The Mythical Biphasic Reaction: Do They Exist and Can We Predict or Prevent Them?

Brian Grunau
Emergency Physician, St. Paul’s Hospital, Vancouver, B.C.
Scientist, Centre for Health Evaluation & Outcome Sciences
Clinical Assistant Professor, UBC Department of Emergency Medicine
UBC School of Population & Public Health
Faculty/Presenter Disclosure

• Relationships with commercial interests:
  • None
Further Disclosures

Chronic sleep deprivation can have serious effects on IQ
Case

• A healthy 25 yo male with a history of peanut allergy anaphylaxis, presents to your ED after eating at a Thai restaurant
• Sx: Had acute onset of dyspnea and throat, lip, and ear swelling and while eating
• Self administered epi auto-injector and 9-1-1 was called
• Now 40 minutes after epi; patient feels well except subtle throat “tickle”
• On exam, patient is calm, in no distress,
  • Other than HR 110, vitals are normal
  • Physical exam reveals subtle rash to thorax with no other findings
• Patient states he feels back to normal and would like to leave
• Resident: “Dr. House, what does the evidence say about how long should you monitor patients after experiencing anaphylaxis?”

• Dr. House: “Good question Resident. You should go look this up and then we can discuss it.”
Further disclosures

“The only thing I know is that I don’t know anything” - Socrates

'The more you know, the more you know you don’t know.' - Aristotle

'The more I learn, the more I realize how much I don't know.' - Albert Einstein
Learning Objectives

• This session will explore the literature of allergic, anaphylactic, and biphasic reactions, with focus on the following questions:
  • Do biphasic reactions actually exist and if so, what is the risk of their occurrence?
  • What is the benefit of prolonged monitoring of anaphylaxis patients? What is the optional duration of observation?
  • Can we predict in whom biphasic reactions will occur? Can we predict the severity?
  • Can we prevent or mitigate the risk of severe biphasic reactions?
Anaphylaxis & Allergic Reactions

• Common!
  • 12.4 million allergy-related ED visits per year in the US (3.8 visits/1000 people per year) \(^1\)
  • ~1% of all ED visits\(^{1-2}\)
  • Anaphylaxis lifetime prevalence 2%\(^3\)

Prospective randomized placebo-controlled trials
What is Anaphylaxis?
What is Anaphylaxis?

** Disclaimer: I have no financial ties to Michelin **
What is Anaphylaxis?

“anaphylaxis is hard to define, but that I know when I see it“

US Supreme Court Justice Potter Stewart, 1964
What is Anaphylaxis?

• 2nd Symposium on the Definition and Mgt of Anaphylaxis: NIAID / FAAN Symposium¹
• Clinical definition: “Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death.”¹
• A criterion was created “to capture more than 95% of cases of anaphylaxis.”

✧ NIAID, National Institute of Allergy and Infectious Disease
✧ FAAN, Food Allergy and Anaphylaxis Network

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

1. Sudden onset of an illness (minutes to several hours), with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, itching or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING:
   - Sudden respiratory symptoms and signs (e.g., shortness of breath, wheeze, cough, stridor, hypoxemia)
   - Sudden reduced BP or symptoms of end-organ dysfunction (e.g., hypotonia [collapse], incontinence)

OR 2. Two or more of the following that occur suddenly after exposure to a likely allergen or other trigger* for that patient (minutes to several hours):
   - Sudden skin or mucosal symptoms and signs (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   - Sudden respiratory symptoms and signs (e.g., shortness of breath, wheeze, cough, stridor, hypoxemia)
   - Sudden reduced BP or symptoms of end-organ dysfunction (e.g., hypotonia [collapse], incontinence)
   - Sudden gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

OR 3. Reduced blood pressure (BP) after exposure to a known allergen** for that patient (minutes to several hours):

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Guideline Methodology: The GOBSAT\textsuperscript{1} Method

\textbf{The Good Old Boys Sat Around a Table}

\textsuperscript{1}Miller et al. Lancet. 2000; 355(9198):82-3.
Biphasic Reactions

• First described in 1984\textsuperscript{1}
  • 3 patients who experienced a 2\textsuperscript{nd} anaphylactic reaction 3-4 hours after initial reaction resolution
• Various definitions however is a recurrence of allergic-related symptoms after the initial symptoms have resolved
• Pathophysiology is unclear
• “may be related to the high-molecular weight neutrophil chemotactic factor-mediated late-phase reaction of the biphasic allergic response”\textsuperscript{2}

\textsuperscript{1}Popa et al. Ann Allergy 1984; 53(2): 151-5.
\textsuperscript{2}Rosen’s Emergency Medicine. 2010. 7th Edition
FATAL AND NEAR-FATAL ANAPHYLACTIC REACTIONS TO FOOD IN CHILDREN AND ADOLESCENTS

Hugh A. Sampson, M.D., Louis Mendelson, M.D., and James P. Rosen, M.D.

