common reason for an elite athlete to seek medical attention either during training or when competing at the summer or winter Olympic Games. In a three-year surveillance study of 322 Olympic athletes, ~70% of illnesses recorded by medical staff resulted in "time loss" (complete absence) from training and competition and the remaining illnesses resulted in "performance restriction" (e.g., reduced volume and/or intensity of training) (Palmer-Green et al., 2013). Clearly, sickness absence from training is incompatible with success in elite sport which demands a consistently high training volume (Table 1). In accordance with this logic, the empirical evidence shows that medal winners at major sporting events, including the Olympics and World Championships, suffer fewer URI and shorter-lasting URI than less successful, national level athletes (Hellard et al., 2015; Svendsen et al., 2016).

Why infection is incompatible with success in elite sport.
• Medal winners suffer fewer and shorter URI
• Infection is the 2nd most common reason to present to a team medic, after injury
• Sickness correlates negatively with training volume
• Illness accounts for 1/3 of all lost training days
• 2/3 of illnesses result in "time loss" from training and competition; 1/3 of illnesses result in "performance restriction"
• Recent below-the-neck symptoms increases the likelihood of not finishing an endurance event
• Heavy exercise can extend an ongoing infection

• Heavy exercise during infection, or after incomplete recovery, can lead to medical emergencies …
  • Rhabdomyolysis[1]
  • Myopericarditis[2]
  • Exertional heat stroke

Table 1. Why infection is incompatible with success in elite sport. URI = upper respiratory infection; [1]Rhabdomyolysis = breakdown of muscle tissue that can lead to renal failure; [2]Myopericarditis = acute inflammation of the pericardium usually caused by an infection.

Risk Factors for Infection and Lowered Immunity in Athletes

Only very recently has research begun to scratch the surface regarding the prominent risk factors for infection in elite athletes (Table 2). Central to the doctrine of early exercise immunology was the concept that heavy exercise temporarily decreases immunity, providing an "open window" for URI and other infections. Periods of overreaching and longer-term maladaptation (coined overtraining) were also associated with neuroendocrine modulation, decreased immunity and increased URI. These findings supported the prevailing notion of the time that accumulated training stress compromised immune health and increased infection risk. As such, for many years exercise immunologists broadly accepted and focused their research efforts toward countering heavy exercise as a prominent risk factor for URI in athletes. In short, both innate and acquired immunity (Figure 1) are often observed to decrease transiently during the recovery period after prolonged heavy exertion; typically of the order 15%–70% (Walsh, 2018). But whether these transient changes in immunity with acute heavy exercise and intensified training are sufficient to increase URI susceptibility in accordance with the "open window" theory has been in doubt for some time (Ekblom et al., 2006). Findings on URI at the 2000 Stockholm marathon provided the first serious challenge to the "open window" theory by showing no increase in URI symptoms post-race. This contrasted earlier findings showing increased URI after endurance races (Peters & Bateman, 1983). In addition, Ekblom et al. (2006) observations supported the idea that pre-race URI symptoms may have accounted for reports of increased URI after endurance events.

Ten risk factors for infection in athletes.
1. Autumn and winter — common cold and flu season
2. Poor hygiene and exposure to sick people
3. Recent symptoms
4. Air travel
5. Life stress, depression and anxiety
6. Low energy availability
7. Poor sleep
8. Increases in training load, e.g., training camp
9. National vs. International level
10. Low mucosal immunity (saliva/tear immunoglobulin-A)

Table 2. Ten risk factors for infection in athletes.

Recent research highlights prominent risk factors for infection in elite athletes and military personnel are broadly similar to those in the wider population (Table 2). Risk factors include, wintertime (common cold and influenza season), high levels of psychological stress, anxiety and depression, poor sleep, and long-haul travel (Drew et al., 2017; Hellard et al., 2015; Svendsen et al., 2016; Wentz et al., 2018). By contrast, increases in training load resulted in relatively small increases in URI and gastrointestinal infection incidence in one study in elite swimmers (Hellard et al., 2015) and no change in infection incidence in another study in elite cross-country skiers (Svendsen et al., 2016). Low energy availability has recently been associated with increased illness symptoms in elite female athletes (Drew et al., 2017). Besides the obvious limitation that this observation was restricted to females, the authors recognized the need for studies to directly assess energy availability (they used the LEAF questionnaire) and perform measures of immunity and pathology, the latter to confirm infection. It is conceivable that poor mental health (e.g., stress, anxiety and depression), highly prevalent in female athletes with low energy availability, also plays a role in the increased URI reports. Psychological stress, anxiety and depression have a well-known and marked influence on immunity and infection resistance (Cohen et al., 1991).

HOW DOES NUTRITION INFLUENCE IMMUNITY AND INFECTION?

