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Cefaclor-induced hypersensitivity: Differences in the incidence of anaphylaxis relative to other 2nd and 3rd generation cephalosporins

Hyo-In Rhyou[1,2], Young-Hee Nam[1,2], Su-Chin Kim[3], Go-Eun Doo[4], Chae-Yeon Ha[4], Hee-Joo Nam[1,2], Sung-Dae Woo[4,5], Youngsoo Lee[4,5], Jae-Hyuk Jang[4,5], Hyun-Young Lee[3], Young-Min Ye[4,5]*

1 Department of Internal Medicine, College of Medicine, Dong-A University, Busan, Korea, **2** Dong-A Regional Pharmacovigilance Center, Dong-A University Hospital, Busan, Korea, **3** Clinical Trial Center, Ajou University Hospital, Suwon, Korea, **4** Ajou Regional Pharmacovigilance Center, Ajou University Hospital, Suwon, Korea, **5** Department of Allergy and Clinical Immunology, Ajou University School of Medicine, Suwon, Korea

* ye9007@ajou.ac.kr

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Abstract

Cefaclor, a second-generation oral cephalosporin, is the most frequently prescribed cephalosporin in Korea. Studies, however, have yet to analyze the incidence of cefaclor-associated adverse drug reactions (ADRs), including hypersensitivity (HS), according to total national usage rates. This study aimed to investigate the incidence rates and clinical features of cefaclor ADRs reported to the Korean Adverse Event Reporting System (KAERS) and Health Insurance Review and Assessment Service (HIRA) database for the most recent 5 years. Reviewing the HIRA database, which contains information on all insurance claims, including prescribed medications and patient demographics, we identified the total number of individuals who had been prescribed cefaclor and other cephalosporins including 2nd generation without cefaclor and 3rd generation antibiotics from January 2014 to December 2018. Additionally, we retrospectively analyzed all ADRs reported to the KAERS for these drugs over the same study period. Incidence rates for ADRs, HS, and anaphylaxis to cefaclor were 1.92/10,000 persons, 1.17/10,000 persons, and 0.38/10,000 persons, respectively, lower than those to other 2nd and 3rd cephalosporins. Among all ADRs, HS (60.9% vs. 43.6% vs. 44.8%, $P<0.001$) and anaphylaxis (19.8% vs. 4.6% vs. 4.7%, $P<0.001$) were more common for cefaclor than for other 2nd and 3rd cephalosporins. Females, individuals under 65 years of age, concomitant use of drugs, and serious ADRs were more strongly associated with HS to cefaclor than with HS to other 2nd and 3rd cephalosporins. In a nationwide database for the Korean population, the incidence of cefaclor-induced ADRs, particularly HS and anaphylaxis, was high. Female sex, age younger than 65 years, and concomitant use of drugs may be associated with HS to cefaclor.

Competing interests: There are no financial or other issues that might confer a conflict of interest.

Introduction

Adverse drug reactions (ADRs) are common and responsible for significant morbidity and mortality. The incidence of ADRs for all hospital admissions has been estimated at approximately 3–10%, varying greatly among reports, and ADRs pose a considerable public health problem [1–3]. ADRs were subdivided into type A and type B reactions as previously described, and type B reactions mainly included hypersensitivity reactions that were subdivided into immediate and delayed HS. Drug hypersensitivity (HS) is unpredictable, dose independent after the dose exceeding the threshold, and potentially life-threatening [4,5]. In addition, diagnosis of anaphylaxis was based on diagnostic criteria set forth in the 2011 World Allergy Organization Anaphylaxis Guidelines [6]. Several studies on the incidence of HS and/or anaphylaxis to cephalosporins have been conducted on large subjects [7,8], and past history of HS to penicillin or cephalosporin is the most important risk factor for reacting to cephalosporins [9]. However, data on the incidence thereof and results on risk factors for drug HS are unclear, because its diagnosis depends on a patient's history and clinical manifestation. Additionally, studies have shown that the incidence of drug HS can be affected by various factors, such as study population, definition, and methods of data analysis [3,10].

Cefaclor is a second-generation oral cephalosporin and is reportedly the most frequently prescribed antibiotic among cephalosporins in Korea [11]. The prescription of cefaclor in Korea has continued to increase since 2015 according to Health Insurance Review and Assessment (HIRA) Service data [12], and cefaclor has been reported to be the most common causative drug of anaphylaxis in a tertiary care hospital in Korea [13]. Although studies on cefaclor-induced ADRs, HS, and/or anaphylaxis have been reported [14–18], the incidences of individual cefaclor associated-ADRs based on total national usage rates have not been analyzed. Accordingly, we sought to investigate the incidence rates and clinical features of cefaclor-induced ADRs in a nationwide database provided by the Korea Adverse Event Reporting System (KAERS) and HIRA for the most recent 5 years.

Materials and methods

Data source on drug prescriptions

We reviewed information from the HIRA database, which contains information on all medical insurance claims, including prescribed medications, for approximately 97% of the entire Korean population covered under the national health insurance system. The HIRA service provided data retrieved from medical facilities and pharmacies, with information on patient demographics, diagnoses, prescriptions, and procedures after de-identification. Therewith, we assessed the total number of individuals who had been prescribed cefaclor and other 2nd (without cefaclor) and 3rd cephalosporin antibiotics from January 2014 to December 2018.

Data source on adverse drug reactions

Introduced in 1988, the KAERS is a spontaneous ADR reporting system in Korea and has been regulated by the Korea Institute of Drug Safety & Risk Management (KIDS) since 2012. ADR reports are submitted to KAERS primarily by regional pharmacovigilance centers, including general hospitals, and associations of pharmacists, pharmaceutical companies, health providers, and even patients via paper forms, telephone, fax, or electronically on the KIDS website using a standardized form. Culprit drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification system, and adverse events are coded according to World Health Organization Adverse Reaction Terminology (WHO-ART) which has been used in Korea since 2006.

