Objectives

- Better understand the differential diagnosis of perioperative anaphylaxis
- Evaluate and manage patients with a history of perioperative anaphylaxis
- Advise patients with a history of perioperative anaphylaxis that need to return to the operating room
Case Presentation

- 28 year old female
- No significant past medical history
- Elective laparoscopic cholecystectomy 6 months ago
- No previous exposure to anesthesia
- No known drug allergies
Patient with History of Perioperative Anaphylaxis

- Received a dose of cefazolin preoperatively
- Received midazolam, fentanyl, propofol, lidocaine, and rocuronium during procedure
- Developed significant hypotension 10 minutes after start of procedure
- No rash, hives or angioedema documented
- Hypotension responded immediately to treatment with epinephrine and benadryl
- Stable in recovery room with no other symptoms
Perioperative Anaphylaxis

- Anaphylaxis during surgical procedures is difficult to evaluate because of the rapid, successive use of multiple agents.

- Careful analysis of anesthesia records is critical to a complete and thorough evaluation.
Epidemiology: Anaphylaxis to General Anesthesia

- Incidence ranges from 1:3500 to 1:20,000
  - Most published reports are from studies in France, Australia, England and New Zealand

- Mortality ranges from 3-6%

- An additional 2% of patients experience significant brain damage

Murat et al, 1999; Fisher et al., 1993; Currie et al., 1993; Mitsuhata et al., 1992
Differential diagnosis of perioperative anaphylaxis

<table>
<thead>
<tr>
<th>Differential diagnosis of anaphylaxis during anesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug overdose and interactions</td>
</tr>
<tr>
<td>Cardiac/vascular drug effects</td>
</tr>
<tr>
<td>Asthma</td>
</tr>
<tr>
<td>Arrhythmia</td>
</tr>
<tr>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Pericardial tamponade</td>
</tr>
<tr>
<td>Pulmonary edema</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Tension pneumothorax</td>
</tr>
<tr>
<td>Hemorrhagic shock</td>
</tr>
<tr>
<td>Venous embolism</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>C1 esterase inhibitor deficiency</td>
</tr>
<tr>
<td>Mastocytosis</td>
</tr>
<tr>
<td>Malignant hyperthermia (succinylcholine)</td>
</tr>
<tr>
<td>Myotonias and masseter spasm (succinylcholine)</td>
</tr>
<tr>
<td>Hyperkalemia (succinylcholine)</td>
</tr>
</tbody>
</table>

Mertes et al., 2010
Differential Diagnosis

- Neuromuscular Blocking Agents
- Latex
- Antibiotics (β-lactams)
- Hypnotics (propofol, thiopental)
- Opiates
- Aspirin and NSAIDs
- Colloids
- Chlorhexidine and other antiseptics
- Local Anesthetics
- Protamine and Heparin
- Dyes (Methylene Blue)
- Oxytocin
- Aprotinin
**Etiology of Perioperative Anaphylaxis**

- NMBAs: 59%
- Latex: 17%
- Antibiotics: 15%
- Hypnotics: 3%
- Opioids: 1%
- Colloids: 4%
- Other Agents: 1%

Ebo et al., 2007
Risk Factors

- Female
- Atopy (not for NMBAs)
- Prior history of anaphylaxis
- Prior history of drug allergy
- History of multiple prior procedures
Predisposing Factors by History

- Spina Bifida
- Health Care Workers with glove dermatitis
- Gelatin Allergy
- Allergy to exotic fruit (kiwi, chestnut, mango, avocado, banana)

→ Latex Allergy
→ Latex Allergy
→ Colloids
→ Latex Allergy
Evaluation

• History, History, History
  • Timing of administration of drug and onset of reaction
Clinical symptoms and reaction severity will not allow one to distinguish between an immune-mediated IgE reaction and an anaphylactoid reaction due to direct mast cell activation.
Important Questions

• Was this a first dose reaction?
  • First dose reactions are not usually IgE mediated unless prior sensitization occurred

• What is the nature of the reaction?
  • Urticaria and angioedema vs. maculopapular rash

• What was the time course of the reaction?
  • Within minutes, hours or days
Time Elapsed between Administration and Onset of Symptoms

- 90% of cases, symptoms usually start within 5-10 minutes after intravenous administration of the responsible agent.