The immune system's ability to clear viruses, bacteria and other pathogens, termed resistance, is dependent upon an adequate supply of energy from important fuel sources, including glucose, amino acids and fatty acids. In addition to fuel requirements, cell proliferation requires nucleotides for DNA and RNA synthesis and amino acids for protein synthesis. An adequate supply of amino acids is also required for the production of proteins such as immunoglobulins, cytokines and acute-phase proteins. The influence of severe restriction of all nutrients (Marasmus) and protein-energy malnutrition (Kwashiorkor) on immunity and infection-related mortality in developing countries is well documented (Woodward, 1998). Severe energy restriction may also influence immunity via activation of the hypothalamic-pituitary-adrenal axis and increases in stress hormones as cortisol, for example, is widely acknowledged to have anti-inflammatory effects.

Micronutrients also play important roles in nucleotide and nucleic acid synthesis (e.g., iron, zinc and magnesium) and antioxidant defenses that limit tissue damage (e.g., vitamins C and E). Antioxidant availability (e.g., vitamin C) may be particularly important during heavy exertion or infection when oxidative stress increases. Some micronutrients can directly influence immune cell functions by regulating gene expression (e.g., vitamin D).

There are other ways in which nutrition may affect immunity and infection; for example, prebiotics and probiotics may influence immunity indirectly by modifying the gut microbiota, and elemental zinc in oral lozenges may directly inhibit viral activity in the oropharyngeal region, with therapeutic benefits for URI. Calder (2013) highlighted the bidirectional link between nutrition, immunity and infection. On the one hand, malnutrition has a well-described negative influence on immunity and resistance to infection, but on the other, the widely reported increase in energy requirements during infection paradoxically coincides with reduced appetite (anorexia) and nutrient malabsorption; hitherto, a poorly described phenomenon. Recent research sheds some light on this paradox by showing that reduced appetite improves immune tolerance and survival during bacterial infection (starve a fever …) yet potentiates the progression and lethality of viral infection (… feed a cold) (Wang et al., 2016).

