Anaphylaxis

Clinical Pathway

Disclaimer

This clinical pathway is intended to provide general guidance and should not replace clinical judgment. It is meant to assist licensed practitioners and other health care providers in clinical decision-making by describing a range of generally acceptable approaches to the diagnosis and management of a particular condition. A particular patient's circumstances should always be taken into account when a practitioner is deciding on a course of management.This clinical pathway is current as of the date of publication and will be reviewed periodically to align with any updated best practices or evidence; however, new development may notbe represented in the published version. The treating practitioner assumes all risks associated with care decisions. Phoenix Children's accepts no liability for the content of this clinical pathway or the outcomes a patient might experience where a practitioner consulted the content of this clinical pathway.

Table of Contents

Pathway Flow Diagram/Algorithm

Table 1. Diagnosis of Anaphylaxis

Anaphylaxis is highly likely when ONE of the following 3 criteria are fulfilled, usually within minutes to 2-3 hours following a possible allergen exposure:	
Criteria 1	• **Acute onset** of an illness with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lip-tongue-uvula) **AND** at least one of the following: o Respiratory compromise o Reduced blood pressure or associated symptoms of end-organ dysfunction o Persistent gastrointestinal symptoms, significant abdominal pain and/or significant vomiting
Criteria 2	• Two or more of the following that occur rapidly after exposure to a **LIKELY ALLERGEN** for that patient: o Involvement of the skin-mucosal tissue o Respiratory compromise o Reduced blood pressure or associated symptoms o Persistent gastrointestinal symptoms
Criteria 3	• Reduced blood pressure after exposure to a **KNOWN ALLERGEN** for that patient

Table 2. Symptoms of Anaphylaxis

System	Symptoms
Mucous Membranes	• Pruritus • Congestion of eyes, nose or mouth
Cutaneous	• Pruritus • Flushing • Erythema • Urticaria • Angioedema
Respiratory – Upper Airway	• Stridor • Difficulty swallowing • Choking
Respiratory – Lower Airway	• Chest tightness • Shortness of breath • Tachypnea • Coughing • Wheezing • Retractions
Gastrointestinal (GI)	• Abdominal pain • Nausea • Vomiting • Diarrhea
Cardiovascular	• Weak pulse • Hypotension
Central Nervous System	• “Sense of impending doom” • Anxiety • Agitation • Loss of consciousness

Table 3. EPINEPHrine Dosing for the Treatment of Anaphylaxis

EPINEPHrine IntraMUSCULAR (IM) Dose *ADMINISTER INTO ANTEROLATERAL THIGH*		
Weight	**Autoinjector (Preferred where available)**	**Syringe**
< 7.5 kg	—	0.01 mg/kg (max 0.5 mg/dose) using EPINEPHrine 1 mg/1 mL concentration*
7.5 to <15 kg	Auvi Q 0.1 mg *or* 0.15 mg by autoinjector	
15 to 24.9 kg	0.15 mg by autoinjector	
≥ 25 kg	0.3 mg by autoinjector	

*See code book for dilution instructions for EPINEPHrine IM dosing in patients weighing <10 kg

Table 4. Duration of Monitoring after Anaphylaxis

Factors that increase the duration of time to monitor after anaphylaxis:
• Patient who previously required intubation • Patient with a history of a biphasic reaction • Patient with a history of a severe asthma • Patient with severe symptomatology such as hypotension or grade 4 anaphylaxis • Patient with delayed administration of epinephrine • Patient who was slow to respond to treatment or required more than 1 dose of epinephrine • Patient whose family was unable to educated on anaphylaxis treatment • Patient distant from a healthcare facility

Note: A 1-hour symptom-free observation after resolution of initial anaphylaxis has been associated with a 95% negative predictive value (95%CI, 90.9%-97.3%) for biphasic anaphylaxis. As such, the minimum symptom free time to monitor a patient without any of the above risk factors after anaphylaxis is 1 hour. If any of the above factors are present, a longer duration of monitoring is appropirate, often up to 4 hours, due to the risk of having a biphasic reaction. In most pediatric studies, timing of biphasic anaphylaxis on average occurred later than the previously standard 4-6 hours waiting period. Hence, provider discretion is advised to determine utility in prolonged observation in pediatric anaphylaxis for whom risk factors for biphasic anaphylaxis are present.

