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Association of Early Antibiotic Exposure with Kawasaki Disease

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Abstract

Background

Kawasaki disease (KD) is an acute febrile vasculitis of unknown etiology that primarily affects children under five years old. Emerging evidence suggests that gut microbiota alterations may contribute to KD pathogenesis. Because antibiotics modify intestinal microbial composition, their inappropriate or repeated use in early childhood may increase KD susceptibility. However, population-based evidence linking antibiotic exposure with KD onset remains limited, and the influence of antibiotic class, number of classes, and administration route has not been systematically evaluated.

Objectives

To examine the association between antibiotic type, number of antibiotic classes, route of administration, and KD onset in a nationwide dataset.

Methods

We conducted a matched case–control study using the JMDC database (2005–2024). Children aged 0–18 years were eligible. Newly diagnosed KD cases (n = 17,410) and controls (n = 68,621) were matched 1:4 by age, sex, and birth year. Antibiotic exposure within 12 months before the KD index date was assessed by class (penicillins, cephalosporins, macrolides, quinolones, others), number of distinct classes, and administration route (oral vs. intravenous). Multivariable conditional logistic regression estimated odds of KD onset adjusted for low birth weight, pneumonia, otitis media, allergic rhinitis, and asthma.

Results

Among 86,031 children, exposure to penicillins (OR, 1.18; 95% CI, 1.11–1.24), cephalosporins (OR, 1.11; 95% CI, 1.05–1.18), quinolones (OR, 1.32; 95% CI, 1.13–1.55), and macrolides (OR, 1.16; 95% CI, 1.05–1.27) was associated with increased KD risk. Risk rose with more antibiotic classes (≥3 classes: OR, 1.20; 95% CI, 1.15–1.26). Oral antibiotic use showed a significant association (OR, 1.22; 95% CI, 1.16–1.27), while intravenous use did not.

Conclusions

Exposure to multiple antibiotic classes, especially via oral administration, was significantly associated with KD development. These findings support a possible link between antibiotic-related microbiome disruption and KD susceptibility and highlight the need for cautious pediatric antibiotic stewardship.

Introduction

Kawasaki disease (KD) is an acute, self-limiting, systemic vasculitis of unknown etiology that predominantly affects children under five years old **[1]**. Alterations in the gut microbial composition have

been linked to the development of various metabolic and immune-mediated disorders, including inflammatory bowel disease, type 1 diabetes, and even neurodevelopmental impairment **[2-4]**. Antibiotics are known to have a profound impact on the composition of the gut microbiota. Antibiotic exposure has also been associated with various long-term adverse health outcomes. These include an increased risk of atopic dermatitis, allergies, wheezing, asthma, obesity, arthritis, idiopathic disorders, psoriasis, and neurodevelopmental impairments **[5]**. Recent small-scale studies have suggested an association between gut microbiota dysbiosis and KD **[6,7]**. Several other studies have reported a potential link between antibiotic exposure and KD **[8-11]**. However, few studies have examined the classes, number, and routes of antibiotic administration (intravenous versus oral) in detail.

The present study therefore investigated whether or not these antibiotic-related factors are independently associated with the KD onset.

Methods

Study design and data source

We conducted a case-control study using the health insurer database provided by JMDC, Inc., an administrative claims database covering the period from January 2005 to July 2024. We chose this study design because it had a relatively low incidence rate, and a case-control approach was considered efficient. JMDC, Inc., has contracts with more than 60 insurers and collects annual health and lifestyle disease-screening records linked to health insurance. The database contained demographic information, medical histories, prescription records, diagnoses recorded using the International Classification of Diseases, 10th Revision (ICD-10) codes, and death information. Drugs were categorized based on the WHO Anatomical Therapeutic Chemical (ATC) classification, and the routes of administration were determined using Japan's national pharmaceutical coding system. Japan has had a universal health insurance system since 1961, under which, in principle, all citizens are covered by health insurance. In addition, many municipalities subsidize medical expenses for children under 15 years old. This institutional background ensures relatively uniform access to medical care across the country; thus, the data used in this study are unlikely to be substantially affected by regional disparities in healthcare delivery.