Classification and assessment of adverse drug reaction data

In this study, we retrospectively reviewed all ADRs to cefaclor and other 2nd and 3rd cephalosporins reported to the KAERS from January 2014 to December 2018. We identified HS and anaphylaxis using WHO-ART terms. Cases of HS were defined according to WHO-ART preferred terms (PTs) as follows: A) ADR reports wherein more than one code listed in S1 Table was present or B) ADR reports wherein two or more of the codes listed in S2 Table were present. Cases of anaphylaxis were defined according to WHO-ART PTs and System Organ Classes (SOCs) as follows (S3 Table): A) ADR reports coded "anaphylaxis" among SOCs; B) ADR reports coded "skin" and "cardiovascular" or "respiratory" among SOCs; and C) ADR reports coded with two or more SOCs of "skin", "cardiovascular", "respiratory", and "gastrointestinal".

All ADR cases included in the present study were assessed as being of possible, probable, or certain cause according to the WHO-Uppsala Monitoring Center criteria by healthcare professionals in regional pharmacovigilance centers. A serious adverse reaction was defined as "one requiring or prolonging hospitalization, causing congenital anomaly, resulting in persistent or significant disability, life-threatening, or resulting in death" [4]. We reviewed information on age, sex, type of reporters, concomitant medications, and indications of drug administration in each ADR case from the KAERS database. Suspected and concomitant medications were identified using ATC classification, and indications of drug administration were identified using International Classification of Diseases 10th Revision (ICD-10). This study was approved by the institutional review boards of both Ajou University Hospital and Dong-A University Hospital (AJRIB-MED-MDB-19-231 and DAUHIRB-19-136), respectively, and all data were fully anonymized before we accessed them.

Statistical analysis

Incidence rates for ADR, HS, and anaphylaxis to cefaclor, other 2nd generation cephalosporins and 3rd generation cephalosporins were calculated as for each category of ADRs in the KAERS database divided by the total number of individuals who had been prescribed these drugs in the HIRA database during the study period, and are expressed as incidence per 10,000 persons. Categorical variables are described as frequencies and proportions, and continuous variables are presented as means ± standard deviations and absolute numbers. Statistical significance was assessed using Student's t-test for continuous variables and Pearson's chi-squared test for categorical variables. $P<0.05$ was considered statistically significant. Statistical analyses were conducted using R program, version 3.6.3 (http://www.r-project.org).

Results

The total numbers of prescriptions of cefaclor, other 2nd cephalosporins, and 3rd cephalosporins during the study period were 35,902,648, 15,619,584, and 17,146,861 respectively, according to the HIRA database. Annual numbers of prescriptions of cefaclor and other 2nd and 3rd cephalosporins are shown in Table 1. Patients who had been prescribed cefaclor or other 2nd and 3rd cephalosporins showed similar distribution of sex and age (Table 1). In total, 6,883, 12,800, and 22,294 cases of ADRs to cefaclor, other 2nd cephalosporins, and 3rd cephalosporins, respectively, were reported in the KAERS database during the study period. All annual reports of ADRs to cefaclor, other 2nd cephalosporins, and 3rd cephalosporins increased continuously, and most of the ADRs to cefaclor, other 2nd cephalosporins, and 3rd cephalosporins were spontaneously reported by regional pharmacovigilance centers (cefaclor vs. other 2nd cephalosporins; 98.3% vs. 96.7%, $P<0.001$, cefaclor vs. 3rd cephalosporins; 98.3% vs. 95.5, $P^{\wedge}<0.001$) (Table 2). The proportion of females experiencing ADRs was statistically

Table 1. Prescriptions of cefaclor and other 2nd and 3rd cephalosporins in the Health Insurance Review and Assessment Service database in Korea for the most recent 5 years.

	Cefaclor N = 35,902,648 (%)	Other 2nd cephalosporins N = 15,619,584 (%)	3rd cephalosporins N = 17,146,861 (%)
Female	18,884,652 (52.6)	8,491,507 (54.4)	9,241,463 (53.9)
Age, years			
0–9	3,937,238 (11.0)	1,910,540 (12.2)	3,826,513 (22.3)
10–19	4,461,479 (12.4)	1,844,820 (11.8)	1,677,280 (9.8)
20–29	5,357,101 (14.9)	1,973,290 (12.6)	1,670,411 (9.7)
30–39	6,137,385 (17.1)	2,560,838 (16.4)	2,287,212 (13.3)
40–49	6,567,638 (18.3)	2,505,652 (16.0)	2,192,517 (12.8)
50–59	6,551,235 (18.2)	2,460,543 (15.8)	2,314,416 (13.5)
60–69	4,319,144 (12.0)	1,778,043 (11.4)	1,859,000 (10.8)
70–79	2,647,211 (7.4)	1,167,898 (7.5)	1,482,109 (8.6)
≥80	1,016,467 (2.8)	467,485 (3.0)	864,976 (5.0)
Report year			
2014	14,511,415	4,429,987	5,061,842
2015	14,346,403	4,483,135	5,223,740
2016	14,772,831	4,737,316	5,619,054
2017	14,572,493	4,714,094	5,506,605
2018	14,804,131	4,921,172	5,960,831

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significantly higher for cefaclor than for other 2nd and 3rd cephalosporins (cefaclor vs. other 2nd cephalosporins; 65.5% vs. 58.5%, $P<0.001$, cefaclor vs. 3rd cephalosporins; 65.5% vs. 52.1%, $P^{\wedge}<0.001$). Age was significantly younger for cefaclor ADRs than for 3rd cephalosporins ADRs (47.6±17.4 years vs. 49.3±23.4 years, $P^{\wedge}<0.001$), but no significant difference in age between cefaclor ADRs and other 2nd cephalosporins (47.6±17.4 years vs. 47.2±19.2 years, $P = 0.251$). Cefaclor ADRs were more common in individuals aged 30 to 50 years than other 2nd and 3rd cephalosporins ADRs with statistical significance (30s: 15.3% vs. 14.1% vs. 9.8%, 40s: 19.3% vs. 15.8% vs. 11.0%, 50s: 23.0% vs. 19.4% vs. 16.3%) (Table 2).