Outpatient Anaphylaxis Pathway

If the patient meets the diagnostic criteria for anaphylaxis, immediately administer EPINEPHrine IM (see Table 3 for dosing)

Assessment/Interventions AFTER EPINEPHrine Administration	
Positioning/General	• Call Code Blue (or dial 911 if not available) • Place patient in Trendelenburg position or, if not feasible, a position of comfort • Obtain vitals and repeat every 5 minutes until emergency response team arrives
Cardiovascular	• Consider inserting a peripheral IV
Respiratory	• Give 10 – 15 L O2 via facemask if sats are < 90% or the patient is in respiratory distress

Has the emergency response team arrived?

- Yes → Sign out and transfer patient
- No → Is the patient responding to EPINEPHrine?
  - Yes → Continue to monitor until arrival of emergency response team
    - Any return of symptoms?
      - Yes → Repeat EPINEPHrine IM every 5 minutes as needed up to 3 doses
      - Continue above listed "Assessment/Interventions After EPINEPHrine Administration" as needed and if available:
        - For shortness of breath, wheezing, dyspnea, and respiratory distress not resolved after EPINEPHrine, give albuterol MDI 4 puffs
        - Consider cetirizine for cutaneous manifestations not resolved after EPINEPHrine

      See Table 5 for adjunctive medication dosing
      - No → Continue to monitor until arrival of emergency response team
  - No → Repeat EPINEPHrine IM every 5 minutes as needed up to 3 doses
    - Continue above listed "Assessment/Interventions After EPINEPHrine Administration" as needed and if available:
      - For shortness of breath, wheezing, dyspnea, and respiratory distress not resolved after EPINEPHrine, give albuterol MDI 4 puffs
      - Consider cetirizine for cutaneous manifestations not resolved after EPINEPHrine

    See Table 5 for adjunctive medication dosing

Emergency Department (ED), Urgent Care (UC), and Infusion Center Anaphylaxis Pathway

If the patient meets the diagnostic criteria for anaphylaxis, immediately administer EPINEPHrine IM (see Table 3 for dosing)

Assessment/Interventions AFTER EPINEPHrine Administration	
Positioning/General	• Place patient in Trendelenburg position or, if not feasible, a position of comfort • Obtain vitals and repeat as needed
Cardiovascular	• Consider inserting a peripheral IV
Respiratory	• Give 10 – 15 L O2 via facemask if sats are < 90% or the patient is in respiratory distress • For shortness of breath, wheezing, dyspnea, and respiratory distress not resolved after EPINEPHrine, give albuterol MDI 4 puffs • If there is evidence of impending airway obstruction, intubate (or call code/911 for assistance) • For upper airway obstruction, consider racemic EPINEPHrine
Cutaneous	• Consider oral cetirizine (preferred) or IV diphenhydramine for cutaneous manifestations not resolved after EPINEPHrine
Gastrointestinal (GI)	• Consider famotidine for patients with GI manifestations

***See Table 5 for adjunctive medication dosing**

Is the patient responding to EPINEPHrine?

Yes

- Once symptom free, monitor for 1 to 4 hours (see Table 4 regarding Duration of Monitoring after Anaphylaxis). If unable to monitor in UC or Infusion Center, transfer to ED. If prolonged monitoring deemed necessary, consider admission to hospitalist service.
- Continue vital sign assessments hourly
- Obtain a **serum tryptase** if available (from 1-4 hours of symptom onset)

Any return of symptoms?

