

Gaps between actual initial treatment of anaphylaxis in China and international guidelines: A review and analysis of 819 reported cases

To the Editor,

Anaphylaxis is a life-threatening clinical emergency, and prompt intramuscular (IM) injection of epinephrine is critical.¹⁻³ Current practices pertaining to the initial treatment of anaphylaxis in China remain unclear. In this study, we assessed the actual initial treatment and the use of epinephrine for anaphylaxis in China by systematic analysis of published case reports between 2014 and 2018.

1 | MATERIALS AND METHODS

An online literature search was performed in PubMed, Web of Science, ScienceDirect, China National Knowledge Internet database (<http://www.cnki.net>), Wanfang database (<http://med.wanfangdata.com.cn>), and VIP database (<http://www.cqvip.com>). The following key words were used: "anaphylaxis," "anaphylactic reactions," "anaphylactic reaction," "anaphylactic shock," "reactions, anaphylactic," "reaction, anaphylactic," "shock, anaphylactic," "kounis," "kounis syndrome," and "china". The inclusion criteria were as follows: (a) diagnosis of anaphylaxis¹; (b) availability of records about the anaphylaxis; (c) published from January 1, 2014, to December 31, 2018; (d) published in English or Chinese. Exclusion criteria were as follows: (a) cases with incomplete data; (b) duplicate publication; (c) cases in which cardiac arrest occurred prior to the administration of epinephrine. Overdose of epinephrine was defined as administration of a dose that exceeded the dose recommended by the guidelines.²⁻⁴

2 | DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

A total of 7579 articles were retrieved on database search, and a total of 819 patients from 748 case reports were included in this review (Figure S1). These patients were distributed across 30/31 (96.8%) provinces in mainland China except Tibet (Figure S2). Patient characteristics are summarized in Table S1. The median age was 46.1 years, and 53.0% patients were male. More than 2/3rd of the episodes of anaphylaxis occurred among inpatients. All the patients except

one (99.9%) presented severe anaphylactic reactions (cardiovascular and/or respiratory compromise). The mortality rate was 5.6%.

3 | ANALYSIS OF THE INITIAL TREATMENT OF ANAPHYLAXIS

Removal of the likely trigger (57.3%) and supplemental oxygen (42.1%) were the 2 most commonly administered initial treatment followed by glucocorticoids (19.8%) and intravenous (IV) fluid support (14.9%; Table 1). Only 14.2% patients were appropriately treated with epinephrine as the first-line intervention. The percentage of patients treated with glucocorticoids was significantly higher than the percentage of those treated with epinephrine as the first-line treatment (19.8% vs. 14.2%; $P < .001$), as the first-line medication (44.3% vs. 38.5%, $P = .016$), or during the course of anaphylaxis (94.7% vs. 70.8%, $P < .001$).

4 | DOSAGE AND ROUTE OF ADMINISTRATION OF EPINEPHRINE

Out of the 580 patients who received epinephrine (Table 2), the initial dosage of epinephrine showed wide variability from 0.03 to 3 mg in children and from 0.01 to 20 mg in adults.⁵⁻⁸

Among children, the two most commonly administered initial doses of epinephrine were 0.3 mg (28.6%) and 0.5 mg (26.5%), and the two most common routes of administration were IV bolus injection (41.2%) and subcutaneous (SC) injection (41.2%). Only seven children (13.7%) received epinephrine by IM route. Most (89.4%) of children were administered an initial overdose of epinephrine. The percentage of children who received epinephrine overdose by IV bolus injection, SC injection, and IM injection was 100.0%, 73.7%, and 71.4%, respectively.

Among adult patients, the percentage of patients who received an initial dose of 1.0 mg (62.5%) was significantly higher than the percentage of those who received 0.5 mg (24.0%; $P < .001$). The percentage of patients who received epinephrine via IM injection (16.3%) was significantly lower than those who received IV bolus (46.0%, $P < .001$) or SC injection (36.1%, $P < .001$). Out of the 476

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TABLE 1 Treatment of patients with anaphylaxis

