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Epidemiology and outcome of patients admitted to intensive care after anaphylaxis in France: a retrospective multicentre study

Philippe Guerci[1,2,*,†], Charles Tacquard[3,†], Laura Chenard[1], David Millard[3], Lila Soufir[4], Jean-Marc Malinovsky[5], Matthias Garot[6], Jean-Marc Lalot[7], Guillaume Besch[8], Guillaume Louis[9], Laurie-Anne Thion[10], Claire Charpentier[11], Antoine Kimmoun[2,12], Marc Danguy Des Déserts[13], Serge Carreira[14], Gaetan Plantefeve[15], Emmanuel Novy[1], Paul Abraham[16], Paul-Michel Mertes[3], and Société Française d'Anesthésie et Réanimation (SFAR) Research Network

[1]Department of Anaesthesiology and Critical Care Medicine, Institut Lorrain du Coeur et des Vaisseaux, University Hospital of Nancy-Brabois, Vandœuvre-lès-Nancy, France, [2]INSERM U1116, Groupe Choc, University of Lorraine, Nancy, France, [3]Service d'Anesthésie-Réanimation Chirurgicale, Nouvel Hôpital Civil, Hôpitaux Universitaires de Strasbourg, Strasbourg, France, [4]Service d'Anesthésie-Réanimation, Groupe Hospitalier Paris Saint Joseph, Paris, France, [5]Département d'Anesthésie-Réanimation, Hopital Maison Blanche, Centre Hospitalier Universitaire de Reims, Reims, France, [6]Département d'Anesthésie-Réanimation, Hopital Huriez, Centre Hospitalier Regional Universitaire de Lille, Lille, France, [7]Réanimation Polyvalente, Centre Hospitalier Emile Durkheim, Épinal, France, [8]Department of Anaesthesiology and Intensive Care Medicine, University Hospital of Besançon, Besançon, France, [9]Réanimation Polyvalente, Hôpital de Mercy, CHR Metz-Thionville, Metz, France, [10]Service d'Anesthésie-Réanimation, Fondation Ophtalmologique Adolphe de Rothschild, Paris, France, [11]Réanimation Chirurgicale Polyvalente, Hôpital Central, Centre Hospitalier Universitaire de Nancy, Nancy, France, [12]Réanimation Médicale, Institut Lorrain du Cœur et des Vaisseaux, Centre Hospitalier Régional Universitaire Nancy-Brabois, Vandœuvre-lès-Nancy, France, [13]Réanimation Polyvalente, Hôpital d'Instruction des Armées Clermont-Tonnerre, Brest, France, [14]Anesthésie-Réanimation, Hôpital Saint Camille, Bry-sur-Marne, France, [15]Service de Réanimation Polyvalente, Centre Hospitalier Victor Dupouy, Argenteuil, France and [16]Département d'Anesthésie-Réanimation, Hôpital Edouard Heriot, Hospices Civils de Lyon, Lyon, France

*Corresponding author. E-mail: phil.guerci@gmail.com

†These authors contributed equally to this work.

Abstract

Background: Few data are available on patients who have experienced anaphylaxis and were admitted to ICUs. The purpose of this observational study was to describe the epidemiology and management of these patients.
Methods: This was a multicentre retrospective study carried out in 23 French ICUs between 2012 and 2017. All patients who suffered anaphylaxis and were transferred to an ICU were included. Data were collected using an electronic database after approval by an ethics committee.
Results: A total of 339 patients were included, and 17 (5%) died secondary to anaphylaxis. The main triggers were drugs (77%), contrast media (11%), and food (7%). Epinephrine was administered before ICU admission in 88% of patients with Grade III anaphylaxis and 100% of patients with Grade IV anaphylaxis. Most patients with Grades III and IV anaphylaxes did not receive the recommended dose of i.v. fluid of 30 ml kg^{-1} within the first 4 h of ICU admission. The time to epinephrine administration was not statistically different between survivors and non-survivors, but non-survivors received a higher dose of epinephrine (median: 5 [3–10] *vs* 3 [2–7] mg; $P<0.0001$), which suggests that some forms of anaphylactic shock may be resistant to epinephrine. In multivariate analysis, only lactate concentration at ICU

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admission was a predictor of death (odds ratio: 1.47 [1.15–1.88]; P=0.002).
Conclusions: Lactate concentration at ICU admission appeared to be the most reliable criterion for assessing prognosis. Epinephrine is widely used during anaphylaxis, but the volume of fluid resuscitation was consistently lower than recommended.
Clinical trial registration: NCT04290507.