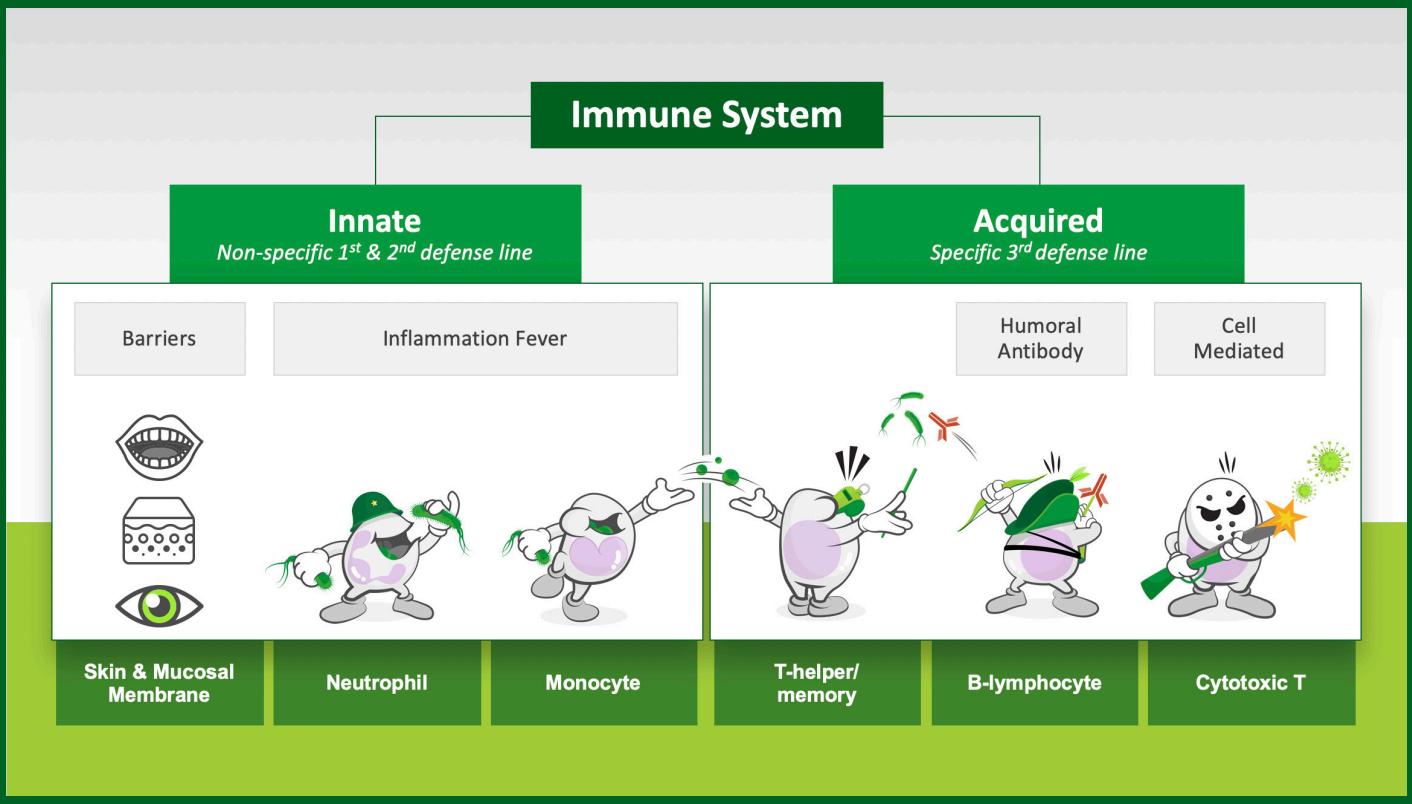

Figure 1. Simple overview of the immune system. The immune system provides a potent, multi-layered defense against attack from pathogenic microorganisms including viruses, bacteria, fungi and protozoa, and provides defense against cancer through anti-tumor activity. The various cellular and soluble elements in the immune system's armory against infectious agents can broadly be divided into innate (non-specific) and acquired (specific) arms. On encountering a pathogen, the first and second lines of defense, the innate immune system is activated. The innate immune system comprises physical and chemical barriers (e.g., the skin and mucosal membranes) and phagocytes (e.g., neutrophils, monocytes, etc.) that ingest and kill microorganisms along with other non-specific killer cells. The third line of defense, the acquired immune system, is highly specialized, yet slower to deploy than the innate immune system. The acquired immune system comprises the lymphocytes; specifically, T and B lymphocytes that proliferate and serve a multitude of roles including B cell antibody production, cytotoxic T cell killing and the development of T memory cells, so that an augmented response can be mounted on subsequent pathogen exposure (the scientific basis for Edward Jenner's discovery of vaccination). Although subdividing the immune system into innate and acquired arms affords a simple description, this distinction is rather crude as the innate and acquired immune systems are very much intertwined. For example, the processes of antigen presentation and recognition and pathogen exclusion require cells of the innate and acquired immune system to work together in harmony.

A NEW THEORETICAL PERSPECTIVE ON NUTRITION AND ATHLETE IMMUNE HEALTH

Traditionally, immunologists have focused their efforts on understanding the immune weaponry at our disposal in the fight against infectious pathogens (termed resistance). Ecological immunologists prefer a model describing not only resistance but also tolerance, defined as the ability to endure a microbe. Ayres and Schneider (2012) elegantly described a paradigm using these concepts of resistance and tolerance to better understand human-pathogen interactions. Using a castle metaphor, they describe the inhabitants of the fortress performing various tasks including repairing the walls, raising offspring and distributing food. At the same time, the inhabitants must decide whether a battle is worth fighting and the appropriate weapons to use, the immune equivalent of "choosing your battles wisely". Key to effective tolerance is a proportionate immune response: an overly exuberant immune response can cause excessive tissue damage and unnecessarily allocate energy resources away from vital functions and vice versa, a weak immune response increases susceptibility to damage from the pathogen (Figure 2). Reactive oxygen species (ROS) play an important role in host defense against infection, but increased oxidative stress during an immune reponse can result in collateral tissue damage, placing an increased demand on antioxidant scavenging during infection. Seminal work in bumblebees has demonstrated the cost of full-blown immune activation for host survival as starvation significantly decreased survival time in immune-activated compared with immune-naïve bumblebees. Given the tissue damage and increased energy cost during a full-blown immune response, the immune system has likely evolved to control persistent infection at a non-damaging level and exhibit tolerance to non-threatening organisms (Figure 2). A prime example is the mutualistic bacteria that reside in the gut; the immune system does not raise a pathogenic response to obliterate the grams of lipopolysaccharide in the intestinal lumen. Homeostasis is achieved by an appropriate balance of resistance and tolerance that allows us to fight infection, where the signals indicate this is necessary, yet maintain a healthy relationship with the mutualistic bacteria in our gut.

This new theoretical perspective may improve our understanding of how sick we will become when we have an infection (in terms of severity and duration), and more clearly elucidate a role for nutrition, particularly in terms of tolerance (Figure 2). Of course, it stands to reason that a

