Anaphylaxis: a ten years inpatient retrospective study

Malee Techapornroong[1,2], Krittapoom Akrawinthawong[1], Wisit Cheungpasitporn[1] and Kiat Ruxrungtham[3]

Summary

Background: **The actual incidence of anaphylaxis is unknown. Periodical study of the anaphylaxis in different countries will raise the awareness to improve further the prevention and care.**

Methods: **To investigate anaphylaxis among inpatients in the previous decade, we conducted a retrospective study of adult patients between 1992 and2001 at a tertiary care center in Bangkok.**

Results: **Of 448,211 admissions, 80 events of anaphylaxis in 79 patients (0.017%) were found. The incidence had increased from 2.6 to 46 per 100,000 inpatients. Mean age±SD was 36±16 years-old, with an equal male:female ratio. Drugs, mainly antibiotics and non-steroidal anti-inflammatory agents, (48%) and food (31%) were the most common causes. Over-the-counter medication and multiple drug use were responsible for up to a half of the unspecified drug causes. There was no fatality. 84% received epinephrine, but in only 7 % it was given intramuscularly. Fifteen cases (20%) had a history of prior anaphylaxis, nonetheless only one had received prefilled epinephrine.**

Conclusions: **the rise in the incidence of anaphylaxis over the two decades of the study period is alarming. Raising the awareness of anaphylaxis management among healthcare providers and the public is warranted. *(Asian Pac J Allergy Immunol 2010;28:262-9)***

Key words: *Anaphylaxis, Thailand, NSAIDs, Antibitotics, Food-induced anaphylaxis*

From the [1]Faculty of Medicine, Chulalongkorn University
[2]Department of Medicine, Prapokklao Hospital, Chantraburi
[3]Division of Allergy and Clinical Immunology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.
Corresponding author: Kiat Ruxrungtham
Email: kiat.r@chula.ac.th
Submitted date: 15/5/2010
Accepted date: 8/9/2010

Introduction

The actual incidence of anaphylaxis is unknown. In the United States of America, it is at least 10 to 21 per 100,000 of population[1]. In Europe, two studies reported the incidence to be 3.2 cases per 100,000 person-years in Denmark[2] and 9.8 cases of out-of-hospital anaphylaxis per 100,000 person-years in Munich, Germany[3]). In Thailand, only few of retrospective studies in university-based hospitals have been conducted. One-year study of patients who attended the emergency department of an university hospital in Thailand found an incidence of up to 223 cases per 100,000 patients[4]. Another study from a university hospital in Bangkok showed an incidence of 55.45 cases per 100,000 admitted persons in 2004[5]. Periodical study of the anaphylaxis in various centers in different countries will further raise the awareness of changes in causative agents among each of the medical communities.

This paper describes the incidence, etiology, clinical manifestations, management and outcome of patients with anaphylaxis over a 10 years-period at a tertiary care center, the King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

Methods

Medical record review

This is a retrospective study performed at the Inpatient Services at the Department of Internal Medicine, King Chulalongkorn Memorial Hospital (data from January 1, 1992, through December 31, 2001). Computerized databases of the division of Clinical Epidemiology, Department of Medicine were searched for discharge diagnostic ICD-10 code for anaphylaxis. All of the cases were reviewed from the medical records and specific data were collected using specially designed data collection sheets, taking account of the objectives of the study.

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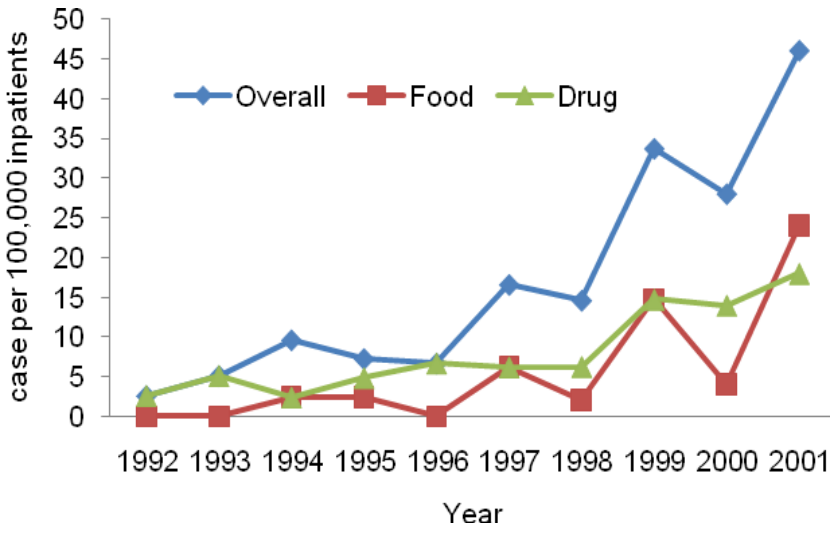

