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In affiliation with the Pacific Rim Association for Clinical Pharmacogenetics (PRACP)

Using Pharmacogenomics to Improve Drug Safety and Efficacy

Preventing and Managing Drug Induced Anaphylactic Shock

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Preventing/managing drug induced anaphylaxis

Depend on a good understanding of the pathophysiology of anaphylaxis, subjects at risk, drugs involved, usual and usual presentation, prospects for prevention, management approach and reasons for continuing morbidity/mortality

- Case reports – avoidable, unusual, fulminant
- Causes and intrinsic/extrinsic risk factors for anaphylaxis
- Mechanisms, clinical features and grading of anaphylaxis
- Management approach – adrenaline as the first-line drug
- Strategies – prevention, recognition and management

Drug-induced anaphylaxis should be avoidable

M/55, allergic rhinitis, asthma, known allergy to aspirin and ibuprofen for ~8 years

Took diclofenac 100 mg (own stock) for left knee pain

Sudden onset of SOB, wheeze and flushing 3 h later

Arrived in ED 40 min after onset of symptoms
BP 142/86 mmHg, pulse 104 bpm, RR 32 breaths/min
SaO_2 95% (O_2 4 L/min), diffuse rhonchi

Adrenaline (1:1000) 0.5 ml i.m.
Hydrocortisone 200 mg i.v., chlorpheniramine 10 mg i.v.
Salbutamol and ipratropium MDI

Home after staying in EMW for 12 hours

Drug-induced anaphylaxis could have been missed

F/55, found collapsed in shopping mall, GCS 3, pupils 3 mm, ambulance arrived in 10 min, spontaneous breathing but cyanosed, bagging (SaO_2 30→85%)

Intubated in A&E, BP 179/98 mmHg, pulse 119 bpm, SaO_2 99%, 4 limb movements, rhonchi, salbutamol/ipratropium

Woke up 1.5 h and extubated 2 h after ICU admission, acute onset of SOB before LOC 1 h after taking levofloxacin 1 tab for toothache, vomited once

Stayed in ICU for 25.5 h and in ward for 2 days

↑ cardiac troponin 79.5 ng/L (<14), ↑ ALT 100 IU/L (<55), ↑ WBC 12.3 x 10^9/L (<9.7), ECG normal

On discharge, BP 118/70 mmHg

Drug-induced anaphylaxis could be rapidly fatal

M/51, IVU as out-patient, iopamidol (water-soluble non-ionic, monomeric, iodinated radiocontrast medium)

After the injection, vomiting, LOC and pulseless, CPR started, pulseless electrical activity on ECG

Adrenaline 1 mg i.v., fluids i.v. ⇒ orientated, SBP ~140 mmHg, chest pain, ST ↓ on ECG, faecal incontinence, very red appearance (vasodilation)

Cardiac arrest, LOC, CPR started, adrenaline 1 mg iv, narrow complex rhythm, asystole or VF on ECG, DC shock given, failed resuscitation

Autopsy ⇒ epiglottis swelling, pulmonary congestion, coronary atherosclerosis and cardiomegaly

What is anaphylaxis

An acute, potentially life-threatening hypersensitivity reaction, involving the release of mediators (e.g. histamine) from tissue mast cells, circulating basophils, recruited inflammatory cells

Multisystem signs and symptoms occurring within minutes or up to a few hours, after exposure to provoking agents – severe allergic reactions with CVS and/or RS features

Can be mild, moderate to severe or severe

Developing rapidly, usually reaching peak severity within 5-30 minutes, and may, rarely, last for several days

3-23% of episodes followed by biphasic reactions hours later

(Adapted from: Lockey RF 2004 and Confino-Cohen R et al. 2010)

What is anaphylactic shock

Anaphylaxis accompanied by hypotension (SBP >30% ↓ from baseline or <90 mmHg in adults)

Rarely, patients present with isolated acute hypotension

The main cardiovascular changes during anaphylaxis = fluid extravasation and vasodilation (causing a mixed distributive–hypovolaemic shock) plus ↓ myocardial contractivity

Blood volume may decrease by up to 35% within 10 minutes due to extravasation; severe vasodilation may only respond to potent vasoconstrictors

Risk factors for shock in anaphylaxis – old age, anti-HT drugs

(Brown SGA. Immunol Allergy Clin N Am 2007; 27: 165-75)
(Lee S et al. J Allergy Clin Immunol 2013; 131: 1103-8)

