



Anaphylaxis Attended in Emergency Departments: a Reliable Picture of Real-world Anaphylaxis

Ana Rosado, MD¹

Mar Moro-Moro, MD, PhD²

Ana Gonzalez-Moreno, MD¹

Teresa Alfaya-Arias, MD¹

Nuria Alberti-Masgrau, MD, PhD³

Miguel A Tejedor-Alonso, MD, PhD^{1,4, *}

Address

^{*,1}Allergy Unit, Hospital Universitario Fundación Alcorcón, C/Budapest 1, 28922, Alcorcón, Madrid, Spain

Email: M914674227@telefonica.net

²Allergy Service, Hospital Virgen del Valle, Toledo, Spain

³Pathology Service, Hospital Universitario 12 de Octubre, Madrid, Spain

⁴Department of Medicine, Surgery and Public Health of University Rey Juan Carlos, Móstoles, Spain

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Abstract

Purpose of review The aim of this document is to review the epidemiology of anaphylaxis in the emergency departments (EDs) (burden and temporal trends), the generally deficient management of anaphylaxis in the ED, and the measures and interventions tested in different settings to improve management of anaphylaxis in the ED.

Recent findings The population attended for anaphylaxis episodes is low (0.009 to 0.4%). Recent studies report an increase in anaphylaxis episodes attended in the ED. Discordance has been observed between the diagnosis of anaphylaxis in the ED and the diagnosis confirmed in allergy units; this can reach 45%. Management of anaphylaxis is not consistent with international guidelines, and the lack of adherence to guidelines affects the use of epinephrine in the ED, prescription of epinephrine autoinjectors, initial advice on avoidance, and referral to an allergist. Measures to improve the management of anaphylaxis have proven effective.

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Summary The low burden of anaphylaxis in the ED and the disappointing landscape of management of this syndrome in the ED should drive strategies aimed at providing staff with key concepts and measures that enable them to manage episodes of anaphylaxis effectively.

Introduction

Anaphylaxis is a potentially life-threatening condition that is usually treated in the emergency department (ED) [1–12, 13•, 14, 15••, 16, 17••, 18, 19••, 20, 21•, 22–25]. Therefore, assessment of episodes of anaphylaxis managed in the ED can provide relevant information on the frequency of this syndrome in the community, and on how it is recognized and managed by physicians

and other health care professionals who are not allergists or specialized in allergic diseases. Patients who experience anaphylaxis are initially managed by professionals not specialized in allergic diseases (ED or critical care physicians, anesthesiologists, and primary care physicians). Therefore, data from the ED can provide us with a real-world picture of anaphylaxis.

Methods of review

The selection of articles for this review was made up of personal files of authors who have used them for other publications on anaphylaxis in emergency departments and a PubMed search of anaphylaxis in emergency departments for the last 5 years (until October 2019) using the chains or words *anaphyla* * and *Emergency*. The articles were selected for review if they contained data on the number of patients treated with anaphylaxis or data on other aspects of the review (use of epinephrine, misdiagnosis, referral to allergists ...). Data on the epidemiological aspects of anaphylaxis in the emergency department are shown in Table 1. The authors did not attempt to make a systematic review, given the wide variety of topics reviewed.

Burden of anaphylaxis in emergency departments

Anaphylaxis accounts for between 0.009 and 0.4% of all visits to the ED in all age groups [1–12, 13•, 14, 15••, 16, 17••, 18, 19••, 20, 21•, 22–25]. Many publications report percentages of under 0.2% of all visits to the ED [7–12, 13•, 14, 15••, 19••, 20, 21•, 22–25]. In the case of children, the range is 0.05–0.1% [1, 10, 13•, 19••, 23]. In our hospital, with an average of 10,000 ED visits per month, an anaphylaxis episode is managed every 3 days and an ED physician treats a patient with anaphylaxis every 2–3 months [12].