Incidence rates of adverse drug reactions, hypersensitivity, and anaphylaxis to cefaclor and other 2nd and 3rd cephalosporins

Incidence rates of ADRs to cefaclor, other 2nd cephalosporins, and 3rd cephalosporins during the study period were 1.92/10,000 persons, 8.19/10,000 persons, and 13.0/10,000 persons, respectively. Incidence rates for HS (and anaphylaxis) to cefaclor, other 2nd cephalosporins, and 3rd cephalosporins were 1.17/10,000 persons (0.38/10,000 persons), 3.57/10,000 persons (0.38/10,000 persons), and 5.82/10,000 persons (0.61/10,000 persons), respectively (Table 3). The majority of incidence rates for ADRs, HS, and anaphylaxis to cefaclor and 3rd cephalosporins showed a tendency to increase gradually during the study period (Fig 1). The proportions of clinical types of ADRs were significantly different between cefaclor and other 2nd and 3rd cephalosporins (Fig 2): HS (60.9% vs. 43.6% vs. 44.8%) and anaphylaxis (19.8% vs. 4.6% vs. 4.7%) were more common for cefaclor than for other 2nd and 3rd cephalosporins with statistical significance.

Comparison of clinical characteristics between hypersensitivity/anaphylaxis to cefaclor and other 2nd and 3rd cephalosporins

Females more commonly experienced HS to cefaclor than to other 2nd and 3rd cephalosporins. Mean age of 3rd cephalosporins HS group was the oldest, followed by cefaclor HS, other 2nd cephalosporins HS group, and so on. However, the proportion of individuals aged ≥65 years

Table 2. Characteristics of adverse drug reaction cases to cefaclor and other 2nd and 3rd cephalosporins in the Korean Adverse Event Reporting System database for the most recent 5 years.

	Cefaclor N = 6,883 (%)	Other 2nd cephalosporins N = 12,800 (%)	3rd cephalosporins N = 22,294 (%)	*P*-value	*P*^-value
Female sex	4,508 (65.5)	7,482 (58.5)	11,618 (52.1)	<0.001	<0.001
Age*, years	47.6±17.4	47.2±19.2	49.3±23.4	0.251	<0.001
0–9	184 (2.7)	341 (2.7)	1,881 (8.4)	>0.999	<0.001
10–19	268 (3.9)	727 (5.7)	935 (4.2)	<0.001	0.289
20–29	554 (8.0)	1,419 (11.1)	1,732 (7.8)	<0.001	0.466
30–39	1,056 (15.3)	1,806 (14.1)	2,177 (9.8)	0.020	<0.001
40–49	1,331 (19.3)	2,017 (15.8)	2,452 (11.0)	<0.001	<0.001
50–59	1,586 (23.0)	2,480 (19.4)	3,736 (16.8)	<0.001	<0.001
60–69	1,086 (15.8)	1,943 (15.2)	3,629 (16.3)	0.276	0.334
70–79	477 (6.9)	1,217 (9.5)	3,135 (14.1)	<0.001	<0.001
≥80	129 (1.9)	372 (2.9)	1,502 (6.7)	<0.001	<0.001
Unknown	212 (3.1)	478 (3.7)	1,115 (5.0)	0.019	<0.001
Report year					
2014	755 (11.0)	2,048 (16.0)	3,367 (15.1)	<0.001	<0.001
2015	1,054 (15.3)	2,319 (18.1)	4,027 (18.1)	<0.001	<0.001
2016	1,333 (19.4)	2,782 (21.7)	4,457 (20.0)	<0.001	0.263
2017	1,696 (24.6)	2,954 (23.1)	4,889 (21.9)	0.015	<0.001
2018	2,045 (29.7)	2,697 (21.1)	5,554 (24.9)	<0.001	<0.001
Reporter					
Regional pharmacovigilance center	6,768 (98.3)	12,382 (96.7)	21,301 (95.5)	<0.001	<0.001
Manufacturer	26 (0.4)	7 (0.1)	160 (0.7)	<0.001	0.003
General hospital	89 (1.3)	407 (3.2)	832 (3.7)	<0.001	<0.001
Pharmacy	0 (0.0)	1 (0.0)	1 (0.0)	>0.999	>0.999
Others	0 (0.0)	3 (0.0)	0 (0.0)	0.506	N/A

* Data are presented as means ± standard deviations.

N/A; not available.

P value: Cefaclor vs. 2nd cephalosporins without cefaclor.

P^ value: Cefaclor vs. 3rd cephalosporins.

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was statistically significantly lower for cases of cefaclor HS than for cases of other 2nd cephalosporins and 3rd cephalosporins HS (14.4% vs. 16.1% vs. 26.4%) (Table 4).

The indication for drug administration were not identified in 48.7% of cases of cefaclor HS, 21.0% of cases of other 2nd cephalosporins HS, and 16.7% of cases of 3rd cephalosporins HS. The three most common indications for cefaclor were diseases of the respiratory system (J00-J99, 12.5%), injury, poisoning and certain other consequences of external causes (S00-T88, 8.6%), and certain infectious and parasitic diseases (A00-B99, 5.7%). Those for other 2nd cephalosporins use were neoplasms (ICD-code: C00-D49) (12.0%); injury, poisoning and certain other consequences of external causes (S00-T88, 8.2%); and certain infectious parasitic diseases (A00-B99, 7.7%). Those for 3rd cephalosporins were certain infectious and parasitic diseases (A00-B99, 12.3%); diseases of the respiratory system (J00-J99, 11.1%); and diseases of the digestive system (K00-K93, 9.6%) (Table 4).

The five most common concomitant medications, including analgesic drugs (7.7% vs. 6.3% vs. 5.2%), antihistamine (8.6% vs. 6.3% vs. 3.0%), gastrointestinal agents (30.0% vs. 22.4% vs. 29.3%), nonsteroidal anti-inflammatory drugs (NSAIDs) (24.3% vs. 13.4% vs. 6.5%), and respiratory agents (12.9% vs. 10.2% vs. 9.0%) were significantly more often prescribed in cefaclor HS than in other 2nd and 3rd cephalosporins HS (Table 4).

Table 3. Incidence rates of adverse drug reactions, hypersensitivity and anaphylaxis to cefaclor and other 2nd and 3rd cephalosporins.

