

# THE IMMUNE SYSTEM AND OVERTRAINING IN ATHLETES: CLINICAL IMPLICATIONS

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**SUMMARY** – The primary objective of this review is to provide an overview of how overtraining and the overtraining syndrome (OTS) affect the immune system of athletes. A secondary objective is to provide sports medicine clinicians with guidance as to how best to prevent and/or treat some of the health consequences of overtraining and the OTS as related to the development of a compromised immune system associated with exercise training. The OTS is a physically debilitating condition that results in athletes being totally compromised in their capacity to perform and compete. Many physiological systems are affected by the process of overtraining and the OTS; but one system in particular, the immune, is highly susceptible to degradation resulting in a reduction in overall health and performance. Monitoring of an athlete's exercise training load and other life stresses is critical to the determination of when their training regimen may be excessive, thereby increasing the risk of OTS developing. Taking steps to mitigate prolonged exposure to extreme stress (training + life or otherwise) in athletes as well as promoting a healthy immune system can significantly aid in the advancement of an athlete's training regimen progression and ultimate physical performance and overall health. In this light, this review provides approaches to aid sports medicine clinicians in promoting a healthy immune system in athletes.

*Key words: Cytokines; Athletes; Stress; Hormones; Sports performance; Overtraining*

## Introduction

The intent of an exercise training program for athletes is to improve their physical performance capacity. In attempting to enhance physical performance and cause positive physiological adaptations, competitive athletes must perform a tremendous amount of exercise on a regular basis. If training regimen stresses are excessive (involving working at too great an intensity, and/or containing too great a volume of work), or an athlete has too many additional life stresses during training, it is possible for physiological mal-adaptations to occur. Such mal-adaptations can lead to phys-

ical performance declines. In the field of exercise and sports physiology, this process of applying excessive training stress is referred to as overtraining (see Table 1 for a detailed operational definition)<sup>1-3</sup>. If overtraining is persistently applied, then there is the potential for the medical condition called the overtraining syndrome (OTS) to develop in the athlete<sup>4-6</sup>. The OTS has been referred to in the past as burnout or staleness and recently it has been proposed that the term unexplained underperformance syndrome be used<sup>1,7,8</sup>.

The OTS is a physically debilitating condition that results in an athlete being totally compromised in their capacity to perform and compete. Table 2 presents some of the signs and symptoms associated with overtraining and OTS development. The information in Table 2 indicates that many physiological systems are affected by the OTS. The primary intent of this paper is to provide an overview on how overtrain-

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*Table 1. Operational definition of overtraining as applied to the exercise training of athletes<sup>1-3</sup>*

Overtraining – a mal-adaptive state related to the physical, behavioral and/or emotional condition of an athlete that occurs when the volume and intensity of his exercise training load becomes excessive and exceeds the individual's ability to recover. It results in a consistent and persistent decline in the physical performance capacity of the athlete relative to their ability to perform training and/or compete in sporting events. The level of decline in physical performance that marks overtraining is highly individualized and dependent upon the observation and interpretation of the athlete, his coach and his athletic trainer.

ing and the OTS affect one system in particular, the immune system. The focus is on the immune system because of new research linking this system to the development of OTS in athletes and due to its over-

*Table 2. Some of the major signs and symptoms of overtraining and the overtraining syndrome*

Physiological function:

- Decreased competitive performance
- Decreased muscular strength
- Increased muscular soreness
- Chronic fatigue
- Reduced tolerance to training overload
- Sleep-wake cycle abnormalities
- Gastrointestinal disturbances
- Reduced testosterone levels
- Reduced thyroid hormone levels
- Elevated cortisol levels
- Elevated creatine kinase
- Altered lactate responses to exercise
- Reduced sexual drive and libido
- Altered heart rate responses to exercise
- Suppressed immune function

Psychological function:

- Increased feelings of depression
- Lethargy and apathy
- Emotional abnormalities
- Loss of appetite
- Lack of competitive drive
- Restlessness
- Difficulty in concentrating

arching impact on so many aspects of human health. To this end, steps toward management and care that sports medicine clinicians can take to prevent and/or treat some of the health consequences of overtraining and OTS as related to the immune system are also presented.

