OPPOSING ARGUMENT AGAINST THE Routine Use of Glucocorticoids For Anaphylaxis

Journal Club

October 30, 2019
A Frequent Call

• Your patient reacted to a peanut. He accidentally ate some old candy. He’s in the emergency room. He got the whole package (epinephrine, steroids, Benadryl) because he didn’t look so good when he rolled in. He looks great now. We’re going to give him some steroids for the road. Can he follow up with you?

• We have all agreed with this plan at one time or another, but are we practicing evidence based medicine and truly helping our patients?
Primum non nocere

• “First, to do no harm.”
• This is embodies the principle of nonmaleficience.
• We all learned this phrase in medical school.
• It is often used in healthcare to caution us that given an existing problem (anaphylaxis), we must consider the potential benefit versus harm of an intervention (glucocorticoids).
We Have the Best Intentions!!

• We hope to treat the acute symptoms of anaphylaxis.
• We hope to prevent biphasic anaphylaxis.
• But are we doing more harm than good?
Let’s Examine the Evidence

• We will review:
  • Categories of evidence.
  • AAAAI Anaphylaxis Practice Parameter from 2014.
  • The role of glucocorticoids in biphasic anaphylaxis.
  • The role of glucocorticoids in hospital length of stay.
  • The role of glucocorticoids in emergency room readmission rates.
  • Side effects of glucocorticoids.
  • The draft of the upcoming Anaphylaxis Practice Parameter.
Categories of Evidence
Types of Recommendations By the Joint Task Force

• Our Joint Task Force for Practice Parameters has a specific set of guidelines when providing recommendations regarding management of allergic disease.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Definition</th>
<th>Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong recommendation</td>
<td>A strong recommendation means the benefits of the recommended approach clearly exceed the harms (or that the harms clearly exceed the benefits in the case of a strong negative recommendation) and that the quality of the supporting evidence is excellent (grade A or B)(^*). In some clearly identified circumstances, strong recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms.</td>
<td>Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.</td>
</tr>
<tr>
<td>Moderate</td>
<td>A recommendation means the benefits exceed the harms (or that the harms clearly exceed the benefits in the case of a negative recommendation), but the quality of evidence is not as strong (grade B or C)(^*). In some clearly identified circumstances, recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits outweigh the harms.</td>
<td>Clinicians also should generally follow a recommendation but should remain alert to new information and sensitive to patient preferences.</td>
</tr>
<tr>
<td>Weak</td>
<td>An option means that the quality of evidence that exists is suspect (grade D)(^<em>) or that well-done studies (grade A, B, or C)(^</em>) show little clear advantage to one approach vs another.</td>
<td>Clinicians should be flexible in their decision making regarding appropriate practice, although they may set bounds on alternatives; patient preference should have a substantial influencing role.</td>
</tr>
<tr>
<td>No recommendation</td>
<td>No recommendation means there is a lack of pertinent evidence (grade D)(^*) and an unclear balance between benefits and harms.</td>
<td>Clinicians should feel little constraint in their decision making and be alert to new published evidence that clarifies the balance of benefit vs harm; patient preference should have a substantial influencing role.</td>
</tr>
</tbody>
</table>
## The Basis of the Recommendation Rating Scale

**Category of Evidence**

Ia  Evidence from meta-analysis of randomized controlled trials  
Ib  Evidence from at least 1 randomized controlled trial  
IIa Evidence from at least 1 controlled study without randomization  
IIb Evidence from at least 1 other type of quasi-experimental study  
III Evidence from nonexperimental descriptive studies, such as comparative studies  
IV Evidence from expert committee reports or opinions or clinical experience of respected authorities or both

**Strength of Recommendation**

A  Directly based on category I evidence  
B  Directly based on category II evidence or extrapolated recommendation from category I evidence  
C  Directly based on category III evidence or extrapolated recommendation from category I or II evidence  
D  Directly based on category IV evidence or extrapolated recommendation from category I, II, or III evidence  
LB Laboratory based  
NR Not rated
AAAAAI Anaphylaxis Practice Parameter
What is the role of glucocorticoids in anaphylaxis?