Keywords: anaphylaxis; epinephrine; fluid resuscitation; intensive care unit; lactate; outcome; vasoplegia

Editor's key points

- A multicentre retrospective study was carried out in 23 French ICUs to describe the epidemiology and management of patients with anaphylaxis who were transferred to an ICU.
- Of 339 patients included, 17 (5%) died secondary to anaphylaxis, with main triggers being drugs (77%), contrast media (11%), and food (7%).
- Epinephrine was administered to 88% of Grade III anaphylaxis and 100% of Grade IV anaphylaxis. More than half of Grades III and IV did not receive the recommended dose of i.v. fluid.
- In a multivariate analysis, only lactate concentration at ICU admission was a predictor of death.
- Given the high mortality rate despite appropriate treatment, further studies are needed to identify new therapeutic targets for anaphylactic shock.

Anaphylaxis is a severe life-threatening reaction after exposure to an antigen. Its incidence is increasing in the general population, accompanied by increasing hospitalisations.[1–3] Although rare, anaphylaxis is often associated with significant morbidity and mortality. The mortality rate has been estimated at 0.84 (95% confidence interval [CI]: 0.79–0.88) per million per year in the French adult population.[4] Age, obesity, and cardiac and pulmonary morbidities have been associated with an increased rate of severe reaction and a higher mortality after anaphylaxis.[5,6] However, the risk factors for death after ICU admission have not yet been elucidated.

Several scientific societies have issued international guidelines to ensure early recognition and prompt management of anaphylaxis.[7–10] Epidemiology reports and national audits have helped substantially improve our knowledge regarding anaphylaxis. Several studies approached the risk factors for ICU admission.[1,11,12] However, data are scarce regarding the management of ICU patients with anaphylaxis. Vascular filling and epinephrine administration are cornerstones of the initial management and may also play an important role after ICU admission, especially for severe anaphylaxis. The use of exceptional therapies, such as extracorporeal life support, has been reported only through case reports. We conducted a large nationwide retrospective study with the main objective being to describe the characteristics, investigate the modalities of management, and analyse the outcomes of patients admitted to the ICU for anaphylaxis graded according to the Ring and Messmer classification.[10]

Methods

Data management and ethics approval

Data were collected and managed using Research Electronic Data Capture software. The database was approved by the local ethics committee (reference no. 147; Centre Hospitalier Régional Universitaire Nancy), which waived the need for signed informed consent of participants in accordance with French legislation on non-interventional studies.[13] This paper was written in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for the reporting of observational studies in epidemiology (STROBE, http://www.strobe-statement.org/). The study was registered on ClinicalTrials.gov (NCT04290507).

Patient population

Eligibility criteria

We included all patients admitted to the ICU with a diagnosis of anaphylaxis or anaphylactic shock regardless of the origin of the shock. Patients were excluded if they were <18 yr old, presented with severe acute asthma, or died before ICU admission. Patients presenting anaphylaxis during their ICU stay were excluded.

Data source and method of selection

The patients' files were extracted through a French hospital discharge database containing individual records of all ICU stays using the International Classification of Diseases, 10th Revision (ICD-10) for the terms *anaphylactic shock* and *anaphylaxis*. In addition, ICU medical charts were cross-checked with final medical reports to ensure exhaustivity.

Conduct of the study

A retrospective, multicentre, observational study was carried out between January 1, 2012 and December 31, 2017. The medical records of patients who experienced anaphylaxis requiring ICU admission were collected from 23 French ICUs. Participating centres and case mixes are listed in the Supplementary material. Collected data concerned both ICU and hospital stays.

Measurements and data handling

Data collected

Patient characteristics data, including age, sex, weight, height, ASA physical status classification, past medical history (cardiac, pulmonary, and allergy history), location, and origin and grade of anaphylaxis according to the Ring and Messmer

grading system[10] (I–IV; see Supplementary Table S1), were collected. The Sequential Organ Failure Assessment (SOFA) score was determined at ICU admission. Laboratory data, such as markers of organ failure (troponin, lactate, and arterial blood gases), were also recorded. Tryptase and specific immunoglobulin E were used to confirm positive diagnosis when available. Management of anaphylaxis, volume of crystalloid and colloid infused, duration and maximum dose of vasopressors infused in 24 h, and various therapeutic products used were collected. Finally, organ failure and outcomes of patients with Grade IV anaphylaxis were documented.

Study endpoints

The primary endpoint was in-hospital mortality during ICU stay. Secondary endpoints included volume of fluid infused during the resuscitation process before ICU admission and during ICU stay, total dose of epinephrine administered, number of patients requiring alternative/rescue therapies to manage severe anaphylaxis, and type of organ failures in Grade IV anaphylaxis.

Sample size calculation

Considering that Grade IV anaphylaxis occurs in 8–17% of patients presenting with perioperative anaphylaxis[14,15] and the need of at least 40 Grade IV anaphylaxis, a convenience sample size of 300 patients was selected.

