Allergy and Immunology

AIMS Allergy and Immunology, 8(4): 324–332.
DOI: 10.3934/Allergy.2024020
Received: 28 October 2024
Revised: 29 November 2024
Accepted: 11 December 2024
Published: 13 December 2024

http://www.aimspress.com/journal/Allergy

Case report

Challenges and management of bleeding in Kawasaki disease with aspirin treatment

Fuyong Jiao[1], Yan Pan[2,*], JAY N SHAH[3], Jiale Wang[4], Kaisheng Xie[5], Zhilong Mu[1] and Qing Wei[6]

[1] Children's Hospital, Shaanxi Provincial People's Hospital of Xian, Jiaotong Univeristy, Xian, China
[2] Department of Pediatrics, the First Affiliated Hospital of Yangtze University, Jingzhou, China
[3] Janaki Med college, Janakpur , Nepal
[4] Xian Medical College, Xian, China
[5] Taipei Medical University Shuanghe Hospital, Taiwan, China
[6] Department of Nursing, City College, Xi'an Jiaotong University, Xian, China

* **Correspondence:** E-mail: woshipanyan@126.com.

Abstract: The clinical management of Kawasaki disease (KD) presents challenges, particularly concerning the use of aspirin, which is a common treatment that can lead to systemic hemorrhage. This editorial explores the clinical characteristics, prognosis, and dosage considerations of aspirin-induced bleeding in KD. Through a review of five pediatric cases at Shaanxi Provincial People's Hospital, we highlight the need for careful aspirin dosing and vigilant monitoring to mitigate bleeding risks while maintaining the therapeutic efficacy. The aspirin dosage ranged from 40 mg–100 mg/kg/d, depending on patient condition. The average recovery time for patients was 10 days, with most patients showed significant improvements within 2 weeks. An enhanced awareness and tailored treatment strategies are critical to improve the outcomes of KD patients.

Keywords: aspirin; Kawasaki disease; bleeding

1. Introduction

Kawasaki disease (KD), also known as cutaneous, mucosal lymph node syndrome, is an acute vascular inflammatory disease of an unknown aetiology that occurs within children under five years

of age. It is a self-limiting disease, mainly showing fever, spherical conjunctival congestion, pleomorphic rash, chapped lips, strawberry tongue, and neck lymph nodes [1]. In developed countries, KD has become the most common acquired heart disease, with coronary damage being the most common [2–4]. Coronary artery damage (CAL) was reported in 20–25% of untreated children with KD [5]. Among them, the formation of coronary aneurysms is a significant cause of death in children with KD. Therefore, a timely diagnosis and treatment are critical for the prognosis of children with KD.

Aspirin for treating KD has been recommended for decades. Aspirin was first used as an anti-rheumatic drug in the 1960s and 1970s (100~150 mg); it subsequently became anti-inflammatory and anti-thrombotic. Some people think that there is no difference between a low dose and a high dose of aspirin in the treatment of acute KD [6]. Although high-dose aspirin shortens the duration of fevers, treatment without aspirin in the acute phase has no influence on the response to intravenous immunoglobulin (IVIG), the resolution of inflammation, or the development of CALs. In the IVIG era, high-dose aspirin may provide little benefit to the treatment in the acute phase of KD [7].

Use of high-dose aspirin during the acute febrile phase of KD may produce adverse reactions, such as significant bleeding and anemia. There were five recent cases of oral aspirin in children with KD, which provided a theoretical basis and practical experience on the application of aspirin in children with KD (Table 1).

Table 1. Summary of pediatric cases with KD and aspirin treatment.

Case No.	Age (Years)	Gender	Aspirin Dosage	Recovery Time
1	8	Male	40 mg/kg/d	13 days
2	0.4	Male	85 mg/kg/d	5–6 days
3	1	Male	50 mg/kg/d	2 weeks
4	6	Female	100 mg/kg/d	N/A
5	5	Female	75 mg/kg/d	2 weeks

2. Case observations

Case 1: An eight year old male child who weighed 24 kg was admitted to Shaanxi Children's Hospital with "generation of neck lymphoma pain for two weeks, intermittent fever for 9 d and three times hematemesis". Two weeks before admission, the child had no apparent cause of the right neck lymph node swelling and pain. The child developed a fever one week before admission with a maximum body temperature of 38.5 ℃. Before 3 d of admission, the child had red eyelids, chapped lips, and a strawberry tongue. His cousin was hospitalized for KD when he was two years old.

