Anaphylaxis Case Management

Elissa M Abrams MD MPH FRCPC

Professor, Department of Pediatrics, Section of Allergy and Clinical Immunology, University of Manitoba
Adjunct Professor, Department of Pediatrics, Division of Allergy and Immunology, University of British Columbia
President, Allergy Section, Canadian Pediatric Society
Board Member, Canadian Society of Allergy and Clinical Immunology
Senior Medical Advisor, Public Health Agency of Canada

LEARNING OBJECTIVES

- Describe the pros and cons of at home anaphylaxis management
- Review the indications and contraindications for use of first generation antihistamines in the treatment of anaphylaxis

A CASE – ALEX

A 26-year-old with food allergy and recurrent anaphylaxis

Reaction History

- Multiple accidental exposures since childhood
- Prior reactions variable; some required ED care and epinephrine (not self-administered)

Past year: increased reaction **frequency and severity**

- Symptoms: GI discomfort, generalized hives
- **Three ED visits** for reactions
- Most recent episode required **2 doses of epinephrine**, IV fluids, and oxygen

All reactions attributed to **milk cross-contamination**

A CASE - ALEX

Preparedness & Risk

- Often forgets epinephrine auto-injector
- Not confident in how to use it properly

Prior Workup

- PCP visit 3 months ago
- Food IgE panel: **milk-specific IgE = 0.38 IU/mL**
- Referred to Allergy/Immunology for evaluation
- Negative to egg, peanut, soy, tree nuts, shellfish, and fish (all < 0.10 IU/ml)

AT HOME ANAPHYLAXIS MANAGEMENT

Anaphylaxis Emergency Plan: _____ *(name)*

This person has a potentially life-threatening allergy (anaphylaxis) to:

PHOTO

(Check the appropriate boxes.)

☐ Food(s): _____

_____

_____

☐ Insect stings ☐ Other: _____

Epinephrine Auto-Injector: Expiry Date: _____ /_____

Dosage:

☐ EpiPen Jr® 0.15 mg ☐ EpiPen® 0.3 mg ☐ ALLERJECT® 0.15 mg ☐ ALLERJECT® 0.3 mg

☐ Emerade™ 0.3 mg ☐ Emerade™ 0.5 mg

Location of Auto-Injector(s): _____

☐ **Previous anaphylactic reaction:** Person is at greater risk.

☐ **Asthmatic:** Person is at greater risk. If person is having a reaction and has difficulty breathing, give epinephrine auto-injector before asthma medication.

A person having an anaphylactic reaction might have ANY of these signs and symptoms:

- **Skin system:** hives, swelling (face, lips, tongue), itching, warmth, redness
- **Respiratory system (breathing):** coughing, wheezing, shortness of breath, chest pain or tightness, throat tightness, hoarse voice, nasal congestion or hay fever-like symptoms (runny, itchy nose and watery eyes, sneezing), trouble swallowing
- **Gastrointestinal system (stomach):** nausea, pain or cramps, vomiting, diarrhea
- **Cardiovascular system (heart):** paler than normal skin colour/blue colour, weak pulse, passing out, dizziness or lightheadedness, shock
- **Other:** anxiety, sense of doom (the feeling that something bad is about to happen), headache, uterine cramps, metallic taste

Early recognition of symptoms and immediate treatment could save a person's life.

Act quickly. The first signs of a reaction can be mild, but symptoms can get worse very quickly.

1. **Give epinephrine auto-injector** (e.g. EpiPen®, ALLERJECT®, Emerade™) at the first sign of a known or suspected anaphylactic reaction. (See attached instructions.)
2. **Call 9-1-1** or local emergency medical services. Tell them someone is having a life-threatening allergic reaction.
3. **Give a second dose of epinephrine** as early as 5 minutes after the first dose if there is no improvement in symptoms.
4. **Go to the nearest hospital immediately (ideally by ambulance),** even if symptoms are mild or have stopped. The reaction could worsen or come back, even after proper treatment. Stay in the hospital for an appropriate period of observation as decided by the emergency department physician (generally about 4-6 hours).

Editorial

Acute At Home Management of Anaphylaxis During the Covid-19 Pandemic

Thomas B. Casale, MD[a,b], Julie Wang, MD[c], and Anna Nowak-Wegrzyn, MD, PhD[d,e] *McLean, Va; Tampa, Fla; New York, NY; and Olsztyn, Poland*

Risk involved in seeking medical care during COVID

“Allergists/immunologists may need to modify recommendations for the acute management of anaphylaxis during these unprecedented times to ensure optimal outcomes of anaphylaxis while weighing the infectious risk and health care burdens associated with the COVID-19 pandemic”

Casale TB, Wang J, Nowak-Wegrzyn A. Acute At Home Management of Anaphylaxis During the Covid-19 Pandemic. J Allergy Clin Immunol Pr. 2020;8:1795–7.

