Allergy, Asthma and the Athlete

Sergio Bonini
Professor of Medicine
Second University of Naples
Institute of Translational Pharmacology
Italian National Research, Rome
se.bonini@gmail.com

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The GA2LEN Olympic Study
Study Protocol

• History
  - Questionnaires (AQUA, SF36, QUAQUA)
• Physical examination
• Skin tests
• Pulmonary function tests
  - Spirometry, Broncho-dialator and –constrictor (methacholine, exercise, EVH, mannitol) tests
• eNO and exhaled breath condensate
• Serum
• Urines
The GA2LEN Olympic Study
Study population by Country

<table>
<thead>
<tr>
<th>Country</th>
<th>Athletes participating in the Olympics</th>
<th>Athletes not qualifying for the Olympics</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denmark</td>
<td>59</td>
<td>17</td>
<td>76</td>
</tr>
<tr>
<td>Finland</td>
<td>25</td>
<td>3</td>
<td>28</td>
</tr>
<tr>
<td>Greece</td>
<td>56</td>
<td>47</td>
<td>103</td>
</tr>
<tr>
<td>Germany</td>
<td>337</td>
<td>0</td>
<td>337</td>
</tr>
<tr>
<td>Norway</td>
<td>59</td>
<td>22</td>
<td>81</td>
</tr>
<tr>
<td>Poland</td>
<td>222</td>
<td>0</td>
<td>222</td>
</tr>
<tr>
<td>Portugal</td>
<td>61</td>
<td>0</td>
<td>61</td>
</tr>
<tr>
<td>Spain</td>
<td>176</td>
<td>0</td>
<td>176</td>
</tr>
<tr>
<td>Italy</td>
<td>208</td>
<td>227</td>
<td>435</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1203</strong></td>
<td><strong>316</strong></td>
<td><strong>1519</strong></td>
</tr>
</tbody>
</table>
The Olympic Study

Sensitizations

- Skin test + athletes: 43%
- Skin test - athletes: 57%

Graph showing sensitizations to various allergens:
- DPF
- DPT
- Graminacee
- Parietaria
- Olea
- Ambrosia
- Cipresso
- Alternaria
- Gatto
- Cane
- Artemisia
- Betulla

Network of Excellence

Global Allergy and Asthma European Network
• Sensitization 32.6%

• Sensitization 56.5% in 84.4% to multiple allergens

World Asthma Congress, Montecarlo 2009
The Olympic Study

30.3
25.3
14.9
12.4
11.3
1.6

Rhinitis
Conjunctivitis
Asthma
Dermatitis
EIB
Anaphylaxis
One in three had respiratory complaints

Cross sectional; n=1662 athletes qualified for the 2008 Olympics

<table>
<thead>
<tr>
<th>Country</th>
<th>Chest tightness</th>
<th>Shortness of breath</th>
<th>Allergic rhinitis</th>
<th>Allergic conjunctivitis</th>
<th>Atopic eczema</th>
<th>Anaphylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norway</td>
<td>23 (30.6%)</td>
<td>35 (44.9%)</td>
<td>17 (21.5%)</td>
<td>5 (6.4%)</td>
<td>23 (29.5%)</td>
<td>6 (7.8%)</td>
</tr>
<tr>
<td>Denmark</td>
<td>41 (56.2%)</td>
<td>41 (56.2%)</td>
<td>20 (27.4%)</td>
<td>9 (12.3%)</td>
<td>21 (28.8%)</td>
<td>11 (15.7%)</td>
</tr>
<tr>
<td>Finland</td>
<td>10 (40.0%)</td>
<td>12 (48.0%)</td>
<td>12 (48%)</td>
<td>10 (40%)</td>
<td>10 (40%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Poland</td>
<td>37 (16.7%)</td>
<td>11 (23.4%)</td>
<td>60 (27%)</td>
<td>27 (12.2%)</td>
<td>59 (26.7%)</td>
<td>38 (17.2%)</td>
</tr>
<tr>
<td>Germany</td>
<td>74 (22.5%)</td>
<td>105 (31.9%)</td>
<td>68 (20.7%)</td>
<td>41 (12.5%)</td>
<td>154 (46.8%)</td>
<td>42 (12.8%)</td>
</tr>
<tr>
<td>Greece</td>
<td>36 (29.3%)</td>
<td>48 (38.7%)</td>
<td>26 (21.0%)</td>
<td>15 (12.1%)</td>
<td>45 (36.3%)</td>
<td>4 (3.2%)</td>
</tr>
<tr>
<td>Italy</td>
<td>37 (12.1%)</td>
<td>46 (15.1%)</td>
<td>46 (15.0%)</td>
<td>38 (12.5%)</td>
<td>61 (20%)</td>
<td>9 (2.9%)</td>
</tr>
<tr>
<td>Spain</td>
<td>57 (30.7%)</td>
<td>60 (34.1%)</td>
<td>46 (26.1%)</td>
<td>36 (20.5%)</td>
<td>51 (29%)</td>
<td>3 (1.7%)</td>
</tr>
<tr>
<td>Portugal</td>
<td>9 (20%)</td>
<td>14 (31.1%)</td>
<td>9 (20%)</td>
<td>2 (4.4%)</td>
<td>11 (24.4%)</td>
<td>2 (4.4%)</td>
</tr>
<tr>
<td>Total</td>
<td>324 (23.6%)</td>
<td>372 (30.9%)</td>
<td>304 (22.0%)</td>
<td>183 (13.3%)</td>
<td>435 (31.6%)</td>
<td>116 (8.5%)</td>
</tr>
</tbody>
</table>