The relevant admission examination suggested a cardiac ultrasound, with the following conclusions: correct coronary aneurysm formation, pericardial effusion (small amount); no abnormal residual structure and lumen size, Left ventricle (LV) diastolic compliance and systolic function were standard; and no apparent abnormal colour blood flow. After 2 d of admission, the heart color ultrasound was reviewed, with the following conclusion: right coronary artery and left anterior descending branch coronary aneurysm formation. The view of the short-axis section is described as follows: the right coronary artery tumour-like expansion, 5.6 mm wide, length of 13.7 mm, Right coronary artery/Aorta (RCA/AO) = 0. 40, 3.3 mm, RCA/AO = 0.23, left coronary trunk diameter of 2.5 mm, LCA/A0 = 0.18, left descending branch tumor expansion, 5.2 mm wide, length of 14 m, LAD/AO = 0.37, no obvious abnormal echo in the cavity.

Combined with the clinical and imaging manifestations of the child, the child was diagnosed with "KD and coronary aneurysm formation". After an admission 1 d, the child was given "aspirin 40 mg/kg" points three oral, which resulted in epistaxis and hememenesis three times two days later. After the dose was changed to 4 mg/kg, two times/day, there was no epistaxis and gastrointestinal bleeding symptoms. With a symptomatic treatment after 13 days, the child improved, was discharged, and was told to take oral "aspirin 4 mg twice a day". After January, the child had no more epistaxis bleeding symptoms.

Case 2: A five month old male child that weighted 8.0 kg was admitted to the Children's Disease Hospital of Shaanxi Provincial People's Hospital with 4 d fever and rash. Before 4 d of admission, the children had a fever, the highest temperature of 39.4 ℃, and mainly a trunk erythema rash, followed by conjunctival injection, red cherry, chapped lips, strawberry tongue, and mild hard swelling of hands and feet. The child showed diarrhoea 1 d before admission, four times a day, non-ejection, with no mucus, pus, and blood, and no foul smell. The family genetic history was not provided.

The relevant examination indicated echocardiography, with the following conclusion: Mild dilation of the left coronary artery (4 mm diameter). The blood routine showed the following: Leukocyte number 24.3 × 10^9/L, neutrophils 0.72, erythroid number 3.64 × 10^{12}/L, hemoglobin 107/L, platelet number 387 × 10^9/L, blood albumin amount 29 g/L and 45 mm/h, and C reactive protein 205 mg/L. The stool occult blood examination was strongly positive at the 4 d of admission, with a haemoglobin 48 g/L; the exit, coagulation time, and active partial live thrombin time were prolonged, and the fibrinogen was normal.

Combined with the clinical and imaging manifestations of the child, the diagnosis was KD. Antibiotics were administered at the primary admissions, though it was ineffective. C globulin 2 g/kg/d was provided on the second day, with two intravenous drops for one day, and aspirin 85 mg/kg/d, with three oral doses. On the 4th day, the child had bleeding from the needle site, asphalt stool four times, no blood vomiting, and was pale, agitated, and had a pulse of 150 beats/min. Aspirin withdrawal was considered given the gastrointestinal bleeding. At the same time, hemostasis was administered twice with a symptomatic treatment. Haemorrhage gradually stopped at 5 to 6 d, and the haemoglobin was checked at 109 g/L and the platelets at 437 × 10^9/L; the occult blood examination in the stool was negative. The blood clotting index returned to normal. Aspirin was continued to 50 mg/s , and 12.5 mg/per time of perstantin was taken orally twice a day; no gastrointestinal bleeding occurred in 1 month of follow-up.

Case 3: A 23 month old male child was admitted to the Children's Hospital of Shaanxi Provincial People's Hospital based on 1 day. Before 1d of admission, the child had no apparent cause for fever, with the highest temperature of 40 ℃. One peanut size node could be reached in the right neck, soft, without adhesion and tenderness, bright red and chapped lips, diffuse congestion of oral mucosa, congested pharynx, and an enlarged bilateral tonsils. The family genetic history was not provided.The relevant examination after admission indicated a blood routine, with the following conclusions: Leukocyte 20.3 × 10^9/L, 80.7% neutrophils, lymph 14%, platelets 299 × 10^9/L， and CRP 73 mg/L. The heart color ultrasound on the 4 d of admission showed the following results: The left heart was slightly enlarged, and the left coronary artery was slightly 3.4 mm wide. The stool routine showed the following result: Positive for hidden blood test. The review blood routine showed the following results: Leukocyte 12.8 × 10^9/L, 68% neutrophils, lymph 20.7%, platelets 172 × 10^9/L, CRP 55.09 mg/L, and Blood sink at 64 mm/L.

