

Repeated epinephrine doses: An analysis of the European Anaphylaxis Registry, 2007-2018

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Clinical Implications

- In the European Anaphylaxis Registry, 3.7% of reactions received a second dose of epinephrine, with a slightly decreasing trend over the past decade. The proportion of second-dose receivers was similar comparing European countries, with higher numbers in Switzerland, Poland, and Spain.

TO THE EDITOR:

Application of intramuscular epinephrine is internationally recommended as the key element for the emergency management of severe allergic reactions, also referred to as anaphylaxis,^{1,2} but not all patients are treated accordingly.³ Depending on the initial severity and response to first-line treatment, repeated application of epinephrine usually in intervals of 5 to 15 minutes is thought to improve the outcome of anaphylactic episodes,⁴⁻⁶ though robust evidence supporting these guidelines is missing.⁴

We used data from the European Anaphylaxis Registry^{7,8} to estimate the proportion of anaphylaxis patients receiving more than 1 dose of epinephrine during their emergency treatment. Split analyses by subgroups of patient and reaction characteristics were performed to better understand which circumstances led to the application of repeated doses. For the purposes of this report, the consideration for additional epinephrine dosing for each incident in the registry requires a complex interplay of knowledge, skill, experience, and clinical decision making to be applied to the clinical scenario for that particular patient.

In short, the European Anaphylaxis Registry started in 2007 to collect anonymized data from tertiary allergy referral centers in European and other countries through a web-based interface. Available information include patients' demographic characteristics, eliciting allergens, symptoms and reaction severity, details of emergency management and follow-up care, results of diagnostic workup, and data about long-term counseling and prophylaxis. The overall severity of the reaction was rated by the health care professional who entered the data on a 10-point rating scale, with higher numbers representing more severe reactions.

Data were collected between July 2007 and March 2019. Anaphylaxis cases presented here are limited to those treated by health professionals, with or without initial lay/self-treatment. Valid information on application of epinephrine autoinjectors (EAIs) in those initially handled by a layperson (including self-treatment) and valid information on professional epinephrine applications was mandatory. More than 1 dose of epinephrine could either occur with lay/self-applied EAI followed by epinephrine applied by health care professionals or repeated

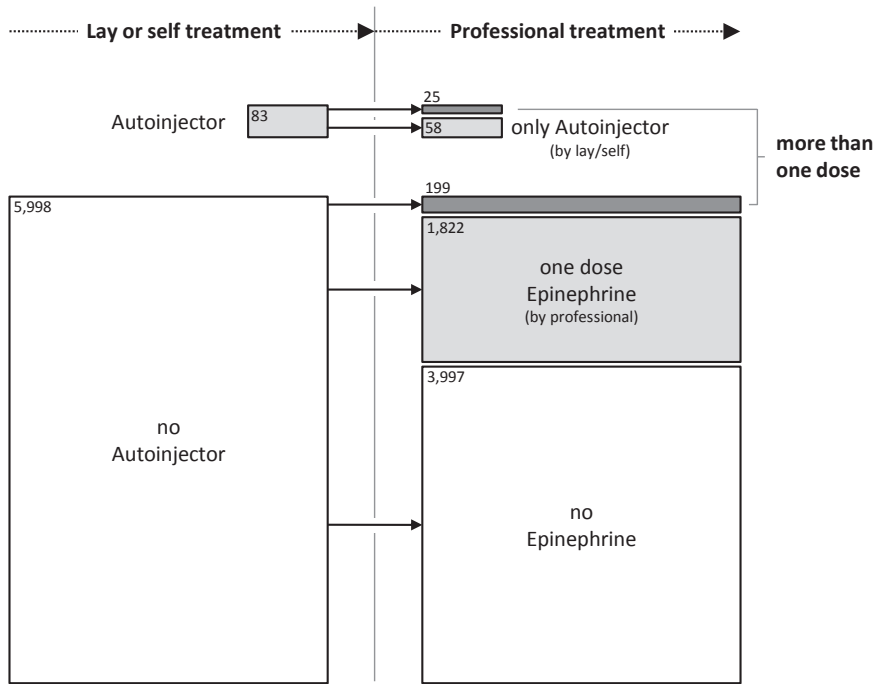


FIGURE 1. History of repeated epinephrine applications in anaphylaxis patients (n = 6081).