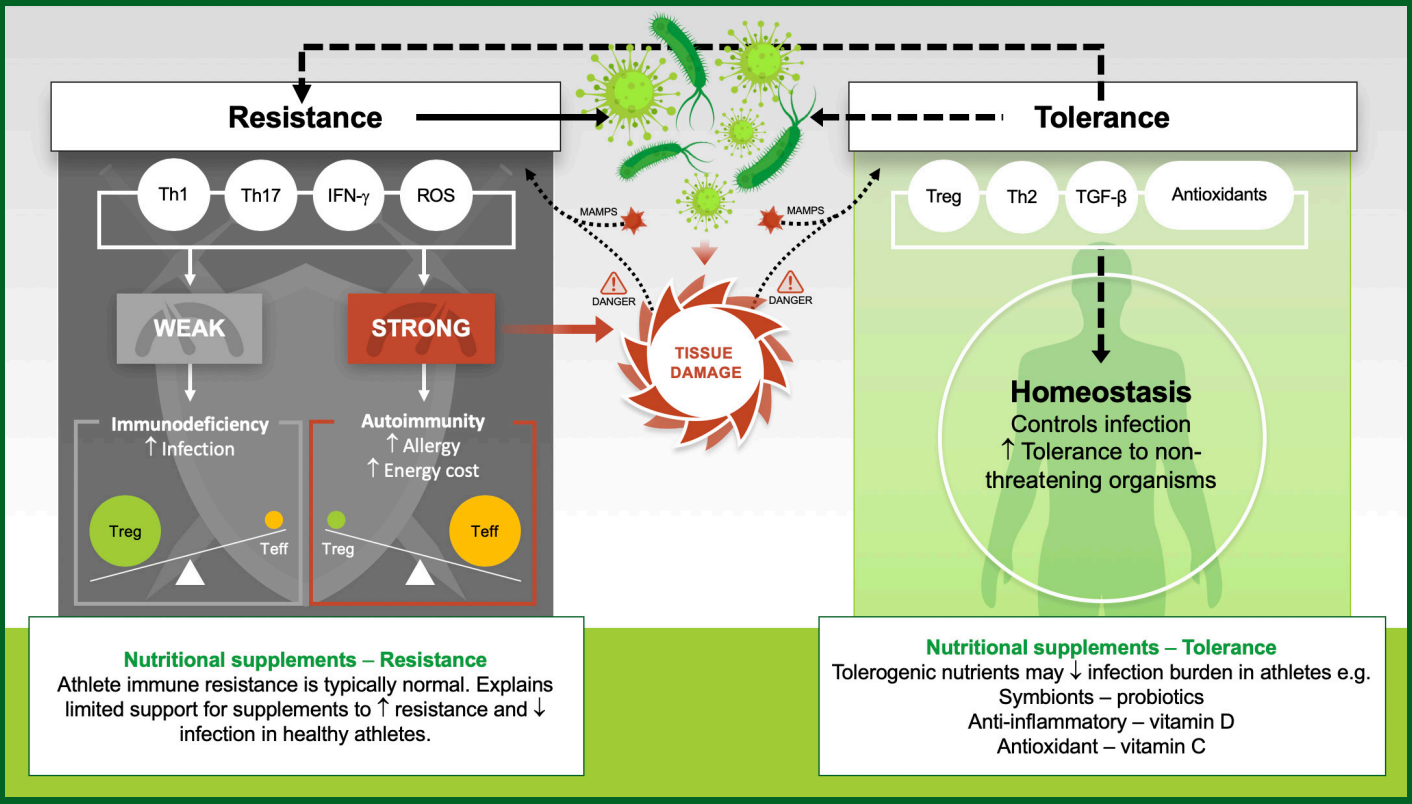

Figure 2. Model of resistance and tolerance in host-pathogen interactions and the value of nutritional supplementation. Dark shaded area on the left (arrows with solid lines) shows classical view of immune resistance where the immune weaponry protects the host by attempting to reduce the pathogen burden, through cell-mediated killing and release of ROS for example. Weak resistance results in immunodeficiency and increased risk of infection. On the other hand, an overly exuberant immune response to a pathogen causes tissue damage and wasteful diversion of energy resources away from other important functions. An overly strong immune response is associated with autoimmunity and allergy. In this simple model, homeostasis is achieved by balancing effector and regulatory sides of the scales. This classical model of immune homeostasis overlooks important tolerogenic interactions with the pathogen. The concept of tolerance, the ability to endure microbes, (light shaded area on the right and arrows with broken lines) has been adopted from ecological immunology where work in invertebrates shows important tolerogenic interactions between the host and microbes, the findings of which are generalizable to vertebrates. Pathogens influence the magnitude of the immune response by displaying conserved molecules called microbe-associated molecular patterns (MAMPS), and by stimulating the release of danger signals from damaged tissue. Tolerance in this model dampens defense activity (upper broken arrow) yet controls infection at a non-damaging level, with the added benefit of a lower energy cost. This explains how we tolerate commensal bacteria rather than eliciting an immune response to obliterate the large abundance of bacteria in the gut. This model also helps to explain why nutritional supplements with tolerogenic effects may reduce the burden of infection (e.g., reduced severity and duration) in otherwise healthy athletes. Adapted from Walsh (2019).

IFN-γ = interferon gamma; ROS = reactive oxygen species; Teff = Effector T cells; Treg = regulatory T cells.

frank deficiency of a nutrient required for proper immune function will decrease immune resistance and increase susceptibility to infection. Examples include the well-known influence of dietary protein deficiency on host defense and evidence that a frank deficiency in zinc decreases immunity (Calder, 2013). But growing evidence indicates that for some nutrients there are times when intake above recommended levels may have beneficial effects on immunity, likely by optimizing the delicate balance between resistance and tolerance. Looking through this new lens, illustrated in Figure 2, brings into sharp focus the previously rather mixed picture presented by studies investigating nutritional supplements and athlete immune health. For example, this model helps to explain why nutritional supplements with tolerogenic effects may reduce the burden of infection in otherwise healthy athletes (e.g., reduced severity and duration). Clearly, it's no longer sufficient to ask only if a nutritional intervention will stop the athlete from getting sick, perhaps it's more pertinent to ask: Will the nutritional intervention reduce how sick the athlete will get?

