Contemporary Diagnosis and Management of Anaphylaxis

The 2020 and 2023 JTFPP Anaphylaxis Practice Parameters At-A-Glance

Marcus S. Shaker, MD, MSc, FAAAAI, FACAAI
Professor of Medicine and Pediatrics
Dartmouth Geisel School of Medicine

Disclosures

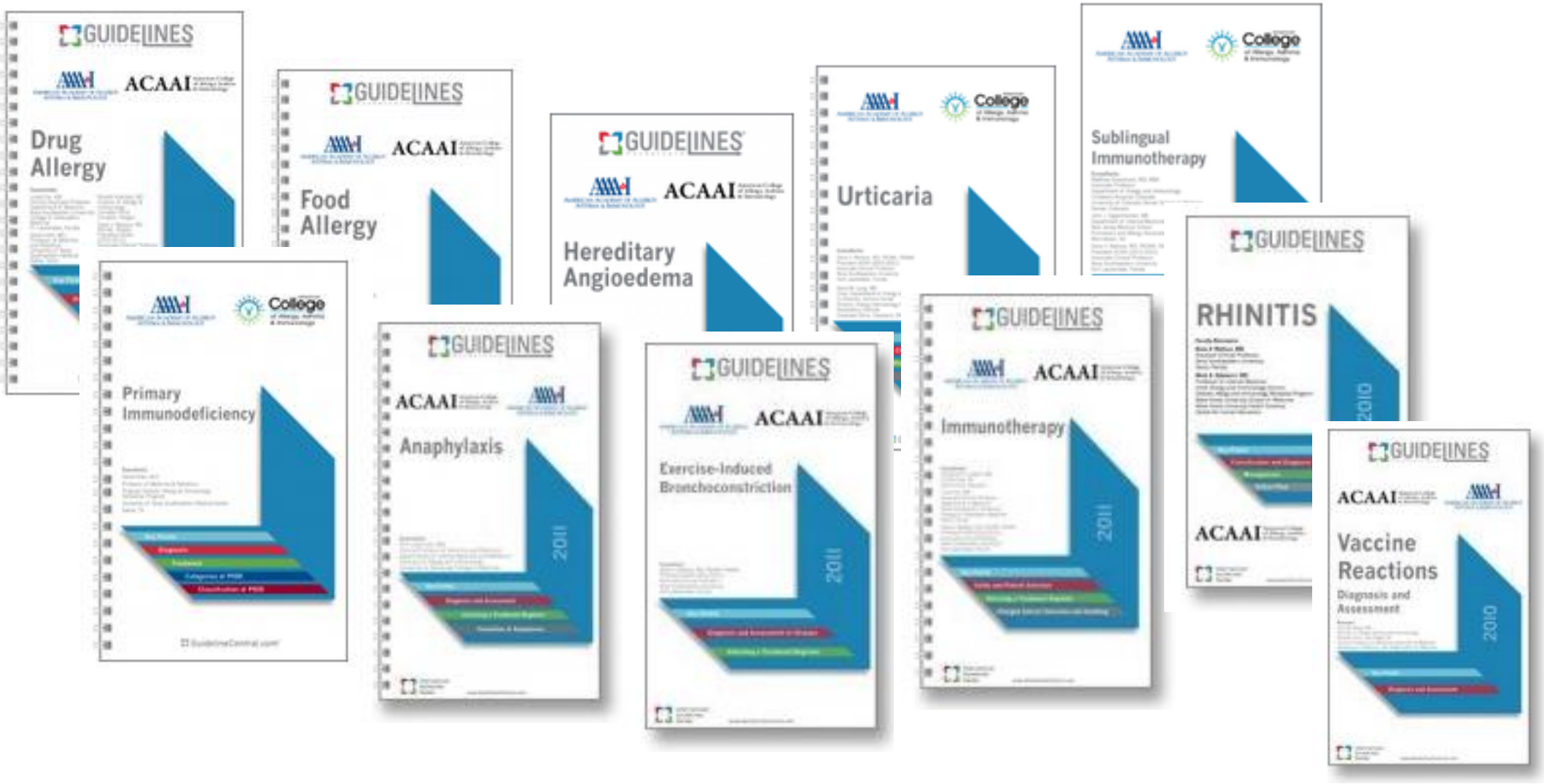
- *I serve on the Joint Task Force on Practice Parameters and the AAAAI Board of Directors, am an Associate Editor for Annals of Allergy, Asthma, and Immunology, and an Editorial Board Member for the Journal of Allergy and Clinical Immunology In Practice and the Journal of Food Allergy. Views expressed are my own*
- *I have participated in research projects that have received funding from DBV but have not received any direct or indirect funds or salary support*

Learning Objectives

- Identify recent topics addressed by anaphylaxis practice parameters
- Leverage shared decision-making (SDM) to provide the right care, at the right time, every time
- Compare and contrast diagnostic criteria for anaphylaxis
- Discuss common causes and subsets of anaphylaxis
- Incorporate anaphylaxis management strategies into practice

Read more at https://www.allergyparameters.org/

Allergy Guidelines and Practice Parameters



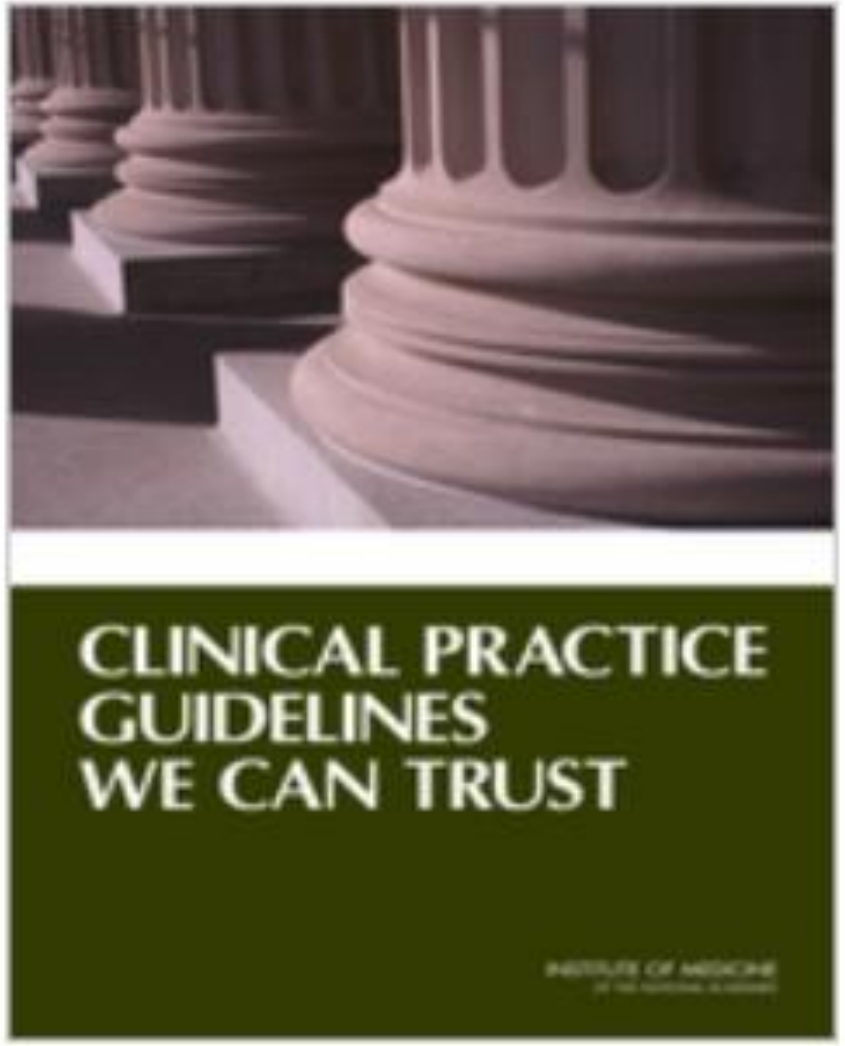
JOINT TASK FORCE ON PRACTICE PARAMETERS

JTF PP

www.allergyparameters.org

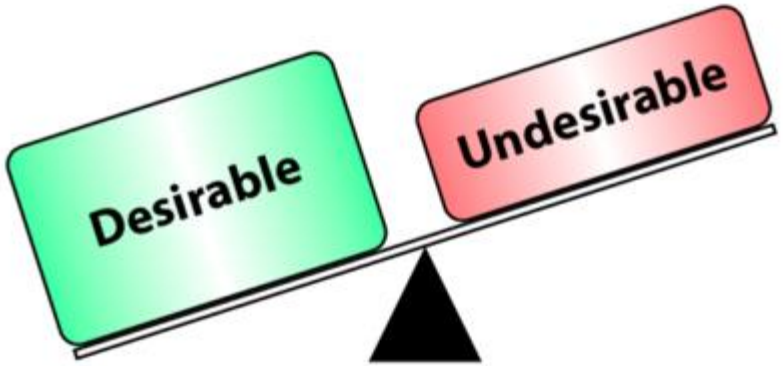
Guidelines and Best Evidence: Institute of Medicine Recommendations

- Clear description of evidence rating
- Transparency
- Up to date
- Balanced
- Contextual
- Unbiased
- Fair
- Actionable
- Cost-effective

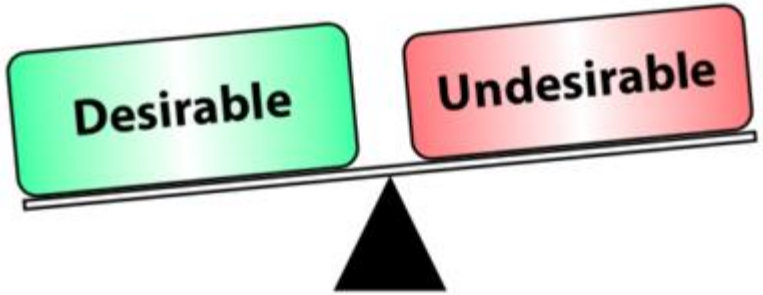


Institute of Medicine 2011

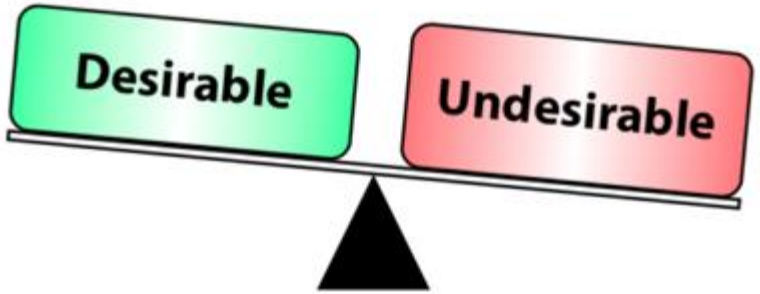
Strength (and directional) of Recommendation



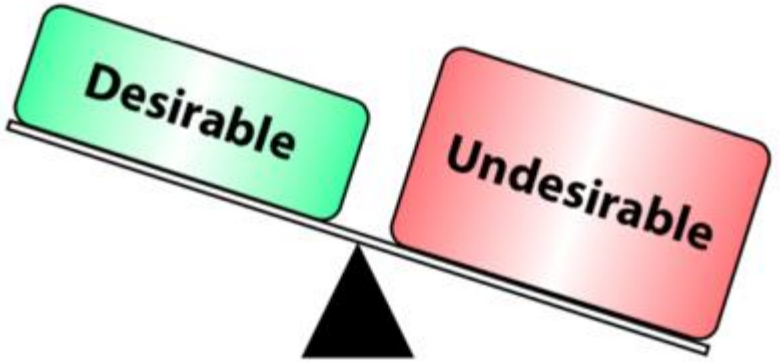
STRONG recommendation
IN FAVOR



CONDITIONAL recommendation
IN FAVOR



CONDITIONAL recommendation
AGAINST



STRONG recommendation
AGAINST

Shaker M et al. Making the Grade. Annals of Allergy, Asthma, Immunology. 2020

What Recommendations Imply

	Strong	Conditional (suggest)
For patients **For clinicians**	Most would adopt the recommendation, but a small proportion would not	While many (and possibly most) would want to follow the course of action, this is a navigational signal for shared decision making
For policy makers	Can be adopted as policy in most situations	Policy making will require substantial debate and may not be appropriate

