ISSN: 2755-0141

Japan Journal of Clinical & Medical Research

SCIENTIFIC Research and Community

Review Article

Open Access

New Advances in the Diagnosis and Treatment of Kawasaki Disease

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ABSTRACT

Objective: To explore the latest research methods and information on the diagnosis and treatment of Kawasaki disease.

Methods: A total of 50 papers related to Kawasaki disease were collected from databases such as CNKI, the Internet, and PubMed for analysis and summary.

Results: In recent years, the research progress in the diagnosis and treatment of Kawasaki disease worldwide has been rapid, mainly focusing on five aspects: etiology and pathogenesis, diagnosis, treatment guidelines, expert consensus, and long-term management. The main pathogenesis theories include genetic susceptibility and infection trigger hypotheses, with the core role of the IL-1 pathway being clarified, and a deeper understanding of incomplete Kawasaki disease relying on ultrasound and biomarkers (NT-proBNP); the Z-score assessment has been promoted. The treatment mainly involves the use of biological agents such as infliximab and anakinra as standard second-line options; for high-risk patients, initial combination with hormones has become a new strategy.

Conclusion: Further strengthening of basic and clinical research on Kawasaki disease is still needed. Future research directions will focus on finding specific etiological factors and diagnostic biomarkers; developing more precise individualized initial treatment plans to minimize drug resistance and coronary artery damage; and deepening the understanding of the mechanisms of long-term sequelae and optimizing management strategies for the pre-adult period.

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Received: November 12, 2025; **Accepted:** November 17, 2025; **Published:** November 30, 2025

Keywords: Kawasaki Disease, Clinical Treatment, Diagnosis, Efficacy

Kawasaki Disease (KD), also known as mucocutaneous lymph node syndrome, is an acute febrile exanthematous disease characterized by systemic vasculitis. It was first reported by Dr. Tomisaku Kawasaki in Japan in 1967. The disease mainly affects children under 5 years old and is a leading cause of acquired heart disease in developed countries. The etiology remains unknown, and diagnosis is mainly based on clinical criteria. The treatment goal is to control inflammation and prevent the formation of Coronary Artery Aneurysms (CAA). Research progress both domestically and internationally has been rapid in recent years, which is summarized as follows.

Progress in Etiology and Pathogenesis Research

The cause remains a mystery, but the mainstream hypothesis is that an abnormal immune response occurs in genetically susceptible individuals triggered by specific environmental factors (such as infection).

Infection Trigger Hypothesis

Multiple studies have suggested that an unknown pathogen (possibly a virus) triggers an immune response through the molecular mimicry theory. The discovery of multisystem inflammatory syndrome (MIS-C) after the COVID-19 pandemic shares many similarities with Kawasaki disease, providing a new model and perspective for studying how viral infections can cause systemic vasculitis.

Deepening of Immune Pathways

IL-1 Pathway: A large amount of evidence indicates that IL-1β plays a core role in acute-phase inflammation, which directly promotes the clinical application of drugs such as anakinra.

Calcineurin-NFAT Pathway: Excessive activation of this pathway may lead to vascular wall inflammation and damage. Related inhibitors (such as tacrolimus and cyclosporine) have also been successfully applied in refractory cases.

Genetic Research

Genome-Wide Association Studies (GWAS) have identified dozens of gene loci associated with Kawasaki disease susceptibility and the risk of coronary artery lesions, involving multiple aspects such as vascular endothelial function, immune regulation, and inflammatory response (such as ITPKC, CD40, BLK, FcγR, etc.). This explains why the incidence is higher in Asian children (especially those of Japanese and Korean descent).

Progress in Diagnosis

The traditional diagnosis mainly relies on fever for at least 5 days and the presence of 4 out of 5 clinical criteria. The progress mainly lies in the deepened understanding of incomplete Kawasaki disease (Incomplete KD) and atypical Kawasaki disease.