Data in file, Olympic Study
The Olympic study

Asthma and exercise induced bronchospasm (EIB)

- Sydney 2000: 10.9% (n = 265)
- Beijing 2008: 21.6% (n = 373)
# Prevalence of asthma among summer sports athletes

<table>
<thead>
<tr>
<th>Athlete group (n)</th>
<th>Method</th>
<th>Prevalence (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australian 1976 Olympic team (185)</td>
<td>Physical examination</td>
<td>9.7</td>
<td>Fitch KD, 1984</td>
</tr>
<tr>
<td>Australian 1980 Olympic team (106)</td>
<td>Physical examination</td>
<td>8.5</td>
<td>Fitch KD, 1984</td>
</tr>
<tr>
<td>US 1984 Olympic team (597)</td>
<td>Questionnaire, treadmill exercise test in selected athletes</td>
<td>4.3</td>
<td>Voy RO, 1984</td>
</tr>
<tr>
<td>1986 Football players from University of Iowa (156)</td>
<td>Questionnaire, methacholine challenge</td>
<td>11.5</td>
<td>Weiler et al., 1986</td>
</tr>
<tr>
<td>Swiss athletes from various sport events (2060)</td>
<td>Questionnaire</td>
<td>3.7</td>
<td>Helbling and Muller, 1991</td>
</tr>
<tr>
<td>Spanish 1982 Olympic team (495)</td>
<td>Questionnaire</td>
<td>4.4</td>
<td>Drobnic F, 1994</td>
</tr>
<tr>
<td>Runners from Finnish national team (103)</td>
<td>Questionnaire</td>
<td>15.5</td>
<td>Tikkanen and Helenius, 1994</td>
</tr>
<tr>
<td>Swimmers from United States (738)</td>
<td>Questionnaire</td>
<td>13.4</td>
<td>Potts J, 1996</td>
</tr>
<tr>
<td>US Track and Field Championship games (73)</td>
<td>Exercise test (competition)</td>
<td>15.1</td>
<td>Schoene RB et al., 1997</td>
</tr>
<tr>
<td>Track and Field athletes, swimmers (162)</td>
<td>Questionnaire, spirometry, histamine challenge</td>
<td>22.8</td>
<td>Helenius et al., 1998</td>
</tr>
<tr>
<td>US 1996 Olympic team (699)</td>
<td>Questionnaire</td>
<td>15.3</td>
<td>Weiler et al., 1998</td>
</tr>
<tr>
<td>Australian 2000 Olympic team (214)</td>
<td>Questionnaire, skin test</td>
<td>21.9</td>
<td>Katelaris et al., 2000</td>
</tr>
<tr>
<td>Italian 2000 Pre-Olympic team (265)</td>
<td>Questionnaire, skin test, spirometry</td>
<td>10.9</td>
<td>Lapucci et al., 2003</td>
</tr>
</tbody>
</table>

Modified from Helenius and Hahtela, 2008
## Prevalence of asthma among winter sports athletes