	Patients with available data, n	Value
First-line treatment, n (%)		
Removal of the trigger	819	469 (57.3)
Oxygen	819	345 (42.1)
Glucocorticoid	819	162(19.8) [†]
Fluid	819	122 (14.9)
Epinephrine	819	116 (14.2)
Vasopressor	819	34 (4.2)
H1-antihistamine	819	25 (3.1)
Atropine	819	5 (0.6)
Calcium gluconate	819	4 (0.5)
Aminophylline	819	2 (0.2)
TCM	819	2 (0.2)
Beta-2-agonist	819	1 (0.1)
NSAIDs	819	1 (0.1)
First-line medication, n (%)		
Glucocorticoid	819	363 (44.3) ^{**}
Epinephrine	819	315 (38.5)
Vasopressor	819	62 (7.6)
H1-antihistamine	819	51 (6.2)
Calcium gluconate	819	7 (0.9)
Atropine	819	5 (0.6)
Aminophylline	819	4 (0.5)
Respiratory stimulant	819	4 (0.5)
TCM	819	3 (0.4)
Beta-2-agonist	819	2 (0.2)
NSAIDs	819	1 (0.1)
Fluid	819	1 (0.1)
No medication	819	1 (0.1)
Treatment during the course of anaphylaxis, n (%)		
Epinephrine	819	580 (70.8)
Oxygen	819	648 (79.1)
Nasal catheter	648	484 (74.7)
Face mask	648	82 (12.7)
Endotracheal intubation	648	77 (11.9)
Noninvasive ventilator	648	3 (0.5)
Tracheotomy	648	2 (0.3)
Fluid support	819	583 (71.2)
Normal saline	583	229 (39.3)
Glucose solution	583	83 (14.2)
Balanced solution	583	71 (12.2)
Colloid solution	583	64 (11.0)
Glucose saline	583	17 (2.9)
TCM solution	583	1 (0.2)
50% Glucose solution	583	1 (0.2)

(Continues)

TABLE 1 (Continued)

	Patients with available data, n	Value
Unspecified	583	117 (20.1)
Inhaled beta-2 agonists	819	10 (1.2)
H1-antihistamines	819	343 (41.9)
H2-antihistamines	819	12 (1.5)
Glucocorticoids	819	776 (94.7) [†]
Dexamethasone	776	683 (88.0)
Methylprednisolone	776	72 (9.3)
Hydrocortisone	776	20 (2.6)
Unspecified	776	1 (0.1)
Vasopressors	819	382 (46.6)

Note: Data presented as frequency (%) unless indicated otherwise. Removal of the trigger (57.3%), oxygen (42.1%), glucocorticoid (19.8%), and IV fluid support (14.9%) were the top 4 most commonly administered first-line interventions. Only 14.2% patients were treated with epinephrine as the initial treatment. In the analysis of first-line medications, 315 patients (38.5%) were administered epinephrine; glucocorticoids (44.3%) were the most commonly used drugs. Compared to the percentage of patients treated with epinephrine that of patients treated with corticosteroids were significantly higher as the first-line treatment ($\chi^2 = 298.029$, $P < .001$), as the first-line medication ($\chi^2 = 5.798$, $P = .016$), or during the course of anaphylaxis ($\chi^2 = 164.557$, $P < .001$), respectively. TCM, traditional Chinese medicine and NSAIDs, nonsteroid anti-inflammatory drugs.

[†] $P < .01$.

^{**} $P < .05$ vs percentage of patients treated with epinephrine.

patients for whom the records of the epinephrine dose and the route of administration were available, 385 (80.9%) patients received an initial overdose of epinephrine. The percentage of overdose was more common with IV bolus injection (99.5%) as compared to IM injection (63.0%; $P < .001$) or SC injection (65.5%; $P < .001$).

5 | ANALYSIS OF THE ADVERSE EFFECTS ASSOCIATED WITH EPINEPHRINE

Out of 580 patients who received epinephrine, 54 (9.3%) developed serious adverse effects associated with epinephrine (Table S2), including ventricular arrhythmias (59.3%), hypertension (20.4%), pulmonary edema (13.0%), myocardial ischemia (5.6%), and stroke (1.9%). Among the 52 patients with complete records of both the dose and route of administration of epinephrine, 50 (96.2%) patients had received an overdose and 45 (86.5%) were administered epinephrine by IV bolus injection.