Nutritional Supplements for Immune Resistance: If it ain't broke, don't fix it!

As logic would dictate, support for nutritional supplements to improve immune resistance (and thus decrease pathogen burden) comes largely from studies in those with impaired immunity, such as the frail elderly and clinical patients, particularly in those with poor nutritional status (Bermon et al., 2017). Over the last 25 years or so, exercise immunologists have actively researched nutritional supplements to improve immune resistance in athletes (Table 3). For much of this period, there was a broad acceptance among exercise immunologists that immunity was impaired in athletes under heavy training, prompting the search for nutritional countermeasures. A more contemporary view is that the evidence supporting immunosuppression in athletes is lacking. So, it is not surprising that supplements targeted toward immune resistance show limited benefits for athlete immunity and host defense: the phrase "if it ain't broke, don't fix it" comes to mind (Table 3). One exception is the therapeutic effect of zinc lozenges for treating the common cold. A recent

meta-analysis showed that dissolving zinc lozenges in the mouth (75 mg/day elemental zinc) reduced URI duration by ~3 days (33%) when taken < 24 h after the onset of symptoms, and for the duration of the illness (Hemila, 2017). The author points out that the optimal zinc lozenge dosage and composition need to be determined, as many over-the-counter lozenges contain too little zinc or contain substances that bind zinc. Although the exact mechanism(s) require elucidation, zinc may act as an antiviral agent by increasing interferon gamma and decreasing the docking of common cold viruses with binding sites. The therapeutic effects of zinc lozenges for treating URI have also been ascribed to antioxidant and anti-inflammatory properties of elemental zinc in the lozenge and as such, zinc lozenges may also have tolerogenic effects on immunity.

Tolerogenic Nutritional Supplements: The New Targets

Tolerance in this model dampens defense activity, yet effectively controls infection at a non-damaging level and it also facilitates homeostatic regulation of beneficial intestinal microbial communities (Figure 2). Looking through this lens, it is easy to see why studies involving nutritional supplements with tolerogenic properties have yielded some positive effects for reducing the burden of infection in otherwise healthy athletes (Table 4). Probiotics (and prebiotics) may have tolerogenic effects by influencing intestinal microbial communities and the common mucosal immune system; the antioxidant effects of vitamin C and the anti-inflammatory effects of vitamin D may improve tolerance, mitigating against excessive tissue damage during infection. As mentioned previously, the therapeutic effects of zinc lozenges for treating the common cold, although principally considered to reduce the pathogen burden (improved resistance), may also be attributed to antioxidant and anti-inflammatory (tolerogenic) properties of zinc.

Probiotics

Probiotics are live microorganisms, which when administered regularly and in adequate amounts are thought to confer a health benefit on the host by modulating gut-dwelling bacteria (the microbiota) and immunity. There are various mechanisms by which probiotics are purported to benefit immunity and infection resistance, particularly respiratory and gastrointestinal infections; however, thus far, these have not been clearly elucidated. Probiotics can improve immune resistance by reinforcing the intestinal barrier and competing with pathogens for both attachment to the gut epithelium and for available nutrients. The products of probiotic metabolism (e.g., lactic acid) can also inhibit pathogen growth in the gut. Probiotics are considered to have important mutualistic benefits for immune health that extend beyond the gut, as these interactions between the commensal microbial community and the host immune system occur via the common mucosal immune system. There is now broad agreement that probiotics exert important anti-inflammatory, tolerogenic, effects that maintain homeostasis (Figure 2). For example, probiotics may prevent unnecessary inflammatory responses to harmless foreign substances in the gut.

Results from studies investigating the influence of probiotics on athlete immune health are promising and have been extensively reviewed elsewhere (Pyne et al., 2015). One placebo-controlled, cross-over trial in 20 elite distance runners showed that probiotic supplementation

Nutritional Supplements and Immune Resistance[1]

