PERIOPERATIVE ANAPHYLAXIS: A BRIEF REVIEW

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DEC 2011

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ADVERSE DRUG REACTIONS (ADR) IN THE PERIOPERATIVE ENVIRONMENT: OVERVIEW

- most perioperative ADR are not allergic
- non-allergic ADR →dose dependent, relatively predictable
  - related to overdose, inadvertent route, drug interaction, side effect, or secondary effect
  - may mimic signs of allergic reaction
- by contrast, allergic reactions in OR are dose independent and unpredictable

EARLIEST RECORDED CASE OF ANAPHYLAXIS

In 2641 B.C.E. the Egyptian King Menes died from the bite of a wasp

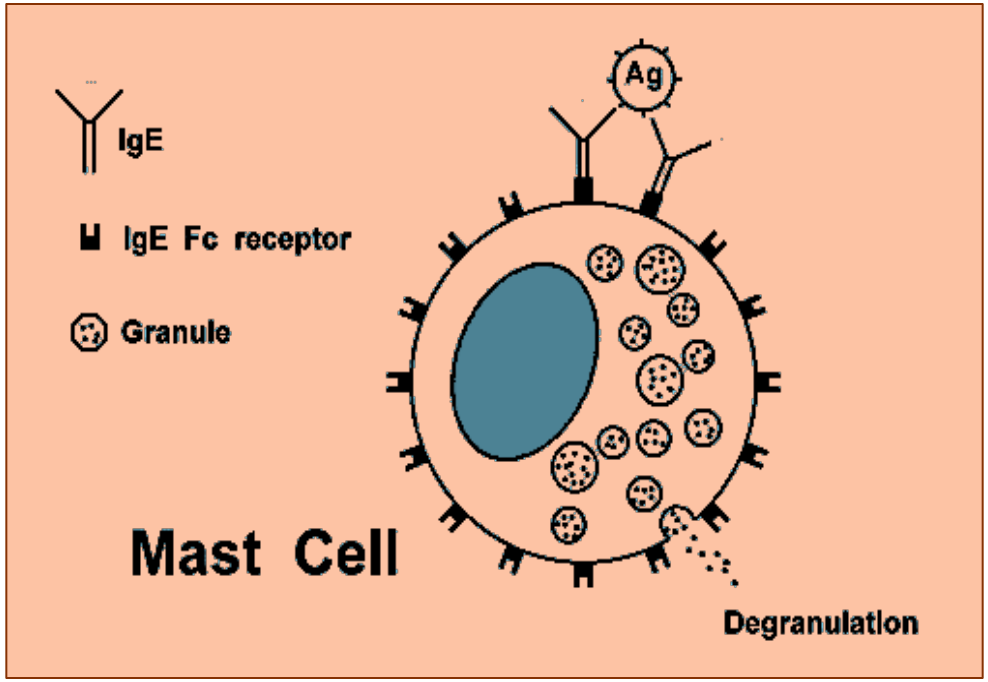
PERIOPERATIVE ANAPHYLAXIS*: OVERVIEW

- allergic reactions in OR→causes include drugs, blood products, environmental agents such as skin prep & latex
- anaphylaxis represents the most serious allergic reaction
- diagnosis may be delayed in perioperative environment
- likely causes of perioperative anaphylaxis have evolved over time and exhibit some regional differences
- treatment remains empirical at best
- standardized approach to evaluation often lacking

* literally, anaphylaxis is "backward protection"

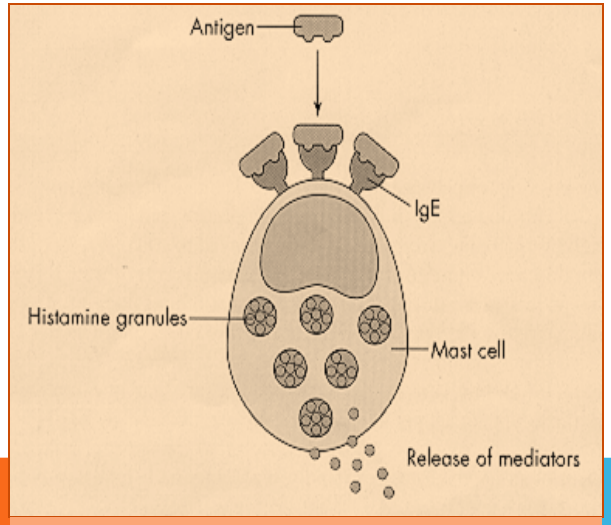
ANAPHYLAXIS IS A TYPE I IMMUNE RELATED ALLERGIC REACTION

- specific IgE elucidated after exposure to allergen
- receptors attach to basophils and mast cells
- re-exposure →IgE bridging with degranulation
- first exposure anaphylaxis due to cross-reactivity