Biphasic Anaphylaxis

Historically estimated at 5-20%

While there is uncertainty regarding actual rate, likely much lower than this (in various studies <1%-5%)

Food allergy NOT a risk factor for biphasic anaphylaxis especially in children

Shaker MS,et al. J Allergy Clin Immunol. 2020;145:1082–123

Kraft M et al J Allergy Clin Immunology: In Practice 2020;8: 3388-3395

Biphasic Anaphylaxis

Risk factors:

- more severe initial presentation of anaphylaxis (odds ratio [OR], 2.11; 95% CI, 1.23-3.61)
- repeated epinephrine doses (ie, >1 dose of epinephrine) required with the initial presentation (OR, 4.82; 95% CI, 2.70-8.58)

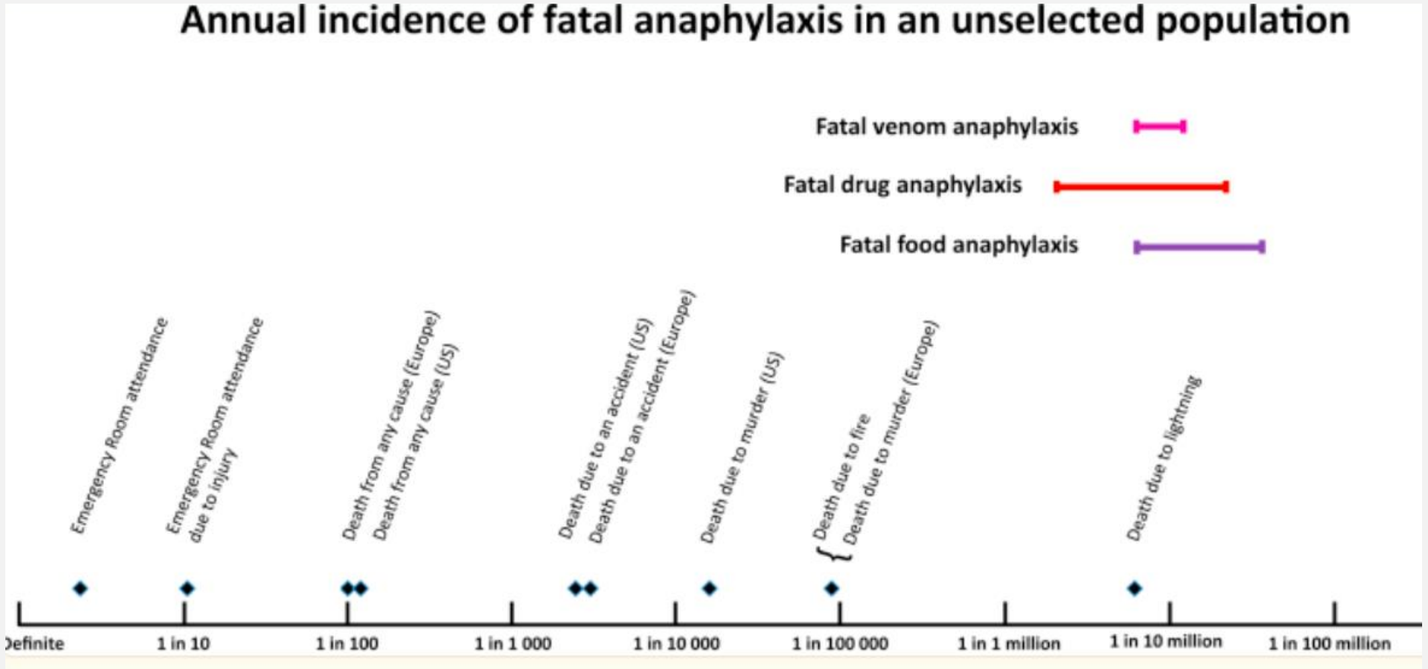
- wide pulse pressure (OR, 2.11; 95% CI, 1.32-3.37),
- unknown anaphylaxis trigger (OR, 1.63; 95% CI, 1.14-2.33)
- cutaneous signs and symptoms (OR, 2.54; 95% CI, 1.25-5.15)
- drug trigger in children (OR, 2.35; 95% CI, 1.16-4.76).

Shaker MS,et al. J Allergy Clin Immunol. 2020;145:1082–123

Anaphylaxis Fatality

Fatality in anaphylaxis is an exceptionally rare outcome, with an overall prevalence of 0.47-0.69 per million persons and case fatality rates at < 0.1% of all ED visits

Biphasic anaphylaxis fatality is exceptionally rare (0.5 to 1 death per million person- years)



Xu YS et al. Allergy Asthma Clin Immunol. 2014;10:38.
Lee JK et al. Clin Exp allergy 2011;41:923–38.
Ichikawa M et al. Acute Med Surg. 2021;8:e689.
Turner PJ et al. J Allergy Clin Immunol Pr. 2017;5:1169–78.