	Cefaclor	Other 2nd cephalosporins	3rd cephalosporins	*P*-value	*P*^-value
ADR	**IR, per 10,000 persons**				
Total	1.92	8.19	13.00	<0.001	<0.001
2014	0.52	4.62	6.65	<0.001	<0.001
2015	0.73	5.17	7.71	<0.001	<0.001
2016	0.9	5.87	7.93	<0.001	<0.001
2017	1.16	6.27	8.88	<0.001	<0.001
2018	1.38	5.48	9.32	<0.001	<0.001
Hypersensitivity	**IR, per 10,000 persons**				
Total	1.17	3.57	5.82	<0.001	<0.001
2014	0.32	2.37	3.09	<0.001	<0.001
2015	0.45	2.55	3.53	<0.001	<0.001
2016	0.57	2.40	3.49	<0.001	<0.001
2017	0.71	2.46	4.00	<0.001	<0.001
2018	0.81	2.19	4.04	<0.001	<0.001
Anaphylaxis	**IR, per 10,000 persons**				
Total	0.38	0.38	0.61	0.937	<0.001
2014	0.11	0.23	0.32	<0.001	<0.001
2015	0.13	0.25	0.40	<0.001	<0.001
2016	0.18	0.28	0.38	<0.001	<0.001
2017	0.23	0.29	0.35	0.020	<0.001
2018	0.28	0.22	0.45	0.012	<0.001

ADR: Adverse drug reaction, IR: Incidence rate.

P value: Cefaclor vs. 2nd cephalosporins without cefaclor.

P^ value: Cefaclor vs. 3rd cephalosporins.

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Similar differences in mean age and age distribution were noted between cefaclor anaphylaxis and other 2nd and 3rd cephalosporins anaphylaxis. Females were more commonly observed in cefaclor anaphylaxis than in other 2nd and 3rd cephalosporins anaphylaxis (60.7% vs. 60.0%, 55.6%). All the concomitant medications were more often prescribed in cases of cefaclor anaphylaxis than in cases of other 2nd and 3rd cephalosporins anaphylaxis (Table 5).

Anaphylaxis (32.7% vs. 10.6% vs. 10.4%), angioedema (7.7% vs. 2.1% vs. 2.1%) were more frequently reported in cases of cefaclor HS, and urticaria was less frequent in cases of cefaclor HS than in cases of other 2nd and 3rd cephalosporins HS (27.0% vs. 31.5% vs. 33.0%). However, among cases of anaphylaxis, urticaria and angioedema were more frequently reported in the cefaclor group than in the other 2nd and 3rd cephalosporins group (urticaria; 28.3% vs. 23.3% vs. 22.0, angioedema; 13.1% vs. 4.2% vs. 4.1%), and all of those differences were statistically significant (Table 5).

Serious ADRs were more common for cefaclor HS than for other 2nd and 3rd cephalosporins HS (20.4% vs. 5.2% vs. 5.9%), with statistical significance. There were four (0.1%), three (0.1%), and seven (0.1%) deaths in cefaclor HS, other 2nd cephalosporins HS, and 3rd cephalosporins HS, respectively (Table 4).

Discussion

This is the first national survey to estimate incidence rates of cefaclor ADR, HS, and anaphylaxis. In the current study, the number of prescriptions of cefaclor was very high which are

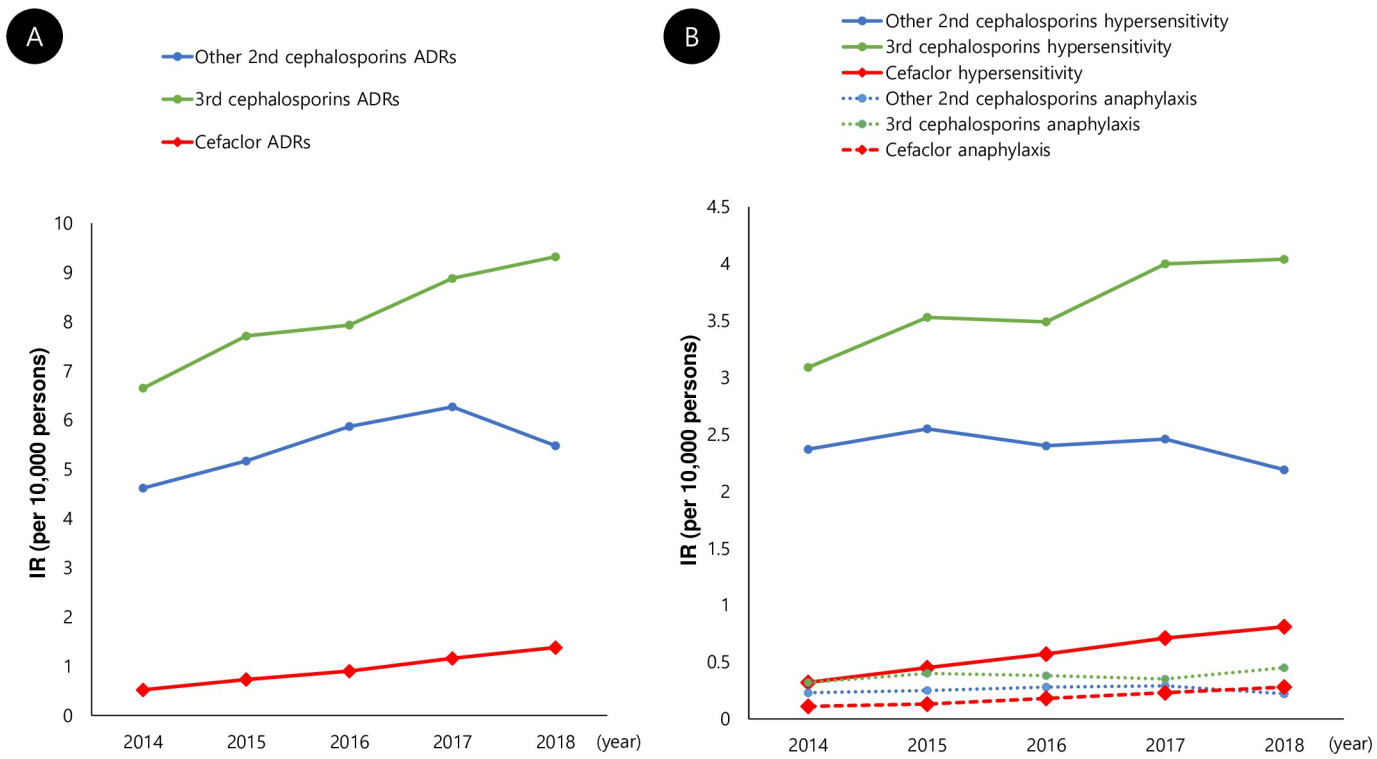

Fig 1. Annual incidence rates of adverse drug reactions, hypersensitivity, and anaphylaxis to cefaclor and other 2nd and 3rd cephalosporins during the study period. ADR: Adverse drug reaction.