- Described 13 children/adolescents who had fatal or near-fatal anaphylaxis
- Biphasic reactions “with a relatively symptom-free interval” in 3.
Key Questions

• How common are biphasic reactions in ED patients?
• How severe are they? Do they have the potential to lead to death?
• When do they occur?
• What are the outcomes of patients who have biphasic reactions after being discharged?
Studies Examining Biphasic Reactions

• Inclusion criteria: anaphylaxis and allergic reactions?
• Anaphylaxis definition?
• Biphasic reaction definition?
• Biphasic Results:
  • Incidence? Severity of Biphasic Reaction?
  • after an allergic reaction or anaphylaxis?
• Timing and ED monitoring:
  • When did the biphasic reaction occur?
  • How long were patients monitored in the ED?
• Deaths?
• Predictors?
Multiphasic Anaphylaxis: An Uncommon Event in the Emergency Department

William J. Brady Jr., MD, Samuel Luber, EMT-P, C. Thomas Carter, MD, Andrew Guertler, MD, George Lindbeck, MD

- Inclusion: Patients with anaphylaxis (67)
- Anaphylaxis: involvement of ≥ 2 organ systems
- Biphasic: recurrent of allergic symptoms & signs
- Biphasic Results:
  - 2 biphasic rxns (both Hymenoptera); only Sx urticaria
  - 0% of patients classified as anaphylaxis
- Timing & ED Monitoring
  - ED monitoring durations: unreported
  - Biphasics @ 26 and 40 hours post-ED discharge
- Deaths: 0
- Predictors: none

Incidence and characteristics of biphasic anaphylaxis: a prospective evaluation of 103 patients
Anne K. Ellis, MD, FRCPC, and James H. Day, MD, FRCPC

- Inclusion: 134 ED Encounters classified as anaphylaxis
- *Anaphylaxis:* as per Allergist using the ≥ system scheme
- *Biphasic Reaction:* same as anaphylaxis
- Biphasic Results: 20/103 (19%)
  - 10 treated with epinephrine
  - 3 did not re-present to ED
  - 4 admitted
- Timing & ED monitoring
  - Mean observation time 3.8 hours
  - 19/20 occurred post-d/c
  - Mean time to biphasic 10 hours (range 2-38)
- Deaths: 0
- Predictors: took longer for the initial reaction to resolve (133 vs 112 minutes)

Annals of Allergy, Asthma & Immunology. 2007; 89;64-69
“The findings from this study suggest that patients treated for anaphylaxis should be monitored for 24 hours or longer.

“This could be accomplished either via ongoing care in the ED or... discharge into an environment with adequate supervision”
• Inclusion: 541 patients with anaphylaxis,
• Anaphylaxis: NIAID/FAAN criteria applied by RA’s
• Biphasic: any recurrent anaphylactic reaction that occurred after initial treatment and resolution of symptoms without re-exposure to the trigger
• Biphasic Results: 21 (4%)
  • 10 treated with epi
  • 4 admitted (2 to the ICU)
• Timing & ED Monitoring
  • Time to biphasic: Median 7 h, mean 17 h (range 1-72),
  • 7/21 occurred post-dc
• Deaths: 0
• Predictors: prior anaphylaxis, unknown ppt, wheeze, diarrhea

“it seems most reasonable to base recommendations for observation on the ... current guidelines [4-6h] and to strongly consider observation longer than 6 hours for patients unable to rapidly access emergency care or with factors that place them at an increased risk of a fatal reaction”
Incidence of Clinically Important Biphasic Reactions in Emergency Department Patients With Allergic Reactions or Anaphylaxis