Ethics

This study protocol was reviewed and approved by the Chiba Cancer Center Ethics Review Committee (approval number A07-1; April 17, 2025). The requirement for informed consent was waived because this study used only anonymized data. The study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Variables of interest

- Source population

Information on each child, including the sex, age, and history of antibiotic prescriptions, was obtained from all available periods in the database. Antibiotic use was identified from the WHO ATC .

- Outcomes

The primary outcome was the occurrence of KD. Specifically, we included patients diagnosed with KD (ICD-10 code M303) who received intravenous immunoglobulin (IVIG) treatment. Cases labelled as “suspected” were excluded, whereas those diagnosed with atypical KD were included. To ensure diagnostic accuracy, patients over six years old were excluded because KD onset is uncommon in this age group, and distinguishing KD from other diseases is challenging.

- Exposures

The exposure variables included age category (0–5 years old), sex (male), presence of complex chronic conditions (CCC) [12], use of antibiotic agents, antiviral agents, antifungal agents, low-birth-weight infants (P07.0–P07.2), and preterm infants (P07.3). For antibiotics, antiviral agents, and antifungal agents, exposure information was collected from birth until one month before the onset of KD. Patients who received antibiotic treatment after the onset of KD symptoms due to cervical lymphadenitis (L04.0) or other infectious diseases were excluded.

With regard to comorbidities and background conditions, the following variables were included in the analysis: severe infections (sepsis [A41/R78.81], meningitis [G00], and septic arthritis [M00]), sinusitis (J01), pneumonia (J18), otitis media (H66), allergic rhinitis (J30), allergic dermatitis (L20), eczema (L50), and asthma (J45). In CCC classification, congenital diseases include congenital heart defects, chromosomal/genetic syndromes, inborn errors of metabolism, and major structural malformations (ICD-10 Q00–Q99, partly E70–E90).

Antibiotics were further classified into the following categories: penicillins, cephalosporins, fluoroquinolones, macrolides, sulfonamide/trimethoprim (ST) agents, and tetracyclines (the latter corresponding to the “Others” category in the regression analysis) (Supplemental table). In cases where multiple antibiotic classes were administered, the patients were classified as exposed to each of the corresponding categories.

Regarding antibiotic types, we examined the number of different classes of antibiotics administered from birth until one month before the onset of KD. The classes included penicillins, cephalosporins, macrolides, and quinolones, and antibiotics were categorized as including 0, 1, 2, or ≥3 classes.

To examine the route of antibiotic administration, we created two exposure variables for oral and intravenous administration with Japan’s national pharmaceutical coding system. . These variables were not mutually exclusive; patients who received both routes were classified as being exposed to both oral and intravenous antibiotics.

Statistical analyses

Categorical variables are indicated as numbers and percentages and were compared using Fisher's exact test. Continuous variables were presented as mean and standard deviation (SD) or median and interquartile range (IQR). The Mann–Whitney U test was used to compare non-normally distributed variables between the two groups. The results of the logistic regression analyses were presented as odds ratios (ORs) and 95% confidence intervals (CIs). Statistical significance was set at $P<0.05$. All statistical analyses were conducted using the Stata software program (version 19.0; Stata Corp LP, College Station, TX, USA).