Certainty of Evidence Adjustment

Certainty can be rated down for	Certainty can be rated up for
Risk of bias	Large magnitude of effect
Imprecision	
Inconsistency	Dose-response gradient
Indirectness	Residual confounding would increase magnitude of effect
Publication bias	

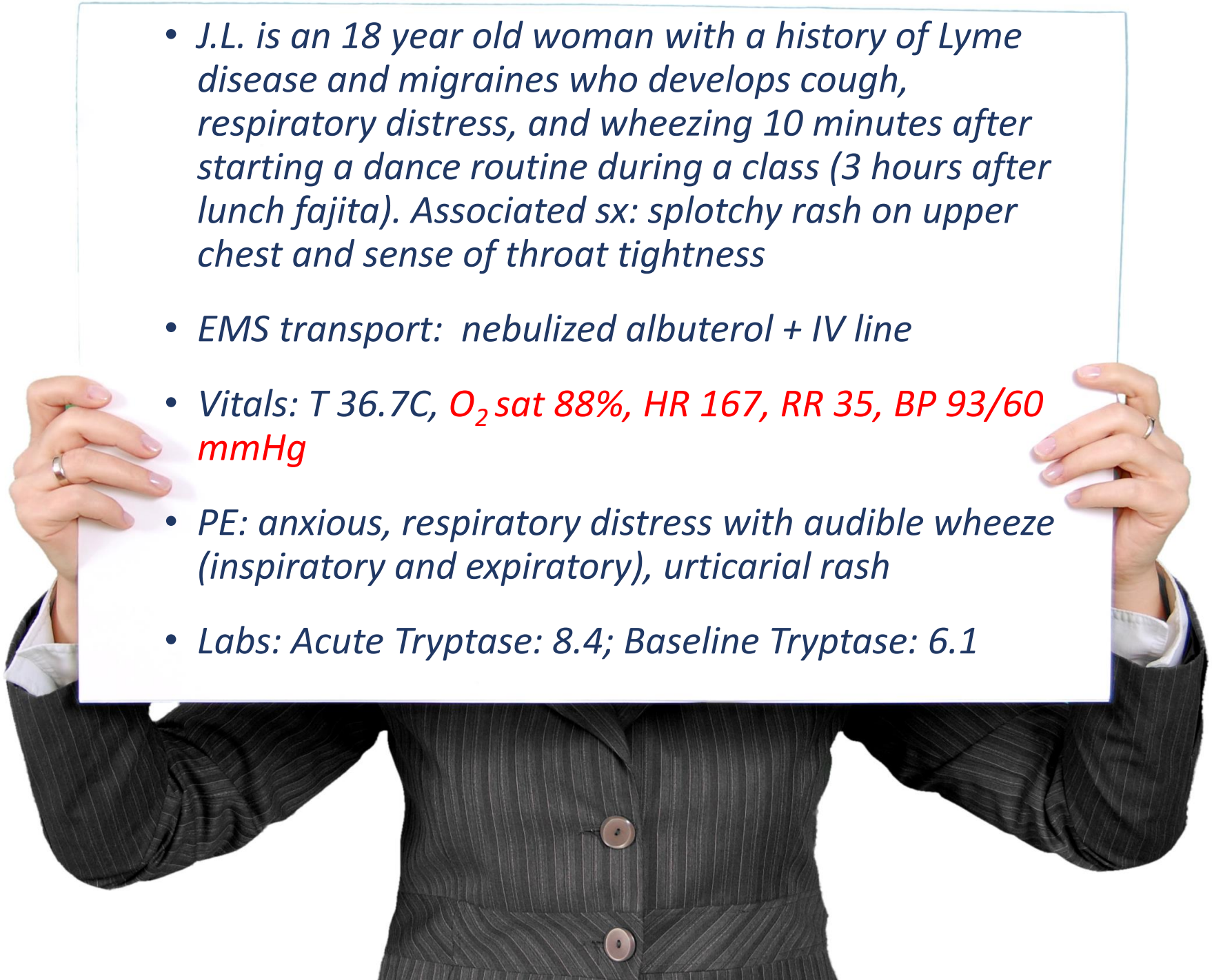
N.B. RCT's start as HIGH and observational studies start as LOW

Siemieniuk R, Guyatt G. What is GRADE? BMJ Best Practice 2019

Recommendations must also incorporate and consider

- Balance between benefits/harms
- Patient values/preferences
- Resource allocation and cost-effectiveness
- Equity

- Feasibility
- Acceptance
- Is the problem a priority?
- Policy Implications



Questions:

1. Is this anaphylaxis?
2. How severe?
3. Risk for biphasic?
4. How long to observe?
5. Switch her propranolol to another migraine therapy?
6. Significance of tick born disease and fajita?
7. Role of tryptase in diagnosis?

Anaphylaxis Practice Parameter Updates

Shaker MS, et al. Anaphylaxis – a 2020 practice parameter update, and GRADE analysis.
J Allergy Clin Immunol 2020;145:1082-1123.

Golden DBK et al. Anaphylaxis: A 2023 practice parameter update.
Ann Allergy Asthma Immunol (in press)

Read more at https://www.allergyparameters.org/

Practice parameter

Anaphylaxis—a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis

Baseline rate of biphasic reactions ~ 4-5%

Kraft et al. JACI IP 2020
Mills et al. JACI IP 2021

Objectives:

(1) To identify risk factors for biphasic anaphylaxis (to inform management, preparedness, and education), and

(2) To understand if giving patients glucocorticoids and/or antihistamines prevents anaphylaxis.

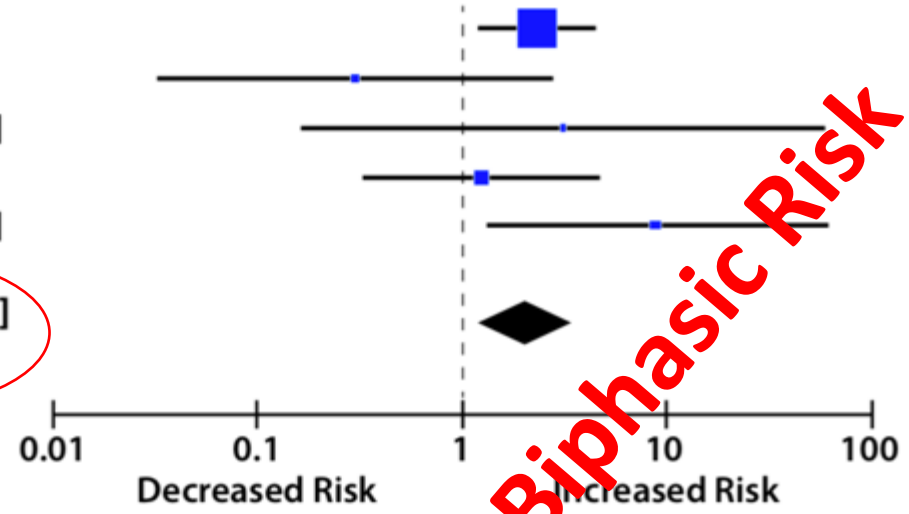
Shaker M, Wallace D, Golden DBK, et al. JACI 2020.
PMID 32001253

Severe anaphylaxis

A

Study or Subgroup	Biphasic Events	Biphasic Total	No Biphasic Events	No Biphasic Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Brown 2013	22	49	72	266	66.0%	2.34 [1.20, 4.54]
Confino-Cohen 2010	0	11	11	120	5.9%	0.31 [0.03, 2.82]
Lee 2000	6	6	90	99	3.4%	3.16 [0.17, 59.06]
Manuyakorn 2015	12	15	47	62	16.6%	1.26 [0.34, 4.73]
Vezir 2013	4	5	28	91	8.1%	8.96 [1.34, 59.87]
Total (95% CI)		**86**		**638**	**100%**	**2.11 [1.23, 3.61]**
Total Events	44		248			

Heterogeneity: $Chi^2 = 5.88$, $df = 4$ ($P = 0.21$); $I^2 = 32\%$
Test for overall effect $Z = 2.70$ ($P = 0.007$)

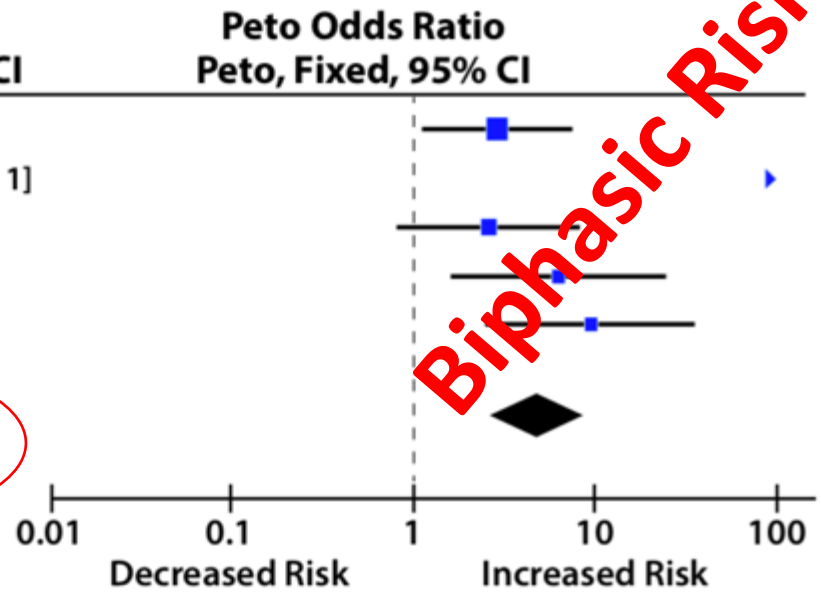


> 1 dose of epinephrine

B

Study or Subgroup	Biphasic Events	Biphasic Total	No Biphasic Events	No Biphasic Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Alqurashi 2015	10	71	27	413	37.2%	2.91 [1.13, 7.49]
Inoue 2013	2	2	1	59	0.8%	9.56E8 [1.49E6, 6.13E11]
Lee 2017	6	36	73	836	24.7%	2.62 [0.82, 8.36]
Mehr 2009	7	12	21	95	18.0%	6.41 [1.65, 24.96]
Scranton 2009	9	14	8	46	19.2%	9.69 [2.60, 36.14]
Total (95% CI)		**135**		**1449**	**100%**	**4.82 [2.70, 8.58]**
Total Events	34		130			

Heterogeneity: $Chi^2 = 36.98$, $df = 4$ ($P < 0.00001$); $I^2 = 89\%$
Test for overall effect $Z = 5.33$ ($P < 0.00001$)



Biphasic Anaphylaxis
Additional Outcomes with statistically significant effect size

Risk Factors	Odds Ratio (CI)	Evidence Certainty	Heterogeneity
Wide pulse pressures	2.11 (1.32, 3.37)	Very low	Low
Drug as trigger in pts <18 yrs.	2.35 (0.16, 4.65)	Very low	Moderate
Unknown trigger	1.63 (1.13, 2.33)	Very low	Moderate
Cutaneous symptoms	2.54 (1.25, 5.15)	Very low	Low

Shaker M, Wallace D, Golden D, et al. Anaphylaxis – A 2020 Practice Parameter Update, Systematic Review, and GRADE Analysis. JACI 2020

Additional Factors Analyzed Without Significant Associations

- Hx of allergy
- Hx of anaphylaxis
- Hx of asthma
- Insect trigger
- Itchy symptom
- Wheezing symptoms

- Hypotension
- Hypertension
- Food trigger
- GI symptoms
- Use of bronchodilator

Triage makes sense…

Dartmouth-Hitchcock
School of Medicine
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

ED observation of resolved anaphylaxis

- **Routine prolonged observation cost $68,411 – $230,202 per additional case of biphasic anaphylaxis observed (1 vs 6-24 hours)**

Shaker M, Wallace D, Golden D, et al. JAMA Network Open 2019; 2(10): e1913951

Practice parameter

Anaphylaxis—a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis

Objectives:

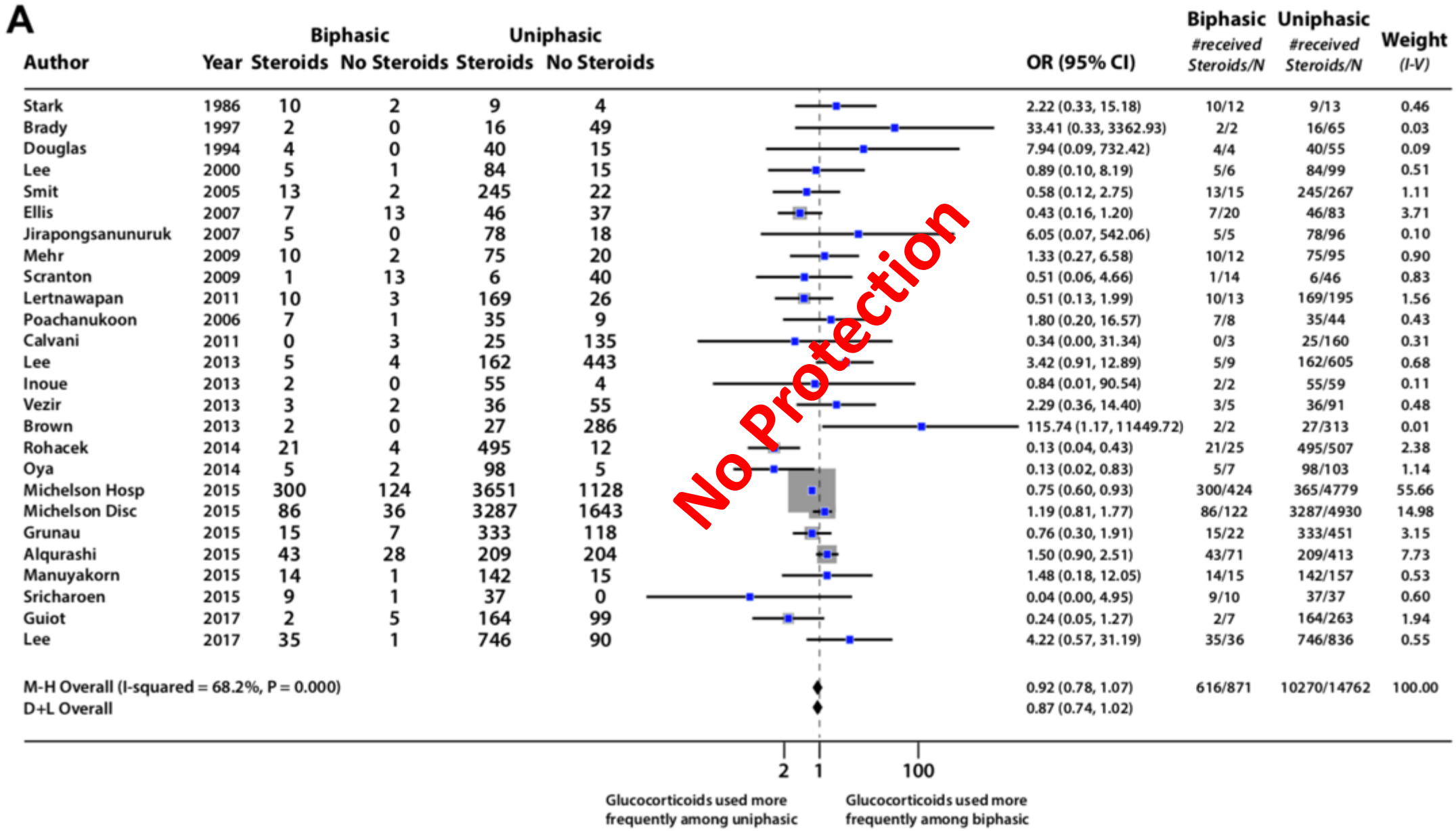
(1) To identify risk factors for biphasic anaphylaxis (to inform management, preparedness, and education), and

(2) To understand if giving patients glucocorticoids and/or antihistamines prevents anaphylaxis.

Shaker M, Wallace D, Golden DBK, et al. JACI 2020.
PMID 32001253

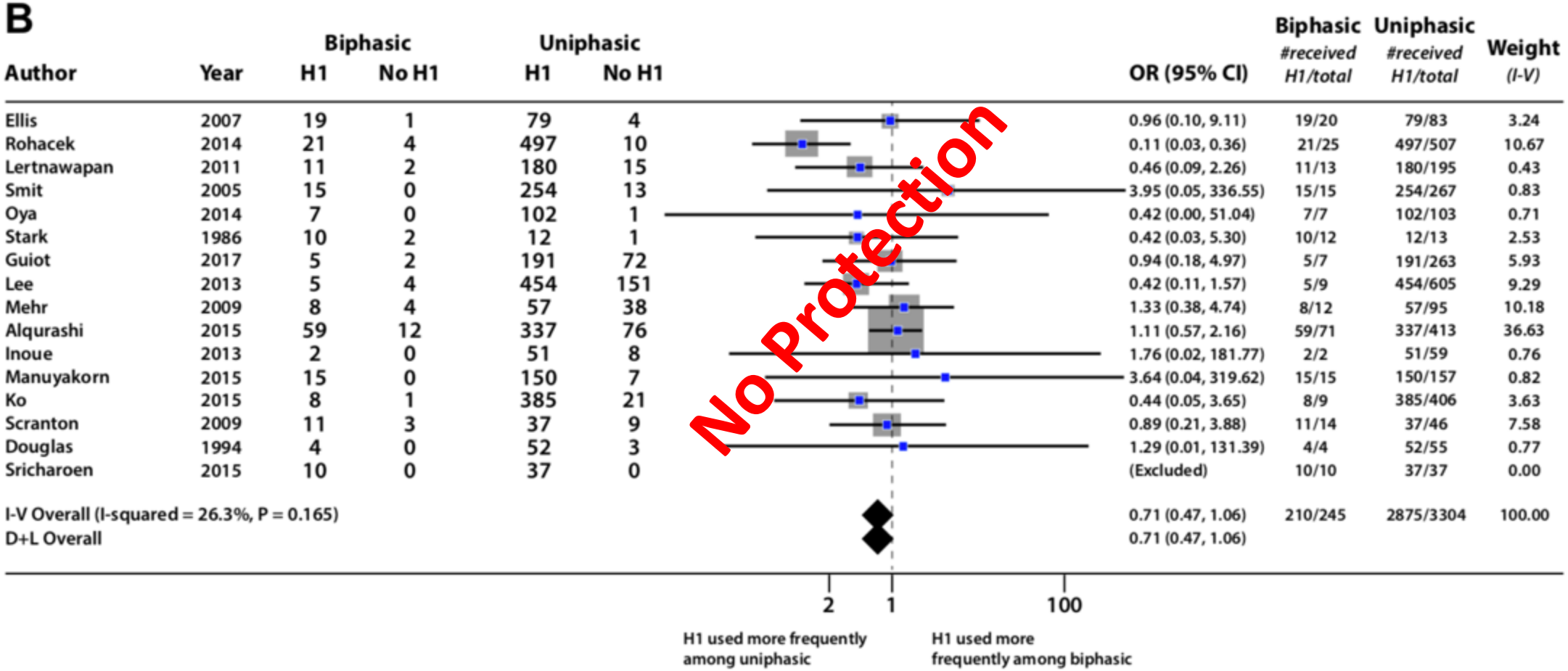
Glucocorticoids

A



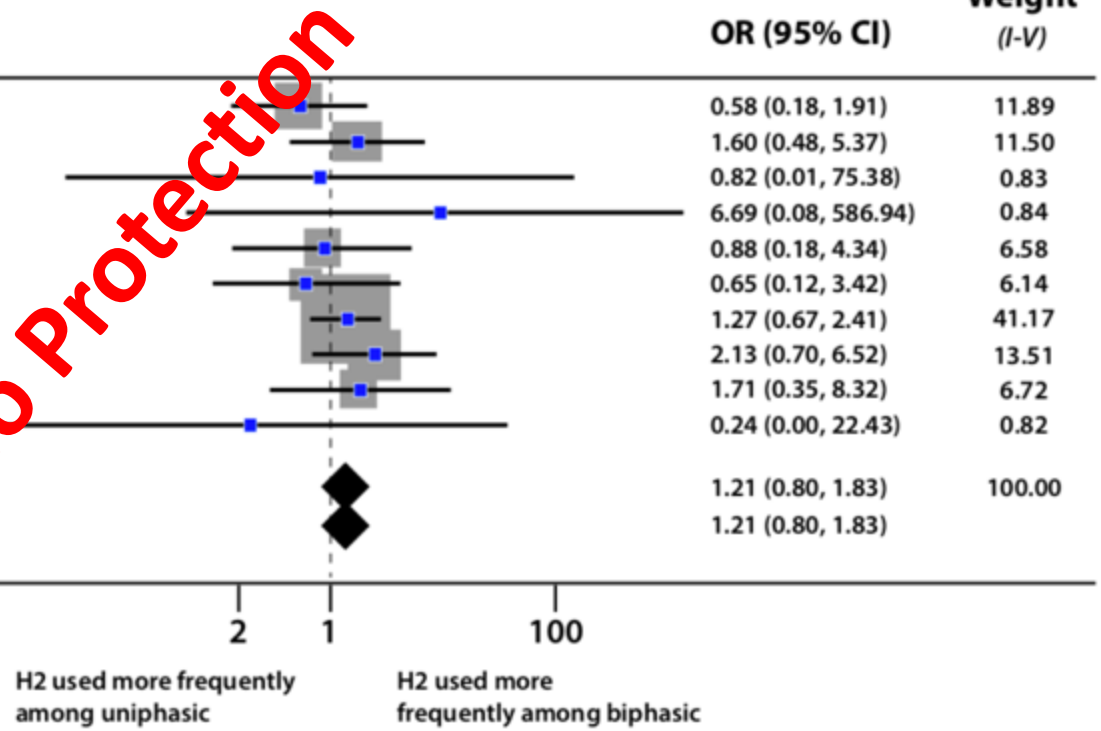
Anti H1 antihistamine

B



C Anti H2 antihistamine

Author	Year	Biphasic H2	Biphasic No H2	Uniphasic H2	Uniphasic No H2	OR (95% CI)	Weight (I-V)
Ellis	2007	4	16	25	58	0.58 (0.18, 1.91)	11.89
Lertnawapan	2011	9	4	114	81	1.60 (0.48, 5.37)	11.50
Smit	2015	0	15	4	263	0.82 (0.01, 75.38)	0.83
Oya	2014	7	0	87	16	6.69 (0.08, 586.94)	0.84
Stark	1996	7	5	8	5	0.88 (0.18, 4.34)	6.58
Guiot	2017	2	5	100	163	0.65 (0.12, 3.42)	6.14
Alqurashi	2015	14	57	67	346	1.27 (0.67, 2.41)	41.17
Manuyakorn	2015	10	5	76	81	2.13 (0.70, 6.52)	13.51
Ko	2015	7	2	273	133	1.71 (0.35, 8.32)	6.72
Douglas	1994	0	4	9	46	0.24 (0.00, 22.43)	0.82
I-V Overall (I-squared = 0.0%, P = 0.751)						1.21 (0.80, 1.83)	100.00
D+L Overall						1.21 (0.80, 1.83)	



Biphasic Anaphylaxis

Question 1	Recommendation 1: **The guideline suggests that a clinician incorporate severity of anaphylaxis presentation and/or the administration of more than one dose of epinephrine for the treatment of initial anaphylaxis as a guide to determining a patient's risk for developing biphasic anaphylaxis**
	Recommendation 2: **The guideline suggests in favor of extended clinical observation in a setting capable of managing anaphylaxis (to detect a biphasic reaction) for patients with resolved severe anaphylaxis and/or those who need more than one dose of epinephrine**
Question 2	Recommendation: **The guideline suggests against glucocorticoids or antihistamines as an intervention to prevent biphasic anaphylaxis**

Conditional Recommendations; Very Low Certainty Evidence

Shaker M, Wallace D, Golden D, et al. Anaphylaxis – A 2020 Practice Parameter Update, Systematic Review, and GRADE Analysis. JACI 2020

Additional Topics

- Should antihistamines and/or glucocorticoids be used to prevent index hypersensitivity/infusion reactions to chemotherapy?
  - Conditional recommendation in favor
- Should antihistamines and/or glucocorticoids be routinely used to prevent recurrent hypersensitivity reactions to radiocontrast media?
  - Conditional recommendation against
- Should antihistamines and/or glucocorticoids be used to prevent hypersensitivity reactions to rush allergen immunotherapy or other agents?
  - Conditional recommendation in favor

Read more at https://www.allergyparameters.org/

JTFPP 2020 Anaphylaxis Guideline Good Practice Statements

1. Administer epinephrine as the only first line pharmacotherapy for uniphasic and/or biphasic anaphylaxis.
2. Do not delay the administration of epinephrine for anaphylaxis, as doing so may be associated with higher morbidity and mortality.
3. After diagnosis and treatment of anaphylaxis, all patients should be kept under observation until symptoms have fully resolved.
4. All patients with anaphylaxis should receive education on anaphylaxis, including avoidance of identified triggers, presenting signs and symptoms, biphasic anaphylaxis, treatment with epinephrine, the use of epinephrine auto-injectors, and referral to an allergist.