The anaphylaxis episodes attended in the ED are usually of moderate severity (7.2 to 76.03%), while severe episodes account for between 3 and 42% of cases [9, 16, 18, 20]. The two most important causes of anaphylaxis managed in the ED are foods and drugs. Studies covering all age groups show drugs to be the main cause (16.7–77.4%) and foods to be the second most frequent cause (6.6–49%) [1, 2, 7, 9, 11, 12, 16, 18, 20, 21•, 24]. Pediatric studies, on the other hand, show the main causes to be foods (72.3–85%), with

Table 1. Main epidemiological data in visits to the emergency department for anaphylaxis. Empty cells in the table mean that there is no data available

Author, country	Publication year/design	Population	Prevalence in emergency departments	Main causes	Severity	Trends in emergency visits
Sørensen, Denmark [8]	1989/retrospective	1 hospital All ages	0.0032%	Drugs 50% Food 10% Hymenoptera 40%	Anaphylactic shock 100%	
Klein, USA [3]	1995/retrospective	1 hospital All ages	0.089%	Food 41.7% Drugs 17.6% Latex 5.9% Exercise 11.8% Unknown 23.5%		
Steward, UK [2]	1996/retrospective	1 hospital All ages	0.016%	Food 33.3% Drugs 20% Hymenoptera 20% Unknown causes 13.3%	Severe 100%	
Pastorello, Italy [9]	2001/restrospective	1 hospital Adults	0.4%	Foods 35% Drugs 31.4% Hymenoptera 5.8% Exercise 2.9% Unidentified causes	Severe 9.3% Females 70.7%	
Bellou, France [5]	2003/retrospective	1 hospital All ages	0.009%	Insect stings 24% Drug 7.7% Food 9.5% Unknown causes 50.9%	Anaphylactic shock	
Brown, Australia [16]	2004/retrospective	1 hospital >17 years	0.18%	Venom stings and bites 30% Iatrogenic 22% Food 18% Other 5% Unidentified 25%	Moderate 76.03% Severe 23.97%	
Braganza, Australia [1]	2005/retrospective	1 hospital 15 years or younger	0.1%	Food 10.3% Drug 16.7 % Insects 12.0% No cause identified 59.5% Miscellaneous 1.5%		

Table 1. (Continued)

Author, country	Publication year/design	Population	Prevalence in emergency departments	Main causes	Severity	Trends in emergency visits
De Villiers Smit, Hong Kong [7]	2005/retrospective	1 hospital >18 years	0.035%	Food 49.6% Drugs 40.5% Bites and stings 7.1% Idiopathic 0.8%		The overall population rate was stable during the 12-year period (3.8 in 1993–1994 to 3.6 in 2003–2004; <i>P</i> for trend 0.39)
Poachanukoon, Thailand [4]	2006/retrospective	1 hospital All ages	0.23%			
Gaeta, USA [6]	2007/retrospective	National Database All ages	0.38%			
De Silva, USA [10]	2008/retrospective	1–17 years 1 Hospital		Food 85% Drugs 6% Insect sting 3% Unknown 7%		The rate of food-induced anaphylaxis cases increased by 62% from 2001 to 2006.
Harduar-Murano, USA [11]	2010/retrospective	Database of State of Florida All ages		Food 18.1% Drugs 5.7% Hymenoptera 1.4% Exercise 0.7% Unknown 20.7%		
Rudders, USA [23]	2010/retrospective	1 hospital <16 years				
Moro, Spain [12]	2011/retrospective	1 hospital All ages	0.09%	Food 28.6% Drugs 28.2% Unknown 27.2% Anisakis 10.8% Hymenoptera 3.3% Exercise 2.4% Latex 0.9%	Severe 26.3%	

Table 1. (Continued)

Author, country	Publication year/design	Population	Prevalence in emergency departments	Main causes	Severity	Trends in emergency visits
Campbell, USA [14]	2011/retrospective	1 hospital All ages	0.74%	Food 33.9% Drugs 34.8% Venom 12.1% Latex 0.4% Contrast 15.8% Other 0.4% Unknown 19.2% Females 58.2% Food 49% Venomous insect stings 29% Drugs 22%		
Harduar-Murano, USA [15••]	2011/retrospective	Database of State of Florida All ages		Food 72.3% Drugs 6.7% Unknown 21% Foods 71% Unknown 15% Drugs 9% Other 5% Males 51%		There was no significant change over 5 years
Arroabarren, Spain [19••]	2011/retrospective	1 hospital <14 years	0.047			
Huang, USA [13•]	2012/retrospective	1 hospital 1–18 years	0.18%			
Ye, Korea [20]	2015/retrospective	15 university hospitals Age 16–86 years	0.048%	Drugs 46.6% Food 24.2% Insect stings 16.4% Exercise 5.9%), Unknown 7.0%),	Mild 19.1% Moderate 38.9% Severe 42%	In adult patients increased from • 7.74 per 100,000 in 2007 • to 11.21 in 2008 ($P < 0.001$), • to 9.65 in 2009 ($P = 0.024$), to 10.40 in 2010 ($P = 0.001$), • and to 13.32 in 2011 ($P < 0.001$).
Alvarez-Perea, Spain [21•]	2015/prospective	1 hospital >18 years	0.13%	Food 25% Drugs 41.7% Hymenoptera 1.7% Unidentified 13.3% Females 49.13%		