Statistical analyses

Statistical analyses were performed using SPSS statistics version 25.0 (IBM, Boigny-sur-Bionne, France). Categorical data were expressed as percentages. Normally distributed quantitative data (Kolmogorov–Smirnov test) were expressed as mean (standard deviation), and non-normally distributed quantitative data were expressed as median (inter-quartile range). Comparisons between groups were made using the χ^2 test for categorical variables and the Wilcoxon rank-sum test for quantitative variables. Prognostic factors associated with time to in-hospital death were studied using multivariate logistic regression analysis. In-hospital death was determined from the diagnosis date of *anaphylaxis* to death or discharge from the hospital or ICU, whichever occurred first. A patient discharged from the hospital was considered alive. Baseline and time-dependent variables associated with outcome in the univariate analysis ($P<0.05$) and that were present during diagnosis were considered for the multivariate model, and the final model was selected using backward stepwise regression ($P<0.05$). Odds ratios (ORs) were calculated accordingly, with 95% CIs. Significance was defined as $P<0.05$.

Results

Population characteristics

We identified 339 patients from 23 French ICUs (13 surgical ICUs and 10 medical or mixed ICUs in the Société Française d'Anesthésie-Réanimation [SFAR] research network were included). The characteristics of patients admitted to the ICU for anaphylaxis are presented in Table 1. Most of the anaphylactic reactions were severe, with 81% Grades III–IV. In-hospital anaphylaxis occurred in 275 patients (81.1%). Drugs were the main suspected trigger for anaphylaxis (77.2%), followed by contrast media (11.5%) and food (6.8%).

Table 1 Patient characteristics of the study population. Data are presented as median [25th–75th percentiles] or number (percentage). ACE, angiotensin-converting enzyme; ASA, American Society of Anesthesiologists; BMI, body mass index; COPD, chronic obstructive pulmonary disease; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment.

Variable	Total (n=339)
Age (yr)	59 [45–68]
BMI (kg m^{-2})	27.2 [23.7–31.8]
BMI ≥30 kg m^{-2}, n (%)	119 (35.1)
Sex, n (%)	
Female	176 (51.9)
Male	163 (48.1)
Medical history, n (%)	
ASA physical status	
1	54 (16)
2	135 (39.9)
3	130 (38.5)
4	19 (5.6)
Cardiovascular conditions	
Hypertension	138 (81.7)
Coronary artery disease	33 (19.5)
Cardiac rhythm disorders	35 (20.7)
Bronchopulmonary disease	
Asthma	25 (30.5)
COPD	43 (52.4)
Chronic respiratory insufficiency	7 (8.5)
Sleep apnoea syndrome	14 (17.1)
History of allergy, n (%)	110 (32.4)
Medication, n (%)	
ACE inhibitor	51 (17.1)
Angiotensin receptor blocker	32 (9.4)
Beta blocker	80 (26.8)
Bronchodilator	26 (8.7)
Corticosteroid	12 (4)
None	103 (34.6)
Location of anaphylaxis, n (%)	
Out of hospital	64 (18.9)
In hospital	
Operating theatre	190 (56)
Medical unit	35 (10.3)
Emergency unit	9 (2.7)
Radiology	40 (11.8)
Clinical investigation centre	1 (0.3)
Suspected triggering agent, n (%)	
Medication	261 (77.2)
Contrast media	39 (11.5)
Food	23 (6.8)
Hymenoptera	9 (2.7)
Materials	6 (1.8)
Undetermined	1 (0.3)
Grade of anaphylaxis, n (%)	
I	8 (2.4)
II	58 (17.1)
III	222 (65.5)
IV	51 (15)
Severity	
SOFA score at admission	4 [1–9]
SOFA score at 24 h	0 [0–2]
SAPS II at 24 h	30 [21–45]
ICU length of stay (days)	2 [2–3]
Hospital length of stay (days)	5 [3–12]

Subgroup analysis by patient origin

Patients admitted to the ICU for anaphylaxis were primarily from the operating theatre (n=190; 56%), pre-hospital setting (n=64; 18.6%), or radiology (n=40; 11.9%). In the operating theatre, neuromuscular blocking agents (NMBAs) were the

first suspected triggering agents (*n*=130; 68%) with a high representation of succinylcholine (*n*=70; 37%) or rocuronium (*n*=37; 19%). Beta lactams were suspected in 43 cases (23%). Drugs, mainly beta lactams (*n*=13; 20%) or NSAIDs (*n*=8; 13%), were also the first suspected agent in the pre-hospital setting (*n*=30; 47%). Food was the second suspected triggering agent (*n*=19; 30%), followed by Hymenoptera (*n*=9; 14%). In radiology, the main suspected triggering agents were contrast media (*n*=34; 85%). Table 2 details the management of these patients before ICU admission.

