41st Annual Refresher Course for the Family Physician
Clinical Pearls in Allergy and Immunology

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Division of Immunology

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Nothing to disclose
Objectives

- Describe current recommendations regarding influenza vaccination for individuals who report an egg allergy
- Familiarize oneself with the new treatment options for hereditary angioedema
- Identify the role for food allergy testing in patients with eosinophilic esophagitis (EoE)
Case 1

- **HPI:** 20 year old male presents to establish care and for refill of his injectable epinephrine. Doing well and has no complaints. Has avoided eggs and has not had to use his injectable epinephrine. Seen by an Allergist years ago. Reaction to egg during childhood consisted of urticaria and breathing problems.
- **PMH:** egg allergy, allergic rhinitis, no surgeries
- **ALL:** NKDA
- **MEDS:** injectable epinephrine PRN, fluticasone nasal spray
- **FH:** father with CAD, HTN
- **SH:** nonsmoker, college sophomore
- **ROS:** all negative
- **PE:** all normal
Case 1

- Assessment/plan:
  - 1. Egg Allergy
    - Continue avoidance
    - Refill of injectable epinephrine
    - ?Allergy evaluation
  - 2. Allergic rhinitis
    - Refill fluticasone
  - 3. Routine health maintenance
    - ?Recommend influenza vaccine
What is your influenza vaccine recommendation?

A. No vaccine
B. Inactivated
C. Live-attenuated
D. Recombinant
Influenza

- Approximately 294,128 hospitalizations yearly in the US (21,156 <5 yrs)
- Average yearly deaths 23,607 (124 children)

Could these have been prevented with influenza vaccine
- Grown in embryonated chicken eggs
- Potential allergic reaction to ovalbumin (egg protein) in egg allergic individuals (0.12-3.6% of the population)
- Studies to date suggest risk low
  - Included patients with histories of anaphylaxis to egg (currently about 13% of the proven egg allergy population studied)
# TABLE VIII. Ovalbumin content of injectable TIVs approved for the 2011-2012 season

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Manufacturer</th>
<th>Approved ages</th>
<th>Ovalbumin content (µg per 0.5 mL dose*)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afluria</td>
<td>CSL Biotherapies (Merck)</td>
<td>≥9 y</td>
<td>≤1</td>
</tr>
<tr>
<td>Fluarix</td>
<td>GlaxoSmithKline</td>
<td>≥3 y</td>
<td>≤0.05</td>
</tr>
<tr>
<td>FluLaval</td>
<td>ID Biomedical Corporation of Quebec (GlaxoSmithKline)</td>
<td>≥18 y</td>
<td>≤1</td>
</tr>
<tr>
<td>Fluvirin</td>
<td>Novartis</td>
<td>≥4 y</td>
<td>≤1</td>
</tr>
<tr>
<td>Fluzone</td>
<td>Sanofi Pasteur</td>
<td>≥6 mo</td>
<td>~0.1</td>
</tr>
<tr>
<td>Fluzone High-Dose</td>
<td>Sanofi Pasteur</td>
<td>≥65 y</td>
<td>~0.1</td>
</tr>
</tbody>
</table>

*Dose: 0.25 mL, 6-35 months; 0.5 mL, ≥3 years.
†Information in package inserts except Fluzone and Fluzone High-Dose from Sanofi Pasteur by telephone (1-800-822-2463) or e-mail (MIS.Emails@sanofipasteur.com).
Published studies (1998, others since 2010)

- >1600 egg allergic patients (mostly children) vaccinated without serious reactions
- 0-6.3% skin reactions (urticaria)
- 0-4.8% mild respiratory or gastrointestinal symptoms
- 0 hypotension
- 0 treatments with epinephrine
- Controls experienced similar rates of reactions
- One study included 3640 individuals with reported but not proven egg allergy
  - 1.2% skin reaction
  - 0.7% respiratory reactions including 2 which were treated with injectable epinephrine (although authors concluded these symptoms were not anaphylaxis)
**FIG 2.** Recommendations regarding influenza vaccination for persons who report allergy to eggs. Advisory Committee on Immunization Practices (ACIP), 2011-2012 influenza season.