Figure 1. Prevalence and incidence of anaphylaxis in the Inpatient Unit, Department of Medicine, and King Chulalongkorn Memorial Hospital, 1992-2001 (per 10,000 inpatients per year)

Definitions

Case definition required one feature of generalized mediator release such as flushing, pruritus or paresthesias of lips, axilla, hands or feet, general pruritus, urticaria or angioedema and at least one additional feature indicating multisystem involvement, as reviewed by Yocum et al in 1999[6] as discussed below. 1. Oral and gastrointestinal: oral mucosal pruritus, intraoral angioedema of buccal mucosa, tongue, palate or oropharynx, nausea, emesis, dysphagia, abdominal cramps or diarrhea. 2. Respiratory: rhinitis, stridor, cough, hoarseness, aphonia, tightness in the throat, dyspnoea, wheezing, hypopharyngeal or laryngeal edema or cyanosis. 3.Cardiovascular : chest pain, arrhythmia, hypotension, presyncope, syncope, tachycardia, bradycardia, orthostasis, seizures, or shock.

However, there were 2 cases which did not meet these criteria, but were considered to have suffered anaphylaxis i.e., one had an immediate syncopal event with hypotension within 30 minutes of receiving medication; the other had acute respiratory symptoms with laboratory evidence of anaphylaxis (in this case was urine histamine positive). Anaphylactoid reaction was also included in this study. Recorded data of systolic blood pressure lower than 90 mmHg and diastolic blood pressure lower than 60 mmHg were considered as hypotension or shock.

Etiology

The definite cause is defined as when the allergic skin prick test is positive or a provocative test is positive with clinical evidence of anaphylaxis. Probable cause is defined as when only one suspected agent was taken at that anaphylactic episode. Possible cause is defined as when the possible causative agent was taken together with multiple agents.

Results

Epidemiology and prevalence of anaphylaxis

Of 448,211 admissions, the computer found 98 cases that had a diagnosis code for anaphylaxis. Seventeen medical records were missing and one case did not meet the criteria for anaphylaxis. This left a total of 80 episodes of anaphylaxis in 79 patients in our review. The annual incidence during the study period increased from 0.26 per 10,000 persons in 1992 to 4.6 per 10,000 persons in 2001. The incidence of each year is shown in Figure 1. Demographic data are summarized in Table 1. Most patients developed anaphylaxis prior to their hospitalization, only 6% (5 cases) developed anaphylaxis during the admission. Two patients received horse serum antivenom for treating snake bite with a record of the antivenom skin tests being negative. Another two received chemotherapeutic agents, L-asparaginase (skin test negative) and carboplatin. The last case was referred for an allergy consultation with a history of recurrent allergic reactions.

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Table 1. Demographic characteristics of 79 patients with 80 episodes of anaphylaxis

Characteristic	Number of patients (%)
Male: Female	39:40
Mean age (range 15-83 years; SD = 16)	36 years
History of atopy *	12/75 (16 %)
Prior anaphylactic reaction *	15/73 (20 %)
History of drug allergy type I *	11/73 (15 %)

* Data not available in few cases

Etiologies

Of 80 episodes, the two most common causes of anaphylaxis were drugs (38 cases, 47.5%) and food (25 cases, 31.3%). Although 95% had a recognizable cause, most were considered as probable or possible causes. Only 3 of 80 cases had a definitive cause. One case developed anaphylactic shock following a rifampicin oral re-challenge test. The second case was from sesame sweets; although the skin prick test for sesame oil was negative, the oral challenge test confirmed an anaphylactic reaction. And the third case was latex allergy with a cross reaction to jackfruit; she developed anaphylaxis 15 minutes after a skin prick test with the dried jackfruit extract. In 21% of drug-induced anaphylaxis the specific causative agent could not be confirmed.Up to a half of the reactions were related to taking unlabeled over-the-counter drugs or taking multiple drug therapy. All causes are summarized in Table 2. Antibiotics that were reported as probable/possible causative agents including: penicillin (3), amoxicillin (1), co-trimoxazole (3), cloxacillin (1), anti-tuberculosis drug, and ciprofloxacin (1). Among patients who had NSAID induced anaphylactoid reactions, the following probable/possible causative agents were reported: Aspirin (ASA,7), ibuprofen (3),