No

No

- Repeat EPINEPHrine IM every 5 minutes as needed up to 3 doses.
- If in UC or Infusion Center and 2nd dose of EPINEPHrine indicated, transfer to ED by EMS or calling a Code Blue
- If in ED and 2nd dose of EPINEPHrine indicated, consider admission to Hospitalist Service
- If in ED and 3rd dose of EPINEPHrine indicated, consider:
  - Glucagon (for patients on beta-blockers) and/or
  - EPINEPHrine continuous IV followed by admission to PICU, and placing a second PIV, if time permits.
- Continue above listed "Assessment/Interventions After EPINEPHrine Administration" as needed

See Table 5 for adjunctive medication dosing

Yes

- Discharge Medications:
  - If persistent rash, consider cetirizine or other non-sedating antihistamines daily, as needed
  - If initial reaction included wheezing, consider albuterol MDI as needed and, if respiratory symptoms were severe and/or persistent, may consider systemic steroids (Class IIb, Level of Evidence B)
- Discharge Criteria:
  - Resolution of symptoms (mild rash may persist)
  - Tolerating PO intake
  - EPINEPHrine autoinjector teaching completed, if indicated (mandatory for anaphylaxis due to food and venom, but optional for drug) and prescription of a 2-pack/kit sent to pharmacy
  - PCP follow-up arranged if indicated
  - Allergist follow-up/referral initiated for anaphylaxis due to food, venom and drug (Note: drug allergy referrals for infusion reactions occurring in CCBD shall be made at the provider's discretion)