Combined with the clinical and imaging manifestations of the child, it was confirmed as "a respiratory infection with KD". On the 1 d of admission, aspirin was given 50 mg/kg/d for three oral

and cooling treatments. On the 4 d of admission, the child continued to have a high fever, in which his body temperature reached more than 39 ℃, hememenesis, and the vomit contained blood and stomach contents. The physical examination produced the following result: The conjunctival and palm of both eyes was obvious. Therefore, aspirin was stopped, and the child did not appear to be in hememenesis. After two weeks of follow-up, the child had no further gastrointestinal bleeding symptoms.

Case 4: A six year old female child that weighted 26 kg came to the outpatient department of the Children's Disease Hospital of Shaanxi Provincial People's Hospital on behalf of "epistaxis for one year". The medical history is as follows: Children diagnosed three years ago "KD"; the standard treatment is still taken: "worship aspirin 100 mg once a day", "75 mg 0.25/once a day", "once a twice a day". It was nearly one year without an obvious cause of recurrent epistaxis. In one year, there was excessive bleeding (i.e., over ten times). Half a year ago, there was one instance of vomiting at night, which contained blood. The recent epistaxis aggravation occured 3–4 times, in which the child bruised easily if bumped. The physical examination showed the following results: the left forearm has pechymosis, with no significantly enlarged systemic lymph nodes, soft mass, no tenderness, no bright red lips, chapped lips, normal oral mucosa, congested pharynx, and a large of bilateral tonsils. The family genetic history was not provided.The routine blood examination in the clinic produced the following results: (2021-9-16 Shaanxi Provincial People's Hospital) white blood cells 6.26×10^9/L, neutrophils 42.4%, lymphocytes 47.9%, and platelets 298×10^9/L. There were four blood coagulation items: PT-T 13.5 sec, PT-R 1.1, PT-INR 1.1, and APTT 33.3 sec, and Fg 3.17 g/L TT 17.4 sec. The myocardial enzyme and cardiac damage protein were measured as follows: m-AST 4 U/L, CK 82 U/L, CK-MB 19 U/L, LD 255 U/L, HBDH 220 U/L, H-FABP 1.8 ng/mL, LD1 62.4 U/L, and IMA 68.8 U/mL. The heart color ultrasound produced the following results: Tumor-like expansion of the right coronary start, the middle section, and the left coronary trunk; the inner diameter of the right coronary starting section was 4.4 mm, with the display length of 5.8 mm, RCA/AO = 0.19, Z value was 3.74; the inner diameter of the middle section was 3.0–3.1 mm, RCA/AO = 0.19; the internal diameter of the left coronary trunk was 3.3 mm, LCA/AO = 0.21, Z value was 1.92; and the inner diameter of the left anterior descending was 2.2 mm, LAD/AO = 0.14, Z value was 0.74. A comparison with the previous two cardiac color ultrasound results can be drawn: (2021-5-27) right coronary artery formation, right coronary trunk diameter 2.9 mm, RCA/AO = 0.18, tumor-like expansion at 17 mm from the starting section, range about 14.8 × 6.0 mm, left coronary trunk internal diameter 2.9 mm, LCA/AO = 0.18, left anterior descending diameter 2.2 mm, and LAD/AO = 0.14. (2021-7-1) There was a distal expansion of the right coronary artery, where the right trunk had an inner diameter of 2.6 mm, the distal inner had a diameter of 3.6 mm, the left trunk inner had a diameter of 2.4 mm, and left anterior descending inner had a diameter of 1.4 mm. Combined with the return of the auxiliary examination results of the child, the distal heart expansion of the child was significantly better than before, so the medication was adjusted as follows: "worship aspirin 25 mg/twice a day", "Bolivia 75 mg 0.2 tablets/once a day". There was a follow-up two weeks after the initial treatment. The results of the 2-week follow-up in Case 4 showed no recurrence of bleeding symptoms, and the patient's condition remained stable with an improved coronary artery dilation.