Table 2. Etiologies of 80 episodes of anaphylaxis

Category	Number of Episode (%)	Specific agent	
		Probable cause	Possible cause
Drug	38 (48 %)	NSAID 12/38 (31.6%) ASA 6, Brufen 3, Unspecified 3 Antibiotic 12/38 (31.6%) Penicillin 2, Cloxacillin 2, Bactrim 2, Amoxycillin 1, Rifampin 1*, Ciprofloxacin 1, Unspecified 3 Chemotherapeutic agent 2/38 (5.3%) L-asparaginase 1, Carboplatin 1 Unidentified 8/38 (21.1%)	Diclofenac / Pethidine (1/38) Penicillin / Naproxen (1/38) Bactrim / ASA (1/38) Antituberculosisagents (1/38)
Food	25 (31 %)	Seafood 5/25 (20%) Shell 2, Fish 1, Shrimp 1, Unspecified 1 Others 13/25 (52%) Grasshopper 3, Beer 2, Alcohol 1, Frog 1, Ice cream 1, commercially packed chicken soup 1**, Dried jackfruit 1*, Dried banana 1, Sesame sweet 1* , Thai papaya salad 1 Unidentified 2/25 (8%)	Multiple kinds of food (5/25) (Alcohol, bean, bread, dessert, egg, pork, grasshopper, pine apple yam, sausage, seafood, squid, Thai papaya salad)
Contrast media	5 (6 %)	Angiograffin 1, Unspecified 4	
Insect sting	3 (4 %)	Centipede 1, Unspecified 2	
Anti-snake venom	2 (2.5 %)		
Immunotherapy	1 (1.3 %)	Aeroallergen 1	
Exercise induced food	1 (1.3 %)	Seafood 1	
Grass-contacted	1 (1.3 %)		
Unknown	4 (5 %)		

** Definite cause* *** Supplement food*

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diclofenac (1), and naproxen (1). Seafood is the most common cause of food-induced anaphylaxis (20%). Interestingly, 3 cases were caused by eating fried insects, in this case, they were grasshoppers.

Clinical manifestations of reported anaphylaxis

Of 80 episodes, 76 had cutaneous (95.0%), 63 had respiratory (78.8%), 56 had cardiovascular (70.0%) and 19 had oral-gastrointestinal (23.8%) manifestations. All clinical presentations are summarized in Table 3. The onset of anaphylaxis was available for more than two-third of the patients (74%). Most of patients (80%) with available recorded data had developed symptoms of anaphylaxis within 30 minutes. In about a third of the events (29%) the symptoms occurred in less than 10 minutes. These patients consist of 9 drug-related (of 38, 24%), 5 food-related (of 25, 20%), 3 contrast media-related (of 5, 60%) and all cases of insect sting (3 cases), snake antivenom (2 cases) and allergen immunotherapy (1 case). Concerning the characteristics of delayed onset of reactions, 12 of 59 cases (20%) developed the reaction after 30 minutes: 7 cases from a drug, 4 cases from food and 1 case from grass-contact. There are 2 interesting cases worth presenting in detail i.e., Case 1 "Topical penicillin-induced anaphylaxis": A female age 24 years had anaphylaxis caused by applying penicillin topically. She used ground penicillin V powder to treat her skin ulcer, 5 minutes later she rapidly developed chest tightness, loss of consciousness and seizure. She was cardiopulmonary resuscitated at a private hospital prior to hospitalization at our hospital. She completely recovered within 48 hours after the standard treatment. Case 2: - A female age 18 years, had grass-contact induced anaphylactic shock. She developed anaphylaxis 30 minutes after sitting on the grass. There was no evidence of an insect sting reaction. She had a previous history of grass-contact induced urticaria. After treatment for 24 hours, she recovered completely.