Supplement[2]	Proposed Mechanism	Evidence for Efficacy[3]
Zinc	Zinc is required for DNA synthesis and is an enzyme cofactor for immune cells. RNI is 7 mg/day for women and 9.5 mg/day for men. Zinc deficiency results in impaired immunity (e.g., lymphoid atrophy) and zinc deficiency is not uncommon in athletes. Antiviral effects of zinc lozenges.	**No support** for "preventing URI." Regular, high-dose zinc supplementation can decrease immune function and should be avoided. **Strong support** for "treating URI." Dissolving zinc lozenges in the mouth (75 mg/day elemental zinc) shortens common cold by ~33%; zinc must be taken < 24 h after onset of URI. Optimal lozenge composition and dosage to be determined. Side effects include bad taste and nausea.
Glutamine	Nonessential amino acid that is an important energy substrate for immune cells, particularly lymphocytes. Circulating glutamine is lowered after prolonged exercise and very heavy training.	**Limited support**. Some evidence of a reduction in URI incidence after endurance events in competitors receiving glutamine supplementation (2 x 5 g). Mechanism for therapeutic effect requires investigation. Supplementation before and after exercise does not alter immune function.
Carbohydrates (drinks, gels)	Maintains blood glucose during exercise, lowers stress hormones, and thus counters immune perturbations.	**Limited support.** Ingestion of carbohydrate (30–60 g/h) attenuates stress hormone and some, but not all, immune perturbations during exercise. Very limited evidence that this modifies infection risk in athletes.
Bovine colostrum	First milk of the cow that contains antibodies, growth factors and cytokines. Claimed to improve mucosal immunity and increase resistance to infection.	**Limited support** that bovine colostrum blunts the decrease in mucosal immunity and *in-vivo* immunity after heavy exercise. Some evidence in small numbers of participants that bovine colostrum decreases URI incidence. Further support required.
ß-glucans	Polysaccharides derived from the cell walls of yeast, fungi, algae and oats that stimulate innate immunity.	**Limited support**. Effective in mice inoculated with influenza virus; however, studies with athletes show no benefit to immunity and equivocal findings for risk of URI.
Echinacea	Herbal extract claimed to enhance immunity via stimulatory effects on macrophages. There is some *in-vitro* evidence for this.	**Limited support.** Small reduction in URI incidence but no influence on URI duration in general population. Ambiguous findings from small number of studies in athletes. Further support required.
Caffeine	Stimulant found in a variety of foods and drinks (e.g., coffee and sports drinks). Caffeine is an adenosine receptor antagonist and immune cells express adenosine receptors.	**Limited support**. Evidence that caffeine supplementation activates lymphocytes and attenuates the fall in neutrophil function after exercise. Efficacy for altering risk of URI in athletes remains unknown..

Table 3. Nutritional supplements and immune resistance[1] in athletes: proposed mechanism of action and evidence for efficacy. Adapted from Walsh (2019). URI = upper respiratory infection; RNI = reference nutrient intake. [1]Resistance reduces the pathogen burden, e.g., immune weaponry protects the host. [2]Supplement must come from a reliable source and be tested by established quality assurance program (Maughan et al., 2018).[3] Readers are directed to the consensus statement of The International Society of Exercise Immunology for further discussion regarding the evidence for efficacy of these supplements (Bermon et al., 2017).

Nutritional Supplements for Improving Immune Tolerance[1]		
Supplement[2]	**Proposed Mechanism**	**Evidence for Efficacy[3]**
Probiotics	Live microorganisms, which when administered orally for several weeks can increase the numbers of beneficial gut bacteria. Associated with a range of potential benefits to gut health and tolerogenic effects. Prebiotics are typically non-digestible carbohydrates that increase beneficial gut bacteria.	**Moderate-strong support in athletes** with daily dose of ~10^{10} live bacteria; meta-analysis shows ~50% decrease in URI incidence and ~2 d shortening of URI; minor side effects. Unclear whether probiotics reduce gastrointestinal distress and infection, e.g., in travelers' diarrhea. Limited support for prebiotics to decrease risk of URI in athletes.
Vitamin C	An essential water-soluble antioxidant vitamin that quenches ROS. Recommended daily intake for adults is 90 mg for males and 75 mg for females (USA).	**Strong support for "preventing URI" in athletes**. Meta-analysis shows ~50% decrease in URI incidence when taking vitamin C (0.25–1.0 g/day). No reported side effects. However, unclear if antioxidants blunt adaptation in well-trained. High vitamin C doses (gram doses) likely required if initiating vitamin C supplementation after onset of URI to compensate for increased inflammatory response. High vitamin C doses during URI have been shown to reduce URI duration. Further research required.
Vitamin D	Anti-inflammatory. An essential fat-soluble vitamin known to influence several aspects of immunity (e.g., expression of antimicrobial proteins). Skin exposure to sunlight accounts for 90% of the annual source of vitamin D. RNI is 5–15 µg/day.	**Moderate-strong support**. Evidence for deficiency in some athletes and soldiers, particularly in the winter (decreased skin sunlight exposure). Deficiency has been associated with increased risk of URI. Meta-analysis shows some benefit of supplementation to decrease URI incidence. Recommend monitoring and 1,000 IU/day D3 autumn-spring to maintain sufficiency where necessary. Increased risk of adverse outcomes supplementing > 4,000 IU/day D_3.
Polyphenols e.g. Quercetin	Plant flavonoids. *In-vitro* studies show strong anti-inflammatory, antioxidant and anti-pathogenic effects.	**Low-moderate support**. Some evidence of reduction in URI incidence during short periods of intensified training; albeit, in small numbers of untrained subjects. Limited influence on markers of immunity. Putative anti-viral effect for Quercetin. Further support required.
Omega-3 PUFAs	Found in fish oil. Claimed to exert anti-inflammatory effects post-exercise by regulating eicosanoid formation, e.g., prostaglandin. Prostaglandin is immunosuppressive.	**Limited support** for blunting inflammation and functional changes after muscle damaging eccentric exercise in humans and no evidence of reducing risk of URI in athletes. Some evidence oxidative stress actually increased in athletes supplementing n-3 PUFA.
Vitamin E	An essential fat-soluble antioxidant vitamin that quenches exercise-induced ROS.	**No support in athletes.** Improved *in-vivo* immunity and reduced URI incidence in the frail elderly but no benefit in young, healthy humans. One study actually showed that vitamin E (and ß-carotene) supplementation increased the risk of URI in those under heavy exertion. High doses may even be pro-oxidative.