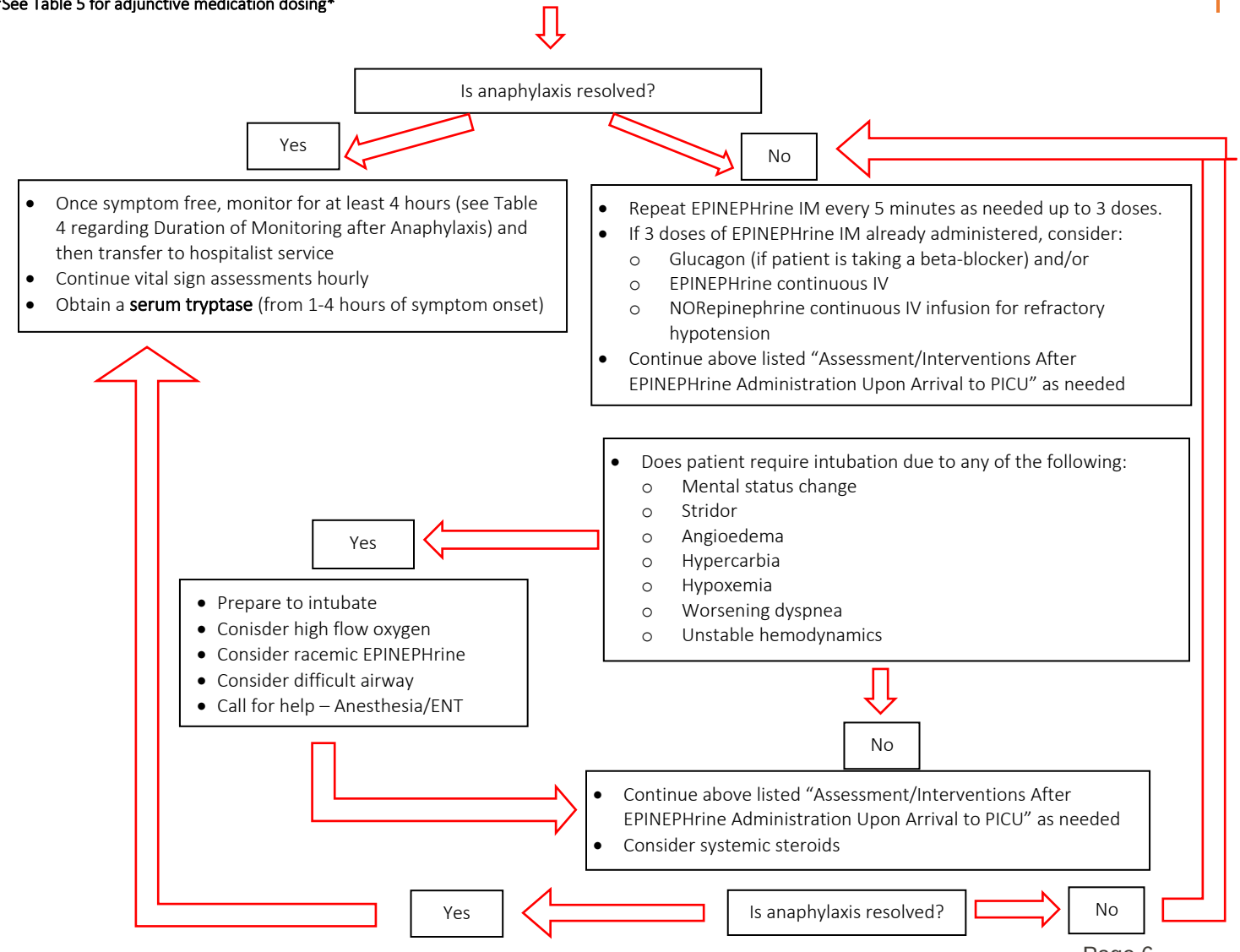
PICU Anaphylaxis Pathway

Assessment/Interventions AFTER EPINEPHrine Administration Upon Arrival to PICU	

Positioning/General	• Place patient in Trendelenburg position. Avoid sudden changes in position.
	• Continuous cardiopulmonary monitoring:
	  ○ Vital (BP, HR, RR) every 5 minutes
	  ○ Skin check every 15 minutes for 1-2 hours
	  ○ Place end tidal monitoring
	  ○ Place second IV if not already done

Cardiovascular	• If MAP < 5% ile, administer crystalloid fluid 20 mL/kg
Respiratory	• Give 10 – 15 L O2 via facemask if sats are < 90% or the patient is in respiratory distress • For shortness of breath, wheezing, dyspnea, and respiratory distress not resolved after EPINEPHrine, give albuterol MDI 8 puffs or NEB • If there is evidence of impending airway obstruction, intubate • For upper airway obstruction, consider racemic EPINEPHrine
Cutaneous	• Consider oral cetirizine (preferred) or IV diphenhydramine for cutaneous manifestations not resolved after EPINEPHrine
Gastrointestinal (GI)	• Consider famotidine for patients with GI manifestations • Consider ondansetron for nausea or vomiting

See Table 5 for adjunctive medication dosing



Inpatient Anaphylaxis Pathway

If the patient meets the diagnostic criteria for anaphylaxis, immediately administer EPINEPHRine IM (see Table 3 for dosing)

Assessment/Interventions AFTER EPINEPHrine Administration	
Positioning/General	• Place patient in Trendelenburg position or, if not feasible, a position of comfort • Obtain vitals and repeat as needed
Cardiovascular	• Consider inserting a peripheral IV (PIV) if not already in place
Respiratory	• Give 10 – 15 L O2 via facemask if sats are < 90% or the patient is in respiratory distress • For shortness of breath, wheezing, dyspnea, and respiratory distress not resolved after EPINEPHrine, give albuterol MDI 4 puffs • If there is evidence of impending airway obstruction, intubate (or call code to aid in such) • For upper airway obstruction, consider racemic EPINEPHrine
Cutaneous	• Consider oral cetirizine (preferred) or IV diphenhydramine for cutaneous manifestations not resolved after EPINEPHrine
Gastrointestinal (GI)	• Consider famotidine for patients with GI manifestations

***See Table 5 for adjunctive medication dosing**

Is the patient responding to EPINEPHrine?

Yes

- Once symptom free, monitor for 1 to 4 hours (see Table 4 regarding Duration of Monitoring after Anaphylaxis).
- Continue vital sign assessments hourly
- Avoid sudden changes in position
- Obtain a **serum tryptase** (from 1-4 hours of symptom onset)

Any return of symptoms?