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nearly same as that of other cephalosporins, and this is consistent with previous reports for Korea [19,20]. While the incidence rates of ADR, HS, and anaphylaxis to cefaclor were lower

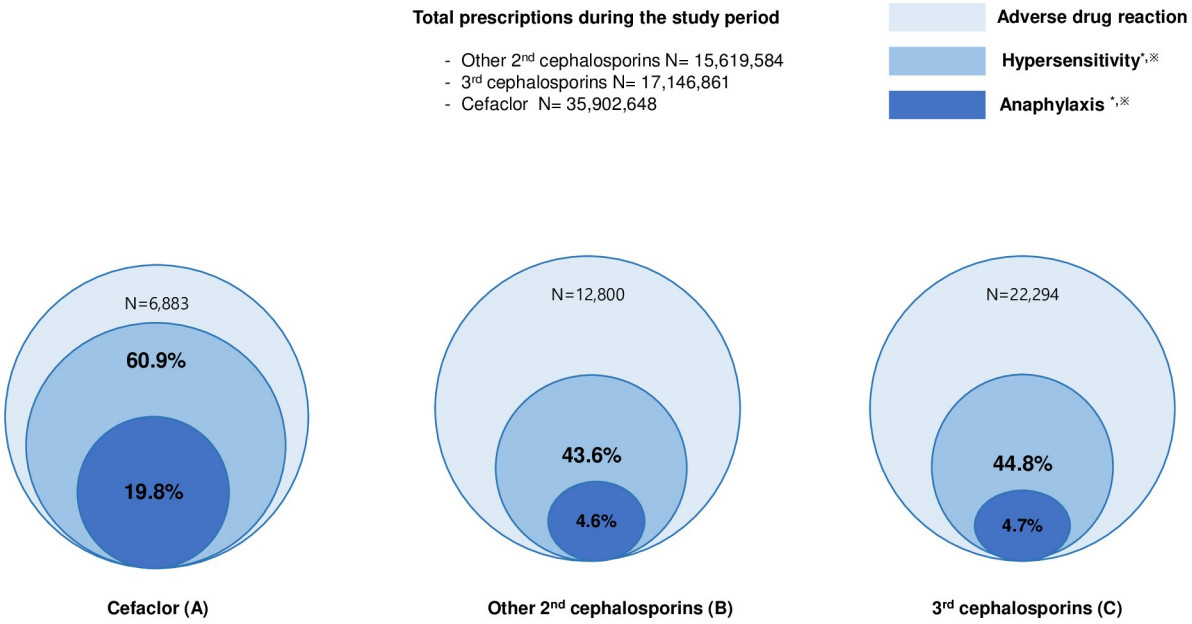

Fig 2. Proportions of hypersensitivity and anaphylaxis among adverse drug reactions to cefaclor (A), other 2nd cephalosporins (B), and 3rd cephalosporins (C). * $P<0.001$ (other 2nd cephalosporins vs. cefaclor). ※ $P^{\wedge}<0.001$ (3rd cephalosporins vs. cefaclor).

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Table 4. Assessment and clinical characteristics of hypersensitivity to cefaclor and other 2nd and 3rd cephalosporins.

	Cefaclor HS N = 4,185 (%)	Other 2nd cephalosporins HS N = 5,569 (%)	3rd cephalosporins HS N = 9,988 (%)	*P* value	*P*^ value
Females, n	2,664 (63.7)	3,259 (59.2)	5,235 (52.4)	<0.001	<0.001
Age*, years	47.7±16.9	46.01±18.50	49.23±22.04	<0.001	<0.001
0–9	91 (2.2)	132 (2.4)	674 (6.7)	0.567	<0.001
10–19	164 (3.9)	340 (6.1)	443 (4.4)	<0.001	0.180
20–29	324 (7.7)	647 (11.6)	826 (8.3)	<0.001	0.309
30–39	648 (15.5)	893 (16.0)	1,086 (10.9)	0.477	<0.001
40–49	823 (19.7)	951 (17.1)	1,279 (12.8)	0.001	<0.001
50–59	989 (23.6)	1,076 (19.3)	1,780 (17.8)	<0.001	<0.001
60–69	672 (16.1)	811 (14.6)	1,681 (16.8)	0.045	0.270
70–79	263 (6.3)	432 (7.8)	1,332 (13.3)	0.006	<0.001
≥80	73 (1.7)	136 (2.4)	554 (5.5)	0.022	<0.001
Unknown	138 (3.3)	151 (2.7)	333 (3.3)	0.103	0.953
Old age					
≥ 65	604 (14.4)	896 (16.1)	2,641 (26.4)	0.027	<0.001
Serious ADR	852 (20.4)	287 (5.2)	591 (5.9)	<0.001	<0.001
Disability	4 (0.1)	2 (0.0)	0 (0.0)	0.445	0.011
Congenital anomaly	0 (0.0)	0 (0.0)	0 (0.0)	N/A	N/A
Life-threatening	118 (2.8)	53 (1.0)	79 (0.8)	<0.001	<0.001
Death	4 (0.1)	3 (0.1)	7 (0.1)	0.704	0.868
Need for or prolongation of hospitalization	180 (4.3)	84 (1.5)	238 (2.4)	<0.001	<0.001
Others	587 (14.0)	162 (2.9)	298 (3.0)	<0.001	<0.001
Clinical manifestations					
Anaphylaxis	1,370 (32.7)	593 (10.6)	1,041 (10.4)	<0.001	<0.001
Urticaria	1,130 (27.0)	1,753 (31.5)	3,293 (33.0)	<0.001	<0.001
Angioedema	322 (7.7)	116 (2.1)	214 (2.1)	<0.001	<0.001
Most common indications of prescription					
1st	Diseases of the respiratory system (J00-J99) 523 (12.5)	Neoplasms (C00-D48) 670 (12.0)	Certain infectious and parasitic diseases (A00-B99) 1,277 (12.3)		
2nd	Injury, poisoning and certain other consequences of external causes (S00-T88) 361 (8.6)	Injury, poisoning and certain other consequences of external causes (S00-T88) 460 (8.2)	Diseases of the respiratory system (J00-J99) 1,109 (11.1)		
3rd	Certain infectious and parasitic diseases (A00-B99) 239 (5.7)	Certain infectious and parasitic diseases (A00-B99) 427 (7.7)	Diseases of the digestive system (K00-K93) 959 (9.6)		
Unknown	2,039 (48.7)	1,171 (21.0)	1,667 (16.7)		
Common concomitant medications					
Analgesic drugs	455 (7.7)	177 (6.3)	240 (5.2)	0.021	<0.001
Antihistamine	511 (8.6)	178 (6.3)	138 (3.0)	<0.001	<0.001
Gastrointestinal agents	1,778 (30.0)	632 (22.4)	1,344 (29.3)	<0.001	0.409
NSAIDs	1,441 (24.3)	377 (13.4)	298 (6.5)	<0.001	<0.001
Respiratory agents	761 (12.9)	286 (10.2)	413 (9.0)	<0.001	<0.001