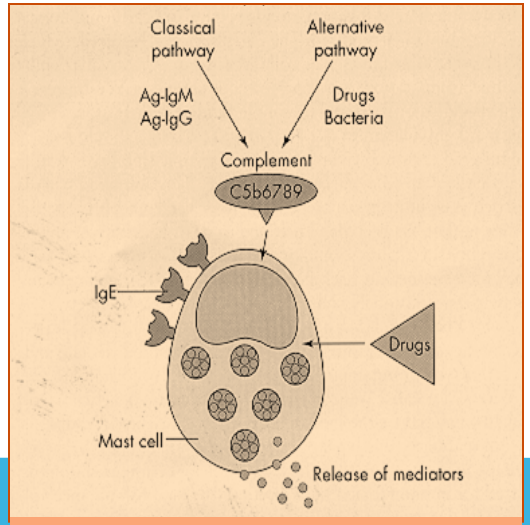


BOTH ANAPHYLACTIC AND ANAPHYLACTOID REACTIONS MAY OCCUR PERIOPERATIVELY

- anaphylactoid reactions are clinically similar to anaphylaxis but mediators are released in absence of IgE
- ~ 2/3 of perioperative allergic reactions are anaphylaxis



anaphylactic



anaphylactoid

CHEMICAL MEDIATORS INVOLVED IN ANAPHYLAXIS

TIMING	MEDIATORS
IMMEDIATE (PREFORMED)	histamine proteases TNF-α heparin
MINUTES (LIPIDS)	prostaglandins leukotrienes
HOURS (CYTOKINES)	IL-4 IL-13

CLINICAL MANIFESTATIONS IN OR: IMMUNE VS. NON-IMMUNE

	immune (%)	non-immune (%)
flushing, urticaria	72	94
angioedema	12	7
bronchospasm	40	19
CARDIOVASCULAR hypotension bradycardia cardiac collapse cardiac arrest	75 17 1.3 51 6	34 18 0.7 11 0