• Anaphylaxis Practice Parameter 2014

• Summary Statement 15: Do not routinely administer antihistamines or corticosteroids instead of epinephrine. There is no substitute for epinephrine in the treatment of anaphylaxis. Administration of H1 and/or H2 antihistamines should be considered adjunctive therapy. (Strong Recommendation; B Evidence)
Evidence Cited in the Practice Parameter

• The 2014 Practice Parameter cites Choo et al.’s study. They conducted a systematic review to determine whether there were randomized controlled trials or even quasi-randomized trials evaluating the use of glucocorticoids in anaphylaxis (Choo, Simons, & Sheikh, 2010).

• They were not able to find any randomized controlled trials or even quasi-randomized trials evaluating the use of glucocorticoids in anaphylaxis.
Is there mechanistic support for the use of corticosteroids?

- Corticosteroids have a slow onset of action (4-6 hours) and therefore, like antihistamines, are not effective in the acute management of anaphylaxis. **There is no strong evidence** that supports the use of corticosteroids in the management of anaphylaxis (Choo, Simons, & Sheikh, 2010; Lieberman, 2006).

- **There is no definitive evidence** to indicate that corticosteroids decrease the risk of biphasic reactions.

- Patients allowed to leave the ED after complete resolution of symptoms of anaphylaxis do not **routinely need further treatment** with corticosteroids.
What is the onset of action for corticosteroids?

- IV methylprednisolone succinate onset of action:
  ● Within 1 hour.

- IV hydrocortisone onset of action:
  ● 1 hour.

- Oral prednisone immediate release tablet time to peak:
  ● 2 hours.

(Pumphrey, 2000)

(Greenberger, Rotskoff, & Lifschultz, 2007)
Biphasic Anaphylaxis
Biphasic Anaphylaxis

• The most widely cited definition of biphasic anaphylaxis is a recurrence of anaphylactic symptoms after initial resolution despite no further exposure to the trigger (Lieberman, 2005).

• Many factors have been postulated to be associated with biphasic anaphylaxis including age, gender, cause of anaphylaxis, severity of initial reaction, length of time monitored in the emergency room, and initial medical management of anaphylaxis.
Prevention of Biphasic Anaphylaxis (BA)

- The data that does exist is composed of prospective reviews, retrospective reviews, and case reports.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Popa &amp; Lerner, 1984</td>
<td>Reports of 3 cases of BA.</td>
</tr>
<tr>
<td>Stark &amp; Sullivan, 1986</td>
<td>Prospective analysis of 25 patients, 5 patients with BA. Presumably receive inpatient care by Internal Medicine service. Had deaths due to anaphylaxis.</td>
</tr>
<tr>
<td>Douglas, Sukenick, Andrade, &amp; Brown, 1994</td>
<td>Chart review of inpatient and outpatient anaphylaxis, 44 cases of anaphylaxis, 2 with BA.</td>
</tr>
<tr>
<td>Lee &amp; Greens, 2000</td>
<td>In pediatric population, 108 cases, 6 had BA. Received inpatient care. Had fatalities.</td>
</tr>
<tr>
<td>Brady, Luber, Carter, Guertler, &amp; Lindbeck, 1997</td>
<td>Retrospective chart review, included patients with anaphylaxis who were admitted to the hospital.</td>
</tr>
<tr>
<td>Ellis &amp; Day, 2007</td>
<td>Will discuss further on next slide.</td>
</tr>
<tr>
<td>Brazil &amp; MacNamara, 1998</td>
<td>Retrospective review of 34 patient, 6 with BA. Admitted to hospital.</td>
</tr>
<tr>
<td>Forrest-Hay, Taylor, Tolchard, 2003</td>
<td>Retrospective analysis, 9 had BA (9% of cohort).</td>
</tr>
</tbody>
</table>
Lessons from Dr. Lieberman’s Review