## Background

Currently, it is unclear as to the exact physiological mechanism responsible for inducing the OTS state; however, there are several prevailing theories. These consist primarily of the muscle glycogen hypothesis, central fatigue hypothesis, glutamine hypothesis, sympathetic-parasympathetic hypothesis, hypothalamic-pituitary hypothesis and the cytokine-tissue trauma hypothesis. The latter one, cytokine-tissue trauma, is currently recognized by many scientists as the prevailing hypothesis in the contemporary understanding of the overtraining phenomenon<sup>6,8</sup>.

### Cytokine hypothesis

Dr. Lucille Lakier Smith of South Africa has developed the main concepts of this hypothesis in which it is proposed that with excessive exercise training (i.e. overtraining) there is a high level of musculoskeletal loading from the exercise which results in tissue damage<sup>9</sup>. This tissue damage in turn results in local and systemic inflammation and the activation of immune system responses. If the athlete is not provided with adequate rest and recovery in the training regimen these responses become disproportionately greater because of subsequent repetitive exercise training sessions. Consequently, inflammatory chemical signaling agents of the immune system (i.e. cytokines [which act to facilitate immune cell components such as lymphocytes, neutrophils and monocytes]) act directly and indirectly upon multiple physiological systems to promote alterations in metabolism, behavior, sexual function, endocrine functions, protein synthesis rates, and other immune functions (see Table 2), which ultimately culminates in the OTS symptoms and compromised physical performance<sup>4,10-16</sup>.

### Immune response overview

A key element in Dr. Lakier Smith's hypothesis is the type and pattern of the cytokine response, which leads eventually to a form of immune system suppres-

sion (i.e. immuno-suppression). A highly detailed, in-depth presentation of the immune basis for the development of this immuno-suppression is beyond the scope of this discussion, mainly because the immune system is a highly complex, integral physiological system. Nevertheless, a brief explanatory overview is warranted and presented here. The human immune system is composed of many interdependent cell types that respond collectively to protect the body from pathogenic (i.e. bacterial, parasitic, fungal, viral) infections and from the growth of tumor cells, as well as to manage tissue inflammation responses. Inflammation is one of the first responses of the immune system to infections<sup>17</sup>. The symptoms of inflammation are redness, swelling, heat, and pain in an area, which are caused in part by increased blood flow into a tissue<sup>17,18</sup>. Inflammation is produced by the eicosanoids and cytokines (see following discussion) which are released by injured or infected cells. Eicosanoids include prostaglandins that produce fever and dilation of blood vessels associated with the inflammation, and the leukotrienes that attract certain white blood cells (leukocytes), specifically neutrophils which are associated with tissue repair<sup>18</sup>.

The actions of the immune system can be divided into what are referred to as the *innate* and *adaptive*

immune responses. The innate responses are the first line of immune defense and are viewed as indiscriminately attacking pathogens, while the adaptive responses (which typically follow those of the innate) tend to target specific pathogens and have an antigen-specific memory of such pathogens<sup>18</sup>. Figure 1 gives a schematic overview of the general aspects of these components to the immune system. Both the innate and adaptive immune responses are associated with the production of cytokines. There are a multitude of cytokines that can be produced, and they are typically classified as either proinflammatory or anti-inflammatory in function, although some cytokines have both pro- and anti-inflammatory actions<sup>18</sup>. In Dr. Lakier Smith's theory, the tissue trauma of excessive exercise results in the production of an abundance of proinflammatory cytokines, which then leads to the development of a sickness response or a chronic fatigue-like behavior in an athlete<sup>19-21</sup>. The key proinflammatory cytokines most associated with the theory are interleukin-1 beta (IL-1 $\beta$ ), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- $\alpha$ )<sup>9</sup>. Research by several investigators, especially Dr. Paula Robson-Ansley of the United Kingdom, has produced findings that substantiate the role of proinflammatory cytokines, especially IL-6, as being the key physiological mediators