No

No

- Repeat EPINEPHrine IM every 5 minutes as needed up to 3 doses
- Admit to PICU
- Place a second PIV if time permits
- Continue above listed "Assessment/Interventions After EPINEPHrine Administration" as needed

Yes

- Resume primary medical condition treatment
- Anaphylaxis Discharge Medications:
  - If persistent rash, consider cetirizine or other non-sedating antihistamines daily as needed
  - If initial reaction included wheezing, consider albuterol MDI as needed and, if respiratory symptoms were severe and/or persistent, may consider systemic steroids (Class IIb, Level of Evidence B)
- Anaphylaxis Discharge Criteria:
  - Resolution of symptoms (mild rash may persist)
  - Tolerating PO intake
  - EPINEPHrine autoinjector teaching completed if indicated (mandatory for anaphylaxis due to food and venom, but optional for drug) and prescription of a 2-pack/kit sent to pharmacy
  - PCP follow-up arranged if indicated
  - Allergist follow-up/referral initiated for anaphylaxis due to food, venom and drug (Note: drug allergy referrals for infusion reactions occurring in CCBD shall be made at the provider's discretion)

Scope

Definition: Anaphylaxis is an acute, potentially life-threatening reaction caused by rapid release of mediators from mast cells and basophils that follows the interaction of an allergen with specific, cell-bound IgE antibodies or nonspecific triggers of mast cells. It is a systemic allergic reaction involving one or more body systems. The reaction may affect the skin, upper and lower airways, gastrointestinal tract, cardiovascular system, and/or any combination of these organ systems.

1. Inclusion Criteria – Adults, children, and infants with suspected anaphylaxis
2. Exclusion Criteria – None

Pathway Goals

The goals of this clinical pathway are to improve the recognition of anaphylaxis across the health system and to provide standardized guidance for timely administration of EPINEPHrine and adjunctive medications to all patients who meet the criteria for anaphylaxis.

Key Clinical Recommendations with Evidence Based Supporting Material

Anaphylaxis is an acute, potentially life-threatening reaction. It is a systemic allergic reaction involving one or more body systems.

ETIOLOGY: Any foreign substance (e.g., medication, food, etc.) is capable of eliciting anaphylaxis under appropriate circumstances. Agents commonly associated with anaphylaxis include the following:

- Drugs – e.g., penicillin, cephalosporins, chemotherapy, sulfonamides, anesthetics
- Foods – e.g., egg, shellfish, tree nuts, cow's milk, peanuts, wheat, soy, finfish, sesame
- Insect stings – e.g., hymenoptera, imported fire ants
- Biological agents – e.g., immunoglobulins, insulin, blood products, allergen extracts, vaccines
- Pseudoallergic/non-immunologic – e.g., iodinated radio-contrast media, opiates (except fentanyl), thiamine, aspirin, captopril, D-tubocaraine, vitamins, NSAIDs, muscle relaxants, plasma expanders
- Idiopathic

SYMPTOMS: Symptoms of anaphylaxis by organ system are summarized in Table 2. Symptoms may include the following:

- Generalized flushing
- Urticaria and/or angioedema
- Nasal congestion, sneezing, excessive tearing and/or periorbital swelling
- Pruritus
- Dyspnea, wheezing, inspiratory stridor, paroxysmal cough, hoarseness, cyanosis
- Abdominal cramps, diarrhea, vomiting
- Cardiac arrhythmias (tachycardia, which can be followed by bradycardia)
- Shock, coma, hypotension

DIAGNOSIS: The diagnosis of anaphylaxis is made by history of symptoms, pattern of occurrence, and physical examination. See Table 1. Diagnostic testing, if performed, may include the following:

- Complete Blood Count/differential
- Serum Tryptase level (obtain within 1-4 hours of anaphylaxis onset). An elevated serum tryptase can help providers confirm mast cell degranulation and hence anaphylaxis. This is a send out lab and turnaround time may take several days to a week. Nonetheless, if it returns as elevated, the information is useful to the Allergy/Immunology specialist in follow up review of the reaction history and ultimately, diagnosis of anaphylaxis.

Medication Recommendations

The mainstay of treatment for anaphylaxis is EPINEPHrine. Intramuscular (IM) injection is recommended over subcutaneous (SQ) injection because it results in a more rapid and higher peak plasma concentration. Compared to intravenous (IV) EPINEPHrine, there is less propensity for dosing errors and cardiovascular adverse effects.

Dosing of IM EPINEPHrine (1 mg/mL) is summarized in Table 3. Autoinjectors are typically used with set dosing and where available, are the preferred modality due to: (1) speed at which they can be administered, (2) reduction in errors, including that of wrong dose, wrong route (IV or SQ), and wrong concentration. In clinic settings where only the solution for injection is available, proper equipment should be available for immediate administration. Providers and staff are encouraged to be well versed in drawing up correct doses of EPINEPHrine. Take note that IV EPINEPHrine solution is (1 mg/10 mL) concentration.

