Urticaria In Athletes

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Publications

1- Allergy Cure!, Massoud Mahmoudi, Author, 2005, Book Surge
2- Allergy and Asthma: Practical Diagnosis and Management: Lange Series, 2008, Mac Graw Hill, Massoud Mahmoudi (Editor and Author)
3- Immunology Made Ridiculously Simple
   Massoud Mahmoudi, 2009, MedMaster, Inc.
4- Challenging Cases in Allergy and Immunology, 2009
   Massoud Mahmoudi, Editor/Author, Springer

Publications

5- Challenging Cases in Allergic Diseases of the Skin
   Massoud Mahmoudi, Editor/Author, Springer, 2010
6- Challenging Case in Pulmonology, Massoud Mahmoudi, Editor/Author, Springer, 2011
7- Challenging cases in Rheumatology and Diseases of the Immune System, Massoud Mahmoudi, Editor/Author, Springer, 2012
Objectives
1-Diagnose urticaria and angioedema in athletes
2-Diagnose Anaphylaxis in athletes
3-Recognize the athletes' risky environment
4-Prevent, treat, and manage urticaria, angioedema, and anaphylaxis in athletes.

Overview
- Urticaria and Angioedema: Definition
- Types of Urticaria
- Urticaria in Athletes
- Exercise-Induced Anaphylaxis
- Prevention-Management

Urticaria & Angioedema
This common disorder affects up to 20% of population some time in life. It presents as pruritic, erythematous papules or plaques, with superficial swelling of the dermis.
Angioedema vs Urticaria

- Urticaria – involving the superficial dermis
  Most often characterized by intense pruritis due to histamine effect
- Angioedema – involving deeper dermal and subcutaneous layers
  - May be pruritic but often characterized as a deeper and dull discomfort – burning quality
  - Level of involvement may dictate detection and subsequent perception by patient
Chronic Urticaria/Angioedema (Mast cell driven)

![Bar chart showing gender distribution]

- 50% Women
- 40% Men

Urticaria 40%
Angioedema 10%
Urticaria & Angioedema

Table 1 - General Classification of Urticaria

<table>
<thead>
<tr>
<th>Type</th>
<th>Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>Duration &lt; 6 wk</td>
</tr>
<tr>
<td>Chronic</td>
<td>Duration &gt; 6 wk</td>
</tr>
<tr>
<td>Physical Urticarias</td>
<td>&quot;Draw on skin,&quot; from mechanical pressure</td>
</tr>
<tr>
<td>Dermatographism</td>
<td>Induced by exposure to cold water/air</td>
</tr>
<tr>
<td>Cold</td>
<td>Hives 4-6 h after applied pressure</td>
</tr>
<tr>
<td>Delayed pressure</td>
<td>Induced by exposure to 2800-5000 A˚ wavelength of sunlight</td>
</tr>
<tr>
<td>Solar</td>
<td>Induced by exposure to heated material</td>
</tr>
<tr>
<td>Heat, localized</td>
<td>Punctate wheals associated with exposure to heat, exercise, and anxiety</td>
</tr>
<tr>
<td>Heat, generalized, or cholinergic</td>
<td></td>
</tr>
<tr>
<td>Exercise-induced (anaphylaxis)</td>
<td>Large hives induced by exercise alone</td>
</tr>
<tr>
<td>Aquagenic</td>
<td>Induced by contact with water</td>
</tr>
<tr>
<td>Vibratory</td>
<td>Induced by vibratory forces</td>
</tr>
<tr>
<td>Collagen vascular disease</td>
<td>Associated with individual lesions lasting &gt; 24 h</td>
</tr>
</tbody>
</table>