## The Immune System

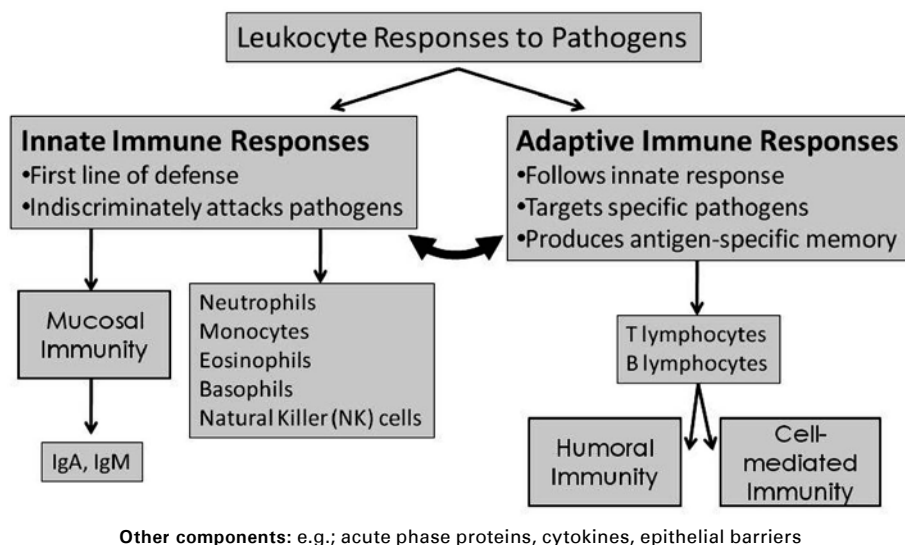


Fig. 1. Schematic overview of the basic components of the immune system (IgA = immunoglobulin A; IgM = immunoglobulin M).

for the development of many of the symptoms associated with OTS<sup>20,21</sup>.

### Immuno-suppression

The production of proinflammatory cytokines also leads to an up-regulation of humoral immunity and suppression of the cell-mediated immunity components of the adaptive immune responses<sup>18</sup>. Because of its immune system role, development of cell-mediated immuno-suppression increases the risk of illness or illness-like symptoms such as upper respiratory symptoms (URS) and infections (URI). The development of such an illness or illness-like symptoms is further associated with compromises in physical performance capacity as athletes find exercise training or competition difficult or impossible under such conditions<sup>22,23</sup>.

This phenomenon of cell-mediated immuno-suppression and increased URS-URI risk is in line with what are referred to as the *Open Window* and *J-Curve response* concepts, which are related to exercise training and illness status as proposed by several eminent health researchers<sup>24-26</sup>. The Open Window concept entails that after an intensive exercise session there is a period of time (3-72 hours) in which there is an increased susceptibility to illnesses, such as URI. With insufficient rest there can be a cumulative effect of consecutive days of intensive training (i.e. the “window” staying open for a longer period of time). This concept of a period of increased susceptibility to illness following exercise has been linked to the occurrence of natural killer (NK) cell inhibition (part of the innate immune responses) that can happen after an exercise session brought on by the increased levels of cortisol, catecholamines, proinflammatory cytokines, and increased prostaglandins (from monocytes) in response to the exercise session<sup>25,27-29</sup>. The NK cell suppression in turn seems to assist in the aspects of the greater adaptive immune responses and the up-regulation of humoral immunity<sup>9,19</sup>. Interestingly, NK cell suppression is especially associated with and found following prolonged-duration aerobic forms of exercise (e.g., marathon training), which have some of the highest incidences of OTS development<sup>5,30,31</sup>. In a similar fashion, the J-Curve response concept states that the risk of URI development initially goes down as a sedentary individual gets involved with light to moderate exercise training for health and fitness, but