*Persons with egg allergy might tolerate egg in baked products (e.g., bread or cake). Tolerance to egg-containing foods does not exclude the possibility of egg allergy.*
Summary

- Patients with egg allergy should receive the vaccine in a medical setting
- Only hives can receive in primary care provider’s office and wait 30 minutes
- If severe symptoms refer to Allergy/Immunology physician
  - Number of patients studied to date (~5000) cannot exclude the possibility of a rare severe reaction
- All influenza vaccines in the US contain low ovalbumin
  - 0.7 μl/0.5mL dose
- Intranasal vaccine does contain albumin and has not been studied therefore egg allergic individuals should not be given this
<table>
<thead>
<tr>
<th>Route</th>
<th>Vaccine</th>
<th>Formulation</th>
<th>Dosage Form</th>
<th>Age Indication</th>
<th>Preservative (thimerosal content)</th>
<th>Latex Content</th>
<th>Ovalbumin (Egg) Content</th>
<th>Other Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intramuscular</td>
<td>FluBlok® (Protein Sciences Corp.)</td>
<td>Recombinant Influenza Vaccine, Trivalent (RIV3)</td>
<td>0.5 ml vial</td>
<td>18 to 49 years</td>
<td>Preservative-free (thimerosal free)</td>
<td>Latex-free</td>
<td>Egg-Free</td>
<td>Sodium phosphate-buffered isotonic sodium chloride solution</td>
</tr>
<tr>
<td></td>
<td>[injection made with DNA/cell culture technology]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Polysorbate 20 (Tween® 20) Residual amounts of: Baculovirus &amp; host cell proteins, Baculovirus and cellular DNA, Triton X-100</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>FluZone® Quadrivalent (Sanofi Pasteur)</td>
<td>Inactivated Influenza Vaccine, Quadrivalent (IV4)</td>
<td>0.25 ml syringe</td>
<td>6 to 35 months</td>
<td>Preservative-free (thimerosal free)</td>
<td>Latex-free</td>
<td>≤ 0.05 mcg/0.25 ml dose</td>
<td>Formaldehyde Octylphenol Ethoxylate Sodium phosphate-buffered isotonic sodium chloride solution</td>
</tr>
<tr>
<td></td>
<td>[standard dose injection]</td>
<td></td>
<td>0.5 ml syringe/vial</td>
<td>≥ 36 months</td>
<td></td>
<td></td>
<td>≤ 0.1 mcg/0.5 ml dose</td>
<td></td>
</tr>
<tr>
<td>Intramuscular</td>
<td>FluZone® High-Dose (Sanofi Pasteur)</td>
<td>Inactivated Influenza Vaccine, Trivalent (IV3), High Dose (IV4)</td>
<td>0.5 ml syringe</td>
<td>≥ 65 years</td>
<td>Preservative-free (thimerosal free)</td>
<td>Latex-free</td>
<td>≤ 0.1 mcg/0.5 ml dose</td>
<td>Formaldehyde Octylphenol Ethoxylate Sodium phosphate-buffered isotonic sodium chloride solution</td>
</tr>
<tr>
<td></td>
<td>[high-dose (4X) injection]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intranasal</td>
<td>FluMist® Quadrivalent (MedImmune)</td>
<td>Live-Attenuated Influenza Vaccine, Quadrivalent (LAIV4)</td>
<td>0.2 ml intranasal sprayer</td>
<td>2 to 49 years</td>
<td>Preservative-free (thimerosal free)</td>
<td>Latex-free</td>
<td>≤ 0.24 mcg/0.2 ml dose</td>
<td>Arginine Dibasic potassium phosphate Ethylenediaminetetraacetic acid (EDTA) (&lt;0.37 mcg/dose) Gentamicin (&lt;0.015 mcg/ml) Monobasic potassium phosphate Monosodium glutamate Porcine gelatin Sucrose</td>
</tr>
<tr>
<td>Intradermal</td>
<td>FluZone® Intradermal (Sanofi Pasteur)</td>
<td>Inactivated Influenza Vaccine, Trivalent (IV3), Standard Dose (IV3)</td>
<td>0.1 ml intradermal syringe</td>
<td>18 to 64 years</td>
<td>Preservative-free (thimerosal free)</td>
<td>Latex-free</td>
<td>≤ 0.02 mcg/0.1 ml dose</td>
<td>Formaldehyde Octylphenol Ethoxylate Sodium phosphate-buffered isotonic sodium chloride solution</td>
</tr>
</tbody>
</table>

Note: None of the vaccines contain aluminum.
New in 2013 trivalent recombinant vaccine

- FluBlok
  - Expression of proteins in insect cells using recombinant baculovirus

