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Risk factors of beta-lactam anaphylaxis in Korea: A 6-year multicenter retrospective adult case-control study

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ABSTRACT

Background: Beta-lactams (BLs) are commonly used antibiotics and leading causative agents of drug-induced anaphylaxis. Few studies on the culprit drugs and risk factors of BL-induced anaphylaxis are available. Our goal was to evaluate the culprit drugs and compare the risk factors in patients with BL-induced anaphylaxis to matched tolerant controls in a hospital setting.

Methods: We retrospectively enrolled all patients who developed anaphylaxis from intravenous BL during hospitalization from 9 Korean hospitals. We compared clinical parameters between patients with BL-induced anaphylaxis and 4-fold BL-tolerant controls matched by age, sex, BL use, and the purpose of BL administration.

Results: Seventy-four cases of BL-induced anaphylaxis and 296 BL-tolerant controls were enrolled. Cephalosporin accounted for 77% of total BL-induced anaphylaxis, and the top derivatives were ceftriaxone (23.0%), cefazedone (10.8%), and cefbuperazone (9.5%). Among penicillin derivatives, piperacillin (16.2%) was the most common, followed by ampicillin (2.7%). History of drug allergy (odds ratio [OR], 19.91; 95% confidence interval [CI] 5.33–74.44), previous exposure to the causative BL (OR, 7.71; 95% CI, 1.62–36.76), and concurrent administration of angiotensin-converting enzyme inhibitors (ACEIs) (OR, 5.97; 95% CI, 1.28–27.91) were independent risk factors associated with BL-induced anaphylaxis. Food allergy (OR, 13.93; 95% CI 1.31–148.9) and previous exposure to BL (OR, 6.59; 95% CI, 1.30–33.31) were identified as risk factors for cephalosporin-induced anaphylaxis.

Conclusions: To prevent BL-induced anaphylaxis, attention should be paid to histories of drug or food allergy, previous exposure to BLs, and ACEI use. The risk factors and clinical outcomes might vary according to the BL classes.

Keywords: Anaphylaxis, Beta-lactams, Cephalosporin, Drug hypersensitivity, Angiotensin-converting enzyme inhibitors, Case-control studies

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INTRODUCTION

Anaphylaxis is a severe, systemic hypersensitivity reaction that is rapid in onset and can be life-threatening. Studies from the United States, Australia, the United Kingdom, and Korea show that the incidence of anaphylaxis has increased over the years.[1–4] Among all causative agents, significant increases in hospital admissions, and fatality rates were reported for drug-induced anaphylaxis.[5,6] Notably, beta-lactams (BLs), including penicillin derivatives, cephalosporins, and carbapenems, have been known as the leading cause of drug-induced anaphylaxis and one of the risk factors for fatal anaphylaxis.[3,6] The exact prevalence and incidence of an allergic reaction to BL in the general population are not clearly known, with a prevalence ranging from 0.7% to 10%, particularly with the prevalence of anaphylaxis ranging from 0.004% to 0.015%.[7] A recent study showed that the incidence of cephalosporin-induced anaphylaxis was 6.8 cases per 100 000 exposures, and the incidence of fatality was 0.1 cases per 100 000 exposures.[8] Given the increasing trend of cephalosporin use, the incidence of anaphylaxis is also expected to increase. Although several studies have investigated drug-induced anaphylaxis, including BLs,[9,10] the number of cases afflicted by BL-induced anaphylaxis was not high enough for a detailed evaluation.

The most practical strategy to prevent anaphylaxis is to avoid causative agents that trigger the reaction because skin tests and *in vitro* IgE tests have limitations in preventing anaphylaxis owing to their low sensitivity.[11] Therefore, it is crucial to identify the triggers and risk factors for anaphylaxis to recognize and monitor at-risk patients. Factors, including old age, cardiopulmonary disease, uncontrolled asthma, mast cell disorders, and several drugs, such as β-blockers and angiotensin-converting enzyme inhibitors (ACEIs), have been suggested to elevate the risk of anaphylaxis as well as fatal outcomes.[6,9,10,12] Since most of the studies on anaphylaxis were conducted as general population-based epidemiological studies, it is doubtful whether those results can identify real risk factors compared with the drug-tolerant controls, and whether these risk factors are the same for all causative agents.

