



ANAPHYLAXIS IN ANESTHESIA

Content

- I. Definition
- II. Epidemiology
- III. Etiology
- IV. Recognition
- V. Diagnosis
- VI. Observation and follow up
- VII. Drugs



Definition

Prophylaxis : protection

Anaphylaxis : against protection

1901 Charles Richet & Paul Portier “immunize”
dogs with venom of sea anemone.

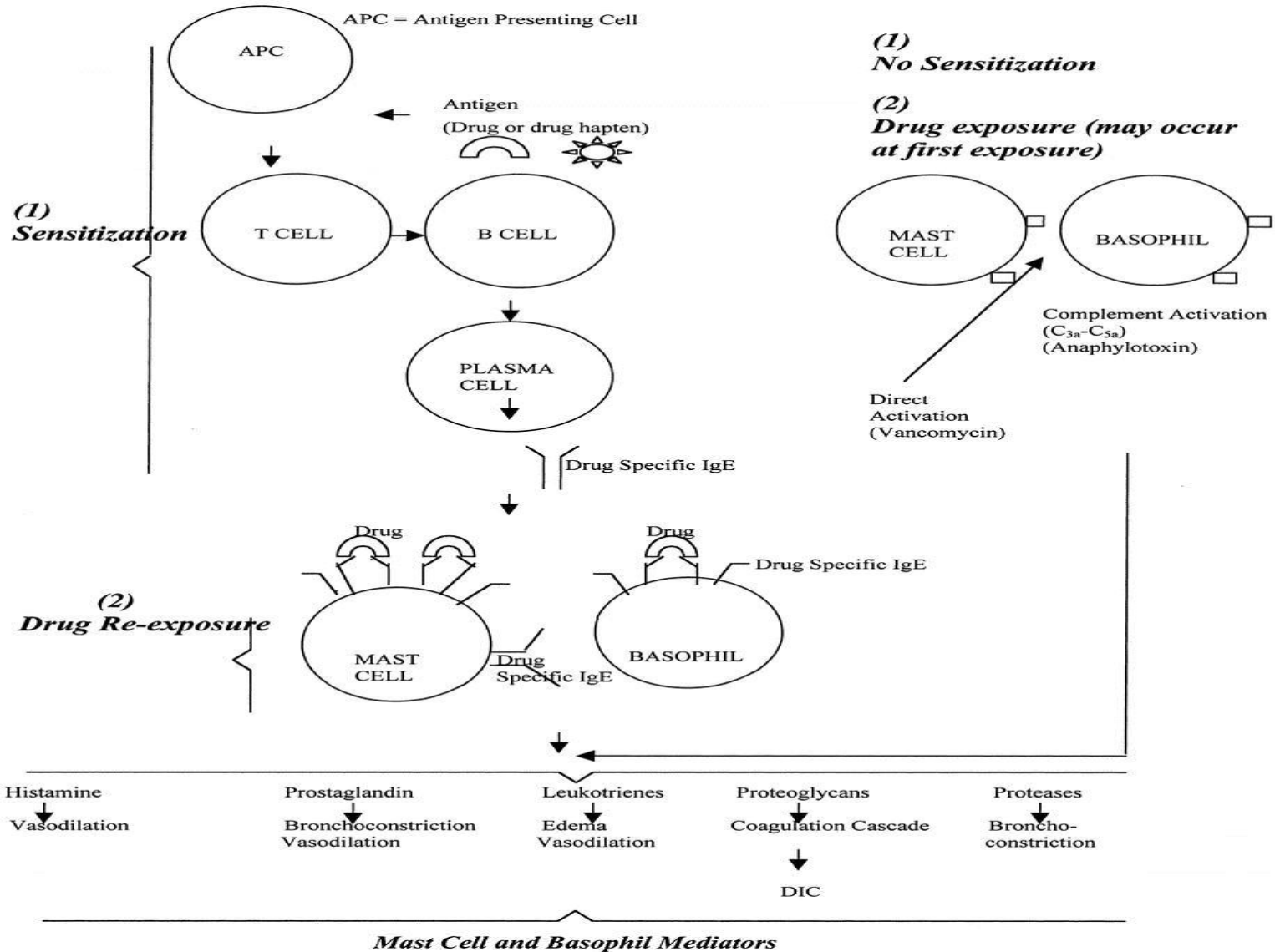
2011 WAO guidelines

“ A serious life-threatening generalized or systemic hypersensitivity reaction” and “a serious allergic reaction that is rapid in onset and might cause death”