Causes of anaphylaxis – Hong Kong

Common causes differ between children (foods) and adults (drugs)

282 patients (166M, 116F) aged 1-91 years (median 28) with anaphylaxis, Prince of Wales Hospital ED, 3/1999 to 2/2003

A precipitant identified in 89%, with 19% of patients claiming a known allergy to the precipitant

Foods = 49.6% of cases (seafoods – 71%)

Drugs = 40.5% of cases (NSAIDs/aspirin – 25.5%, antibiotics – 23.5%, Chinese medicines – 21.6%)

Insect bites/stings = 7.1%

Plants/hair dye = 1.6%, gas inhalation = 0.4%, idiopathic = 0.8%

(Smit DV et al. J Emerg Med 2005; 28: 381-8)

Drugs causing anaphylaxis – Europe

National Pharmacovigilance System, Portugal

1/2000-10/2010, 918 anaphylaxis cases (6% of ADR reports)

Age 7 days-91 years, mean 48 years, 9% ≤18 years

F = 70% of adults, M = 56% of paediatric population

Antibiotics (17%), NSAIDs/paracetamol (13%), cytotoxic drugs (12%), immune-modulators (9%), vaccines (7%) and radiocontrast media (4 %)

19% led to hospitalisation, 24 (3%) had a fatal outcome

Anaphylaxis can occur at any age and is mostly caused by widely used drugs (e.g. antibiotics and analgesics)

(Ribeiro-Vaz I et al. Eur J Clin Pharmacol 2013; 69: 673-81)

Intrinsic risk factors for anaphylaxis

- Previous history of anaphylaxis – however, at least 25% of adults and 65% of children with anaphylaxis do not report a previous episode
- Atopy – orally administered drugs, radiocontrast media, latex, exercise, idiopathic anaphylaxis
- Female gender – aspirin, muscle relaxants, diagnostic agents, idiopathic anaphylaxis
- Increased socio-economic status
- ↓ vitamin D level (sunlight exposure) – a strong north-south gradient in the US for EpiPens prescriptions

(Lee JK et al. Clin Exp Allergy 2011; 41: 932-8; Ben-Shoshan M et al. Allergy 2011; 66: 1-14)

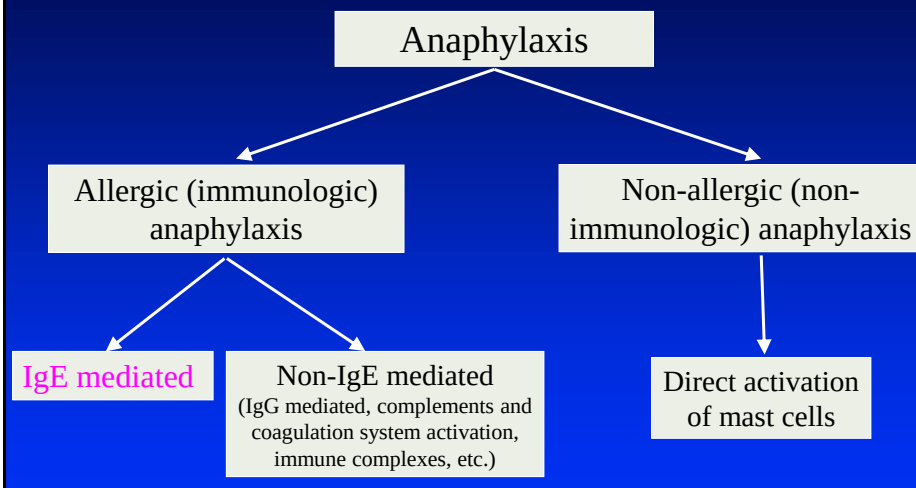
Genes implicated in the pathogenesis of anaphylaxis

