Emergency Allergy-Immunology Conditions

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• I have no conflicts to report.
TODAY’S TOPICS

• ANAPHYLAXIS- PEANUT, PENICILLIN
• ANGIOEDEMA- ACE INHIBITORS
Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death*

Epidemiology

- We do not know for sure how many are at risk
- National, cross-sectional survey based on self-report
  - 1.6 to 5.1% prevalence among adults in US
- Most common triggers
  - Medications (34%)
  - Foods (31%)
  - Insect stings (20%)

Wood RA et al., J Allergy Clin Immunol 2014;133:461-7
Epinephrine

- The most effective treatment for anaphylaxis
- α and β adrenergic receptor agonist
  - α reverses peripheral vasodilatation, hence increasing BP and coronary artery perfusion
  - β-1 inotropic/chronotropic effects increase heart rate, contraction strength
  - β-2 relaxes smooth muscle around airways (bronchodilator)
- **No absolute contraindication** for treatment of anaphylaxis
- Failure to administer early in reaction repeatedly linked with fatalities
- Do not rely on antihistamines, bronchodilators

Epinephrine

• Many deaths in anaphylaxis, especially from food allergy, are due to obstruction to airflow in the upper and/or lower respiratory tract that result in respiratory failure and vascular collapse

• If you wait for the patient to develop shock, you have waited too long!

• Treat long before signs and symptoms of cardiovascular collapse occur!

Management: Immediate Treatment

- **EPINEPHRINE**
  - Primary and most important treatment
  - Dose
    - Adults 0.3-0.5 mg of 1:1000 IM; max of 0.5 mg
    - Children 0.01 mg/kg of 1:1000 IM; max 0.3 mg
  - Repeat doses every 5 min or sooner if needed
  - Call 911/activate EMS after administration
    - For observation/continued treatment, NOT because epinephrine is dangerous
- **Place patient in comfortable position**
  - Lying flat helpful if hypotension
  - Place on side if breathing and unconscious or vomiting
First-aid treatment of anaphylaxis to food: Focus on epinephrine

F. Estelle R Simons, MD, FRCPC

Journal of Allergy and Clinical Immunology
Volume 113, Issue 5, Pages 837-844 (May 2004)
DOI: 10.1016/j.jaci.2004.01.769
Simons FER: J Allergy Clin Immunol 2004;113:837-44
Please remember....

When in Doubt, Inject Epinephrine!
Peanut Allergy

- Prevalence has more than tripled, from 0.4% in 1997 to 1.4% in 2008
- Onset of symptoms usually by age 2 yrs; 75% of reactions may occur with first exposure
- The food allergy most commonly associated with anaphylaxis
- 150 deaths / year, predominantly from peanut and tree nut anaphylaxis
- ~20% peanut allergy resolution; relapse rate ~ 9%

Evaluation: Interpretation of Laboratory Tests

• Positive skin prick test or food-specific IgE
  • Indicates presence of IgE antibody **NOT** clinical reactivity
  • ~90% sensitivity; ~50% specificity
  • ~50% asymptomatic sensitization
  • Larger skin tests/higher sIgE levels correlate with increased likelihood of reaction but not severity

• Negative skin prick test or food-specific IgE
  • Essentially excludes IgE antibody (>95% specific)


Summary Statement 23: The clinician should use specific IgE tests (skin prick tests, serum tests, or both) to foods as diagnostic tools; however, testing should be focused on foods suspected of provoking the reaction, and test results alone should not be considered diagnostic of food allergy. [Strength of recommendation: Strong; B Evidence]
Diagnostic Approach: Suspicion of IgE-Mediated Allergy

• If test for food-specific IgE is
  • Negative: reintroduce food*
  • Positive: food avoidance recommended
• If elimination diet is associated with
  • No resolution: reintroduce food*
  • Resolution
    • Open / single-blind challenges to “screen”
    • DBPCFC for equivocal open challenges

* Unless convincing history warrants supervised challenge

Penicillin Allergy

• 10% of patients report a penicillin allergy, >95% of these patients can tolerate penicillin

• Skin testing has an established and validated negative predictive value >95%

• Majority of penicillin reactions are due to beta-lactam ring, although it is possible to be allergic to a side chain (e.g. amoxicillin, ampicillin)

Penicillin Allergy

• Penicillin “allergic” patients receive broad spectrum antibiotics that can be more toxic, less effective, and more costly

• “Clearing” a penicillin allergy is important for patients and society to decrease antibiotic resistance
  – Aligns with Executive Order of the President 2014 (PCAST)
  – Highlighted by AAAAI statement 2015
  – “Public Health Measure” 2014
Penicillin Allergy Referrals

• Any patient with penicillin allergy can benefit
• Patients who specifically benefit include patients with:
  – Recurrent infections/hospitalization
  – Current or past infection where best therapy includes a beta-lactam
  – Planned surgical procedure where a beta-lactam antibiotic is the drug of choice
  – Upcoming chemotherapy or transplantation
ACE-I Angioedema (Bradykinin-mediated)

Photo courtesy of Dr. David Khan 7/28/2015
ACE Inhibitors

• Increased use of ACE inhibitors in US

• Angioedema occurs in 0.1% to 0.7% of patients treated with ACE inhibitors
  – 4 to 5-fold higher risk in African Americans, hereditary or idiopathic angioedema, females and older age

