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Review Article

Clinical Advances in Pharmacotherapy for Acute Kawasaki Disease

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Abstract

Kawasaki disease (KD) is an acute, self-limiting vasculitis that predominantly affects children under 5 years old. The precise etiology and pathogenesis of KD remain incompletely understood. This multisystem disorder represents the most common cause of acquired heart disease in children and may lead to coronary artery lesions (CALs), with severe complications including myocardial infarction and sudden cardiac death. Consequently, standardized treatment during the acute phase is of paramount importance to reduce coronary complications. This article focuses on recent advances in pharmacotherapy for acute-phase KD, aiming to inform clinical management strategies.

Keywords: Kawasaki disease, Pharmacotherapy, Clinical Advances, Heart disease, Children, Heart disease, Coronary artery lesions.

Introduction

Since its initial description in 1967, Kawasaki disease (KD) has been studied for over five decades, yet its precise etiology and pathogenesis remain incompletely elucidated. Current evidence suggests that KD arises from complex interactions among genetic, environmental, and immunological factors. The incidence rate of KD in East Asian children is far higher than that in European and American children, and the report also shows with surveillance data indicating a rising trend in China [1]. Untreated acute-phase KD can lead to serious complications, most notably coronary artery abnormalities including coronary artery aneurysms (CAAs), thrombosis, stenosis, and even sudden cardiac death. KD has become the leading cause of acquired heart disease in children across developed countries and regions [2], with approximately 25% of untreated patients developing coronary artery lesions (CALs) [3]. The main goal of acute phase treatment is to alleviate or terminate inflammatory reactions, neutralize antibodies and toxins, and prevent the occurrence and development of CAL. Consequently, acute-phase management is critically important in KD. Multiple international guidelines have been established to standardize diagnosis and treatment., including the Scientific Committee of the Japanese Society of Pediatric Cardiology and Cardiac Surgery (JSCCCS) jointly published the "Medical (Drug) Treatment Guidelines for Acute Kawasaki Disease (Revised 2020 Edition)" in 2021, and China also published the "Evidence based Guidelines for the Diagnosis and Treatment of Kawasaki Disease in Children (2023)" in 2023. These consensus documents aim to: Optimize diagnostic and therapeutic protocols, standardize pharmacotherapy, reduce acute KD complications, decrease hospitalization costs. This article synthesizes contemporary global research to provide a comprehensive review of acute KD management, especially in terms of clinical medication selection, dosing optimization, and medical cost-effectiveness.

Acute Phase Treatment Evaluation of KD

KD is a self-limiting systemic vasculitis predominantly affecting children under 5 years of age. Its exact pathogenesis and

etiology remain elusive, and the absence of specific diagnostic tests necessitates clinical diagnosis based on characteristic features combined with manifestations of multisystem vasculitis, supported by laboratory investigations and echocardiography. Diagnosis mainly relies on clinical features combined with the manifestations of systemic vasculitis and auxiliary examinations such as laboratory and echocardiography for clinical diagnosis [4]. For patients diagnosed with KD, early intervention is imperative to mitigate acute-phase inflammation and prevent coronary artery lesions (CALs). Japanese guidelines [5] recommend that IVIG treatment should be given no later than the 7th day before the onset of extensive arteritis. Even in IVIG-nonresponsive patients and has persistent or recurrent fever, treatment should strive to start on the 9th day of the disease, before coronary artery dilation, to reduce fever and inflammatory markers that cause vasculitis as early as possible, such as C-reactive protein (CRP). Current primary treatments for acute KD includes standard therapy, initial combination therapy, additional therapy, and complementary therapy. High-dose IVIG plus aspirin remains the standard initial regimen. However, approximately 10-20% of patients exhibit IVIG resistance. With the continuous deepening of research, second-line and third line treatment drugs have also achieved good therapeutic effects. So far, drugs used for acute KD treatment include immunoglobulin, steroids, immunosuppressants, biologics, etc. Notably, Kawasaki disease shock syndrome (KDSS) is a critical variant of KD, presents with hypotensive shock, impaired left ventricular systolic function, consumptive coagulopathy, multiorgan dysfunction [5]. Due to its stronger inflammatory response and high proportion of incomplete KD, it is easy to miss diagnosis, resulting in an increased incidence of CAL and requiring intensive treatment. Since the outbreak of COVID-19, a disease similar to Kawasaki disease like children's multiple system inflammatory syndrome (MIS-C) has been more and more reported. MIS-C is a serious high inflammatory reaction state that occurs 2-6 weeks after the infection of COVID-19 in children, mainly manifested as damage to digestive tract, skin mucous membrane and cardiovascular system [6]. With the normalization of the COVID-19, we also need to pay attention to the identification of two diseases in clinical practice to prevent some children with Kawasaki disease from being misdiagnosed as MIS-C. At present, there is still no consensus on the treatment of MIS-C, which mainly includes pathogenic microorganism therapy, supportive therapy, and immune regulation therapy, while IVIG and steroid hormones are still used as first-line treatments.