Group	Name of gene	Comments
Anatomic barrier genes	Filaggrin	Increased risk of developing allergic sensitisation and not necessarily anaphylaxis
Innate immunity genes	NLRP3: SNPs (rs4612666 and rs10754558)	Significantly associated with susceptibility to food-induced anaphylaxis
Innate immunity and mast cells genes	C-KIT	Mutations associated with anaphylaxis after hymenoptera stings and may also underlie cases of idiopathic anaphylaxis
	SWAP-70	Anaphylactic responses are strongly reduced in mice with mutations in this gene
	PAF V279F (>30% of Japanese subjects)	Mutations increase the risk for various inflammatory diseases in Japanese subjects PAF and PAF-AH activity affect severity of anaphylaxis
	Sphk1	Sphingosine 1-phosphate receptors play a critical role in regulating human mast cell functions, including degranulation and cytokine and chemokine release
	Rcan	Rcan1 is a novel negative regulator in FcεRI-induced mast cell activation
	CCRL2	Enhance tissue swelling and leucocyte infiltrates
Adaptive immunity	STAT-6 (13/15-GT repeat heterozygosity and the 15GT repeat homozygosity)	Polymorphisms higher in children in Japanese population with allergic disease
	IL-4 (Ile75Val variant of IL-4Rα gene)	Polymorphisms of IL-4 have been implicated in drug allergy especially in women
	IL-10 (-819 C>T and -592 C>A variants)	Polymorphisms of IL-10 promoter associated with β-lactam anaphylactic reactions
	IL-13, 18 (promoter polymorphisms in IL13-1055, IL18-607 and IL18-656)	Latex allergy phenotype significantly associated with polymorphism in the promoter site of these cytokines
Unknown function	DOCK8	Absence of DOCK8 protein associated with severe atopy and anaphylaxis

Adapted from: Ben-Shoshan M al el. Allergy 2011; 66: 1-14

Mechanisms of anaphylaxis

Most cases are IgE mediated, but it is not possible to distinguish IgE from non-IgE cases



Excessive amounts of IgE are produced during sensitisation. Specific IgE binds to high affinity IgE receptors (FcεRI) on mast cells and basophils. Re-exposure to allergen leads to cross-linking of receptor-bound IgE, triggering cell activation and release of mediators.

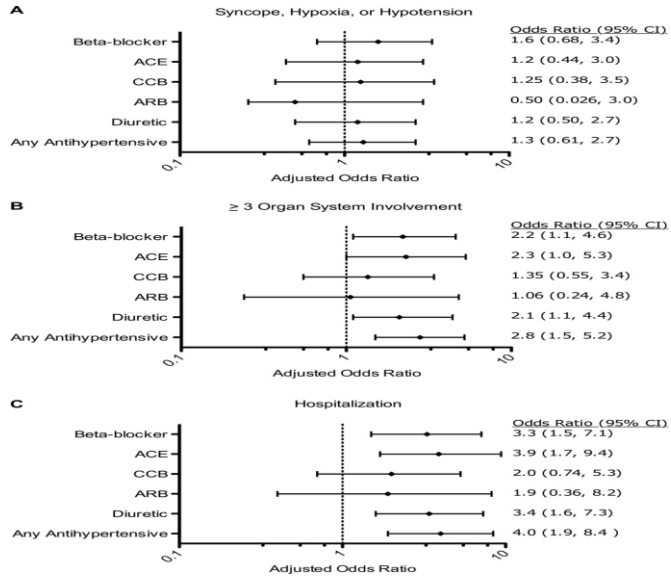
Mediators of anaphylaxis	Known/possible effects – the lungs and the heart are the major shock organs
Preformed for immediate release	
Histamine	Vasodilation and oedema, bronchoconstriction, mucus secretion, nerve stimulation, ↓ myocardial contractility (H_1 receptor), ↑ myocardial contractility (H_2 receptor)
Heparin	Anticoagulant, anti-inflammatory, mediates capillary leakage and oedema formation by initiating the formation of bradykinin (a vasoactive and proinflammatory peptide hormone)
Tryptase	Amplification of allergic response (+ve feedback on effector cells), leucocyte migration and activation, bronchoconstriction, vasodilation and oedema, tissue degradation and cell proliferation
Chymase	Vasodilation and oedema, mucus secretion, leucocyte activation, tissue degradation
Tumour necrosis factor (TNF-α)	Bronchoconstriction, leucocyte adhesion, leucocyte migration and activation, possible role in delayed-phase reactions
Newly generated over minutes	
Cyclooxygenase products, mainly PGD_2	Vasodilation and oedema, bronchoconstriction, mucus secretion, nerve stimulation (vasodilation, itching, bronchoconstriction)
Lipoxygenase products: LTB_4, LTC_4, LTD_4, LTE_4	Vasodilation and oedema, mucus secretion, bronchoconstriction, leucocyte recruitment
Platelet-activating factor (PAF)	Platelet activation/microthrombi, leukocyte migration/activation, histamine release (indirectly by neurogenic activation), ↓ myocardial contractility
Newly generated over hours	
IL-5, GM-CSF	Leucocyte adhesion, leucocyte migration and activation
IL-4, IL-13	IgE production and upregulation of FcεRI expression
IL-10	Anti-inflammatory, ↓ activation and degranulation of mast cells, induces ↑ numbers of Tregs
IL-6	Proinflammatory cytokine; correlates with the extent of erythema and inversely related to MAP; correlates strongly with occurrence of hypotension; causes ↑ expression of FcεRI, ↑ intracellular histamine, and prevents mast cell apoptosis
sTNFRI	Surrogate marker for TNF-α activity, may have anti-inflammatory effects
PAF-AH	Enzyme that inactivates PAF, low levels reported in fatal anaphylaxis
Anaphylatoxins (C3a, C4a, C5a)	Complement activation products, mast cell and neutrophil degranulation and smooth muscle contraction
Chemokines (ie, RANTES, IL-8, MCP-1)	Chemotaxis and activation of immune cells, histamine and serotonin release from mast cells