6 | DISCUSSION

To the best of our knowledge, this is the first study that evaluated the actual initial treatment of anaphylaxis in China based on a literature review. Due to the space limitation, only four of the

TABLE 2 Initial dosage and route of administration of epinephrine

Administration of epinephrine in patients with available data									
Group (n)	Dosage (mg)	Route (n)						Total (n)	Overdose (n)
		IM	SC	IV injection	IV infusion	Intra-tracheal	unspecified		
Children (54)	>0.5	1	2	4	0	0	0	7	7
	0.5	2	7	4	0	0	0	13	13
	0.4	0	0	0	1	0	0	1	1
	0.3	4	5	5	0	0	0	14	12
	<0.3	0	5	6	1	0	2	14	9
	Unspecified	0	2	2	0	0	1	5	NA
	Total	7	21	21	2	0	3	54	42
Adults (526)	>1.0	1	1	13	0	0	1	16	16
	1.0	50	115	135	1	1	0	302 ^a	302
	0.7	0	0	1	0	0	0	1	1
	0.5	24	52	37	0	0	3	116	37
	<0.5	6	9	27	3	0	3	48	29
	Unspecified	0	2	15	3	0	23	43	NA
	Total	81	179	228 ^{b,c}	7	1	30	526	385
Total		88	200	249	9	1	33	580	427

Note: Data presented as frequency (n) unless indicated otherwise. In children, the top 2 common doses of epinephrine were 0.3 mg (28.6%) and 0.5 mg (26.5%), and the top 2 common routes of epinephrine were IV bolus injection and SC injection (both 41.2%). In children, the percentage of epinephrine overdose by IM injection, SC injection, IV bolus injection, and IV infusion was 71.4%, 73.7%, 100.0%, and 100%, respectively. In adults, the percentage of patients who received a dose of 1.0 mg (62.5%) was significantly higher than that of 0.5 mg (24.0%; $\chi^2 = 129.391$, $P < .001$). The number of patients who received IM, SC, IV bolus injection and IV infusion was 81 (16.3%), 179 (36.1%), 228 (46.0%), and 7 (1.4%), respectively. Among the 476 patients with record of both the epinephrine dose and the route, 385 (80.9%) patients received an overdose of epinephrine. The percentage of overdose was significantly more likely with IV bolus injection (99.5%) as compared to that with IM injection (63.0%; $\chi^2 = 89.064$, $P < .001$) or SC injection (65.5%; $\chi^2 = 85.639$, $P < .001$). IM, Intramuscular; SC, Subcutaneous; IV, intravenous; NA, not available.

^a $P < .01$ vs 0.5 mg.

^b $P < .01$ vs IM injection.

^c $P < .01$ vs SC injection.

748 studies included in this review were referenced. Our results indicated considerable underuse of epinephrine as the initial treatment of anaphylaxis. In contrast, glucocorticoids were inappropriately used as the first-line drug in place of epinephrine. Moreover, 81.6% patients had received an overdose of epinephrine, and 45.5% patients received IV bolus injection, both of which were proved to be significantly associated with serious adverse effects of epinephrine. Our findings suggest that the actual initial treatment of anaphylaxis in China does not comply with the international anaphylaxis guidelines. Of note, none of these problems was discussed or mentioned in these reports. This implies a general lack of awareness about the gaps in the initial treatment of anaphylaxis among many Chinese healthcare professionals.⁹ Our findings call for concerted efforts to remedy the current situation and to promote the safety of Chinese patients with anaphylaxis.

7 | LIMITATIONS

The study has a selection bias because the cases come from published reports. However, a large enough sample size helped negate

this limitation to a certain extent. We established rigorous inclusion/exclusion criteria to minimize the risk of bias, and a thorough literature search was performed to include more cases of anaphylaxis. Moreover, Inclusion of Chinese literature helped increase the yield of cases and improved the representativeness of our findings.

8 | CONCLUSION

Our study highlights some critical gaps in the initial treatment of anaphylaxis in China when compared against the international guidelines. Underuse, overdose, and inappropriate route of administration of epinephrine, as well as overuse of glucocorticoids, are the major problems. The epinephrine overdose and administration of IV bolus injection significantly increase the risk of serious adverse effects of epinephrine. Targeted training on the initial treatment of anaphylaxis is strongly suggested for healthcare providers in China.

CONFLICT OF INTEREST

There are no conflicts of interest to declare.