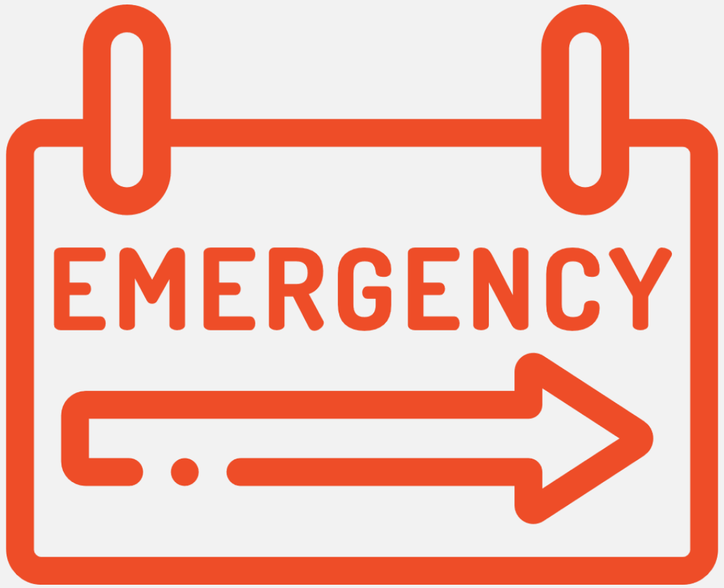
Risk Factors for Anaphylaxis Fatality and Severe Outcomes

Cardiovascular comorbidity, beta-blocker use, prior severe anaphylaxis, lack of access to epinephrine, lack of access to emergency medical services

The delayed use of epinephrine, identified as a significant feature in several reports of fatal food anaphylaxis, is perhaps the risk factor most amenable to modification

Turner PJ et al. J Allergy Clin Immunol Pr. 2017;5:1169–78.
Mullins R.J. et al. Clin Exp Allergy. 2016;46:1099–1110
Xu Y.S. et al. Allergy Asthma Clin Immunol. 2014;10:38
Sampson H.A. et al. N Engl J Med. 1992;327:380–384.
Bock S.A. et al. J Allergy Clin Immunol. 2007;119:1016–1018.
Pumphrey R.S. et al. J Allergy Clin Immunol. 2007;119:1018–1019.

The mandatory requirement to activate EMS may lead to an association of the use of epinephrine with EMS activation, and so result in non-use or delayed use of intramuscular epinephrine



Gabrielli S et al. Ann Allergy Asthma Immune 2021;8: 496
Glassberg B et al. Ann Allergy Asthma Immunol 2021; 126:175-179.e3.

> Int Arch Allergy Immunol. 2017;173(3):171-177. doi: 10.1159/000477566. Epub 2017 Aug 9.

Safety of Adrenaline Use in Anaphylaxis: A Multicentre Register

Victòria Cardona [1], Laia Ferré-Ybarz, Mar Guilarte, Nuria Moreno-Pérez, Catalina Gómez-Galán, Eva Alcoceba-Borràs, Maria Belén Delavalle, Teresa Garriga-Baraut; AdreSCAIC Research Group

A common misconception is that the administration of intramuscular epinephrine requires cardiac monitoring. Since the vast majority of complications due to epinephrine use in anaphylaxis are following intravenous epinephrine use, clinical practice guidelines clearly associate the need for cardiac monitoring with intravenous epinephrine use. Intramuscular epinephrine is extremely safe and does not require cardiac monitoring.

Adverse Events with Epinephrine Use

Serious adverse reactions to intramuscular epinephrine are very rare and should not pose a barrier to the prescription or early administration of EAIs when indicated.

The adverse effects associated with EAI use ar
typically mild and transient. When cardiac adve
events do occur, they are rarely associated with
intramuscular administration.

Table 20
Proposed Strategies to Reduce the Risk of EAI-Related Injury[303]

1. Restrain the patient and firmly immobilize their leg before administering the EAI
2. Control the action of administration as much as possible, using a place and press motion rather than a swing and jab motion
3. Hold the EAI in place for the shortest period of time recommended by the manufacturer
4. Avoid reinserting the needle if it dislodges before the recommended hold time passes

Abbreviation: EAI, epinephrine autoinjector.

Golden DBK et al. Ann Allergy Asthma Immunol. 2023 Dec 5:S1081-1206(23)01304-2

Adjunct Anaphylaxis Therapies

Practice parameter

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

Question 2. Should antihistamines or glucocorticoids be used to prevent biphasic anaphylaxis?

Recommendation. We suggest against administering glucocorticoids or antihistamines as an intervention to prevent biphasic anaphylaxis. Conditional recommendation.

Clinical Commentary Review

Do Corticosteroids Prevent Biphasic Anaphylaxis?

