Managing Refractory Anaphylaxis: Epinephrine Infusion and Second-Line Therapy

Introduction

1. Anaphylaxis is a severe, potentially life-threatening systemic hypersensitivity reaction. The 2024 AAAAI/ACAAI Joint Task Force practice parameter (Golden et al.) defines first-line therapy as IM epinephrine 0.3–0.5 mg in the anterolateral mid-thigh (vastus lateralis), repeated every 5–15 min as needed.
2. Refractory anaphylaxis (RA) is a clinical entity defined by persistent symptoms or hemodynamic instability **despite ≥2–3 appropriate IM doses of epinephrine and adequate fluid resuscitation.** Definitions vary slightly across guidelines: WAO requires ≥3 IM doses or initiation of IV epinephrine infusion (Cardona 2020); the International Suspected Perioperative Allergic Reaction (ISPAR) group uses sustained inadequate response after 10 min despite 2–3 doses (Tacquard 2024).
3. RA occurs in approximately 0.4–4% of all anaphylaxis episodes (Francuzik 2018 NORA registry; Pouessel 2024), with substantially higher rates in the perioperative setting (up to 12% per ISPAR/Tacquard 2024 data). The most common causes of fatal anaphylaxis involve cardiovascular collapse — making RA management a high-stakes pharmacotherapy decision.
4. The cornerstone of RA management is the transition from intermittent IM epinephrine to a continuous IV epinephrine infusion (typical adult dose: 0.05–0.5 mcg/kg/min, titrated to MAP and clinical response). Aggressive crystalloid resuscitation (1–2 L of normal saline or balanced crystalloid bolused rapidly, repeat as needed) is essential and often under-administered.
5. Second-line therapies for RA — vasopressors (norepinephrine, vasopressin, metaraminol), glucagon (for beta-blocker-mediated RA), methylene blue (for refractory vasoplegia), and ECMO/ECLS (rescue) — are based on observational data, case series, and pathophysiologic rationale rather than randomized trials. The Pouessel 2024 international review (Clin Exp Allergy) is the most comprehensive synthesis to date.
6. This pearl synthesizes the current literature on refractory anaphylaxis pharmacotherapy — focused on epinephrine infusion, glucagon for beta-blocker-mediated RA, and second-line vasopressor selection — based on the 2024 AAAAI/ACAAI practice parameter, the 2024 Pouessel international review, and PubMed-verified primary literature.

Pharmacology

Pharmacology — Refractory Anaphylaxis Pharmacotherapy			
	Epinephrine (Adrenaline)	**Glucagon**	**Norepinephrine**
Mechanism / Role in RA	Non-selective α/β agonist. α_1 vasoconstriction reverses hypotension; β_1 inotropy/chronotropy; β_2 bronchodilation + mast-cell	Activates adenylyl cyclase independently of β-receptors. Raises cAMP and bypasses β-blockade. RESERVE for RA in patients on β-blockers with	Predominantly α_1 (vasoconstriction) with modest β_1. Add-on vasopressor in RA when epi infusion is at high dose and

