# Anaphylaxis

Chapter 364 | Part 11: Immune-Mediated, Inflammatory, and Rheumatologic Disorders

### KEY CLINICAL POINTS

1. Anaphylaxis is a potentially life-threatening systemic allergic reaction involving one or more organ systems, typically occurring within seconds to minutes of exposure to triggers like drugs, food, or Hymenoptera stings.
2. Approximately 80–90% of episodes are uniphasic; 10–20% are biphasic (symptoms recur ≥ 1 hour after initial resolution).
3. First-line treatment is intramuscular (IM) epinephrine (0.3–0.5 mL of 1:1000), repeated at 5- to 20-minute intervals as needed.
4. Serum tryptase peaks 60–90 min after onset and remains measurable for up to 5 hours; a level ≥ 20% above baseline + 2 ng/mL confirms significant mast cell activation.
5. Non-IgE-mediated reactions can occur via MRGPRX2 (e.g., NMBDs, quinolones) or complement activation (e.g., paclitaxel/Cremophor, heparin/OSCS).
6. Alpha-gal syndrome causes delayed anaphylaxis (3–6 h) after consuming mammalian meat (beef, lamb, pork) in patients with anti-alpha-gal IgE.
7. Preexisting asthma and cardiovascular disease are major risk factors for rapid decompensation and increased mortality.
8. Scombroid poisoning mimics anaphylaxis but is distinguished by a lack of tryptase elevation and negative skin tests; it results from histamine accumulation in fish.
9. Beta-blockers may attenuate the response to epinephrine; alternative antihypertensives should be considered in high-risk patients.
10. Hereditary alpha-tryptasemia (HAT) is a common, mostly benign condition with elevated baseline tryptase that can complicate the interpretation of anaphylactic events.

## 1. DEFINITION & OVERVIEW

- **Definition:** Anaphylaxis is a potentially life-threatening systemic allergic reaction involving one or more organ systems that typically occurs within seconds to minutes of exposure to the anaphylactic trigger (most commonly drug, food, or Hymenoptera sting).
- **Clinical Course:**
  - **Uniphasic:** 80–90% of cases.
  - **Biphasic:** 10–20% of cases → symptoms return ≥ 1 hour after resolution of initial symptoms.
- **Critical Risks:** Reactions are particularly dangerous when hypotension or hypoxia occurs, potentially leading to cardiovascular collapse or respiratory failure.

### 1.1 Clinical Presentation

- **Upper Airway:** Laryngeal edema may present as a 'lump' in the throat, hoarseness, or stridor.
- **Lower Airway:** Bronchial obstruction is associated with chest tightness and/or audible wheezing.

• **Asthma Link:** Patients with underlying asthma are predisposed to severe lower airway involvement and increased mortality.

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# 2. EPIDEMIOLOGY

• **Predisposing Factors:**

– **Asthma & Cardiovascular Disease:** Lead to rapid decompensation.

– **Atopy:** Not a general risk factor for drug or Hymenoptera anaphylaxis; however, it is associated with radiocontrast sensitivity, exercise-induced anaphylaxis, idiopathic anaphylaxis, food allergy, and latex allergy.

– **Mastocytosis:** Significant risk for severe Hymenoptera-induced anaphylaxis (prominent hypotension). Baseline tryptase should be checked in these patients.

– **Occupational Exposure:** Higher incidence in beekeepers, trash haulers, and landscape workers.

## 2.1 Drug-Related Incidence

• **Carboplatin:**

– ≥ 7 lifetime infusions → 27% hypersensitivity.

– ≥ 15 lifetime infusions → 46% hypersensitivity.

– **Cystic Fibrosis:** High incidence of allergic reactions to IV antibiotics (especially beta-lactams) during periodic 'clean-outs'.

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# 3. ETIOLOGY & PATHOPHYSIOLOGY

• **Mast Cell Mediators:**

– **Preformed Granules:** Histamine, proteases (tryptase, chymase), proteoglycans (heparin, chondroitin sulfate), and TNF-α.

– **Histamine Effects:** Flushing, urticaria, pruritus; high concentrations → hypotension and tachycardia.