Waleed Alqurashi, MD, MSc, FAAP, FRCPC[a], and Anne K. Ellis, MD, MSc, FRCPC, FAAAAI[b] *Ottawa and Kingston, Ontario, Canada*

A total of 31 appropriate studies were identified. 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. (J Allergy Clin Immunol Pract 2017;5:1194-205)

Adjunct therapies provided in the ED such as antihistamines and steroids have not been demonstrated to reduce the risk of a biphasic reaction nor of fatality

Shaker MS et al. J Allergy Clin Immunol. 2020;145:1082–123.
Alqurashi W et al. J allergy Clin Immunol Pract. 2017;5:1194–205

An economic evaluation of immediate vs non-immediate activation of emergency medical services after epinephrine use for peanut-induced anaphylaxis

Marcus Shaker, MD, MS*,†; Tsuzumi Kanaoka, BA†; Lynn Feenan, RN*;
Matthew Greenhawt, MD, MBA‡

Performed a cost-effectiveness analysis using Markov modeling simulated over a 20-year horizon comparing activating EMS immediately after epinephrine use for allergic reactions to peanut vs a "wait and see" approach in which EMS was only activated if symptoms of the reaction did not promptly resolve after treatment

Medical observation of a treated and promptly resolved peanut allergic reaction has minimal benefit and excessive costs. Immediately activating EMS after using epinephrine for a peanut allergic reaction in this context is not cost-effective

Shaker M et al. Ann Allergy Asthma Immunol 2019:122; 79-85

Rationale

The mandatory requirement to activate EMS may lead to an association of the use of epinephrine with EMS activation, and so result in non-use or delayed use of intramuscular epinephrine

Fatality in anaphylaxis is an exceptionally rare outcome

Severe biphasic anaphylaxis is uncommon and biphasic anaphylaxis fatality is exceptionally rare

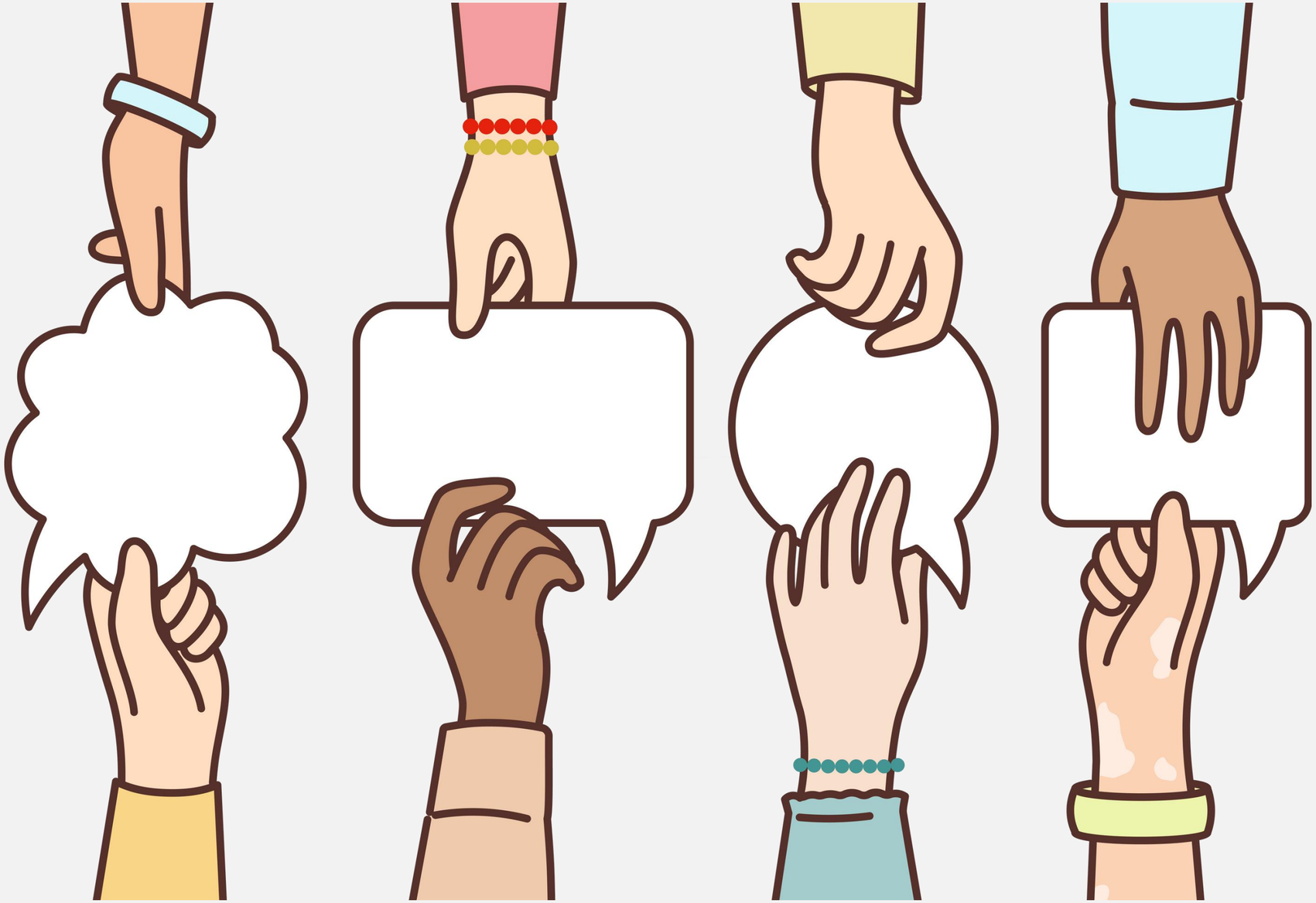
Biphasic anaphylaxis and other severe anaphylaxis outcomes are most effectively prevented by early epinephrine administration