Open Window Theory: After intense exercise increased susceptibility to illness

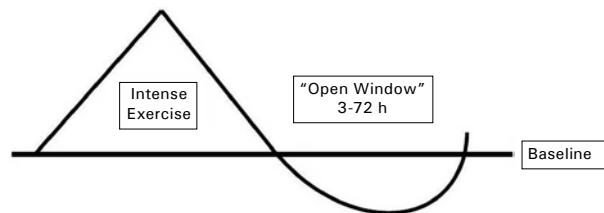


Fig. 2. Open Window theoretical concept associated with immune responses to acute exercise ( $h = \text{hours}$ ).

substantially increases as they move their training to higher levels of volume and/or intensity such as occurs in individuals wanting to compete in sporting activities. Diagrammatic depictions of these concepts are shown in Figures 2 and 3.

An additional final point to consider is “the chicken or the egg” argument about the development of the OTS and immuno-suppression. That is, does the immune system become suppressed and this leads to the OTS, or does an athlete develop the OTS and it results in immuno-suppression? Dr. Lakier Smith’s hypothesis most certainly proposes it is the former scenario and not the latter. However, not all researchers who study overtraining in athletes are in total agreement on this point and further research is needed to rectify this question and devise an answer<sup>5,6,12,22,23</sup>.

The proposed cytokine-tissue trauma theory by Dr. Lakier Smith, while not perfect, does reconcile and connect many of the major pathogenic and clinical

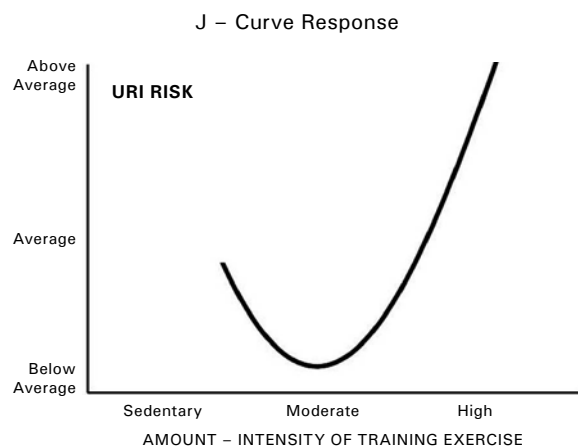


Fig. 3. J-Curve response concept associated with the immune responses to exercise training (URI = upper respiratory infections).

cal manifestations typically seen in athletes who have been diagnosed with the OTS. It is important to recognize, however, that this entire line of research is hampered because the systematic research on overtraining, for ethical reasons, is very limited and in many situations findings consist of case study-like reports. That is, it would be ethically inappropriate to take an athlete who perhaps makes their livelihood through sports participation and intentionally overtrain them and compromise their ability to compete and raise financial sponsorship.

### Training Load: Overload – Over-Reaching – Overtraining

In the last few years, there has been a re-defining of some of the terminology associated with training and the development of OTS. In particular, it is important to this discussion that the reader recognizes the distinctions between the different terms used for the types of training loads. The concept of overload in exercise training progression is typically well understood – i.e. the principle of overload states that a greater than normal exercise load on the body is required for training adaptations to take place and as one adapts to this exercise load it must be progressed to a greater load in order to continually stimulate and induce physical improvement<sup>32,33</sup>. What is typically less clear is the distinction between over-reaching training and overtraining. Over-reaching training is considered a short-term excessive training overload that can actually result in a short-term transient decline in physical performance. However, over-reaching is usually administered for a very short period of time, its training intensity is only slightly excessive, and it is followed by a period of reduced training (~2 weeks) and is done in an attempt to achieve a greater adaptive compensation. Some coaches and sports physiologists feel that cycles of over-reaching are necessary in a training program to produce a super-compensation, which allows the athlete to reach higher levels of competitive performance<sup>8,31</sup>. A task force of the leading scientists from the European Congress of Sports Science (ECSS) have termed this scenario as *functional* over-reaching. In contrast, overtraining is viewed as an exercise training load that is extremely excessive and results in large, more long-lasting performance declines, even when periods of rest and

recovery are allowed, and culminates in persistent declines in physical performance and the potential development of OTS. This scenario has been termed a form of *non-functional* over-reaching by the ECSS task force<sup>31</sup>. According to the task force, if the OTS stage is allowed to be developed in an athlete, the only known course of treatment action appears to be a substantial-extended period of rest for the athlete and removal from the training and competitive environments<sup>4,5,12,34</sup>.