– **Leukotrienes & Prostaglandins:**

– Cysteinyl leukotrienes and Prostaglandin D → bronchoconstriction and increased microvascular permeability.

– Prostaglandin D → cutaneous flushing, recruits eosinophils/basophils.

– **Tryptase & Chymase:** Activate complement and coagulation pathways → production of anaphylatoxins (C3a, C5a) and activation of the kallikrein-kinin system.

– **Platelet-Activating Factor (PAF):** Serum levels correlate with severity; inversely proportional to constitutive PAF acetylhydrolase.

## 3.1 Non-IgE Mechanisms

• **MRGPRX2 Activation:** G protein–coupled receptor on skin mast cells → activation by NMBDs, quinolones, and icatibant.

– **Complement Activation:**

– **Paclitaxel:** Solubilized by Cremophor → complement-dependent histamine release.

→ **Abraxane** (albumin-bound) has a lower rate of hypersensitivity.

– **Heparin:** Contamination with oversulfated chondroitin sulfate (OSCS) → activates contact activation system → bradykinin and anaphylatoxins (C3a, C5a).

– **Scombroid Poisoning:**

– Cause: Histine-rich fish (mahi-mahi, mackerel, tuna) + bacteria → histamine.

– Characteristics: Symptoms include flushing, pruritus, nausea; **Tryptase not elevated**; negative skin test.

– **Other Non-IgE:** Radiocontrast, opiates, vancomycin, and NSAIDs.

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# 4. CLINICAL FEATURES

• **Cutaneous Manifestations:** >90% of cases; urticarial eruptions (intensely pruritic), flushing, and diffuse erythema.

– **Duration:** Urticarial plaques seldom persist > 48 h.

– **Histopathology:** Wide separation of collagen fibers/glandular elements; vascular congestion and eosinophilic infiltration.

## 4.1 Respiratory & Cardiovascular

• **Respiratory:**

– Laryngeal edema → 'lump' in throat, hoarseness, or stridor.

– Bronchial obstruction → chest tightness and audible wheezing.

– Fatal cases with bronchial obstruction show marked hyperinflation on gross/microscopic exam.

– **Cardiovascular:**

– Hypotension or hypoxia → cardiovascular collapse or respiratory failure.

– Vascular collapse without prior hypoxia may involve visceral congestion and loss of intravascular volume.

## 4.2 Gastrointestinal Manifestations

• **Symptoms:** Nausea, vomiting, crampy abdominal pain, fecal incontinence.

– **Mechanism:** Angioedema of the bowel wall → intravascular volume depletion → cardiovascular collapse.

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# 5. DIFFERENTIAL DIAGNOSIS

• **Key Distinctions (Table 364-1):**

– **Mastocytosis:** Elevated baseline tryptase, spindle-shaped mast cells (MCs) on bone marrow.

– **Pheochromocytoma:** [No specific marker provided in source]

– **Carcinoid syndrome:** [No specific marker provided in source]

– **Hereditary angioedema:** [No specific marker provided in source]

– **Acquired angioedema:** Decreased C1q.

– **Systemic capillary leak syndrome:** [No specific marker provided in source]

– **Scombroid poisoning:** Tryptase not elevated; negative skin test and oral challenge to fish.

– **Drug-specific (opiates, NMBDs, vancomycin):** Direct mast cell degranulation via MRGPRX2.

– **Radiocontrast:** Unknown mechanism.

## 5.1 Diagnostic Strategy

• **Identification:** Attempt to identify specific cause to minimize recurrence risk.

– **Confirmation:** Use skin or serum-specific IgE testing for suspected drugs/foods.

– **Broad Workup:** If trigger unknown, evaluate underlying atopic diatheses.