Adapted from: Stone SF al el. Curr Allergy Asthma Rep 2012; 12: 33-41

Patient-specific risk factors for anaphylaxis severity and fatality

Age	Comorbidities	Concurrent medications / recreational drugs
• Infant: cannot describe symptoms and difficult to diagnose anaphylaxis • Adolescent / young adult: ↑ risk of anaphylaxis triggered by foods - Inconsistent behaviour regarding allergen avoidance and carrying adrenaline autoinjector • Elderly: greater risk of fatality from insect venom anaphylaxis and concomitant diseases (e.g. COPD, CVD)	• Asthma especially if severe or uncontrolled • CVD • Allergic rhinitis and eczema: atopic diseases are a risk factor for anaphylaxis triggered by foods, exercise and latex • Psychiatric disease (may impair recognition of symptoms)	• May affect recognition of anaphylaxis: sedatives, hypnotics, antidepressants, alcohol narcotics, recreational drugs • May increase the severity of anaphylaxis: β blockers, ACE inhibitors • May affect responses to adrenaline: β blockers

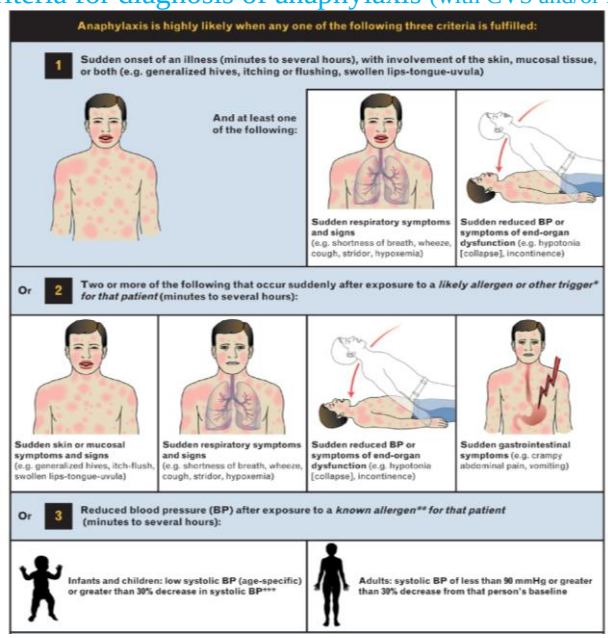
Adapted from: Stoloff SW. J Fam Pract 2010; 59: S1-8



Multiple logistic regression analysis adjusted ORs (95% CI) in 302 ED adult cases for the association between antihypertensive drugs and markers of severe anaphylaxis (syncope, hypoxia or hypotension) (A); 3 or more organ system involvement (B); and hospitalisation adjusted for gender, age, suspected trigger and preexisting lung disease (C).

Lee S et al. J Allergy Clin Immunol 2013; 131: 1103-8

Clinical criteria for diagnosis of anaphylaxis (with CVS and/or RS features)



In infants and children, respiratory compromise is more likely than hypotension or shock, and shock is more likely to be manifest initially by tachycardia than by hypotension.