Case and control definition

Patients with KD were identified as cases, and the index date for each case was defined as the date on which KD was first recorded. Four controls were randomly selected from each case. Controls were selected using risk set sampling from individuals who had not yet developed KD at the index date of each case. Therefore, individuals selected as controls at one point in time may later become cases. As this database is based on insurance claims rather than hospital registries, the control group included a broad range of children, from those with no history of medical visits to those who had received outpatient or inpatient care for conditions other than KD, including various infectious diseases. Randomization was performed using a random number table to sequentially select candidate numbers with the aid of a software program. All children were observed from birth to six years old, and cases and controls were matched by age, sex, and year of birth **[13,14].**

Univariate analyses were conducted to examine the association between each factor and KD. A multivariable conditional logistic regression analysis was then performed to identify factors independently associated with KD onset. Dependent variables were selected based on previous studies and included the child's sex, presence of older siblings, preterm birth, low birth weight, antibiotic use, and history of infectious diseases **[11,15-17]**. To further explore the relationship between antibiotic exposure and KD, three multivariable models were constructed: Model 1 evaluated the *type of antibiotics used* (penicillin, cephalosporin, macrolide, quinolone, or others); Model 2 examined the *number of antibiotic types prescribed* (none, one, two, or three or more types); and Model 3 assessed the *route of administration* (intravenous vs. oral).

Results

Table 1 summarizes the characteristics of case-control matched children with and without KD. A total of 17,410 patients and 68,621 matched controls (1:4 matching ratio) were included. There were no significant differences in the proportion of preterm infants between the two groups, whereas the proportion of low-birth-weight infants was significantly higher among the KD cases. Several comorbidities including sinusitis, pneumonia, otitis media, and asthma were significantly more prevalent in the KD group than in the control group. Children with KD were significantly more likely to have received antibiotics and to have been prescribed multiple antibiotic classes. Both oral and intravenous antibiotic use was also significantly more frequent in KD patients than in controls.

Across all three multivariable models, low birth weight was consistently associated with an increased risk of KD onset (odds ratio [OR] range: 1.12–1.13). Among the comorbidities, pneumonia, otitis media, allergic rhinitis, and asthma were significantly associated with KD. In **Model 1** (antibiotic type), the use of penicillins (OR: 1.18; 95% confidence interval [CI]: 1.11–1.24), cephalosporins (OR: 1.11; 95% CI: 1.05–1.18), quinolones (OR: 1.32; 95% CI: 1.13–1.55), and macrolides (OR: 1.16; 95% CI: 1.05–1.27) was significantly associated with KD compared with no antibiotic use. In **Model 2** (number of antibiotic classes), the risk of KD increased in a dose-dependent manner, with adjusted ORs of 1.10 (95% CI: 1.03–1.17), 1.11 (95% CI: 1.03–1.19), and 1.20 (95% CI: 1.15–1.26) for one, two, and three or more antibiotic classes, respectively. In **Model 3** (route of administration), oral antibiotic use was significantly associated with KD (OR: 1.22; 95% CI: 1.16–1.27), whereas intravenous antibiotic use showed no significant association (OR: 1.03; 95% CI: 0.98–1.08). The use of antifungal or antiviral agents was not significantly associated with KD onset in any of the models (**Tables 2–4**).

Discussion

In this study, a case–control design was used to investigate the association between antibiotic exposure and KD onset. The findings demonstrated that antibiotic use was associated with an increased risk of KD, particularly with the use of specific antibiotic classes, administration of multiple antibiotic classes, and oral antibiotic use.

In the analysis by antibiotic class, fluoroquinolone antibiotics showed the strongest association with the onset of KD. In contrast, the use of ST combinations was not significantly associated with KD occurrence. In Japan, oral fluoroquinolone antibiotics have been approved for pediatric use. It is widely prescribed for infections caused by *Streptococcus pneumoniae* (including penicillin-resistant strains), *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, and *Haemophilus influenzae*. Previous studies have reported a strong association between fluoroquinolone use and the onset of inflammatory bowel disease **[18]**. Commonly used agents in Japan, such as tosufloxacin, may reduce gut microbial diversity and potentially contribute to KD onset through the disruption of immune homeostasis. In contrast, ST combinations used for prophylactic purposes have been reported to have relatively minor effects on gut microbiota **[19].** These findings underscore the importance of avoiding the unnecessary use of broad-spectrum antibiotics and promoting appropriate antibiotic stewardship. Fluoroquinolone antibiotics have broad activity against intestinal bacteria, including *Escherichia coli*, and therefore, should be used cautiously and only when clinically indicated.