Table 3. Symptoms and signs of anaphylaxis

Symptom or sign	% total episodes (N=80)
Cutaneous	95.0
Urticaria	61.3
Angioedema	57.5
Flushing	11.3
Pruritus	8.8
Rash	5.0
Respiratory	78.8
Chest tightness	71.3
Wheezing	33.8
Dyspnea	8.8
Cough	3.8
Rhinitis	2.5
Apnea	1.3
Cardiovascular	70.0
Hypotension	60.0
Syncope	25.0
Presyncope	13.8
Oral-gastrointestinal	23.8
Nausea and vomiting	17.5
Abdominal pain	8.8
Diarrhea	7.5

Management and clinical outcomes

Five cases were transferred from other hospitals after the specific management had been given. The other five cases were referred from private clinics. In respect to treatment (Table 4), most of the patients received appropriate standard treatment: 83.8%, 83.8% and 76.3% were treated with adrenaline, corticosteroid and antihistamine respectively. However only 1% of the patients received adrenaline intramuscularly, in most cases it was given either subcutaneously or intravenously. Interestingly, of 15 patients who had a history of prior anaphylaxis or food anaphylaxis, only 1 had received an adrenaline kit. No biphasic and protracted cases were noted. None of the patients in this study died.

Causes and the management of very severe anaphylactic reactions

Fourteen cases had very severe anaphylaxis as defined by "patients who required continuous inotropic and/or vasoactive agent infusion or cardiopulmonary resuscitation (CPR)". (Table 5) 14/80 cases (17.5%) developed severe anaphylaxis with profound shock (needing an IV inotropic drug), apnea and cardiac arrest. Almost all (12/14 or 86%) were drug-induced, whereas 2

Table 4. Treatment in anaphylaxis

Treatment	% of total
Duration of admission	
< 24 hrs	58.7
24-72 hrs	30.0
> 72 hrs	11.3
Hospital medication	
Adrenaline	83.7
Corticosteroid drug	83.7
Antihistamine drug	76.3
Home medication	
Adrenaline kit	1.3
Corticosteroid drug	23.8
Antihistamine drug	55.0

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Table 5. Data of 14 cases with very severe anaphylaxis (mean age was 35 years)

Case	Cause	Clinical feature	Management
1	Shell	Profound hypotension	Epinephrine IM, Dopamine IV infusion
2	Multiple kinds of food	Profound hypotension	Epinephrine IM, Dopamine IV infusion
3	Penicillin / Naproxen	Profound hypotension	Epinephrine IM, Dopamine IV infusion
4	Cloxacillin	Profound hypotension	Epinephrine IV, Dopamine IV infusion
5	L-asparaginase	Profound hypotension	Epinephrine IV, Dopamine IV infusion
6	Rifampicin	Profound hypotension	Epinephrine IV, Dopamine IV infusion
7	AntiTB drug	Profound hypotension	Epinephrine IM, Dopamine IV infusion
8	Contrast media	Profound hypotension	Epinephrine IV, Dopamine IV infusion, ICU admission
9	Contrast media	Profound hypotension	Epinephrine IV, Dopamine IV infusion
10	Contrast media	Profound hypotension	Epinephrine IV, on endotracheal tube, Dopamine IV infusion, ICU admission
11	Contrast media	Severe bronchospasm	Epinephrine IV, ICU admission
12	Penicillin	Cardiac arrest	Epinephrine IV, on endotracheal tube, Dopamine IV infusion, ICU admission
13	Cloxacillin	Apnea	Epinephrine IV, on endotracheal tube
14	Unspecified drug	Profound hypotension	Epinephrine IM, Dopamine IV infusion

cases were caused by food. Of note, radiological contrast media and penicillin-derivatives (4 cases of each) were the most common causative agents. Eight of ten cases which had received drugs by the intravenous route suffered severe anaphylaxis. An 81 years-old female with underlying hypertension developed atrial fibrillation with hemodynamic instability after the slow intravenous injection of 0.5 ml epinephrine diluted in 2 ml normal saline. Nonetheless, after cardioversion, no other serious complication was observed. Two cases required CPR, nonetheless there was no fatality.

Discussion

This 10 years study of anaphylaxis has given us an insight into anaphylaxis among hospitalized patients in our tertiary care center. We have reported the results based on only the inpatient databases of the Department of Medicine, King Chulalongkorn Memorial Hospital (A medical school affiliated tertiary care center to the Faculty of Medicine, Chulalongkorn Univeristy, Bangkok). As a retrospective study, a number of limitations need to be taken into consideration, including the high possibility of under-reporting and incomplete data recording. The evaluation of morbidity and mortality may be incomplete as well. In addition, anaphylaxis is a clinical diagnosis and has a wide variety of clinical presentations. There is no universally accepted definition[7] and no clear classification of symptoms and signs or degree of clinical presentation[8, 9].