MERTES ET AL 2003

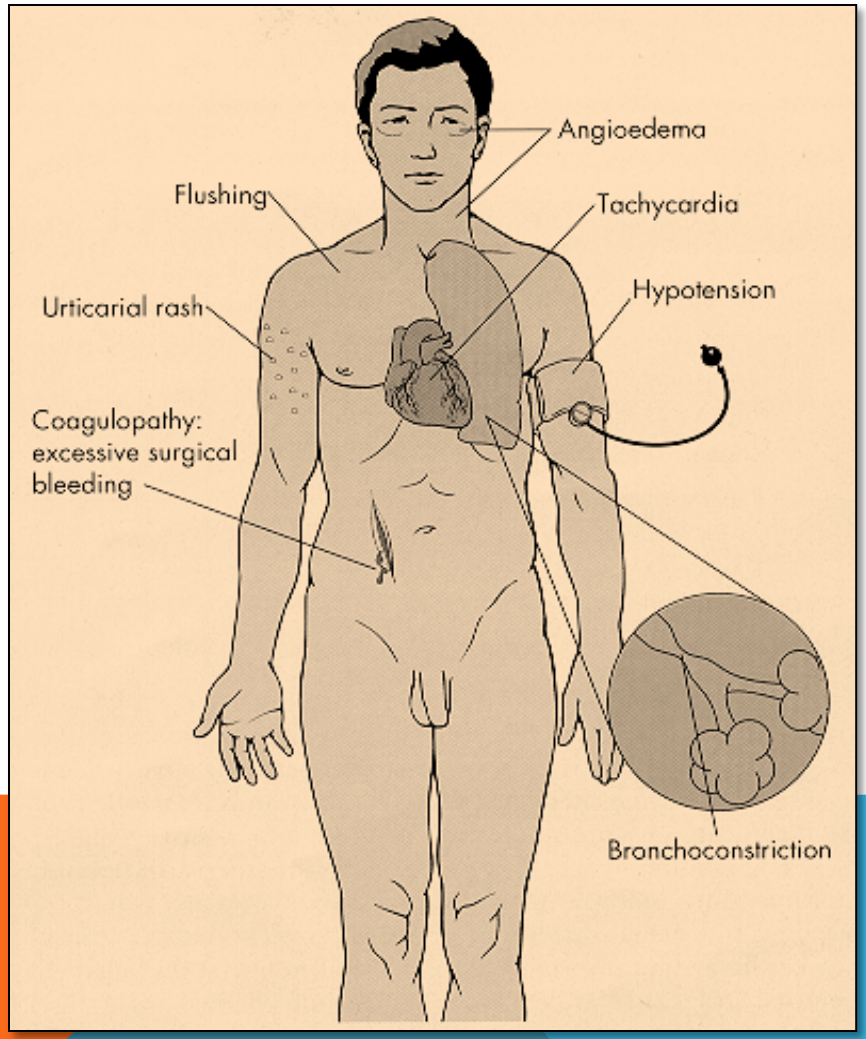
A RARE EVENT → HIGH INDEX SUSPICION REQUIRED TO PREVENT MORBIDITY

- incidence 1:3500-20,000* →most anesthesiologists will witness only a few such reactions in a lifetime
  - mortality 3-4% CNS sequelae 5-6%
- Jacobsen et al 2001 [1]
  - simulator study: 0 of 42 anesthesiologists made the correct dx during the first 10 minutes of anaphylaxis

* *Anesth Analg* 2003;97:1381

1 *ACTA ANAESTHESIOLOGICA SCANDINAVICA* 2001;45:315

INITIAL CLINICAL MANIFESTATIONS OF ALLERGIC REACTION MAY BE MISSED



- most common are CV and cutaneous BUT
- CV ↓ common after anesthesia induction
- and cutaneous signs may be missed due to draping of the patient

SUSPECTED ANAPHYLAXIS: PRIMARY TREATMENT

- remove exposure; decrease or remove anesthetic
- ABC's
  - 100% oxygen and definitive airway support
  - volume expansion (25-50 ml/kg)
- epinephrine (titrate infusion, as needed)
  - 0.1 µg/kg hypotension and 1 µg/kg cardiac collapse
  - ∂_1 effects support BP and ß$_2$ effects bronchodilate

SUSPECTED ANAPHYLAXIS: SECONDARY TREATMENT

- H-1 and H-2 blockers
- bronchodilators as needed
- corticosteroids (0.5-1 mg/kg methlyprednisolone)
- supportive ICU care
- tryptase level within 2 hours; definitive in-vitro (RAST) or in-vivo (skin, intradermal) allergy testing recommended
  - skin test deferred 4-6 wks due to mediator depletion

ROLE OF VASOPRESSIN IN REFRACTORY ANAPHYLACTIC SHOCK

- 6 case reports of shock unresponsive to “standard” therapy with epinephrine / fluid and steroid
- 2 units vasopressin stabilized all 6 patients
- vasoconstriction ↑ in skin, SSM, intestine and fat, less coronary renal vasoconstriction, cerebral vasodilatation
- accompanying editorial →therapies for anaphylaxis are class C or D at best (Cochrane criteria); so in refractory shock, vasopressin is as indicated as any other Rx

SCHUMMER C. *ANESTH ANALG* 2008;107:620

EVOLVING CAUSES OF PERIOPERATIVE ANAPHYLAXIS: I (FRANCE 1984-1989)

ALLERGEN	INCIDENCE (%)
muscle relaxants	81
natural rubber latex	0.5
antibiotics	2
hypnotics	11
colloids	0.5
opioids	3
other	2

LAXENAIRE. *ANN FR ANESTH REANIM* 1990;9:501

EVOLVING CAUSES OF PERIOPERATIVE ANAPHYLAXIS: II (FRANCE 1992-1994)

ALLERGEN	INCIDENCE (%)
muscle relaxants	59.2
natural rubber latex ***	19
antibiotics	3.1
hypnotics	8
colloids	5
opioids	3.5
other	2.2

*** marked increase

LAXENAIRE. *ANN FR ANESTH REANIM* 1996;15:1211

EVOLVING CAUSES OF PERIOPERATIVE ANAPHYLAXIS:III (FRANCE 1999-2000)

ALLERGEN	INCIDENCE (%)
muscle relaxants	58.2
natural rubber latex	16.7
antibiotics ***	15
hypnotics	3.7
colloids	2.7
opioids	1.4
other	2.9

*** marked increase

MERTES. *ANESTHESIOLOGY* 2003; 99:521

PERIOPERATIVE ALLERGIC REACTIONS MAYO CLINIC DATA BASE 1992-2010 (I)