Simons FE et al. Curr Opin Allergy Clin Immunol 2012; 12: 389-99

282 patients with anaphylaxis, Prince of Wales Hospital, 3/1999 to 2/2003

History of asthma	54 (19.1%)
History of allergy	116 (41.1%)
Clinical features	
• Urticaria	223 (79.1%)
• Angioedema	171 (60.6%)
• Flushing or general pruritus	209 (74.1%)
• Dyspnoea	185 (65.6%)
• Wheeze/bronchospasm	85 (30.1%)
• Laryngeal oedema	31 (11%)
• Tongue swelling	21 (7.5%)
• Chest pain – non-specific	16 (5.7%)
• Angina	1 (0.35%)
• Abdominal pain or diarrhoea	27 (9.6%)
• Vomiting	23 (8.2%)
• Dysphagia	1 (0.35%)
• Headache	2 (0.71%)
• Syncope	16 (5.7%)
• Dizziness	39 (13.8%)
• Systolic BP (mmHg)	129 [108.5-150]
• Diastolic BP (mmHg)	68 [55.5-81]
• Peak expiratory flow rate (L/min)	300 [220-400]

Numbers (%) of patients or medians (IQR [25–75])

Smit DV al el. J Emerg Med 2005; 28: 381-8

Severity of generalised hypersensitivity reactions

Severity	Defined by
Mild (skin and subcutaneous tissues only)†	Generalised erythema, urticaria, periorbital oedema or angioedema
Moderate (features suggesting respiratory, cardiovascular or gastrointestinal involvement)	Dyspnoea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), diaphoresis, chest or throat tightness or abdominal pain
Severe (hypoxia, hypotension or neurological compromise)	Cyanosis or SpO2 ≤92%, hypotension (SBP <90 mmHg in adults), confusion, collapse, loss of consciousness or incontinence

†The Mild grade does not represent anaphylaxis according to the National Institute of Allergy and Infectious Disease-Food Allergy and Anaphylaxis Network and World Allergy Organization definitions.

Adapted from: Brown SGA. Emerg Med Australas 2006; 18: 155-69

294 Korean subjects admitted to the ED with anaphylaxis, 1/2000-12/2009

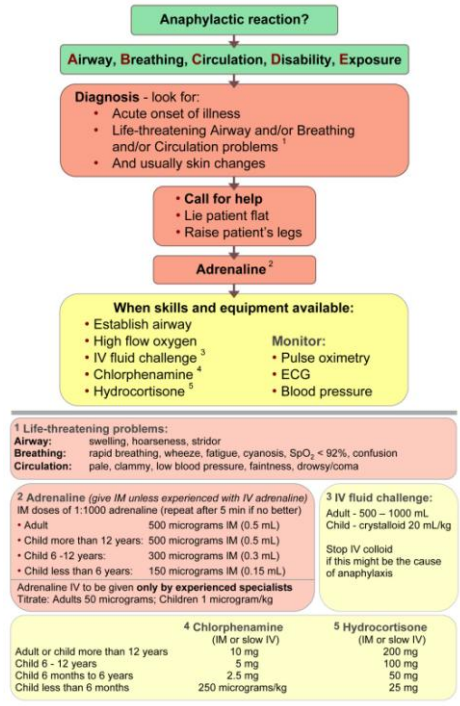
Symptoms or signs, n (%)	Non-shock (n=175)	Shock (n=119)	P value
Cutaneous	166 (94.9)	97 (81.5)	<.001
Urticaria	99 (56.6)	50 (42.0)	.014
Itching	69 (39.4)	61 (51.3)	.045
Flushing	41 (23.4)	32 (26.9)	.500
Angioedema	28 (16.0)	15 (12.6)	.419
Respiratory	100 (57.1)	68 (57.1)	1.000
Dyspnoea	93 (53.1)	65 (54.6)	.803
Hoarseness	6 (3.4)	2 (1.7)	.480
Cyanosis	2 (1.1)	21 (17.6)	<.001
Laryngeal oedema	5 (2.9)	1 (0.8)	.407
Cough	5 (2.9)	1 (0.8)	.407
Wheezing	5 (2.9)	5 (4.2)	.533
Cardiovascular	50 (28.6)	102 (85.7)	<.000
Syncope	3 (1.7)	45 (37.8)	<.001
Chest discomfort	40 (22.9)	16 (13.4)	.044
Palpitation	3 (1.7)	3 (2.5)	.689
Sweating	4 (2.3)	15 (12.6)	<.001
Cardiac arrest	0 (0.0)	1 (0.8)	.405
Gastrointestinal	56 (32.0)	34 (28.6)	.531
Nausea	22 (12.6)	21 (17.6)	.227
Vomiting	19 (10.9)	21 (17.6)	.096
Abdominal pain	25 (14.3)	10 (8.4)	.126
Diarrhoea	19 (10.9)	4 (3.4)	.019
Neurologic	27 (15.4)	61 (51.3)	<.001
Dizziness	23 (13.1)	59 (49.6)	<.001
Headache	6 (3.4)	3 (2.5)	.743
Seizure	0 (0.0)	2 (1.7)	.163