ANAPHYLACTIC REACTION

ANAPHYLACTOID REACTION



Incidence

- The incidence of anaphylaxis related to anesthesia is not precisely known.
- More common with general anesthesia than with local or spinal anesthesia.
- The anaphylaxis incidence with general anesthesia varies from 1:10,000 to 1:20,000
- Estimated mortality ranging from 1.4% to 6%
- Anaphylaxis during anesthesia can present as cardiovascular collapse, airway obstruction, and/or skin manifestations. C



Etiology

Table 2. Drugs and related compounds involved in perioperative anaphylaxis (not exhaustive)

Substance	%*	Examples
NMBA	58.2	Succinylcholine <i>Benzylisoquinolines</i> : atracurium, cisatracurium, doxacurium, mivacurium <i>Aminosteroids</i> : pancuronium, rapacuronium, rocuronium, vecuronium
NRL	16.7	Gloves, tourniquets, catheters
Antibiotics	15.1	β -lactams (penicillins, cephalosporins), vancomycin, quinolones <i>Cave</i> : locally applied antibiotics
Colloids	4	Gelatine, hydroxyethyl starch, dextrans, albumins
Hypnotics	3.4	Barbiturates: thiopental, methohexital Nonbarbiturates: propofol, midazolam, etomidate, ketamine
Opioids	1.3	Phenanthrenes: morphine, codeine Phenylpiperidines: alfentanil, fentanyl, remifentanyl, sufentanyl and meperidine
Miscellaneous	1.3	Antiseptics: chlorhexidine, povidone iodine Iodinated radiological contrast and dyes (patent and isosulphan blue) Local anaesthetics: benzoic acid esters and amides Aspirin, NSAID and paracetamol (acetaminophen) Ethylene oxide Protamine and heparins

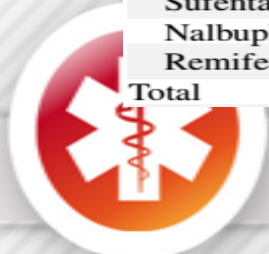
NMBA, neuromuscular blocking agent; NRL, natural rubber latex; NSAID, nonsteroidal anti-inflammatory drugs.



Etiology

TABLE I. Agents involved in IgE-mediated anesthesia (1816 patients, 1851 subjects, 1997, and December 31, 2004)

Causal agent			
	Colloids	3.43	63
	Gelatin	88.9	56
	Hetastarch	9.5	6
	Albumin	1.6	1
	Total	100	
	Local anesthetics	0.33	6
	Bupivacaine	50.0	3
	Lidocaine	33.3	2
	Mepivacaine	16.7	1
	Total	100	
	Other agents	2.40	44
	Patent blue	25.0	11
	Methylene blue	2.3	1
	Propacetamol	20.5	9
	Aprotinin	11.4	5
	Protamine	9.1	4
	Nonsteroidal anti-inflammatory drugs	6.8	3
	Papain	6.8	3
	Nefopam	4.5	2
	Ethylene oxide	2.3	1
	Steroids	2.3	1
	Hyaluronidase	2.3	1
	Metabisulfite	2.3	1
	Povidone	2.3	1
	Contrast media	2.3	1
	Total	100	
NMBAs			
Succinylcholine			
Rocuronium			
Atracurium			
Vecuronium			
Pancuronium			
Mivacurium			
Cisatracurium			
Total			
Latex			
Antibiotics			
Penicillin			
Cephalosporin			
Others			
Total			
Hypnotics			
Propofol			
Midazolam			
Pentothal			
Ketamine			
Total			
Opioids			
Morphine			
Fentanyl			
Sufentanil			
Nalbuphine			
Remifentanil			
Total			