In the present study, we investigated clinical characteristics of patients with BL-induced anaphylaxis compared to their matched controls. Moreover, we determined the risk factors for BL-induced anaphylaxis and identified the contributing factors to anaphylaxis severity.

MATERIALS AND METHODS

Study design and data collection

We performed a multicenter case-control study of patients with BL-induced anaphylaxis and those who tolerated BL without adverse reactions. A thorough retrospective chart review was performed on all patients who developed anaphylaxis with intravenous BL antibiotics during their admission period at 9 university hospitals in Korea between January 1, 2010, and December 31, 2015. The cases were obtained from the individual case safety report (ICSR) systems at each hospital or by searching candidate cases based on International Classification of Diseases (ICD)-10 codes. Although electronic medical records were used by all institutions participating in the study, they were not part of the same program. In the research planning stage, a unified case report form was created and distributed. Allergy specialists reviewed each ICSR for anaphylaxis according to the World Allergy Organization (WAO) guidelines.[13] Causality assessment was conducted using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) criteria, and "certain" or "probable" cases were enrolled. When multiple drugs were co-administered, the culprit drugs included those evaluated as "certain" and "probable" in the causality assessment. For each patient, 4 BL-tolerant controls were selected within the same hospital using caliper-matching for age by 5 years, exact matching for sex, use of drugs identical to culprits, and purpose of antibiotics use classified by prophylactic or therapeutic use. The patients were selected by random draw if there were over at least 4 cases. The Ethics Committee from each hospital approved the study (HPIRB 2016-05-006-003). Patient consent was not required, because this research was a retrospective medical record study of patients.

We evaluated the demographic and clinical characteristics, such as age, sex, body mass index, the purpose of BL usage, history of allergic

diseases, including asthma and allergic rhinitis, food allergy, drug allergy, comorbidities, such as hypertension, diabetes, chronic liver disease, and malignancy, and medications including ACEIs, angiotensin receptor blockers (ARBs), beta-blockers, and proton pump inhibitors (PPIs). The previous history of BL exposure and its derivatives were verified. We analyzed the diagnostic criteria for anaphylaxis, the time interval between drug exposure and symptoms, and clinical manifestations, including cutaneous, respiratory, gastrointestinal, cardiovascular symptoms, and related outcomes. Variables from laboratory findings, including complete blood count, creatinine, and liver function tests, were obtained. We compared these variables between BL-induced anaphylaxis cases (anaphylaxis group) and BL-tolerant controls (control group).

Cephalosporins and penicillin are the 2 main classes of BLs. Cephalosporins are subclassified into 4 groups according to the similarity of their side-chain structures.[8] In addition, anaphylaxis cases are divided into 2 groups according to their severity, and compared using Brown's grading system for generalized hypersensitivity reactions.[14] "Moderate" reactions comprised skin and subcutaneous manifestations and symptoms suggesting respiratory, cardiovascular, or gastrointestinal system reactions, and "severe" reactions comprised hypoxia, hypotension, or neurologic compromise. The potential risk factors for the development and severity of anaphylaxis were assessed.

Statistical analysis

All statistical analyses were performed using the SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as the means with standard deviations or medians with ranges according to whether they were normally distributed or not, respectively, and analyzed by nonparametric methods (Wilcoxon two-sample test with continuity correction of 0.5) when the variables were not normally distributed. The variables were compared by univariate analysis, using the *t*-test, Pearson's chi-squared test, and Fisher's exact test. Conditional logistic regression analysis was performed to evaluate the prognostic factors for the development of BL-induced anaphylaxis. Values were considered statistically significant at a *P*-value less than 0.05.

RESULTS

Demographic and clinical characteristics of patients with BL-induced anaphylaxis

A total of 74 patients with BL-induced anaphylaxis and their matched 296 tolerant controls were enrolled (Table 1). The mean age was 47.2 ± 23.5 years, and 51.4% were females. The purpose of BL administration was prophylaxis in 54.1% of patients, and infection treatment in 45.9% of patients.