- Of the eight studies, only one showed a significant association between decreased corticosteroid administration and anaphylaxis (Ellis & Day, 2007).
- In biphasic reactors:
  - There was a lower rate of corticosteroid use ($P = 0.07$).
  - The corticosteroid dose tended to be lower in those having biphasic reactions ($P = 0.06$).
  - There was less administration of epinephrine ($P = 0.048$).
  - The majority of analyses suggest a $P$ value of less than 0.05 is statistically significant.
A 10 Year Follow Up

• A.K. Ellis actually conducted a systematic review on the same topic 10 years later (Alqurashi & Ellis, 2017).

• Concluded that:
  ● Biphasic anaphylactic reactions are more likely to occur in moderate to severe anaphylaxis or when anaphylaxis is not treated with timely epinephrine.
  ● Because of the potential detrimental adverse effects of corticosteroids and lack of compelling evidence demonstrating an effective role in reducing anaphylaxis severity or preventing biphasic anaphylaxis, we do not advocate for their routine use in anaphylaxis.
If we gave everyone glucocorticoids, could we prevent biphasic anaphylaxis?

• Ko et al. examined the incidence of biphasic anaphylaxis in 415 patients treated with glucocorticoids for anaphylaxis.

• 9 of the 415 patients experienced biphasic anaphylaxis (2.2% of the study population).
Glucocorticoids in Hospital Admissions
Glucocorticoids Thought to Reduce Length of Hospital Admission??

• They found that glucocorticoid use was associated with reduced length of stay for children hospitalized for anaphylaxis.

• Their definition of glucocorticoid use was receiving 1 or more doses of dexamethasone, methylprednisolone, prednisolone, or prednisone intravenously or orally on the day of presentation.

• This is in line with our con argument that glucocorticoids should not routinely be used for the management of anaphylaxis after resolution of the initial symptoms of anaphylaxis.
But Do They Really?

• A 2018 Japanese study by Okubo et al. found that glucocorticoid administration on admission for pediatric anaphylaxis was actually associated with increased length of hospital admission (0.39 more days in the steroid group, \( P < 0.001 \)) and increased cost (¥ 3896 = $35 more in the steroid group, \( P < 0.001 \)).

• Therefore the evidence is equivocal. Medically, legally, and conscionably can we justify the routine use of glucocorticoids for anaphylaxis?
Glucocorticoids in Emergency Room Admissions
Use of Glucocorticoids for Anaphylaxis in the Emergency Room

• Grunau et al. examined the use of glucocorticoids in anaphylaxis in patients >17 years (Grunau et al., 2015).

• Neither the one time dose of glucocorticoids while in the emergency room or separate analysis in patients prescribed glucocorticoids on discharge (all were prescribed prednisone) significantly prevented emergency room readmission rates in the 7 days after initial admission compared to patients who did not receive glucocorticoids.
Side Effects of Glucocorticoids
## Side of Effects of Glucocorticoids

(Waljee et al., 2017)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>No of participants</th>
<th>Median dose (mg/day)</th>
<th>Median No of days using steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>All doses v no corticosteroids:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>1556</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>4343</td>
<td>17.5</td>
<td>6</td>
</tr>
<tr>
<td>Fracture</td>
<td>20090</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>Dose: &lt;20 mg/day v 0 mg/day:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>708</td>
<td>17.5</td>
<td>6</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>2139</td>
<td>17.5</td>
<td>6</td>
</tr>
<tr>
<td>Fracture</td>
<td>9941</td>
<td>17.5</td>
<td>6</td>
</tr>
<tr>
<td>Dose: 20-39 mg/day v 0 mg/day:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>652</td>
<td>32</td>
<td>7</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>1713</td>
<td>35</td>
<td>7</td>
</tr>
<tr>
<td>Fracture</td>
<td>8009</td>
<td>35</td>
<td>7</td>
</tr>
<tr>
<td>Dose: ≥40 mg/day v 0 mg/day:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>196</td>
<td>60</td>
<td>5</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>491</td>
<td>60</td>
<td>5</td>
</tr>
<tr>
<td>Fracture</td>
<td>2140</td>
<td>60</td>
<td>5</td>
</tr>
</tbody>
</table>
A Rare, But Reported Side Effect