Recognition

Grade I	Grade II	Grade III	Grade IV
Cutaneous	Cutaneous	Cardiovascular	Cardiovascular
Erythema	Grade I signs	Grade II signs plus	Pulseless electrical activity
Pruritis	Cardiovascular	Cardiovascular collapse	Cardiac arrest
Urticaria	Hypotension	Profound hypotension	Death
Angioedema	Tachycardia	Bradycardia	
	Presyncope	Dysrhythmia	
	Respiratory	Respiratory	
	Dyspnea	Bronchospasm	
	Wheezing	Hypoxia (SaO ₂ < 92%)	
	Gastrointestinal	Gastrointestinal	
	Nausea	Grade II signs plus	
	Vomiting	Incontinence	
	Diarrhea	Neurologic	
	Abdominal pain	Confused	
		Unconscious	



Recognition

Table 2 Clinical features of anaphylaxis during anaesthesia in 477 patients in France between January 1997 and December 1998

Clinical symptoms	Number of cases (%)	Sole feature (number of patients)
Cardiovascular symptoms		
Arterial hypotension	85 (17.8%)	
Cardiovascular collapse	256 (53.7%)	
Bradycardia	10 (2.1%)	
Cardiac arrest	19 (4.0%)	
Bronchospasm	211 (44.2%)	
Cutaneous symptoms	332 (69.6%)	
Angio-oedema	56 (11.7%)	

Br J Anaesth 2001; 87: 549-558

Table 1 Presenting signs of 76 severe anaphylactic reactions

Presenting signs	Number
Hypotension	31*
Hypotension + skin signs	21†
Hypotension + bronchospasm + skin signs	12
Hypotension + bronchospasm	4
Skin/mucosal signs	4
Bronchospasm	2
Bronchospasm + skin signs	2
Total	76

*One also reported "difficult ventilation".

†Two also reported "difficult ventilation".

Hypotension: includes a documented fall in systolic blood pressure, unrecordable blood pressure, and impalpable pulses.

Bronchospasm: includes documented bronchospasm or difficulty with ventilation.

Skin/mucosal signs: includes rash, urticaria, oedema, or swelling of any part of the patient (including tongue and airway).

Qual Saf Health Care 2005;14:e19



Recognition

Table 1. Differential diagnosis of anaesthesia-related anaphylaxis

Symptoms and signs	Cause
Skin and mucosa: (hives, flush, erythema, urticaria), swelling head and neck	Direct histamine release Venous obstruction Head down position C1-esterase inhibitor deficiency Mastocytosis
Airway compromise, dyspnoea, wheeze, bronchospasm, stridor, difficulty in inflating the lungs	Direct histamine release (e.g. propofol) Acid aspiration Exacerbation of asthma Intubation Oesophageal or bronchial intubation Difficult airway
Fall in blood pressure	Direct histamine release Visceral traction Vasodilatation by drugs (e.g. oxytocin) Cardiac drug effects Concealed hypovolaemia Drug overdose and interactions Gas embolism Hypoxemia Neurocardiogenic syncope Vasovagal reaction Electrolyte disorders



Allergy 2007; 62: 471–487

Diagnosis

- There is a broad spectrum of anaphylaxis presentations that require clinical judgment. Do not rely on signs of shock for the diagnosis of anaphylaxis.
(Moderate Recommendation; C Evidence)
- During acute management, no test is needed to confirm the diagnosis.



Diagnosis

- There is a broad spectrum of anaphylaxis presentations that require clinical judgment. Do not rely on signs of shock for the diagnosis of anaphylaxis.
(Moderate Recommendation; C Evidence)



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Diagnosis

Anaphylaxis is likely when any one of the three criteria is fulfilled:

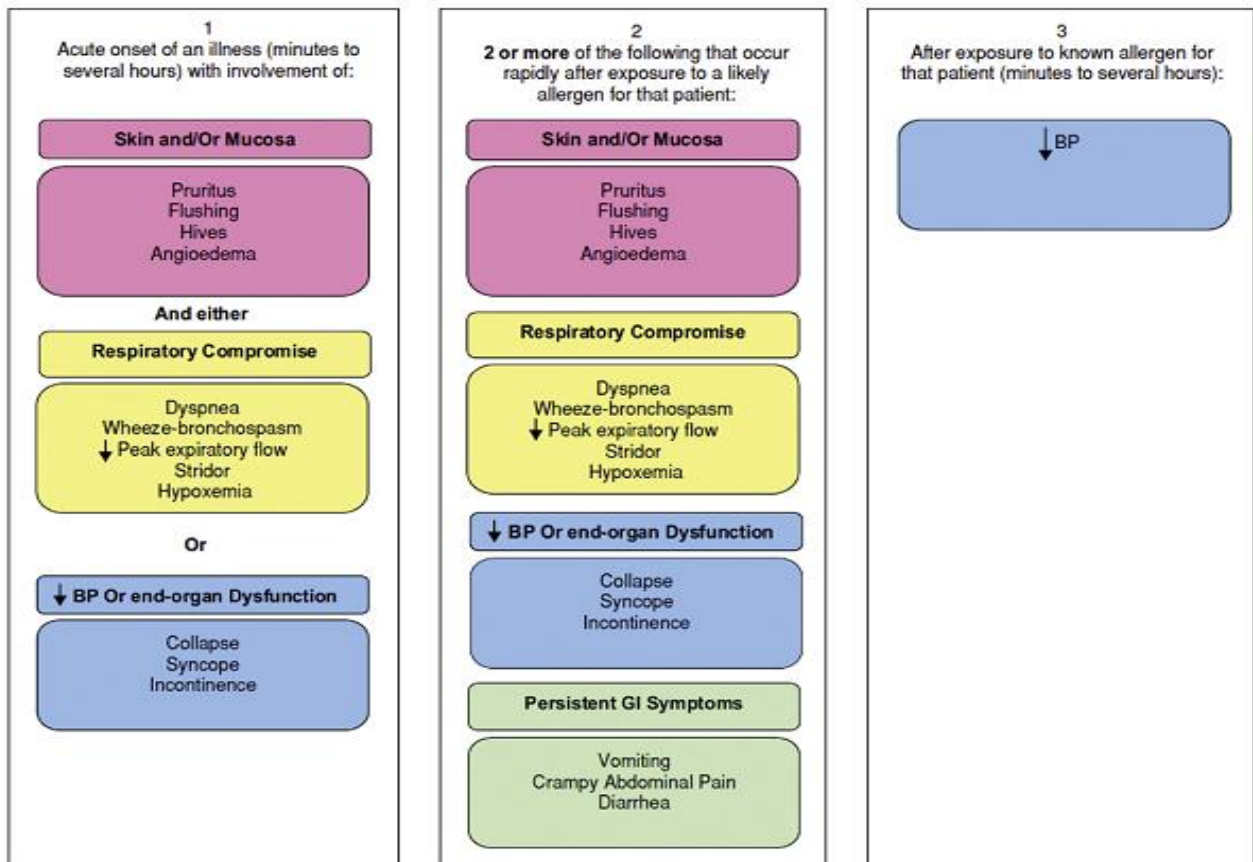


Figure 1. Visual representation of the NIAID/FAAN criteria. Reprinted with permission from the Internal Journal of Emergency Medicine.⁸



Diagnosis

TABLE IV. Test characteristics of NIAID/FAAN criteria for the diagnosis of anaphylaxis compared with the reference standard of allergist's diagnosis

Test characteristics	Criterion 1, 2, or 3	Criterion 1	Criterion 2	Criterion 3
Patients meeting criterion (n)	86	79	71	5
Patients given diagnosis of anaphylaxis (n)	59	53	53	5
Sensitivity, % (95% CI)	96.7 (88.8-99.1)	86.9 (76.2-93.2)	86.9 (76.2-93.2)	8.9 (4.0-18.5)
Specificity, % (95% CI)	82.4 (75.5-87.6)	83.0 (76.3-88.1)	88.2 (82.2-92.4)	99.7 (97.0-100)
Positive predictive value, % (95% CI)	68.6 (58.2-77.4)	67.1 (56.1-76.4)	74.6 (63.4-83.3)	91.7 (51.7-99.1)
Negative predictive value, % (95% CI)	98.4 (94.5-99.6)	94.1 (88.7-97.0)	94.4 (89.3-97.1)	73.1 (66.7-78.6)
Likelihood ratio of a positive test result	5.48	5.1	7.39	27.32
Likelihood ratio of a negative test result	0.04	0.16	0.15	0.91