Management modalities of anaphylaxis according to the grade of severity

Management of anaphylaxis according to the grade of severity is presented in Table 3. Half of patients with Grade II anaphylaxis received epinephrine. In Grades III and IV anaphylaxes, more than half of patients did not receive the recommended dose of i.v. fluids of 30 ml kg^{-1} within the first 4 h after ICU admission. The volume of fluids was higher in patients with haemodynamic monitoring (3500 [500–1500] *vs* 3000 [250–750] ml; *P*=0.04), regardless of the monitoring used. At ICU admission, epinephrine was continuously infused in 78% of patients with Grade IV. Norepinephrine was chosen as an alternative to, or together with, epinephrine in 19% and 55%, respectively, of patients with Grades III and IV.

Fatal cases

Of the 17 patients (5%) who died during their ICU stay, two presented with Grade III and 15 with Grade IV anaphylaxis. There was a majority of men (73%), and there was no significant difference between survivors and non-survivors regarding medical history or medication except for corticosteroids as regular medication (3.2% in survivors *vs* 17.6% in non-survivors; *P*=0.017). The SOFA score at admission and the Simplified Acute Physiology Score II at 24 h were higher in non-survivors than in survivors (10 [9–13] *vs* 4 [1–8]; *P*<0.0001 and 87 [73–94] *vs* 30 [20–43]; *P*<0.0001, respectively). Non-survivors required significantly more renal replacement therapy than did survivors (33.3% *vs* 5.6%; *P*=0.014). Most patients died from multi-organ failure (*n*=10; 59%) or brain death (*n*=3; 18%). The median delay between admission and death was 3 [1–8] days. Table 4 shows a comparison between survivors (*n*=36) and non-survivors (*n*=15) in patients with Grade IV anaphylaxis. Organ failure during ICU stay in survivors is presented in Supplementary Table S2.

Factors associated with death in Grade IV anaphylaxis

Lactate concentration at ICU admission, duration of no flow (defined as the reported time from cardiac arrest to start of bystander cardiopulmonary resuscitation) and low flow (defined as time with active cardiopulmonary resuscitation by a bystander or a medical provider to return of spontaneous circulation or full extracorporeal membrane oxygenation support if needed), epinephrine dose before ICU admission, and SOFA score at ICU admission were significantly higher amongst non-survivors with Grade IV anaphylaxis. After multivariate logistic regression analysis, lactate concentration at ICU admission was the only variable identified as an independent risk factor for in-ICU mortality after Grade IV anaphylaxis (OR: 1.47 per unit; 95% CI [1.15–1.88]; *P*=0.002). Figure 1 shows the receiver operating characteristic (ROC) curves of the same factors for predicting death of patients admitted for Grade IV anaphylaxis in ICU. The largest area under ROC curves were 0.83 (95% CI: 0.70–0.97) for lactate concentrations at ICU admission and 0.72 (95% CI: 0.48–0.96) for duration of low flow. Lactate >6.9 mM at ICU admission predicted death with a sensitivity of 70%, specificity of 87.5%, and positive predictive value of 80%.

Allergic workup

Plasma tryptase concentration was assessed for 163 (48%) patients. The median tryptase was 31 [10–82] μM. Baseline

Table 2 Management of anaphylaxis before ICU admission according to patient origin. Data are presented as median [25th–75th percentiles] or number (percentage).

	Operating theatre	Radiology	Out of hospital
Number of patients	190	40	64
Grade II	17	6	27
Grade III	137	26	31
Grade IV	36	5	4
Epinephrine dose before admission (mg)			
Grade II	0.5 [0.1–2]	0.2 [0.1–0.3]	0.3 [0.1–0.5]
Grade III	0.5 [0.2–1]	0.2 [0.1–0.4]	0.3 [0.1–1]
Grade IV	4 [2–8]	4 [1–8]	3 [2–4]
Delay before epinephrine administration (min)			
Grade II	28 [2–128]	5 [5–5]	70 [40–120]
Grade III	5 [3–10]	10 [5–28]	40 [30–50]
Grade IV	2 [1–5]	7 [3–10]	23 [15–35]
Delay before ICU admission (min)			
Grade II	120 [48–288]	62 [38–90]	165 [120–330]
Grade III	120 [76–201]	49 [30–128]	150 [90–222]
Grade IV	148 [75–237]	60 [54–85]	140 [120–183]
Fluid resuscitation before ICU admission (ml kg^{-1})			
Grade II	17.0 [0.0–36.0]	6.5 [0.0–8.8]	0.0 [0.0–9.5]
Grade III	16.0 [8.4–24.0]	0.0 [0.0–10.0]	6.7 [0.0–18.0]
Grade IV	16.0 [0.0–23.0]	0.0 [0.0–0.0]	5.4 [1.2–18.0]
Number of deaths	10	2	3

Table 3 Initial management of anaphylaxis according to anaphylaxis grade before admission and within the first 24 h of ICU stay. Data are presented as median [25th–75th percentiles] or number (percentage). *Details on fluid resuscitation volumes are available in Supplementary Table S4. †Corticosteroids include methylprednisolone (most commonly used), hydrocortisone, prednisolone, and dexamethasone. NA, not available.