An increasing number of antibiotic classes was associated with a stepwise increase in the risk of KD. Similar findings have been reported in previous studies, suggesting that this association may reflect the effect of antibiotic exposure itself, rather than the underlying infection **[10].** Furthermore, antibiotic use has been shown to induce not only transient but also long-lasting alterations in the gut microbiota, persisting for one to two years **[20,21].** In children, the impact of antibiotic exposure on gut microbial composition may persist for up to 3 years **[19]**. Because early childhood is a critical period for the development of gut microbiota and coincides with the peak age of KD onset, antibiotic use during this

period should be carefully evaluated for its potential long-term effects. These findings highlight the importance of avoiding unnecessary broad-spectrum antibiotic use and promoting appropriate antibiotic stewardship in clinically indicated cases.

In the analysis according to route of administration, oral antibiotic use was significantly associated with an increased risk of KD, whereas intravenous antibiotic use showed no significant association. In a univariate analysis, the frequency of intravenous antibiotic use was higher among patients with KD. However, this association disappeared after adjusting for the patient background in the multivariate analysis. This finding suggests that the higher frequency of intravenous antibiotic use in KD cases reflects differences in underlying clinical conditions rather than the onset of KD itself. In contrast, oral antibiotic use remained significantly associated with KD onset, even after adjustment, suggesting a potential mechanism mediated by direct effects on the gut microbiota. Therefore, unnecessary antibiotic use should be avoided, particularly in cases without clear bacterial indications such as viral infections, and appropriate antibiotic stewardship should be strongly promoted.

Several infections, including pneumonia, otitis media, allergic rhinitis, and asthma are independently associated with an increased risk of KD. However, the effect sizes were relatively modest (ORs ranging from 1.04 to 1.09). In contrast, antibiotic exposure demonstrated stronger associations with KD (ORs ranging from 1.11 to 1.32 across different classes of antibiotics). These findings suggest that the observed risk of KD cannot be fully explained by preceding infection alone. Instead, the use of antibiotics, potentially through their impact on the gut microbiota, may play a more independent and substantial role in KD susceptibility than previously considered.

Limitations

Several limitations associated with the present study warrant mention. First, disease identification in the administrative claims database used in this study was based on diagnostic codes such as ICD-10, and diagnostic misclassification cannot be completely excluded. Compared to prospective studies, any misclassification in diagnostic coding could have affected the results if it occurred disproportionately between the KD and control groups. Second, due to the nature of database research, detailed clinical information, such as laboratory findings, clinical indications, or potential confounding factors influencing the gut microbiota, including dietary habits, was not available for the analysis. Third, because this was a case-control study, only relative risks could be assessed; absolute risks could not be calculated. Therefore, validation through future cohort studies is required. Fourth, the study population consisted almost entirely of Japanese individuals; therefore, generalizability of the findings to other ethnic or racial groups may be limited. Fifth, owing to limitations inherent in claims data, patient follow-up was not possible if an individual changed insurers, so some KD cases might not have been captured in the database. Hence, caution should be exercised when interpreting the generalizability of these findings. Sixth, information regarding the duration or cumulative number of antibiotic prescriptions was unavailable.

Nevertheless, this study is the first to examine the association between KD onset and both class and route of antibiotic administration (oral versus intravenous). Importantly, intravenous antibiotic use was not associated with an increased risk of KD, whereas fluoroquinolone use was significantly associated with an increased risk of KD. These findings provide valuable insights into antibiotic prescription practices and their potential impact on KD development.

Conclusions

Antibiotic exposure, particularly multiple classes and oral administration, was associated with an increased KD risk, suggesting a role for gut microbiota disruption in its pathogenesis. These findings emphasize the importance of appropriate antibiotic stewardship in children to prevent unnecessary exposure, especially in cases of viral infection.