Supplement and Optimization of Diagnostic Criteria

Emphasis on the core role of echocardiography: For suspected incomplete Kawasaki disease, even if the clinical criteria are not met, treatment can be initiated if echocardiography indicates coronary artery abnormalities (such as Z-score ≥ 2.0). This enables more atypical cases to be identified and intervened early.

- **Application of Biomarkers:** In addition to traditional erythrocyte sedimentation rate (ESR) and C-Reactive Protein (CRP), indicators such as N-terminal pro-B-type natriuretic peptide (NT-proBNP) and Hepatocyte Growth Factor (HGF) have been confirmed to be related to disease activity and the risk of coronary artery damage, and their value as auxiliary diagnostic tools is increasingly prominent.
- **New Scoring Systems:** Such as the Kawasaki Disease Japan (KDJ) scoring system, which integrates clinical symptoms and laboratory indicators, aims to improve the diagnostic accuracy of incomplete Kawasaki disease.

Progress in Imaging Techniques

Standardized application of coronary artery Z-score: By correcting for body surface area to assess coronary artery diameter, it is more accurate than the absolute value of the inner diameter and can detect mild dilation earlier and more sensitively. Cardiac Magnetic Resonance (CMR) and CT angiography (CTA): For complex coronary artery lesions, such as giant aneurysms, thrombosis, or stenosis, these techniques can provide more detailed anatomical information and assess myocardial perfusion and fibrosis.

Advances in Treatment

The standard treatment protocol is Intravenous Immunoglobulin (IVIG) combined with high-dose aspirin. The most significant breakthrough in recent years has been in the management of patients who do not respond to IVIG (IVIG-resistant patients).

Consolidation and Optimization of First-line Treatment

Risk prediction of IVIG resistance: Various scoring systems (such as the Kobayashi score and Egami score, which are more commonly used in Japan) have been developed to predict high-risk patients for IVIG resistance before treatment, providing a basis for early intensified treatment. However, it should be noted that the predictive efficacy of these scores is limited in other populations in Europe, America, and Asia.

Major Breakthroughs in Second-line/Salvage Treatment

- Biologics have become the standard second-line treatment [7].
- **Tumor Necrosis Factor-α (TNF-α) Inhibitors:** Infliximab is the most thoroughly studied and widely used biologic. Multiple Randomized Controlled Trials (RCTs) have confirmed that for IVIG-resistant patients, infliximab is superior to a second IVIG infusion in terms of reducing fever, lowering inflammatory markers, and reducing coronary artery abnormalities.
- **IL-1 Receptor Antagonists:** Anakinra has shown great potential. It directly targets the IL-1 inflammasome, one of the core pathways in the pathogenesis of Kawasaki disease. For refractory patients, especially those with giant aneurysms, anakinra has demonstrated significant efficacy and good safety.
- **The Role of Glucocorticoids (GCs) has Changed:** Previously, they were only used in salvage treatment. Now, for high-risk IVIG-resistant patients (identified through scoring systems), the initial treatment with the addition of glucocorticoids (such as methylprednisolone) has been proven to significantly reduce the rate of IVIG resistance and the incidence of coronary artery lesions [8]. The Japanese Circulation Society guidelines have recommended initial combined treatment for high-risk patients.
- **Antiplatelet and Anticoagulant Therapy:** For patients with medium to large coronary artery aneurysms, treatment plans have become more refined. Dual antiplatelet therapy with aspirin and clopidogrel is usually adopted, or anticoagulation with warfarin or low-molecular-weight heparin is added on this basis to prevent myocardial infarction. Data on the use of novel oral anticoagulants (NOACs) such as rivaroxaban in children are also accumulating.