- Developed due to:
  - Specialized facilities
  - Decreased ability to scale up egg production rapidly
  - Poultry potentially vulnerable to influenza viruses
  - Time consuming adaption of candidate vaccine viruses for high yield growth

- Low rates of local and systemic reactions
  - Systemic reactions similar to placebo

- Safe, immunogenic and effective in the prevention

- Approved in >18 years (18-49)

- SAFE BUT LESS IMMUNOGENIC IN CHILDREN
$$$$ (to patient)

- Fluzone
  - $30
- High dose Fluzone
  - $40
- Flumist
  - $35
- Flublok
  - $50
Case 2

- **HPI:** 21 year old male presents for treatment of hereditary angioedema (HAE) dx at 2y/o. Weekly episodes (↑ severity frequency). No ICU admissions but numerous emergency department visits. Does not take danazol due to concern of long term side affects. Lost to follow up many years.

- **PMH:** HAE, depression/anxiety

- **ALL:** NKDA

- **MEDS:** danazol

- **FH:** mother and brother with HAE

- **SH:** unemployed, lives with mother

- **ROS:** negative

- **PE:** normal

<table>
<thead>
<tr>
<th>Labs</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C4 complement</td>
<td>11 (16-47 mg/dL)</td>
</tr>
<tr>
<td>C1-inhitor functional assay</td>
<td>32 (≥40%)</td>
</tr>
<tr>
<td>C1-inhibitor protein</td>
<td>9 (21-39 mg/dL)</td>
</tr>
<tr>
<td>C1q</td>
<td>6.7 (5.0-8.6 mg/dL)</td>
</tr>
</tbody>
</table>
Which is the most appropriate prophylactic therapy?

A. Attenuated androgens
B. Fresh frozen plasma
C. Antifibrinolytic agents
D. C-1 inhibitor concentrate
Hereditary Angioedema (HAE)

- Autosomal dominant
- Presents in late childhood or adolescence
- Prevalence
  - 1:10,000 to 1:150,000
  - Equal among races; Women = Men
- Attacks build in severity over 12-36 hours
- Resolution: 24-72 hours
- Unpredictable, waxing/waning, delayed diagnosis
- Significant morbidity
- Treatment:
  - Response is variable
  - Antihistamines, glucocorticoids, or epinephrine are ineffective
HAE Morbidity

- Web-based survey of 457 HAE patients found:
  - 100% felt disease prevented them from advancing in school
  - 69% felt unable to consider certain jobs
  - 58% affected career advancement

- Impact of last HAE attack:
  - 51% missed ≥1 work day
  - 44% missed ≥1 school day
  - 59% missed ≥1 leisure day

- Attacks result in 20-100 days of incapacitation annually
  - Approximately 15,000 to 30,000 ER visits/yr

- Unpredictability of attacks causes significant psychological burden

Pathophysiology

Mutation of C1 esterase inhibitor gene (C1-INH)

Inhibition of the kallikrein-kinin system

Increased **bradykinin** production

Vasodilation and increased permeability

Localized subcutaneous or submucosal swelling
Diagnosis Criteria

- **Clinical criteria**
  - Recurrent angioedema that is self-limiting, non-pitting, non-pruritic, non-erythematous
  - Edema usually lasts for more than 12 h with no major urticaria
  - Family history of hereditary angioedema

- **Laboratory criteria**
  - C1 inhibitor <50% of normal values obtained on two separate occasions after first year of age
  - Functional levels of C1 inhibitor <50% (chromogenic assay) or <84% (ELISA assay; local normal ranges might vary) of normal values obtained on two separate occasions after first year of age
  - Mutation in C1-inhibitor gene that modifies protein synthesis or function

*Need one clinical and one laboratory criterion*
Common HAE Triggers

- Trauma
- Menstruation
- Infection
- Medications
- Stress

Angioedema attack
HAE Treatment: U.S. Timeline

Prevention: Androgen derivatives, anti-fibrinolytics
Acute: FFP, supportive care

C1 Esterase Inhibitor (Berinert)  
**ACUTE**

Oct 2008
Dec 2009
Oct 2009
Aug 2011

C1 Esterase Inhibitor (Cinryze)  
**PREVENTION**

Icatibant (Firazyr)

Ecallantide (Kalbitor)
Prophylactic Treatment of HAE

Prophylaxis typically used for:
- Short-term: Planned exposure to a trigger situation
  - Dental work
  - Invasive medical procedures
  - Surgery
- Long-term: Frequent attacks (i.e. ≥2 attacks/month or several times per year causing decreased QOL)