However, it is also critical to recognize that other life stresses encountered by the athletes, besides that of training load alone, have influences on their adaptive responses. Athletes may experience many psychosocial stresses within their educational, personal, occupational, and financial situations<sup>5,7,31</sup>. There is also the stress of traveling to sporting competitions, as well as different cultural settings, competing too frequently, ambient environmental factors, medical/medication conditions or treatments, and poor dietary practices that can all influence how a training load is perceived and tolerated by the athlete<sup>8,22,30,31</sup>. Relative to this last point (diet), it is especially important for the athlete to maintain an adequate daily carbohydrate intake, as insufficient carbohydrate intake will exacerbate the risk of immuno-suppression development<sup>35-38</sup>. All of these aforementioned factors combine to add to the total stress placed upon the athlete and, in doing so, can impact the effectiveness of a training plan to ensure the desired overall performance outcomes are reached. Thus, what may be an appropriate overload or functional over-reaching training dosage could become excessive and inappropriate when combined with the influence of other daily life stresses being placed upon the athlete's physiology. This makes it critical for the coach and athletic trainer to understand and appreciate what are the "events happening" in the life of the athlete besides just what is occurring on the practice field.

### Practical Aspects of Dealing with Immuno-Suppression

Evidence demonstrates that development of exercise training induced immuno-suppression is associated with compromised physical performance<sup>22,25</sup>. But, development of an infection of any type, for any reason, in an athlete can lead to inability to train or

compete at an optimal level<sup>22,26</sup>. Hence, it is important for sports medicine clinicians to recognize preventative and treatment steps and actions to allow for maintenance of appropriate immune function and health in athletes<sup>39</sup>.

### Prevention

As with nearly all medical and health conditions, prevention is far superior to treatment in providing for a more successful overall maintenance of the athlete's training regimen and physical performance capacity. Research supports that there are several proactive steps and actions that athletes and sports medicine clinicians can take to reduce the risk of development of an infection or a compromised immune system<sup>22,40</sup>. These include such items as the athletes should:

- keep vaccine(s) administration updated
- attempt to minimize contact with known infected or sick people
- wash hands frequently throughout the day
- limit mouth/nose contact when with infection symptoms (i.e. URS)
- do not share drinks with other athletes
- do not share towels or washcloths with other athletes
- isolate team members from others if displaying infection symptoms
- protect airway from very cold or dry air when performing strenuous exercise
- maintain adequate daily dietary carbohydrate intake (~60% daily caloric intake)
- wear proper clothing for weather conditions and avoid getting cold-wet after exercise
- attempt to get a minimum of 7-hours sleep a night
- avoid rapid weight loss and "crash" dieting approaches to weight loss
- wear clothing to prevent unnecessary hazardous dermatological exposures (e.g., shower shoes)
- whenever possible minimize other life stressors

Evidence-based findings support that following these steps can significantly decrease the risk of infections developing in athletes<sup>18,22</sup>. Obviously, it may not be completely realistic to incorporate all of the above into daily behaviors and lifestyles of every athlete.

### Treatment

Even with compliance to all of the abovementioned preventative steps and actions there is always the likelihood that an athlete will develop an infection of some type. This condition would be apparent if they display symptoms such as sore throat, coughing, runny/congested nose, muscle/joint pain-edema, headache, fever, malaise, diarrhea and vomiting<sup>18</sup>. Recently, a group of leading exercise immunologists have recommended the following course of action when clinicians are dealing with an athlete displaying overt signs of an infection and/or inflammation<sup>22,40</sup>.

