WISC 2014
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Advancing the Borders of Allergy:
From Treatment to Prevention by Targeting the Environment, Infections and the Susceptible Patient

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ADVERSE REACTIONS TO IMMUNOTHERAPY

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ADVERSE REACTION

WHO, Definitions (1972)

'A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease or for the modifications of physiological function'
• Subcutaneous allergen immunotherapy (SCIT) is an effective treatment for allergic rhinitis, asthma and venom hypersensitivity and has the potential of producing serious life-threatening anaphylaxis.

• New indications of Immunotherapy
  – Atopic Dermatitis
  – VIT for LLRS (large local reaction) (Immunotherapy Practice Parameters - 3rd edition)
<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
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<tbody>
<tr>
<td><strong>Cutaneous</strong></td>
<td></td>
<td><strong>Lower respiratory</strong></td>
<td></td>
<td><strong>Death</strong></td>
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<tr>
<td>Generalized pruritus, urticaria, flushing or sensation of heat or warmth</td>
<td>Asthma: cough, wheezing, shortness of breath (e.g., less than 40% PEF or FEV1 drop, responding to an inhaled bronchodilator)</td>
<td>Asthma (e.g., 40% PEF or FEV1 drop, NOT responding to an inhaled bronchodilator)</td>
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<tr>
<td>Angioedema (not laryngeal, tongue or uvular)</td>
<td><strong>Gastrointestinal</strong></td>
<td><strong>Upper respiratory</strong></td>
<td>Lower or Upper respiratory</td>
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<td>or</td>
<td>Abdominal cramps, vomiting, or diarrhea</td>
<td>Laryngeal, uvula or tongue edema with or without stridor</td>
<td>Respiratory failure with or without loss of consciousness</td>
<td>Hypotension with or without loss of consciousness</td>
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<tr>
<td>or</td>
<td><strong>Conjunctival</strong></td>
<td>or</td>
<td>or <strong>Cardiovascular</strong></td>
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<tr>
<td>Conjunctival erythema, pruritus or tearing</td>
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<tr>
<td><strong>Other</strong></td>
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<td>Nausea, metallic taste, or headache</td>
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ADVERSE REACTIONS: SUMMARY

• Local Reactions
• Generalized Pruritus
• Rhinitis
• Angioedema
• Itchy throat
• Cough
• Conjunctival symptoms
• Nausea
ADVERSE REACTIONS: SUMMARY

• Asthma
• Abdominal cramps
• Uterine cramps
• Laringeal, uveal and tongue edema
• Respiratory failure
• Hypotension
• Death
FATAL REACTIONS TO IMMUNOTHERAPY (SCIT) IN THE USA

• 1973 – 18 deaths
• 1984 – 17 deaths
• 1989 – 41 deaths
• 2001 – 6 deaths
• 2007 – 0 (zero) deaths
• 2011 – Locker et al. JACI 1987, Reid et al JACI 1993, Bernstein Jaci 2004 Jaci 2010
Why deaths are decreasing in immunotherapy?

- Better quality and standardized antigens
- Awareness of the risks
- Increased prophylactic measures
- Adequate facilities for delivering immunotherapy
- Guidelines on Immunotherapy
- Guidelines on Anaphylaxis
- Better trained allergy specialists
• 17 deaths from anaphylaxis after allergen injection occurred from 1985 through 1989.

- Only one patient received house mite antigens injections. All the others received different pollen antigens mixtures.

- Most of the deaths occurred due to:
  - New vial, overdose,
  - personal aggravating circumstances like obesity, asthma,
  - multiple extracts,
  - use antigen in the middle of the pollen season.

- Only one patient was using the extract at home.
Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001

David I. Bernstein, MD et al
The Immunotherapy Committee of the American Academy of Allergy, Asthma and Immunology
Journal of Allergy and Clinical Immunology
Volume 113, Issue 6, Pages 1129–1136, June 2004

• Dosing errors and β-blockers were not major contributing factors, as in previous surveys.\(^6\)
• Delay or failure to administer adequate doses of epinephrine is a common feature of fatal reactions.
• This highlights the need to prohibit injection therapy in any clinic that is not fully equipped and staffed to treat severe anaphylaxis.

**OUR COMMENT:** all patients were on pollen extracts. Some also received house mite ag. All of them received multiple antigens injections. It seems pollens antigens may be a risk factor
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- 273 incidents of near fatal reactions
- 5,4 events per 1000 000 injections
  - 46% occurred during the height of the allergy season (Pollen season in USA)
  - 25% were due to dose errors
  - 4 out 5 near fatal reactions were asthma patients
  - FEV1 < 70% in 4 out 7 near fatal patients who had asthma
RISK FACTOR FOR ADVERSE REACTIONS

- Severe asthma specially with FEV1 <70%
- B blockers and ECA inhibitors
- Polen season
- Route of delivery (SCIT more than SLIT)
- Patients sensibility to the allergen
- Dose of the allergen
- Non standarized antigen
- New vial
- Rush and cluster immunotherapy
WHAT TO DO ABOUT IMMUNOTHERAPY IN CASE OF ADVERSE REACTIONS?

- Previous local reactions are not indicative of future more severe reactions BUT
  - Review the causes of adverse reactions
  - Review the antigen concentration
  - If there is a suspicion switch the vial for a new one
  - Keep the patient under observation for a longer period (1h) next time
COMPLICATIONS MOSTLY OCCUR DUE TO:

- Delay in recognizing the severity or potential severity of the initial reaction
- Delay in the use of Epinephrine
- Asthma
- Lack of resources of life support
- Untrained professional
PROPHYLAXIS MEASURES

- **Antihistamines** decrease local reactions in cluster and rush immunotherapy
- **Antileucotriens** have a protective effect on rush protocol
- **An assessment of patients health**
- **Peak flow, Blood pressure** level measurement
- **Local life support resources** available such as:
  - Drugs: epinephrine, antihistaminic, corticosteroids, betaadrenergics, oxygen, dopamine, atropine, Glucagon
  - ACLS training or equivalent training for professionals
- **Reliable antigens** in standardized vials, individualized for the patient
- Check for usage of **prohibited drugs** such as betablockers and ECA inhibitors
- Keep **patient under observation** for at least 30 min
INCREASED SAFETY AND/OR EFFICACY WITH CURRENTLY AVAILABLE EXTRACTS

• Delayed absorption
  – Aluminum
  – Tyrosine

• Reduced levels of IgE
  – Omalizumab

• Alternative routes of delivery
  – Oral
  – Bronchial
  – Nasal
  – Epicutaneous
  – Intralymphatic
  – Intradermal
  – Sublingual
THE FUTURE

Molecular allergology, the science that describes the detailed structure of the molecules that cause allergies, is expected to take the field to the next step, as the components of treatment will be defined to precision in quality and quantity. (EAACI)
ASBAI2015
XLII Congresso Brasileiro de Alergia e Imunologia
De 03 a 06 de outubro - Centro de Convenções Vitória - ES