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# Anaphylactic deaths in Maryland (United States) and Shanghai (China): A review of forensic autopsy cases from 2004 to 2006

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### ABSTRACT

Anaphylaxis is a life threatening allergic reaction that is rapid in onset and may cause sudden death. A retrospective study was performed using the database from the Office of the Chief Medical Examiner (OCME) in the State of Maryland and the Department of Forensic Medicine in Shanghai Medical College (DFM-SMC) to examine the etiology and forensic investigation findings of anaphylactic deaths from 2004 to 2006. Details of the medical history, agent responsible for the allergic reaction, death scene investigation and postmortem examination findings were reviewed for all cases.

A total of 28 cases of anaphylactic death were identified for the study period, 17 from Maryland and 11 from Shanghai. Of the 17 Maryland cases, 6 (35%) involved allergic reaction to food, 5 (25%) to drugs, 2 to bee stings, 1 to hair dye, and 3 to unknown allergens. Investigation revealed that 9 of 17 cases had a history of asthma and 8 had previous allergic reactions to certain foods and / or drugs. In Shanghai, all 11 deaths resulted from anaphylactic reaction to antibiotics, 10 of which occurred in clinics illegally operated by unlicensed physicians.

The interval between the onset of symptoms and death ranged from less than 1 min to 3 days after initially contacting the allergen. In the majority (68%) of cases, death occurred within 8 h after the onset of symptoms. Postmortem findings were relatively non-specific, and included pharyngeal/laryngeal edema 14/28 (50%), mucus plugging in the airways 11/28 (39%), and pulmonary congestion and edema 28/28 (100%). Serum tryptase concentrations were measured in 14 cases in Maryland and the concentration ranged from 3.3 ng/ml to 200 ng/ml.

There were significant differences with regards to allergen type and the circumstances of death between these two regions. Inappropriate use of antibiotics and illegal medical practices were the main causes of identified anaphylactic death in Shanghai. In Maryland anaphylactic deaths were mainly caused by food reactions. This study indicates that the postmortem diagnosis of anaphylactic death is usually based on exclusion and circumstantial evidence. Knowledge of the patient's history and circumstances of death is of major importance for the forensic pathologist when investigating suspected anaphylactic death.

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## 1. Introduction

Anaphylaxis is a serious systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance and may cause death. Affecting children and adults, anaphylactic reaction is

a well recognized cause of sudden death. Current data suggest that there are approximately 1500 deaths annually from anaphylaxis in the United States, and between 2.8 million and 42.7 million Americans are at risk of experiencing an episode of anaphylaxis during their lives [1]. Data regarding the incidence and prevalence of anaphylaxis and the number of deaths caused by it in China could not be found in the published literature. Sudden anaphylactic deaths that occur outside hospital, sometimes in the emergency room, or during medical treatment usually are subject to forensic autopsies. These cases are a source of frustration to the forensic pathologist because postmortem diagnosis of anaphylaxis can be very difficult due to the non-specific pathologic findings and

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the diagnosis of anaphylactic shock is one of exclusion and is often based circumstantial evidence [2–4].

The Office of the Chief Medical Examiner (OCME) is responsible for investigation of all the violent deaths, sudden and unexpected deaths, suspicious deaths, deaths without a physician in attendance, and deaths in a penal institution in the State of Maryland. The Department of Forensic Medicine, Shanghai Medical College (DFM-SHMC) is an institution, which assists the police and local health departments to do medicolegal investigation of certain deaths, mainly sudden and unexpected deaths, suspicious deaths, and deaths due to possible therapeutic misadventures. A respective study of anaphylactic deaths occurring in the State of Maryland (United States) and Shanghai City (China) was conducted. The purpose of our study was to determine the etiology and circumstances of anaphylactic deaths in these two different regions. This study focuses on the characteristics of anaphylactic deaths investigated by OCME in the State of Maryland and DFM-SHMC in Shanghai City.

## 2. Materials and methods

This study was a retrospective review of all deaths due to anaphylactic reaction investigated by the Office of the Chief Medical Examiner for the State of Maryland (OCME-MD) and the Department of Forensic Medicine at Shanghai Medical College (FM-SHMC) over a three-year-period from January 2004 to December 2006.