Read more at https://www.allergyparameters.org/

What about many other areas of anaphylaxis that have advanced?

- Diagnostic evaluation
- Anaphylaxis in infants and toddlers
- Anaphylaxis in community settings
- Epinephrine autoinjectors
- Beta-blockers and ACE inhibitors
- Mast cell disorders
- Peri-operative anaphylaxis

Read more at https://www.allergyparameters.org/

Anaphylaxis: A 2023 Practice Parameter Update

Golden DBK, Wang J, Waserman S, Akin C, Campbell RL, Ellis AK, Greenhawt M, Lang DM, Ledford DK, Lieberman J, Oppenheimer J, Shaker MS, Wallace DV, Abrams EM, Bernstein JA, Chu DK, Horner CC, Rank MA, Stukus DR, Burrows AG, Cruickshank H.

Annals of Allergy Asthma and Immunology 2023; (in press)

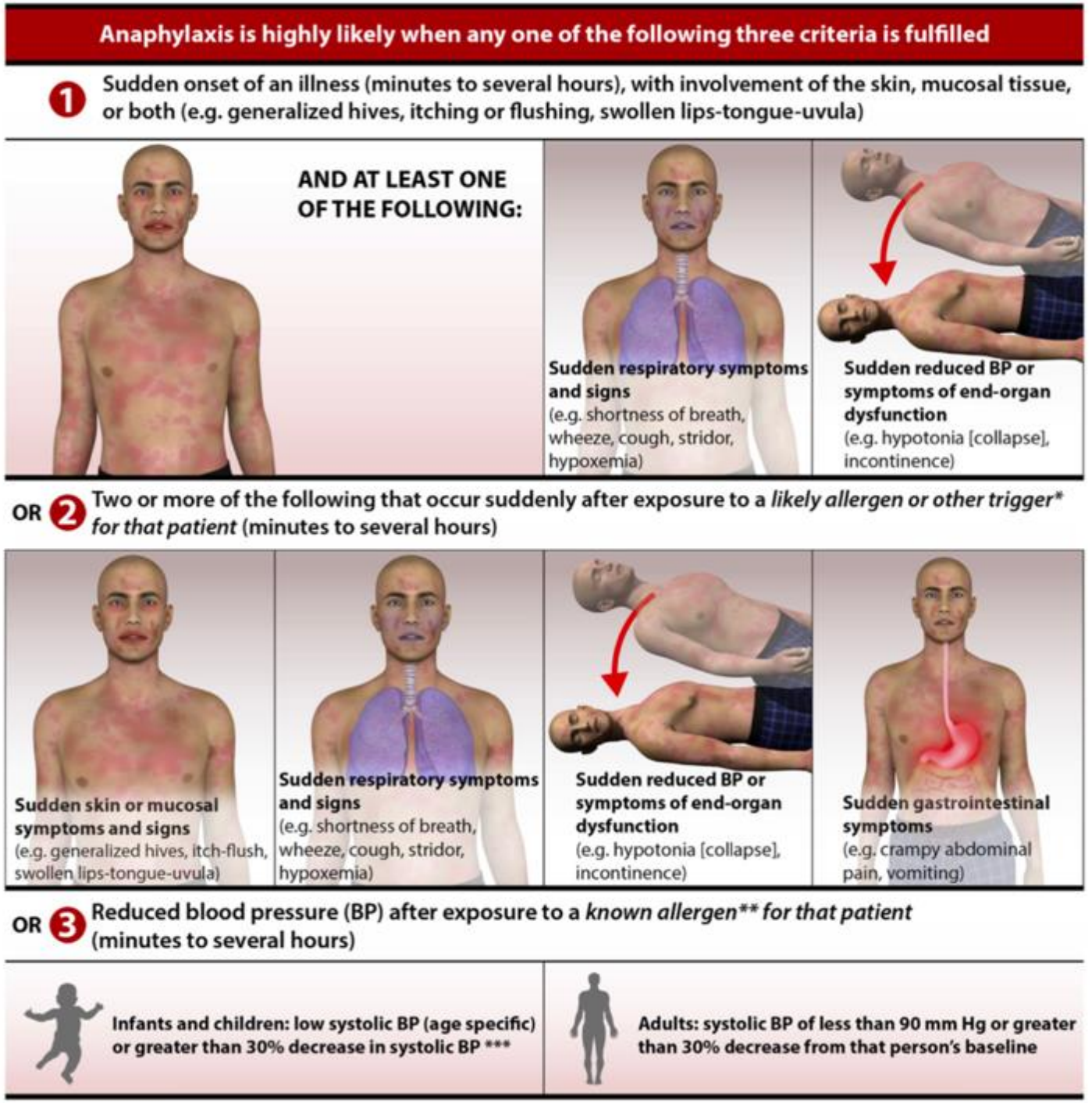
48 recommendations

9 strong (s)

39 conditional (c)

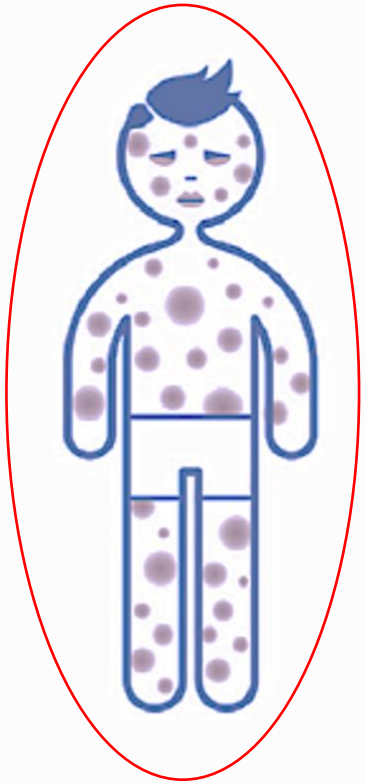
Anaphylaxis

- An acute, potentially life-threatening systemic allergic reaction
- Diagnostic criteria are not perfect and fulfilling diagnostic criteria are not required for epinephrine use to treat an allergic reaction.
- Lifetime prevalence: 1.6% - 5.1%



Shaker M, Wallace D, Golden DBK, et al. JACI 2020. PMID 32001253

1 Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, pruritus or flushing, swollen lips-tongue-uvula)



and at least one of the following

A. Airway/Breathing: Respiratory compromise.

(e.g. dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

B. Circulation: Reduced BP or associated symptoms of end-organ dysfunction.

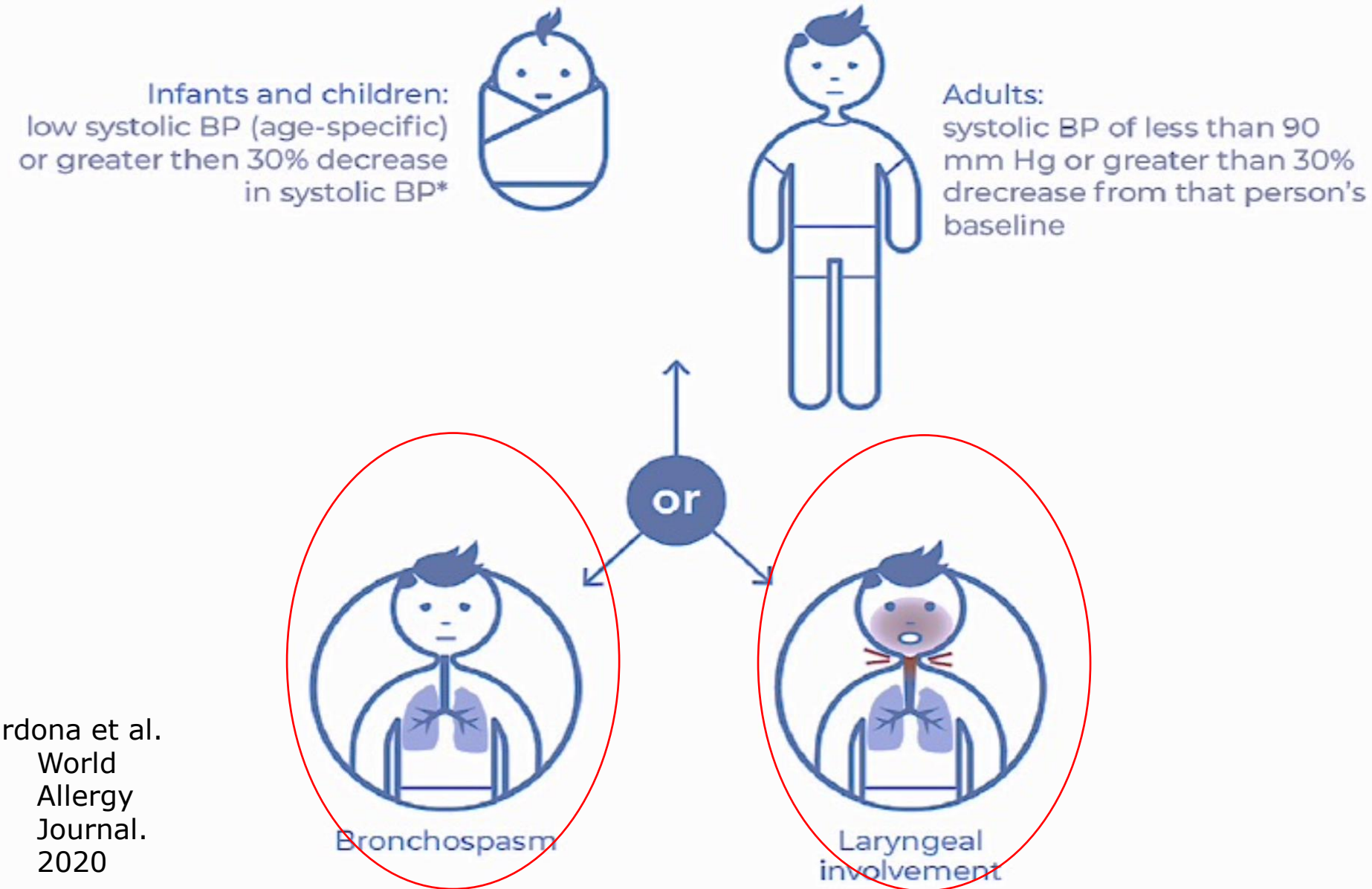
(e.g. hypotonia [collapse], syncope, incontinence)

C. Other: Severe gastrointestinal symptoms.

(e.g. severe crampy abdominal pain, repetitive vomiting), especially after exposure to non-food allergens)

Cardona et al. World Allergy Journal. 2020

2 Acute onset of **hypotension*** or **bronchospasm** or **laryngeal involvement#** after exposure to a known or highly probable allergen for that patient (minutes to several hours), **even in the absence of typical skin involvement.**