HS: Hypersensitivity; NSAIDs: Non-steroidal anti-inflammatory drugs; N/A: Not available.

* Data are presented as means ± standard deviations.

P value: Cefaclor vs. 2nd cephalosporins without cefaclor.

P^ value: Cefaclor vs. 3rd cephalosporins.

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Table 5. Assessment and clinical characteristics of anaphylaxis to cefaclor and other 2nd and 3rd cephalosporins.

	Cefaclor anaphylaxis N = 1,370 (%)	Other 2nd cephalosporins anaphylaxis N = 593 (%)	3rd cephalosporins anaphylaxis N = 1,041 (%)	*P* value	*P*^ value
Females, n	837 (60.7)	356 (60.0)	579 (55.6)	0.811	0.013
Age*, years	47.2±14.8	44.4±18.62	47.84±22.33	0.001	0.467
0–9	13 (0.9)	14 (2.4)	69 (6.6)	0.024	<0.001
10–19	45 (3.3)	46 (7.8)	71 (6.8)	<0.001	<0.001
20–29	94 (6.9)	73 (12.3)	88 (8.5)	<0.001	0.165
30–39	234 (17.1)	92 (15.5)	111 (10.7)	0.430	<0.001
40–49	318 (23.2)	104 (17.5)	135 (13.0)	0.006	<0.001
50–59	356 (26.0)	95 (16.0)	160 (15.4)	<0.001	<0.001
60–69	195 (14.2)	84 (14.2)	174 (16.7)	>0.999	0.105
70–79	51 (3.7)	45 (7.6)	123 (11.8)	<0.001	<0.001
≥80	15 (1.1)	9 (1.5)	57 (5.5)	0.576	<0.001
Unknown	49 (3.6)	31 (5.2)	53 (5.1)	0.115	0.084
Old age					
≥ 65	147 (10.7))	88 (14.8)	269 (25.8)	0.012	<0.001
Clinical manifestations					
Urticaria	388 (28.3)	138 (23.3)	229 (22.0)	0.024	0.001
Angioedema	180 (13.1)	25 (4.2)	43 (4.1)	<0.001	<0.001
Most common indications of prescription					
1st	Diseases of the respiratory system (J00-J99) 286 (20.9)	Certain infectious and parasitic diseases (A00-B99) 51 (8.4)	Certain infectious and parasitic diseases (A00-B99) 124 (11.9)		
2nd	Injury, poisoning and certain other consequences of external causes (S00-T88) 221 (16.1)	Diseases of the respiratory system (J00-J99) 50 (8.4)	Diseases of the respiratory system (J00-J99) 111 (10.7)		
3rd	Certain infectious and parasitic diseases (A00-B99) 120 (8.8)	Injury, poisoning and certain other consequences of external causes (S00-T88) 48 (8.3)	Diseases of the genitourinary system (N00-N99) 91 (8.7)		
Unknown	337 (24.6)	140 (23.6)	207 (19.9)		
Common concomitant medications					
Analgesic drugs	85 (7.9)	14 (5.7)	24 (5.7)	0.301	0.165
Antihistamine	56 (5.2)	6 (2.4)	12 (2.8)	0.095	0.064
Gastrointestinal agents	311 (28.9)	53 (21.6)	103 (24.3)	0.027	0.085
NSAIDs	325 (30.2)	40 (16.3)	24 (5.7)	<0.001	<0.001
Respiratory agents	121 (11.2)	15 (6.1)	33 (7.8)	0.024	0.059

NSAIDs: Non-steroidal anti-inflammatory drugs.

* Data are presented as means ± standard deviations.

P value: Cefaclor vs. 2nd cephalosporins without cefaclor.

P^ value: Cefaclor vs. 3rd cephalosporins.

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than those to other 2nd and 3rd cephalosporins, the proportions of HS and anaphylaxis to cefaclor among cefaclor ADRs were significantly higher than the proportions thereof to other 2nd and 3rd cephalosporins ADRs. Overall, the incidence rates of ADR, HS and anaphylaxis to both cefaclor and 3rd cephalosporins increased consistently over the study period, although there is the possibility that this merely reflects increases in spontaneous reporting to the KAERS.