	Grade I (*n*=8)	Grade II (*n*=58)	Grade III (*n*=222)	Grade IV (*n*=51)
Fluid resuscitation (ml kg^{-1})				
Before admission*				
Total (ml)	0 [0–0]	500 [0–1000]	1000 [0–1638]	500 [0–1500]
Total (ml kg^{-1})	0.0 [0.0–0.0]	6.1 [0.0–15.0]	13.0 [0.0–22.0]	7.9 [0.0–19.0]
H+1*				
Total (ml)	0 [0–113]	725 [0–2000]	2000 [500–3000]	1105 [82–3000]
Total (ml kg^{-1})	0.0 [0.0–0.8]	9.8 [0.0–30.0]	22.0 [7.6–38.0]	18.0 [0.5–31.0]
H+4*				
Total (ml)	0 [0–413]	914 [500–2390]	2175 [1000–3330]	1750 [828–4328]
Total (ml kg^{-1})	0.0 [0.0–3.8]	12.0 [5.8–35.0]	28.0 [11.0–46.0]	23.0 [10.0–38.0]
H+24*				
Total (ml)	325 [0–875]	2000 [875–3625]	3125 [1975–4500]	3500 [2000–5500]
Total (ml kg^{-1})	1.5 [0.0–10.0]	25.0 [10.0–44.0]	39.0 [24.0–63.0]	41.0 [26.0–67.0]
Epinephrine				
Before admission				
n treated patients (%)	2 (25)	29 (50)	195 (88)	51 (100)
Total dose (mg)	0.325 (0.15–0.5)	0.3 (0.1–0.53)	0.4 (0.2–0.8)	4.0 (2.0–8.5)
At admission				
Continuous infusion, *n* (%)	0 (0)	13 (22)	100 (45)	40 (78)
Dose (μg min^{-1} kg^{-1})	N/A	0.08 (0.02–0.25)	0.13 (0.10–0.2)	0.29 (0.11–0.68)
Maximum dose in first 24 h (μg min^{-1} kg^{-1})	0.15 (0.15–0.15)	0.23 (0.12–0.79)	0.13 (0.1–0.28)	0.39 (0.21–0.68)
Norepinephrine				
Continuous infusion, *n* (%)	0 (0)	7 (12)	42 (19)	28 (55)
Maximum dose in first 24 h (μg min^{-1} kg^{-1})	NA	0.13 (0.05–0.95)	0.21 (0.13–0.54)	0.27 (0.2–0.88)
Corticosteroids†				
n (%)	7 (88)	41 (71)	150 (68)	19 (38)
Dose (mg kg^{-1})	1.0 (0.4–1.4)	1.3 (0.95–2.4)	1.4 (1.0–2.0)	1.4 (0.9–2.2)
Antihistamines				
n (%)	4 (50)	27 (47)	47 (21)	4 (8)

tryptase (at least 24 h after the reaction) was assessed for only 93 patients (27%). Consultation in an outpatient allergy clinic was scheduled for 248 patients (73%).

Discussion

This study is one of the largest nationwide reports focused on the epidemiology and more specifically on management of anaphylactic reactions in patients admitted to ICU. Drugs were the main trigger for anaphylaxis. In accordance with international guidelines, epinephrine was used as the first-line treatment for anaphylaxis. However, management was suboptimal, with insufficient fluid resuscitation in the early phase and underuse of epinephrine in Grade III anaphylaxis. Mortality was significant (5%) despite rapid recognition of anaphylaxis and administration of epinephrine within minutes of onset of anaphylaxis. This suggests that some forms of anaphylactic shock may be resistant to epinephrine. Lactate concentration at ICU admission appears to be a good predictor of ICU mortality. Blood sampling for tryptase and referral to the allergy clinic for an allergic check-up after anaphylactic shock could be further improved.