Diagnostic Evaluation

<table>
<thead>
<tr>
<th>Type of Urticaria</th>
<th>Diagnostic Testing</th>
<th>Additional Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>Skin prick testing or ImmunoCAP (Phadia AB, Uppsala, Sweden)/RAST for foods, elimination of eliciting factor when indicated</td>
<td>Food challenge when indicated</td>
</tr>
<tr>
<td>Chronic</td>
<td>Complete blood count, ESR or CRP, total IgE, autoimmune tests, anti-thyroid antibodies, ANA, chronic infections, ie, Helicobacter pylori</td>
<td>Autologous serum skin test, basophil mediator assay, flow cytometry using basophil activation markers: CD63 or CD203c</td>
</tr>
<tr>
<td>Physical urticarias</td>
<td>Linear stroking of skin causes a wheal</td>
<td></td>
</tr>
<tr>
<td>Dermatographism</td>
<td>5- to 15-min application of ice cube causes a wheal on removed within 5 min</td>
<td></td>
</tr>
<tr>
<td>Cold</td>
<td>Application of pressure perpendicular to skin over specified time causes a wheal</td>
<td></td>
</tr>
<tr>
<td>Delayed pressure</td>
<td>Irradiation with UV solar stimulator or Evaluate for other photosensitivities visible light</td>
<td></td>
</tr>
<tr>
<td>Solar</td>
<td>Apply warm material to arm</td>
<td></td>
</tr>
<tr>
<td>Local heat</td>
<td>Exercise challenge</td>
<td></td>
</tr>
<tr>
<td>Cholinergic</td>
<td>Intradermal injection of methacholine produces a localized hive</td>
<td></td>
</tr>
<tr>
<td>Aquagenic</td>
<td>Exposure to water for an min</td>
<td></td>
</tr>
<tr>
<td>Vibratory</td>
<td>Vortex for several minutes</td>
<td></td>
</tr>
<tr>
<td>Collagen vascular disease</td>
<td>Skin biopsy, complete blood count, ESR, AHA</td>
<td></td>
</tr>
<tr>
<td>Urticarial vasculitis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Pharmacotherapeutic Management of Urticaria

<table>
<thead>
<tr>
<th>H1 Antagonists</th>
<th>Drug (Example)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antihistamines are first-line treatment for acute and chronic urticaria.</td>
<td></td>
</tr>
<tr>
<td>Sedating</td>
<td>Diphenhydramine</td>
<td>Side effects include sedation, cognitive impairment, dry mouth, and urinary retention especially at higher doses.</td>
</tr>
<tr>
<td></td>
<td>Hydroxyzine</td>
<td>Doxepin is a tricyclic antidepressant and an H1 and H2 antagonist.</td>
</tr>
<tr>
<td></td>
<td>Cetirizine</td>
<td>Cyproheptadine is the drug of choice for cold-induced urticaria.</td>
</tr>
<tr>
<td></td>
<td>Fexofenadine</td>
<td>Ranitidine, Cimetidine</td>
</tr>
<tr>
<td></td>
<td>Desloratadine</td>
<td>Recommended in conjunction with an H1 antagonist.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>H2 Antagonists</th>
<th>Drug (Example)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ranitidine, Cimetidine</td>
<td>Generally effective in severe episodes of acute and chronic urticaria.</td>
</tr>
<tr>
<td></td>
<td>Pseudocholinesterase</td>
<td>Often required to control urticarial vasculitis.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Corticosteroids</th>
<th>Drug (Example)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>Generally effective in severe episodes of acute and chronic urticaria. Often required to control urticarial vasculitis. Titrates to most effective lowest dose or alternate-day dose for long term. Monitor for long-term corticosteroid-induced side effects.</td>
<td></td>
</tr>
</tbody>
</table>
Leukotriene Receptor Antagonist

- Montelukast
- Zafirlukast

Efficacy in treatment of urticaria has not been established.

Other Immunomodulatory/Anti-inflammatory Agents

- Thyroxine
  May be effective in patients with chronic urticaria and thyroid autoimmunity
- Cyclosporine
  Effective in treatment of chronic urticaria
  Monitor blood pressure and renal function
- Methotrexate
  Cyclophosphamide
  Dapsone
  Colchicine
  Efficacy not established
  Significant potential side effects
- Rofecoxib
  Safety and efficacy not established
- Intravenous immunoglobulin
  May be effective in chronic autoimmune urticaria
  Plasmapheresis
  May be effective in hypocomplementemic urticarial vasculitis
- Hydroxychloroquine
  May be effective in delayed-pressure urticaria

Anaphylaxis

Anaphylaxis is an allergic reaction that is a result of an exposure to a specific allergen resulting in a multiple organ failure and death. An immediate intervention is a key to abortion of the condition.