Domestic and International Guidelines for the Diagnosis and Treatment of Kawasaki Disease

Chinese experts have published the Evidence-based Guidelines for the Diagnosis and Treatment of Kawasaki Disease in Children (2023) [9] in the Chinese Journal of Contemporary Pediatrics and three expert consensuses: Expert Consensus on the Use of Intravenous Immunoglobulin in Children with Kawasaki Disease, Expert Consensus on the Use of Aspirin in Children with Kawasaki Disease, and Pediatric Expert Consensus on the Use of Glucocorticoids in the Treatment of Kawasaki Disease. They have also published guidelines for incomplete Kawasaki disease in the British Journal of Pediatrics. Guidelines from various countries classify Kawasaki disease into complete and incomplete types based on clinical symptoms and laboratory tests [9]. The guidelines from Argentina and Italy also include "atypical Kawasaki disease," such as meningitis, epilepsy, acute abdomen, pancreatitis, nephritis, cardiogenic shock, cholestatic jaundice, arthritis, and pneumonia. There are differences in the diagnostic criteria for Kawasaki disease among various guidelines, such as the Japanese guideline no longer emphasizing a fever duration of more than 5 days, and the American guideline has developed a diagnostic flowchart based on expert consensus.

There are also differences in the specific treatment methods for Kawasaki disease among various guidelines, such as the definition and treatment plans for IVIG-resistant Kawasaki disease. The diagnosis of complete Kawasaki disease requires a fever duration of more than 5 days and at least 4 major clinical features, including: (1) Non-exudative conjunctival injection of both eyes; (2) Chapped, red lips and strawberry tongue; (3) Acute non-suppurative cervical lymphadenopathy (usually with a diameter > 1.5 cm); (4) Polymorphic rash, including erythema around the scar; (5) Acute stage of the disease presents with acral erythema and hard edema of the hands and feet, and during the recovery stage, there is membranous desquamation around the nails of the fingers (toes), with or without CAL.

The Japanese guidelines have redefined the fever duration of Kawasaki disease, no longer emphasizing a fever duration of more than 5 days, and have removed the requirement for the specific duration of fever [10]. The American guidelines have developed a diagnostic flowchart based on expert consensus for suspected incomplete Kawasaki disease in children, combining laboratory test results, clinical symptoms, and echocardiography results. The KD guidelines of Spain, Europe, and China have recommended this flowchart.

The Chinese guidelines have optimized the American diagnostic flowchart, emphasizing dynamic observation for 2 days when the C-reactive protein is < 30 mg/L and the erythrocyte sedimentation rate is < 40 mm/h. The Japanese guidelines use similar laboratory and echocardiography results when diagnosing incomplete Kawasaki disease, including gallbladder effusion, elevated brain natriuretic peptide or N-terminal pro-brain natriuretic peptide, but have not formed a diagnostic flowchart.

The definitions of IVIG non-responsive Kawasaki disease in the guidelines of various countries are different. For example, the Chinese guidelines define IVIG non-responsive KD as a body temperature still higher than 38°C 36 hours after the initial treatment of KD; or a recurrence of fever within 2 weeks after medication (mostly occurring within 2 to 7 days), accompanied by at least one major clinical manifestation of KD, and excluding other causes of fever, which is called IVIG non-responsive KD. The American and Spanish KD guidelines define IVIG non-responsive KD as persistent or recurrent fever (> 38°C) 36 hours after the end of IVIG infusion. The Argentine guidelines define IVIG non-responsive KD as persistent or recurrent fever or a decrease in CRP < 50% 36 to 48 hours after the end of IVIG infusion. The Italian and European guidelines define IVIG non-responsive KD as persistent or recurrent fever 48 hours after the end of IVIG infusion [12-14].