J Allergy Clin Immunol 2012;129:748-52



Diagnosis

Laboratory test

- Establishing anaphylaxis as a cause
 - ✓ Plasma Histamine
 - ✓ Serum Tryptase
 - ✓ 24-h urinary histamine metabolites

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TABLE 3. Role of Laboratory Tests in the Diagnosis of Anaphylaxis

Total tryptase (pro, pro', and mature forms of alpha/beta tryptases)

Obtain blood sample within 15 minutes to 3 hours of symptom onset^{a,b}

Consider measuring levels in accurately timed serial blood samples during the anaphylactic episode

Consider comparing levels measured during the episode with a baseline level^{c,d}

Histamine

Obtain blood sample within 15 minutes to 1 hour of symptom onset^a

Special handling of the blood sample is required (use wide-bore needle, keep sample at 4°C and centrifuge it promptly, freeze plasma promptly)

Measure histamine and its metabolite *N*-methylhistamine in a 24-hour urine sample

Other^e



Diagnosis

Diagnostic Value of Histamine and Tryptase Concentrations in Severe Anaphylaxis with Shock or Cardiac Arrest during Anesthesia

Dominique Laroche, M.D., Ph.D., Philippe Gomis, M.D., Emmanuel Gallimidi, M.D., Jean-Marc Malinovsky, M.D., Ph.D., Paul Michel Mertes, M.D., Ph.D.

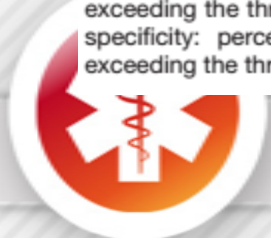
Table 4. Diagnostic Performances of Plasma Histamine and Tryptase Measurements for the Diagnosis of Allergic Immediate Hypersensitivity, According to Different Thresholds

	Threshold	Se % (95% CI)	Sp % (95% CI)
Histamine (nmol/l)	6.35	90.7 (81.7–96.1)	91.7 (73.0–98.9)
	9	84.0 (73.7–91.4)	91.7 (73.0–98.9)
Tryptase (µg/l)	7.35	92.0 (83.4–97.0)	92.0 (73.9–99.0)
	12.5	82.7 (73.7–91.4)	96.0 (79.6–99.9)
	25	68.0 (56.2–78.3)	100 (86.2–100)

Performances are expressed as percentage and 95% CI.

Se = sensitivity: percentage of patients with mediator concentrations exceeding the threshold among patients with proved allergic shock; Sp = specificity: percentage of patients with mediator concentrations not exceeding the threshold among patients with shock unrelated to allergy.

	PPV	NPV
Histamine (9nmol/L)	99.4%	28.6%
Tryptase 12.5mcg/l 25mcg/l	99.7% 100%	27.9% 17.9%



Diagnosis

- Expediently consider conditions other than anaphylaxis that might be responsible for the patient's condition. Obtain a serum tryptase level to assist in this regard after effective treatment has been rendered.
- (Moderate Recommendation; C Evidence)

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Diagnosis

ORIGINAL RESEARCH



Can serum mast cell tryptase help diagnose anaphylaxis?

Simon GA Brown,^{1,2} Konrad E Blackman¹ and Robert J Heddle²

¹Department of Emergency Medicine, Royal Hobart Hospital, Hobart, Tasmania, ²Department of Immunology, Allergy and Arthritis, Flinders Medical Centre and Flinders University, Bedford Park, South Australia, Australia

Results:

Excluding mild reactions from the analysis, peak tryptase readings had sensitivity of 0.36 and specificity of 0.93 using the recommended cut-off range ($< 12.0 \mu\text{g/L}$). Receiver-operator curve analysis found a cut-off of $9.0 \mu\text{g/L}$ would improve diagnostic performance (sensitivity 0.55, specificity 0.93). Serial tryptase measurement was significantly more discriminatory; an increase in tryptase of $2.0 \mu\text{g/L}$ or greater had a sensitivity of 0.73 and specificity of 0.98. The addition of histamine measurements, defining a positive result by either a rise in tryptase or a rise in histamine, appeared to further increase sensitivity (0.90).