The high safety profile of intramuscular epinephrine does not require any ED monitoring

Adjunct therapies have not been demonstrated to reduce the risk of a biphasic reaction

Routine activation of EMS for resolved anaphylaxis after epinephrine therapy is a low value practice

There remains significant healthcare utilization issues in the EDs



Factors to Consider

Patient/caregiver comfort level with recognition/management of anaphylaxis

Immediate access to ≥2 up to date, weight-appropriate dose of autoinjectors

Absence of risk factors for a biphasic reaction

Absence of risk factors for severe anaphylaxis outcomes

Symptom resolution with one dose of epinephrine administration

Patient/caregiver preference

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, or the 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 may continue to observe at home if comfortable	Signs and symptoms that had emerged prior to administration of the first dose of epinephrine 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.

Figure 5. General guidance for activation of EMS and administration of a second dose of epinephrine. EMS, emergency medical services.

Golden DBK et al. Ann Allergy Asthma Immunol. 2023 Dec 5:S1081-1206(23)01304-2

We suggest that clinicians counsel patients that immediate activation of EMS may not be required if the patient experiences prompt, complete, and durable response to treatment with epinephrine, provided that additional epinephrine and medical care are readily available, if needed. We suggest that clinicians counsel patients to always activate EMS after epinephrine use if anaphylaxis is severe, fails to resolve promptly, fails to resolve completely or nearly completely, or returns or worsens after a first dose of epinephrine.

Golden DBK et al. Ann Allergy Asthma Immunol. 2023 Dec 5:S1081-1206(23)01304-2

SEDATING ANTIHISTAMINES

Patients are very familiar with them and consider that ‘they must be both effective and safe’

- MOST PRESCRIBED

First generation antihistamines remain the most commonly prescribed antihistamines by both practitioners and pharmacists

- LEAST RIGOROUSLY STUDIED

Available since 1946, a time at which medications were not required to pass rigorous drug safety or efficacy testing

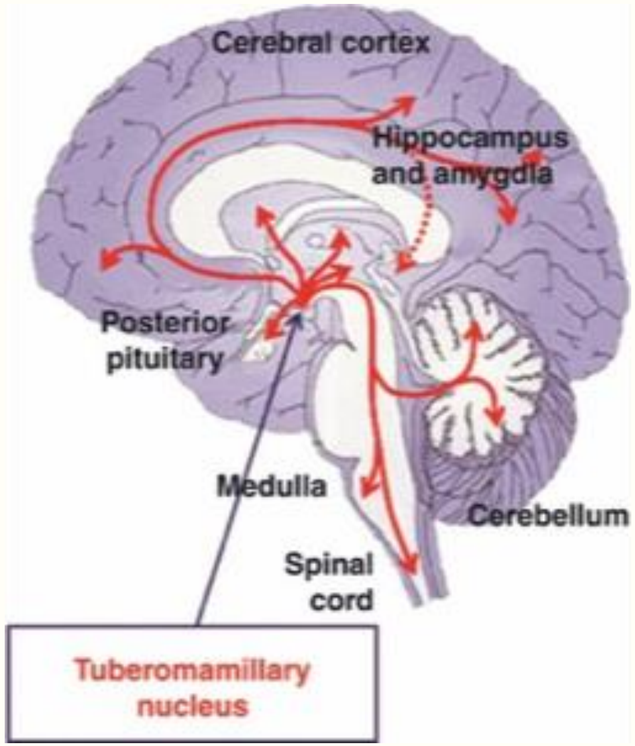
- STRONG BRAND RECOGNITION

Patients will often choose first generation antihistamines based on brand recognition and comfort as tbey have been using it since their own childhoods

Emanuel MB. Clin Exp Allergy 1999
Cburcb MK et al. Allergy 2010

HISTAMINE RECEPTORS IN THE BRAIN

THERE ARE APPROXIMATELY 64000 HISTAMINE-PRODUCING NEURONES, LOCATED IN THE TUBEROMAMILLARY NUCLEUS OF THE HUMAN BRAIN.