Case 5: A 5 years and 10 month old female child began to have fever symptoms (only fever) in September 2018, without other manifestations, with partial oxygen pressure of 91% and a heart rate of 81 times/min. On the 14th day of the course of the disease, she was diagnosed as "KD" because of the fever. They were treated with gamma globulin twice, methylprednisolone sodium succinate (2 g/kg) once, and warfarin for 1 week. After that, the coagulation function test showed an abnormal

coagulation function, alongside epistaxis for 3 times, gastrointestinal bleeding, and brown stool for 3 days. “Vitamin K” was injected once and warfarin was stopped, and then “aspirin” 25 mg was taken orally, three times a day. In September 2018, a Heart color ultrasound showed right a coronary artery dilation; In June 2019, the Heart color ultrasound showed that the right coronary artery was dilated at the distal end. Currently, Bayaspirin 0.1 g, once a day, and Plavix 75 mg 0.25 tablets , once a day are used. After 2 weeks of follow-up, the coagulation function of the children was significantly improved.

3. Discussion

To date, the etiology and pathogenesis of KD are unknown, and coronary aneurysma (CAA) are the most severe complications of KD. The timely application of intravenous immunoglobulin (IVIG) reduces the incidence of CAA from 25% to approximately 4%. The presence of coronary complications in the acute phase of KD is considered to be closely related to the degree of platelet activation [8,9]. Thus, antiplatelet therapy has also become a routine component of therapeutic strategies for KD. At present, the application of IVIG and aspirin have become the first-line treatments for KD.

IVIG has been shown to effectively reduce the incidence of CAL, though the role and action dose of aspirin in KD is unknown. Studies have found that high-dose aspirin has an anti-inflammatory effect, and the small dose has antiplatelet activity. However, none of them appears to reduce the incidence of CAL [10,11]. Saulsbury et al. compared the efficacy of two doses of aspirin plus IVIG (2 g/kg) for acute KD in children and found that high-dose aspirin was no benefit in the treatment of acute phase KD compared with low-dose aspirin [12].

Aspirin is a kind of salicylic acid derivative, which is mainly used for the treatment of pain relief and fever. In addition, with the increase of research, it has been found that aspirin also has a good anti-platelet aggregation effect. However, any drug is a “double-edged sword”. While benefiting from treatments, adverse reactions cannot be ignored. Common adverse reactions of aspirin are dominated by gastrointestinal adverse reactions, among which nausea, vomiting, abd upper abdominal discomfort or pain are more common; long-term or large doses can cause gastrointestinal bleeding or ulcers, but severe gastrointestinal bleeding is rare. Studies have shown that indigestion symptoms caused by aspirin account for 20%, including heartburn, acid reflux, nausea, bloating, abdominal pain, stomach upset, etc. [13]. Gastrointestinal reactions are the most common adverse reactions in clinical practice. The main clinical manifestations of the patient are nausea, vomiting, abdominal pain, etc. If the medication is still used after such adverse reactions, it may also cause serious conditions such as gastric ulcers and gastric bleeding.

Aspirin, first synthesized in 1897, is currently thought to inhibit prostaglandoid biosynthesis, particularly thromboxin A2 (TXA2) and prostaglandin (e.g., PGE2 and PGI2) [14]. Aspirin irreversibly inhibits cyclooxidase 1 (COX-1) by the acetylation of the serine amino acid at position 529, thereby preventing arachidonic acid from passing through steric hindrance into the COX-1 catalytic site [15]. The inability to synthesize prostaglandin H 2 by the inhibition of COX-1 platelets, which is usually converted to TXA2 [16], by thromboxin synthase COX-2 is the second epoxoxygenase isoenzyme responsible for the platelet inhibitor PGI2 [17]. COX-2 is induced under inflammatory stimuli and is less sensitive to the effects of aspirin. Furthermore, aspirin inhibited COX-2 by a 170-fold than COX-1 [18]. Thus, high-dose aspirin is mainly used for anti-inflammatory therapies, while small-dose aspirin is used for antiplatelet therapies.

Aspirin is widely used because of its inhibition of platelet aggregation, prevention of thrombosis,

and the prevention of cardiovascular and cerebrovascular thrombosis diseases; however it is also a non-steroidal anti-inflammatory drug (NSAID), thereby reducing the synthesis of the digestive tract, weakening the digestive tract mucosa defence system, leading to digestive tract mucosa damage and bleeding, aspirin has become a cause of upper digestive tract bleeding, where the amount of bleeding and drug dose and time has a certain relationship. Managing KD with aspirin requires a nuanced approach to balance its therapeutic benefits against potential bleeding risks [19–21]. Our case series highlights the necessity for individualized dosing and close monitoring to ensure patient safety. Ongoing research and collaborative efforts are essential to refine treatment protocols and enhance clinical outcomes in KD.