- In contrast, anaphylaxis from latex and antiseptics (chlorhexidine) is usually 20-40 minutes later.
  - Slower absorption through skin or other mucosal surfaces.
Evaluation

- History, History, History
  - Timing of administration of drug and onset of reaction

- Caveats of skin testing
  - Not indicated for non-IgE mediated reactions
  - Often uninformative if negative
  - Must rule-out an irritant reaction if positive
What can an Allergist Provide?

GENERAL GUIDANCE BASED ON KNOWN INFORMATION

- Skin testing using non-irritating concentrations
- NMBAs
- Antibiotics
- Latex
- Local Anesthetics
- Propofol
- Fentanyl
- Clorhexidine
- Protamine
- Oxytocin
Allergy to NMBAs

- IgE antibodies to the two quaternary or tertiary ammonium ions mediate anaphylaxis

- Many OTC drugs, cosmetics, and food products contain quaternary or tertiary ammonium ions that can lead to sensitization

- Therefore, can often see reactions with “first” exposure to NMBAs
NMBAs (N=336)

- Rocuronium 29%
- Succinylcholine 23%
- Vecuronium 18%
- Mivacurium 18%
- Pancuronium 7%
- Cisatracurium 4%
- Atracurium 1%

Laxenaire et al., 2001
## Skin Testing Concentrations

<table>
<thead>
<tr>
<th>Available Agents</th>
<th>Concentration (mg/mL)</th>
<th>SPT</th>
<th>IDT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Dilution</td>
<td>$C_{\text{max}}$ (mg/mL)</td>
</tr>
<tr>
<td>NMBAs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atracurium</td>
<td>10</td>
<td>1/10</td>
<td>1</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>2</td>
<td>Undiluted</td>
<td>2</td>
</tr>
<tr>
<td>Mivacurium</td>
<td>2</td>
<td>1/10</td>
<td>0.2</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>2</td>
<td>Undiluted</td>
<td>2</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>10</td>
<td>Undiluted</td>
<td>10</td>
</tr>
<tr>
<td>Suxamethonium</td>
<td>50</td>
<td>1/5</td>
<td>10</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>4</td>
<td>Undiluted</td>
<td>4</td>
</tr>
</tbody>
</table>

Mertes et al., 2010
Latex Allergy

- Derived from the Hevea brasiliensis tree
- Universal precautions by the FDA in the 1980s in the setting of HIV led to a dramatic increase in the use of latex gloves
  - The high demand led to a decrease in manufacturing time and therefore increased protein content in gloves
- Latex allergy is decreasing due to increased awareness and avoidance
- High risk groups include health-care workers, patients with a history of multiple procedures
Latex Skin Testing Protocol

1. Soak a latex glove in saline for one hour and perform an epicutaneous test with the extract

2. If negative, apply a wet latex glove to the forearm for 30 minutes

3. If negative prick the ski through the wet latex glove

Lieberman P. AAAAI ask the expert
www.aaaaai.org
Antibiotics

- Penicillins and cephalosporins elicit approximately 70% of perioperative anaphylactic reactions to antibiotics.

- Quinolones are the third most important group of antibiotics involved in perioperative anaphylaxis.