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REFERENCES

1. Muraro A, Roberts G, Worm M, et al. Anaphylaxis: guidelines from the European academy of allergy and clinical immunology. *Allergy*. 2014;69(8):1026-1045.
2. Simons FER, Arduzzo LRF, Bilo MB, et al. World allergy organization guidelines for the assessment and management of anaphylaxis. *J Allergy Clin Immunol*. 2011;127:587-593.
3. Lieberman P, Nicklas RA, Randolph C, et al. Anaphylaxis – a practice parameter update 2015. *Ann Allergy Asthma Immunol*. 2015;115(5):341-384.
4. Campbell RL, Bellolio MF, Knutson BD, et al. Epinephrine in anaphylaxis: higher risk of cardiovascular complications and overdose after administration of intravenous bolus epinephrine compared with intramuscular epinephrine. *J Allergy Clin Immunol*. 2015;3(1):76-80.
5. Jiang YP. Emergency treatment and nursing care of a case of anaphylactic shock induced by chloral hydrate enema. *J SNAKE (Sci & Nature)*. 2015;27(4):462-463.
6. Liu X. A case of anaphylactic shock induced by liposoluble vitamin (I). *Chin Hosp Pharm J*. 2015;35(19):1800-1801.
7. Chen Q, Tang M. Analysis of anaphylactic shock caused by cefazolin sodium pentahydrate. *Pharm Care Res*. 2016;16(1):63-66.
8. Dai BB, Zhao TY, Dai HY. A case of anaphylactic shock induced by bleomycin. *Anhui Med and Pharm J*. 2018;22(10):2064-2066.
9. Jiang C, Li H. Electrocardiographic changes after overdose of epinephrine in a patient with anaphylaxis: kounis syndrome or epinephrine? *JAMA Intern Med*. 2019;179(7):973-974.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Figure S1. PRISMA flow diagram of the selection of studies.