The anaphylactic death in our study is defined as a death caused by a serious allergic reaction that occurs rapidly (minutes to several hours) after exposure to a likely allergen. The postmortem diagnostic criteria of anaphylactic death were similar in these two institutions. They were based on (1) the circumstantial evidence, including history of exposure to a likely allergen prior to death, clinical presentation of an allergic reaction, such as involvement of skin-mucosal surface (e.g., generalized hives, pruritus, swollen lip–tongue–uvula), respiratory compromise (e.g., dyspnea, wheeze, hypoxia), and reduced blood pressure or associated symptoms that occur rapidly (minutes to several hours) after exposure to a likely allergen; (2) postmortem findings suggesting an allergic reaction, such as laryngeal edema, mucous plugging in the airways, erythematous skin rash and edema, eosinophilia in the mucosa and submucosa of the respiratory and the gastrointestinal tracts, and marked pulmonary congestion and edema, (3) exclusion of other possible cause of death based on the circumstances of death and autopsy examination including toxicology test. In addition, the serum alpha and beta tryptase were tested by Enzyme Immunoassay (EIA) with fluorescent substrate on the suspected anaphylactic cases in the State of Maryland. The normal upper limit of total serum tryptase level had been established and was set at 11.4 ng/ml in the Office of the Chief Medical Examiner.

A total of 28 cases of anaphylactic death were identified for the study period, 17 from Maryland and 11 from Shanghai. In Maryland, all of the autopsies were performed within 24 h after death was determined. The autopsies in Shanghai were performed between 36 h and 10 days after death.

The cases were analyzed as to (1) general characteristics of the victims (age, gender, and race); (2) personal information from interview of the victim's relatives, acquaintances, witnesses, or doctors (including any allergic symptoms prior to death, medical history, history of allergies, current medications, or history of drug or alcohol abuse); (3) postmortem examination findings including histological study and toxicology testing; (4) cause of death. The data that were analyzed were extracted from the police investigation report, medical record, interviews of the victim's family members, witnesses, or doctors by forensic pathologists or investigators, and forensic autopsy protocols.

## 3. Results

Between 2004 and 2006 a total of 28 deaths (17 from Maryland and 11 from Shanghai) were caused by anaphylactic reaction. The general characteristics of these 28 cases are summarized in Table 1. With regard to gender, the study cases were evenly split, with males (14) and females (14), each comprising 50% of the total. Of the 17 cases in Maryland, 11 decedents were African-American and 6 were white. Of the white decedents, 4 were male (66.7%) and 2 were female (33.3%). Three of the African-American decedents were male (27.3%) and 8 were female (72.7%). All 11 decedents in Shanghai were Han, of which 7 were male (63.6%) and 4 were female (36.4%). Overall, the age distribution of anaphylactic deaths in this study ranged from 1 to 81 years, with a median age of 37 years.

**Table 1**  
General characteristics.

|                              | Maryland  | Shanghai  |
|------------------------------|-----------|-----------|
| Gender (Female:male)         | 10:7      | 4:7       |
| Race (White:Black:Asian)     | 11:6:0    | 0:0:11    |
| Age in years, range (median) | 1–81 (43) | 2–49 (31) |

### 3.1. Clinical history and presentation

Analysis of the data revealed that 12 out of 17 cases (70.1%) in Maryland had history of asthma and/or previous allergic reactions to certain food or drugs. Four cases did not have reported history of allergy and the history was unknown in one case. In Maryland, six cases had significant history of hypertension, three had heart disease, and two had Chronic Obstructive Pulmonary Disease (COPD). Regarding the Shanghai cases, all individuals were reportedly healthy, with no history of asthma or allergy (Table 2).

The symptoms and signs of anaphylactic reactions varied across the study cases, ranging from shortness of breath ( $N = 15$ ), failure of endotracheal intubation due to severe swelling of the upper airways ( $N = 2$ ), urticaria of the skin and facial swelling ( $N = 2$ ), vomiting ( $N = 2$ ), and sudden shock ( $N = 1$ ). Two individuals reported mild discomfort. Five people were found deceased without obvious signs of anaphylactic reaction.