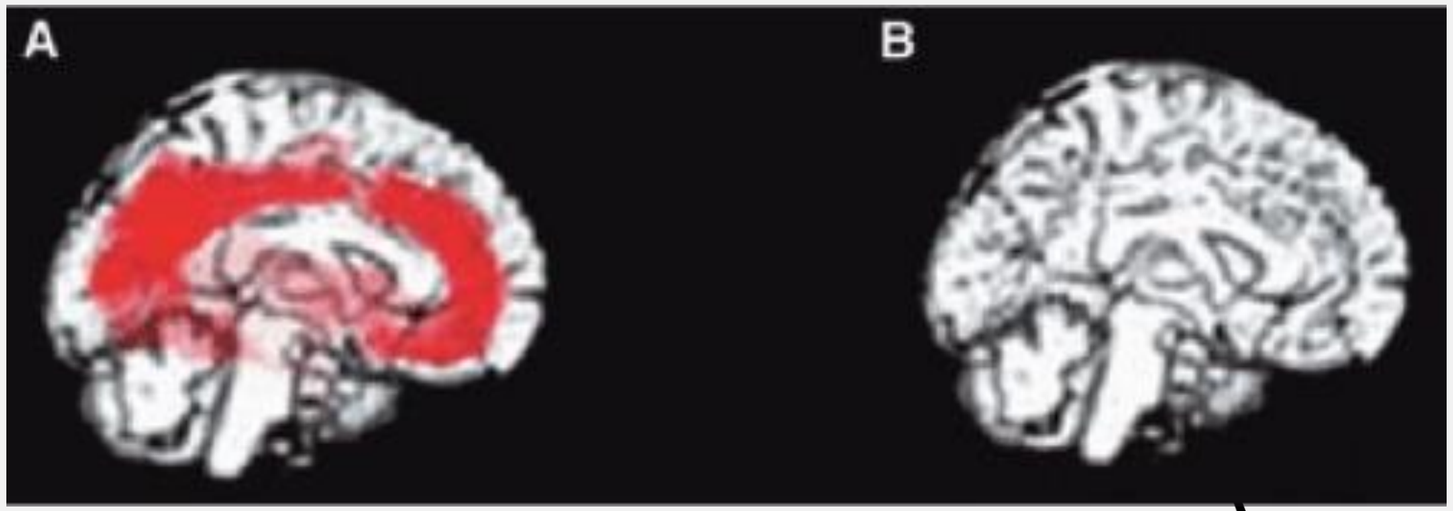


THE PROBLEM

When activated, these neurons stimulate H1-receptors in all of the major parts of the cerebrum, cerebellum, posterior pituitary and spinal cord

Tashiro M, Duan X, Kato M, Miyake M, Watanuki S, Ishikawa Y et al. Br J Clin Pharmacol 2008

PET Scan



The penetration (red colouring) of (A) diphenhydramine, a first-generation H1-antihistamine, and (B) bepotastine, a second-generation H1-antihistamine, into human brain

Tashiro M, Duan X, Kato M, Miyake M, Watanuki S, Ishikawa Y et al. Br J Clin Pharmacol 2008

Sedation

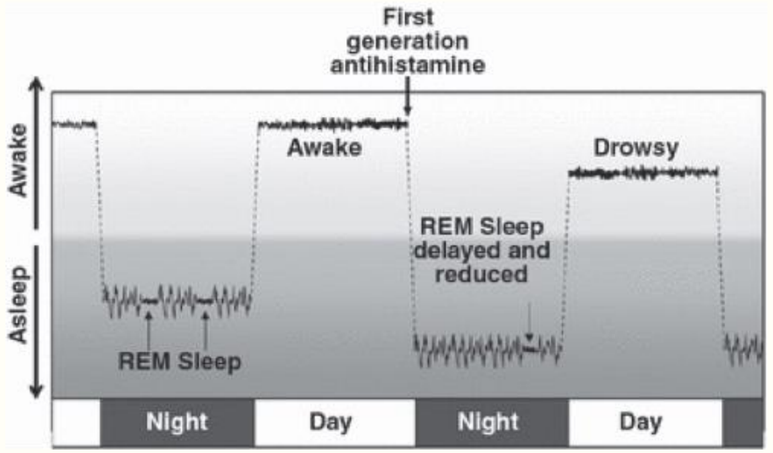
1. Sleepy during the day
2. Sleepy - but poor sleep quality - at night

DAYTIME SOMNOLENCE, SEDATION, DROWSINESS, FATIGUE AND IMPAIRED CONCENTRATION AND MEMORY

At night increase the latency to the onset of rapid eye movement (REM) sleep and reduce the duration of REM sleep