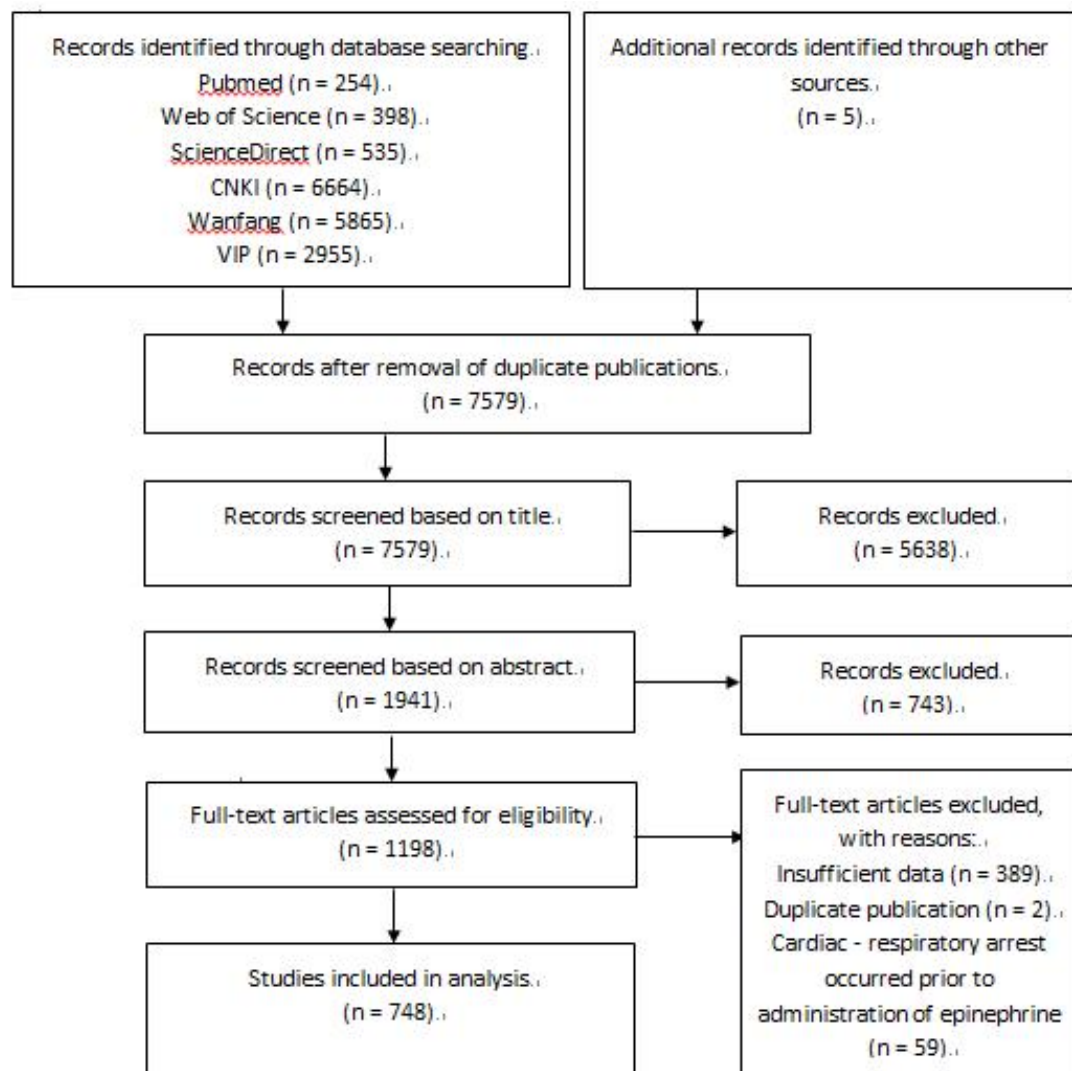
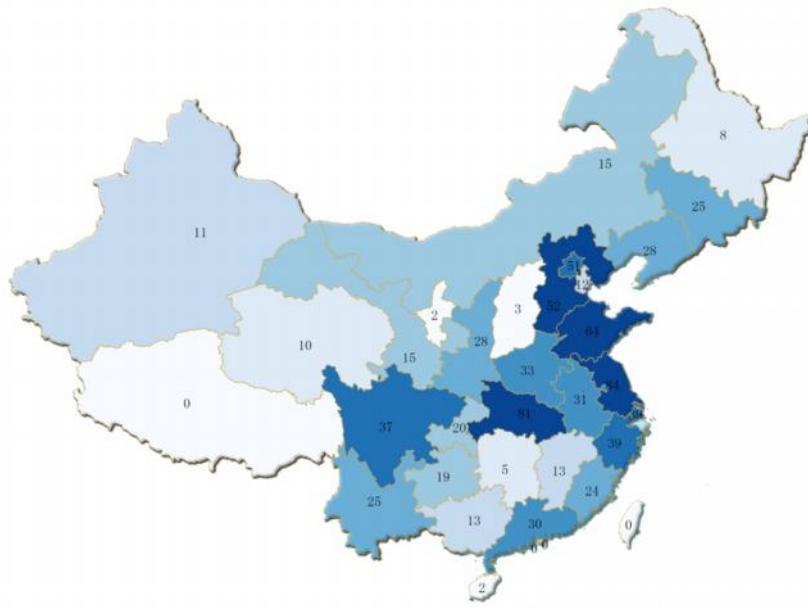


Figure S2. Geographic distribution of the included patients with anaphylaxis



The patients were widely distributed across 30 provinces/autonomous regions /municipalities in mainland China except Tibet. Jiangsu, Hubei, Shandong, Hebei and Beijing were the top 5 provinces/municipalities where the most number of patients with anaphylaxis (84, 81, 64, 52, and 51, respectively) were included in this study.

Table S1. Characteristics of patients with anaphylaxis

	Patients with available data, n	Value
Age, median (minimum-maximum), years	804	46.1 (0.3–91.0)
<18, n (%)	804	74 (9.2)
18–44 n (%)	804	250 (31.1)
45–64, n (%)	804	341 (42.4)
≥65, n (%)	804	139 (17.3)
Male, n (%)	815	432 (53.0)
Origin, n (%)		
Inpatient	800	542 (67.8)
Outpatient	800	159 (19.9)
Emergency patient	800	99 (12.4)
Department, n (%)		
Internal Medicine	743	243 (32.6)
Surgery	743	137 (18.4)
ED	743	88 (11.8)
Primary care	743	77 (10.4)
Gynecology and Obstetrics	743	60 (8.1)
Pediatrics	743	49 (6.6)
Neurology	743	40 (5.4)
Dermatology	743	19 (2.6)
E.N.T.	743	13 (1.7)
Ophthalmology	743	9 (1.2)
Stomatology	743	5 (0.7)
Rehabilitation	743	3 (0.4)
Positive allergic history, n (%)	819	145 (17.7)
Risk factors, n (%)		
Acute infection	819	219 (26.7)
CVD	819	68 (8.3)
Asthma	819	14 (1.7)
Previous severe reaction	819	12 (1.5)
ACEI	819	5 (0.6)
Beta-blocker	819	2 (0.2)
exercise	819	2 (0.2)
Asthma + acute infection	819	1 (0.1)
ACEI + beta-blocker	819	1 (0.1)
CVD + acute infection	819	1 (0.1)
Triggers		
Type, n (%)		
Antibiotics	819	192 (23.4)
TCM (injection)	819	107 (13.1)
Antineoplastic drugs	819	73 (8.9)