Histories of allergic diseases, such as asthma, allergic rhinitis, atopic dermatitis, and food allergy, were not significantly different between the groups. However, the number of patients with previous history of drug and BL allergies was markedly higher in the anaphylaxis group than in the control group (drug allergy 17.2% vs. 1.4%, $P < 0.0001$; BL allergy 6.8% vs. 0.3%, $P = 0.001$). In addition, a history of drug allergy other than one induced by BLs (non-BL) was also significantly more prevalent in the anaphylaxis group (8.1% vs. 1.0%, $P = 0.003$). In the 11 patients with a history of drug allergy in the BL-induced anaphylaxis group, the causative agents of drug allergy included other BLs (5), the radiocontrast media (2), unknown drugs (2), ibuprofen (1), and oseltamivir (1). In the 4 patients with a history of drug allergy in the BL-tolerant control group, the causative agents were meropenem (1), dexamethasone (1), rituximab (1), and cytosine arabinose (1). Of the 6 cases of non-BL allergies available for the evaluation of the clinical manifestation, half showed an immediate reaction.

Regarding previous exposure to BLs, patients in the anaphylaxis group had a higher chance of asymptomatic exposure to the same causative drug (13.5% vs. 5.1%, $P = 0.01$) than that in case of the control group. Interestingly, exposure to other BLs and the causative drug also tended to be higher in the anaphylaxis group than in the control group, but the difference was not statistically significant.

When the administered concurrent medications were analyzed, the administration of ACEIs was significantly higher in the anaphylaxis group than

Variables	Anaphylaxis (n = 74) n (%)	Control (n = 296) n (%)	*P*-value
Demographic variables			
Age (years)	47.2 ± 23.5	46.1 ± 22.6	0.70
Sex, n (%)			
Female	38 (51.4)	154 (52.0)	0.92[a]
Purpose of BL antibiotics administration			
Prophylaxis	40 (54.1)	151 (51.2)	0.66[a]
Infection treatment	34 (45.9)	144 (48.8)	-
Allergic disease			
Asthma	2 (2.7)	4 (1.6)	0.63[b]
Allergic rhinitis	1 (1.4)	3 (1.2)	1.00[b]
Atopic dermatitis	0 (0.0)	1 (0.3)	1.00[b]
Food allergy	4 (5.5)	5 (1.9)	0.11[b]
Drug allergy			
Drug allergy to any drugs	11 (17.2)	4 (1.4)	<0.0001[b]
Drug allergy to BLs	5 (6.8)	1 (0.3)	0.001[b]
Drug allergy to non-BL	6 (8.1)	3 (1.0)	0.003[b]
Previous exposure to BLs			
Causative drug	10/74 (13.5)	15/296 (5.1)	0.01[a]
Any BLs	16/74 (21.6)	45/296 (15.2)	0.18[a]
Penicillin group	3 (4.1)	6 (2.0)	0.39[b]
Cephalosporin group	8 (10.8)	38 (12.8)	0.65[b]
Interval from previous exposure to BLs (d)	274.2 ± 405.6	276.6 ± 511.4	0.39
Co-medication			
ACEI	5 (6.8)	4 (1.4)	0.02[b]
Beta-blocker	11 (14.9)	26 (8.8)	0.12[a]
ARB	7 (9.5)	19 (6.4)	0.36[a]
PPI	12 (16.2)	31 (10.5)	0.17[a]

Table 1. Baseline characteristics of patients in the anaphylaxis and control groups. *BL: beta-lactam; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; PPI: proton pump inhibitor. Values are either frequency with percentage in parentheses or mean ± standard deviation. The Shapiro-Wilk's test was employed to test the normality assumption* [a] *P values were derived from chi-square tests.* [b] *P values were derived from Fisher's exact tests.*

in the tolerant control group (6.8% vs. 1.4%, respectively; $P = 0.02$). However, there were no significant differences in the use of other medications, such as beta-blockers, ARBs, and PPIs between the 2 groups. Comorbidities of chronic diseases, including diabetes mellitus, hypertension, liver disease, malignancy, and obesity, were not different between the 2 groups. The laboratory findings, including leukocytosis, eosinophil count, anemia, thrombocytopenia, aspartate aminotransferase, alanine aminotransferase, creatinine, and C-reactive protein, did not show any difference between the 2 groups (Supplement Table 1).