Several studies on the incidence of HS and/or anaphylaxis have been conducted. In a retrospective population-based analysis [7] in the United States, physician-documented cephalosporin-associated anaphylaxis occurred in five oral exposures (95% confidence interval, 1/1,428,571–1/96,154) among 622,456 patients exposed to 901,908 courses of treatment with oral cephalosporins and in eight parenteral exposures (95% confidence interval, 1/200,000–1/35,971) among 326,867 patients exposed to 487,630 courses of treatment with parenteral cephalosporins. In a large multicenter retrospective cohort study [8] in Korea, the incidence of intravenous cephalosporins-induced anaphylaxis was 6.8 per 100,000 exposures, and this is similar to our results on the incidence rate of anaphylaxis to cephalosporins (0.82 per 10,000 persons). Meanwhile, several studies on cefaclor-induced anaphylaxis have, however, reported inconsistent results for various populations [15,16,21–24], and incidence rates of cefaclor HS and anaphylaxis are unclear. The incidence rate of cefaclor HS was reported at 1.1% among 3,000 patients taking cefaclor in a previous study by Kammer et al. [25], and this is higher than the incidence rate for cefaclor anaphylaxis (0.0038%) in our study.

Various risk factors for drug HS have been reported previously and have largely been divided into drug-related factors and host-related factors. Drug-related risk factors include the chemical properties and molecular weights of a drug, dose, route of administration, treatment duration, and frequency of exposure. Host-related factors include age, sex, atopy, specific genetic polymorphism, and comorbidity [3,26,27]. When we compared clinical characteristics for cefaclor and other 2nd and 3rd cephalosporins HS groups, we noted female sex and age under 65 years to be potential risk factors for cefaclor HS. Also, we found that the proportions of cases in patients aged 40 to 50 years were much higher for HS to cefaclor than for HS to other 2nd and 3rd cephalosporins. These results are comparable to previously reported risk factors for drug allergy, especially IgE-mediated hypersensitivity reactions [17,28].

Cefaclor has a simple structure composed of an aminobenzyl (R1) side chain and Cl at R2, and researchers have indicated that IgE binding determinants on cefaclor encircle the whole molecule [29]. This structure may be related with the relatively high proportion of HS and anaphylaxis to cefaclor compared to other 2nd and 3rd cephalosporins among ADRs to them. In addition, in our study, serious ADRs were significantly more common among cases of HS to cefaclor than to other 2nd and 3rd cephalosporins. Although we are unable to state that serious ADRs are a cefaclor-specific problems, we do suggest that cefaclor HS could potentially pose a significant socioeconomic burden and public health problem and that further research is needed to determine whether these severe reactions are associated with structural features of cefaclor.

The use of concomitant medications, including analgesic drugs, antihistamine, gastrointestinal agents, NSAIDs, and respiratory agents, were more frequently prescribed in cases of cefaclor HS than in cases of other 2nd and 3rd cephalosporins HS. These medications were generally prescribed to patients with respiratory disease, in particular upper respiratory infections, and diseases of the respiratory system were the most common indications for cefaclor administration in this study. This difference could affect the difference in concomitant medications between cefaclor HS and other 2nd and 3rd cephalosporins HS.

There are several limitations to this study. First, this study was conducted retrospectively for data reported to a national spontaneously reporting system, and there were some ADRs that were not reported in this study. In addition, prescriptions of cefaclor and other 2nd and 3rd cephalosporins from the HIRA database were ascertained from de-identified data, and we were unable to confirm the exact number of patients exposed to each drug. Therefore, the incidence rates of ADRs may not be exact. However, we compared the incidence rates of cefaclor ADRs with those of other 2nd and 3rd cephalosporins ADRs, which were estimated using same method. Although the exact incidences of ADRs were not obtained in this study, our results

can emphasize relatively higher proportions of HS and anaphylaxis to cefaclor than to other 2nd and 3rd cephalosporins among ADRs to them using nationwide data. Second, the KAERS database contained almost all spontaneous ADR reports from mainly 27 pharmacovigilance centers, other general hospitals, pharmaceutical companies, and pharmacies. Therefore, assessment of ADRs, including causality and seriousness could differ depending on the reporter. To offset this difference as much as possible, healthcare specialists and/or professional pharmacists at regional pharmacovigilance centers conduct a final review before inclusion in the database. However, in this study, the proportions of urticaria in the clinical manifestations of anaphylaxis to cefaclor and other 2nd and 3rd cephalosporins were significantly lower than what is commonly known [30]. This may be because of missing information in the ADR reports. In addition, information on concomitant medications and indications for drug administration were not exact. Systematic approaches to improve the quality of the reports of ADRs are necessary. Finally, we could not evaluate potential risk factors for ADRs, including prior exposure history or exposed intensity, because the individual patients were not identified.

Notwithstanding, this is the first study to estimate incidence rates of cefaclor ADR, HS, and anaphylaxis from a nationwide pharmacovigilance database of the Korean population. Compared to other 2nd cephalosporins and 3rd cephalosporins, cefaclor induced relatively high proportions of HS and anaphylaxis among ADRs in this study. Female sex and age under 65 years and concomitant administration of drugs were found to be potential risk factors for cefaclor HS. Physicians should be cautious about prescribing cefaclor to patients who may be fatal to anaphylaxis or are at a relatively high risk of developing hypersensitivity reaction. Further studies to obtain the exact incidence rates of cefaclor ADRs and to confirm risk factors thereof are needed.

Supporting information

S1 Table. WHO-ART codes for hypersensitivity.
(DOCX)

S2 Table. WHO-ART codes for hypersensitivity.
(DOCX)

S3 Table. WHO-ART codes for anaphylaxis.
(DOCX)

Author Contributions

Conceptualization: Young-Hee Nam, Young-Min Ye.

Data curation: Hyo-In Rhyou, Young-Hee Nam, Su-Chin Kim, Go-Eun Doo, Chae-Yeon Ha, Hee-Joo Nam, Sung-Dae Woo, Youngsoo Lee, Jae-Hyuk Jang, Hyun-Young Lee, Young-Min Ye.

Formal analysis: Hyo-In Rhyou, Go-Eun Doo, Chae-Yeon Ha.

Funding acquisition: Young-Hee Nam, Young-Min Ye.

Investigation: Hyo-In Rhyou, Su-Chin Kim, Go-Eun Doo, Chae-Yeon Ha, Sung-Dae Woo, Youngsoo Lee, Jae-Hyuk Jang, Hyun-Young Lee.

Writing – original draft: Hyo-In Rhyou.

Writing – review & editing: Young-Hee Nam, Young-Min Ye.