- day 1 of illness – no strenuous exercise or competition; they should drink plenty fluids; keep from getting wet/cold; minimize life stress. If feverish – induce nasal drainage, and use decongestants-analgesics;
- day 2 of illness – if symptoms worsen – no exercise, rest. If no fever or worsening of symptoms, then light-easy exercise (30-45 minutes) allowed;
- day 3 of illness – if fever, symptoms persist, consult physician. If no fever or worsening of symptoms, then light-moderate exercise (45-60 minutes) allowed; and
- day 4 of illness – if no symptom relief, no exercise – continued rest; have an office visit with a physician. If relief (1<sup>st</sup> day of improved symptoms) and no fever, then light-easy exercise (as noted above). Use the same number days as off to return and step up to normal training; monitor tolerance to gradually increasing exercise intensity, take additional days off if poor tolerance (if necessary).

Finally, in order to optimize treatment, it is critical that all members of the healthcare team treating the athlete have good communication with one another concerning the progression and responses of the athlete if symptoms develop and persist<sup>41-43</sup>.

### Conclusions

In conclusion, competitive athletes subject themselves to a high level of exercise training stress in order to enhance their physical performance capacity. This training stress, as well as the other stresses of life these athletes encounter, places them at a great risk of developing the OTS. The physiological cause(s) of the OTS is presently uncertain, but one of the leading

theories is the “cytokine tissue-trauma” hypothesis. This hypothesis proposes that undue proinflammatory cytokine responses to excessive exercise training (overtraining) creates a “sickness behavior” response, development of immuno-suppression, and ultimately leads to a decline in physical performance capacity of the athlete. This hypothesis presents one of the most encompassing and complete perspectives on how exercise training and development of the OTS are explicitly linked mechanistically to a compromised physiological system – i.e. the immune system. Additional future research, however, is necessary and warranted to collect further evidence to substantiate or refute this hypothesis.

Steps to prevent and reduce the risk of infection involve sports medicine clinicians helping foster and develop appropriate behaviors and actions in athletes (as noted above). Likewise, once an infection-inflammation response is manifested in the athlete, it is critical for clinicians to take the actions to mitigate the severity and impact of the illness development through the recommended intervention steps. By doing so, the clinician can promote a more rapid return to normal health and exercise training level in the athlete.

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## Sažetak

## IMUNI SUSTAV I PREKOMJERAN TRENING KOD ŠPORTAŠA: KLINIČKE IMPLIKACIJE

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Primarni cilj ovoga rada je dati pregled načina na koje prekomjerman trening i sindrom prekomjernog treninga utječu na imuni sustav športaša. Sekundarni cilj je pružiti kliničarima koji se bave športskom medicinom smjernice kako najučinkovitije spriječiti i/ili liječiti neke od zdravstvenih posljedica prekomjernog treninga i sindroma prekomjernog treninga u odnosu na razvoj poremećaja imunog sustava udruženih s treningom. Sindrom prekomjernog treninga je stanje onemoćalosti koje kod športaša potpuno onemogućava športske aktivnosti i natjecanje. Proces prekomjernog treninga i sindroma prekomjernog treninga utječe na mnoge fiziološke sustave, no jedan od tih sustava, tj. imuni sustav, osobito je osjetljiv na te utjecaje, što dovodi do poremećaja općeg zdravstvenog stanja i smanjene sposobnosti za športske aktivnosti. Ključno je pratiti opterećenje treningom i drugim životnim stresnim situacijama kod pojedinog športaša kako bi se utvrdilo kad je režim treniranja možda pretjeran pa postoji opasnost od razvoja sindroma prekomjernog treninga. Poduzimanjem mjera za ublažavanje izloženosti krajnjem stresu (trening + životne situacije ili drugo) kod športaša te podržavanjem zdravog imunog sustava može se značajno pomoći u promicanju progresivnog režima treniranja i krajnje fizičke učinkovitosti, kao i zdravlja općenito. U tom smislu ovaj pregled upućuje kako pomoći kliničarima koji se bave športskom medicinom u promicanju zdravog imunog sustava kod športaša.

Ključne riječi: *Citokini; Športaši; Stres; Hormoni; Uspjeh u sportu; Prekomjerman trening*