Acute Phase Medication for KD

Intravenous Immunoglobulin (IVIG)

Since Furusho et al. first reported the use of IVIG for Kawasaki disease (KD) treatment in 1984 [7], IVIG remains the safest and most reliable treatment method for KD. The most dependable anti-inflammatory therapy for acute KD is the early administration of high-dose intravenous immunoglobulin. IVIG therapy is also the most effective method for reducing the risk of coronary artery abnormalities (CAA) development [8]. IVIG is indicated in virtually all patients with typical febrile acute KD meeting diagnostic guidelines who are at risk for CAA complications. Guidelines also recommend initiating high-dose IVIG treatment as soon as possible after KD diagnosis to maximally reduce the risk of CAA occurrence [4]. Historically IVIG dosing regimens included a single-dose protocol (2 g/kg/day) and a divided-dose protocol (200–400 mg/kg/day for 3–5 days). Extensive clinical research has been conducted regarding IVIG dosage and administration methods. Current clinical findings demonstrate that the single-dose regimen significantly reduces CAA incidence, shortens fever duration, and decreases the need for additional treatments [9]. Consequently, high-dose IVIG therapy is now universally recommended for KD patients. Although high medical costs have prevented a consensus on the maximum therapeutic dose for larger and more severely affected children, a single 2 g/kg dose is recommended. Infusion rates vary among different IVIG preparations. In Japan and China, a single dose of IVIG (2 g/kg) is typically administered intravenously over 12–24 hours, while in the US, it is given over 10–12 hours. The recommended initial infusion rate is 0.01 mL/kg/min [equivalent to 30 mg/kg/h for 5% IVIG], maintained for 15–30 minutes. The rate can then be increased to 0.02 mL/k/min. If well tolerated, it may be adjusted to 0.04 mL/kg/min, and finally to a maximum rate of 0.08 mL/kg/min. During IVIG administration, physicians should closely monitor for the development or worsening of heart failure due to rapid volume load and ensure the infusion is not administered too quickly. For patients who are non-responsive to initial IVIG therapy defined as those with persistent or recurrent fever of any degree occurring between 36 hours and 2 weeks after starting initial IVIG treatment early retreatment with IVIG (again at 2 g/kg) is still recommended. Alternatively, infliximab may be combined with this second IVIG dose. Studies have shown that combination therapy with infliximab is more beneficial for IVIG-resistant KD patients [10]. However, as IVIG is a blood product, although complications are infrequent, potential side effects include chills, shock (cyanosis, hypotension), allergic reactions, aseptic meningitis, hemolytic anemia, jaundice, acute renal failure, thrombocytopenia, and pulmonary edema. It is particularly crucial to monitor immediately after starting the intravenous infusion for symptoms such as chills, shivering, coma, restlessness, tremor, cyanosis, hypotension, or shock [11]. To be aware of potential myocardial damage and heart failure during the acute phase, close attention should be paid to the rapid increase in circulating blood volume and changes in vital signs during intravenous infusion [12].

Antiplatelet Agents

Aspirin (ASA)

The combination of IVIG and ASA currently serves as the standard treatment for KD. ASA is a non-selective cyclooxygenase (COX) inhibitor. Its primary mechanism involves the irreversible acetylation of the serine residue at position 529 of COX-1, thereby inactivating COX-1. This inhibits arachidonic acid metabolism, leading to reduced production of its metabolite thromboxane A2 (TXA2), and consequently suppresses platelet aggregation [13]. There is debate regarding the optimal ASA dose during the acute phase of KD, as high-dose ASA exerts non-specific anti-inflammatory effects, while low-dose ASA primarily exhibits antiplatelet activity.