Cardona et al. World Allergy Journal. 2020

Anaphylaxis Triggers and Risks

Leading anaphylaxis triggers

- Adults: Medications
  - Antibiotics, NSAIDS, Immunomodulators, Biologics, Anesthetics
- Children/Adolescents: Foods
- All ages: Stinging Insects
- Idiopathic

Risk factors for severe anaphylaxis include

- Cardiovascular disease
- Asthma
- Older age
- Co-morbid conditions
  - Mast cell disorder, beta-blocker use, ACEi use

Shaker M, Wallace D, Golden DBK, et al. JACI 2020. PMID 32001253

How Often Does Seve
The Cross-Car

- The 2019 Cross-Canada Anaphy
  anaphylaxis cases presenting to
  a 6-year period, enrolling 3,498

Anaphylaxis Severity
Mild
Moderate
Severe

Note

The literature estimates are severity are variable, for example

- **Using, "severe enough to be hospitalized" Clark et al estimated a 22% rate of those with anaphylaxis of patients seen in the ED or hospital**
- **Francuzik estimated a 42% rate of severe anaphylaxis from the European Anaphylaxis Registry in children and adolescents**
- **Worm et al estimated a 40-70% rate of severe anaphylaxis from the European Anaphylaxis Registry with higher rates in older adults**

Clark et al JACI 2014
Francuzik et al Frontiers 2019
Grabenenrich et al JACI 2016
Worm et al Allergy 2018

Gabrielli et

e. 2019

Potential risk factors and co-factors for severe or fatal anaphylaxis

Drug-Induced	Food-Induced	Venom-Induced	Non-Trigger-Related
• Age > 60 years • Cardiovascular diseases • Respiratory diseases • Antihypertensive drugs	• Adolescence • Uncontrolled asthma • Alcohol consumption • Peanut or tree-nut induced reaction • Exercise	• Older age • Male sex • Hereditary alpha tryptasemia • Mast cell disorders • Cardiovascular diseases • NSAIDs • Antihypertensive drugs	• Mast cell disorders • Infections • Perimenstrual period • NSAIDs • Alcohol • Psychological burden • Exercise • Unknown cause

Read more at https://www.allergyparameters.org/

Severity of Anaphylaxis –

PMID: 33476673

Severity grading system for acute allergic reactions: A multidisciplinary Delphi study

Timothy E. Dribin, MD,[a,b] David Schnadower, MD, MPH,[a,b] Jonathan M. Spergel, MD, PhD,[c] Ronna L. Campbell, MD, PhD,[d] Marcus Shaker, MD, MSc,[e,f] Mark I. Neuman, MD, MPH,[g,h] Kenneth A. Michelson, MD, MPH,[g,h] Peter S. Capucilli, MD,[i] Carlos A. Camargo, Jr, MD, DrPH,[j] David C. Brousseau, MD, MS,[k] Susan A. Rudders, MD, MS,[h,l] Amal H. Assa'ad, MD,[b,m] Kimberly A. Risma, MD, PhD,[b,m] Mariana Castells, MD, PhD,[n] Lynda C. Schneider, MD,[h,l] Julie Wang, MD,[o] Juhee Lee, MD,[c] Rakesh D. Mistry, MD, MS,[p] David Vyles, DO, MS,[k] Michael Pistiner, MD, MMSc,[q] John K. Witry, MS,[a] Yin Zhang, MS,[r] and Hugh A. Sampson, MD[o]

Cincinnati, Ohio; Philadelphia, Pa; Rochester, Minn; Hanover, NH; Boston, Mass; and Rochester and New York, NY

Dribin T, Schnadower D, Spergel J, et al. Journal of Allergy Clin Immun 2020

Severity grading system for acute allergic reactions

**Grading system application is INDEPENDENT of whether reactions fulfill NIAID/FAAN anaphylaxis diagnostic criteria*
(e.g. a reaction can be either Grade 5 anaphylaxis or a Grade 5 non-anaphylactic reaction)**

Severity grades**

Life threatening allergic reactions

5 ANY Severe:
Cardiovascular, Neurologic, Respiratory

4 ANY Moderate:
Cardiovascular, Neurologic, Respiratory
OR
Severe: *Mucosal/angioedema*

3 ANY Mild:
Cardiovascular, Neurologic, Respiratory

2 2 or more Mild, ANY Moderate:
Skin, Gastrointestinal, Mucosal/angioedema

1 ANY Mild:
Skin, Gastrointestinal, Mucosal/angioedema

Mild allergic reactions

Terms: ***Symptoms***: patient and/or family reported symptoms, not observed by clinicians; ***Signs:*** clinical and/or examination findings; ***Infants***: signs and symptoms of allergic reactions in infants and young children may overlap with normal behavior. Mild/moderate respiratory, neurologic or CV symptoms may represent increased reaction severity in infants and young children.

Definitions

Hypotension:
Pediatric: systolic BP < 5th percentile for age or < 2 standard deviations below normal for age **or** systolic BP < 70 mm Hg from 1 month to 1 year, < (70 mm Hg + [2 X age]) from 1 to 10 years, and < 90 mm Hg from 11 to 17 years. Hypotension is a late phase sign in young children; consider use of HR and other CV symptoms in infants. Do not delay management of anaphylaxis for acquisition of BP.
Adult: estimated or calculated mean arterial pressure (MAP=1/3[systolic BP]+2/3[diastolic BP]) < 65; **or** systolic BP < 90 mm Hg or > 30% decrease from baseline

Anaphylactic shock: anaphylaxis with an IV vasopressor infusion requirement to maintain a MAP ≥ 65 mmHg or systolic BP ≥ 90 mm Hg among adults, and age appropriate BPs among children (see pediatric definitions of hypotension above)

Increased work of breathing (WOB): retractions, use of accessory muscles, nasal flaring or grunting (infants), age defined tachypnea that is not brief or self-resolved

Hypoxemia: SpO2 ≤ 92% on room air

Respiratory failure: impaired oxygenation or ventilation requiring use of non-invasive and/or invasive ventilatory support (bag mask ventilation, high flow nasal cannula, continuous positive airway pressure, bi-level positive airway pressure, mechanical ventilation, extracorporeal membrane oxygenation)

Clinical criteria (sub-grading system)

Cardiovascular†
MILD: *Symptoms* - weak, dizzy, pre-syncope, palpitations, blurred vision; *Infants* - tachycardia not related to other causes such as crying, discomfort, or medications
MODERATE: hypotension, syncope (collapse); *Infants* - mottling, cyanosis
SEVERE: anaphylactic shock, cardiac arrest; *Infants* - hypotension

Neurologic†
MILD: *Symptoms* - confusion, drowsy, sense of impending doom; *Infants* - persistent and unexplained irritability, inconsolability, crying, or decreased activity
MODERATE: GCS (Glasgow Comma Scale; https://www.mdcalc.com/glasgow-coma-scale-score-gcs) 13-14; *Infants* - lethargic
SEVERE: GCS <13, seizure; *Infants* - new onset hypotonia

Respiratory
General
MILD: *Symptoms* - chest tightness, dyspnea; *Signs* - new onset cough
MODERATE: new onset persistent cough, increased WOB, hypoxemia
SEVERE: respiratory failure
Laryngeal
MILD: *Symptoms* - throat tightness or discomfort; *Signs* - voice change; *Infants* - barky or croup like cough, hoarse cry
MODERATE: stridor w/o increased WOB
SEVERE: stridor with increased WOB (partial or complete upper airway obstruction)
Lower airway
MILD: wheezing w/o increased WOB
MODERATE: wheezing with increased WOB
SEVERE: bronchospasm with minimal or no air movement on auscultation AND increased WOB

Mucosal/angioedema (see Figure E1 in the online repository for example images of mucosal/angioedema severity)
MILD: *Symptoms* - mouth tingling, itchy mouth or throat, metallic taste; *Signs* - facial swelling, conjunctival injection, chemosis, nasal congestion, rhinorrhea, throat clearing, lip swelling, mild tongue, soft palate, and/or uvula swelling (anatomical landmarks preserved); *Infants* - tongue thrusting or pulling, repetitive lip, ear or eye rubbing
MODERATE: drooling, moderate tongue, soft palate, and/or uvula swelling (anatomical landmarks obscured); *Infants* - marked increase in drooling
SEVERE: severe tongue, soft palate, and/or uvula swelling (complete loss of anatomical landmarks)

Skin
Pruritus
MILD: *Symptoms* - pruritus, skin discomfort; *Signs* - occasional scratching, localized scratching or excoriations (< 50% body surface area [BSA])
MODERATE: continuous scratching, generalized scratching or excoriations (≥ 50% BSA)
Urticaria, rash
MILD: localized urticaria (< 50% BSA), localized erythema (< 50% BSA)
MODERATE: generalized urticaria (≥ 50% BSA), flushing, generalized erythema (≥ 50% BSA)

Gastrointestinal
MILD: *Symptoms* - nausea, abdominal pain††; *Signs* - 1-2 episodes of emesis or diarrhea; *Infants* - new onset spitting up, hiccups, or back arching
MODERATE: *Symptoms* - frequent or continuous nausea or abdominal pain, distressed due to GI symptoms; *Signs* - ≥3 episodes of emesis or diarrhea or 2 of each

Anaphylaxis Subsets

TABLE II. Clinical criteria for diagnosing persistent, refractory, and biphasic anaphylaxis

Persistent anaphylaxis is highly likely when the following criterion is fulfilled*:

Presence of symptoms and/or examination findings that fulfill the 2006 NIAID/FAAN anaphylaxis criteria that persist for at least 4 hours.[1]

Refractory anaphylaxis is highly likely when *both* of the following 2 criteria are fulfilled†:

1. Presence of anaphylaxis following appropriate epinephrine dosing *and* symptom-directed medical management (eg, intravenous fluid bolus for hypotension).
2. The initial reaction must be treated with 3 or more appropriate doses of epinephrine (or initiation of an intravenous epinephrine infusion).‡

Biphasic anaphylaxis is highly likely when *all* of the following 4 criteria are fulfilled§:

1. New /or recurrent symptoms and/or examination findings must fulfill the 2006 NIAID/FAAN anaphylaxis criteria.[1]
2. Initial symptoms and/or examination findings must completely resolve before the onset of new or recurrent symptoms and/or examination findings.
3. There cannot be allergen reexposure before the onset of new or recurrent symptoms and/or examination findings.
4. New or recurrent symptoms and/or examination findings must occur within 1 to 48 hours from complete resolution of initial symptoms and/or examination findings.

- **<u>Knowledge Gap:</u> After 3 doses of epinephrine and appropriate symptom directed therapy, o**ptimal management for refractory anaphylaxis is not well studied

Dribin T, Sampson H, Camargo C, et al. Journal of Allergy Clin Immun 2020

Refractory anaphylaxis

Establish dedicated peripheral IV or IO access

Seek expert[1] help early
Critical care support is essential

Give rapid IV fluid bolus
e.g. 0.9% sodium chloride

&

Start adrenaline infusion
Adrenaline is essential for treating all aspects of anaphylaxis

Give IM* adrenaline every 5 minutes until adrenaline infusion has been started
*IV boluses of adrenaline are not recommended, but may be appropriate in some specialist settings (e.g. peri-operative) while an infusion is set up

Give high flow oxygen
Titrate to SpO_2 94–98%

Monitor HR, BP, pulse oximetry and ECG for cardiac arrhythmia
Take blood sample for mast cell tryptase

Follow local protocol
OR
Peripheral low-dose IV adrenaline infusion:
- 1 mg (1 mL of 1 mg/mL [1:1000]) adrenaline in 100 mL of 0.9% sodium chloride
- Prime and connect with an infusion pump via a dedicated line

DO NOT 'piggy back' on to another infusion line
DO NOT infuse on the same side as a BP cuff as this will interfere with the infusion and risk extravasation

- In both adults and children, start at 0.5–1.0 mL/kg/hour, and **titrate according to clinical response**
- Continuous monitoring and observation is mandatory
- ↑↑ BP is likely to indicate adrenaline overdose

Continue adrenaline infusion and treat ABC symptoms
Titrate according to clinical response

[1]Intravenous adrenaline for anaphylaxis to be given only by experienced specialists in an appropriate setting.