TABLE I. Number of anaphylaxis patients receiving no, 1, or more than 1 dose of epinephrine, by patient and reaction characteristics

Characteristic	n	No epinephrine, n (%)	One dose epinephrine, n (%)	More than 1 dose epinephrine, n (%)	More than 1 dose epinephrine vs no/1-dose epinephrine		
					OR	95% CI	P value
Total	6081	3977 (65.4)	1880 (30.9)	224 (3.7)			
Sex: female	3052	2092 (68.5)	855 (28.0)	105 (3.4)	0.98	0.73-1.32	.903
Age (y)							
<18	1944	1097 (56.4)	758 (39.0)	4.6 (89)	1.47	0.99-2.19	.059
18-64	3472	2439 (70.2)	932 (26.8)	2.9 (101)	Reference		
65+	665	441 (66.3)	190 (28.6)	34 (5.1)	1.40	0.90-2.17	.134
Country*							
Germany	2816	2110 (74.9)	621 (22.1)	85 (3.0)	Reference		
Austria	227	173 (76.2)	46 (20.3)	8 (3.5)	1.57	0.71-3.48	.262
Switzerland	748	514 (68.7)	198 (26.5)	36 (4.8)	1.86	1.20-2.89	.006
Poland	216	111 (51.4)	89 (41.2)	16 (7.4)	2.02	1.11-3.68	.021
Spain	346	145 (41.9)	177 (51.2)	24 (6.9)	3.33	1.95-5.69	<.001
France	803	413 (51.4)	361 (45.0)	29 (3.6)	0.87	0.53-1.42	.581
Italy	391	272 (69.6)	118 (30.2)	1 (0.3)	0.18	0.02-1.36	.098
Year of reaction							
2010-2012	1808	1259 (69.6)	478 (26.4)	71 (3.9)			
2013-2015	2328	1561 (67.1)	691 (29.7)	76 (3.3)	0.44	0.29-0.66	<.001
2016-2018	1945	1157 (59.5)	711 (36.6)	77 (4.0)	0.60	0.40-0.90	.014
Symptoms							
Skin	5445	3607 (66.2)	1654 (30.4)	184 (3.4)	0.92	0.60-1.40	.686
Gastrointestinal	2504	1584 (63.3)	821 (32.8)	99 (4.0)	0.97	0.71-1.33	.849
Respiratory	4246	2685 (63.2)	1385 (32.6)	176 (4.1)	1.34	0.93-1.92	.113
Cardiovascular	3592	2196 (61.1)	1222 (34.0)	174 (4.8)	2.45	1.68-3.58	<.001
Severity							
Grade I + II	3399	2518 (74.1)	819 (24.1)	62 (1.8)	0.56	0.40-0.80	.001
Grade III	2506	1389 (55.4)	998 (39.8)	119 (4.7)	Reference		
Grade IV	140	43 (30.7)	56 (40.0)	41 (29.3)	4.17	2.49-6.98	<.001
Rating scale 1-4	104	88 (84.6)	16 (15.4)	0 (0.0)	†		
Rating scale 5 + 6	359	266 (74.1)	88 (24.5)	5 (1.4)	†		
Rating scale 7 + 8	459	244 (53.2)	195 (42.5)	20 (4.4)	†		
Rating scale 9 + 10	163	48 (29.4)	97 (59.5)	18 (11.0)	†		
Time to symptoms							
≤10 min	2848	1759 (61.8)	964 (33.8)	125 (4.4)	1.17	0.87-1.58	.303
Location							
Work, school, home	2419	1574 (65.1)	767 (31.7)	78 (3.2)	Reference		
Health care facility	915	487 (53.2)	351 (38.4)	77 (8.4)	2.14	1.40-3.28	<.001
Public place	1764	1212 (68.7)	505 (28.6)	47 (2.7)	1.04	0.69-1.57	.844
Reacted before (same allergen)	1671	1032 (61.8)	570 (34.1)	4.1 (69)	1.07	0.77-1.47	.690
Elicitor							
Food	2191	1365 (62.3)	742 (33.9)	84 (3.8)	Reference		
Drugs	1293	813 (62.9)	418 (32.3)	62 (4.8)	0.61	0.36-1.04	.067
Insect venom	1978	1420 (71.8)	512 (25.9)	46 (2.3)	0.69	0.42-1.13	.143
Emergency drugs received							
Antihistamines	4658	3250 (69.8)	1264 (27.1)	144 (3.1)	0.69	0.48-0.98	.037
Beta-2-mimetics	713	396 (55.5)	272 (38.1)	45 (6.3)	1.34	0.91-1.98	.132
Corticosteroids	5113	3454 (67.6)	1491 (29.2)	168 (3.3)	0.90	0.61-1.34	.615
Postreaction care							
Hospital admission	2611	1427 (54.7)	1034 (39.6)	150 (5.7)	2.26	1.57-3.27	<.001
Intensive care unit	579	257 (44.4)	256 (44.2)	66 (11.4)	2.08	1.37-3.17	<.001

OR, Odds ratio.

Only selected symptoms; respiratory and cardiovascular symptoms combined. Adjusted OR, 95% CI, and P values from multivariate logistic prediction model.

*Countries with less than 200 cases omitted.

†Only in most recent questionnaire version, thus omitted from model.

professional applications. A predictive multivariate logistic model was used to estimate (mutually) adjusted odds ratios and 95% CIs for patient and reaction characteristics. The analytic approach cannot be interpreted causally, because it is inherently confounded by indication (mainly reaction severity). Missing information on symptom details, time to symptoms, previous reactions, emergency drugs, and postreaction care was assumed to indicate absence of the assessed characteristic; missing severity grade and location data were imputed with the reference category; missing elicitor data or other elicitors were modeled together (data not shown). Cases were analyzed from 105 hospitals/centers from Austria, Brazil, Bulgaria, France, Germany, Greece, Italy, Ireland, Poland, Spain, and Switzerland.