Causative agents for BL-induced anaphylaxis

Ceftriaxone (23.0%) was the most common causative drug, followed by piperacillin (16.2%), cefazedone (10.8%), cefbuperazone (9.5%), and ceftizoxime (6.8%). Among the different subgroups (groups 1–4) of cephalosporins, group 1 accounted for 36.5% of all cephalosporin-induced anaphylaxis cases, followed by group 4 (33.8%)

and group 3 (5.4%). Cefbuperazone and cefotetan from group 4 contributed to a relatively high proportion of severe reactions without statistical significance. Among the different penicillin derivatives, piperacillin was the primary causative drug responsible for 70.6% of penicillin derivative-induced anaphylaxis, and 9 of 12 (75%) piperacillin-induced anaphylaxis cases were severe. However, there were no statistically significant differences in the proportion of individual culprit BLs among those in the severe groups (Table 2).

Clinical manifestations according to the classes of the culprit drug

When subgroups were compared according to drug classes (penicillin and cephalosporin) (Table 3), the history of food allergy as well as drug allergy was significantly higher in the cephalosporin-induced anaphylaxis group than in the cephalosporin-tolerant control group (food allergy 7.1% vs. 0.5%, $P = 0.01$; drug allergy 20.0% vs. 0.0%, $P < 0.0001$, respectively). However, there was no difference in number of patients with comorbid allergic diseases in the penicillin-induced anaphylaxis group compared to the control group. The previous history of asymptomatic exposure to the causative drug and BLs was also significantly more frequent in the cephalosporin-induced anaphylaxis group than in the cephalosporin-tolerant control group (exposure to the causative drug 15.8% vs. 6.1%, $P = 0.02$; exposure to BL 24.6% vs. 11.0%, $P = 0.01$, respectively). Concurrent ACEI administration was significantly higher in the cephalosporin-induced

BL Class	Total (n = 74)	Moderate (n = 27)	Severe (n = 47)
Penicillin derivatives, n (%)	**17 (23.0)**	**5 (18.5)**	**12 (25.5)**
Piperacillin	12 (16.2)	3 (11.1)	9 (19.1)
Ampicillin	2 (2.7)	1 (3.7)	1 (2.1)
Amoxicillin	1 (1.4)	0 (0.0)	1 (2.1)
Penicillin	1 (1.4)	1 (3.7)	0 (0.0)
Ticarcillin	1 (1.4)	0 (0.0)	1 (2.1)
Cephalosporins, n (%)	**57 (77.0)**	**22 (81.5)**	**35 (74.5)**
Group 1	27 (36.5)	14 (51.9)	13 (27.7)
Ceftriaxone	17 (23.0)	8 (36.4)	9 (25.7)
Ceftizoxime	5 (6.8)	3 (13.6)	2 (5.7)
Cefotaxime	3 (4.1)	1 (4.5)	2 (5.7)
Cefepime	1 (1.4)	1 (4.5)	0 (0.0)
Cefmenoxime	1 (1.4)	1 (4.5)	0 (0.0)
Group 2	1 (1.4)	0 (0.0)	1 (1.4)
Cefoxitin	1 (1.4)	0 (0.0)	1 (1.4)
Group 3	4 (5.4)	3 (11.1%)	1 (2.1)
Cefazolin	3 (4.1)	2 (9.1)	1 (2.9)
Ceftezole	1 (1.4)	1 (4.5)	0 (0.0)
Group 4	25 (33.8)	5 (18.5)	20 (42.6)
Cefazedone	8 (10.8)	3 (13.6)	5 (14.3)
Cefbuperazone	7 (9.5)	1 (4.5)	6 (17.1)
Cefotetan	4 (5.4)	0 (0.0)	4 (11.4)
Cefoperazone	2 (2.7)	1 (4.5)	1 (2.9)
Cefminox	1 (1.4)	0 (0.0)	1 (2.9)
Cefotiam	1 (1.4)	0 (0.0)	1 (2.9)
Ceftazidime	1 (1.4)	0 (0.0)	1 (2.9)
Flomoxef	1 (1.4)	0 (0.0)	1 (2.9)