Emergency Medicine Australasia (2004) 16, 120–124



Diagnosis

- Establishing the etiology of anaphylactic events
 - ✓ Skin tests to foods to drugs when indicated
 - ✓ Serum-specific IgE to foods and drugs when indicated
 - ✓ Oral challenge
 - ✓ Galactose-1,3-a-galactose
 - ✓ Baseline serum tryptase
 - ✓ Baseline 24-h urinary histamine metabolites
 - ✓ Prostaglandin D2
 - ✓ Blood determination for 816V mutation
 - ✓ Bone marrow



Diagnosis

Serum specific IgE test	Skin test
<i>Favour serum IgE testing:</i>	
<ul style="list-style-type: none"> ▪ Widely available in any medical setting 	<ul style="list-style-type: none"> ▪ Available only where equipment, reagents and trained staff are on hand
<ul style="list-style-type: none"> ▪ Minor pain - venesection 	<ul style="list-style-type: none"> ▪ Minor discomfort, itching
<ul style="list-style-type: none"> ▪ Little patient effort or cooperation required 	<ul style="list-style-type: none"> ▪ Requires patient cooperation
<ul style="list-style-type: none"> ▪ No risk to patient; may be first line with certain high-risk allergens 	<ul style="list-style-type: none"> ▪ Slight risk of systemic allergic reaction, more so in some situations
<ul style="list-style-type: none"> ▪ Can be done where there is extensive skin disease 	<ul style="list-style-type: none"> ▪ Require areas of normal skin for testing
<ul style="list-style-type: none"> ▪ Can be done where the patient has taken antihistamines or is unable to stop certain medications which might interfere with SPT 	<ul style="list-style-type: none"> ▪ Must stop antihistamines and some antidepressants and other drugs several days before test (see appendix 2)
<ul style="list-style-type: none"> ▪ Many allergens available, including some which are not available for skin testing or not routinely carried in skin test settings. Some laboratories may send away samples for rarer allergens 	<ul style="list-style-type: none"> ▪ Many allergens available, but some low-demand allergens will not be carried by individual practices
<ul style="list-style-type: none"> ▪ Laboratory test, subject to quality control and standardization 	<ul style="list-style-type: none"> ▪ Methodology and result quality variable, no standardization or formal quality control at the current time



Diagnosis

Favour skin prick testing:

<ul style="list-style-type: none"> ▪ Venesection may be painful or anxiety-provoking particularly in children 	<ul style="list-style-type: none"> ▪ Minor scratch, itch if positive
<ul style="list-style-type: none"> ▪ Results may take days or weeks 	<ul style="list-style-type: none"> ▪ Results in half an hour
<ul style="list-style-type: none"> ▪ Results are not directly meaningful to patients 	<ul style="list-style-type: none"> ▪ Results are visible and compelling to patients; may have value in ensuring compliance with allergen avoidance measures
<ul style="list-style-type: none"> ▪ Reasonably good sensitivity 	<ul style="list-style-type: none"> ▪ In most cases, shown to have better sensitivity for clinically valid allergies
<ul style="list-style-type: none"> ▪ Some food allergens, drugs, rarer pollens not available for testing 	<ul style="list-style-type: none"> ▪ Can extemporaneously prepare allergens (with appropriate considerations; specialist practice)
<ul style="list-style-type: none"> ▪ Some allergens particularly foods may show low sensitivity in certain clinical situations 	<ul style="list-style-type: none"> ▪ Freshly prepared food allergens may show more sensitivity in certain circumstances (caution- risk of anaphylaxis)
<ul style="list-style-type: none"> ▪ False positives possible with high total IgE levels 	<ul style="list-style-type: none"> ▪ No interference from high total IgE
<ul style="list-style-type: none"> ▪ Numerical results obtained on different types of equipment are not directly comparable 	<ul style="list-style-type: none"> ▪ Numerical measurements may vary by different operators



Diagnosis

- The diagnosis of a specific cause of anaphylaxis
 - ✓ Skin tests,
 - ✓ In vitro IgE tests
 - ✓ Challenge tests (particularly double-blinded, placebo-controlled challenge tests)

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Observation and follow up

- The first 30 minutes of surgery is more likely due to
 - ✓ Antibiotics
 - ✓ Neuromuscular blocking agents, or
 - ✓ Hypnotic inducing agents.
- After 30 minutes of anesthesia is more likely due to
 - ✓ Latex
 - ✓ Protamine
 - ✓ Supravital dyes
 - ✓ Plasma expanders
 - ✓ Blood transfusion.