Literature on the epidemiology of anaphylactic shock for patients admitted to intensive care is scarce, especially in France. Most of the studies on severe anaphylaxis focus on risk factors for ICU admission or fatal anaphylaxis.[1,5,16] In our study, operating theatres were the main source of patients admitted for anaphylaxis, followed by the pre-hospital and radiology settings. The major triggers of perioperative anaphylaxis for patients admitted to ICU were NMBAs and antibiotics. This is consistent with other studies evaluating the epidemiology of perioperative anaphylaxis, including the latest Groupe d'étude des réactions anaphylactiques périopératoires study in France in 2011–2, in which 60.6% of perioperative allergic reactions were caused by NMBAs, followed by antibiotics (18.2% of reactions).[17] Consistent with previous studies, succinylcholine and rocuronium were the most common triggers of NMBA-related anaphylaxis.[18,19] Amongst antibiotics, beta lactams were common triggers.[17,20] In pre-hospital settings, antibiotics were also the most common triggers of anaphylactic shock in patients admitted to the ICU, followed by food and bite by Hymenoptera. This differs slightly from the epidemiology of patients admitted for anaphylaxis in the emergency department, where food allergens are the usual triggers.[21] This could be explained by a particular severity of reactions triggered by drugs and Hymenoptera. Radio contrast media are, by far, the leading causes of anaphylaxis in radiology. Our study clearly shows that these reactions represent an important cause of ICU admission. There may be room for improvement in their management especially in fluid resuscitation.

Subgroup analysis of anaphylaxis management before ICU admission shows that when anaphylaxis occurs in the operating theatre, where patients are fully monitored and treated by trained anaesthetists, recognition of anaphylaxis is prompt and epinephrine is administered within minutes after onset of anaphylaxis. However, time to ICU admission is delayed by ~2 h, probably because of the time required to complete the

Table 4 Comparison between survivors and non-survivors with Grade IV anaphylaxis (n=51). Data are presented as median [25th–75th percentiles] or number (percentage). BMI, body mass index; ECMO A/V, arteriovenous extracorporeal membrane oxygenation.

Variable	Survivors (n=36)	Non-survivors (n=15)	P-value
Age (yr)	61 [51–69]	66 [63–68]	0.189
Sex			0.125
Female	19 (53)	4 (27)	
Male	17 (47)	11 (73)	
BMI (kg m^{-2})	31 [25.9–35.9]	31.3 [27.1–34.3]	0.939
Location of shock			0.059
Out of hospital	1	3	
Operating theatre	27	9	
Radiology	3	2	
Ward	5	1	
Cause of anaphylaxis			0.041
Medication	33	10	
Hymenoptera	0	2	
Contrast media	3	2	
Material	0	1	
Cardiac arrest			
No-flow duration (min)	0 [0–0]	0 [0–1]	0.060
Low-flow duration (min)	9 [3.5–15]	40 [11–60]	0.003
Delay from anaphylaxis to epinephrine administration (min)	3 [1–6]	2.50 [1.25–18.8]	0.892
Initial shockable rhythm, n (%)	13 (37)	8 (57)	0.222
Epinephrine			
Before admission (mg)	3 [2–7.3]	5 [3–10]	<0.0001
Continuous infusion at admission, n (%)	19 (54)	11 (79)	0.194
Dose at admission (μg min^{-1} kg^{-1})	0.2 [0.1–0.4]	0.6 [0.3–2]	0.012
Maximum dose within first 24 h (μg min^{-1} kg^{-1})	0.3 [0.2–0.4]	0.7 [0.6–1]	0.001
Fluid resuscitation (ml kg^{-1})			
Before ICU admission	13.0 [0.0–18.0]	0.0 [0.0–23.0]	0.756
1 h after admission	17.0 [0.7–29.0]	19 [0.0–44.0]	0.812
4 h after admission	20.6 [10.4–30.9]	31.6 [5.6–54.1]	0.575
24 h after admission	39.5 [26.3–57.5]	52.9 [12.2–76.9]	0.453
Norepinephrine			
Continuous infusion, n (%)	19 (54)	9 (64)	0.750
Maximum dose within first 24 h (μg min^{-1} kg^{-1})	0.2 [0.2–0.4]	0.8 [0.3–1]	0.014
Rescue therapies			
Methylene blue	0 (0)	3 (20)	0.020
ECMO A/V	0 (0)	3 (20)	0.019
Biological parameters at admission			
Lactate (mM)	4.5 [3.1–5.6]	10.0 [6.5–13.4]	<0.0001
Troponin I–C (pg ml^{-1})	0.74 [0.23–3.74]	13.8 [1.3–51.7]	0.046
pH	7.24 [7.18–7.32]	7.08 [6.90–7.34]	0.206
Peak tryptase concentration (μg ml^{-1})	77 [35–168]	100 [18–200]	0.950

surgical procedure for resuscitation in the operating theatre. By contrast, in radiology, where patients are supervised by physicians who are trained to recognise anaphylaxis, but who have no particular experience in resuscitation, the time to first injection of epinephrine is short and patients are quickly transferred to the ICU for resuscitation. In pre-hospital settings, the time to first injection of epinephrine is longer: 23 min for Grade IV anaphylaxis and 40 min for Grade III anaphylaxis. This delay represents the time that the medical team requires to reach the patient, and illustrates the need to prescribe an epinephrine auto-injector to reduce the time to first injection in patients with a history of severe anaphylaxis. Unlike patients in the operating theatre, i.v. fluid resuscitation was rare in radiology and pre-hospital settings because of a lack of emphasis in guidelines from the emergency medicine society.[9] This gap should be addressed in future guidelines.