Table 2. Causative drugs for BL-induced anaphylaxis

Variable	Penicillin		P-value	Cephalosporin		P-value
	Anaphylaxis (n = 17) n (%)	Control (n = 68) n (%)		Anaphylaxis (n = 57) n (%)	Control (n = 228) n (%)	
Underlying disease						
Allergic disease						
Asthma	1 (5.9)	1 (1.5)	0.37[a]	1 (1.8)	3 (1.6)	1.00[a]
Allergic rhinitis	0 (0.0)	0 (0.0)	-	1 (1.8)	3 (1.6)	1.00[a]
Atopic dermatitis	0 (0.0)	0 (0.0)	-	0 (0.0)	1 (0.5)	1.00[a]
Food allergy	0 (0.0)	4 (5.9)	0.56[a]	4 (7.1)	1 (0.5)	0.01[a]
Drug allergy to any drug	1 (5.9)	4 (5.9)	1.00[a]	10 (20.0)	0 (0.0)	<0.0001[a]
Drug allergy to BL	0	1 (1.5)	1.00[a]	5 (8.8)	0	0.000
Drug allergy to non-BL	1 (5.9)	3 (4.4)	1.00[a]	5 (8.8)	0	0.000
Previous exposure to BLs						
Causative drug	1 (5.9)	1 (1.5)	0.36[a]	9 (15.8)	14 (6.1)	0.02[a]
Any BLs	2 (11.8)	20 (29.4)	0.23[a]	14 (24.6)	25 (11.0)	0.01[b]
Penicillin group	1 (5.9)	3 (4.4)	1.00[a]	2 (3.5)	3 (1.3)	0.26[a]
Cephalosporin group	0 (0.0)	17 (25)	0.018[a]	8 (14)	21 (9.2)	0.28[b]
Interval from previous exposure to BLs (d)	40.0 ± 5.7	91.8 ± 150.1	0.51	313.3 ± 427.5	433.7 ± 648.0	0.94
Co-medication						
ACEI	1 (5.9)	1 (1.5)	0.36[a]	4 (7.0)	3 (1.3)	0.01[a]
Beta-blocker	3 (17.6)	10 (14.7)	0.73[a]	8 (14.0)	16 (7.0)	0.11[a]
ARB	0 (0.0)	5 (7.4)	0.58[a]	7 (12.3)	14 (6.1)	0.15[a]
PPI	7 (41.2)	18 (26.5)	0.23[b]	5 (8.8)	13 (5.7)	0.37[a]

Table 3. Subgroup analysis of underlying allergic disease and previous exposure to BLs according to the drug class. *BL: beta-lactam; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; PPI: proton pump inhibitor. Values are either frequency with percentage in parentheses or mean ± standard deviation.* [a] *P values were derived from Fisher's exact tests.* [b] *P values were derived from chi-square tests.*

anaphylaxis group, but not in the penicillin-induced anaphylaxis group, compared to their respective drug-tolerant control groups.

