Increasing incidence of anaphylaxis in Hong Kong from 2009 to 2019 – discrepancies of anaphylaxis care between adult and pediatric patients

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Abstract

Background: Anaphylaxis has been increasing in developed countries but there is very little published data on the burden of anaphylaxis and the pattern of adrenaline autoinjector (AAI) prescription from Asia. Objectives: We aim to determine the incidence rates of anaphylaxis and prescription rates of AAI over the past decade in Hong Kong. Methods: Using a centralized electronic database of Hong Kong's sole public-funded healthcare provider, we obtained and analysed all patients between 2009 and 2019 with physician-reported diagnosis of anaphylaxis. Incidence rates were calculated using population statistics as the denominator. Patients' prescriptions on discharge were collected to determine the AAI prescription rates. Results: The overall 10-year estimated incidence rate of anaphylaxis was 3.57 per 100,000 person-years. An increasing trend over time across both pediatric and adult populations from 2009 to 2019 was found which was more marked among the pediatric population. There was an overall increasing rates of AAI prescription for patients admitted for anaphylaxis, but the overall AAI prescription rate was less than 15% and was significantly less likely to be prescribed for the adult compared to pediatric patients (36.5% vs. 89.4%, $p<0.001$). Conclusions: An increasing trend of anaphylaxis incidence rates over the past decade is evident in Asian populations, with a discrepantly low rate of AAI prescription, particularly in the adult patients.

Introduction

Anaphylaxis is defined as a potentially fatal, severe and systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance [1]. Although rare, deaths caused by food-induced anaphylaxis are continuing to occur at an estimated rate of 5 to 200 cases per year in the United States[2]. Anaphylaxis registries and prospective studies from the West have reported an increasing trend of anaphylaxis incidence over time [3-5]. In contrast, the burden of anaphylaxis was thought to be lower in Asia and different from the West in terms of varying age distribution, anaphylaxis triggers and low usage of adrenaline auto-injectors (AAI) as first-line treatment[6,7]. However, a more recent study suggested that children of Asian ethnicity born in Australia may conversely be at higher risk of anaphylaxis compared to other ethnicities[8]. This discrepancy highlights the need for more accurate estimates of the true anaphylaxis burden in Asian countries. Time-trend analyses of anaphylaxis incidence across longer time periods, using a unifying methodology on a territory-wide population, have never previously been reported.

In this study, we took an advantage of a comprehensive electronic records system to determine the incidence rates of anaphylaxis between 2009 and 2019 in Hong Kong and investigated the longitudinal trends of AAI prescriptions.

Methods

The Hospital Authority (HA) of Hong Kong has established a comprehensive clinical information system with a unified medical record database encompassing more than 7.1 million unique patients across the entire territory. Data were obtained from the Clinical Data Analysis and Reporting System (CDARS) – a centralized electronic database of the HA which captures patients' data from all public hospitals in the territory. The HA is the sole public-funded healthcare provider, which provides about 90% of in-patient care services across the territory. It serves a population of more than 7 million through 18 Emergency Departments (ED) among the 43 hospitals [13]. These hospitals are organized into 7 clusters based on geographical locations[9,10]. As most patients with anaphylaxis in Hong Kong will be admitted to ED, our data likely captures the vast majority of patients with anaphylaxis in the territory during the study period.

Data were extracted by a standardized protocol and cross-checked independently by two physicians. All in-patient records between 1st January 2009 and 31st December 2019 with physician-reported diagnosis of anaphylaxis, as classified by the International Classification of Diseases, Ninth Revision (995.0, 995.60-995.69), were extracted from the CDARS, anonymized and analysed. Since CDARS has been built to automatically map the ICD-10 coded diagnoses with that coded by ICD-9, our database search captures all anaphylaxis cases coded by physicians during the study period. Data obtained included patients' age, gender, admission date, length of stay, and list of prescription medications at time of discharge. Pediatric patients are defined as those less than 18 years of age.

Statistical analysis

Categorical variables are expressed as number (percentage), and continuous variables are expressed as either mean (standard deviation) or median (range) when appropriate. Univariate and multivariate analyses were used to identify independent associations between demographics and clinical characteristics with AAI prescription. The chi-squared statistic and independent samples t-test were used to compare categorical and continuous variables between groups in univariate analysis, respectively. Variables with a P value of 0.1 or less from univariate analysis were included in multivariate logistic regression to determine which variables were independently associated. A P value of less than 0.05 was considered statistically significant for the multivariate analysis. SPSS Statistics version 20 (IBM, Armonk, NY, USA) was used for all analyses. The incidence rates were calculated by the number of patients divided by the number of total estimated population of Hong Kong between 2009 and 2019. The AAI prescription rates were calculated by dividing the number of AAI prescriptions by the number of patients with anaphylaxis. Population statistics from the Census & Statistics Department (Hong Kong Government) were extracted for calculations[11]. Our Census used 19 years old as the cut-off age for pediatric population, thus estimates for the breakdown of pediatric and adult anaphylaxis incidence rates were calculated using population data for <20 and [?]20 years, respectively. This study was reviewed and approved by the Institutional Review Board of the Joint Chinese University of Hong Kong – NTEC Clinical Research Ethics Committee.