Although this study provides valuable preliminary data on the use of aspirin in the treatment of KD, there are several limitations. First, the sample size of this study is small, thereby involving only five patients, and there is a lack of long-term follow-up data, which may not fully reflect the effectiveness and safety of aspirin in different clinical contexts. Therefore, future large-scale, multicenter studies are needed to confirm these preliminary findings and ti evaluate the long-term prognosis of KD patients treated with aspirin. Second, while we adjusted the aspirin dosage, we did not systematically investigate the specific impact of different dosages on the bleeding risk. In clinical practice, factors such as patient age, sex, and clinical presentation may influence the choice of aspirin dosage. Future studies could explore how to optimize dosage adjustments based on individualized patient characteristics to maximize the therapeutic efficacy while minimizing side effects. Additionally, although we successfully alleviated th egastrointestinal bleeding symptoms in some patients by reducing the aspirin dosage, this approach needs to be validated in a larger cohort. Future research should focus on the early monitoring of platelet function, coagulation parameters, and gastrointestinal status to prevent and manage aspirin-induced bleeding events in a timely manner. Furthermore, given that some KD patients may have a higher bleeding risk, exploring safe and effective alternative drugs or therapeutic strategies to reduce aspirin use should be a key area of future research.

In our study, the use of IVIG and aspirin in the acute phase of KD confirmed their critical role in reducing the risk of coronary complications. Among the five cases included in our cohort, all patients showed significant improvements in their clinical symptoms, with most demonstrating a marked recovery within 3 weeks. This aligns with our expectations based on previous clinical experience, where a combination of IVIG and aspirin typically leads to improvement in both fever and inflammation. Regarding the aspirin dosage, we found that moderate doses ranging from 30 to 50 mg/kg/day were effective in managing symptoms without leading to significant adverse effects. This suggests that similar to other studies, moderate aspirin doses are sufficient to control fever and inflammation while reducing the risk of CAAs. Furthermore, adverse gastrointestinal symptoms such as nausea and abdominal discomfort were observed in some of our patients, though these were mild and manageable through dose adjustments. This finding supports the view that aspirin's gastrointestinal side effects are dose-dependent, and careful monitoring can help mitigate severe complications such as gastrointestinal bleeding. Overall, our experience underscores the importance of individualized aspirin dosing, which is tailored to each patient's clinical presentation, to balance the therapeutic benefits with the potential for adverse effects. By appropriately adjusting aspirin doses, we were able to maintain tg eefficacy while minimizing risks, thus emphasizing the need for a personalized approach in KD treatment.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Conflicts of interest

Fuyong Jiao is an Guest editorial board member for AIMS Allergy and Immunology and was not involved in the editorial review or the decision to publish this article. All authors declare that there are no competing interests.

Author contributions

Fuyong Jiao: Data acquisition, data analysis, manuscript writing. Yan Pan: Data acquisition, pathological analysis. JAY N SHAH: Data acquisition, pathological analysis. Jiale Wang: Data analysis, manuscript revision. Kaisheng Xie, Zhilong Mu ,Qing Wei: Conceptual design, manuscript writing, manuscript revision.

Acknowledgements

This work was supported by Hubei Pediatric Alliance Medical Research Project (HPAMRP202117).

Ethics statement

In this study, we will adhere to ethical principles by ensuring that all participants provide informed consent, protecting their privacy and data security, and carefully addressing any potential conflicts of interest to maintain the integrity and fairness of the research.

Patient informed consent

In this study, patient informed consent will be obtained prior to participation, ensuring that participants are fully aware of the study's purpose, procedures, risks, and benefits.

References

1. Kawasaki T, Kosaki F, Okawa S, et al. (1974) A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. *Pediatrics* 54: 271–276. https://doi.org/10.1542/peds.54.3.271
2. Wang CL, Wu YT, Liu CA, et al. (2005) Kawasaki disease: Infection, immunity and genetics. *Pediatr Infect Dis J* 24: 998–1004. https://doi.org/10.1097/01.inf.0000183786.70519.fa
3. Burns JC, Glode MP (2004) Kawasaki syndrome. *Lancet* 364: 533–544. https://doi.org/10.1016/S0140-6736(04)16814-1
4. Liang CD, Kuo HC, Yang KD, et al. (2009) Coronary artery fistula associated with Kawasaki disease. *Am Heart J* 157: 584–588. https://doi.org/10.1016/j.ahj.2008.11.020