Table 1. (Continued)

Author, country	Publication year/design	Population	Prevalence in emergency departments	Main causes	Severity	Trends in emergency visits
Motosue, USA [17●●]	2017/retrospective	National administrative claims database including commercially insured and Medicare Advantage patients	0.3%			- Increases in all age groups (101%) - The greatest increase was in children aged 5 to 17 years (196% increase; $P<0.001$). - The rate of food-related anaphylaxis increased by 124% ($P<0.001$), - the rate of medication-related anaphylaxis increased by 212% ($P<0.001$). 1 case of mortality
Oropeza, Denmark [25]	2017/prospective	1 hospital All ages	All ages = 0.04% Children =0.06%	Drugs 44% Foods 22% Venom 21% Children Drugs 22% Food 61% Venom 4% Unknown 9% Adults Drugs 48% Food 17% Venom 24% Unknown 11%		
Alkanhal, Saudi Arabia [24]	2018/retrospective	2 hospitals All ages	All 0.026% Pediatric cases 0.05% Adult cases 0.02%	Environment triggers 5% Insect bites 38.5% Foods 39.1% Drugs 17.4% Females (38.8%)	25% of the cases were classified as level 1 severity (mild), 72% were level 2 (moderate),	

Table 1. (Continued)

Author, country	Publication year/design	Population	Prevalence in emergency departments	Main causes	Severity	Trends in emergency visits
Corrigan, France [18]	2019/retrospective	7 French public hospitals All ages	0.16%	Drugs 6.6% Food 77.4% Insect sting 9.4% Undetermined 3.8%	and 3% were level 3 (severe) Grade I 20.8% Grade II 34.9% Grade III 44.3% Grade IV 0%	
Lacombe-Barrios, Spain [22]	2019/retrospective	1 hospital >14 years	0.025			

drugs accounting for a notably lower percentage of cases (6–16%) [1, 10, 19••]. The frequency of anaphylaxis of unknown origin is remarkable (3.8–59.5%) [1, 3•, 7, 9–12, 13•, 14, 16, 18, 19••, 20, 21•, 25], thus emphasizing the importance of referral to the allergy department for subsequent assessment.

In two studies from the USA carried out in the 1990s and the first decade of the current century (12 and 5 years, respectively) [6, 13•], the authors did not find any increase in visits to the ED because of anaphylaxis. However, three recent multicenter studies from Korea and the USA [17••, 20, 26•], which reported ED visits from 2005 to 2010 and 2010 to 2015, noted increases in visits to the ED due to anaphylaxis. In the Korean study [20], an increase of almost 50% was recorded between 2004 and 2008 in 15 teaching hospitals, while in the US study, based on data from a national administrative claims database [17••], the frequency of anaphylaxis treated in the ED increased by 100% in all age groups, with the greatest increase in children aged 5 to 17 years (increase of almost 200%). With respect to the main causes of anaphylaxis, the rate of food-related anaphylaxis also increased by almost 125%, and the rate of medication-related anaphylaxis increased by 200%. A recent study in EDs in the USA [26•] carried out during 2008–2015 showed that anaphylaxis increased 3.2-fold among children from 2008 to 2016, while for adults it increased 1.9-fold. The incidence of food and idiopathic anaphylaxis also increased. The three studies discussed above show an increase in the number of patients seen in the ED for anaphylaxis. This increase parallels results from other studies in patients admitted to hospital, especially in children and food-induced anaphylaxis [27–29].