Brian E. Grunau, MD; Jennifer Li, BSc; Tae Won Yi; Robert Stenstrom, MD, PhD; Eric Grafstein, MD; Matthew O. Wiens, PhamD; R. Robert Schellenberg, MD; Frank Xavier Scheuermeyer, MD, MHSc

- **Inclusion:** Anaphylactic (496) or Allergic Rxns (2323)
- **Anaphylaxis:** Adapted NIAID/FAAN definition to incorporate objective findings (kappa 0.83-1.00)
- **Clinically important biphasic reaction:** recurrent S/Sx occurring after the initial presentation, which satisfy the definition for anaphylaxis, without any obvious re-exposure
- **Biphasic Results:** 5/2995 (0.18%)
  - Anaphylaxis (0.4%): 2 biphasics within the ED stay (longest 200 min)
  - Allergic Rxn (0.1%): 3 biphasics post-discharge at 28, 35, and 143 hours
- **Timing & ED Monitoring:** Median LOS 1.78h (IQR 1.2-2.9h); For Anaphylaxis Grp 2.85 (1.9-4.2)
- **Deaths**
- **Predictors:** None

“Although extended observation would be justified in patients with severe or protracted anaphylaxis, the added costs and resource use involved in routine prolonged monitoring of patients whose symptoms have resolved may worsen ED crowding while likely adding little to individual patient safety.

“A careful discussion on when to return to the ED and the importance of an epinephrine auto-injector, however, is essential before discharge.”
• Inclusion: Anaphylactic (532) and allergic reactions (802)
• Anaphylaxis: NIAID/FAAN definition
• Clinically Important Biphasic Rxn: worsening symptoms or new symptoms fulfilling the definition of anaphylaxis, after resolution of the primary reaction
• Biphasic Results: 12 “clinically important biphasic reactions” (2.3%)
  • Anaphylaxis: 7 (1.3%)
  • Allergic Reaction: 5 (0.6%)
• Time & ED Monitoring:
  • ED monitoring: Median of 7.8 h (IQR 2.5-22)
  • Median time to biphasic 12h (1-36h); occurred post-d/c in 10/12
• Predictive factors: No dyspnea
• No deaths

Allergy. 2014; 69:791-797.
“Clinically important biphasic reactions... were exceedingly rare. During 13 years, only one patient had to be transferred to ICU because of a secondary reaction, and there were no deaths due to anaphylaxis, irrespective of early discharge.

“Our study could motivate physicians to consider discharging patients after complete resolution of an anaphylactic reaction and to dispense with prolonged monitoring”
- Initial hypotension (pooled OR 2.18, 95% CI: 1.14 to 4.15)
Biphasic Prevention: Corticosteroids

- **No evidence** to support this practice
- Commonly used
- Although short duration likely safe, short courses may cause hyperglycemia, boney necrosis, Ψ symptoms
Glucocorticoids for the treatment of anaphylaxis (Review)

Choo KJL, Simons FER, Sheikh A

“We are, based on this review, unable to make any recommendations for the use of glucocorticoids in the treatment of anaphylaxis”
Attention Patients:

Please note that at this time St. Paul’s Emergency Department is unable to treat any patients whose conditions are not informed by randomized or quasi-randomized clinical trials.
Emergency Department Corticosteroid Use for Allergy or Anaphylaxis Is Not Associated With Decreased Relapses

Brian E. Grunau, MD*; Matthew O. Wiens, PharmD; Brian H. Rowe, MD, MSc; Rachel McKay, MSc; Jennifer Li, MD; Tae Won Yi, MD; Robert Stenstrom, MD, PhD; R. Robert Schellenberg, MD; Eric Grafstein, MD; Frank X. Scheuermeyer, MD, MHS C

<table>
<thead>
<tr>
<th>Variable</th>
<th>Steroid Group (n=1,288)</th>
<th>No-Steroid Group (n=1,413)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n or Median</td>
<td>Missing (%)</td>
</tr>
<tr>
<td>Steroids used in ED (%)</td>
<td>1,181 (92)</td>
<td>0</td>
</tr>
<tr>
<td>Hydrocortisone, IV (%)</td>
<td>269 (21)</td>
<td>0</td>
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<tr>
<td>Methylprednisolone, IV (%)</td>
<td>192 (15)</td>
<td>0</td>
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<tr>
<td>Dexamethasone, IV (%)</td>
<td>10 (0.8)</td>
<td>0</td>
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<tr>
<td>Prednisone, PO (%)</td>
<td>786 (61)</td>
<td>0</td>
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<tr>
<td>Postdischarge prednisone, PO (%)</td>
<td>813 (63)</td>
<td>0</td>
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<tr>
<td>Anaphylaxis (%)</td>
<td>348 (27)</td>
<td>0</td>
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</tbody>
</table>
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Table 2. Outcomes and propensity score analysis.