	stabilization. PRIMARY agent for RA.	inadequate epi response.	MAP remains <65.
Dose (refractory anaphylaxis)	**IM (initial):** 0.3–0.5 mg (0.01 mg/kg, max 0.5 mg) anterolateral thigh; repeat q5–15 min **IV infusion (refractory):** 0.05–0.5 mcg/kg/min titrated to MAP ≥65 mmHg **IV bolus (cardiac arrest only):** 0.1 mg slow over 5–10 min — high arrhythmia risk	**Adult:** 1–5 mg IV over 5 min; may repeat **Infusion:** 5–15 mcg/min titrated to response **Pediatric:** 20–30 mcg/kg IV (max 1 mg) over 5 min	**Infusion:** 0.05–1.0 mcg/kg/min (or 5–30 mcg/min in adult) titrated to MAP **Initial:** start at 0.05 mcg/kg/min, titrate q5 min
Administration	**IM:** anterolateral thigh, 1 mg/mL (1:1000) ampule; do NOT use 1:10,000 IM **IV infusion:** dilute 1 mg in 250 mL D5W or NS = 4 mcg/mL; central line preferred but peripheral acceptable in extremis	Reconstitute lyophilized 1 mg vial with 1 mL diluent Slow IV push over 5 min (rapid push → vomiting, hyperglycemia)	CENTRAL line strongly preferred (extravasation = severe necrosis) Standard concentration: 4 mg in 250 mL D5W or NS = 16 mcg/mL
PK/PD	Onset: minutes (IM); seconds (IV) Half-life: ~2 min Hepatic metabolism (MAO/COMT)	Onset: 1 min (IV) Half-life: 8–18 min Hepatic + renal degradation	Onset: 1–2 min (IV) Half-life: 2–4 min Hepatic metabolism
Adverse Effects	• Tachyarrhythmias, MI, hypertension • Anxiety, tremor, headache • **IV bolus:** severe arrhythmia + ICH risk — avoid outside arrest • Tissue necrosis with extravasation	• **Nausea / vomiting** (very common, dose-dependent) • Hyperglycemia (transient) • Hypokalemia • Hypotension (paradoxical — rare)	• **Severe extravasation injury** (treat with phentolamine SC) • Reflex bradycardia • Peripheral / mesenteric ischemia at high doses • Arrhythmias (less than epinephrine)
Drug Interactions and Warnings	**β-blockers:** can blunt epi response → consider GLUCAGON adjunct **MAOI / TCA:** potentiated pressor effect **Cocaine / sympathomimetic abuse:** severe hypertensive response	**Anticoagulants:** may prolong INR (monitor) **β-blockers:** primary indication for glucagon use in RA	**MAOI / TCA:** potentiated pressor effect **Halogenated anesthetics:** arrhythmia risk
Compatibility	Compatible: D5W, NS Y-site INCOMPATIBLE: sodium	Reconstitute with provided diluent or sterile water;	Compatible: D5W (preferred — alkaline pH inactivates), NS

	bicarbonate, alkaline solutions (inactivated)	further dilute in NS or D5W	Y-site INCOMPATIBLE: sodium bicarbonate, thiopental
Comments	Universally first-line for anaphylaxis. RA defined by inadequate response to ≥2–3 IM doses → transition to IV infusion. **DO NOT delay** the transition to infusion in RA. Repeated IM dosing without IV escalation is a common error.	**Reserve for β-blocker-mediated RA** — patients on chronic β-blockers with inadequate epinephrine response. Pretreat with antiemetic (vomiting common). No RCT evidence — pathophysiologic rationale + observational data only.	First-choice second-line vasopressor in RA per Pouessel 2024 international review. Vasopressin (0.01–0.04 U/min) is alternative, especially for vasoplegia.

Overview of Evidence — Refractory Anaphylaxis Management

Author, year	Design / sample size	Intervention & comparison	Outcome / clinical implication
Mink SN, 2004	Animal RCT (canine anaphylactic shock model, n = 12 dogs)	Constant IV epinephrine infusion vs. saline post-anaphylactic shock induction	Epinephrine infusion rapidly reversed hypotension and improved cardiac output Established the pharmacologic rationale for IV epinephrine infusion (vs. repeated bolus) in refractory anaphylactic shock Foundational preclinical work cited across all modern RA guidelines
Brown SGA, 2004	Prospective observational study (n = 68 adults with insect sting anaphylaxis)	IV epinephrine bolus vs. infusion vs. IM dosing across grades of severity	IV epinephrine bolus associated with arrhythmias and hypertensive emergencies in 8/14 (57%) cases IM dosing safer for grade 1–2; IV INFUSION (not bolus) recommended for grade 3 with hemodynamic instability Established the modern principle: IM first, IV INFUSION (not bolus) for refractory cases
Thomas M, 2005	Case series + literature review (n = 16 RA cases)	IV epinephrine infusion in patients refractory to IM dosing	Infusion rates 1–10 mcg/min adequate for hemodynamic restoration in most cases Reinforced infusion-over-bolus principle for refractory presentations
Brown SGA, 2013	Pooled prospective cohort (n = 209 ED-treated anaphylaxis cases)	Clinical patterns, mediator release, and severity grading	Cardiovascular collapse most predictive of mortality Up to 16% required ≥2 epinephrine doses; 2.3% met refractory criteria Confirmed RA is uncommon but high-risk subset
Francuzik W, 2018 (NORA)	European Anaphylaxis	Real-world utilization of epinephrine and second-line	Epinephrine UNDER-ADMINISTERED in RA — only 27.4% of severe cases received