Misdiagnosis of anaphylaxis in emergency departments and its repercussions

The reported incidence of visits to the ED is likely to have been underestimated owing to the difficulty in diagnosing anaphylaxis.

A study performed in the USA showed that only 43% of cases that the researchers considered to have fulfilled the criteria for anaphylaxis were actually diagnosed as anaphylaxis by ED physicians [30]. A study performed in Spain showed that only 44% of events meeting anaphylaxis criteria were correctly diagnosed as such and reported in clinical registries [21•]. The same under-reporting was observed in an Australian pediatric study, where only 49% of cases were identified as anaphylaxis [31].

Anaphylaxis may be misdiagnosed for several reasons, the main one being inaccurate coding. The 9th Edition of the International Classification of Diseases (ICD-9-CM), which is the clinical administrative coding for discharges (emergency or hospitalized patients) most widely used by the allergy community worldwide, was not considered appropriate for clinical practice [32]. ICD-9 and ICD-10 are not suitable for classifying hypersensitivity reactions, particularly anaphylaxis; ICD-9 and ICD-10 codes only consider “allergy” and “anaphylactic shock” and exclude all other types of anaphylactic reaction. Therefore, physicians and coders have difficulty attributing a specific code to an anaphylaxis event, and mild reactions are attributed to another code for anaphylactic reaction, thus leading cases of anaphylaxis to go unnoticed [33••]. Physicians interested in allergic diseases and

allergists hope that the new ICD-11 [34–36] will provide an adequate classification of anaphylaxis and thus ensure greater visibility of this syndrome.

Another reason for misdiagnosis is the limited time available to make a correct diagnosis or exclude alternative disorders. This problem is related to the rapid progression of the conditions treated in the ED and the characteristics of ED work, where the focus is on stabilizing the patient. The lack of specific diagnostic markers that enable rapid diagnosis of anaphylaxis in the ED is a key reason for misdiagnosis. Serum tryptase level is not very useful for diagnosing anaphylaxis at the time of the clinical presentation. In addition, tryptase is elevated in only 60% of adults with anaphylaxis [37], and a normal value does not rule out the diagnosis.

Another possible reason for the misdiagnosis of anaphylaxis in the ED is that some physicians may not be familiar with the complete spectrum of anaphylaxis, which may not be limited to anaphylactic shock. Most authors report a gap in knowledge of anaphylaxis in ED staff and recommend training programs to improve adherence to anaphylaxis guidelines [8–12, 13•, 14, 15••, 16]. Solid evidence of this gap can be seen in the experience of hospitals where interventions that improved professionals' knowledge of anaphylaxis led to an improvement in the management of anaphylaxis [19••].

Misdiagnosis of anaphylaxis not only leads to under-reporting but also generates major problems in patient management. Alvarez-Perea et al. [21•] reported that epinephrine was used more frequently in the ED in patients correctly identified as having anaphylaxis.

Use of epinephrine in emergency departments

Intramuscular epinephrine is the first choice for the treatment of anaphylaxis and is more effective than subcutaneous injection and safer than intravenous injection [38••]. Early administration of epinephrine before admission to the ED makes admission to hospital less likely than when the first epinephrine dose is administered after admission to the ED [39]. Early administration can also decrease the probability of death [40].

Guidelines recommend intramuscular epinephrine administered in the mid-anterolateral thigh at a dose of 0.01 mg/kg of a 1:1000 (1 mg/ml) solution up to a maximum of 0.5 mg in adults and 0.3 mg in children. The dose can be repeated every 5–15 min if necessary [41, 42]. Guidelines recommend that an episode of anaphylaxis should be followed by prescription of an epinephrine autoinjector, referral to an allergist, and a treatment plan [43].

Despite the various recommendations, intramuscular use of epinephrine is not widespread. In a Korean study, the frequency of use of epinephrine in hospitals was 31.5% in 2010, rising to 39.7% in 2014 [44] (10% in children under 6 years, 25–35% in middle-aged adults, and 17% in patients aged above 80 years). According to a French epidemiological study, epinephrine was prescribed in only 32.4% of cases of anaphylaxis. Most patients received epinephrine intravenously (41.7%), and the drug was used more often in children than in adults [18]. In the study by Cohen et al. [44], intramuscular administration of epinephrine was reported in only 54% of patients, and an epinephrine autoinjector for use after discharge from the ED was prescribed in 73%.