<table>
<thead>
<tr>
<th>Athlete group (n)</th>
<th>Method</th>
<th>Prevalence %</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-country skiers (42)</td>
<td>Questionnaire, spirometry, methacholine challenge</td>
<td>54.8</td>
<td>Larsson et al., 1993²⁵</td>
</tr>
<tr>
<td>Cross-country skiers (171)</td>
<td>Questionnaire, spirometry, methacholine challenge</td>
<td>12 (Norway) 42 (Sweden)</td>
<td>Sue-Chu et al., 1996²⁶</td>
</tr>
<tr>
<td>Figure skaters</td>
<td>Exercise test</td>
<td>35 (exercise-induced bronchospasm)</td>
<td>Mannix et al., 1996²⁷</td>
</tr>
<tr>
<td>Ice hockey players</td>
<td>Questionnaire, spirometry, methacholine challenge, exercise test</td>
<td>19.2 11.5 (exercise-induced bronchospasm)</td>
<td>Leuppi et al., 1998²⁸</td>
</tr>
<tr>
<td>US 1998 winter Olympic team (196)</td>
<td>Questionnaire</td>
<td>21.9 60.7 (cross-country, etc.) 24 (alpine, etc.) 2.8 (bobsled, etc.)</td>
<td>Weiler et al., 2000²⁷</td>
</tr>
<tr>
<td>US 1998 winter Olympic team</td>
<td>Exercise challenge, spirometry</td>
<td>23 (all, exercise-induced bronchospams) 50 (cross-country)</td>
<td>Wilber et al., 2000²⁹</td>
</tr>
<tr>
<td>Ice hockey players</td>
<td>Questionnaire, spirometry, histamine challenge</td>
<td>22 (total asthma) 13 (current asthma)</td>
<td>Lumme et al., 2003³⁰</td>
</tr>
</tbody>
</table>
Prevalence of allergic rhinitis in athletes

16.8%  Helbling et al. 1991
29.0%  Katelaris et al. 2000
25.3%  Bonini et al. 2003
30.3%  Bonini et al. 2008
Allergic skin diseases

• Exercise-induced urticaria
  (cold, aquagenic, solar, pressure)

• Contact dermatitis
  (from rubber masks, dresses, instruments)
Exercise-induced anaphylaxis

- Often associated with food allergy
- Consider allergens contaminating food
- Consider in polysensitized subjects cross-reacting or pan-allergens (PR-10 proteins, profilins, tropomyosins, etc) or molecular allergens potentially responsible for severe allergic reactions (Ara h 1,2,3; Pru p 3; Cor a 8)
Why Allergy and Asthma are so frequent in athletes?
Allergens responsible for sensitisation

- Dermatophagoides pteronyssinus (2)
- Grasses (2)
- Cat dander (2)
- Olive tree (2)
- Pellitory (2)
- Alternaria tenuis (2)
- Wormwood (2)
- Ragweed (2)

(1) % of athletes, (2) % of positive skin tests
Physical exercise induces a neuro-endocrine-immune adaptative response aimed at maintaining homeostasis.
Physical exercise

Risk of infections

Hook Hypothesis

Physical exercise

Overtraining

Immune response

Open Window Hypothesis

Transient immunodeficiency
Effect on T helper sub-populations balance

Higher susceptibility to infections

Higher prevalence of atopy
Infectious diseases

AIDA study: Allergy and Infectious Diseases in Athletes

• 265 pre-Olympic athletes
• 3 or more than 3 URTI episodes in the last 12 months in 15.9%
• More than 1 Herpes labialis episode in the last 12 months in 12.1%
• Decreased number of CD3+ lymphocytes in 17.0% of athletes with a preferential reduction of CD4+ subpopulation (40.7+/−8.2), well related to clinical picture
Cytokine serum profile in allergic and non-allergic top athletes