40-80%

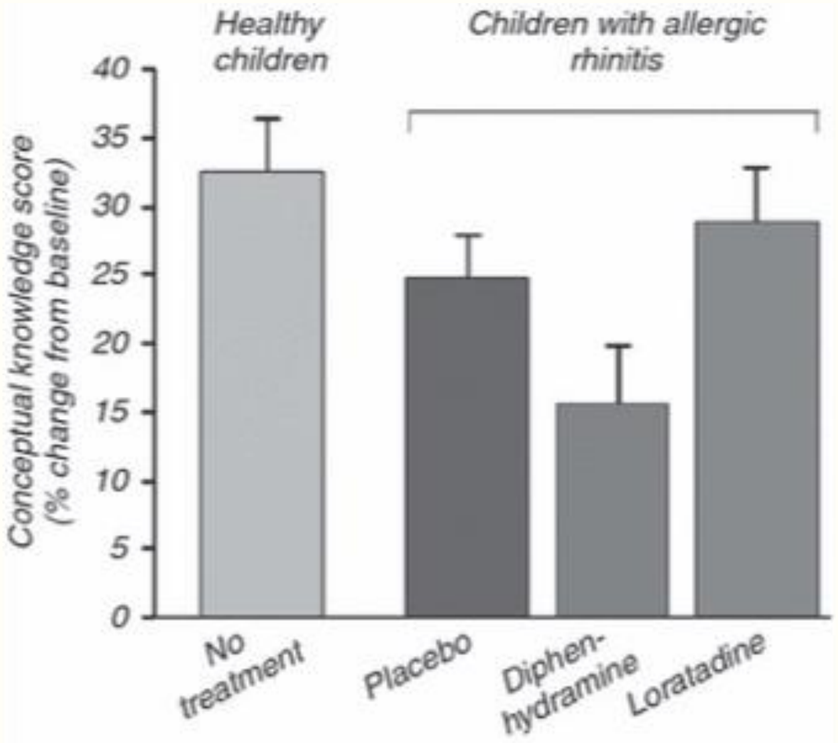
Objective sedation >Subjective symptoms



Tashiro M, Duan X, Kato M, Miyake M, Watanuki S, Ishikawa Y et al. Br J Clin Pharmacol 2008

SCHOOL

Performance



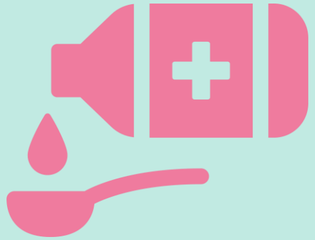
Tashiro M et al. Br J Clin Pharmacol 2008
Walker S et al. JACI 2007

WORK
Performance

Review of toxicology testing profiles from 6677 fatally injured civil aviation pilots (US;1990-2012): diphenhydramine was the drug most commonly found on autopsy that was capable of causing impairment (7.3%). Due to the increased risk, first-generation AHs are banned for use by commercial and military airline pilots before or during flights.

TFein MN et al. AACI 2019
McKay MP et al. Accid Anal Prev. 2016

Impairment of function is produced even by the lowest doses of first-generation H1-antihistamines that are recommended by manufacturers



Effects on the CNS are similar to and additive with those produced by alcohol or other CNS-sedatives, such as benzodiazepines

Bedtime dosing may not decrease functional impairment because of long elimination half-life values

Some patients are especially vulnerable to the CNS effects: CNS disorders, extremes of age, renal/liver dysfunction

Simons FE. N Engl J Med 2004
Juniper EF et al. J Allergy Clin Immunol 2005
Cockburn IM et al. J Occup Environ Med 1999
Shamsi Z et al. Hum Psychopharmacol 2000

Drugs of Abuse

Documented drugs of abuse
Overdose can result in anti-cholinergic effects including fever, flushing, pupillary dilatation, urinary retention, tachycardia, hypotension and coma
Infants and children who experience accidental or intentional overdose may present with paradoxical excitation including irritability, hallucinations, and seizures followed by drowsiness, delirium, respiratory depression and coma

Diphenhydramine overdoses are so frequently reported to poison control centres in the United States that evidence-based guidelines have been published to facilitate their management

Canadian, American, and British health care agencies recommending against these over-the-counter medications not being used for children younger than 5 years.

In 2003, 28,092 exposures to diphenhydramine were reported to poison control centres in the United States—11,355 (40.4%) of these cases were in children under the age of six, resulting in at least six fatalities

Boyle J et al. Curr Med Res Opin 2006
Pragst F et al. Forensic Sci Int 2006
Page CB et al. QJM 2009
Scharman EJ et al. Clin Toxicol 2006

Cardiac toxicity

- May be associated with a prolonged QTc and cardiac arrhythmias when taken in large doses or overdoses
- Cardiac safety of first generation antihistamines was never studied as this was an unknown risk when introduced
- In June 2016, Health Canada released a safety recall regarding hydroxyzine and issued a “black box” warning hydroxyzine can increase the risk of QT prolongation and torsade de pointes

Fein MN et al. AACI 2019
Woosley RL. Annu Rev Pharmacol Toxicol 1996

INFANTS

“Even more alarming is the practice of using first-generation H1-antihistamines as sedatives/sleeping aids in infants.”

Although reports of fatal intoxications are uncommon and are usually accidental, infant homicides have also been reported.

Over-the-counter cold medications can also contain first-generation antihistamines and their use in children may also be potentially lethal, even when the manufacturer’s instructions are followed

OLDER ADULTS

25% of individuals older than 65 years of age have some cognitive impairment and histamine neurotransmission is disrupted in individuals with neurodegenerative disease.