Current Chinese guidelines recommend:

Acute phase: 30–50 mg/(kg·d), divided into 2–3 oral doses.

After fever subsides for 48–72 hours or by day 14 of illness: Reduce to 3–5 mg/(kg·d), administered as a single daily dose (SID).

Duration: Maintain low-dose ASA for 6–8 weeks. Children who develop coronary artery lesions (CAL) require continued ASA until coronary arteries normalize.

Potential complications of ASA include hepatic impairment, shock, allergic reactions, gastrointestinal ulcers, recurrent epistaxis (nosebleeds), and melena (black, tarry stools). If these complications occur, dose reduction or discontinuation of ASA is necessary. ASA can be routinely used in patients presenting with abnormal liver function on admission, **but requires close monitoring** of liver enzymes. If significant liver dysfunction develops during ASA therapy**, dose reduction or discontinuation should be considered. Crucially, KD patients concurrently infected with influenza or varicella (chickenpox) are at risk of developing Reye's syndrome when treated with high-dose ASA. Therefore, IVIG alone is recommended for initial treatment in these cases. Subsequent antiplatelet therapy should utilize dipyridamole or clopidogrel instead of ASA. For children on long-term low-dose ASA if they develop symptoms of influenza or varicella, or have close contact exposure to these infections, it is advisable to discontinue ASA for 2 weeks and substitute with clopidogrel during this period. Children receiving long-term low-dose ASA are advised to receive prophylactic influenza vaccination, and close monitoring for relevant clinical symptoms is essential [14].

Other Antiplatelet Agents

Anti-platelet agents with different mechanisms include clopidogrel and dipyridamole. Clopidogrel, an adenosine diphosphate (ADP) receptor P2Y12 antagonist, is converted to its active metabolite by the cytochrome P450 enzyme system in hepatocytes. The active metabolite irreversibly binds to the platelet surface ADP receptor P2Y12, inhibiting ADP-mediated activation of the glycoprotein IIb/IIIa complex, thereby suppressing platelet activation and aggregation. It also possesses fibrinolytic and thrombolytic effects with minimal adverse reactions [15]. The recommended dosage is 0.2 mg/kg once daily for children under 2 years old and 1 mg/kg once daily for children aged 2 years and above. Adverse effects of clopidogrel may include fatigue, dizziness, gastrointestinal reactions, and bleeding, though hepatic impairment is rare.

Dipyridamole primarily inhibits platelet adhesion and aggregation through multiple mechanisms. However, due to its vasodilatory effect, it may reduce blood flow in distal aneurysms, leading to a steal phenomenon. Thus, it is not recommended for children with severe coronary obstruction or for long-term use. Adverse reactions such as chest pain, angina, and headache may occur. If adverse reactions develop, the dose may be reduced or discontinued as appropriate. The recommended dosage is 3–5 mg/(kg·d), administered orally in three divided doses.