Prophylaxis options
- Androgen derivatives (Danazol)
- Antifibrinolytic agents
- Nanofiltered C1 inhibitor concentrate (Cinryze®)
Androgen Derivatives: Danazol

- Androgen derivatives: 17-α-alkylated androgen
  - Danazol
  - Stanazol – compounded only
    - Average dose 2mg daily
  - Oxandrolone
    - Approved for pediatric use

- Mechanism of action
  - Thought to increase hepatic synthesis of C1-INH

- Pharmacokinetics of danazol
  - Onset: Slow ~4 weeks
  - Time to peak: 2 hours
  - Half-life: 4.5 hours (variable)
Danazol (cont.)

Effects on C1-Inhibitor

Danazol (cont.)

❖ Adverse effects
  o Virilization
  o Weight gain
  o Menstrual disorders/amenorrhea
  o Psychological disorders
  o Headache
  o Myalgia
  o Acne
  o Increased sweating
  o Diminished libido
  o Hepatocellular adenoma
  o Hirsutism
  o Hyperlipidemia

❖ Frequency and severity of adverse effects with danazol increase with dosage strength and duration of therapy
Danazol: Hepatocellular Adenomas

- Hepatocellular adenomas have been associated with long-term (>10 years) danazol prophylaxis
  - In some of these cases, the adenomas regressed 18-24 months after discontinuation of danazol

- Fatal hepatic failure has also been reported

- Therefore, periodic liver function monitoring has been strongly advocated (i.e. annually)

Gompels MM et al., Clin Exp Immunol. 2005
Crampon D et al., J Hepatol. 1998
Bork K et al., J Hepatol. 2002
Danazol: \textit{Dosing}

- Not for acute treatment, several days for efficacy

- \textbf{Short-term prophylaxis:}
  - 200mg TID for 5-10 days before event, may continue after for a few days

- \textbf{Long-term prophylaxis (if \textgreater{}1 attack every 3 months):}
  - Use the lowest effective dose
  - Usual dose: 200mg/day (Range 100mg every 3 days to 600mg daily)
  - Options
    - High dose of 400-600 mg daily, then taper down every 2-4 weeks to a dose that achieves symptomatic control \textbf{OR}
    - Start a low dose of 50 mg daily, then taper up every 2-4 weeks to an effective dose

- \textbf{Cost:} $55.99 for 30 capsules (50 mg)
Danazol: Efficacy in Long-term Prophylaxis

Freedom from HAE Attacks vs Placebo

Danazol Dosage (mg/d)

<table>
<thead>
<tr>
<th>Dosage (mg/d)</th>
<th>200</th>
<th>300</th>
<th>400</th>
<th>600</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freedom from HAE Attacks</td>
<td>11%</td>
<td>56%</td>
<td>88%</td>
<td>95%</td>
</tr>
</tbody>
</table>

Frank M. Immunol Allergy Clin N Am. 2006
Antifibrinolytic Agents

- Aminocaproic acid and tranexamic acid
- Not for acute treatment, several days for efficacy
- Possibly not as effective as androgen derivatives
- Better safety than androgens in pregnancy and children
- Most common side effects
  - Nausea and diarrhea
  - Vertigo
  - Postural hypotension
  - Fatigue
  - Muscle cramps/weakness (increased muscle enzyme concentrations)
  - Risk of vascular thrombosis
  - Teratogenicity?
### Antifibrinolytic Agents (cont.)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Usual Prophylactic Adult Dose (Range)</th>
<th>Usual Prophylactic Pediatric Dose (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminocaproic acid</td>
<td>2g TID (1g BID – 4g TID)</td>
<td>0.05 g/kg BID (0.025 g/kg BID–0.1 g/kg BID)</td>
</tr>
<tr>
<td>Tranexamic acid</td>
<td>1g BID (0.25g BID – 1.5g TID)</td>
<td>20 mg/kg BID (10 mg/kg BID–25 mg/kg TID)</td>
</tr>
</tbody>
</table>

*NOT FDA Approved for HAE in either adults or children

C1-Inhibitor Concentrate: Cinryze®

- Nanofiltered, highly purified human C1 esterase inhibitor
- First C1 esterase inhibitor therapy for **routine PREVENTION**
  - FDA approved in October 2008 (adults and adolescents)
  - UIHC formulary for prevention *(past agent for acute)*
- Pharmacokinetics
  - Onset of action: ~1 hour; Peak: ~4 hours; Half-life: 56 hours
- Adverse effects
  - Headache, upper respiratory infections, sinusitis, rash, DVT/TIA, MI, thrombosis
- Dosing: 1000 units IV infusion every 3-4 days
  - 1 mL/minute over 10 minutes at room temperature
  - **May also give 500 - 1500 units <24 hrs (best 1 hour) prior to provoking event**
- Cost:
  - ~$2,900/500 units (Dose = $5,800)
C1-Inhibitor Concentrate: Cinryze® (cont.)