Results

More than 2-fold increase in anaphylaxis incidence between 2009 and 2019

Between 2009 and 2019, there were a total of 2,854 patients admitted 2,961 times with a physician-reported diagnosis of anaphylaxis over the span of 11 years. Detailed breakdown of the demographics, admissions and rates of AAI prescriptions of patients per year is shown in Table 1. The number of admissions (per geographical locations) and proportion of patients discharged with AAI per year are displayed in Figure 1. The overall 10-year estimated incidence rate was 3.57 per 100,000 person-years; the male to female ratio was 0.52 and the median age was 46 years (range 0-98 years). The estimated incidence rates per year are shown in Table 2. The increase in the anaphylaxis incidence rates was more than 2-fold from 2009 to 2019, with a particularly marked increase between 2013 and 2014 (2.80 to 4.44 per 100,000 population, respectively). The increased incidence was also much greater among the paediatric population (pediatric vs adult: 2.11 vs 2.30 per 100,000 population in 2009 to 7.40 vs 4.18 per 100,000 population in 2019).

Fewer than 15% of anaphylaxis survivors prescribed AAI and adult patients significantly less likely to have prescriptions

Overall, 14.8% (422/2,854) patients admitted for anaphylaxis had prescribed AAI on their medication record prior to discharge. To identify factors associated with AAI prescription, the demographics and clinical demographics (including age, gender, number of admissions, length of stay) were included in univariate analysis. Male gender (59.0% vs 50.3%, P =0.001) and adult age group (36.5% vs. 89.4%, P <0.001) were found to be significant factors in univariate analysis (P <0.10), but other variables including number of admissions and length of stay did not reach statistical significance (data not shown). Further multivariate analysis confirmed that only age group was independently associated with AAI prescription while gender was not. Pediatric patients admitted for anaphylaxis were significantly more likely to be prescribed AAI compared to adult patients (OR=14.434, 95% CI=11.378-183.310,P <0.001).

Increasing trend of AAI prescription, especially among adult patients admitted for anaphylaxis

There was an overall increasing rate of AAI prescription for patients admitted for anaphylaxis during the study period. The AAI prescription rates among adult and pediatric patients with anaphylaxis are displayed longitudinally in Figure 2. Patients admitted for anaphylaxis in the year 2019 were significantly more likely to be prescribed an AAI compared to those admitted in 2009 (27.9% vs. 5.1%; OR=7.263, 95% CI=3.436-15.352; P <0.001). This difference was more marked in subgroup analysis of adult patients (16.2% vs. 0.8%; OR=25.180, 95% CI=3.427-185.020; P <0.001), but also held true for pediatric patients (64.0% vs. 25.9%; OR=5.069, 95% CI=1.928-13.329; P =0.001) between 2009 and 2019 .

Discussion

We present a comprehensive longitudinal study of anaphylaxis in Hong Kong over a span of 11 years. With the availability of our territory-wide electronic clinical information system, we were able to calculate the near-absolute anaphylaxis incidence of 3.57 per 100,000 person-years, with an apparent rise in anaphylaxis incidence over the past decade from 2009 to 2019. In contrast to previous reports, this incidence is comparable to Western populations and we identified a discrepancy of AAI prescription rates between adult and paediatric anaphylaxis survivors.

Although it is difficult to directly compare between studies due to differences in study design and anaphylaxis definitions, our findings are consistent with reports from Western cohorts. For example, the national anaphylaxis data from the UK between 1992 to 2012 found an increase in anaphylaxis admissions from 1 to 7 cases per 100,000 population per annum [12]. The estimated anaphylaxis incidence rates were 1.75 per 100 000 person-years from the Spanish hospital system during the period 1998-2011 and 1.41 per 100,000 person-years from the Chile's hospital discharge database between 2001 and 2010 [13,14]. The incidence rate of anaphylaxis in Olmsted County, Minnesota of the United States was, however, much higher at 42 per 100,000 person-years from 2001 to 2010 [15]. Our novel findings show that Asian populations have also seen a parallel and comparable rise in anaphylaxis incidence to Western cohorts over the past decade. Well-designed prospective studies using a standardized working definition as well as a unified reporting and collection method of anaphylaxis data are much needed in Asia to better understand how genetic and environmental factors modulate anaphylaxis susceptibility. Identification of potential ethnic- or population-specific modulators may elucidate novel protective or pathomechanisms of anaphylaxis. For example, differences in susceptibility to specific co-factors or adherence to allergen avoidance among different ethnicities have been implicated [16]. Such findings would be invaluable to inform future allergy prevention or treatment strategies both locally and internationally.