The European guidelines recommend the use of the Kobayashi scoring system for the prediction of IVIG non-responsive Kawasaki disease, while the Italian guidelines consider that all scoring systems are not suitable for the white population. The guidelines all recommend an IVIG dose of 2 g/kg, given as a single intravenous infusion. The Italian KD guidelines require IVIG treatment to be given before the 7th day of the disease course. The KD guidelines of other countries/regions all require IVIG treatment to be given before the 10th day of the disease course to reduce inflammation and prevent CAA. In addition, the Argentine KD guidelines suggest using diphenhydramine (1 mg/kg) 1 hour before IVIG infusion. The Chinese and Japanese guidelines recommend completing IVIG treatment within 12 to 24 hours, while the Argentine and American guidelines recommend completing it within 10 to 12 hours. The Italian guidelines suggest that when the heart function is normal, it should be completed within 12 hours, and in the case of heart failure, it can be extended to 16 to 24 hours. The Chinese guidelines describe the IVIG infusion rate in detail, recommending an initial infusion rate of 0.01 mL/(kg·min) [5% IVIG 30 mg/(kg·h)] for 15 to 30 minutes, then increasing to 0.02 mL/(kg·min), and if well tolerated, adjusting to 0.04 mL/(kg·min), and finally adjusting to the maximum rate of 0.08 mL/(kg·min). The Chinese guidelines recommend a medium dose of aspirin in the acute stage, that is, 30 to 50 mg/(kg·d), divided into 2 to 3 oral doses, and changing to 3 to 5 mg/(kg·d) 48 to 72 hours after the fever subsides or 14 days after the onset of the disease. The Argentine guidelines recommend high-dose aspirin during the acute phase, that is, 80-100 mg/(kg·d), and switch to low-dose aspirin 72 hours after defervescence. The American and European guidelines consider that moderate-dose and high-dose aspirin have the same effect. The American KD guidelines recommend switching aspirin to 3-5 mg/(kg·d) 48-72 hours after defervescence or 14 days after onset. The European KD guidelines recommend reducing aspirin to 3-5 mg/(kg·d) 48 hours after defervescence and when inflammation subsides. The Italian, Spanish and Japanese KD guidelines recommend moderate-dose aspirin during the acute phase, that is, 30-50 mg/(kg·d), and switch to low-dose aspirin, that is, 3-5 mg/(kg·d), once a day, for 6-8 weeks. If coronary artery lesions (CAL) occur, oral aspirin should be continued until the coronary arteries return to normal.

For IVIG-resistant KD, the Chinese KD guidelines recommend prednisone 1-2 mg/(kg·d), taken once in the morning, with a total dose < 60 mg/d, or methylprednisolone 1-2 mg/(kg·d), intravenous infusion, 1-2 times a day. After body temperature and CRP return to normal, switch to oral prednisone [1-2 mg/(kg·d), taken once in the morning] and start reducing the dose gradually within 15 days [1-2 mg/(kg·d), 5 days; 0.5-1 mg/(kg·d), 5 days; 0.25-0.5 mg/(kg·d), 5 days]. The Chinese guidelines are the only ones that involve the treatment of glucocorticoids in cases of KD combined with Kawasaki Disease Shock Syndrome (KDSS) or macrophage activation syndrome (MAS). It is recommended to use methylprednisolone 10-30 mg/(kg·d) for KDSS, with a course of 1-3 days, and each intravenous infusion lasts 2-3 hours. It is recommended to use heparin anticoagulation or low-molecular-weight heparin calcium anticoagulation at the same time, and monitor coagulation function, echocardiography and blood pressure. For MAS, it is recommended to use methylprednisolone at a dose of 10-30 mg/(kg·d) for 3 consecutive days, and then switch to oral prednisone [1-2 mg/(kg·d)], and gradually reduce the dose until the condition improves.

The European KD guidelines recommend two regimens. Regimen 1

Intravenous injection of methylprednisolone 0.8 mg/kg daily for 5-7 days or until CRP returns to normal, then switch to oral prednisone 2 mg/(kg·d) and gradually reduce the dose over the next 2-3 weeks. Regimen 2: High-dose methylprednisolone pulse therapy [10-30 mg/(kg·d)] for 3 consecutive days, then switch to oral prednisone [2 mg/(kg·d)] until the 7th day or until CRP returns to normal, and gradually reduce the dose over the next 2-3 weeks.