• ACE inhibitors are the most common cause of angioedema seen in the hospital and emergency room

Banerji A  Annals Allergy Immunol 2008; Apr;100(4):327-32
Sondhi  D Chest 2004 Aug;126(2):400-4
ACE Inhibitor Angioedema

- Usually presents as angioedema of the face and neck (throat, tongue, lips, eyes)

- Studies suggest that bradykinin is likely the mediator responsible for ACE inhibitor related angioedema

- New therapies targeting bradykinin pathway are useful
Drug Induced Urticaria / Angioedema

Bradykinin responsible for swelling in angioedema in patients with HAE

Angiotensin converting enzyme (ACE) inhibitors interfere with metabolism of bradykinin via interference with kininase II

Patients on angiotensin converting enzyme blockers (ARBs) may not be at risk for angioedema
Gavras I Arch Int Med 2003; 163: 240-1
ACE Inhibitor Angioedema

- Typically angioedema occurs shortly after start
  Slater E et al JAMA 1988; 260: 967-70

- Several reports of angioedema after several months
  - Angioedema after 13 months of enalapril therapy
    Venable RJ  J Fam Pract 1992; 34: 201-4

- Report of angioedema after stopping and then restarting ace-inhibitor within 72 hours
  Dyer PD  J Allergy Clin Immunol 1994; 93: 947-8
Meta-analysis of randomized trials of angioedema as an adverse event of renin-angiotensin system inhibitors.

Weighted incidence of angioedema with ACE inhibitors was 0.30% (95% CI 0.28 to 0.32) compared to 0.11% (95% CI 0.09 to 0.13) with ARBs, 0.13% (95% CI 0.08 to 0.19) with DRIs, and 0.07% with placebo (95% CI 0.05 to 0.09). In conclusion, incidence of angioedema with ARBs and DRI was <1/2 than that with ACE inhibitors and not significantly different from placebo.
Safety of ARBs in Pts. With ACE-I Angioedema

• Mechanism of action of ACE-I angioedema- increased bradykinin levels
• ARBs not associated with increased bradykinin levels
• Incidence of angioedema with ARBs no greater than placebo
• Data on ARB related angioedema in pts. With ACEI angioedema- retrospective, mixed. (http://www.aaaai.org/ask-the-expert/angiotensin-receptor-blocker)

FDA-approved Newer Treatments

- Trauma
- Factor XIIa
- Prekallikrein
- Kallikrein
- C1 INH
- Kininogen
- Bradykinin
- Ecallantide
- Icatibant

Vasodilation, Edema, Nonvascular Smooth Muscle Contraction
Original Article

A Randomized Trial of Icatibant in ACE-Inhibitor–Induced Angioedema

Murat Baş, M.D., Jens Greve, M.D., Klaus Stelter, M.D., Miriam Havel, M.D., Ulrich Strassen, M.D., Nicole Rotter, M.D., Johannes Veit, M.D., Beate Schossow, Alexander Hapfelmeier, Ph.D., Victoria Kehl, Ph.D., Georg Kojda, Pharm.D., Ph.D., and Thomas K. Hoffmann, M.D.

N Engl J Med
Volume 372(5):418-425
January 29, 2015
## Clinical Outcomes.

### Table 2. Clinical Outcomes.*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Icatibant</th>
<th>Standard Therapy</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>Median (IQR) time to complete resolution of edema:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>primary end point — hr</td>
<td>8.0 (3.0–16.0)</td>
<td>27.1 (20.3–48.0)</td>
<td>0.002†</td>
</tr>
<tr>
<td>Patients with complete resolution of edema at 4 hr</td>
<td>5 (38)</td>
<td>0</td>
<td>0.02‡</td>
</tr>
<tr>
<td>after treatment — no. (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Median (95% CI) time to onset of symptom relief — hr§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>According to composite investigator-assessed symptom score</td>
<td>2.0 (1.0–8.1)</td>
<td>11.7 (8.0–18.0)</td>
<td>0.03¶</td>
</tr>
<tr>
<td>According to composite patient-assessed VAS score</td>
<td>2.0 (2.0–6.3)</td>
<td>7.9 (1.2–11.8)</td>
<td>0.36¶</td>
</tr>
<tr>
<td>According to composite investigator-assessed angioedema score</td>
<td>2.0 (2.0–12.0)</td>
<td>12.0 (11.3–NE)</td>
<td>0.003¶</td>
</tr>
</tbody>
</table>

*Clinical outcomes were assessed in the per-protocol population. CI denotes confidence interval, IQR interquartile range, and NE not estimable.

† The P value was calculated with the use of the Wilcoxon rank-sum test.

‡ The P value was calculated with the use of Fisher’s exact test.

§ The time to the onset of symptom relief was defined as the time to the first improvement (i.e., decrease) of at least 1 point in the composite score.

¶ The P value was calculated with the use of the Peto–Peto–Prentice test.

Conclusions

• Among patients with ACE-inhibitor–induced angioedema, the time to complete resolution of edema was significantly shorter with icatibant than with combination therapy with a glucocorticoid and an antihistamine.