Anaphylaxis management is based on epinephrine administration and fluid resuscitation (Supplementary Table S3).[7,10,22] Epinephrine has been consistently used in Grade IV anaphylaxis, but 12% of Grade III anaphylaxis cases did not receive epinephrine, although it is recommended. Two patients with Grade I reactions were treated with epinephrine. This may be the result of physician overreaction. Although we focused on the most severe patients (admitted to ICU), the median dose of epinephrine was high in patients with Grade II reactions. High doses of epinephrine, especially intravenously, are associated with severe complications, such as arrhythmia, myocardial infarction, and stress cardiomyopathy.[23] Use of i.v. epinephrine must therefore be in strict compliance with current guidelines with dose adjustments based on severity of the reaction.

As proposed in the most recent guidelines,[7] continuous infusion of epinephrine was used in 45% and 78% of Grades III and IV anaphylaxes, respectively. Norepinephrine was used in 55% of Grade IV anaphylaxis. Use of norepinephrine is recommended as a second-line agent in several guidelines, but has never been scientifically evaluated. It could represent an interesting alternative strategy when vasoplegia is

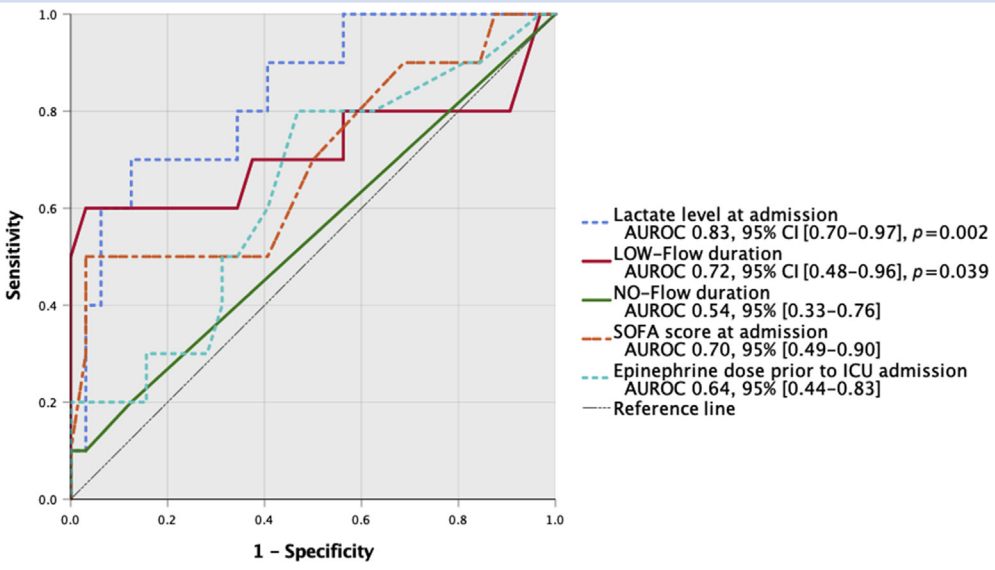

Fig 1. Area under receiver operating characteristic (ROC) curves for main factors differing between survivors and non-survivors with Grade IV anaphylaxis admitted to ICU. AUROC, area under ROC curve; CI, confidence interval; SOFA, Sequential Organ Failure Assessment.

predominant, or when tachycardia or arrhythmia is deleterious. Further studies are needed to assess whether norepinephrine is a suitable alternative to epinephrine in anaphylaxis.

Fluid resuscitation of 10–30 ml kg^{-1} is currently recommended for the initial management of anaphylaxis.[10,24] However, in our study, the median volume of fluid was <30 ml kg^{-1} at 4 h after ICU admission in Grades III and IV anaphylaxes (Table 3). Experimental studies suggest that infusion of i.v. fluids should be rapid, within 1 h of onset of anaphylaxis.[25,26] Hypovolaemia occurs within minutes after onset of anaphylaxis and is often profound, with severe reduction in tissue perfusion.[26,27] Volume loading with crystalloids is recommended, but may not be effective in restoring cardiac preload because of persistent high vascular leakage and vascular hyporesponsiveness.[26] Colloids, if not suspected of being a trigger for anaphylaxis, could be used as second-line therapy in cases of persistent hypovolaemia. Clinical data are lacking on which type of colloid should be used.[25] In the event of persistent haemodynamic instability at ICU admission, haemodynamic monitoring should be considered to assess preload dependency and to adjust the fluid resuscitation. Infused volume was higher when cardiac output was monitored in our study, suggesting that patients were hypovolaemic.