<table>
<thead>
<tr>
<th>Primary Outcome, Secondary Outcomes, Secondary Analysis</th>
<th>Steroids (%)</th>
<th>No Steroids (%)</th>
<th>Unadjusted OR</th>
<th>95% CI</th>
<th>Adjusted OR</th>
<th>95% CI</th>
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<tr>
<td><strong>Primary outcome: allergy-related visits</strong></td>
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<tr>
<td>Full cohort (n=2,701)</td>
<td>75 (5.82)</td>
<td>95 (6.72)</td>
<td>0.86</td>
<td>0.63–1.17</td>
<td>0.91</td>
<td>0.64–1.28</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary outcomes (all examining full cohort)</th>
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<tbody>
<tr>
<td>Any subsequent ED visit within 7 days</td>
<td>128 (9.94)</td>
<td>170 (12.03)</td>
<td>0.81</td>
<td>0.63–1.03</td>
<td>0.87</td>
<td>0.67–1.14</td>
</tr>
<tr>
<td>Clinically important biphasic reactions</td>
<td>4 (0.31)</td>
<td>1 (0.07)</td>
<td>4.38</td>
<td>0.43–215.80</td>
<td></td>
<td></td>
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<tr>
<td>Mortality</td>
<td>0</td>
<td>0</td>
<td></td>
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<td></td>
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<tr>
<td>Secondary analysis</td>
<td></td>
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<td></td>
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<tr>
<td>Extended course vs only ED steroids</td>
<td>43 (6.09)</td>
<td>25 (5.26)</td>
<td>1.17</td>
<td>0.71–1.96</td>
<td>1.10</td>
<td>0.66–1.86</td>
</tr>
</tbody>
</table>

• NNT = 176 (95% CI: NNT to benefit 39, to infinity, to NNT to harm 65)
• ENGLISH: the lower bound of the 95% CI indicates that a minimum of 39 patients would have to be treated with steroids to prevent 1 relapse to additional ED care within 7 days
• Likely “clinically insignificant”
Theories: Biphasic Reactions are real

- Immune-mechanisms involving delayed release of mediators
- Individual patient factors / Genetic pre-disposition
  - Could explain different rates of biphasic reactions in different populations
- Different regions may lead to different rates of biphasic reactions due to different allergen exposure allergens

Figure 2. Time course of selected inflammatory mediators.
Theories: Biphasic Reactions are not real

- A biphasic within the first few hours:
  - Epinephrine and/or other treatments wearing off
  - Persistent evolving symptoms that haven’t truly resolved
- Delayed delayed reactions (ie. after 6-12 hours):
  - Re-exposure to the offending allergen (which may have been unknown or perhaps mistaken)
  - A heightened state of reactivity (the person may be more likely to react to this, or other allergens, due to the most recent reaction)
Summary: Biphasic Reactions

• Rare
• They may be a result of primary delayed or “rebound” immune or may be due to other factors, however the etiology is likely clinically unimportant
• No reliable predictive factors of occurrence or severity
• Can occur after mild allergic reactions
• ~50% of biphasic reactions will occur after 10 hours
• Many biphasic reactions described in the literature occurred after ED discharge, however no studies have reported deaths
Strategy

• Anaphylaxis is indeed life-threatening! Consider prolonged observation or admission if symptoms are:
  • Severe (especially hypotension)
  • persistent
  • refractory to treatment (require >1 epinephrine)
  • slow resolution

• For uncomplicated cases: those who would not satisfy definition of anaphylaxis or those who resolve rapidly
  • Acknowledge that a “biphasic reactions” may occur
  • Consider a short period of observation
  • Ensure epinephrine auto-injector! Consider even in mild cases
  • Clear instructions of when to return
  • Consider: reliability, lives alone, distance from hospital