A = Airway

Partial upper airway obstruction/stridor:
Nebulised adrenaline (5mL of 1mg/mL)

Total upper airway obstruction:
Expert help needed, follow difficult airway algorithm

B = Breathing

Oxygenation is more important than intubation

If apnoeic:
- Bag mask ventilation
- Consider tracheal intubation

Severe/persistent bronchospasm:
- Nebulised salbutamol and ipratropium with oxygen
- Consider IV bolus and/or infusion of salbutamol or aminophylline
- Inhalational anaesthesia

C = Circulation

Give further fluid boluses and titrate to response:
Child 10 mL/kg per bolus
Adult 500–1000 mL per bolus
- Use glucose-free crystalloid (e.g. Hartmann's Solution, Plasma-Lyte®)

Large volumes may be required (e.g. 3–5 L in adults)

Place arterial cannula for continuous BP monitoring

Establish central venous access

IF REFRACTORY TO ADRENALINE INFUSION
Consider adding a second vasopressor **in addition** to adrenaline infusion:
- Noradrenaline, vasopressin or metaraminol
- In patients on beta-blockers, consider glucagon

Consider extracorporeal life support

Cardiac arrest – follow ALS ALGORITHM
- Start chest compressions early
- Use IV or IO adrenaline bolus (cardiac arrest protocol)
- Aggressive fluid resuscitation
- Consider prolonged resuscitation/extracorporeal CPR

Poussel, Deschildre, Dribin, et al. Refractory Anaphylaxis. JACI IP 2023
PMID: 37172716

Anaphylaxis Diagnosis: Additional Pearls

- Anaphylaxis may be persistent, refractory, and biphasic
- Severity is a continuum
- Consider obtaining a tryptase (bST) for severe or recurrent presentations (s)
- Consider evaluation of HαT in patients with an elevated bST (8ng/ml or greater) and consider alpha-gal based on exposure history (c)
- Meeting diagnostic criteria is not required before use of epinephrine for a severe allergic reaction (c)

(s) Strong recommendation; (c) conditional recommendation

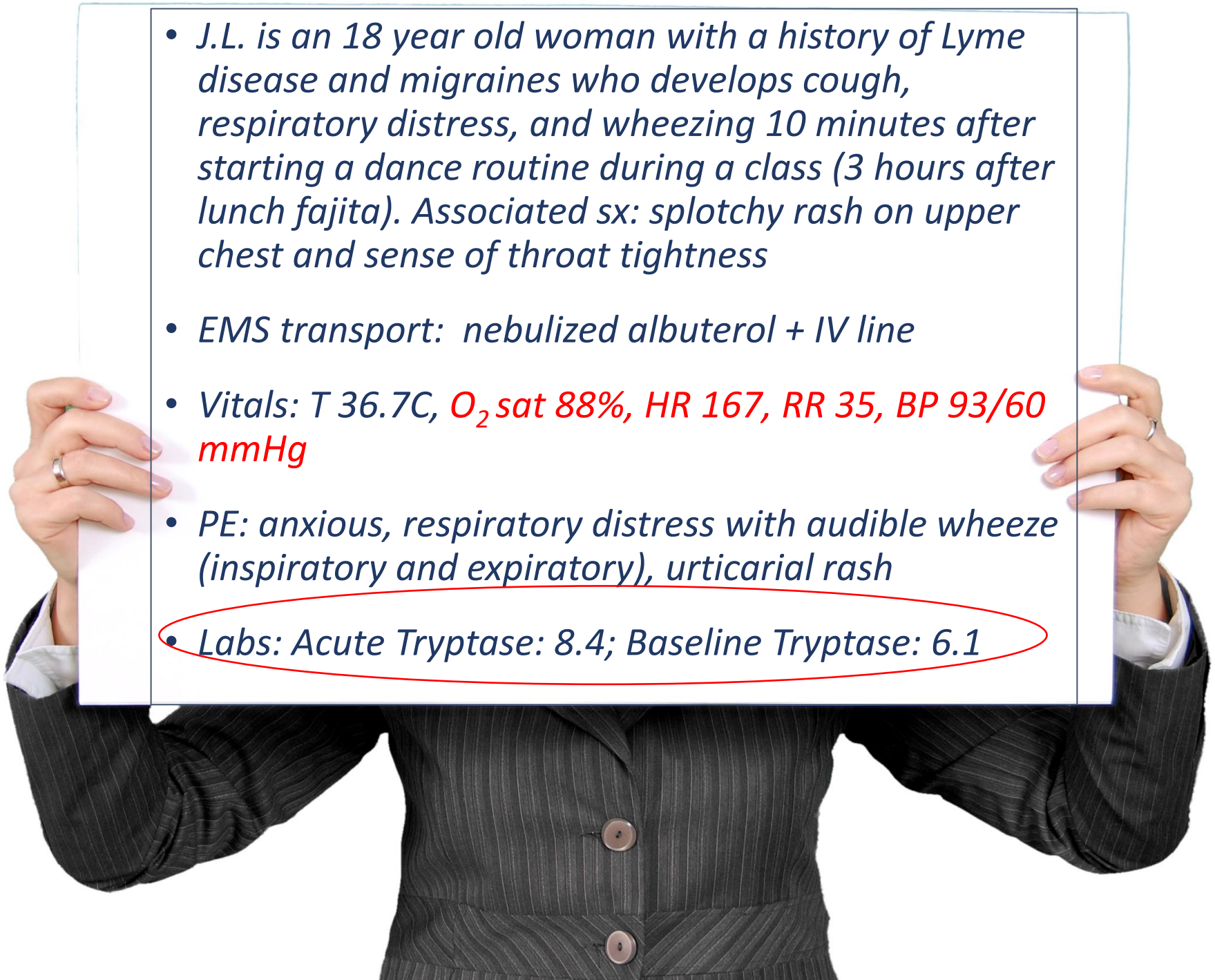
Read more at https://www.allergyparameters.org/

When is Tryptase Elevated? The Evolving Tryptase Rule

- Classic evidence of mast cell activation:
  - Acute tryptase 20% plus 2ng/ml over baseline
- Validated in perioperative anaphylaxis
  - **Sn 98%, Sp 44%**
  - PPV 98%, NPV 44%
- Variability limits rule
  - ¼ of individuals may exceed this variability on serial measures

- Alternative thresholds with the ratio of acute to baseline levels
- Ratio 1.685
  - Modeled **Sn 94.4%, Sp 94.4%**
- High vs. Low Clinical Suspicion
  - High: 1.374
    - Modeled **Sn 97.5%,** Sp 76.5%
  - Low: 1.868
    - Modeled Sn 92.4%, **Sp 97.5%**

Read more at https://www.allergyparameters.org/


• J.L. is an 18 year old woman with a history of Lyme disease and migraines who develops cough, respiratory distress, and wheezing 10 minutes after starting a dance routine during a class (3 hours after lunch fajita). Associated sx: splotchy rash on upper chest and sense of throat tightness
• EMS transport: nebulized albuterol + IV line
• Vitals: T 36.7C, O_2 sat 88%, HR 167, RR 35, BP 93/60 mmHg
• PE: anxious, respiratory distress with audible wheeze (inspiratory and expiratory), urticarial rash
• Labs: Acute Tryptase: 8.4; Baseline Tryptase: 6.1

National Institute of Allergy and Infectious Diseases
Leading research to understand, treat, and prevent infectious, immunologic, and allergic diseases

Total Rise In Peripheral Tryptase After Systemic Event (TRIPTASE) Calculator

Baseline Tryptase (ng/mL):
6.1

Acute tryptase measurement* (ng/mL):
8.4

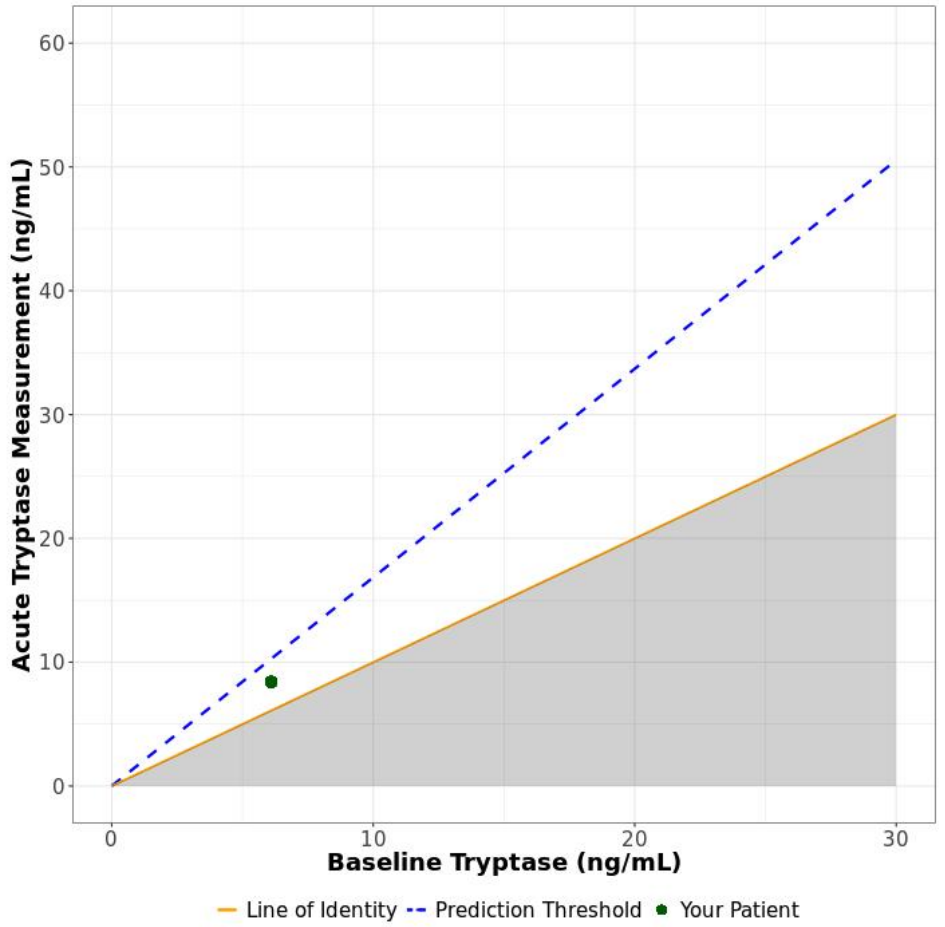
Clinical Suspicion
Possible

*Total serum tryptase measured within 4 hours of symptom onset during an episode suggestive of a systemic immediate hypersensitivity reaction.

Disclaimer: A failure to detect a significant increase in serum tryptase during an acute event does not rule out the diagnosis of anaphylaxis.

Analyze my data | Reset

The change in total serum tryptase is NOT consistent with the clinical diagnosis of anaphylaxis.



Classic rule (Sn 98%; Sp 44%):
(6.1 ng/mL * 1.2) + 2 = 9.32 ng/mL = NO

Ratio threshold of 1.685 (Sn 97.5%; Sp 97.5%):
8.4/6.1 = 1.377 = NO

https://triptase-calculator.niaid.nih.gov.

This tool was developed by Translational Allergic Immunopathology Unit in collaboration with Bioinformatics and Computational Biosciences Branch (BCBB). For any questions regarding this tool, please contact Dr. Jonathan Lyons or Qinlu Wang.

Our manuscript describing the design and development of this tool can be found here.