This 10 years observation has shown that this life-threatening systemic reaction is not uncommon in an inpatient setting. 79 anaphylaxis cases with 80 episodes of the attack were found with the estimated overall prevalence of 1.78 per 10,000 inpatients person-year. In comparison to other countries, the incidence of anaphylaxis varies between countries and clinical settings. In the study conducted by Yocum et al in the U.S.[6], the occurrence rate was 21 cases per 100,000 person-years. In the European studies, the incidence ranges from 1 to 3 cases per 10,000 patients[2, 3]. With regard to other retrospective studies in Thailand, a 1-year study of patients who attended the emergency department at Thammasat University Hospital found an occurrence rate of 223 cases per 100,000 patients per year [4]. Another study of patients with anaphylaxis admitted to Siriraj Hospital showed that the annual occurrence of anaphylaxis increased from 9.16 per 100,000 admitted persons in 1999 to 55.45 per 100,000 admitted persons in 2004[5].

This 10 years observation has shown that this life-threatening systemic reaction is not uncommon in an inpatient setting. We found an overall prevalence of 17.8 per 100,000 inpatients person-year with a 4.8 folds rise in the incidence. Sheikh et al had reported a similar finding with a two-fold increase in hospital admissions for anaphylaxis between 1991 and 1995[9]. Recent Thai studies have also reported a similar increased hospital incidence to more than 50 per 100,000 patients [5, 10]. Better development both in medical and non-medical aspects of society in the past

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decades may have led to more exposure to therapeutic agents, changes in life-style and diet. These factors may be associated with the rise of anaphylaxis. However, better patient education and improved skills of health-care providers in diagnosing anaphylaxis may also have contributed to the increase in these life-threatening systemic reactions.

For this inpatient setting, up to 50% and one-third of incidents were caused by drugs and food respectively, which was similar to the results reported in the other 2 previous studies from Bangkok, Thailand. Drug-induced anaphylaxis seems to be more common in Thailand than in Europe and America. (Table 6) Considering the age group, drug and food were predominant in younger patients (mean age was 36.57 and 31.52 years respectively) whereas contrast medium was found to be a common cause in the older age group (mean age was 48.8 years). With regard to drug-induced anaphylaxis, antibiotic and NSAID (31.6% for both) were the two leading causes, which was also the case in the previous studies (Table 7)

We could not specify the causative drugs in 21 % (8/38) of patients. Other studies have reported that the causative agent could not be definitely identified in 0-17% of drug-induced anaphylaxis (Table 6). Besides concurrent multiple drugs exposure, the habit of using non-prescribed drugs or herbal medicine in the Thai population may contribute to the gaps in our data collection. Consequently, legal actions are required for reinforcing a clear label of medications being sold in the market, over-the-counter in particular.

Atopy was not believed to be a predisposing factor for greater risk of anaphylaxis[11]. Other studies found that atopy might be an important risk factor of anaphylaxis or for more severe anaphylactic episode[12] [13]. The other study had shown high prevalence of atopic disease in idiopathic anaphylaxis[14]. However, with limitations of a small sample size (only 16% reported underlying allergy) and as a retrospective study, our study could not draw any conclusion regarding the role of atopy on anaphylaxis.

On the basis of the clinical diagnosis and the lack of a universal consensus on the definition of anaphylaxis[7], the frequency of allergic drug reactions has been overestimated[15, 16]. This inevitably results in higher cost of medication for the patient who cannot use the first line drug because of the false history of drug allergy. Ideally physicians should be aware of a previous history of anaphylaxis to avoid the risk of re-exposure. In reality however, 10% (8/79) of patients in our study, who had a history of previous anaphylaxis, had been re-exposed to the same causative agent. Three of them developed anaphylactic shock. This finding was consistent with data from a population-based study which revealed that the non-first time anaphylaxis can occur up to 17% of cases (23/133) [6].

Most of patients (80%) developed symptoms of anaphylaxis within 30 minutes. This data further supports the recommendation of a close observation period of least 30 minutes for the patient who receives therapeutic or diagnostic agents with a high risk for anaphylaxis. Nonetheless, one must be aware that one-fifth of