• **The Italian KD guidelines recommend:** Methylprednisolone 30 mg/kg, intravenous injection, once a day for 3 consecutive days; or prednisone 2 mg/(kg·d), intravenous injection. After body temperature and CRP return to normal, switch to oral prednisone and start reducing the dose gradually within 15 days [2 mg/(kg·d), 5 days; 1 mg/(kg·d), 5 days; 0.5 mg/(kg·d), 5 days].

• **The American KD guidelines recommend:** Methylprednisolone 20-30 mg/(kg·d) for 3 consecutive days, with or without subsequent oral prednisone; or prednisone 2 mg/(kg·d) intravenous injection every 8 hours until defervescence, then switch to oral prednisone until CRP returns to normal, and gradually reduce the dose over the next 2-3 weeks.

• **The Spanish KD guidelines recommend:** methylprednisolone 3 mg/(kg·d) for 3 consecutive days. Then, methylprednisolone or prednisone 2 mg/(kg·d) by intravenous injection or oral administration, with gradual tapering based on the disease course; or methylprednisolone 2 mg/(kg·d) by intravenous injection until the body temperature returns to normal and CRP decreases, followed by gradual tapering based on the disease course.

• **The Argentine KD guidelines recommend:** methylprednisolone at a dose of 30 mg/kg by intravenous injection once daily for 3 consecutive days. The Italian guidelines recommend the web-based Z-score calculator (www.parameterz.com) for convenient use by clinicians. The American guidelines list the main formulas for calculating Z-scores but do not provide the specific website for calculation. The Italian guidelines recommend the web-based Z-score calculator (www.parameterz.com) for convenient use by

clinicians. In the future, it is necessary to strengthen international cooperation in the formulation of guidelines and multi-center clinical research to promote the formation of high-level expert consensus, optimize the global diagnosis and treatment practice of Kawasaki disease, and improve the treatment outcomes and quality of life of patients.

Long-term Management and Follow-up Progress Understanding Kawasaki disease as a lifelong condition, even without acute coronary injury during the acute phase, patients may still face increased cardiovascular risks in adulthood. 1. Risk Stratification Management Patients are categorized into different risk levels (I-V) based on acute-phase coronary status, with corresponding long-term follow-up plans, activity recommendations, and examination frequencies established [15].2. Establishment of Adult Kawasaki Disease Outpatient Services As the first cohort of Kawasaki disease patients enters middle age, multidisciplinary clinics specializing in "adult Kawasaki disease" (integrating cardiology, rheumatology, and pediatrics) have emerged to manage long-term complications such as early-onset atherosclerosis and coronary artery stenosis [16].3. Interventional and Surgical Treatments For patients with severe coronary stenosis, techniques like Percutaneous Coronary Intervention (PCI) and Coronary Artery Bypass Grafting (CABG) have become more advanced. Arterial grafts using vessels like the internal mammary artery demonstrate superior long-term patency rates compared to venous grafts. VI. Summary and Prospects Diagnosis Deepening understanding of incomplete Kawasaki disease through ultrasound and biomarkers (NT-proBNP); promoting Z-score assessment. Treatment Biologics (infliximab, anadecylchelate) have become standard second-line regimens; initial combination with corticosteroids serves as a novel strategy for high-risk patients. Mechanism Genetic susceptibility + infection-triggered hypothesis; clarifying the central role of IL-1 pathway; MIS-C provides new research models. Management Emphasizing lifelong follow-up and risk stratification; adult Kawasaki disease management emerging as a new focus; advancements in interventional and surgical techniques. Future research will focus on: 1) identifying specific etiological and diagnostic biomarkers; 2) developing more accurate individualized initial treatment regimens to minimize drug resistance and coronary artery damage; 3) understanding the mechanisms of long-term sequelae and optimizing adult management strategies.

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