- **CHANGE Trial**: C1-inhibitor in Hereditary Angioedema Nanofiltration Generation evaluating Efficacy
  - N=22 patients with at least 2 HAE attacks/month
  - 24-week double-blind, placebo-controlled cross-over study
  - Randomized to 12 weeks of C1-INH 1000 units or placebo
    - Prophylactic infusions every 3-4 days
    - After 12 weeks patients switched treatment arms

CHANGE Trial (cont.)

- C1 inhibitor concentrate had significant reductions vs. placebo in the following:
  - Severity of attacks
    • Score: 1.3 vs 1.9
  - Duration of attacks
    • 2.1 vs 3.4 days
  - Need for open-label rescue therapy
    • N=11 vs N=22
  - Total number of days with swelling
    • 10 vs 30 days

Acute Treatment for HAE

- Purified C1 inhibitor concentrate (Berinert®)
  - Cinryze studied but not FDA approved
- Ecallantide (Kalbitor®)
- Icatibant (Firazyrr®)
- Others
  - FFP
    - May worsen symptoms due to contact-system proteins
  - Supportive therapy during acute attacks
    - Airway management
    - Pain management, opioids often required
    - Anti-emetics for nausea/vomiting
    - IV fluids

*Corticosteroids, antihistamines, and epinephrine not effective in aborting acute attacks and should generally not be given for HAE*
Purified C1 Inhibitor Concentrate: Berinert®

- Purified human C1-INH from plasma donors
  - FDA Approved for ACUTE treatment abdominal/facial attacks in adults and adolescents - October 2009
  - UIHC Formulary agent for Acute Attacks (Feb 2012)

- Pharmacokinetics
  - Onset: ~1 hr; Time to peak: ~4 hrs; Half-life: 22 hours

- Adverse effects
  - Headache, abdominal pain, nausea, muscle spasm, pain, diarrhea, vomiting, injection site reaction, fever, chills, hypersensitivity

- Dose: 20 units/kg IV (~4 ml/min), repeat after 30 min if needed
  - Ex: 50 kg = 1000 units, 75 kg = 1500 units, 100 kg = 2000 units, 125 kg = 2500 units
  - Consider rounding dose up

- Cost: ~$1,400 for 500 units
Purified C1 Inhibitor Concentrate: Berinert® (cont.)

- IMPACT Trial: International Multicenter Prospective Angioedema C1-INH Trial

- Randomized, double-blind, placebo-controlled study
- 125 HAE patients enrolled (45 centers, 15 countries)
  - Acute facial or abdominal HAE attacks
  - Age range: 6-72
- C1 inhibitor concentrate (Berinert) 10 U/kg and 20 U/kg vs. placebo within 5 hours of attack
  - Rescue dose: if no relief in 4 hrs gave Berinert 20 U/kg for placebo group, 10 U/kg in 10 U/kg group, or placebo in 20 U/kg group
- Primary endpoint: time to onset of symptom relief

IMPACT Trial (cont.)

Ecallantide: Kalbitor®

- Highly selective recombinant kallikrein inhibitor
  - FDA Approved Dec 2009 (>16 yo)
- Pharmacokinetics
  - Onset: 30 min - 4 hrs; Time to peak: ~2-3 hrs; Half-life: ~2 hrs
Ecallantide: Kalbitor® (cont.)