National Institute of Allergy and Infectious Diseases
Leading research to understand, treat, and prevent infectious, immunologic, and allergic diseases

Total Rise In Peripheral Tryptase After Systemic Event (TRIPTASE) Calculator

Baseline Tryptase (ng/mL):
6.1

Acute tryptase measurement* (ng/mL):
8.4

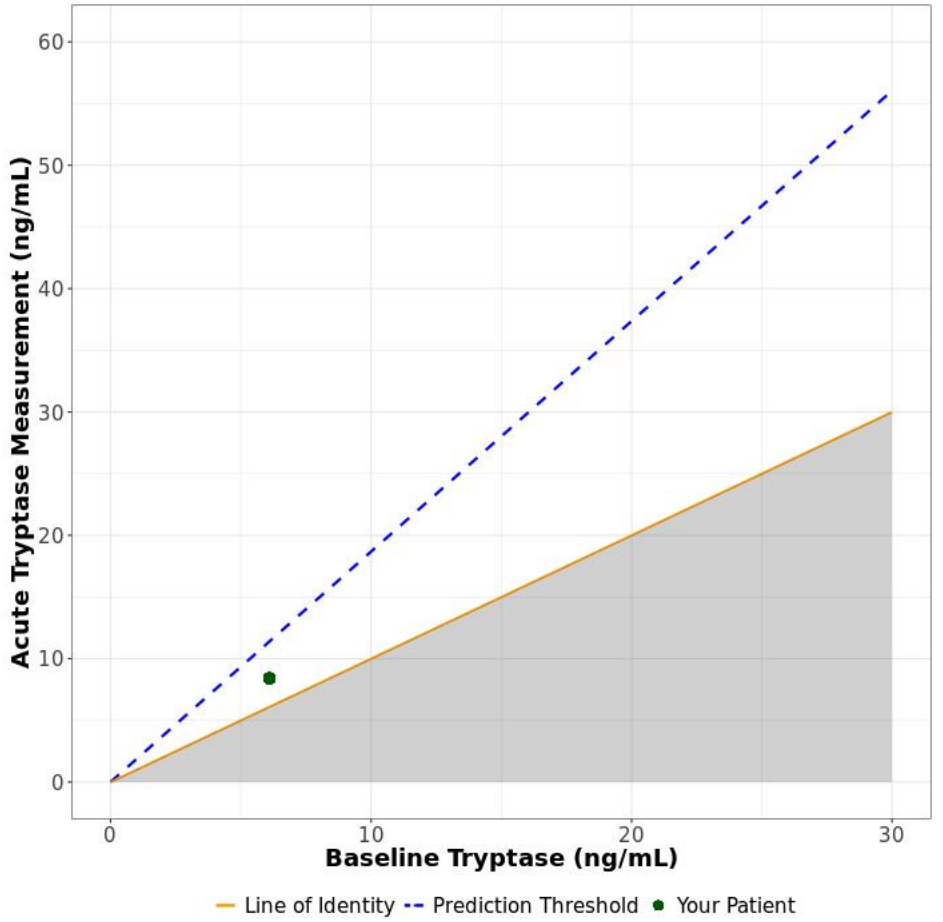
Clinical Suspicion
Less Likely

*Total serum tryptase measured within 4 hours of symptom onset during an episode suggestive of a systemic immediate hypersensitivity reaction.

Disclaimer: A failure to detect a significant increase in serum tryptase during an acute event does not rule out the diagnosis of anaphylaxis.

Analyze my data | Reset

The change in total serum tryptase is NOT consistent with the clinical diagnosis of anaphylaxis.



Classic rule (Sn 98%; Sp 44%):
(6.1 ng/mL * 1.2) + 2 = 9.32 ng/mL = NO

High ratio threshold of 1.868
8.4/6.1 = 1.37 = NO

https://triptase-calculator.niaid.nih.gov.

This tool was developed by Translational Allergic Immunopathology Unit in collaboration with Bioinformatics and Computational Biosciences Branch (BCBB). For any questions regarding this tool, please contact Dr. Jonathan Lyons or Qinlu Wang.

Our manuscript describing the design and development of this tool can be found here.

National Institute of Allergy and Infectious Diseases
Leading research to understand, treat, and prevent infectious, immunologic, and allergic diseases

Total Rise In Peripheral Tryptase After Systemic Event (TRIPTASE) Calculator

Baseline Tryptase (ng/mL):

6.1

Acute tryptase measurement* (ng/mL):

8.4

Clinical Suspicion

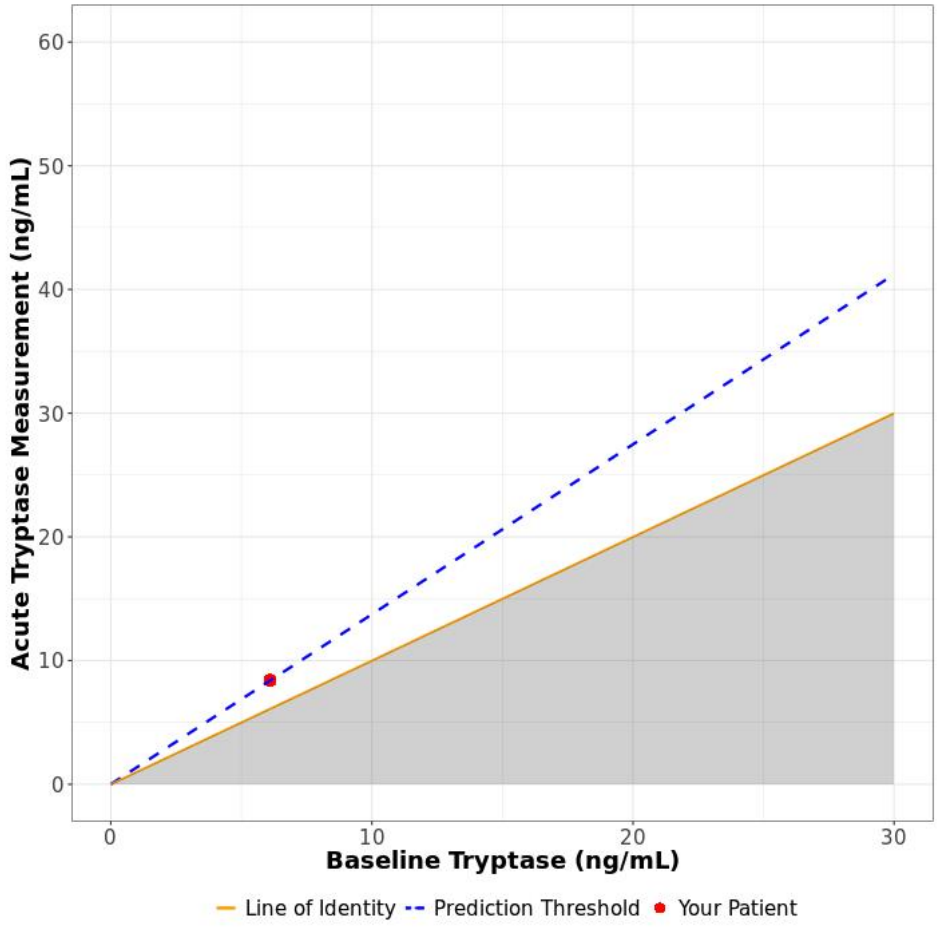
Likely

*Total serum tryptase measured within 4 hours of symptom onset during an episode suggestive of a systemic immediate hypersensitivity reaction.

Disclaimer: A failure to detect a significant increase in serum tryptase during an acute event does not rule out the diagnosis of anaphylaxis.

Analyze my data | Reset

The change in total serum tryptase is consistent with the clinical diagnosis of ANAPHYLAXIS.



Classic rule (Sn 98%; Sp 44%):
(6.1 ng/mL * 1.2) + 2 = 9.32 ng/mL = NO

Low ratio threshold of 1.374 (Sn 97.5%; Sp 97.5%):
8.4/6.1 = 1.377 = YES

https://triptase-calculator.niaid.nih.gov.

This tool was developed by Translational Allergic Immunopathology Unit in collaboration with Bioinformatics and Computational Biosciences Branch (BCBB). For any questions regarding this tool, please contact Dr. Jonathan Lyons or Qinlu Wang.

Our manuscript describing the design and development of this tool can be found here.

Infant/Toddler Anaphylaxis

- Anaphylaxis is unlikely to be the first reaction of a food or medication on initial exposure in infants (c)
- Anaphylaxis is not more severe in younger children (c)
- Food is the most likely trigger of anaphylaxis in this age range
- There are several age-specific presentations that the clinician should be aware of in infants:
  - More likely to have skin symptoms than older children
  - More likely to manifest subtle behavioral changes than older children
  - Less likely to have respiratory or subjective symptoms than older children
  - Tachycardia, coughing, vomiting all can be multi-factorial in this age range

Read more at https://www.allergyparameters.org/

Anaphylaxis in Community Settings

- Patients at high-risk for anaphylaxis should have self-injectable epinephrine (SIE) available; SDM may be appropriate for patients at lower risk for anaphylaxis (c)
- Patient preferences can inform the number of SIE's to prescribe (c)
- Use epinephrine promptly if anaphylaxis is suspected, but pre-emptive use of epinephrine is discouraged in an asymptomatic patient, even if an allergen exposure has occurred (c)
- Emergency medical services may not be required if signs and symptoms promptly resolve with epinephrine use and do not recur (c)
- School-wide allergen bans are not recommended (c)
- Stock epinephrine programs are encouraged (c)

Read more at https://www.allergyparameters.org/

“Time is on my side…” or “Call 911”?

Dartmouth-Hitchcock

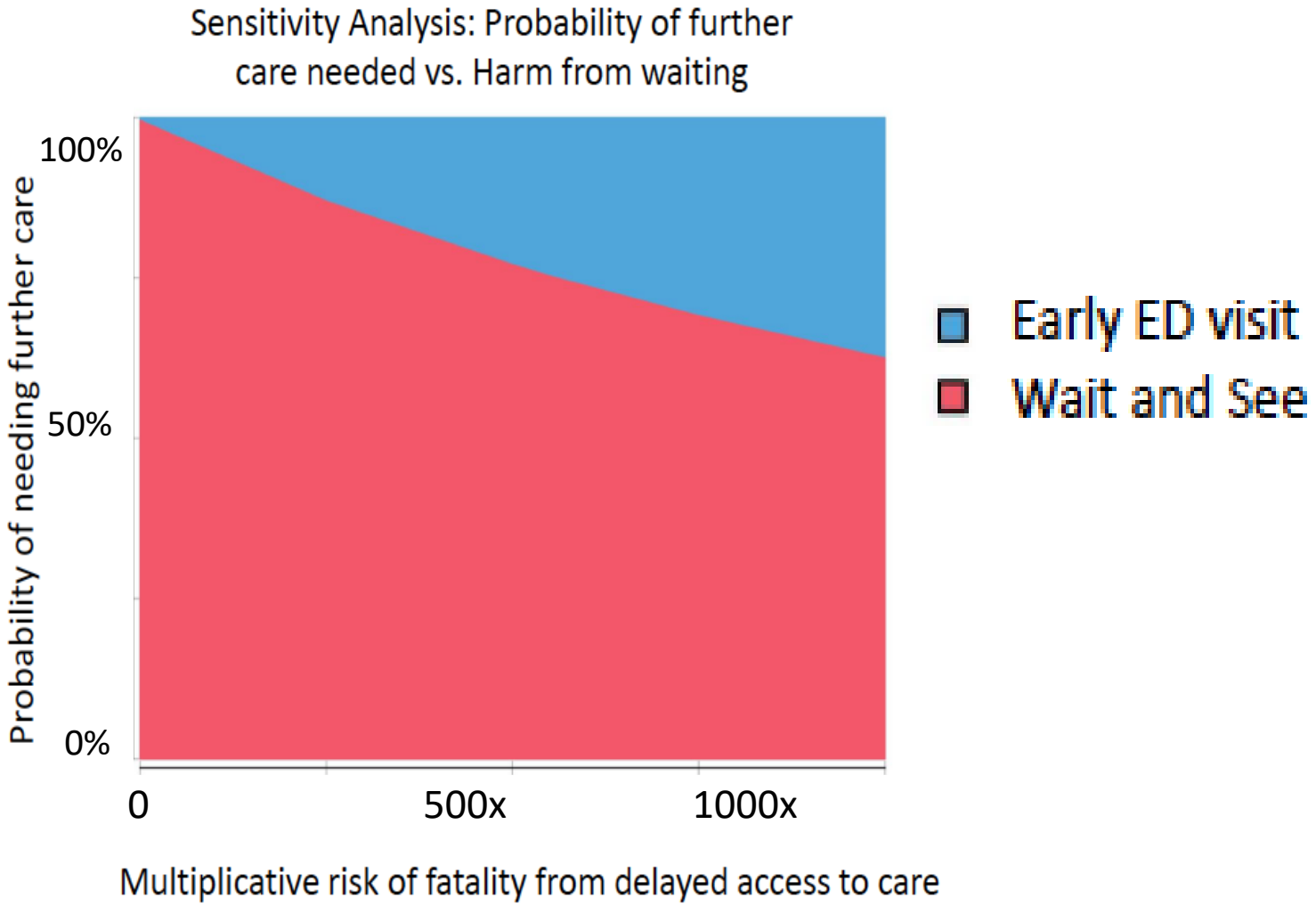
School of Medicine
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

