Anaphylaxis

Anaphylaxis is a life threatening manifestation of antigen-antibody interaction characterized by IgE mediated degranulation of mast cells and basophils causing release of vasoactive mediators. The release of histamine, tryptases, leukotrienes, kinins, prostaglandins and other vasoactive mediators causes a symptom complex characterized by bronchospasm, increased capillary permeability and edema, vasodilation and cardiovascular collapse and urticaria.

ANESTHETIC CONSIDERATIONS:

Management of Intraoperative Anaphylactic Reaction:

- Recognize the symptom complex: (may range from minor clinical changes to death)
  - Urticaria
  - Pruritis
  - Primary vascular collapse and hypotension
  - Laryngeal edema
  - Bronchospasm
  - Arterial hypoxemia
- Stop the administration of the antigen.
- Maintain and secure the airway – risk of upper airway edema and impending airway obstruction
- Ventilate with 100% oxygen
- Discontinue all anesthetic agents.
- Establish large bore IV access and bolus crystalloid solution (2-4L bolus of fluid with hypotension)
- Give epinephrine 5-10mcg IV bolus and titrate as needed – dose of epi should be doubled and repeated every 1-2 minutes until satisfactory blood pressure response has been obtained. If anaphylaxis is not life threatening, subcutaneous Epi may be used in a dose of 0.3-0.5mg sc. Increase IV dose range to 100mcg-1mg IV with cardiovascular collapse.
- Secondary treatments:
  - Antihistamines (0.5-1mg/kg diphenhydramine)
  - Catecholamine infusions (epi, norepi, isoproterenol; titrate to desired effects)
  - Bronchodilator therapy: ventolin, and/or anticholinergic agents for refractory bronchospasm.
  - Corticosteroids (0.25-1g hydrocortisone, 1-2g methylprednisolone)
  - Sodium bicarbonate if refractory hypotension or acidosis
  - Vasopressin for refractory shock
- Post-anaphylaxis care in ICU x 24h
- Check for airway obstruction prior to extubation
- Diagnosis of anaphylaxis:
  - Increased plasma tryptase if drawn within 1-2h of suspected allergic drug reaction
  - Increased plasma histamine if drawn within 30 minutes of suspected allergic reaction
  - Intradermal test (should not be performed within 6 weeks of anaphylactic reaction because of mast cell and basophil mediator depletion and possible false negative result)
  - RAST/ELISA

ANESTHETIC GOALS:

- Maintain oxygenation, ventilation and perfusion by treating cardiopulmonary collapse with a secured airway, volume resuscitation and inotropes/vasopressors as necessary.
- Confirm immunlologically mediated reaction with immunologic and biochemical lab assays and differentiate between immunologically mediated reaction and anaphylactoid reaction.

HISTORY

- History of allergic reaction?
  - Drug/Food/Latex/Contrast allergy
  - Type of reaction to allergen
- History of asthma, atopy or allergy
- History of latex exposure
  - Reaction to latex exposure:
    - Itching
    - Conjunctivitis
    - Rhinitis
    - Rash
- History of spina bifida

PHYSICAL

- Routine preoperative examination including:
  - Focused airway exam
  - Focused cardiorespiratory exam
  - GI/GU/Neurological examination as indicated

LABS (AFTER A SUSPECTED ANAPHYLACTIC REACTION)

- CBC with differential – eosinophilia
- Serum histamine and tryptase after allergic reaction
- RAST immunoassay or ELISA
- Intradermal skin testing

INVESTIGATIONS

- Routine preoperative tests

OPTIMIZATION

- Remove known allergens from the operating room environment
- Preoperative administration of H1 or H2 antagonists may be beneficial in attenuating the severity of vasodilation and hypotension

ANESTHETIC OPTIONS

- None
- Regional
- Neuraxial

- General

ANESTHETIC SETUP

- Standard emergency drugs
- Emergency drugs readiily available including:
  - Epinephrine
  - Antihistamines
  - Inhaled B2 agonists
  - Corticosteroids
  - NaHCO3
  - Vasopressin

MANAGEMENT OF ANESTHESIA

INDUCTION

- Be aware that NMBAs are the most commonly implicated agent in perioperative allergic reactions
- Cross reactivity between succinylcholine and non-depolarizing agents
- IV induction agents (barbiturates, etomidate, propofol) have all been implicated
- Opioids (meperidine, morphine, fentanyl) have all been implicated

MAINTENANCE

- Nothing specific

EMERGENCE

- Nothing specific
- If a perioperative anaphylactic/anaphylactoid reaction has occurred, be aware that recurrence of symptoms in a treated patient may persist for up to 24h

POSTOPERATIVE DISPOSITION

- Consider ICU if a perioperative anaphylactic/anaphylactoid reaction has occurred

COMPLICATIONS

- Recurrence of symptoms

PATHOPHYSIOLOGY

Anaphylaxis:

- Overall incidence of perioperative allergic reactions is 1:5000-25000 anesthetics
- 3.4% mortality rate
- Most common manifestation under general anesthesia is circulatory collapse, usually within 5 minutes of administration of IV drug
- More likely to occur in patients with a history of allergy, atopyy or asthma.
- Antigen binding to IgE antibodies initiates anaphylaxis.
- Prior exposure to the antigen or to a substance of similar structure is needed to provide sensitization, although an allergic history may be uknown to the patient.
- On reexposure, bining of the antigen to bridge two immunospecific IgE antibodies found on the surfaces of mast cells and basophils releases stored mediators
- The released mediators produce a symptom complex of bronchospasm and upper airway edema in the respiratory system, vasodilation and increased capillary permeability with possible cardiovascular collapse, and urticaria in the cutaneous system.
  - Histamine**: increased capillary permeability** (via H1 mediated stimulation of NO release from vascular endothelium), **peripheral vasodilation**, **bronchoconstriction**, vascular smooth muscle constriction
  - Leukotrienes: inceased capillary permeability, intense bronchoconstriction, **negative inotropy**, coronary artery vasoconstriction
  - Prostaglandins: bronchoconstriction, vasodilation, pulmonary hypertension, increased permeability
  - Eosinophil chemotactic factor: attraction of eosinophils
  - Neutrophil chemotactic factor: attraction of neutrophils
  - Platelet activating factor: platelet aggregation and release of vasoactive amines (smooth muscle contraction and increased capillary permeability)
- **Non-IgE mediated reactions:**
  - Other immunologic and nonimmunologic mechanisms release many of the mediators previously discussed, independent of IgE, creating a clinical syndrome identical with anaphylaxis.
    - Complement activation follows both immunologic (antibody mediated) and nonimmunologic pathways to include a series of multimolecular, selfassembling proteins that release biologically active complement fragments of C3 and C5.
      - C3a and C5a are called anaphylatoxins because they release histamine from mast cells and basophils, contract smooth muscle, increase capillary permeability and cause interleukin synthesis.
    - Nonimmunologic release of histamine
      - Many diverse molecules administered during the perioperative period release histamine in a dose-dependent nonimmunologic fashion
        - Antibiotics (vancomycin, pentamidine)
        - Basic compounds
        - Hyperosmotic agents
        - Muscle relaxants (d-tubocurarine, metocurine, atracurium, mivacurium, doxacurium)
        - Opioids (morphine, meperidine, codeine)
        - thiobarbiturates
      - Mechanism not well understood but involves selective mast cell and NOT basophil activation
      - Mast cell activation may be through specific cell signaling activation.
      - Antihistamine pretreatment before administration of drugs that are known to release histamine in humans does not inhibit histamine release, rather they compete with histamine at the H1/H2/H3 receptor and may attenuate decreases in SVR
- Treatment:
  - Secure Airway and ventilate with 100% O2
    - Profound VQ abnormalities can occur, producing hypoxemia
  - Discontinue all anesthetic drugs and offending agent
    - Inhalational anesthetic drugs are not the bronchodilators of choice to treat bronchospasm during anaphylaxis
    - Patients may not tolerate vasodilation and myocardial depression from volatile anesthetics
    - Interfere with body's compensatory response to cardiovascular collapse
    - Halothane sensitizes myocardium to epinephrine

- Volume
  - Up to 40% loss of intravascular fluid into interstitial space
  - Initial 2-4 L bolus of crystalloid; may require additional 25-50mL/kg if persistent hypotension
  - Consider TEE
  - May also lose significant volume into lungs secondary to increased capillary permeability
  - Colloid volume expansion has not proved to be more effective than crystalloid for treating anaphylaxis
- Epinephrine
  - Drug of choice in resuscitation of anaphylactic shock
  - Alpha adrenergic effects vasoconstrict to reverse hypotension
  - Beta receptor stimulation causes bronchodilation
  - Beta receptor stimulation attenuates mediator release by increasing cyclic AMP in mast cells and basophils
  - Infusion is an ideal method to administer EPI
  - Patients without hypotension (even if laryngeal edema) should receive subcutaneous epi
  - IV epi should not be given to normotensive patients
- Antihistamines
  - H1 receptors mediated may of the adverse effects of histamine
  - H1 antagonists may be useful in treating acute anaphylaxis
  - Do not inhibit anaphylactic reactions or histamine release but compete with histamine at H1 receptor after histamine is released
  - H2 antagonist administration is controversial
- Catecholamine infusion
  - For persistent hypotension or bronchospasm after initial resuscitation
- Bronchodilators
  - Useful if bronchospasm is a major feature
- Corticosteroids
  - Anti-inflammatory effects mediated by multiple mechanisms
  - Beneficial effects are delayed at least 4-6h
  - Though never proven to be effective, often given to treat refractory bronchospasm or refractory shock
  - 0.25-1g IV of hydrocortisone or equivalent
  - may be useful in reactions believed to be complement mediated
  - may be important in attenuating the late phase reactions that are reported to occur 12-24h after anaphylaxis
- Bicarbonate
  - Acidosis develops rapidly in patients with persistent hypotension
  - Acidemia reduces efficacy of epinephrine
  - With refractory hypotension or acidemia, $NaHCO_3$ may be indicated and given up to q5min
- Vasopressin
  - May attenuate pathologic vasodilation
  - Works via non-adrenergic receptor

- Agents implicated in allergic reactions
  - Muscle relaxants
    - Most common drugs responsible for evoking intraoperative allergic reactions
    - Aminosteroids more common than benzylisoquinonamines
    - Cross sensitivity between succinylcholine and NDNMBAs
    - All NMBAs are functionally divalent and capable of cross linking cell surface IGE and causing mediator release from mast cells and basophils without binding or haptenating to larger carrier molecules
  - Induction agents
  - Local anesthetics
  - Opioids
  - Antibiotics
  - Aprotinin
  - Colloid volume expanders (dextrans, albumin, HES)
  - Bonecement
  - Drug additives (preservatives)
  - Mannitol
  - Vascular graft material
  - NSAIDS
  - Latex
    - Milky sap derived from hevea brasiliensis
    - Present in variety of different products
    - Health care workers and children with congenital abnormalities are at risk
    - Spina bifida patients at increased risk
    - History of atopy significant risk factor
    - Allergy to bananas, avocados, kiwis
    - Latex induced allergic reaction is characterized by delayed onset of reaction – typically >30min after exposure to latex
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REFERENCES:

Stoelting's Anesthesia and Coexisting Disease Page 526-530
Barash Chapter 12