- **Administration**
  - Subcutaneous injection in abdomen, upper arm, or thigh
  - **Must be administered by a healthcare worker**

- **Dosing: 30 mg per dose**
  - Administered as three 10mg/mL doses
  - Repeat dose may be given within 24 hours

- **Adverse effects**
  - Headache (8%), nausea (5%), diarrhea (4%), fever (4%), injection site reaction (3%)

- **Black box warning: Anaphylaxis**
  - 5 of 187 patients (3%)
  - Typically appears within 1 hour

- **Cost:** $9,540 per 30 mg treatment
### Ecallantide: Kalbitor® - EDEMA Studies

#### Phase III, double-blind, placebo-controlled trials

<table>
<thead>
<tr>
<th>STUDY</th>
<th>EDEMA3¹ (N=72)</th>
<th>EDEMA4² (N=96)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion</strong></td>
<td>Age ≥10 ≤8hrs of moderate-severe^ attack</td>
<td>Age ≥10 ≤8hrs of moderate-severe attack</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Ecallantide 30mg SC vs Placebo</td>
<td>Ecallantide 30mg SC vs Placebo</td>
</tr>
<tr>
<td><strong>Median patient-reported</strong></td>
<td>50.0 vs 0.00 (P=0.004)</td>
<td>53.4 vs 8.1 (P=0.003)</td>
</tr>
<tr>
<td><strong>Median change in</strong></td>
<td>-1.00 vs -0.50 (P=0.14)</td>
<td>-0.8 vs -0.4 (P=0.01)</td>
</tr>
<tr>
<td>symptom severity score at 4 hours from baseline</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

^Moderate: Intervention highly desirable, impedes ADLs; Severe: necessitates treatment, inability to do ADLS
*TOS: 100=sig improvement, 50=improvement, 0=same, -50=worsening, -100 sig worsening

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Icatibant: Firazyr®

- **Selective Bradykinin β₂ Receptor Antagonist**
  - FDA Approved August 2011 (≥18 yo)

- **Pharmacokinetics:**
  - Onset: ~2 hours; Time to peak: 45 minutes; Half-life: 1-2 hours
Icatibant: Firazyr® (cont.)

- **Administration**
  - Subcutaneously into abdomen
  - **May be self-administered at home**

- **Dosing**
  - Inject 30 mg over ≥ 30 seconds
  - May repeat every 6 hours; max of 3 doses/ 24 hours

- **Adverse Effects:**
  - **Injection site reaction** (97%), fever (4%), elevated transaminase levels (4%), dizziness (3%)

- **Cost:** $2500 for 30 mg dose
# Icatibant: Firazyr® - FAST Studies

<table>
<thead>
<tr>
<th>STUDY</th>
<th>FAST-1&lt;sup&gt;1&lt;/sup&gt; (N=56)</th>
<th>FAST-2&lt;sup&gt;1&lt;/sup&gt; (N=74)</th>
<th>FAST-3&lt;sup&gt;2&lt;/sup&gt; (N=88)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion</strong></td>
<td>Age ≥18 ≤6hrs of mod-severe cutaneous/abd attack</td>
<td>Age ≥18 ≤6hrs of mod-severe cutaneous/abd attack</td>
<td>Age ≥18 ≤6hrs of moderate-severe cutaneous attack OR ≤12hrs abdominal attack</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Icatibant 30mg SC vs Placebo</td>
<td>Icatibant 30mg SC vs Tranexamic acid</td>
<td>Icatibant 30mg SC vs Placebo</td>
</tr>
<tr>
<td><strong>Median time to clinically significant relief of index symp.</strong></td>
<td>2.5 vs 4.6 hrs (P=0.14)</td>
<td>2.0 vs 12.0 hrs (P&lt;0.001)</td>
<td>1.5 vs 18.5 hrs (P&lt;0.001)</td>
</tr>
<tr>
<td><strong>Median patient-assessed time to improvement</strong></td>
<td>0.8 vs 16.9 hrs (P&lt;0.001)</td>
<td>0.8 vs 7.9 hrs (P&lt;0.001)</td>
<td>2.0 vs 19.8 hrs* (*50% improvement) (P&lt;0.001)</td>
</tr>
<tr>
<td><strong>Median physician-assessed time to improvement</strong></td>
<td>1.0 vs 5.7 hrs (P&lt;0.001)</td>
<td>1.5 vs 18.5 hrs (P&lt;0.001)</td>
<td>NA</td>
</tr>
</tbody>
</table>