Other Anticoagulant and Thrombolytic Agents

Anticoagulants

Anticoagulants primarily include warfarin and heparin. Warfarin exerts its anticoagulant effect by inhibiting the synthesis of coagulation factors II, VII, IX, and X, thereby preventing thrombus formation in coronary artery aneurysms (CAAs) [16]. The dosage is 0.16 mg/kg/d once daily for children under 12 months of age, and 0.04–0.10 mg/kg/d once daily for children aged 1 to 15 years. According to guidelines [17], patients with coronary artery lesion (CAL) risk classification grade IV or higher require combined therapy with low-dose aspirin and warfarin. The dosage should be adjusted based on PT-INR, with a target range of 1.5–2.5. During the acute phase, warfarin is less effective in controlling inflammatory responses, and time is needed for disease stabilization. Low molecular weight heparin (LMWH) is preferred in the acute phase due to its rapid onset and anti-inflammatory effects. Once the condition stabilizes and coronary aneurysm expansion ceases, LMWH may be switched to oral warfarin. Since warfarin takes 3–7 days to take effect, the two agents should overlap for 3–7 days. The most significant side effect of warfarin is bleeding (e.g., nasal, gingival, intracranial, or intra-abdominal hemorrhage). Warfarin is also considered teratogenic; administration 6–9 weeks before pregnancy may cause skeletal malformations, cartilaginous deformities, and microcephaly [18]. Heparin is indicated for giant CAAs, myocardial infarction, and thrombosis within CAAs. For thrombolysis, heparin is administered as a continuous infusion at 10–20 U/kg/h, with close monitoring of coagulation parameters and bleeding. Physicians should monitor for heparin-induced thrombocytopenia (HIT), bleeding, hepatic dysfunction, alopecia, rash, and diarrhea during use [19]. Generally, anticoagulants are unnecessary for patients without CAAs, but combined aspirin (ASA) and anticoagulant therapy in patients with giant CAAs can prevent long-term cardiac complications.

Direct Oral Anticoagulants (DOACs)

This class of drugs directly inhibits thrombin and factor Xa to exert anticoagulant effects, primarily used for preventing thrombosis in atrial fibrillation and venous thromboembolism [20]. In adults, they are indicated for preventing hemorrhagic stroke and systemic embolism in non-valvular atrial fibrillation, as well as for treating and preventing recurrent deep vein thrombosis and pulmonary embolism. Adult dosages include: dabigatran ester 150 mg twice daily, rivaroxaban 15 mg once daily, apixaban 5 mg twice daily, and edoxaban 60 mg once daily (30 mg for patients weighing <60 kg). Pediatric dosages have not yet been established. In the future, DOACs may serve as alternatives to warfarin and heparin.

Thrombolytic Agents

Myocardial infarction frequently occurs within 2 years after Kawasaki disease (KD) onset, primarily due to acute coronary obstruction caused by intraluminal thrombosis in aneurysms. The Japan Pediatric Society guidelines recommend thrombolytic therapy as more suitable for children due to their smaller body size and lower risk of bleeding complications. Thrombolysis is indicated for acute coronary obstruction in KD and should ideally be initiated within 12 hours of acute myocardial infarction onset; efficacy diminishes significantly beyond this timeframe. The most commonly used thrombolytic agents in pediatrics include:

Tissue plasminogen activator (tPA): 0.5 mg/(kg·h) for 6 hours.

Urokinase: Single bolus of 4,400 U/kg over 10 minutes, or 1,000–4,000 U/kg over 30 minutes (less effective than tPA).

Concomitant aspirin and low-dose heparin (10 U/kg/h) should be administered during thrombolysis. Coagulation parameters and bleeding must be monitored, with fibrinogen maintained >1.0 g/L and platelets >50×10⁹/L. Clinical experience with thrombolytic agents in pediatrics remains limited. Potential complications include intracranial hemorrhage, hemorrhagic infarction, gastrointestinal bleeding, pulmonary hemorrhage, allergic reactions, and shock [21].

Glucocorticoids

The role of glucocorticoids in Kawasaki disease (KD) treatment has evolved significantly in recent years. Initially used cautiously due to concerns about increased coronary aneurysm risk, they are now increasingly recommended in guidelines for refractory KD as part of combination therapy. Monotherapy with glucocorticoids is not advised as first-line treatment for KD.

Glucocorticoids exert potent anti-inflammatory and immunosuppressive effects, rapidly and effectively controlling KD vasculitis and mitigating the risk of coronary artery remodeling [22]. Their mechanism involves binding to cytoplasmic steroid receptors to inhibit gene transcription of inflammatory proteins while promoting transcription of anti-inflammatory proteins. This suppresses the production of inflammatory cytokines (e.g., TNF-α, IL-6, IL-8, G-CSF), chemokines, and cell adhesion molecules, while enhancing anti-inflammatory proteins (e.g., lipocortin), thereby attenuating vasculitis [23].

For IVIG-nonresponsive KD or children with persistent inflammation markers complicated by CAA or peripheral aneurysms, glucocorticoids are recommended as first-line therapy.

Dosage:

Prednisone: 1–2 mg/(kg·d) as a single morning dose (max. 60 mg/d).