The interval between the onset of symptoms and death ranged from less than 1 min to 3 days after initially contacting the allergen (Table 3). In the majority (68%) of cases, death occurred within 8 h after the onset of symptoms.

### 3.2. Allergens

Of the 17 Maryland cases, 6 (35.3%) involved allergic reaction to food: 3 to seafood, 2 to peanuts, and 1 to uncertain allergen(s) of ice cream. Five (29.4%) cases involved reaction to drugs: 2 to antibiotics (1 to Ceftriaxone, and 1 to Penicillin), 1 to Dilaudid, 1 to Lisinopril, and 1 to anesthesia (Propofol, Succinylcholine, Medazolam, Vecuronium, Fentanyl). Of the remaining 6 cases, 2 involved reaction to bee stings, 1 to hair dye, and 3 to unknown allergens (Table 4).

All 11 (100%) cases from Shanghai involved allergic reaction to antibiotics. Six of these cases involved reaction to a specific antibiotic: 4 to Cephalosporin, 1 to Lincomycin, and 1 to Penicillin. Five of the 11 cases involved reaction to combined use of antibiotics, including 3 cases to Cephalosporin and Lincomycin, 1 to Cephalosporin and Gentamicin, and 1 to Cephalosporin and Bupleurum (a Chinese herb) (Table 4). Of the 11 Shanghai cases, 10 deaths occurred in clinics illegally operated by unlicensed physicians and one death occurred in a major hospital. The route of antibiotic administration in the Shanghai cases is showed in Table 5. Seven out of the 11 deaths occurred after intravenous injection (IV), followed by intramuscular injection (IM) ( $N = 3$ ), and

**Table 2**  
Clinical history—Maryland and Shanghai.

|                              | Maryland  | Shanghai  | Total      |
|------------------------------|-----------|-----------|------------|
| History of allergy           |           |           |            |
| Asthma and food or drug      | 5 (29.4%) | 0         | 5 (17.9%)  |
| Asthma                       | 4 (23.5%) | 0         | 4 (14.3%)  |
| Food, drug, or hair dye      | 3 (17.7%) | 0         | 3 (10.7%)  |
| No history of allergy        | 4 (23.5%) | 11 (100%) | 15 (53.6%) |
| Unknown                      | 1 (5.9%)  | 0         | 1 (3.6%)   |
| History of medical condition |           |           |            |
| Hypertension                 | 6         | 0         | 6 (21.4%)  |
| Heart disease                | 3         | 0         | 3 (10.7%)  |
| COPD                         | 2         | 0         | 2 (7.1%)   |

**Table 3**

The interval between the onset of symptoms and death.

| Time interval  | Maryland  | Shanghai  | Total     |
|----------------|-----------|-----------|-----------|
| Within 1 min   | 4 (23.5%) | 1 (9.1%)  | 5 (17.9%) |
| Within 1 h     | 6 (35.3%) | 2 (18.2%) | 8 (28.6%) |
| 1–8 h          | 1 (5.9%)  | 5 (45.4%) | 6 (21.4%) |
| 16 h to 3 days | 0 (0.0%)  | 2 (18.2%) | 2 (7.1%)  |
| Unknown        | 6 (35.3%) | 1 (9.1%)  | 7 (25.0%) |

**Table 4**

Allergens—Maryland and Shanghai.

| Allergens                                                               | Maryland | Shanghai | Total |
|-------------------------------------------------------------------------|----------|----------|-------|
| Drugs                                                                   | 5        | 11       | 16    |
| Antibiotics                                                             | 2        | 11       | 13    |
| Penicillin                                                              | 1        | 1        | 2     |
| Cephalosporin                                                           | 1        | 4        | 5     |
| Lincomycin                                                              | 0        | 1        | 1     |
| Cephalosporin/Lincomycin                                                | 0        | 3        | 3     |
| Cephalosporin/Getamycin                                                 | 0        | 1        | 1     |
| Cephalosporin/Buplaurum                                                 | 0        | 1        | 1     |
| Other drugs                                                             | 3        | 0        | 3     |
| Dilaudid                                                                | 1        | 0        | 1     |
| Lisinopril                                                              | 1        | 0        | 1     |
| Anesthesia (Propofol, Succinylcholine, Medazolam, Vecuronium, Fentanyl) | 1        | 0        | 1     |
| Foods                                                                   | 6        | 0        | 6     |
| Hair dye                                                                | 1        | 0        | 1     |
| Bee sting                                                               | 2        | 0        | 2     |
| Unknown                                                                 | 3        | 0        | 3     |