Recurrence of anaphylaxis increases the use of epinephrine (two administrations for every three cases) compared with the first anaphylaxis episode (one administration for every three cases) [45]. Hypotension and respiratory symptoms were significantly associated with more frequent use of epinephrine [46, 47].

Epinephrine is frequently administered intravenously despite international recommendations to the contrary [18]. This can lead to serious complications, such as acute pulmonary edema, ventricular arrhythmia, hypertensive crisis, and acute coronary events. Intravenous epinephrine is recommended only in cases of severe hypotension, cardiac arrest, and under-response to intramuscular epinephrine [48]. The study by Corrigan et al. [18] reports a high frequency of intravenous epinephrine.

The low incidence of anaphylaxis can explain the low use of epinephrine in EDs and the low rate of referral to allergy departments for further assessment [12]. There are no absolute contraindications for the use of epinephrine in anaphylactic reactions.

Lack of recognition of the features of anaphylaxis or concerns about the adverse effects of epinephrine could account for nonuse of the drug when necessary. However, adverse reactions to epinephrine are associated with dosing errors, cardiovascular disease, and intravenous administration [49]. Underuse of epinephrine in anaphylactic reactions is related to development of biphasic reactions [50].

In children, improvement of symptoms before admission to the ED and the absence of hemodynamic and respiratory dysfunction can account for underuse of epinephrine [51]. Early use of epinephrine is recommended in mild-to-moderate anaphylactic reactions (e.g., urticaria with mild abdominal pain) [52]. Providing training for physicians, nurses, and other health care providers can help to ensure adequate use of epinephrine when an anaphylactic reaction occurs.

Prescription of epinephrine autoinjectors in emergency departments

Guidelines recommend that before discharge, the risk of future reactions should be assessed and an epinephrine autoinjector (EAI) prescribed to patients at risk of recurrence [41, 42, 52]. Recommendations are necessary, since the risk of recurrence has been estimated to be between 30 and 42.8% [53, 54]. In most studies, prescription of EAIs in the ED is infrequent, ranging from 6 to 63% [12, 47, 51, 55–59]. In a review study that evaluated post-discharge care in anaphylaxis [60], prescription rates for EAIs varied from 0 to 68%, with a mean of 44%.

During the last decade [61], annual rates of filled EAI prescriptions and follow-up by an allergist have not changed. Overall rates of filled prescriptions were higher in patients with venom-induced and food-induced anaphylaxis, while the lowest rates were reported for drug-related anaphylaxis.

Trigger avoidance

ED physicians should provide complete recommendations about avoidance of drugs, foods, and other allergens (e.g., latex, hymenoptera venom, and

vaccines) depending on clinical suspicion, until the patient can be evaluated by an allergist. A large discrepancy has been observed between recommendations in guidelines and actual management of anaphylaxis. In one study [47], 51% of patients received written instructions for recognition of warning signs of anaphylaxis, although only 29% received instructions about avoidance of triggers.

The patient should receive an emergency personalized action plan covering instruction about avoidance of triggers and recognition of warning signs [41, 42, 52].

Remission to an allergist for assessment

Guidelines recommend referring all patients treated in the ED to an allergist for follow-up and for confirmation of the cause of anaphylaxis. In many cases, the physician's impression in the ED does not correspond to the diagnosis confirmed after the allergology work-up [60]. The allergist can investigate cross-reactivity with other allergens, for consideration in the management of possible recurrences.

In a review study [60], allergist referral rates ranged from 0 to 84%, with a mean of 33%, and in a Belgian study [59], the referral rate was over 74%. However, the frequency of referral varies with geographic area, although it is generally below 60%, and attendance at allergy services is less than 50% [47, 51, 56, 59, 62–64]. However, patients referred by the ED more frequently undergo an allergology work-up than those referred by other care settings [12].

Experiences from several countries [19••, 65] show that greater knowledge of the management of anaphylaxis significantly improves treatment in the ED.

The low rate of EAI prescriptions reveals a need to train ED physicians in the importance of prevention and treatment of a new episode, which could potentially prove to be fatal.