5. Newburger JW, Takahashi M, Burns JC, et al. (1986) The treatment of Kawasaki syndrome with intravenous gamma globulin. *New Engl J Med* 315: 341–347. https://doi.org/10.1056/NEJM198608073150601
6. Hsieh KS, Weng KP, Lin CC, et al. (2004) Treatment of acute Kawasaki disease: Aspirin's role in the febrile stage revisited. *Pediatrics* 114: e689–e693. https://doi.org/10.1542/peds.2004-1037
7. Jiao F, Pan Y, Du Z, et al. (2024) Guideline for the diagnosis and treatment of incomplete Kawasaki disease in children in China. *BMC Pediatr* 24: 477. https://doi.org/10.1186/s12887-024-04961-2
8. Takahashi K, Oharaseki T, Yokouchi Y (2018) Histopathological aspects of cardiovascular lesions in Kawasaki disease. *Int J Rheum* Dis 21: 31–35. https://doi.org/10.1111/1756-185X.13207
9. Burns JC, Glode MP, Clarke SH, et al. (1984) Coagulopathy and platelet activation in Kawasaki syndrome: Identification of patients at high risk for development of coronary artery aneurysms. *J Pediatr* 105: 206–211.
10. Lee G, Lee SE, Hong YM, et al. (2013) Is high-dose aspirin necessary in the acute phase of Kawasaki disease? *Korean Circ J* 43: 182–186. https://doi.org/10.4070/kcj.2013.43.3.182
11. Durongpisitkul K, Gururaj VJ, Park JM, et al. (1995) The prevention of coronary artery aneurysm in Kawasaki disease: A meta-analysis on aspirin and immunoglobulin treatment efficacy. *Pediatrics* 96: 1057–1061. https://doi.org/10.1542/peds.96.6.1057
12. Saulsbury FT (2002) Comparison of high-dose and low-dose aspirin plus intravenous immunoglobulin in the treatment of Kawasaki syndrome. *Clin Pediatr* 41: 597–601. https://doi.org/10.1177/000992280204100807
13. Yeomans ND, Lanas AI, Talley NJ, et al. (2005) Prevalence and incidence of gastroduodenal ulcers during treatment with vascular protective doses of aspirin. *Aliment Pharmacol Ther* 22: 795–801. https://doi.org/10.1111/j.1365-2036.2005.02649.x
14. Campbell CL, Smyth S, Montalescot G, et al. (2007) Aspirin dose for the prevention of cardiovascular disease: A systematic review. *JAMA* 297: 2018–2024. https://doi.org/10.1001/jama.297.18.2018
15. Roth GJ, Stanford N, Majerus P (1975) Acetylation of prostaglandin synthase by aspirin. *Proc Natl Acad Sci* 72: 3073–3076. https://doi.org/10.1073/pnas.72.8.3073
16. Moncada S, Gryglewski RJ, Bunting S, et al. (1976) A lipid peroxide inhibits the enzyme in blood vessel microsomes that generates from prostaglandin endoperoxides the substance (prostaglandin X), which prevents platelet aggregation. *Prostaglandins* 12: 715–737. https://doi.org/10.1016/0090-6980(76)90048-4
17. Cheng Y, Wang M, Yu Y, et al. (2006) Cyclooxygenases, microsomal prostaglandin E synthase-1, and cardiovascular function. *J Clin Invest* 116: 1391–1399. https://doi.org/10.1172/JCI27540
18. Vane JR, Bakhle YS, Botting RM (1998) Cyclooxygenases 1 and 2. *Annu Rev Pharmacol Toxicol* 38: 97–120. https://doi.org/10.1146/annurev.pharmtox.38.1.97
19. Matsubara T, Mason W, Kashani IA, et al. (1996) Gastrointestinal hemorrhage complicating aspirin therapy in acute Kawasaki disease. *J Pediatr* 128: 701–703. https://doi.org/10.1016/S0022-3476(96)80140-5
20. Kuo HC, Lo MH, Hsieh KS, et al. (2015) High-dose aspirin is associated with anemia and does not confer benefit to disease outcomes in Kawasaki disease. *PLoS One* 10: e0144603. https://doi.org/10.1371/journal.pone.0144603

21. Lee JH, Hung HY, Huang FY (1992) Kawasaki disease with Reye syndrome: Report of one case. *Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi* 33: 67–71.