Table 4. Nutritional supplements for improving immune tolerance[1] in athletes: proposed mechanism of action and evidence for efficacy. Adapted from Walsh (2019). URI = upper respiratory infection; RNI = reference nutrient intake; ROS = reactive oxygen species; PUFA = polyunsaturated fatty acids. [1]Tolerance dampens defense activity yet controls infection at a non-damaging level. [2]Supplement must come from a reliable source and be tested by established quality assurance program (Maughan et al., 2018). [3]Readers are directed to the consensus statement of The International Society of Exercise Immunology for further discussion regarding the evidence for efficacy of these supplements (Bermon et al., 2017).

(*Lactobacillus fermentum*) for 28 days reduced the number of days of URI and the severity of URI symptoms (Cox et al., 2010). Another randomized, placebo-controlled trial in 64 university athletes reported a lower incidence of URI during a four-month winter training period in athletes receiving daily probiotic (*Lactobacillus casei Shirota*) compared with placebo (Gleeson et al., 2011). This study also reported better maintenance of saliva secretory immunoglobulin-A (SIgA) in the probiotic group. Four weeks of supplementation with a multi-species probiotic formulation (*Lactobacillus, Bifidobacterium and Streptococcus*) reduced markers of gut permeability and symptoms of gastrointestinal discomfort during exercise heat stress (Shing et al., 2014). Whether probiotics and prebiotics can prevent travelers' diarrhea remains unclear as prophylaxis may be dependent upon the strain of probiotic given. Notwithstanding, results from general population studies show some beneficial effects of probiotics on URI (Table 4). A recent meta-analysis showed that probiotic supplementation reduced the incidence of URI by ~50%, shortened URI duration by ~2 days, reduced antibiotic prescription rates and resulted in only minor side effects (Hao et al., 2015). However, only 12 studies were included in the meta-analysis (n=3,720) and the quality of evidence was rated as low. Limitations included the relatively small sample sizes, poor controls and unclear procedures for randomization. Although the available evidence supporting probiotics to reduce the infection burden in athletes is by no means definitive, studies to date indicate some benefit with little evidence of harm. Athletes might therefore consider probiotic supplementation particularly during periods of increased URI risk, as in the weeks before and during foreign travel (Pyne et al., 2015).

Vitamin C

Vitamin C (ascorbic acid) is a major water-soluble antioxidant that is effective as a scavenger of ROS in both intracellular and extracellular fluids. Good sources of vitamin C include fruit and vegetables and the recommended daily dietary intake for adults is 90 mg for males and 75 mg for females (USA). Vitamin C is found in high concentration in leukocytes, but the level falls dramatically during a common cold when oxidative stress increases. As such, there is a sound scientific basis for vitamin C supplementation to improve tolerance by mitigating against excessive tissue damage during infection (Ayres & Schneider, 2012). There is also a strong rationale for anticipating benefits to reduce URI in athletes who experience increased oxidative stress during heavy exercise. A meta-analysis examined the evidence that daily doses of vitamin C of more than 200 mg have prophylactic and therapeutic effects for the common cold (Hemila & Chalker, 2013). In a subgroup of five placebo-controlled trials in heavy exercisers (n=598), including marathon runners, skiers and soldiers, vitamin C (0.25–1.0 g/day) decreased URI incidence by 52%. For example, in a double-blind, placebo-controlled design, Peters et al. (1993) showed that 600 mg/day of vitamin C for three weeks prior to a 90 km ultramarathon reduced the incidence of URI symptoms in the two-week post-race period (33% vs. 68% in age- and sex-matched control runners). Whether the observed benefit of vitamin C for preventing URI symptoms in those under heavy exertion represents a real decrease in respiratory viral infection is an important avenue for inquiry. The rather high URI symptom incidence in this study (68% in placebo) and the observed benefit of vitamin C might relate to exercise-induced

bronchoconstriction caused by airway inflammation and injury, which is common during heavy exercise. Regardless of the mechanism, there are clear benefits of vitamin C supplementation (0.25–1.0 g/day) to reduce URI symptoms in athletes (Table 4).

Determining whether initiating vitamin C supplementation after the onset of URI has therapeutic effects is complicated by methodological differences between studies, including differences in the timing of initiating vitamin C supplementation and in the duration and dosage of supplementation (Table 4). Hemila and Chalker (2013) suggest that higher daily vitamin C doses may be required for treating URI and that future therapeutic trials in adults should use doses that exceed 8 g/day vitamin C. Another area of uncertainty is whether regular high-dose vitamin C supplementation (1 g/day) blunts some of the adaptations to endurance training. The authors of one study caution against high-dose antioxidant supplementation during endurance training to avoid blunting cellular adaptations (Paulsen et al., 2014). But whether high-dose antioxidant supplementation blunts training adaptations in highly trained athletes remains unclear. As vitamin C supplementation (0.25–1.0 g/day) is cheap, safe and can prevent URI symptoms in those under heavy exertion, athletes should consider vitamin C supplementation during periods of heightened infection risk, e.g., foreign travel for important competition.