Clinical manifestations according to anaphylaxis severity

The clinical manifestation and laboratory findings associated with the severity of anaphylaxis are presented in Supplement Tables 1 and 2 Of the 74 patients with BL-induced anaphylaxis, 47 were severe cases (severe group), and 27 were moderate cases (moderate group). Most patients (78.7%) that were classified as severe had cardiovascular symptoms. In contrast, cutaneous symptoms were less frequently observed in the severe group than in the moderate group (57.4% vs. 88.9%, $P = 0.02$). However, there was no difference in demographic characteristics, underlying diseases, including allergic diseases and comorbidities, and concurrent medications. There was no difference in the time interval from the administration of the causative drug to the onset of symptoms between the severe and moderate groups. However, previous exposure to BLs showed an increase in the number of patients in the severe group compared with those in the moderate group without statistical significance (19.1% vs. 3.7%, $P = 0.082$). There were no significant differences among the laboratory findings, including leukocytosis, peak eosinophil count, and platelet count between the 2 groups. However, the proportion of patients with anemia was remarkably increased in the severe group (29.4% in the moderate group vs. 65.7% in the severe group, $P = 0.014$). Similarly, hemoglobin levels were significantly decreased in the severe group compared with that in the moderate group ($P = 0.02$) (Supplement Table 1).

Variable	OR	95% CI	*P*-value
Total BL anaphylaxis			
History of drug allergy	19.91	5.33–74.44	<0.0001
Previous exposure to BLs	2.25	0.53–119.16	0.13
Previous exposure to the causative drug	7.71	1.62–36.76	0.01
ACEI	5.97	1.28–27.91	0.02
Cephalosporin anaphylaxis			
History of food allergy	13.93	1.31–148.90	0.03
Previous exposure to BLs	6.59	1.30–33.31	0.02
Previous exposure to the causative drug	5.33	0.54–52.79	0.15
ACEI	9.47	1.51–59.32	0.02

Table 4. Risk factors for the development of BL-induced anaphylaxis. *BL: beta-lactam; OR: odds ratio; CI: confidence interval; ACEI: angiotensin converting enzyme inhibitor. The effect of independent variables on response variables was analyzed using the multivariate logistic regression, and the statistically significant variables were selected in a backward elimination method with 0.05 alpha level*

Approximately 88% of total cases (65/74) recovered in a general ward, whereas 9 (12.2%) patients from severe group were transferred to an intensive care unit owing to insufficient response to initial resuscitation. In the 9 severe patients who did not sufficiently respond to the initial treatment, ceftriaxone was the most common causative drug (4), followed by piperacillin (2), ceftazidime (1), cefbuperazone (1), and cefoperazone (1), respectively. One case of anaphylaxis triggered by cefobactam (a combination of cefoperazone and sulbactam) was fatal despite intensive resuscitation. A total of 16 mg of epinephrine was administered to the patients via intramuscular and intravenous injection. Despite these treatments, the patient did not recover from the shock and was given 120 mg of norepinephrine and 20 units of vasopressin. Therefore, the fatality of BL-induced anaphylaxis was 1.4% in this study.

Risk factors of BL-induced anaphylaxis

Regarding risk factors for BL-induced anaphylaxis (Table 4), the history of drug allergy (odds ratio [OR], 19.91; 95% confidence interval [CI], 5.33–74.44; $P < 0.01$), previous exposure to the causative drug (OR 7.71; 95% CI, 1.62–36.76; $P = 0.01$), and concurrent administration of ACEIs (OR 5.97; 95% CI, 1.28–27.91; $P = 0.01$) were significantly associated with the development of BL-induced anaphylaxis.

Additionally, the history of food allergy, previous exposure to BL, and the administration of ACEI were remarkably associated with cephalosporin-induced anaphylaxis (OR, 13.93; 95% CI, 1.31–148.9; $P = 0.03$ in history of food allergy; OR, 6.59; 95% CI, 1.30–33.31; $P = 0.02$ in previous exposure to BL, and OR, 9.47; 95% CI, 1.51–59.32; $P = 0.02$ in ACEI). Our results suggest that there was a slight difference between the risk factors associated with total BL- and cephalosporin-induced anaphylaxis.

DISCUSSION

This study analyzed the major causative drugs, clinical manifestations, outcomes, and risk factors associated with BL-induced anaphylaxis by comparing the results to matched controls. To date, no study has investigated the clinical risk factors for BL-induced anaphylaxis by comparing data with drug-tolerant matched controls. Interestingly, our main finding in this study demonstrates that history of drug allergy, previous exposure to the causative drug, and administration of ACEIs were risk factors for developing BL-induced anaphylaxis.