**Table 5**

Route of administration of antibiotics in Shanghai.

| Antibiotics              | IV | IM | IM/P.O. |
|--------------------------|----|----|---------|
| Penicillin               | 1  | 0  | 0       |
| Cephalosporin            | 2  | 2  | 0       |
| Cephalosporin/Lincomycin | 2  | 0  | 1       |
| Cephalosporin/Getamycin  | 1  | 0  | 0       |
| Cephalosporin/Buplaurum  | 0  | 1  | 0       |
| Lincomycin               | 1  | 0  | 0       |
| Total                    | 7  | 3  | 1       |

IM and by mouth/per os (P.O.) in one. None of the patients received an antibiotic skin test prior to the administration.

### 3.3. Postmortem findings

Table 6 displays the autopsy findings including histological examination. Fourteen cases (50%) had laryngeal edema, 11 (39.3%) had mucous plugging in the airways, and 4 (14.3%) showed erythematous skin rash and edema. Eosinophilia was seen in the mucosa and submucosa of the respiratory tract in 18 cases (64.3%), and in the gastrointestinal tract in 10 cases (35.7%). All of the 28 cases showed marked pulmonary congestion and/or edema. Other significant pathologic changes identified at autopsy included emphysema ( $N=8$ ), atherosclerotic coronary artery disease ( $N=2$ ), and acute gastritis ( $N=1$ ).

**Table 6**

Autopsy findings.

| Autopsy findings                       | Maryland | Shanghai | Total |
|----------------------------------------|----------|----------|-------|
| Erythematous skin rash                 | 3        | 1        | 4     |
| Pharyngeal/laryngeal edema             | 5        | 9        | 14    |
| Mucous plugging in the airways         | 1        | 10       | 11    |
| Eosinophilia in respiratory tract      | 8        | 10       | 18    |
| Eosinophilia in gastrointestinal tract | 5        | 5        | 10    |
| Pulmonary congestion and/or edema      | 17       | 11       | 28    |

**Table 7**

Concentration of total serum tryptase in Maryland cases.

| Cases | Allergen                         | Tryptase level (ng/ml) |
|-------|----------------------------------|------------------------|
| 1     | Hair dye                         | 18.0                   |
| 2     | Uncertain component of ice cream | 200.0 <sup>a</sup>     |
| 3     | Unknown                          | 16.2                   |
| 4     | Bee sting                        | 200.0 <sup>a</sup>     |
| 5     | Chinese food                     | 7.3                    |
| 6     | Peanuts                          | 15.0                   |
| 7     | Anesthesia                       | 3.9                    |
| 8     | Bee sting                        | 200.0 <sup>a</sup>     |
| 9     | Chinese food                     | 3.3                    |
| 10    | Recephin                         | 27.1                   |
| 11    | Sea food                         | 8.5                    |
| 12    | Sea food                         | 8.0                    |
| 13    | Penicillin                       | 18.0                   |
| 14    | Unknown                          | 26.9                   |

<sup>a</sup> Upper reported limit for the tryptase tests.

Routine toxicology tests were performed in all 28 cases. Only one case from Maryland had blood alcohol of 0.09%w/v and positive benzoylecgonine (metabolite of Cocaine). The rest of the cases were negative for alcohol and drugs. Moreover, the drug allergens could not be detected by the routine toxicological tests. The serum alpha and beta tryptase were tested by Enzyme Immunoassay (FEIA) with fluorescent substrate in 14 out of the 17 Maryland cases. The range of total tryptase concentration was from 3.3 ng/ml to 200 ng/ml (upper reported limit for the test) in 14 cases. In 9 cases, the tryptase level was higher than 10 ng/ml. Table 7 showed the concentration of the total serum tryptase with the corresponding allergens. In 2 cases serum tryptase could not be tested because the blood samples were unsuitable due to hemolysis. The tryptase test was not requested in one case.