Park HJ et al. Am J Emerg Med 2012; 30: 1674-8

208 cases of anaphylaxis with or without biphasic reactions, Thailand, 2004-2008

Characteristics	Non-biphasic (n=195)	Biphasic (n=13)	P value
Male (%)	106 (54.4)	4 (30.8)	0.173
Median age, years	22	18.5	0.564
Atopy (%)	118 (60.5)	4 (30.8)	0.069
- Allergic rhinitis (%)	47 (22.6)	4 (30.8)	0.526
- Asthma (%)	31 (15.9)	3 (23.1)	0.771
- Food allergy (%)	45 (23.1)	2 (15.4)	0.764
Drug allergy (%)	36 (18.5)	0	0.13
Previous allergic reactions (%)	78 (40)	5 (38.5)	0.855
Underlying disease (%)	87 (44.6)	5 (38.5)	0.885
Presenting symptoms:			
• Urticaria/angioedema (%)	169 (86.7)	12 (92.3)	1.00
• Bronchospasm (%)	100 (51.3)	4 (30.8)	0.252
• Abdominal pain (%)	57 (29.2)	7 (53.8)	0.121
• Hypotension (%)	63 (32.3)	5 (38.5)	0.879
• Shock (%)	56 (28.7)	5 (38.5)	0.665
• Unconsciousness (%)	7 (3.6)	1 (7.7)	0.409
Treatment:			
• Intramuscular injection of adrenaline (%)	170 (87.2)	13 (100)	0.467
• Adrenaline use (%)	192 (98.5)	12 (92.3)	0.229
• Injected H_1 antagonist (%)	180 (92.30	11 (84.6)	0.288
• Injected H_2 antagonist (%)	114 (58.5)	9 (69.2)	0.636
• Steroid use (%)	169 (86.7)	10 (76.9)	0.398
• β-agonist use via nebuliser (%)	59 (30.3)	4 (30.8)	1.00
Time interval	Median (IQR)	Median (IQR)	
• Time from contact – onset (minutes)	30 (17.5-107.5)	120 (10-240)	0.501
• Time from onset – hospital arrival (minutes)	60 (30-120)	180 (105-360)	0.002
• Time from onset – adrenaline (minutes)	70 (40-135)	240 (122.5-380)	0.002
• Time from hospital arrival – adrenaline (minutes)	15 (10-15)	25 (16.5-30)	0.001

Lertnawapan R al el. Allergol Int 2011; 60 :283-9



Soar J et al. Resuscitation 2008; 77: 157-69.

Adrenaline – pros / cons of intramuscular administration in anaphylaxis

Pros

- Adrenaline has a vasodilation effect in skeletal muscle
- Skeletal muscle is highly vascular, leading to rapid absorption
- Drug injected into vastus lateralis reaches central circulation promptly
- Peak pharmacologic effects are achieved promptly
- Benefit-to-risk ratio perceived to be optimal when this route is used for first-aid treatment
- Most commonly recommended route worldwide

Cons

- Currently available auto-injector needle lengths and gauges are not optimal for intramuscular injection in overweight or obese people
- Not effective if muscle perfusion is poor or absent due to shock or cardiorespiratory arrest

Simons KJ et al. Curr Opin Allergy Clin Immunol 2010; 10: 354-61

Adrenaline – pros / cons of intravenous administration in anaphylaxis

Pros

- Optimal route of administration for patients with severe anaphylaxis who have not responded to intramuscular adrenaline and/or are experiencing profound hypotension or shock, or in whom cardiorespiratory arrest is imminent

Cons

- Establishing a peripheral intravenous route for adrenaline administration may be difficult in the above patients
- Narrower benefit-to-risk ratio than adrenaline administered by other routes, partly attributed to iatrogenic error
- For safe administration in hypotension or shock, it is optimally given through an infusion pump and central line by physicians trained and experienced in continuous dose titration of vasopressors against continuously monitored heart rate and function, blood pressure and oxygenation
- Errors in adrenaline dosing combined with errors in assessment of cardiac rate and function and blood pressure can be catastrophic for the patient