Mechanisms and triggers of anaphylaxis in the community

Immunologic mechanisms (IgE-dependent)

- Foods, such as peanut, tree nut, shellfish, fish, milk, egg, sesame, and food additives
- Medications, such as β-lactam antibiotics and NSAIDs, and biological agents
- Venoms, such as stinging insects (Hymenoptera)
- Natural rubber latex
- Occupational allergens
- Animal danders (prostate-specific antigens)
- Inhalants, such as horse, hamster, and other animal danders and grass pollen (rare)
- Radiocontrast media

Immunologic mechanisms (IgE-independent, formerly classified as anaphylactoid reactions)

- Dextran, such as high-molecular-weight iron dextran
- Infusions
- Radiocontrast media
- Nonimmunologic mechanisms
- Physical factors, such as ozone, cold, heat, and sunlight/UV radiation
- Ethanol
- Medications, such as opioids

Idiopathic anaphylaxis

Consider the possibility of hidden or previously unrecognized allergens

Mastocytosis/clonal mast cell disorder

Consider the possibility of mastocytosis/clonal mast cell disorder
### Patient factors that increase risk of anaphylaxis severity and fatality

<table>
<thead>
<tr>
<th>Age</th>
<th>Infants: Underrecognition, underdiagnosis; no appropriate epinephrine auto-injector dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adolescents and young adults: Risk-taking behavior, sedatives/hypnotics/antidepressants/ethanol/recreational drugs</td>
</tr>
<tr>
<td></td>
<td>Pregnancy: During labor and delivery, antibiotic prophylaxis against neonatal group B streptococcal infection is a common trigger</td>
</tr>
<tr>
<td></td>
<td>Elderly: Risk of fatality from medication and venom-triggered anaphylaxis</td>
</tr>
</tbody>
</table>

### Comorbidities

- Asthma and other respiratory diseases, especially if severe or uncontrolled
- CVDs, including hypertension
- Mastocytosis and clonal mast cell disorders
- Depression and other psychiatric diseases (might impair recognition of symptoms)
- Thyroid disease (some patients with idiopathic anaphylaxis)
- Concurrent medication/chemical use: Potentially affect recognition of anaphylaxis

### Symptoms and Signs of Anaphylaxis

#### Cutaneous/subcutaneous/mucosal tissue

- Flushing, pruritus, hives (urticaria), swelling, eczematous rash, pilo-erection

#### Respiratory

- Pruritus and swelling of lips, tongue, oral/pharyngeal
- Pruritus in the external auditory canals
- Pruritus of genititalia, palms, soles

#### Gastrointestinal

- Nausea, vomiting, cramping abdominal pain, constipation (stringy mucus), diarehes

#### Cardiovascular

- Feeling faint, altered mental status, hypotension, loss of sphincter control, shock, cardiac arrest
Symptoms and Signs of Anaphylaxis

CNS
Aura of impending doom, unusualness, throbbing headache, dizziness, confusion, tunnel vision; in infants and children, sudden behavioral changes, such as irritability, cessation of play, and clinging to parent

Other
Metallic taste in the mouth
Dysphagia
Uterine contractions in postpubertal female patients

Sudden onset of symptoms and signs is characteristic of anaphylaxis.

Differential Diagnosis of Anaphylaxis

Common entities
Acute generalized hives
Acute asthma
Syncope (faint, vasovagal episode)

Panic attack
Aspiration of a foreign body
Cardiovascular event (myocardial infarction, pulmonary embolism)

Neurologic event (seizure, stroke)
Postpartum syndromes
Pollen-food syndrome
Scombroidosis

Mastocytosis
Hypersensitivity (eg, spinal cord injury) Septic (might involve all of the above)

Other
Nonallergic angioedema
Red-Man syndrome (vancomycin)

Pericardial syndrome
Hypersensitivity angioedema

Urticarial vasculitis
Hyper IgE syndrome
Pseudotumor cerebri
Phenomenal systemic capillary leak syndrome

Excess endogenous histamine
Mastocytosis/clonal mast cell disorders
Basophilic leukemia
Flush syndromes
Premenopause
Carcinoid
Autonomic epilepsy
Medullary carcinoma
Exercise-Induced Anaphylaxis (EIA)

- Described in 1970's
- A rare form of allergic reaction that is precipitated by exercise.
- Over 1000 cases have been reported; however, the actual number of cases are a lot higher.
- A sub-type of EIA is precipitated with certain food or medications (mostly NSAIDs).

Patterns of Exercise-Induced Anaphylaxis

<table>
<thead>
<tr>
<th>Type</th>
<th>Precipitating event</th>
<th>Urticarial morphology</th>
<th>Vascular collapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholinergic</td>
<td>Passive warming, Emotional stress, Exercise</td>
<td>2 to 5 mm</td>
<td>Rare</td>
</tr>
<tr>
<td>Classic</td>
<td>Exercise only</td>
<td>Conventional 10-15 mm</td>
<td>Yes</td>
</tr>
<tr>
<td>Variant</td>
<td>Exercise only</td>
<td>2 to 5 mm; may progress to larger lesion</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Cholinergic Urticaria