Allergic reaction was the single cause of death in 23 cases (82.1%). In 5 cases the cause of death was determined as anaphylactic reaction complicated by natural diseases, including atherosclerotic coronary artery disease ( $N=2$ ), COPD ( $N=2$ ), and myotonic dystrophy ( $N=1$ ).

## 4. Discussion

The incidence of all types of anaphylaxis has experienced upward trends in the United States and in the world [5,6]. Food-related reactions are now the leading cause of anaphylactic reactions treated in the emergency departments in the United States, accounting for approximately 30,000 emergency department visits and 150–200 deaths each year [7,8]. In Maryland between 2004 and 2006, foods were the most common allergen to cause anaphylactic death (35.3%), followed by drugs (29.4%) and bee stings (11.8%). Among the foods, seafood and peanuts were the most common agents. There were considerable difference between Maryland and Shanghai with regard to the types of allergens. In Shanghai, all of the cases involved anaphylactic reactions to drugs, such as antibiotics, especially Cephalosporins (81.8%). Four cases involved Cephalosporin alone and 5 cases involved a combination of Cephalosporin and other antibiotics. Compared to Shanghai, deaths from anaphylactic reaction to antibiotics were relatively rare in Maryland. There were only 2 cases from antibiotic anaphylaxis, one case involving Penicillin and the other involving Ceftriaxone. Since our study only involved the autopsied cases conducted by the OCME in Maryland, the fewer number of drug-induced anaphylactic deaths in Maryland when compared with Shanghai city may be partly due to under-reporting of events, particularly those deaths occurred in hospital. This would suggest that the data we presented, may have underestimated the true incidence of this problem in the Maryland.

There have been no reported data regarding the incidence and prevalence of lethal anaphylaxis in China. However, drug-induced anaphylaxis, especially among the hospital patients and the patients treated by illegally practicing physicians, is the leading cause of anaphylaxis and a major public health concern in China [9–10]. Our study shows that all deaths in Shanghai resulted from anaphylactic reaction to antibiotics and 10 of the 11 deaths occurred in the care of illegally practicing physicians. The current medical practice in China accounts for the higher incidence of antibiotic-induced anaphylaxis. First, there is extensive, inappropriate use of broad-spectrum antibiotics. Currently, doctors prefer to use new, expensive, highly efficient antibiotics as a first line of therapy. Cephalosporins are one of the antibiotics used as a first line of treatment, and are often combined with other antibiotics, thus increasing the potential for cross-reactivity [11–13]. Second, there are problems with the quality and purity of drugs used in China. Driven by financial interests and seeking to lower costs, some small manufacturers compromise drug quality. Third, illegal medical practices are not uncommon in China, despite prohibitions by the government. In recent years, large numbers of people, especially those from poor, rural areas, have moved to big cities seeking employment. When ill, many of these people, unable to afford legitimate medical care, seek treatment at the “cheaper” illegal medical clinics. Typically, illegal clinics are poorly equipped, lacking the necessary first aid equipment and medicine. Illegal practitioners often have limited medical knowledge and render treatments that are not standardized. When allergic reactions occur during medical treatment, practitioners find that they are helpless. Because of their fear of being held responsible, practitioners do not always immediately call for help from emergency centers, resulting in delays of treatment. All of the 10 cases occurring in illegal clinics in Shanghai involved relatively poor, migrant farmers. Fourth, the increased therapeutic use of cephalosporins, the appearance of selective allergic response to these compounds, and the lack of standardized skin tests for cephalosporins allergy have been reported to be the major factors accounting for the increase in the incidence of anaphylactic reactions to cephalosporins and the number of deaths associated with cephalosporins anaphylactic reaction since 1990s [9,10,14–19]. Our study showed that 82% (9/11) of the drug-related anaphylactic deaths in Shanghai were associated with cephalosporin use. Because there was no history of previous drug allergy among the patients, none of the nine patients received skin tests for penicillin or cephalosporins. It is the opinion of other authors [19,20], and authors of this study, that histories and penicillin skin test results do not reliably predict the likelihood of allergic reactions to cephalosporins. Therefore, standardized skin tests with cephalosporins are needed to prevent anaphylactic reactions to cephalosporins.