- retrospective data base postoperative referrals for allergy testing

maintenance 74%
induction 18%
PACU 8%

clinical presentation consistent with immediate-type allergic reaction

38 patients (20 female)
1:34,000 incidence

Ig-E
+ skin test
↑ tryptase
N = 18

non Ig-E
- skin test
↑ tryptase
N = 6

possible non Ig-E
- skin test
tryptase either nl or not obtained
N = 14

GURRIERI C. *ANESTH ANALG* 2011;113:1202

PERIOPERATIVE ALLERGIC REACTIONS MAYO CLINIC 1992-2010 (II)

- causative agent NOT identified in 53% of cases

+ SKIN TEST (18 patients)	N (%)
antibiotics cefazolin levofloxacin / ampicillin	9 (50) 7 1
neuromuscular blockers vecuronium, succinylcholine	2 (11)
latex	3 (17)
other / multiple propofol; isosulfan blue; midazolam; fentanyl; flumazenil	4 (22)

GURRIERI C. *ANESTH ANALG* 2011;113:1202

PERIOPERATIVE ALLERGIC REACTIONS MAYO CLINIC 1992-2010 (III): OBSERVATIONS

- though causative agent often lacking, unlike European studies, antibiotics >cause of anaphylaxis than NMB's
  - different testing methods ?? vs. geographical differences
- opioids rare cause, in contrast to Danish study (Garvey)
- severity of rxns: 58% abortion of case / 40% ICU
- elevation of tryptase (t ½ 2 hours) depends on sampling
- lack of causative agents in > 50% suggests need for standardized protocols to investigate anaphylaxis

GURRIERI C. *ANESTH ANALG* 2011;113:1202

MUSCLE RELAXANTS & ANAPHYLAXIS

- sux > benzylisoquinolium > aminosteroid
  - histamine release w/benzylisoquilium compounds such as atracurium is not immune mediated
- IgE to 4°or 3° ammonium ions mediate anaphylaxis
  - prior sensitization may be due to OTC meds, cosmetics, foods
- cross-sensitivity between muscle relaxants in 60%
- rocuronium ↑ incidence anaphylaxis in Norway, but not in US; may represent false + testing vs. population based differences in sensitization

NATURAL RUBBER LATEX AND ANAPHYLAXIS

- milky sap produced by *Hevea brasiliensis* tree
- frequent exposures to latex in the OR, although many OR environments now going latex-free.... as a result →
- incidence ↓ but still probably ~ 10% periop anaphylaxis
- increased risk health care workers, spina bifida, G-U anomalies, rubber workers, patients with atopy / eczema
- certain food allergies (banana, kiwi, avocado) associated

PROPOFOL & ANAPHYLAXIS

- **lipid vehicle w/soybean oil, egg lecithin and glycerol**
  - egg lecithin from yolk; most egg allergy related to ovalbumin in egg white / -'ve allergy testing w/propofol in 25 pts with egg allergy
- **Laxenaire : 2.1% of perioperative anaphylaxis; most Ig-E related** [1]
  - sensitization from isopropyl groups in dermatologic products
- **estimated incidence in French study 1:60,000**
  - compares favorably to 1:30,000 incidence with thiopental
- **bottom line – "safe" in egg allergy but is allergenic and could be increased incidence if atopy, multiple food allergies**

1 *BR J ANAESTH* 2001;87:549

ANTIBIOTICS AND ANAPHYLAXIS

- Mayo series, antibiotics → 50% IgE-mediated anaphylaxis
  - cephalosporins caused majority of these
- PCN most common cause anaphylaxis in US overall (75% anaphylactic deaths) but only 10-20% PCN allergy is true
- cross-sensitivity between PCN and cephalosporins reported (~10%); usually non-immunologic rash, most authors "OK" with cephalopsporins unless PCN allergy true anaphylaxis
- recommend that antibiotics be given prior to other agents to facilitate diagnosis should allergic reaction occur

PERIOPERATIVE ANAPHYLAXIS: FINAL OBSERVATIONS

- myriad exposures in the perioperative environment
  - IV drugs, blood products, contrast, latex, colloids
  - NMB's and antibiotics most likely causes at present time
- allergic reaction may occur on 1st exposure
- when in doubt, discontinue latex
- recommend: standardized protocols to test all agents administered during anesthesia, including medications and occult antigens such as latex and chlorhexidine