[picture of skin with urticaria]
<table>
<thead>
<tr>
<th>Contemporary hypotheses for EIAn</th>
<th>Physiological basis of hypotheses</th>
<th>Exercise physiology in context of EIAn</th>
<th>Likelihood of occurrence in context of EIAn</th>
<th>Future research direction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changes in plasma osmolality during exercise increases basophil histamine release, 320 mOsm associated with increase in basophil histamine release in FDEIAn (n = x)</td>
<td>Exercise can increase plasma osmolality.</td>
<td>Plasma osmolality is relatively stable during short-term, low intensity exercise. 5% loss of body mass through dehydration required to achieve osmolality of 330 mOsm.</td>
<td>Unlikely Effect of minor shifts in osmolality on basophil degranulation warrants further investigation</td>
<td></td>
</tr>
<tr>
<td>Increased acidity in blood results in increased mast cell degranulation as shown by protective effect of sodium bicarbonate in FDEIAn during exercise</td>
<td>Exercise induces metabolic/lactic acidosis, pH 7.2. Provides optimal conditions for mast cell degranulation.</td>
<td>Supramaximal exercise associated with lactic acidosis. Acidosis is unlikely to occur in the context of EIAn.</td>
<td>Possible Changes in muscle pH greater than blood, prophylactic effect of sodium bicarbonate warrants further investigation</td>
<td></td>
</tr>
<tr>
<td>Increased exercise-induced gut permeability (GI) results in appearance of gliadin peptides in WKDEIA</td>
<td>Exercise can increase GI and potentially increase the absorption of allergenic peptides</td>
<td>Only very prolonged exercise is associated with increases in GI. Exercise for 90 min at 70% VO2max increase GI. Increased GI is unlikely to occur in the context of EIAn</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise-induced increases in tissue transglutaminase (tTG) activity results in post-digestion allergen peptide aggregation</td>
<td>tTG activity increase by severe homeostatic disruption and associated increase in inflammatory cytokines, free radicals, and cortisol release. Dysregulated tTG results in fibrosis, autoimmune disorders</td>
<td>Short-term, low intensity exercise results in slight, transient increase in inflammatory cytokines, free radicals, or cortisol. No evidence of tTG/allergen complexes in circulation in EIAn.</td>
<td>Unlikely Determination of lowest concentration of cytokines to increase tTG required</td>
<td></td>
</tr>
<tr>
<td>Redistribution of blood flow from viscera to active tissues results in exposure of allergen to phenotypically different mast cells</td>
<td>Exercise results in altered blood flow from the viscera to the active tissues. Mast cell heterogeneity has been demonstrated in a number of tissues in humans</td>
<td>Mild to severe exercise alters blood flow distribution with greater percentage of cardiac output going to active tissues and reduction in viscera.</td>
<td>Possible Hypothesis warrants further investigation in EIAn patients vs. healthy controls</td>
<td></td>
</tr>
</tbody>
</table>
Food–Dependent Exercise-Induced Anaphylaxis (FDEIAAn)

- A sub type of Exercise-Induced Anaphylaxis
- A unique phenomenon where two conditions of food and exercise have to be present for the symptoms to occur.
- The allergic reaction/anaphylaxis starts after ingesting the food and subsequent exercise.

Pathophysiology

- Unknown
- One hypothesis is that the affected individuals have mild allergy to a specific food and exercise helps the increase of absorption of food allergens in the GI tract and the degranulation of mast cells.
Precipitating Food
- Seafood
- Celery
- Wheat
- Cheese
- Any food?

Wheat
- The most studied food item in Exercise-induced food anaphylaxis
- Is wheat unique to this type of anaphylaxis?
- Wong and Krishna, 2013 reported Wheat-dependent exercise–induced anaphylaxis by is by no means a unique condition.

A 16-year-old soccer player presents with recurrent anaphylaxis. Anaphylaxis occurs during exercise, but only occasionally. Symptoms include flushing, shortness of breath, wheezing, lightheadedness and vomiting. No consistent precipitant was apparent to the athlete or to his parents or coach. Episodes only occur when exercise follows a meal. A specific food could not be identified by history. Prophylactic medications were not effective at preventing anaphylaxis, which often required an epinephrine injection for rescue. Past history revealed well-controlled asthma and rhinitis that rarely interfered with exercise. Medications include cetirizine (10 mg/day), EpiPen® (0.3 mg IM PRN anaphylaxis), budesonide/formoterol (80 μg/4.5 μg 2 doses BID), and albuterol (2 puffs PRN and pre-exercise). The physical exam at baseline was normal.
Assessment: Spirometry was within normal limits. Immediate hypersensitivity skin testing for possible foods was positive to wheat, but historic information to support consumption of wheat before anaphylaxis was inconsistent. Open food challenge to wheat was negative. Exercise challenge while fasting 6 h per ATS guidelines for EI-asthma was negative. Exercise challenge with food excluding wheat resulted in an 8% reduction in FEV₁, without symptoms, interpreted as negative. Exercise challenge following wheat consumption induced anaphylaxis with presyncope, nausea and a significant drop in blood pressure that responded to epinephrine. FEV₁ could not be obtained because of nausea and the need for immediate therapy.