The postmortem diagnosis of fatal anaphylaxis presents a challenge to forensic pathologists. The pathologic findings seen in these cases at autopsy were relatively nonspecific. Sometimes swelling of larynx and accompanying pulmonary emphysema are seen along with the perhaps more common non-specific findings of visceral congestion and pulmonary edema [21,22]. Often no significant pathologic findings are discovered at autopsy [4]. In this study, features suggesting allergic reactions such as erythematous skin rash and edema, laryngeal edema, mucous plugging in the airways, and eosinophilia seen in the mucosa and submucosa of the respiratory tract were present in 64% of all cases. None of the features alone are diagnostic. The diagnosis of fatal anaphylactic reaction requires a detailed death scene investigation, including interviews of the victim's relatives, acquaintances, witnesses, and/or doctors to obtain any history of allergy, any allergic symptoms prior to death, medical history, current medications, or history of drug or alcohol abuse. A complete postmortem examination including histological study and toxicology testing is also

necessary. In the presence of a typical clinical history, absence of postmortem findings does not exclude the diagnosis of anaphylaxis.

Postmortem serum concentrations of tryptase (a mast cell product released during anaphylaxis) have been used after death as an indicator of possible antemortem anaphylaxis [23–25]. However, the reliability of measuring mast cell tryptase in postmortem blood to diagnose anaphylactic death has been questioned because moderate elevation of tryptase can be seen in other known causes of death, such as trauma and myocardial infarction [26,27]. The reference values for postmortem serum tryptase have been difficult to establish [28]. An early study by Yunginger et al. had suggested that 10 ng/ml of  $\beta$ -tryptase as a cut-off point for anaphylactic or anaphylactoid death [23]. Another study by Edston et al. had showed that a reference cut-off value of 10 ng/ml of  $\beta$ -tryptase gave a sensitivity of 86% and a specificity of 88%, while either the sensitivity or the specificity decreased at a lower or higher cut-off value [28]. In our institute, 11.4 ng/ml of total serum tryptase was established as a reference cut-off point for anaphylactic death. It has been reported that many factors, such as (1) postmortem interval; (2) sampling site (i.e., heart blood vs. femoral blood); (3) hemolysis and trauma; (4) prolonged agonal asphyxia; (5) resuscitation efforts by means of external cardiac massage, may have some influence on postmortem tryptase concentrations [25,27–29]. A more recent study by Edston et al. recommended that postmortem alpha and beta tryptase measurements should be done in serum from femoral blood, and that the normal upper limit was set at 44.3 ng/ml [29]. In Maryland, 14 out of 17 suspected anaphylactic deaths had suitable serum samples for tryptase tests with tryptase concentrations ranging from 3.3 ng/ml to 200 ng/ml. Of these, 9 cases had tryptase levels which were more than 11.4 ng/ml, and only 3 cases had tryptase levels more than 44.3 ng/ml. The lower value of tryptase was seen mostly in cases of food allergy. Our report is consistent with findings of two previous studies [23,28], which reported tryptase values below 10 ng/ml in cases of anaphylaxis due to food allergy. This implies that tryptase might not be significantly elevated even in clear-cut cases of anaphylactic death, and with a well-defined allergenic agent. Despite these limitations to the usefulness of serum tryptase tests in the postmortem anaphylactic diagnosis, the test may still be helpful in confirming suspected anaphylaxis in autopsy cases with an undetermined cause of death [25,28,30]. We conclude that in suspected anaphylactic deaths, postmortem tryptase test is a useful indicator, but the diagnosis should not be based on the tryptase test alone.

## 5. Conclusion

Antibiotics-induced anaphylaxis, especially among the patients treated by illegally practicing physicians, is the leading cause of anaphylaxis and a major public health concern in China. Ensuring the appropriate use of antibiotics and prohibiting illegal medical practice are important measurements to prevent the occurrence of deaths resulting from this type of allergic reaction. The classic postmortem findings of anaphylaxis, such as laryngeal edema, pulmonary hyperinflation, and tissue eosinophilia, are subjective and inconstant. The postmortem diagnosis of anaphylactic death is usually based on exclusion and circumstantial evidence. Knowledge of the patient's history and circumstances of death is of major importance for the forensic pathologist when investigating suspected anaphylactic death.

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