First generation antiH in this population associated with increased risk of inattention, disorganized speech, altered consciousness and impaired function or alertness

Fein MN et al. AACI 2019
Church MK et al. Allergy 2010
Nine JS et al. Am J Forensic Med Pathol 2006
Agostini JV et al. Arch Intern Med 2001

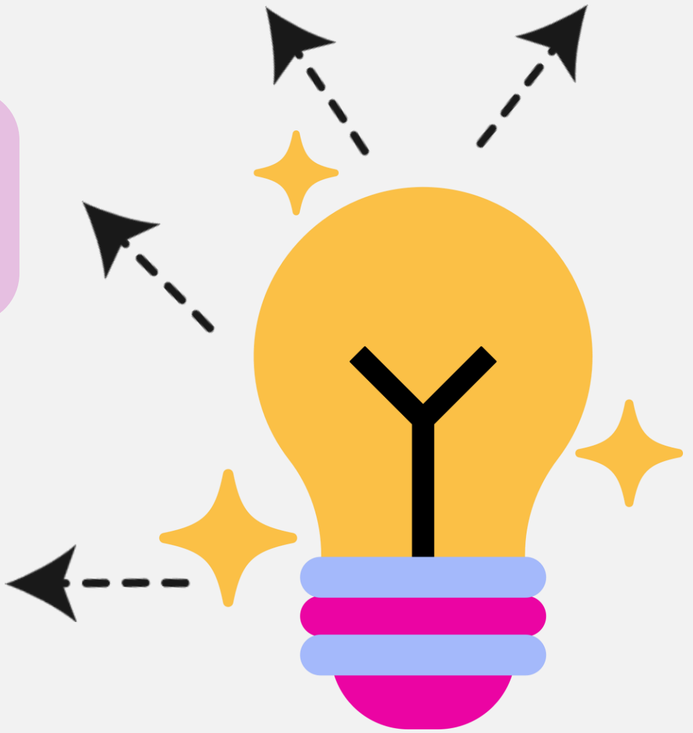
SECOND GEN ANTIH

Improved receptor specificity

Better efficacy

Longer duration of action

Less adverse effects



Wolfson A et al. JACI: IP 2022

Second Generation Safety

Within the second-generation antihistamines, cetirizine was found to cause more sedation when compared with loratadine

Loratadine, fexofenadine, desloratidine, rupatadine, and bilastine are considered the least-sedating antihistamines.

Multiple studies have noted no clinically significant electrocardiogram changes associated with second-generation antihistamines

Minimal safety concerns as compared with the first-generation antihistamines. Even up to 30-fold accidental overdoses of cetirizine, loratadine and fexofenadine have not resulted in serious adverse events or deaths

Studies have not found any increased risk of accident or injury associated with loratadine, cetirizine, bilastine, or fexofenadine

In addition to the minimal sedation and proven cardiac safety, multiple clinical trials of second-generation antihistamines have demonstrated that other side effects such as dry mouth, nausea, urinary retention, headache and dizziness are not significantly different when compared with placebo

Ten Eick AP et al. Drug Saf, 2001
Rodriguez M et al. Eur J Pediatr 2020
Santamaria F et al. PLoS One 2017
Simons FE et al. J Allergy Clin Immunol 1990
Breneman DL. Ann Pharmacother 1996
Park JH et al. J Allergy Clin Immunol 2011
Raphael GD et al. Ann Allergy Asthma Immunol 2006
Alper BS. Arch Fam Med 2000

THE MYTH THAT DIPHENHYDRAMINE HAS A FASTER ONSET OF ACTION AND BETTER EFFICACY THAN SECOND-GENERATION ANTIHISTAMINES IS OFTEN THE REASON CITED BY PATIENTS FOR THEIR CHOICE OF MEDICATION. THE SEDATIVE SIDE EFFECT IS ALSO SOMETIMES MISTAKEN OR PERCEIVED BY PATIENTS AS BETTER EFFECTIVENESS.

STUDIES:

CETIRIZINE AND LORATADINE > CHLORPHENIRAMINE (ONSET OF ACTION, POTENCY, DURATION OF ACTION)

CETIRIZINE > HYDROXYZINE (ONSET OF ACTION)

CETIRIZINE > DIPHENHYDRAMINE (ONSET OF ACTION, EFFICACY)

Ten Ek AP et al. Drug Saf, 2001
Rodriguez M et al. Eur J Pediatr 2020
Santamaria E et al. PLoS One 2017
Simons FE et al. J Allergy Clin Immunol 1990
Breneman DL. Ann Pharmacother 1996
Park JH et al. J Allergy Clin Immunol 2011
Raphael GD et al. Ann Allergy Asthma Immunol 2006
Alper BS. Arch Fam Med 2000

TAKE HOME POINTS

AT HOME ANAPHYLAXIS IS A GOOD OPTION IN MANY CIRCUMSTANCES

NEVER USE FIRST GENERATION ANTIHISTAMINES


THANK
YOU