## 6. INVESTIGATIONS & DIAGNOSIS

1. **Clinical Assessment:** Identify symptoms (urticaria, hypotension) occurring within seconds to minutes of exposure.
   – Exception: Alpha-gal syndrome → delayed onset (3–6 h).
2. **Biomarker Collection:** Measure serum tryptase in acute setting.
   – Timing: Peak 60–90 min; measurable for up to 5 hours post-onset.
3. **Interpretation of Tryptase:**
   – Rule: "20% + 2" rule.
   – Calculation: Current value ≥ (Patient Baseline + 20%) + 2 ng/mL → Diagnosis of significant mast cell activation.
4. **Baseline Establishment:** Follow up with a second measurement when stable to establish baseline serum tryptase (BST) for future comparison.

## 7. MANAGEMENT & TREATMENT

1. **First-Line Therapy:**
   – Action: Intramuscular (IM) epinephrine.
   – Dose: 0.3–0.5 mL of 1:1000.
   – Frequency: Repeat every 5–20 minutes as needed for severe reaction.
   – Timing: Failure to use within first 20 min → risk factor for poor outcome.
   – Mechanism: α- and β-adrenergic effects → vasoconstriction, bronchial relaxation, reduced permeability.
2. **Supportive Care:**
   – **Hypotension:** IV fluids and vasopressor agents.
   – **Respiratory Distress:** Oxygen via nasal catheter or nebulized albuterol.
   – **Critical Airway:** Endotracheal intubation or tracheostomy if progressive hypoxia develops.
3. **Adjunctive Therapies (Post-Stabilization):**
   – Antihistamines, glucocorticoids, and bronchodilators for urticaria/angioedema and bronchospasm.
4. **Beta-Blocker Management:**
   – Note: Beta-blockers may attenuate the response to epinephrine; use alternative antihypertensives in patients at high risk of needing emergency epinephrine.

## 8. PROGNOSIS & COMPLICATIONS

- **Biphasic Reaction:** 10–20% of cases → symptoms return ≥ 1 hour after resolution.
  – Risk: Particularly dangerous when hypotension or hypoxia is present.
  – Outcome: Potential for cardiovascular collapse or respiratory failure.
  – **Mortality Factors:**
  – Presence of underlying asthma (severe lower airway involvement).
  – Clinical bronchial obstruction (marked hyperinflation on imaging/gross exam).
  – Vascular collapse without preceding hypoxia → visceral congestion and volume loss.

## 9. SPECIAL CONSIDERATIONS

- **Alpha-Gal Syndrome:** Delayed anaphylaxis (3–6 h) to mammalian meat; associated with anti-alpha-gal IgE.
  - **Drug-Specific Risks:**
  - Carboplatin: High incidence of hypersensitivity in multiple infusions.
  - Cystic Fibrosis: High risk for beta-lactam reactions during airway clear-outs.
  - **Non-IgE Drug Reactions:** Radiocontrast, opiates, vancomycin, and NSAIDs.
  - **Occupational Risk:** Higher incidence of Hymenoptera allergy in beekeepers, trash haulers, and landscape workers.

## 10. KEY PEARLS & CLINICAL TRAPS

- **Tryptase Rule:** Use the "20% + 2" rule to distinguish significant mast cell activation from high baseline tryptase (e.g., in HAT).
  - **HAT:** ~6% of Western population; benign but can be a risk factor for severe anaphylaxis.
  - **Scombroid Distinction:** Tryptase is NOT elevated in scombroid poisoning because the source of histamine is exogenous.
  - **Epinephrine Timing:** Delay > 20 minutes in administering epinephrine is linked to poorer outcomes.
  - **Beta-Blocker Interaction:** Be aware that beta-blockers can blunt the effect of epinephrine; plan for alternative antihypertensives if needed.

REFERENCE TABLES

TABLE 364-1

**Differential Diagnoses for IgE-Mediated Anaphylaxis CONDITION Mastocytosis Pheochromocytoma Carcinoid syndrome...**

| CONDITION | DISTINGUISHED BY |
|---|---|
| **Mastocytosis** | Elevated baseline tryptase, spindle-shaped mast cells (MCs) on bone marrow |
| **Carcinoid syndrome** | Elevated urine 5-hydroxyindoleacetic acid |
| **Acquired angioedema** | Decreased C1q |
| **Scombroid poisoning** | Tryptase not elevated; negative skin test and oral challenge to fish |