### Summary: Acute HAE Treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Indication</th>
<th>Dose</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ecallantide&lt;sup&gt;9,24&lt;/sup&gt;</td>
<td>Kallikrein inhibition</td>
<td>Acute attacks of HAE at any location in patients &gt;16 yr of age</td>
<td>30 mg s.c.</td>
<td>Headache, nausea, vomiting, diarrhea, injection-site reactions, anaphylaxis, antibody development</td>
</tr>
<tr>
<td>C1 esterase inhibitor (human)&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Replacement of C1 esterase inhibitor; inhibits bradykinin activation</td>
<td>Acute abdominal or facial attacks of HAE in adults</td>
<td>20 units/kg i.v.</td>
<td>Headache, nausea, vomiting, diarrhea, anaphylaxis, transmission of infectious agents</td>
</tr>
<tr>
<td>Icatiban&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Bradykinin-2 receptor antagonist</td>
<td>Acute attacks of HAE at any location in adults</td>
<td>30 mg s.c.</td>
<td>Dizziness, headache, injection site reactions, rash</td>
</tr>
</tbody>
</table>
Acute HAE Attacks: Emerging Therapy

- **Recombinant Human C1-INH (Conestat alfa - Rhucin™)**
  - From the milk of transgenic female rabbits
  - DNA contains an extra bovine milk-specific promoter sequence (alpha-S1 casein) functionally linked to the gene encoding human C1 inhibitor
  - Induces production of rhC1INH in milk at levels of 12 g/L

- **Phase I trial of 12 subjects results**
  - Reported no adverse events
  - Showed no evidence of immune rejection
  - Demonstrated evidence of systemic availability and activity

- **Ongoing phase II/III trials in patients age 12 or older**

- **Dosing:**
  - <84 kg = 50 U/kg
  - ≥84 kg = 4200 U in adults
Summary

- Recurrent episodes of non-pruritic swelling without hives warrants further evaluation for hereditary angioedema
- Newer therapies offer patients significant hope
- 1st line prevention OR acute attacks: C1-inhibitor
- 2nd line for acute attacks: ecallantide or icatibant
- Considerations for choice of therapy:
  - Route of administration
  - Patient preference
  - Efficacy
  - Safety and tolerability
  - Cost
Case 3

- HPI: 35 year old male seen in consultation from gastroenterology for evaluation of eosinophilic esophagitis (EoE) Recently had an EGD for impaction. History of dysphagia the prior 3-5 years.
- PMH: Allergic rhinitis
- ALL: NKDA
- MEDS: omeprazole 20 mg daily
- FH: brother with asthma
- SH: degree in finance and law
- PE: normal
- Review of epic revealed 40 – 60 eosinophils/hpf on distal esophageal biopsy “some” in proximal
- Labs: no eosinophilia, mildly elevated IgE
What is the next best step?

A. Watch and wait
B. Order IgG to foods
C. Aeroallergen testing
D. Skin prick test to foods
Eosinophilic esophagitis

- Esophageal eosinophilia
- Emerging disease
  - 1977 (Dobbins, et al.)
- Male predilection
- Affects both children and adults
  - Adults commonly present in the third decade
- Symptoms of heartburn, dysphagia, food impaction, CP
  - Children present with feeding difficulties, FTT, food aversion, regurgitation, abdominal pain, emesis, GERD symptoms
- Current diagnostic criteria
  - Symptoms
  - 15 eosinophils/hpf
  - Exclusion of other disorders

TABLE I. Diseases associated with esophageal eosinophilia

<table>
<thead>
<tr>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>GERD</td>
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<tr>
<td>EoE</td>
</tr>
<tr>
<td>Eosinophilic gastrointestinal diseases</td>
</tr>
<tr>
<td>Celiac disease</td>
</tr>
<tr>
<td>Crohn disease</td>
</tr>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Hypereosinophilic syndrome</td>
</tr>
<tr>
<td>Achalasia</td>
</tr>
<tr>
<td>Drug hypersensitivity</td>
</tr>
<tr>
<td>Vasculitis</td>
</tr>
<tr>
<td>Pemphigoid vegetans</td>
</tr>
<tr>
<td>Connective tissue disease</td>
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<tr>
<td>Graft-versus-host disease</td>
</tr>
</tbody>
</table>