Adjunctive medications may be considered, but will not sufficiently treat anaphylaxis. Use of adjunctive medications should not delay EPINIEPHrine administration. Corticosteroids have a slow onset of action (4 – 6 hours) and are therefore not effective in the acute management of anaphylaxis. Giving corticosteroids has not shown to aid in rates of readmission and has overall low level of evidence in anaphylaxis (Class IIb, Level of Evidence B). It may be considered in critically ill patients or those with asthma and/or severe and persistent respiratory symptoms. Adjunctive medications with dosing recommendations are listed in Table 5.

Table 5: Adjunctive Medication Dosing in Anaphylaxis

Medication	Dosing Recommendations
Albuterol	- MDI: 4 inhalations; repeat as needed; up to every 20 minutes - Nebulization: 2.5-5 mg; repeat as needed; up to every 20 minutes or continuously, if needed
Cetirizine	- PO: o <2 years: 2.5 mg once o 2 to 5 years: 2.5-5 mg once o >5 years: 5-10 mg once
Dexamethasone	- PO: IV inj 0.6 mg/kg x 1, max 16mg; Note – only for severe respiratory symptoms requiring albuterol
DiphenhydrAMINE	- IV: 0.5-1 mg/kg/dose, max 50 mg; Note – only to be given when oral cetirizine isn't feasible
EPINEPHrine Infusion	- Continuous Infusion: 0.01-0.2 mcg/kg/min - See Table 3 for IM dosing recommendations
Famotidine	- IV/PO: 1 mg/kg/dose once (max: 20 mg/dose IV; 40 mg/dose PO)
Fluids (crystalloid)	- IV: 20 mL/kg bolus
Glucagon	- IV: 0.02-0.03 mg/kg over 5 min once (max: 1 mg)
Hydrocortisone	- IV: 2mg/kg/dose once (max: 100mg); Note – only for patients with adrenal insufficiency
NORepinephrine Infusion	- Continuous infusion: 0.01-0.2 mcg/kg/min (titrate to effect every 5 mins)
Ondansetron	- IV/IM: 0.15 mg/kg/dose once; max: 8 mg/dose - PO: o <15 kg: 0.2 mg/kg/dose once o 15-30 kg: 4 mg once o >30 kg: 8 mg once
Racemic EPINEPHrine	- Nebulization: 0.05-0.1 mL/kg (max: 0.5 mL) diluted in 2 mL NS; may repeat every 15 to 20 minutes if needed

ED Criteria

As per the Outpatient Pathway, consider calling the Code Team (or 911 if not available) for outpatients with anaphylaxis followed by transfer to the Emergency Department. Exceptions may occur for patients in the Allergy/Immunology Clinic. As per the ED, Urgent Care and Infusion Center pathway, if a 2nd dose of EPINEPHrine is indicated, transfer to ED by EMS or calling a Code Blue.

Discharge Criteria

Factors that may increase the duration of time to monitor after anaphylaxis are summarized in Table 4. Discharge criteria are summarized in the respective pathways, but include:

- Clinical resolution of serious symptoms
- Tolerating PO intake
- Autoinjector teaching completed when indicated (mandatory for food and stinging insect prophylaxis; optional and typically not indicated for drug induced anaphylaxis) with prescription sent to pharmacy
- Allergy/immunology consultation or follow-up order placed (mandatory for food, stinging insect and drug allergy, though drug allergy referrals for infusion reactions occurring in the CCBD shall be made at the provider's discretion)
- PCP follow-up arranged within 72 hours if indicated
- Patients must be warned of potential recurrences of acute episodes several hours after the initial onset and ideally have an epinephrine autoinjector prescribed and filled (or in process) at time of discharge.