- Survive all-cause mortality
  - Spontaneous tolerance?
    - Allergic reaction from accidental exposure?
      - Use of self-injectable epinephrine?
        - “Call 911” OR “Wait and see"
          - Additional hospitalization and/or follow-up care
            - Risk of fatality from peanut allergy

- **The incremental cost per life year saved was nearly $150M/QALY for reflex EMS**
- **With the cost per death prevented reaching $1.3B**

Shaker MS, Kanaoka T, Feenan L, Greenhawt M. Ann Allergy Asthma Immunol. 2018

Reflex EMS



- Early EMS activation could be cost-effective when the **fatality risk increased 500-fold** over a "wait and see" approach, combined with eventual care being required in the "wait and see" cohort 75% of the time

Willingness to pay threshold is $100,000 per life year saved over model horizon

Shaker MS, Kanaoka T, Feenan L, Greenhawt M. Ann Allergy Asthma Immunol. 2018

Considerations for Home Management

- ✓ Patients / caregivers engaged in shared decision making
- ✓ Immediate access to at least 2 epinephrine autoinjectors
- ✓ Immediate access to person(s) who can help
- ✓ Clear understanding of thresholds for further care
- ✓ Understanding of how to use epinephrine device

- ✗ Patient/caregiver not comfortable with home observation
- ✗ No extra epinephrine on hand
- ✗ No access to additional help
- ✗ Unsure (or unwilling) to use epinephrine
- ✗ History of near fatal anaphylaxis
- ✗ Poor adherence to recommendations

Casale TB, Wang J, Oppenheimer J, Nowak-Wegrzyn. Acute At-Home Management of Anaphylaxis: 911: What is the Emergency? J Allergy Clin Immunol Pract 2022

Contextual Considerations

Home observation following first dose of epinephrine	Signs and symptoms that had emerged prior to epinephrine administration resolve within minutes of epinephrine administration, without recurrence. Patient is asymptomatic. Patients with scattered residual hives or other rash (including erythema), even those with newly emerging but isolated hives or erythema without other symptoms occurring after epinephrine administration may be observed at home provided no additional new symptoms develop.
Consider EMS activation and possibly second dose of epinephrine but can continue to observe at home if comfortable	Signs and symptoms that had emerged prior to epinephrine administration are improving or resolving within minutes of epinephrine administration. For example, persistence of a mild sensation of globus, nausea, coughing, or stomachache may be closely observed at home provided symptoms are improving (not worsening and are perceived to be getting better) and do not persist for longer than 10-20 minutes without any additional signs of improvement.
Activate EMS immediately, consider second dose of epinephrine, do not observe at home	Signs and symptoms that had emerged prior to epinephrine administration are not resolving. Particularly concerning symptoms would include respiratory distress, stridor, altered consciousness, cardiovascular instability, cyanosis, or incontinence not typical for their age. This would also include non-skin symptoms that fail to resolve or worsen, including but not limited to repeated (>2 total episodes of vomiting), persistent hoarseness, cough, dysphagia, wheezing, or lightheadedness.

Beta-blockers, ACEi, and Anaphylaxis

- BB/ACEi may be continued in patients with prior stinging insect anaphylaxis, depending on medical necessity and alternative options (c)
- SDM may be used to inform BB/ACEi use in patients beginning VIT (c)
- In most cases, BB/ACEi can be continued for patients receiving maintenance VIT (c)
- If possible, use a BB/ACEi alternative when starting AIT but with maintenance AIT it is not unreasonable to continue BB/ACEi (c)
- Similar risk/benefit and SDM frameworks for planned procedures with risk of anaphylaxis and conditions that increase anaphylaxis risk (c)

Heavy Reliance on SDM

Read more at https://www.allergyparameters.org/

BB/ACEi: High Risk Conditions/Patients

- Some conditions are associated with greater frequency or severity of anaphylactic reactions, often at unpredictable times
  - Such as idiopathic anaphylaxis, underlying mast cell disorders, severe food allergy, or severe insect sting allergy (prior to VIT)
- Such patients should be counseled to take special measures to mitigate this risk
  - Caution regarding contributing factors (eg, alcohol, vigorous exercise, medications)
  - Increased vigilance for the earliest signs of the beginning of a reaction, and ready availability of treatment with epinephrine
- There could reasonably be increased concern in these patients for the potential risk associated with BB or ACEi

An Interesting Perspective: Weighing Risks and Benefits

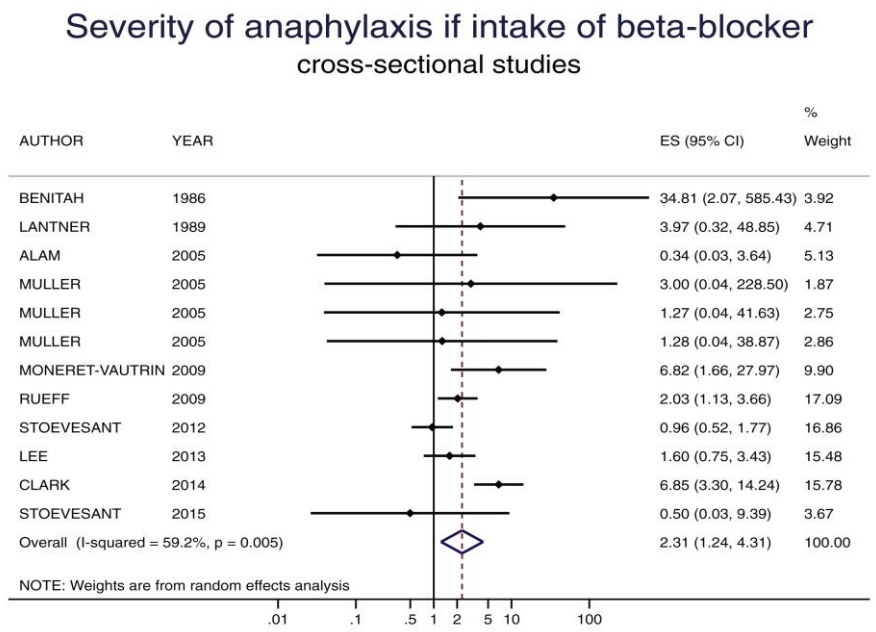
- In a Markov model of patients with heart disease (post-MI or CHF) at risk for peanut anaphylaxis who did or did not receive a beta-blocker
- **Heart disease benefit of BB outweighs risk of anaphylaxis**
  - BB increased life expectancy by 9.4 months (post-MI) and 17.4 months (CHF), on average
- BB preferred unless
  - Annual Risk of anaphylaxis exceeded 6% (post-MI) or 15% (CHF)
  - BB increased risk of moderate to severe anaphylaxis >2.5-fold (post-MI) or > 5.8-fold (CHF)
  - Anaphylaxis case fatality exceeded 6.5% post-MI
  - BB increased anaphylaxis case-fatality > 25-fold post MI

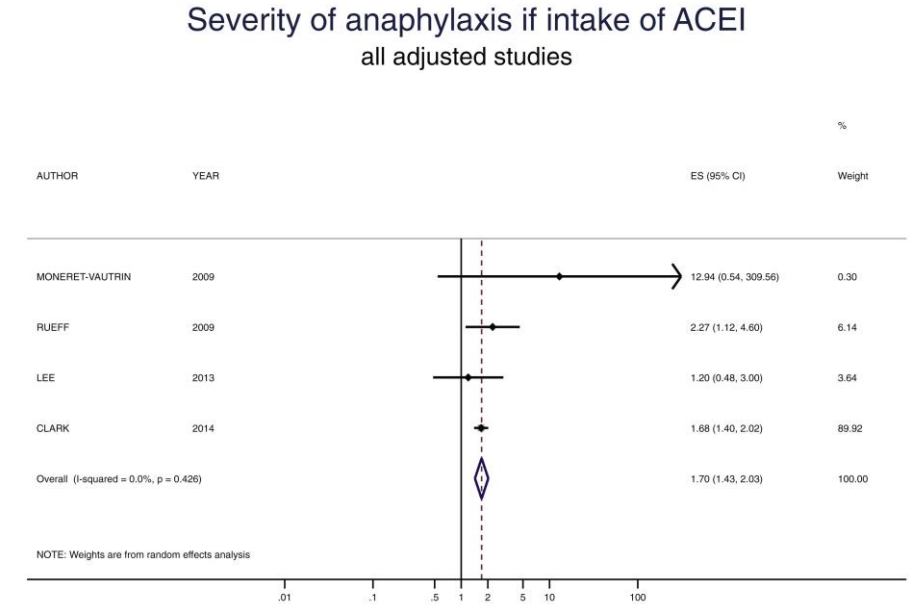
TenBrook et al. Journal of Allergy and Clinical Immunology In Practice. 2004

Beta blocker and ACEi: May increase anaphylaxis severity, but probably not incidence…

…and, it is difficult to distinguish between underlying CV risk and risk of BB and ACEi

- Trejador Alonso 2019
- Systematic review episodes of anaphylaxis for differences in severity (>22K) & incidence (>18K)
- Increased severity (OR 2.19 BB, 1.56 ACEi)
- No significant difference in incidence
- Odds for severe anaphylaxis was more associated with CV dz than BB or ACEi use





Tejador-Alonso JACI 2019; Francuzik et al. JACI 2020; Sturm et al. Allergy 2021

Mast cell disorders and anaphylaxis

- Serum tryptase alone is not a sensitive enough marker for mastocytosis (s)
- Consider a bone-marrow evaluation in patients with a predictive REMA score (c)

Variable		REMA score	NICAS score
Gender	Male	+1	+1
	Female	-1	-1
Clinical Symptoms During Attack	Absence of urticaria and angioedema	+1	--
	Presence of urticaria and/or angioedema	-2	--
	Presyncope or syncope	+3	
	Absence of angioedema	--	+1
	Flushing	--	-1
	Urticaria	--	+1
	Syncope	--	+3
Tryptase	< 15 ng/mL	-1	--
	>25 ng/ml	+2	---
	< 11.4 ng/mL	--	-1
	> 11.4 ng/mL	--	+3
Allele-specific PCR (D816V)	Negative	--	-1
	Positive	--	+3

Peri-operative anaphylaxis

- Skin testing to culprit agents endorsed and encouraged, although accuracy of such testing for many agents remains poorly defined (c)
- Supervised challenges can be combined with future procedures in partnership with a willing and collaborative anesthesiologist (c)

POA: Repeat anesthesia following appropriate evaluation

Citation	Cases of (Suspected) POA	Contactable and Confirmed POA Cases	Cases of Subsequent Anesthesia	Procedures Performed without POA	Recurrent POA
Fisher 2011	606	246	183	183	0
Guyer 2015	73	73	47	45	2
Miller 2018	174	70	70	67	3
TOTAL	853	389	300	295	5

Total cases with recurrent POA: 5/300 (1.7%)

Take Home Points

- Epinephrine is the first line pharmacotherapy for uniphasic and biphasic anaphylaxis
- Anaphylaxis severity is a spectrum; most cases of anaphylaxis are non-severe but the condition can be life-threatening
- Using antihistamines and/or glucocorticoids to prevent anaphylaxis is a low value practice, in general

Take Home Points

Using antihistamines and/or glucocorticoids to prevent anaphylaxis is a low value practice, in general

Strong and conditional recommendations allow a paradigm of care in which evidence can be appropriately applied to each patient within the context of individual circumstances, risk-tolerances, and preferences

In the setting of conditional recommendations, SDM can inform practice around both anaphylaxis prevention and management

Thank You