The 17 patients (5%) who died during their ICU stay is consistent with the mortality rate reported in the literature, and shows that anaphylaxis remains a serious disease.[6,20,28] Non-survivors were more critically ill at ICU admission (higher SOFA score and lactate concentrations) and presented with longer low-flow duration. In the multivariate logistic regression analysis, only the lactate concentration at ICU admission was identified as an independent risk factor for in-ICU mortality. This situation differs slightly from that described for the perioperative period, in which age, high ASA physical status, obesity, and use of beta blockers and angiotensin-converting enzyme inhibitors were identified as prognostic indicators.[29] Although our cohort had a significant proportion of perioperative anaphylaxis, we also identified a significant proportion of patients who experienced anaphylaxis in a pre-hospital setting or during injection of radiocontrast media. Triggers for these were different, with a higher proportion of protein allergens (in the pre-hospital setting) and different routes of administration, which could lead to differences in prognostic factors, and thus mask those specifically related to perioperative anaphylaxis. Only non-moribund patients admitted to ICU were considered in our cohort. Prognostic indicators previously identified could be related to early mortality with failure of initial resuscitation manoeuvres and less to late mortality.

The patients included in this study died despite rapid administration of high-dose epinephrine. Fluid resuscitation could have been insufficient with a median volume of 17 ml kg^{-1} at 1 h after ICU admission; however, there was no difference between survivors and non-survivors. Rescue therapies with methylene blue or extracorporeal life support were used unsuccessfully in three cases each. As previously observed specifically in the perioperative period and in the general population, these data suggest that some cases of anaphylactic shock are resistant to epinephrine. This suggests that new therapeutic targets should be considered to reduce the mortality of anaphylaxis.[6,20]

Anaphylaxis is also associated with significant morbidity amongst survivors (Supplementary Table S2), including coagulopathy, hepatitis, and acute coronary syndromes. These complications cannot be directly attributed to anaphylaxis, but might result from the severe haemodynamic impairment in patients with pre-existing co-morbidities. Nevertheless, these complications were observed only in Grades III and IV anaphylaxes, which confirms that severe anaphylactic shock should be monitored in the ICU for at least 24 h after the reaction.

Our study suffers from several limitations. Over-representation of perioperative anaphylaxis was attributable to our method of recruitment through the SFAR network, which resulted in over-representation of surgical ICUs compared with medical ICUs. However, 10 ICUs were mixed or medical, which allowed us to include a significant number of non-perioperative anaphylaxis cases. Moreover, perioperative anaphylaxis is particularly severe and is associated with a high mortality rate, which may contribute to the high prevalence of perioperative anaphylaxis in the ICU.[6,28]

We identified anaphylaxis cases using ICD-10 codes, which have been found to be imprecise,[30] so each case was then reviewed manually. The diagnosis was considered as probable when clinical signs of anaphylaxis occurred in a concordant time frame after exposure to an antigen and when other suspected diagnoses were ruled out by attending physicians. Tryptase concentrations were considered when available. Because of the lack of allergy investigation in some cases, uncertainties about the diagnosis might remain.

We studied only anaphylactic shock cases admitted to ICU. Thus, patients who died before admission to the ICU were not included. This could lead to an underestimation of the mortality rate for anaphylaxis.

The patients were insufficiently referred to an allergy outpatient clinic for investigation. An allergy workup is the only way to confirm the mechanism of the reaction and to identify the culprit agent. This is also critical in assessing cross-reactivity to avoid a new reaction with a similar agent.[31]

In conclusion, this is one of the largest studies available evaluating the epidemiology and management of anaphylactic shock in patients admitted to ICU. Drugs, in particular NMBAs, were the leading triggers of these reactions. Epinephrine was widely used during anaphylaxis, but the volume and rate of fluid resuscitation were insufficient. Mortality rate remains high at 5% despite appropriate treatment. Further studies, both experimental and clinical, are needed to identify new therapeutic targets. Each patient who has suffered anaphylactic shock should be referred to an allergy clinic for proper study.

Authors' contributions

Study conception/design: PG, CT, P-MM
Data acquisition: PG, CT, LC, DM, LS, J-MM, MG, J-ML, GB, GL, L-AT, AK, MDD, SC, GP, PA
Data analysis/interpretation: PG, CT, LC, P-MM
Drafting of paper: PG, CT
Critical revisions of paper: LC, DM, LS, J-MM, MG, J-ML, GB, GL, L-AT, AK, MDD, SC, GP, PA, P-MM
Final approval of paper: all authors

Declarations of interest

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Appendix A. Supplementary data

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