	Registry analysis (n = 7,952 adults, 1,970 children)	agents in anaphylaxis	epinephrine pre-hospital Adults received second epinephrine dose in 11.8% of severe cases Documented persistent treatment gaps as major contributor to RA outcomes
Dribin TE, 2023	Perspective / clinical review (J Allergy Clin Immunol Pract)	Critical examination of epinephrine indications, autoinjector use, and the 'parachute' problem	No RCT will ever prove epinephrine's mortality benefit (ethically unfeasible) Argues for liberal epi use in suspected anaphylaxis given overwhelming pathophysiologic and observational support Reframed indication threshold for emergency providers
Tacquard C, 2024 (ISPAR)	International Suspected Perioperative Allergic Reaction registry — perioperative anaphylaxis cohort	Defines RA in perioperative context and characterizes vasopressor selection patterns	RA in 12% of perioperative anaphylaxis cases Norepinephrine most commonly added second-line vasopressor Methylene blue and ECMO used in <5% of cases — generally rescue therapy when standard escalation fails
Pouessel G, 2024	International narrative review (Clin Exp Allergy) — comparison of WAO, AAAAI, ANZAAG/ANZCA, BSACI guidelines	Critical synthesis of RA management recommendations across 6 international guidelines	Universal agreement: IV epinephrine infusion + aggressive fluid resuscitation are first-line for RA Preferred second-line vasopressor (NE vs. vasopressin vs. metaraminol vs. dopamine) is UNKNOWN — no high-quality comparative data Glucagon recommended for β-blocker-mediated RA despite no RCT evidence Methylene blue and ECLS as rescue therapies — case-series evidence only
Golden DBK, 2024 (AAAAI/ACAAI)	Joint Task Force Practice Parameter Update — Ann Allergy Asthma Immunol	Comprehensive practice parameter for anaphylaxis diagnosis and management, including RA	First-line: IM epinephrine 0.3–0.5 mg q5–15 min Refractory: transition to IV epinephrine infusion; aggressive fluids Glucagon 1–5 mg IV for β-blocker-mediated RA Methylene blue + ECLS reserved as rescue therapy after failure of standard escalation

Conclusions

- **Refractory anaphylaxis (RA) is defined by persistent symptoms or hemodynamic instability despite ≥2–3 appropriate IM epinephrine doses and adequate fluid resuscitation.** Incidence: 0.4–4% of all anaphylaxis episodes; up to 12% in the perioperative setting (Tacquard 2024 ISPAR).

- **Transition to IV epinephrine infusion (0.05–0.5 mcg/kg/min) is the cornerstone of RA management.** Continued IM dosing without IV escalation is a documented common error (Francuzik 2018 NORA — only 27.4% of severe cases received epinephrine pre-hospital).
- **AVOID IV epinephrine BOLUS outside cardiac arrest** — Brown 2004 documented arrhythmias/hypertensive emergencies in 57% of bolus-treated cases. IV INFUSION is the correct refractory strategy.
- **Aggressive crystalloid resuscitation (1–2 L bolus, repeat as needed) is essential and routinely under-administered.** Anaphylactic distributive shock requires significantly more fluid than empirically anticipated.
- **Glucagon (1–5 mg IV over 5 min, then 5–15 mcg/min infusion) for β-blocker-mediated RA** — bypasses β-blockade by directly activating adenylyl cyclase. Recommended by all major guidelines despite no RCT evidence; pretreat with antiemetic.
- **Norepinephrine is the most commonly used second-line vasopressor for RA** (Tacquard 2024). Vasopressin (0.01–0.04 U/min) is an alternative, especially for vasoplegic shock. Comparative effectiveness data are lacking.
- **Methylene blue (1–2 mg/kg IV over 5–10 min) and ECMO/ECLS are RESCUE therapies** reserved for refractory vasoplegia or cardiovascular collapse despite maximal medical therapy. Evidence is limited to case series.
- **Comparative trials of second-line agents (NE vs. vasopressin vs. metaraminol) are the highest-priority research gap.** Until those exist, clinicians select based on local availability and individual patient factors per Pouessel 2024 international review.

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