Table 6. Reported causes of anaphylaxis from previous studies

Study	Setting	No. of cases (episodes)	Cause of anaphylaxis (%)						
			Drug	Food	Insects	Anti venom	Exercise	Radiographic Contrast media	Idiopathic
Brown et al, 2001 [7]	ER	142	28	17	18	NA	NA	NA	27
Cianferoni et al, 2001 [18]	ER	113	49	8	NA	29	2	NA	6
Yocum et al, 1999 [6]	OPD,ER	154	17	36	15	NA	NA	NA	32
Kemp et al, 1995 [8]	OPD	266	20	34	NA	NA	7.1	NA	37
Yocum et at, 1994 [32]	OPD	179	16	42	18	NA	8.5	NA	24
This study (Thailand) 1992-2001	IPD	79 (80 episodes)	48	31	3.8	2.5	1.3	6.3	5
Bunsawansong et al, (Thailand) 2003-2004[33]	-	28	36	29	11	NA	NA	NA	15

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Table 7. Drug-induced anaphylaxis from previous studies

Study	No. of case	Antibiotics* (%)	NSAIDs* (%)	Unidentified cause* (%)
Brown et al, 2001[7]	142	42.5	25.0	17.6
Cianferoni et al, 2001[18]	113	48.0	35.0	-
Kemp et al, 1995 [8]	266	25.0	52.0	0
This study, 1992-2001	80	31.6	31.6	21.1

*Percentage is calculated only from the drug induced anaphylaxis group.

our patients developed the reaction after 30 minutes[17]. Similarly to other studies, we found cutaneous features are the most common manifestations (95%)[6, 18]. Up to 50% of the patients had hypotension, and up to 20% had very severe anaphylaxis that required CPR or continuous vasoactive agent infusion. Drugs and radiological contrast media are the main causative agents. Although our data showed that at least a half of those with very severe anaphylaxis developed the reaction within 30 minutes and a third developed it within 10 minutes, but some of them had took longer than 30 minutes to develop symptoms. Biphasic anaphylaxis has been reported vary from 5% to 23% [5, 19, 20], however there was no report found in this study. The reasons are not well understood; it may due to under reporting, missing records, or early epinephrine treatment.

Appropriate administration of epinephrine is safe and valuable [21, 22]. In this study, the rate of prescribing epinephrine was a bit higher than in other recent studies (75-78%) [5, 10] i.e., 84% of overall patients and 94% of patients with shock received epinephrine. Although the current evidence-based recommendation is to give epinephrine intramuscularly in the lateral aspect of thigh [23], only 7% of patients in this study received an intramuscular epinephrine injection. The intravenous route of administration is acceptable in severe case with EKG monitoring [24, 25]. However, the risk of cardiac arrhythmia and/or myocardium ischemia needs to be taken into the consideration. Rapid intravenous bolus administration of epinephrine therefore should be avoided. In this study, 8 cases received intravenous epinephrine. A 81 years-old female with underlying hypertension developed atrial fibrillation with hemodynamic instability after the slow intravenous injection of epinephrine, however she recovered after the cardioversion with no complication.

Emergency preparedness and self first-hand management is critical when faced with recurrent anaphylaxis, as the onset of anaphylactic reaction is usually very rapid and life threatening and patients may not have enough time to obtain treatment [26-29]. Thus patients with a history of recurrent anaphylaxis, insect sting or food-induced anaphylaxis in particular, should be prescribed a self-injectable epinephrine kit [30]. In this study of, only 1 out of 15 cases with a history of prior anaphylaxis received epinephrine in the form of a set of epinephrine prefilled syringes, whereas another study reported that 92% of their patients carried an epinephrine autoinjector [13]. In settings where commercial autoinjector epinephrine kits are not widely available, a prefilled epinephrine set is the only option. Its stability and sterility have recently been confirmed for up to 3 months after preparation [31]. This useful information supports the reliability of such a cost-effective emergency life-saving epinephrine prefilled set.

Conclusions

Anaphylaxis is not uncommon in an inpatient setting in Bangkok, Thailand. There has been a 4.8 fold increase in the incidence of anaphylaxis during the 10 year study period. Drug and food are the most common causative agents. Antibiotics and NSAID were found in high proportion of drug related cases. The leading causes of very severe anaphylaxis were drugs and radiological contrast media. Over-the-counter medication and multiple drug use were responsible for up to half of unspecified drug related cases. Proper drug labeling and use should lessen the risk of drug-induced anaphylaxis.

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Patient close observation for 30 minutes after administration of any high risk or unknown risk new agent is required for early detection and management of the life threatening anaphylaxis. To further improve anaphylaxis care, we need to continue raising the awareness among health care providers and the general public of the proper detection and management of anaphylaxis is warranted.

Acknowledgements

This work and KR is supported in part by the Research Team Strengthening Grant from the National Center for Genetic Engineering and Biotechnology (BIOTEC), Thailand. The authors declare no conflict of interest.

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