Treatment: avoid ingesting wheat products for at least 6 h before exercise. Always have EpiPen® available, and train the player and his coach and parents to use it properly. Continue current asthma treatment.

Follow-Up: soccer playing resumed without recurrence of anaphylaxis. Occasional EI-asthma occurred but responded well to inhaled albuterol.

Lesson: Food-dependent EI-anaphylaxis can be diagnosed or suspected based on the history, and confirmed by objective tests. Treatment includes prophylaxis (food-allergen avoidance for at least 6 h or general food avoidance for at least 2 h before exercise), and being prepared for rescue interventions (immediate availability and use of intramuscular epinephrine, and Trendelenburg position).

Exercise-Induced Anaphylaxis (EIAn & Literature

- Bonini & Palange, 2014 report, reviewed the literature form 02-01-2013 to 01-31-2014.
- Initially identified 138 articles. Finally 17 articles met the criteria for inclusion in the review.
- Conclusions:
  There were no randomized controlled trials.
  The overall collected evidence appeared to be very low quality.
Except the five experimental studies (3 case-control studies, one cohort study, and retrospective study), all other data derived from reports performed in extremely small population samples or even in individual cases.

The authors noted two interesting papers. One was about genetic results showing the influence of the IL-4 C590T polymorphism on the onset of WDEIA.

Literature

The other paper was related to reliability of the ISAC (Immuno solid-phase allergen chip microarray technique) in the allergic screening of athletes, especially if polysensitized and at risk of severe reactions.

The author suggested a need for trials based on more robust study designs and should consider the creation of multicenter networks to increase the number of the poser of trials.

Prevention Strategies for Anaphylaxis in Community Settings

Allergen-specific trigger avoidance based on history of exposure and confirmation of sensitization (strength of recommendation = C)

Foods, including additives and contaminants
Medications and biological agents,
Insect stings and bites
Natural rubber latex
Inhalants
Seminal fluid
Occupational allergens
Other
Nonimmunologic triggers: avoid relevant exposure (strength of recommendation = C)

Exercise-induced anaphylaxis
Prevention........

Cold air or water
Heat
Sunlight/UV radiation
Medications, such as opioids
Ethanol
Immunomodulation
Food: Currently, oral immunotherapy is a research procedure supervised by physicians in specialized food allergy centers (strength of recommendation pending).
Insect venoms: allergen-specific immunotherapy (strength of recommendation = A)
Medications: desensitization (strength of recommendation = B)
Seminal fluid: desensitization (strength of recommendation = C)
Idiopathic anaphylaxis (for frequent episodes only; strength of recommendation = C)
Oral glucocorticoid, such as prednisone; H1-antihistamine, such as cetirizine (used for prophylaxis)

Prevention & Treatment

• Do not exercise for 4-6 hours after a meal
• Do not take Aspirin and NSAIDs before exercising
• Do not exercise alone
• Leukotriene receptor antagonist (e.g. montelukast)
• Antihistamines
• Epinephrine (treatment)

References-Credits
1-Exercise-Induced Anaphylaxis and Urticaria
2-Combined Effects of Food and Exercise on Anaphylaxis, Cheol Woo Kim, et al. Nutrition Research and Practice, 2003; 7 (5)
3-Exercised-Induced Anaphylaxis, Up To Date, accessed 09-30-2014
4-Food-Dependent Exercise-Induced Anaphylaxis: Is What Unique?
5-Anaphylaxis and Sport, Matteo Bonini and Palange; Curr Opin Allergy Clin Immunology, Vol 14; N 4; August 2014
6-Allergy and Sports in Children, Sefanbo R. Del Giacco; Kai-Hakon Carlson and Geroge Da Ttili; Pediatric Allergy and Immunology 2012: 23:10-20
7-American Academy of Allergy, Asthma, and Immunology, teaching slide series (Urticaria)
Thank You