Contrast agents	819	66 (8.1)
Anesthetic agents	819	46 (5.6)
Colloid plasma expanders	819	37 (4.5)
Vitamins	819	27 (3.3)
Haemocoagulase Agkistrodon	819	23 (2.8)
Venom	819	21 (2.6)
NSAIDs	819	20 (2.4)
Foods	819	20 (2.4)
Vaccines	819	19 (2.3)
Others	819	168 (20.5)
Route, n (%)		
IV infusion	819	475 (58.0)
IV injection	819	130 (15.9)
PO	819	74 (9.0)
IM	819	53 (6.5)
Sting	819	21 (2.6)
SC	819	16 (2.0)
ID	819	16 (2.0)
Others	819	34 (4.2)
Time of exposure to onset, median (minimum - maximum), min	727	15.3 (1-590)
Severity of the anaphylaxis, n (%)		
Severe	819	818 (99.9)
Moderate	819	1 (0.1)
Outcome, n (%)		
Death	819	46 (5.6)
HIE	819	5 (0.6)
Referral	819	3 (0.4)
Discharge without treatment	819	1 (0.1)

Data presented as frequency (%) unless indicated otherwise. Data for the analysis of age, gender, origin, administrative department, allergic history, risk factors, triggers, time of exposure to onset, and outcomes, were available for 804, 815, 800, 743, 819, 819, 819, 727, and 819 patients, respectively. ED, emergency department; E.N.T., ear-nose-throat department; CVD, cardiovascular disease; ACEI, angiotensin-converting enzyme inhibitor; TCM, traditional Chinese medicine; NSAIDs, nonsteroidal anti-inflammatory drugs non-steroid anti-inflammatory drugs; IV, intravenous; PO, per oral; IM, intramuscular; SC, subcutaneous; ID, intradermal; HIE, hypoxic ischemic encephalopathy.

Table S2. Serious adverse effects associated with epinephrine administration

Serious Adverse effects, n (%)	IM injection (n=2)		SC injection (n=5)		IV bolus injection (n=45)		NA (n=2)	Total (n=54)
	overdose	non-overdose	overdose	non-overdose	overdose	non-overdose		
Ventricular arrhythmia	0	1 (50.0)	1 (20.0)	1 (20.0)	28 (63.6)	0	1 (50.0)	32 (59.3)
Hypertension	1 (50.0)	0	1 (20.0)	0	8 (18.2)	0	1 (50.0)	11 (20.4)
Pulmonary edema	0	0	2 (40.0)	0	5 (11.4)	0		7 (13.0)
Myocardial ischemia	0	0	0	0	3 (6.8)	0		3 (5.6)
Stroke	0	0	0	0	1 (2.3)	0		1 (1.9)

Data presented as frequency (%) unless indicated otherwise. Out of a total of 580 patients who received epinephrine, 54 patients (9.3%) developed serious adverse effects associated with epinephrine. The initial epinephrine dosing was categorized as non-overdose or overdose (>0.01 mg/kg of 1:1000 solution with a maximum dose of 0.5 mg in adults or 0.3 mg in children for IM and SC routes, or 0.001 mg/kg of 1:10,000 solution or 1:100,000 solution with a maximum dose of 0.1 mg for slow IV injection) ²⁻⁴. Out of the 52 patients for whom data pertaining to both the dose and the route of administration of epinephrine were available, 50 (96.2%) received an overdose, and 45 (86.5%) of these were administered by IV bolus injection. IM, Intramuscular; SC, Subcutaneous; IV, intravenous; NA, not available.