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Observation and follow up

- Observing for at least 4 to 8 hours
- Observe patients with a history of risk factors for severe anaphylaxis (eg, asthma, previous biphasic reactions, or protracted anaphylaxis) for a longer period.
- (Moderate Recommendation; C Evidence)



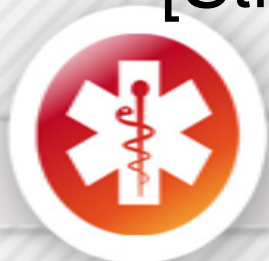
Prevent

- Perform skin testing for suspected reactions to neuromuscular blocking agents, b-lactam antibiotics, and barbiturates.

[Recommendation; C Evidence]

- Consider in the evaluation of perioperative anaphylaxis medications (opioids, neuromuscular agents, antibiotics, ...) blood transfusions, supravital dyes, and latex.

[Strong Recommendation; B Evidence]



Drugs

- Mivacurium and atracurium are associated with non-allergic anaphylaxis.
- Cisatracurium, is not associated with non-allergic anaphylaxis
- Succinylcholine, can cause non-immunologic histamine release, but there have also been reports of IgE-mediated reactions in some patients. B
- Cross-sensitivity between different NMBAs is relatively common.
- The patient should undergo skin prick testing with all the NMBAs in current use.



Drugs

Table VI-2

Latex-containing articles potentially used for anesthesia or surgery

Adhesive tape
Airway masks
Ambu-bag
Anesthesia bags and tubing
Self-adhesive bandages
Blood pressure cuffs
Bulb syringes
Catheter leg bag straps
Catheters
Condoms
Indwelling
Straight
Elastic bandages
Electrode pads
Endotracheal tubes
Gloves, sterile and exam
Intravenous bags, ports, infusion sets
Penrose drains
Rubber pads
Stethoscope tubing
Suction catheters
Syringes
Tourniquets

Current free of latex items:

- ✓ Ambu-bags,
- ✓ Catheter leg bag straps,
- ✓ Bandages
- ✓ Adhesive pads, tape,
- ✓ Electrode pads
- ✓ Endotracheal tubes
- ✓ Infusion sets
- ✓ Ports
- ✓ Suction catheters



Drugs

- Perform skin tests patients who present with possible anaphylaxis to penicillin recognizing that the negative predictive value is 95% to 99%. [B Evidence]
- Patients with a history of penicillin induced-anaphylaxis, recognizing that lifethreatening reactions have occurred when patients allergic to penicillin are given cephalosporins. [B Evidence]
- Vancomycin can produce manifestations similar to anaphylaxis that are not mediated by IgE and can be prevented by slow infusion of the drug. [C Evidence]



Drugs

- Induction agents are responsible for no more than 2% of anaphylaxis episodes related to anesthesia.
- Barbiturates generally cause IgE-dependent reactions.
- Benzodiazepines, propofol, etomidate and ketamine, do not generally cause reaction
- Narcotics when administered intravenously will commonly cause flushing and urticaria and could cause anaphylactoid reactions.
- There are rare reports of IgE-mediated anaphylaxis to morphine and fentanyl.
- Skin testing with narcotics is of limited value



Drugs

- Blood transfusions can result in anaphylactoid reactions.
- Protamine can cause IgE-dependent and IgE independent anaphylaxis.
- Neither skin testing nor in vitro testing of IgE specific for protamine is available.



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Drugs

Table VI-3

Skin testing concentrations for anesthetic agents

Medication	Intradermal skin test concentration (mg/mL)
Alcuronium	0.005
Methohexital	0.1
Metocurine	0.002
Pancuronium	0.002
Succinylcholine	0.02, 0.05
Thio amyl	0.1
Thiopental	0.20
Tubocurarine	0.0003, 0.001
Rocuronium	0.01
Vecuronium	0.004



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Drugs