- Bacitracin and rifamycin applied locally to irrigate wounds also can cause anaphylaxis.
# Antibiotic Skin Testing

<table>
<thead>
<tr>
<th>Available Agents</th>
<th>Concentration (mg/mL)</th>
<th>SPT</th>
<th>IDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPL</td>
<td>Undiluted</td>
<td>0.035</td>
<td>Undiluted</td>
</tr>
<tr>
<td>MDM (penicillin)</td>
<td>Undiluted</td>
<td>1</td>
<td>Undiluted</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>Undiluted</td>
<td>$20 - 25 \times 10^3$</td>
<td>Undiluted</td>
</tr>
<tr>
<td>AX, AMP</td>
<td>Undiluted</td>
<td>20 - 25</td>
<td>Undiluted</td>
</tr>
<tr>
<td>Other penicillins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Undiluted</td>
<td>1 - 2</td>
<td>Undiluted</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>500</td>
<td>$1/5 \times 10^6$</td>
<td>0.1</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>40</td>
<td>$1/10^2$</td>
<td>400</td>
</tr>
</tbody>
</table>

Mertes et al., 2010
Value of Skin Testing

- **NMBAs**
  - 60-70% cross-reactivity among agents
  - Literature suggests 80-90% sensitivity and specificity

- **Latex**
  - No standardized extract for skin testing available
  - RAST test 20% false negative rate

- **Antibiotics**
  - Lack of major and minor determinants
  - Use of non-irritating skin testing concentrations

Fisher et al., Anest Analg 1983
Evaluation

- History, History, History
  - Timing of administration of drug and onset of reaction
- Caveats of skin testing
  - Not indicated for non-IgE-mediated reactions
  - Often uninformative if negative
  - Must rule-out an irritant reaction if positive
- Delay skin testing 4-6 weeks to avoid refractory period
- RAST testing often not available or sensitive/specific
- IgG, IgA and IgM to specific drugs are not useful
- Serum tryptase within 2-4 hours
Serum Tryptase Levels

- Half-life is approximately 120 minutes
- Tryptase level suggested within 4 hours of reaction
Tryptase

- Marker of mast cell activation
- Pro-tryptase (β) is constitutive and elevated in mastocytosis
- Total tryptase elevated with mast cell activation

<table>
<thead>
<tr>
<th>Clinical condition</th>
<th>Tryptase levels (ng/mL)</th>
<th>Tryptase ratio (total/mature)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Mature</td>
</tr>
<tr>
<td>Normal</td>
<td>1–15</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Systemic anaphylaxis (acute)</td>
<td>&gt; Baseline</td>
<td>&gt; 1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Systemic mastocytosis (nonacute)</td>
<td>&gt; 20&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;1 to small elevations</td>
</tr>
</tbody>
</table>
28 year old female with perioperative anaphylaxis

- Skin testing to midazolam, fentanyl, propofol, lidocaine, rocuronium and cefazolin was negative
- RAST Latex was negative
- Skin testing to all agents including latex was negative
Skin Testing is Negative: Next Steps?

- Comprehensive allergy evaluation is unable to identify causative agent
- Review differential diagnosis
- Create list of high vs. low likelihood agents responsible for perioperative anaphylaxis
Management

- Recommend an unrelated alternative medication
  - Most common approach

- Recommend a medication not identical to, but potentially cross-reactive with the drug in question
  - Low cross-reactivity between PCNs and cephalosporins
  - Significantly less with 3rd and 4th generation cephalosporins
What is the Value of Prophylaxis?

- No data exist in the current literature for standard prophylaxis prior to anesthesia

- Data exist for steroid and antihistamine prophylaxis for patients with IV contrast allergy
  - Mechanism of prophylaxis not well understood
  - Not IgE mediated

- Antihistamine prophylaxis may be helpful to reduce the incidence of adverse effects due to direct histamine release, but no data for anaphylaxis
Subsequent Anesthesia in Patients with Prior Anaphylaxis

- No subsequent anaphylaxis in 7 patients with negative skin testing (Thacker et al., 1999)

- 43 NMBA skin test positive patients, 19 had uneventful anesthesia with negative skin testing to NMBAs (Soetens et al., 2003)

- Evaluated 27 patients, no subsequent anaphylaxis in 3/11 with negative skin testing and 8/16 with positive skin testing that returned to the OR (Moscicki et al., 1990)
Conclusions

- Review the history, clinical symptoms, anesthesia record and consider differential diagnosis

- Comprehensive allergy evaluation is helpful in evaluation of perioperative anaphylaxis