A total of 6081 anaphylaxis patients were treated by a health professional, of which 83 (1.4%) already received epinephrine from a layperson or themselves by EAI. Of these, 25 (30.1%) received a second dose from a health professional. Of the 5998 patients who did not receive epinephrine before the start of professional emergency management, 1822 (30.4%) received only 1 dose and 199 (3.3%) more than 1 epinephrine application by health professionals. For these patients, the interval between doses was less than 10 minutes in 59 cases (46.1% of those with documented time interval). Of patients who received their first (or only) dose by a professional (2021), 1012 (50.1%) received it intramuscularly and 734 (36.3%) through an intravenous route (not differentiating between bolus and continuous application); the latter were more often treated with a second dose (8.4% and 13.6%, respectively). Overall, 2104 (34.6%) received any epinephrine and 224 (3.7%) more than 1 dose (Figure 1).

Young (<18 years) and elderly (65+) patients received a second dose slightly more often than did adults, with no difference between female and male patients. Comparing robust country estimates (based on at least 200 cases), Spain, Poland, and Switzerland reported the highest proportion of second-dose receivers, and a low in Italy, which reported only 1 case in 391. Over the past decade, the proportion of patients receiving more than 1 dose of epinephrine seemed to decrease slightly, especially when adjusting for the changing distribution of reactions reported over the years (Table I, upper).

Not unexpectedly, the severity of the reaction had the most pronounced impact on the health care professional's decision to apply consecutive doses, with 29.3% of patients with grade IV reactions (based on Ring and Messmer⁹) receiving epinephrine more than once (adjusted odds ratio, 4.17, compared with no/1-dose receivers). In addition, cardiovascular symptoms led to slightly higher proportions of second-dose receivers.

Anaphylaxis incidents occurring within health care facilities (medical practices, hospitals) were considerably more often treated with 2 or more doses of epinephrine (8.4%), in contrast to insect venom-induced reactions, which were more often not treated or received only 1 dose. As indicators of reaction severity, treatment with beta-2-mimetics and being admitted to a hospital and/or an intensive care unit after the reaction were associated with receiving more than 1 dose (Table I, lower).

About 4% of all anaphylaxis patients documented in the European Anaphylaxis Registry received more than 1 dose of epinephrine. The proportion of reactions requiring a second dose is presumably higher; for example, 16% to 36% of immunotherapy-related anaphylaxis patients were assessed to merit more than 1 epinephrine application.¹⁰ Of those

experiencing near-fatal reactions (grade IV), only one-third were treated with a second dose, despite international recommendations to apply epinephrine repeatedly during the emergency management of anaphylaxis. A phenomenon relatively stable over time, application of more than 1 dose of epinephrine by health care professionals seems not to correspond to the recent dissemination of guidelines and awareness campaigns. It highlights the current role of expertise, experience, and scenario-specific decision making of health care professional.

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REFERENCES

1. Simons FE, Arduzzo LR, Bilo MB, Cardona V, Ebisawa M, El-Gamal YM, et al. International consensus on (ICON) anaphylaxis. *World Allergy Organ J* 2014;7:9.
2. Adrenaline auto-injectors - EMA/478468/2015. London, United Kingdom: European Medicines Agency; 2015.
3. Grabenhenrich LB, Dolle S, Rueff F, Renaudin JM, Scherer K, Pfohler C, et al. Epinephrine in severe allergic reactions: the European Anaphylaxis Register. *J Allergy Clin Immunol Pract* 2018;6:1898-1906.e1.
4. Muraro A, Roberts G, Worm M, Bilo MB, Brockow K, Fernandez Rivas M, et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy* 2014;69:1026-45.
5. Simons FE, Arduzzo LR, Bilo MB, El-Gamal YM, Ledford DK, Ring J, et al. World Allergy Organization anaphylaxis guidelines: summary. *J Allergy Clin Immunol* 2011;127:587-593.e1-22.
6. Lieberman P, Nicklas RA, Oppenheimer J, Kemp SF, Lang DM, Bernstein DI, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol* 2010;126:477-480.e1-42.
7. Grabenhenrich LB, Dolle S, Moneret-Vautrin A, Kohli A, Lange L, Spindler T, et al. Anaphylaxis in children and adolescents: the European Anaphylaxis Registry. *J Allergy Clin Immunol* 2016;137:1128-1137.e1.
8. Worm M, Moneret-Vautrin A, Scherer K, Lang R, Fernandez-Rivas M, Cardona V, et al. First European data from the network of severe allergic reactions (NORA). *Allergy* 2014;69:1397-404.
9. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet* 1977;1:466-9.
10. Kelso JM. A second dose of epinephrine for anaphylaxis: how often needed and how to carry. *J Allergy Clin Immunol* 2006;117:464-5.