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>A vsCTRL</th>
<th>AA vs NAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1ra</td>
<td>↓ &lt; 0.0001</td>
<td>↑ NS (0.9280)</td>
</tr>
<tr>
<td>IL-4</td>
<td>↓ &lt; 0.05</td>
<td>↑ NS (0.0784)</td>
</tr>
<tr>
<td>IL-6</td>
<td>↓ &lt; 0.0001</td>
<td>↑ NS (0.1882)</td>
</tr>
<tr>
<td>IL-7</td>
<td>↓ &lt; 0.0001</td>
<td>↑ NS (0.3663)</td>
</tr>
<tr>
<td>IL-8</td>
<td>↓ &lt; 0.0001</td>
<td>↑ NS (0.9875)</td>
</tr>
<tr>
<td>IL-12</td>
<td>↓ &lt; 0.0001</td>
<td>↑ NS (0.9093)</td>
</tr>
<tr>
<td>IL-13</td>
<td>NS (0.1659)</td>
<td>NS (0.9436)</td>
</tr>
<tr>
<td>IL-17</td>
<td>↓ &lt; 0.0001</td>
<td>↑ NS (0.3984)</td>
</tr>
<tr>
<td>Eotaxin</td>
<td>↓ &lt; 0.0001</td>
<td>↑ NS (0.9749)</td>
</tr>
<tr>
<td>IFN-gamma</td>
<td>↓ &lt; 0.0001</td>
<td>↑ NS (0.8752)</td>
</tr>
<tr>
<td>IP-10</td>
<td>↓ &lt; 0.0001</td>
<td>↑ NS (0.5584)</td>
</tr>
<tr>
<td>MCP-1</td>
<td>↓ &lt; 0.0001</td>
<td>↑ NS (0.5427)</td>
</tr>
<tr>
<td>MIP-1alfa</td>
<td>NS (0.0852)</td>
<td>NS (0.9187)</td>
</tr>
<tr>
<td>MIP-1beta</td>
<td>↓ &lt; 0.0001</td>
<td>↑ NS (0.2979)</td>
</tr>
<tr>
<td>RANTES</td>
<td>↓ &lt; 0.05</td>
<td>↑ NS (0.8690)</td>
</tr>
</tbody>
</table>

- AA = 41; NAA = 51; CTRL = 49
- Luminex assay
- For all cytokines measured, apart from IL-13 and MIP-1a, serum levels in athletes were significantly lower than in controls
- No differences were observed between allergic and non-allergic athletes
- The median value of the IFNg/IL-4 ratio was lower in athletes than in controls (33.0 vs. 37.9), particularly in the allergic ones (27.8)

Bonini M. et al.
Abs. presented to the 2011 AAAAI Congress
Physical exercise as a trigger on target organs

- Increased ventilation
- Nasal filter by-pass
- Climate condition (cold-dry air)
- Exposure to indoor and outdoor allergens
- Exposure to pollutants ($O_3$, $PM_{2.5-10}$, $NO_2$, $SO_2$)
- Exposure to irritants (chlorine)
Epithelium dysfunction in asthma

Stephen T. Holgate, MD, DSc  Southampton, United Kingdom
Potential role of epithelium damage in EIB

The Role of the Airway Epithelium and its Interaction with Environmental Factors in Asthma Pathogenesis

Stephen T. Holgate¹, Graham Roberts¹, Hasan S. Arshad¹, Peter H. Howarth¹, and Donna E. Davies¹

DOI: 10.1513/pats.200907-072DP
Internet address: www.atsjournals.org

A new look at the pathogenesis of asthma

Stephen T. Holgate,¹ Hasan S. Arshad,¹ Graham C. Roberts,¹ Peter H. Howarth,¹ Philipp Thurner,† and Donna E. Davies²

NGF serum levels in elite athletes

Allergic athletes: n = 44
Non allergic athletes: n = 52
Healthy controls: n = 49

470.7 ± 882.2 pg/ml
281.7 ± 670.7 pg/ml
174.1 ± 483.7 pg/ml

AA + AnA vs HC
P < 0.001
Airway inflammation in asthmatic competitive swimmers may result of mixed type effects

Sputum eosinophilia and increased $F_{E_{NO}}$ of the allergic inflammation

Sputum neutrophils and airway responsiveness of training/environment exposure

A Moreira; L Delgado; C Palmares, T Haahtela. Eur Respir J. 2008;31(5):1139-41
Allergic rhinitis in 16/40 (40.0%)
NARES in 2/40 (5.0%)
Infective rhinitis 2/40 (5.0%)
“Swimmer’s nose” in 20/40 (50.0%)