Abbreviations

ATC = Anatomical Therapeutic Chemical classification; CCC = Complex chronic conditions; CI = Confidence interval; ICD-10 = International Classification of Diseases, 10th Revision; IQR = Interquartile range; IV = Intravenous; IVIG = Intravenous immunoglobulin; JMDC = Japan Medical Data Center; KD = Kawasaki disease; OR = Odds ratio; SD = Standard deviation.

Declarations

Data sharing statement: The datasets analyzed during the current study are not publicly available because the JMDC database is a commercial database. Access to the data can be obtained from JMDC, Inc., through a paid licensing agreement. Interested researchers may contact JMDC, Inc. via the official inquiry form (https://www.phm-jmdc.com/inquiry) or through the JMDC database website (https://www.jmdc.co.jp/jmdc-claims-database/).

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Conflict of Interest Disclosures:

The authors have no potential conflicts of interest to disclose.

Consent statement:

The requirement for informed consent was waived because of the anonymity of the data.

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Author Contribution

Takanori Suzuki and Jumpei Yoshida wrote the first draft of this manuscript. Nobuaki Michihata conceptualized and designed the study and reviewed and revised the manuscript. Kazuyoshi Saito, Hidetoshi Uchida, Arisa Kojima, Yumiko Asai, Tadayoshi Hata, and Tetsushi Yoshikawa conceptualized and designed the study and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work. Takanori Suzuki and Jumpei Yoshida contributed equally to this study.

Data Availability

The datasets analyzed during the current study are not publicly available because the JMDC database is a commercial database. Access to the data can be obtained from JMDC, Inc., through a paid licensing agreement. Interested researchers may contact JMDC, Inc. via the official inquiry form (https://www.phm-jmdc.com/inquiry) or through the JMDC database website (https://www.jmdc.co.jp/jmdc-claims-database/).

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randomized, placebo-controlled trial. EBioMedicine. 2018 Dec;38:265–72.

Tables

Table 1. Characteristics of case-control-matched children with and without KD

	Cases (with KD)	Controls	p-value
	(n=17,410)	(n=68,621)	
Patient characteristics			
Age, year of the KD diagnosis*	2.1 (1.2-3.5)	2.1 (1.2-3.5)	0.85
Male (%)*	9,964 (57.2%)	39,311 (57.3%)	0.89
Low birth weight infants	929 (5.3%)	3,315 (4.8%)	0.006
Preterm infants	534 (3.1%)	2,018 (2.9%)	0.38
Comorbidities and prior conditions			
Severe infections†	74 (0.4%)	258 (0.4%)	0.35
Sinusitis	3,885 (22.3%)	14,343 (20.9%)	<0.001
Pneumonia	1,610 (9.2%)	5,576 (8.1%)	<0.001
Otitis media	4,332 (24.9%)	15,311 (22.3%)	<0.001
Allergic rhinitis	32,422 (47.2%)	32,422 (47.2%)	<0.001
Allergic dermatitis	5,355 (30.8%)	20,958 (30.5%)	0.58
Eczema	3,528 (20.3%)	13,541 (19.7%)	0.12
Asthma	7,776 (44.7%)	29,045 (42.3%)	<0.001
Congenital anomalies	205 (1.2%)	816 (1.2%)	0.90
CCC	1,309 (7.5%)	4,855 (7.1%)	0.043
Antibiotics			
Type of antibiotics			
No antibiotics	7,052 (40.5%)	29,903 (43.6%)	<0.001
Penicillin	5,876 (33.8%)	21,305 (31.0%)	
Cephalosporin	3,403 (19.5%)	13,443 (19.6%)	
Quinolones	228 (1.3%)	685 (1.0%)	
Macrolides	705 (4.0%)	2,638 (3.8%)	
ST	3 (0.0%)	10 (0.0%)	
Others	143 (0.8%)	637 (0.9%)	
Number of antibiotic classes			
0	7,052 (40.5%)	29,368 (42.8%)	<0.001