Methylprednisolone: 1–2 mg/(kg·d) IV, 1–2 times daily. Transition to oral prednisone (1–2 mg/(kg·d) once stabilized, followed by a 15-day taper.

For IVIG-nonresponsive KD, options include a second IVIG dose or IVIG combined with prednisone/methylprednisolone at the above doses, with close monitoring for adverse effects.

For KD Shock Syndrome (KDSS) or KD with Macrophage Activation Syndrome (MAS): High-dose methylprednisolone pulse therapy is recommended for its potent and rapid immunosuppressive effect on vasculitis [24]. This therapy significantly suppresses cytokine production and modulates inflammatory gene transcription, controlling inflammation and CAA development. It is used either: As initial therapy for predicted IVIG non-responders. As rescue therapy for confirmed IVIG non-responders.

Dosage: 10–30 mg/(kg·d) IV over 2–3 hours for 1–3 days.

Adverse effects: Sinus bradycardia (6–82%), hypertension (10–91%), hyperglycemia (6–55%), and hypotension (6–9%). Prophylactic H_2 blockers or antacids may be considered for gastric protection, though evidence is limited [25].

Important considerations:

Anticoagulation with heparin (10 U/(kg·d) continuous infusion over 24 hours) or LMWH is recommended 2 hours before initiating pulse therapy [4]. Disease activity monitoring is challenging during glucocorticoid therapy, as they mask inflammatory markers (e.g., fever, CRP). Regular blood tests, echocardiography, and coagulation monitoring are essential. Suspected relapse warrants prompt intervention.

Biologic Agents

Infliximab (IFX)

Infliximab, a monoclonal antibody against tumor necrosis factor-alpha (TNF-α), has become a crucial rescue or adjunctive therapy for KD, particularly refractory cases. It inhibits inflammatory pathways and controls vasculitis by specifically blocking TNF-α [26]. Growing evidence confirms the safety and efficacy of IFX in IVIG-nonresponsive KD, with some studies suggesting superior outcomes compared to IVIG combined with glucocorticoids [27]. Optimal timing and indications for use vary regionally. A retrospective Chinese study of 68 children demonstrated favorable efficacy and safety in IVIG/glucocorticoid-nonresponsive KD patients with progressive CAAs [28], though large-scale randomized controlled trials (RCTs) are needed to refine treatment timing.

Dosage: 5 mg/kg as a single 2-hour intravenous infusion.

Adverse effects: Infusion reactions, rash, viral infections, transient hepatomegaly, reactivation of latent tuberculosis or viral hepatitis, exacerbation of heart failure, and infections linked to live attenuated vaccines [29].

Etanercept

Etanercept is a dimeric fusion protein combining the extracellular domain of the human TNF receptor (p75) with the Fc segment of immunoglobulin G (IgG1). It functions as a soluble "decoy receptor," binding TNF-α with high affinity in circulation to prevent its interaction with cell-surface receptors. It features a short half-life and low side-effect profile. Preliminary RCTs suggest etanercept as adjunctive therapy to IVIG may reduce IVIG resistance and mitigate coronary dilation, but optimal dosing and efficacy require further prospective studies. Anti-IL-6 receptor antibody (tocilizumab) and IL-1 antagonist (anakinra) have also been reported in KD treatment but warrant further investigation.

Immunosuppressive Agents

Cyclosporine A (CsA)

CsA is a calcineurin inhibitor that suppresses T-cell activation by binding calcineurin, a key signaling molecule in immune cell activation. This blocks transcription of pro-inflammatory cytokines implicated in KD vasculitis [30], positioning CsA as a potential agent to halt arterial inflammation. The American Heart Association suggests CsA for refractory KD after failure of second IVIG, IFX, or glucocorticoids, but not as routine therapy.

Dosage: Oral CsA 5 mg/(kg·d) divided twice daily before meals for 5 days. Trough plasma concentration (day 3 predose) should be maintained at 60–200 ng/mL, with dose adjustments based on levels.

Monitoring: Watch for hyperkalemia, hypomagnesemia, and hirsutism. No severe KD-specific adverse events reported to date [31].