History of drug allergy is a known risk factor of anaphylaxis. In this study, the development of BL-induced anaphylaxis was increased by approximately 20-fold in patients with a history of drug

allergy. Generally, previous exposure to drugs without a hypersensitivity reaction is often regarded as evidence of tolerance to those drugs in practice; therefore, there is a tendency to pay less attention to drugs that were safely administered without an initial adverse reaction in real-world practice. However, this study showed that previous asymptomatic exposure to BLs could be a risk factor for developing BL-induced anaphylaxis, particularly as repeated administration of the same BL significantly increased the risk of related anaphylaxis by ~8 fold. Histories of previous asymptomatic exposure events to certain drugs may imply a duality of tolerance and silent sensitization as the possibility of sensitization increases with subsequent exposures to the causative antigen in patients susceptible to drug allergy. Therefore, it is recommended that patients be closely monitored during BL administration, even if there is no history of hypersensitivity reactions.

In our dataset, we could not find any difference in patients with cardiovascular disease or those taking beta-blockers, which are known risk factors for severe anaphylaxis.[15–17] Age is a crucial risk factor for anaphylaxis, particularly old age, owing to the increased chance of repeated exposure to causative allergens.[18,19] Cardiovascular diseases and treatments with beta-blockers also increase with age. Therefore, these results suggest that these known risk factors might have acted as confounding variables. Notably, ACEIs, food allergy, and previous exposure to BLs were risk factors for cephalosporin-induced anaphylaxis. Our findings were consistent with previous studies that showed ACEIs were risk factors for drug-induced anaphylaxis.[20–23] Meanwhile, studies have shown that antihypertensive drugs, including ACEIs, are associated with severity and hospitalization rates in anaphylactic patients. Since ACE breaks down bradykinin, ACEIs can increase bradykinin levels by blocking its breakdown, subsequently leading to angioedema, hypotension, and broncho spasm.[24] In addition, bradykinin formation has been found in the human plasma of anaphylactic patients and experimental animal model of anaphylaxis.[25] Another research published that ACEI and beta-blockers augment the anaphylaxis reaction caused by direct mast cell priming in mouse models.[17] Therefore, ACEIs may contribute to increasing the risk of anaphylaxis by inhibiting bradykinin degradation. However, ACEIs were not found to be risk factors for penicillin-induced anaphylaxis in this study. One possibility is that the number of penicillin-induced anaphylaxis cases was too small to reach statistical significance. Further studies are needed with larger sample sizes to elucidate these findings.

In this study, no significant differences were observed in the history of allergic diseases, comorbidities, and concomitant medications between the moderate and severe groups, which is consistent with findings from previous reports.[9,20,26,27] Previous studies showed that factors, including old age, cardiovascular disease status, male sex, known drug allergy, chronic lung disease, obesity, and some drugs, e.g., ACEIs, ARBs, beta-blockers, or PPIs, affected anaphylaxis severity.[5,6,18–20,28–30] Furthermore, drug-induced anaphylaxis, history of allergic disease, multi-organ involvement, and old age were reported as predictors of severe outcomes of anaphylaxis in Korean adults.[3]

In this study, ceftriaxone, piperacillin, cefazedone, cefbuperazone, and ceftizoxime were the most common causative drugs for BL-induced anaphylaxis. In Korea, a recent report showed that ceftizoxime had the highest incidence of anaphylaxis (13.0 cases per 100,000 exposures) followed by cefotetan, cefoperazone, and cefotaxime (11.6, 9.6, and 9.5 cases per 100,000 exposures, respectively) in intravenously administered cephalosporin-induced anaphylaxis.[8] Although the actual incidence of anaphylaxis owing to each drug was not evaluated in the present study, it may be affected by differences in prescription patterns by doctors as well as between hospitals.

Interestingly, cefbuperazone, cefotetan, and piperacillin correlated with severe reactions. Cefbuperazone and cefotetan share an identical R2 side chain, whereas cefbuperazone and piperacillin have a similar R1 side chain.[30] The observation that drugs causing severe reactions have structural similarity potentially indicates that the severity of BL-induced hypersensitivity may correlate with the structural properties of

individual drugs. In the future, it will be necessary to verify this finding through a large-scale study.