Simons KJ et al. Curr Opin Allergy Clin Immunol 2010; 10: 354-61

282 patients with anaphylaxis, Prince of Wales Hospital, 3/1999 to 2/2003

ED management	
• IV fluids	88 (31.2%)
• Adrenaline (i.v., i.m., s.c.)	188 (66.7%)
• H_1 antagonists	269 (95.4%)
• H_2 antagonists	4 (1.4%)
• Steroids	258 (91.5%)
• Salbutamol	95 (33.7%)
• Ipratroprium	44 (15.6%)
• Intubation	4 (1.4%)
Disposition	
• Discharge ED	4 (1.4%)
• Discharge against advice	9 (3.2%)
• Observation ward	154 (54.6%)
• General ward	93 (33%)
• Intensive care unit	27 (7.8%)

Smit DV et al. J Emerg Med 2005; 28: 381-8

Follow-up care of patients with anaphylaxis

Patients should understand their drug allergy status and action plans in case of emergency

Further work up and referral to the experts

Skin prick testing is useful to help identify the cause of anaphylaxis, but does not predict the severity of reactions Except for β-lactam antibiotics and a few other drugs, such allergens are generally not available for skin testing or in vitro testing

The level of serum specific IgE does not correlate with reaction severity and cannot be used to identify subjects at risk for anaphylaxis

(Lee JK et al. 2011 and Simons FER 2009)

Anaphylaxis management gaps categorised by a Canadian panel of allergy experts in a systematic review

Theme	Description	Gap
Anaphylaxis management	Lack of knowledge to identify the signs and symptoms, or correctly diagnose anaphylaxis	Patients are not diagnosed accurately Lack of awareness and adequate knowledge of anaphylaxis
	Adrenaline is not the most commonly prescribed treatment	No published criteria or professional consensus on prescribing adrenaline for severe allergy Infrequent, inappropriate or no use of adrenaline Auto-injector prescription is low
Adrenaline use	Inadequate or no training provided to patients on how to use adrenaline auto-injectors	Parents of children with allergies have unmet information needs from their physicians, including not knowing the definition of anaphylaxis and the symptoms requiring epinephrine Patients receive infrequent or no instruction, demonstration, or training on how to use auto-injectors Patients unsure when or how to use an auto-injector
	Adrenaline administration is inadequate or delayed	Adrenaline either not given or administration was delayed
	Physicians lack knowledge on epinephrine use	Lack of knowledge or consensus on appropriate dosage of adrenaline Few physicians have or know how to use an auto-injector training device In acute severe reactions, differences exist on treatment recommendations, and adrenaline is used less than other medications (e.g. steroids, β blockers)
Follow-up care	Infrequent or no referral to an allergy specialist after acute reaction	Few patients are being referred to an allergy specialist after an allergic reaction Lack of follow-up is common in patients who experienced an acute reaction
	Patients are not given enough information about how to manage anaphylaxis	Physicians did not think that advising patients to go to the hospital after taking adrenaline was necessary Few patients are given accurate information and advice by their family physicians about managing anaphylaxis Few patients with acute allergic reactions were given discharge instructions Poor identification of or provision of guidance of which allergens to avoid
	Patients do not have an anaphylaxis action plan	Patients do not have action plans or there is no consensus on what should be included in action plans; missing essential components or auto-injector instructions

Waserman S et al. Allergy 2010; 65: 1082-92

Anaphylaxis – Prevention, Recognition, Management

Anaphylaxis can occur at any age and is mostly caused by widely used drugs (e.g. antibiotics, analgesics, cytotoxic drugs, RCM)

Drug induced anaphylaxis is preventable by checking and clearly documenting drug allergy status and educating patients

Drug induced anaphylaxis can have unusual clinical presentations, biphasic reactions, rapid clinical deterioration and fatal outcome

Patient-specific risk factors for anaphylaxis severity and fatality – age, comorbidities (CVD, COPD) or concomitant drugs

Markers of severe anaphylaxis – including very rapid onset, shock, cyanosis, syncope, neurological compromise

Adrenaline i.m. and fluids i.v. – first-line treatment of anaphylaxis

Continuing training to address gaps in knowledge and management