Reports on the adherence of AAI prescriptions across different centres and countries. For example, the rates of AAI prescription or retrieval were 54-68% in Olmsted County of the United States; 69.9% in Manitoba, Canada; and 76% in a report from Denmark [17,18]. In contrast, we identified that fewer than 15% of our anaphylaxis patients were prescribed with AAI. We were also able to confirm that all AAI prescriptions were dispensed and retrieved by patients due to the integration of pharmacies into our public healthcare system. Although there was a gradual improvement in AAI prescription rates (especially in adults) over the

past decade, over 70% of patients surviving anaphylaxis in 2019 were still not prescribed with AAI. Since our study only reviewed patients' discharge medications, the true rate of AAI possession by anaphylaxis patients may be under-estimated as AAI may be prescribed upon subsequent review by allergists. However, as per most international recommendations, AAI should be prescribed for at-risk patients upon discharge from the ED or hospital [19-21]. This is particularly important when there is a time lag between the allergic or anaphylaxis episode and subsequent allergy consultation. The alarmingly low rate of AAI prescription in Hong Kong was, however, worrisome as more than 10% of adult patients with anaphylaxis did not have an identifiable cause and were reported to have lower adherence to dietary avoidance compared to Western cohorts [16]. Our findings therefore heed for an urgent call to improve allergy resources and physician education for anaphylaxis. For example, local or institutional recommendations need to be available and reinforced to optimize the rate of AAI prescription and training among anaphylaxis survivors before discharge. All at-risk patients should also be referred (and timely reviewed) by allergists for accurate diagnosis and counselling to prevent recurrent life-threatening episodes in the future.

Our study identified a discrepancy of anaphylaxis care between adult and pediatric patients. During the past decade, pediatric patients were significantly more likely to be prescribed AAI compared to adult patients as shown in our multivariate analysis. In 2009, less than 1% of adult anaphylaxis patients was prescribed an AAI, compared to more than 25% of pediatric patients. Although the rate of AAI prescription subsequently improved for both adult and pediatric patients, only 16% of adult anaphylaxis patients in 2019 had AAI compared to 64% of pediatric patients. We postulate that this may be due to perception of hospital-based physicians that adult patients may be at lower risk of anaphylaxis recurrence due to better allergen avoidance, or lack of local adult allergists [22]. It may also be attributed by the heightened awareness of anaphylaxis in pediatric physicians as allergic diseases, particularly food allergy and eczema, usually occur in the first few years of life [23]. Survivors of anaphylaxis are at continuous risk of repeated life-threatening episodes, with previous studies reporting one in twelve patients experiencing recurrence and one in fifty requiring adrenaline or hospital attention [24]. Food-induced, exercise, and "idiopathic" anaphylaxis have been reported to have even higher recurrence rates [24-26]. Our study highlights the dire demand of allergy services, especially for adult patients presented to ED and hospitals for anaphylaxis.

Our study also noted a sharp increase in anaphylaxis incidence from 2013 to 2014. This coincides with the year with the most marked anaphylaxis fatalities in the United States, and the year when the updated practice parameter for food allergy was issued [2,27]. Altogether this might have led to the heightened awareness of anaphylaxis in the community and related professions, as well as a shifting behaviour and practice in our patients and health care providers. This demonstrates the importance of continued physician education and promoting anaphylaxis awareness in the community.

The strength of this study is that we used a population-based data set with detailed time-trend, age and sex distribution analyses. However, one of the limitations of this study was the inability to capture information about the anaphylaxis triggers due to the privacy regulations in a deidentified study. Also, data may be incomplete if we identify anaphylaxis triggers based on ICD-9 coding, since causes of anaphylaxis may not be apparent upon initial presentation, but only confirmed after detailed allergy assessment. Our study could not capture patients who do not present to emergency services, but would only be a small proportion and is a limitation common in other studies[28]. Another limitation of this study is that anaphylaxis-related fatalities were not identified/reported, again highlighting the under-recognition of anaphylaxis in our community.

Conclusion

In conclusion, we report an increase in anaphylaxis incidence between 2009 and 2019 in Asian populations, comparable to the Western world. Fewer than 15% of anaphylaxis patients were prescribed with AAI, which was low compared to countries with similar disease burden. AAI was less likely to be prescribed to the adult patients, highlighting the discrepancy in anaphylaxis care between adult and pediatric patients. These findings highlight the urgent need for enhanced allergy education for both hospital-based physicians and family physicians in the community in order to optimize management of anaphylaxis and timely prescription of AAI. Local or regional anaphylaxis registries using standardized anaphylaxis definition, methodology and

data collection are in dire need.