ED physicians have limited time to assume new knowledge about anaphylaxis, which accounts for less than 0.5% of ED demand. Therefore, they should be provided with tools that allow rapid dissemination of key concepts to ensure urgent management.

Interventions to improve management of anaphylaxis in emergency departments

Guidelines aim to improve management of anaphylaxis; however, several studies reveal a lack of adherence to guidelines in EDs and a knowledge gap with respect to anaphylaxis in ED staff. Consequently, training programs are necessary to improve adherence to guidelines [13•, 18, 22, 24, 46, 47, 66–69]. Unfortunately, few data are available on the effect of education in improving management of anaphylaxis.

In their multicenter study performed in the USA, Jongco et al. [70] found that an educational intervention on anaphylaxis for pediatrics, internal medicine, and emergency medicine residents resulted in improved knowledge, competence, and confidence in the management of anaphylaxis, which remained

solid 12 weeks after the intervention. The authors concluded that these types of interventions may be effective in improving management of anaphylactic reactions.

Arroabarren et al. [19••] applied an updated protocol for management of children with anaphylaxis in the pediatric ED of a Spanish hospital. The protocol was aimed at physicians and nurses within the hospital's continuing medical education program. The authors found that the intervention led to a significant improvement in adherence to guidelines in the form of more frequent administration of epinephrine (from 27 to 57.6%), longer observation periods, and more frequent prescription of EAI at discharge and referrals to allergy specialists.

Rueter et al. [71••] showed that anaphylaxis training programs in a pediatric ED, with online access to guidelines and management and training information, as well as collaboration between pediatricians and allergists, significantly improved correct identification of anaphylaxis (from 67.6 to 89.8%) and increased the frequency of administration of epinephrine, EAI prescription, and referral to an allergist [71••].

Cohen et al. [44] found that despite the implementation of reviewed diagnostic and treatment anaphylaxis guidelines in a pediatric ED, the percentage of misdiagnosed cases remained unchanged, although referral to an allergist improved. The authors discussed institutional coding limitations and concluded that additional cases would have been correctly identified if a separate code for anaphylaxis had been added to the discharge forms.

At the Children's Hospital of Philadelphia, USA, a multidisciplinary team including physicians, nursing staff, and registered nurses from the division of pediatric emergency medicine and allergy created a clinical pathway to guide management of anaphylaxis in the ED. The authors were able to safely reduce the period of observation from 8 to 4 h in cases of complete resolution and absence of severe symptoms, and thus to decrease unnecessary hospitalizations. The strategy significantly reduced the percentage of admissions from 58.2 to 25.3%, although no differences in the rate of administration of epinephrine or referral to an allergist were recorded [45].

In conclusion, training programs can ensure that anaphylaxis is managed in the ED in accordance with guidelines.

Conclusions

Sciar and Lieberman [32] state that anaphylaxis is an under-recognized, under-reported, and under-treated condition. The results of the present review support this observation. Although reported data indicate that it is possible to increase the quality of care provided to anaphylaxis patients in the ED, many doubts remain on the permanence of these improvements once the initial interventions are complete. On the other hand, if we examine our experience, the low incidence of anaphylaxis episodes attended in our ED (one episode of anaphylaxis every 3 days and one physician treating one anaphylaxis episode every 2 or 3 months) can help to explain the low use of epinephrine in our ED and the low rate of referral to our Allergy Unit. Consequently, we should rethink strategies to improve management of anaphylaxis in the ED. Since ED physicians are probably more

motivated to improve their knowledge of clinical events that are more prevalent than anaphylaxis, these strategies should involve the transmission of key concepts and measures.

Compliance with Ethical Standards

Conflict of Interest

Ana Rosado declares that she has no conflict of interest. Maria Moro-Moro declares that she has no conflict of interest. Ana Gonzalez-Moreno declares that she has no conflict of interest. Teresa Alfaya-Arias declares that she has no conflict of interest. Nuria Alberti-Masgrau declares that he has no conflict of interest. Miguel Tejedor-Alonso declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Epinephrine is increasingly used for treatment of anaphylaxis in several European countries. Have national and international campaigns promoting better management of anaphylaxis proven successful?

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