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S1 Table. WHO-ART codes for hypersensitivity

WHO-ART	ARRN	SEQ
Immediate type hypersensitivity reaction grade I	2237	003
Documented hypersensitivity to administered drug	2268	001
Rash acneiform	0001	004
Angioedema	0003	001
Quincke's oedema	0003	003
Giant urticaria	0003	004
Angioneurotic oedema	0003	005
Giant hives	0003	006
Angioneurotic oedema aggravated	0003	007
Angioedema aggravated	0003	008
Epidermal necrolysis	0013	001
Dermatitis necrotising	0013	003
Lyell syndrome	0013	004
Toxic epidermal necrolysis	0013	005
Erythema multiforme	0014	001
Erythema annulare	0014	003
Erythema nodosum	0015	001
Itching	0024	003
Pruritus	0024	001
Rash	0027	001
Eruption	0027	004
Itching	0027	003
Toxicoderma	0027	005
Dermatitis medicamentosa	0027	009
Skin eruption	0027	002
Erythema	0028	003
Rash erythematous	0028	001
Rash maculo-papular	0030	001
Measly rash	0030	003
Morbilliform rash	0030	004
Macular rash	0030	005
Papular rash	0030	006
Papulosquamous rash	0030	007
Papulovesicular rash	0030	008
Vesicobullous rash	0030	010
Vesicopustular rash	0030	011
Vesicopustular rash aggravated	0030	012
Rash pustular	0032	001
Stevens Johnson Syndrome	0042	001
Erythema multiforme severe	0042	003
Mucocutaneous ulceration	0042	004
Urticaria	0044	001
Urticaroa vesiculosa	0044	003
Wheals	0044	004
Hives	0044	005
Urticaria aggravated	0044	006
Urticaria pigmentosa	0044	008
Urticaria localized	0044	009
Acute urticaria	0045	001
Systemic erythematous rash	0081	011
Vasculitis	0085	001
Vasculitis allergic	0086	001
Purpura allergic	0460	001
Purpura anaphylactoid	0460	003
Henoch-Schonlein purpura	0460	004
Purpura vascular allergic	0460	005
Allergic vascular purpura	0460	006

Anaphylactoid vascular purpura	0460	007
Allergic reaction	0712	001
Hypersensitivity	0712	004
Anaphylactic shock	0713	001
Immediate type hypersensitivity reaction grade IV	0713	002
Anaphylactoid reaction	0714	001
Fever	0725	001
Drug fever	0725	006
Bullous eruption	0871	001
Fixed eruption	1249	001
Rash vesicular	1443	001
Vesicular eruption	1443	003
Mucosa vesicle	1443	004
Varicellar-like eruption	1443	005
AGEP	1846	003
Anaphylaxis	2237	002
Anaphylactic reaction	2237	001
Immediate type hypersensitivity reaction grade II	2237	004
Immediate type hypersensitivity grade III	2237	005
Epidermolysis bullosa	2259	001
Drug hypersensitivity syndrome	2309	001
DRESS Syndrome	2309	002

ARRN: adverse reaction record number; SEQ: **sequence** number, WHO-ART; World Health Organization- adverse reaction terminology

S2 Table. WHO-ART codes for hypersensitivity

WHO-ART	ARRN	SEQ
Neck oedema	0003	009
Dizziness	0101	001
Faintness	0101	003
Headache	0109	001
Smarting	0137	013
Tingling skin	0137	015
Electric shock sensation	0137	021
Consciousness decreased	0151	009
Altered state of consciousness	0151	011
Vertigo	0158	001
Drowsiness	0197	008
Flushing	0207	001
Bradycardia	0208	001
Blood pressure systolic decrease	0210	011
Hypotension	0212	001
Pallor	0220	001
Syncope	0223	001
Tachycardia	0224	001
Hyperaemia	0225	003
Conjunctival hyperaemia	0238	002
Conjunctival congestion	0238	004
Vision abnormal	0257	001
Vision decreased	0257	003
Heartburn	0279	007
GI distress	0279	014
Oral ulceration	0328	005
Tongue oedema	0331	001
Oedema	0398	001
Oedema generalised	0400	001
Shock	0499	003
Wheezes	0511	006
Coughing	0513	001
Dyspnoea	0514	001
Breath shortness	0514	003
Respiration labored	0514	005
Breath difficult	0514	008
Throat irritation	0521	003
Laryngeal oedema	0522	005
Laryngotracheal oedema	0522	006
Tachypnoea	0536	003
Oxygen saturation decreased	0537	005
Nose congestion	0539	004
Rhinorrhoea	0539	006
Sneezing excessive	0539	007
Nose oedema	0539	008
Nasal congestion	0539	011
Nasal dryness	0539	012
Stridor	0542	001
Eosinophilia	0571	001
Face oedema	0602	001
Chest pain	0718	001
Chest discomfort	0718	003
Thoracic pain	0718	012
Chest distress	0718	013
Pyrexia	0725	004
Shivering	0731	003
Oedema periorbital	1009	001

Oedema orbital	1009	002
Oedema eyelid	1009	003
Skin test positive	1058	004
Allergy test positive	1058	005
Skin peeling	1199	003
Oedema pharynx	1395	001
Oedema mouth	1485	001
Oedema circumoral	1485	006
Burning sensation	1491	003
Feeling of warmth	1705	005
Hot flushes	1705	008
Hyperpnoea	1711	001
Pharyngeal disorder	2211	001
Pruritus eyelid	2253	003

S3 Table. WHO-ART codes for anaphylaxis

	SOC	ARRN
Anaphylaxis	1810	2237, 713-714, (712 or 1027 or 1058) & (212 or 213)
Skin	0100	3, 7, 8, 24-28, 43-45, 1123, 1129, 207, 1009, 602
Cardiovascular	1010	108, 212-213, 220-221, 223-225, 229, 496, 499, 501-503, 1762, 1899, 398-401, 716, 718-719, 929
Respiratory	1100	144, 507, 511, 513-514, 519, 521-522, 536-537, 539, 541-542, 1367, 1466, 1490, 1565, 1711, 1749
Gastrointestinal	0600	268, 205, 228