Patient and Family Education/Discharge Planning

1. How to Use AUVI-Q® (epinephrine injection, USP)
2. EPIPEN® (epinephrine injection, USP) Auto-Injectors| How to use
3. Kyah Rayne Foundation – information regarding food allergy and anaphylaxis
4. Food Allergies | FDA

References

1. Campbell RL, Li JT, Nicklas RA, Sadosty AT; Members of the Joint Task Force; Practice Parameter Workgroup. Emergency department diagnosis and treatment of anaphylaxis: a practice parameter. Ann Allergy Asthma Immunol. 2014 Dec;113(6):599-608. doi: 10.1016/j.anai.2014.10.007. PMID: 25466802.
2. Turner PJ, Ansotegui IJ, Campbell DE, Cardona V, Carr S, Custovic A, et al. WAO Anaphylaxis Committee and WAO Allergen Immunotherapy Committee. Updated grading system for systemic allergic reactions: Joint Statement of the World Allergy Organization Anaphylaxis Committee and Allergen Immunotherapy Committee. World Allergy Organ J. 2024 Feb 10;17(3):100876. doi: 10.1016/j.waojou.2024.100876. PMID: 38361745; PMCID: PMC10867340.
3. Simons FE, Ardusso LR, Bilò MB, Cardona V, Ebisawa M, El-Gamal YM, et al. International consensus on (ICON) anaphylaxis. World Allergy Organ J. 2014 May 30;7(1):9. doi: 10.1186/1939-4551-7-9. PMID: 24920969; PMCID: PMC4038846.
4. Cardona V, Ansotegui IJ, Ebisawa M, El-Gamal Y, Fernandez Rivas M, Fineman S, et al. World allergy organization anaphylaxis guidance 2020. World Allergy Organ J. 2020 Oct 30;13(10):100472. doi: 10.1016/j.waojou.2020.100472. PMID: 33204386; PMCID: PMC7607509.

5. Golden DBK, Wang J, Waserman S, Akin C, Campbell RL, Ellis AK, et al. Anaphylaxis: A 2023 practice parameter update. Ann Allergy Asthma Immunol. 2024 Feb;132(2):124-176. doi: 10.1016/j.anai.2023.09.015. Epub 2023 Dec 18. PMID: 38108678.
6. Muraro A, Worm M, Alviani C, et al. EAACI guidelines: Anaphylaxis (2021 update). Allergy 2022; 77:357.
7. Cox L, Larenas-Linnemann D, Lockey RF, et al. The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System. J Allergy Clin Immunol 2010;125:569-574.
8. Sicherer SH, Simons FER; SECTION ON ALLERGY AND IMMUNOLOGY. Epinephrine for First-aid Management of Anaphylaxis. Pediatrics. 2017 Mar;139(3):e20164006. doi: 10.1542/peds.2016-4006. Epub 2017 Feb 13. PMID: 28193791.
9. Chime NO, Riese VG, Scherzer DJ, et al. Epinephrine Auto-Injector versus Drawn up Epinephrine for Anaphylaxis Management: A Scoping Review*. Pediatric Critical Care Medicine. 2017;18(8):764-769. doi:10.1097/pcc.0000000000001197.
10. Kim TH, Yoon SH, Hong H, Kang HR, Cho SH, Lee SY. Duration of observation for detecting a biphasic reaction in anaphylaxis: a meta-analysis. IntArchAllergyImmunol. 2019;179(1):31–36.41.
11. Pourmand A, Robinson C, Syed W, Mazer-Amirshahi M. Biphasic anaphylaxis: A review of the literature and implications for emergency management. Am J Emerg Med. 2018 Aug;36(8):1480-1485. doi: 10.1016/j.ajem.2018.05.009. Epub 2018 May 9. PMID: 29759531.

Pathway Champions & Committee Approvals

Allergy and Immunology: Cindy Salm Bauer, MD; Ifat Zerin Krase, MD, PharmD
Hospitalist Medicine: Tim Raghib, MD; Mahesh Kafle, MD
Emergency Medicine: Cherisse Mecham, MD; Kaleena Patel, MD
CCBD: Alexandra Walsh, MD
PICU: Sreya Devabhaktuni, MD; Elizabeth Zorn, MD

P&T – Approved Dec 2024
CEC – Approved Feb 2025