Negative Skin Prick-test

Prevaling symptoms

- Nasal Obstruction
- Sneezing
- Rhinorrea
- Itching
- Burning

Bonini M. et al. JACI 2007; 119: S163
Diagnosis of allergy in athletes
AQUA©: Allergy Questionnaire for Athletes: Development and Validation

MATTEO BONINI1,10, FULVIO BRAIDO1,10, ILARIA BAIARDINI1,10, STEFANO DEL GIACCO2, CLAUDIA GRAMICCIIONI3,10, MASSIMO MANARA4, GIULIA TAGLIAPIETRA5, ANNA SCARDIGNO6, VITTORIO SARGENTINI7, MARIO BROZZI8, GUIDO RASI3,10, and SERGIO BONINI3,9,10

1Department of Internal Medicine, University of Genoa, ITALY; 2Department of Medical Sciences, University of Cagliari, ITALY; 3Italian National Research Council, Institute of Neurobiology and Molecular Medicine (CNR-INMM, ARTOV), ITALY; 4F.C. Parma Calcio, Parma, ITALY; 5Brescia Calcio, Brescia, ITALY; 6Centro Studi di Medicina dello Sport, Università Cattolica del Sacro Cuore, Rome, ITALY; 7ASL Roma A, Rome, ITALY; 8A.S. Roma (RomaLab), Rome, ITALY; 9Department of Internal Medicine, Second University of Naples, ITALY; and 10Member of GA2LEN Unit, ITALY

ABSTRACT

BONINI, M., F. BRAIDO, I. BAIARDINI, S. DEL GIACCO, C. GRAMICCIONI, M. MANARA, G. TAGLIAPIETRA, A. SCARDIGNO, V. SARGENTINI, M. BROZZI, G. RASI, and S. BONINI. AQUA©: Allergy Questionnaire for Athletes: Development and Validation. Med. Sci. Sports Exerc., Vol. 41, No. 5, pp. 000–000, 2009. Purpose: Despite the high and increasing prevalence of allergic diseases in athletes, allergy diagnostics is not part of the routine medical examination in sports medicine. This study reports the development and validation of an easy and reliable questionnaire for screening allergy in athletes. Methods: AQUA© was derived from the European Community Respiratory Health Survey Questionnaire. On the basis of open interviews with team doctors, coaches, and athletes, questions were added about: the type, duration, and intensity of training; exercise-related allergic and infectious symptoms; social habits (smoking); drug and food supplements intake; antidoping regulations. The final version of the questionnaire, made of 25 selected questions, was validated in 128 professional soccer players who underwent accurate history taking, medical examination, skin prick testing, and/or specific IgE determination. On the basis of the correlation with objective allergy (positive skin tests to at least one allergen), questions were scored from 1 to 5 according to their positive likelihood ratio. Results: Skin tests (gold standard for validation) were positive in 46.8% of soccer players. Mean total AQUA© score was 9.4 ± 7.8 in allergic athletes versus 1.3 ± 2.3 in nonallergic athletes. A total AQUA© score of ≥5 was shown to have the best positive predictive value for allergy (0.94) with a specificity of 97.1% and a sensitivity of 58.3%. Conclusions: AQUA©, produced in 10 European languages, is a validated, easy, and reliable tool for calling attention on the high prevalence of allergy in athletes. Key Words: SOCCER PLAYERS, SPORTS ALLERGY, EXERCISE-INDUCED ASTHMA, EXERCISE-INDUCED BRONCHOCONSTRICTION, UPPER RESPIRATORY TRACT INFECTIONS
AQUA (Methodology)

- Derived from the ECRHS questionnaire
- On the basis of interviews with team doctors, coaches and athletes specific questions were added
- Preliminary administration to verify comprehensiveness and reproducibility
- Administration to 128 professional soccer players of 6 elite teams
- Validation against documented clinical allergy (Anamnensis, OE, Skin-prick-test and/or Phadiatop)
- Key-questions scored from 1 to 5 on the basis of their positive likelihood ratio
AQUA: total score
AQUA
(Results)

• A total score > 5 showed the best positive predictive value for allergy (0.93) with a specificity of 97.1% and a sensitivity of 58.3%.

• The questionnaire, translated in 10 languages was used in the framework of the GA2LEN Olympic Study.

• The questionnaire, protected by copyright, is available on request (free for non-commercial use).