A 2019 case report by Patil and Jadhav reported that a 25 year old male treated for anaphylaxis after multiple bee stings with IV methylprednisolone 125 mg on admission and 40 mg daily for 3 days of hospital admission who developed reactivation of latent tuberculosis infection (Patil & Jadhav, 2019).

Figure 3: Radiological features of right middle lobe collapse with effusion.
(Patil & Jadhav, 2019)
Upcoming Anaphylaxis Practice Parameter
2019 Practice Parameter Draft

• The new guidelines recommend against glucocorticoids for prevention of biphasic anaphylaxis.

• Although glucocorticoids are frequently used as an adjunctive therapy for anaphylaxis they should also not be administered in place of epinephrine in the treatment of acute anaphylaxis.
Joint Task Force Practice Parameter Systematic Review

• We suggest against glucocorticoids or antihistamines as an intervention to prevent biphasic anaphylaxis. As a secondary therapy, antihistamines and corticosteroids may be considerations in anaphylaxis treatment. Glucocorticoids can also effectively prevent delayed urticaria which could confound the assessment and treatment of anaphylaxis.

• No significant benefit in prevention of biphasic anaphylaxis was found from glucocorticoids (OR 0.87, 95% CI 0.74-1.02).
Studies Included in Review

- Alqurashi 2015 (156)
- Brady 1997 (183)
- Brown 2013 (20)
- Calvani 2011 (159)
- Douglas 1994 (162)
- Ellis 2007 (35)
- Grunau 2015 (184)
- Guiot 2017 (185)
- Inoue 2013 (163)
- Jirapongsanunuruk 2007 (164)
- Kawano 2017 (186)
- Ko 2015 (187)
- Lee 2017 (188)
- Lee 2000 (131)
- Lee 2013 (166)
- Lertnawapan 2011 (167)
- Lin 2000 (189)
- Manuyakorn 2015 (169)
- Mehr 2009 (190)
- Michelson 2015 (148)
- Oya 2014 (191)
- Poachanukoon 2006 (173)
- Rohacek 2014 (37);
- Scranton 2009 (192)
- Smit 2005 (175)
- Sricharoen 2015 (52)
- Stark 1986 (33)
- Vezir 2013 (176)
Our Duty as Physicians

- Glucocorticoids are not a risk free intervention.
- There is no high quality evidence showing a benefit of glucocorticoids for the acute management of anaphylaxis and the prevention of biphasic anaphylaxis.
- So I ask you, can we truly continue to recommend, in good faith, that glucocorticoids should routinely be given for the management of anaphylaxis? Medically, legally, and conscientiously, I do not think we can.
Lack of Evidence Supporting the Use of Glucocorticoids in Anaphylaxis

• The practice of prescribing glucocorticoids for anaphylaxis is extrapolated from treatment for asthma exacerbations.

• We have to realize that we are applying it to management of anaphylaxis based on lore.

(Djulbegovic & Guyatt, 2017)
Cases Which Prolonged Courses of Corticosteroids Can Be Given

• We are opposed to the routine use of glucocorticoids for anaphylaxis, but for certain cases it may be necessary.
  ● Our trainings as physician necessitates that we do not blindly prescribe glucocorticoids.
Our Role As Allergists

• In the last year and a half, other physicians and most importantly patients seek out the allergists opinion for the OPTIMAL management of anaphylaxis.
Con Argument

We propose that glucocorticoids should not be used for the routine management of anaphylaxis after initial resolution of symptoms.
References


References (continued)