Vitamin D

In 1981, the British general practitioner and celebrated epidemiologist, R. Edgar Hope-Simpson was the first to hypothesize that respiratory viral infections (e.g., epidemic influenza) have a "seasonal stimulus" intimately associated with solar radiation. The nature of this "seasonal stimulus" remained undiscovered until the important immunomodulatory effects of the sunlight-dependent secosteroid vitamin D were fully recognized (Berry et al., 2011). Vitamin D production as a result of sunlight ultraviolet (UV)B radiation penetrating the skin typically provides 80%–100% of the body's vitamin D requirements, with a small amount typically coming from the diet (good sources include oily fish and egg yolks). The recommended daily dietary intake of vitamin D for adults (5 µg or 200 IU in the European Union and 15 µg or 600 IU in the USA) assumes that no synthesis occurs and all of a person's vitamin D is from food intake, although that will rarely occur in practice. It is now clear that vitamin D has important roles beyond its well-known effects on calcium and bone homeostasis. Immune cells express the vitamin D receptor, including antigen presenting cells, T cells and B cells, and these cells are all capable of synthesizing the biologically active vitamin D metabolite, 1, 25 hydroxy vitamin D. It is widely accepted that vitamin D plays an important role in enhancing innate immunity via the induction of antimicrobial proteins, yet many of the actions of vitamin D on acquired immunity are anti-inflammatory in nature. Tolerogenic effects of vitamin D (Figure 2) prevent overly exuberant immune responses following T cell activation (e.g., 1, 25 hydroxy vitamin D induces development of regulatory T cells and inhibits production of interferon gamma) (He et al., 2016). There has been growing interest in the benefits of supplementing vitamin D as studies report vitamin D insufficiency (circulating 25(OH)D < 50 nmol/L) in more than half of all athletes and military personnel tested during the winter, when skin sunlight UVB is negligible (Carswell et al., 2018; Close et al., 2013). The overwhelming evidence supports avoiding vitamin D deficiency (circulating 25(OH)D < 30 nmol/L) to maintain immunity and reduce the burden of URI in the general population, athletes and military personnel (He et al., 2016). A recent meta-analysis reported protective effects of oral vitamin D supplementation on respiratory infection (odds ratio 0.88), particularly in those deficient for vitamin D at baseline (odds ratio 0.30) and in those who received oral vitamin D daily or weekly, but not in those receiving one or more large boluses (Martineau et al., 2017). Vitamin D sufficiency can be achieved by safe sunlight exposure in the summer and where screening indicates insufficiency 1,000 IU/day vitamin D_3 supplementation in the winter (Table 4) (Carswell et al., 2018).

SUMMARY

This review provides a new theoretical perspective on how nutrition influences athlete immune health. A paradigm adopted from ecological immunology is presented that includes immune resistance (ability to destroy microbes) and immune tolerance (ability to dampen an immune response and control infection at a non-damaging level). Through this new lens, it is easy to see why studies investigating nutritional supplements targeted at improving immune resistance in athletes show limited benefits: evidence supporting immune suppression in athletes is lacking; that is, if it ain't broke, don't fix it! This new perspective sharpens the focus on nutritional supplements with beneficial tolerogenic properties that reduce the infection burden in otherwise healthy athletes, including probiotics, vitamin C and vitamin D. Further research is required demonstrating the benefits of candidate tolerogenic nutritional supplements to reduce the infection burden in athletes, without blunting training adaptations and side effects. When considering nutritional supplementation, athletes must check the supplement comes from a reliable source and is tested by an established quality assurance program (Maughan et al., 2018). Finally, to limit the infection burden and maintain immune health, athletes should follow the practical recommendations in Table 5.

Ten recommendations to limit the infection burden and maintain immunity in athletes.
1. Where possible, avoid sick people, particularly in the autumn-winter
2. Ensure appropriate vaccination schedule[1]
3. Ensure good hand hygiene[2] and avoid self-inoculation by touching the eyes, nose and mouth
4. Do not train or compete with *below-the-neck* symptoms
5. Monitor and manage all forms of stress including psychosocial and physical
6. Aim for 7–9 h sleep each night
7. Eat a well-balanced diet with adequate protein intake (1.2–1.7 g/kg/BM/day)
8. At the onset of a common cold dissolve zinc lozenges in the mouth (75 mg/day elemental zinc)
9. Consider vitamin C supplementation during heightened infection risk, e.g., traveling for important competition (0.25–1.0 g/day)
10. Consider probiotic supplementation for illness prone/traveling athlete (~10^{10} live bacteria/day)

Table 5. [1]Appropriate vaccination schedule should be discussed with the general practitioner; resources include www.cdc.gov/vaccines and www.nhs.uk/conditions/vaccinations. [2]Hand hygiene advice can be found at www.cdc.gov/handwashing.

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