2.6.2 Methotrexate (MTX)

Low-dose MTX, an antimetabolite used in oncology and rheumatology, shows promise in suppressing vasculitis in IVIG-nonresponsive KD. It rapidly reduces fever, improves symptoms, and normalizes acute-phase inflammatory markers [32].

Dosage: Oral MTX 10 mg/m² weekly (max. 16 mg).

Response: Fever typically resolves within 24 hours; CRP declines significantly within a week.

Adverse effects: Nausea and vomiting are common concerns. Evidence is limited to retrospective studies, with no RCTs conducted.

Protease Inhibitors

Ulinastatin (UTI)

UTI, a human urinary trypsin inhibitor produced by multiple organs (e.g., liver, kidneys, pancreas), reduces vascular endothelial damage by inhibiting proteolytic enzymes and inflammatory cytokines released by neutrophils [33]. It may be used alongside IVIG as initial therapy or as adjunctive treatment for IVIG non-responders.

Dosage: Optimal pediatric dosing is undefined. Studies report 5,000 U/kg/dose IV (half-life ~40 minutes), administered 3–6 times daily (max. 300,000 U/day). According to records, the purpose of the first combination therapy of UTI and IVIG is to reduce IVIG resistance and CAA incidence. When patients with drug allergies or urinary tract infection history, they should use medication with caution [34].

Others

Sivelestat Sodium Hydrate (SSH): A selective neutrophil elastase inhibitor and protease inhibitor [35]. Primarily used for acute lung injury/ARDS in systemic inflammatory response syndrome.

KD Application: Limited reports describe SSH combined with IVIG for initial or rescue therapy in KD. But there are several reports showing continuous intravenous infusion of 0.2mg/kg/h in KD. There is currently no evidence regarding the indications, dosage, and prescription of medication.

Plasma Exchange (PE)

PE reduces the incidence of coronary artery lesions by directly removing inflammatory cytokines from the blood [36]. Primarily used for IVIG-nonresponsive patients, PE is an invasive procedure associated with side effects such as hypotension/shock, bleeding, anemia, hypothermia related to extracorporeal circulation, coagulopathy due to albumin replacement, allergic reactions, and hypocalcemia. This treatment often requires deep sedation and management in an intensive care unit with mechanical ventilation. Regular monitoring of calcium levels and electrolyte adjustment is essential. PE has a long history, dating back to the pre-IVIG era, but it is typically reserved as a last resort for severe cases when other therapies fail, with limited prospective clinical trial data [37].

Anti-Anginal Agents and Coronary Vasodilators

Beta-Blockers

Beta-blockers are first-line anti-anginal agents. Propranolol is the only safe option for children with coronary stenosis accompanied by myocardial ischemia, post-myocardial infarction, heart failure, and arrhythmias (but not angina) [38]. Carvedilol may be used in children but carries a risk of worsening heart failure; treatment should start at low doses and be titrated based on tolerance and therapeutic benefit.

Calcium Channel Blockers

These agents inhibit calcium influx into vascular smooth muscle cells and prevent coronary spasm, making them first-line treatments for angina. Amlodipine is approved for hypertension in children aged ≥6 years, while nifedipine and diltiazem are not approved for pediatric use.

Nitrates

Nitrates increase coronary blood flow via coronary vasodilation and reduced preload, while decreasing left ventricular preload and afterload to alleviate myocardial ischemia. Tolerance develops with prolonged use, so indiscriminate administration should be avoided.

Sublingual nitroglycerin: Adults: 1–2 tablets (0.3–0.6 mg); Children: ½–⅓ tablet (dose adjusted based on body size).

Continuous intravenous infusion: 0.1–20 μg/kg/min.

Conclusion

The primary goal of acute-phase Kawasaki disease (KD) treatment is to reduce the incidence of coronary artery lesions. High-dose intravenous immunoglobulin (IVIG) combined with oral aspirin remains the first-line therapy. However, some patients may require adjunctive agents such as glucocorticoids or infliximab. This review summarizes acute-phase therapeutic options to assist domestic clinicians in managing KD. Nevertheless, certain treatment strategies still lack robust evidence. We anticipate updated guidelines with higher-quality recommendations to advance optimal KD management.

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