**TABLE E3.** Histologic features of EoE

<table>
<thead>
<tr>
<th>Feature</th>
</tr>
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<tbody>
<tr>
<td>Mucosal eosinophilia</td>
</tr>
<tr>
<td>Eosinophil microabscess formation</td>
</tr>
<tr>
<td>Superficial layering of eosinophils</td>
</tr>
<tr>
<td>Extracellular eosinophil granules</td>
</tr>
<tr>
<td>Epithelial desquamation</td>
</tr>
<tr>
<td>Basal zone hyperplasia</td>
</tr>
<tr>
<td>Rete peg elongation</td>
</tr>
<tr>
<td>Dilated intercellular spaces</td>
</tr>
<tr>
<td>Subepithelial fibrosis/sclerosis–lamina propria fibrosis</td>
</tr>
<tr>
<td>Mastocytosis and mast cell degranulation</td>
</tr>
<tr>
<td>CD8⁺ lymphocytes and B cells</td>
</tr>
<tr>
<td>TABLE E2. Endoscopic and radiologic features of EoE</td>
</tr>
<tr>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>Isolated stricture (proximal or distal)</td>
</tr>
<tr>
<td>Longitudinal narrowing (small or narrow-caliber esophagus)</td>
</tr>
<tr>
<td>Longitudinal shearing (crepe paper esophagus)</td>
</tr>
<tr>
<td>White exudates</td>
</tr>
<tr>
<td>Linear furrows or vertical lines</td>
</tr>
<tr>
<td>Fixed esophageal rings (corrugated rings or trachealization)</td>
</tr>
<tr>
<td>Transient esophageal rings (feline folds or felinization)</td>
</tr>
</tbody>
</table>
Role for allergy

- Aeroallergen sensitivity in majority of adults/older children
  - Role controversial
  - Seasonal pattern to diagnosis of EoE
  - May act directly causing allergic inflammation or systemically

- Rare history of food-induced anaphylaxis

- Strictures may cause dysphagia and impaction therefore identification of food triggers difficult

- Delayed reaction to foods
  - Patch testing not currently validated or standardized

- Food allergy testing (specific IgE)
  - Guide food elimination/reintroduction
  - Clinical utility for identification of triggers largely unknown
  - Adults have fewer positives to foods
Case 3

- Positive skin prick testing to the following aeroallergens:
  - Lamb’s quarter, ragweed, Russian thistle, Timothy, numerous trees
- Positive skin prick testing to the following foods:
  - Almond, hazelnut, peanut, soybean, milk and eggs
- Positive specific IgE:
  - Pork, soybean, egg, rice, almond, hazelnut, peanut (negative to milk)
- IgE 900 IU/mL
- Treatment
  - Swallowed fluticasone, 1-2 puffs daily; increased PPI
  - Elimination diet (rice, pork, boiled eggs, soy, dairy, nuts)
    *not strictly avoiding
- Repeat EGD:
  - No eosinophils in proximal esophagus, 20 Eos/hpf in distal
- Asymptomatic
### TABLE III. Recommended doses of corticosteroids for EoE

**Topical swallowed corticosteroids**
- **Initial doses** (see references for preparation and administration information)
  - Fluticasone (puffed and swallowed through a metered-dose inhaler)
    - Adults: 440-880 µg twice daily
    - Children: 88-440 µg twice to 4 times daily (to a maximal adult dose)
  - Budesonide (as a viscous suspension)
    - Children (<10 y): 1 mg daily
    - Older children and adults: 2 mg daily

**Systemic corticosteroids**
- For severe cases (eg, small-caliber esophagus, weight loss, and hospitalization)
  - Prednisone: 1-2 mg/kg

### TABLE IV. Major unresolved issues affecting the diagnosis and treatment of EoE

1. Optimization of methodologies for histologic analysis of mucosal samples
   A. Number of biopsy specimens
   B. Proximal versus distal biopsy specimens
   C. Number of hpfs that need to be examined
   D. Effect of associated histologic features on diagnostic sensitivity
   E. Mean versus peak number of eosinophils
   F. Size of hpf used to quantitate eosinophils
   G. Use of completely filled versus partially filled hpfs
   H. Reporting eosinophil density as number per hpf versus number per unit area (mm²)
   I. Eosinophil degranulation and optimal markers (MBP, EPO, and EDN)
2. Exclusion of esophageal acid/nonacid disease (PPI therapy and diagnostic testing)
3. Lack of consensus on criteria to diagnose eosinophilic disease in the remainder of the gastrointestinal tract
4. Allergy testing in adults and children in guiding dietary exclusions
5. Optimal end points of treatment (eg, symptom relief and histologic normalcy)
6. Frequency of endoscopy in follow-up (Is it needed in asymptomatic patients?)
7. Maintenance treatment (dose and duration)
8. Validated measurements of symptoms, endoscopic findings, histology, and quality of life

*EDN*, Eosinophil-derived neurotoxin; *EPO*, eosinophil peroxidase; *MBP*, major basic protein.
Questions?