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Table 1: Demographics and rates of AAI prescriptions of patients admitted for anaphylaxis from 2015-2019

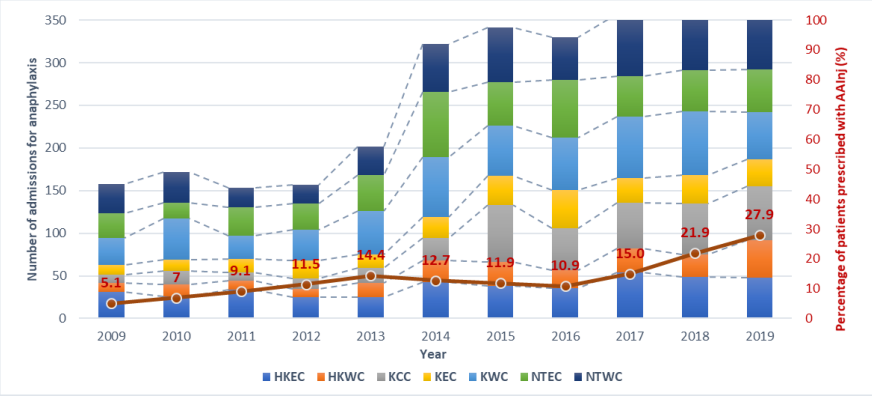
	2009	**2010**	**2011**	**2012**	**2013**	**2014**
Total patients	158	172	153	157	202	322
Total admissions	164	180	162	161	209	329
Male gender	92 (58.2%)	106 (61.6%)	91 (59.5%)	78 (49.7%)	108 (53.5%)	159 (49.4%)
Median age (IQR)	47 (38)	45 (32)	45 (31)	46 (32)	49 (35)	45 (32)
Paediatric (<18 years)	27 (17.1%)	32 (18.6%)	21 (13.7%)	20 (12.7%)	32 (15.8%)	60 (18.6%)
Adult ([?]18 years)	131 (82.9%)	140 (81.4%)	132 (86.3%)	137 (87.3%)	170 (84.2%)	262 (81.4%)
AAI prescriptions						
Total patients prescribed AAI	8 (5.1%)	12 (7.0%)	14 (9.2%)	18 (11.5%)	29 (14.4%)	41 (12.7%)
- Paediatric	*7* (25.9%)	*8* (25.0%)	*10* (47.6%)	*9* (45.0%)	*15* (46.9%)	*32* (53.3%)
- Adult	*1* (0.8%)	*4* (2.9%)	*4* (3.0%)	*9* (6.6%)	*14* (8.2%)	*9* (3.4%)

Table 2: Estimated incidence rate of anaphylaxis from 2015-2019

	2009	**2010**	**2011**	**2012**	**2013**
Population of Hong Kong [11]	6,966,400	7,052,100	7,109,500	7,171,000	7,210,9
- Aged 0-19	1,281,000 (18.4%)	1,257,600 (17.8%)	1,236,900 (17.4%)	1,220,100 (17.0%)	1,194,6

	2009	2010	2011	2012	2013
Estimated incidence rates (per 100,000 population)					
Total incidence rate	2.27	2.44	2.15	2.19	2.80
- Paediatric	2.11	2.54	1.70	1.64	2.68
- Adult	2.30	2.42	2.25	2.30	2.83

Figure 1: Number of admissions for anaphylaxis (by cluster) and rate of AAI prescription from 2009-2019



HKEC = Hong Kong East Cluster, HKWC = Hong Kong West Cluster, KEC = Kowloon Central Cluster, KEC = Kowloon Easter Cluster, KWC = Kowloon West Cluster, NTEC = New Territories Easter Cluster, NTWC = New Territories Easter Cluster

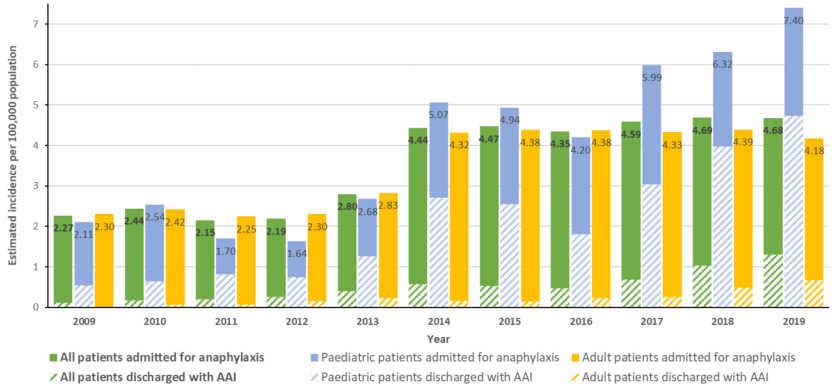


Figure 2: Incidence rates of anaphylaxis (by age group) and rates of AAI prescription from 2009-2019