1	1,793 (10.3%)	7,097 (10.3%)	
2	1,284 (7.4%)	5,052 (7.4%)	
≥3	7,281 (41.8%)	27,104 (39.5%)	
Route of administration			
Oral	10,235 (58.8%)	38,229 (55.7%)	<0.001
Intravenous	3,758 (21.6%)	13,975 (20.4%)	<0.001
Antiviral agents	2,351 (13.5%)	9,302 (13.6%)	0.86
Antifungal agents	153 (0.9%)	565 (0.8%)	0.47

CCC, complex chronic conditions; IQR, interquartile range; KD, Kawasaki disease; SD, standard deviation; ST: Sulfamethoxazole/trimethoprim

*Cases and controls were matched for age and sex.

†Severe infections included sepsis, meningitis, and septic arthritis.

Table 2. Factors associated with the onset of KD according to antibiotic type (Model 1)

Variables	Multivariable analyses*			
	Odds ratio	95% confidence interval		p-value
Patient characteristics				
Low-birth-weight infants	1.13	1.03	1.23	0.013
Preterm infants	0.93	0.82	1.04	0.207
Comorbidities and prior conditions				
Severe infections†	1.04	0.80	1.36	0.761
Sinusitis	1.02	0.97	1.07	0.447
Pneumonia	1.09	1.02	1.16	0.007
Otitis media	1.08	1.03	1.13	0.001
Allergic rhinitis	1.07	1.02	1.11	0.003
Allergic dermatitis	0.99	0.95	1.03	0.541
Eczema	1.01	0.96	1.05	0.706
Asthma	1.04	1.00	1.09	0.036
CCC				
0	reference			
1	1.03	0.96	1.10	0.375
Antibiotics				
Type of antibiotics				
No antibiotics	reference			
Penicillin	1.18	1.11	1.24	<0.001
Cephalosporin	1.11	1.05	1.18	<0.001
Quinolones	1.32	1.13	1.55	<0.001
Macrolides	1.16	1.05	1.27	0.002
ST	1.25	0.34	4.56	0.735
Others	0.99	0.82	1.19	0.920
Antiviral agents	0.95	0.90	1.01	0.082
Antifungal agents	1.02	0.85	1.22	0.842

CCC: Complex chronic conditions, KD: Kawasaki disease, ST: Sulfamethoxazole/trimethoprim

*Cases and controls were matched for age and sex.

†Severe infections included sepsis, meningitis, and septic arthritis.

Table 3. Factors associated with the onset of KD according to the number of antibiotics (Model 2)

Variables	Multivariable analyses*			
	Odds ratio	95% confidence interval		p-value
Patient characteristics				
Low-birth-weight infants	1.12	1.02	1.23	0.015
Preterm infants	0.93	0.82	1.05	0.225
CCC				
0	reference			
1	1.03	0.97	1.10	0.366
Antibiotics				
Number of antibiotic classes				
0	reference			
1	1.10	1.03	1.17	0.003
2	1.11	1.03	1.19	0.004
≥3	1.20	1.15	1.26	<0.001
Antiviral agents	0.97	0.91	1.02	0.219
Antifungal agents	1.03	0.86	1.23	0.764

CCC: Complex chronic conditions, KD: Kawasaki disease

*Cases and controls were matched for age and sex.

Table 4. Factors associated with the onset of KD according to route of administration (Model 3)

Variables	Multivariable analyses*			
	Odds ratio	95% confidence interval		p-value
Patient characteristics				
Low birth weight infants	1.12	1.02	1.23	0.015
Preterm infants	0.93	0.82	1.05	0.222
CCC				
0	reference			
1	1.03	0.97	1.10	0.336
Antibiotics				
Route of administration				
Oral	1.22	1.16	1.27	<0.001
Intravenous	1.03	0.98	1.08	0.188
Antiviral agents	0.97	0.92	1.02	0.240
Antifungal agents	1.03	0.86	1.23	0.768

CCC: Complex chronic conditions, KD: Kawasaki disease

*Cases and controls were matched for age and sex.

Supplementary Files

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- SupplementaryTable1.xlsx