Mortality from anaphylaxis is extremely rare, with 0.12–1.06 cases per 1,000,000 people each year.[4] Although there is no evidence that the overall rate of fatal outcomes has increased and is inconsistent between regions, the mortality estimate is 0.5%–1% of total hospitalization outcomes owing to anaphylaxis.[1] The mortality in the present study is relatively higher at 1.4% than that in the previous report,[1] which may be attributed to several factors. First, the drugs used in this study may affect the outcomes of anaphylaxis. There are certain high-risk drugs that have been well-known to trigger fatal anaphylaxis.[9,10,18] Second, the route of drug administration could affect the development and severity of anaphylactic reactions. For instance, intravenous administration produced more frequent and severe anaphylaxis than that by oral administration in an outpatient setting, which is in line with a previous report.[20]

Our study has several limitations. First, the present study was a retrospective cohort study. Therefore, we could not obtain a complete dataset, including a past medical history, comorbidities, and drug exposure. Moreover, it could not be ruled out that the specific history, such as food/drug allergy, has been overestimated in patients with anaphylaxis. We tried to investigate the risk factor by comparing the anaphylaxis patients with drug-tolerant matched controls. Therefore, acquiring a detailed and thorough history was essential. Unlike outpatient clinics and emergency departments, inpatients are required to assess their food/drug allergy history for dietary and medication prescriptions mandatorily at admission. We could comprehensively review the detailed medical records and provide an in-depth analysis of the risk factors for BL-induced anaphylaxis and clinical courses. Interestingly, the prevalence of allergic comorbidities such as allergic rhinitis, asthma, and atopic dermatitis was relatively low in this study. The average age was approximately 47 years, middle-aged in this study; it might have influenced the relatively low prevalence of allergic disease. To counter this limitation, a large-scale prospective cohort study is needed in the future.

Second, determination of an accurate diagnosis and the causal factor through immunological investigations such as a skin test and specific IgE test was not carried out in most patients. After the anaphylaxis reaction, 12 patients (16%) were referred to an allergy specialist. Except for the patient refusing additional testing, the skin test for the determination of the causal drug was performed in 6 out of 12 patients; of these 6 patients, 4 tested positive, and 2 tested negative. In addition, the sIgE test for BLs was performed in 6 patients, with 4 testing negative and 2 weakly positive. Meanwhile, anaphylaxis mainly occurs immediately after administering the drug, and clinical diagnosis is critical We included cases assessed as only "certain" or "probable" in the causality assessment and excluded drugs with a "possible" causality.

Third, the severity of all patients included in this study was more than moderate. The first thing to explain was anaphylaxis that occurred during hospitalization. The severity estimation may have increased because the response was such that the medical staff took action to report it to the pharmacovigilance system or enter a hypersensitivity code. Furthermore, the route of drug administration should be considered. In this study, patients were given intravenously beta-lactam antibiotics, contributing to the increased severity of anaphylaxis. Finally, the limitations of the retrospective design and the consideration of selection bias might affect severity.

In conclusion, the history of drug allergy, previous exposure to the causative drug, and concomitant administration of ACEI are risk factors for BL-induced anaphylaxis. Therefore, more attention should be paid to a patient's medication history before the administration of BLs.

Abbreviations

ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blockers; BL: Beta-lactam; CI: Confidence interval; ICSR: Individual case safety report; OR: Odds ratio; PPI: Proton pump inhibitor; WHO-UMC: World Health Organization-Uppsala Monitoring Centre.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Authors' contributions

All authors have made substantial contributions to all of the following:

1. The conception and design of the study, or acquisition of data, or analysis and interpretation of data
2. Drafting the article or revising it critically for important intellectual content
3. Final approval of the version to be submitted.

Ethics approval

The Ethics Committee from each hospital approved the study (approval number: HPIRB 2016-06-023-001). Patient consent was not required, because this research was a retrospective medical record study of patients.

Declaration of competing interest

The authors report no competing interests. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2021.100580.

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