Chinese National Consensus Committee of Experts on Kawasaki Disease and Chinese Journal of Contemporary Pediatrics: The expert consensuses on Intravenous Immunoglobulin, aspirin, and Glucocorticoid

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Abstract

Kawasaki disease (KD) is an acute vasculitis with unknown etiology usually occurring in children under 5 years old. It is one of the common acquired heart diseases in children and can cause serious complications such as coronary injury. Although Intravenous immunoglobulin (IVIG) combined with oral aspirin (Asp) is currently recognized as the most effective treatment in KD acute stage and also the first-line treatment to prevent the cardiovascular complications of KD, Glucocorticoid (GC) is mainly used for KD patients with the high risk of Coronary artery aneurysm, no immunoglobulin response and confirmed Coronary artery aneurysm (CAA). There are already consensus guidelines on the diagnosis and treatment of KD at home and abroad, but there are inconsistent opinions in the literature on the mechanism, optimal timing, and dosage of drug treatment for KD. This article will summarize the three consensuses. This review will summarize three consensus items.

Introduction

Kawasaki disease, also known as cutaneous mucosal lymph node syndrome, is a common febrile disorder in children, commonly seen in children under the age of 5. The main pathological feature is systemic vasculitis, and the clinical features include terminal changes in the extremities, bilateral bulbar conjunctival congestion, lip, and oral changes, and non-purulent enlargement of the cervical lymph nodes in addition to fever. KD is mainly complicated by damage to the cardiovascular system, such as coronary artery dilation and thrombosis In addition, KD can also cause multi-system complications such as pulmonary nodules, arthritis, hepatitis, urethritis, and Kawasaki disease shock syndrome (KDSS), etc[1, 2].

The prevalence of KD varies widely among countries, and the prevalence of KD is 10-30 times higher in East Asian countries, including Japan, Korea, and China than in the United States or Europe, and the prevalence is increasing year by year [3]. In 2015, the prevalence of KD among children under 5 years of age was 19.1/100,000 in the United States and 19.6/100,000 in Canada 2014 [4]. The countries of Japan, Korea, and China have the highest KD prevalence rates in the world (>50/100,000 among children under 5 years of age) and are increasing year by year [5-7]. Japan is reported to have the highest KD mortality rate in the world, estimated at approximately 264/100,000 deaths in children under 5 years of age; the recurrence rate of KD is 3.5%, the mortality rate is <0.02%, and 17.0% of children develop resistance to IVIG [7]. In China, the incidence of KD is on the rise, with a prevalence of approximately 7.06-55.1/100,000 children <5 years of age [8, 9], and in Taiwan, the prevalence of KD among children <5 years of age was 82.8/100,000 in 2010 [10], and Hong Kong has the highest prevalence of KD in China (74/100,000 among children <5 years of age) [11].

Epidemiological studies in some regions of China have shown that the incidence of KD combined with coronary artery lesion (CAL) is as high as 15.9% and the incidence of combined CAA is 1.8% [12]. Standardized treatment with IVIG can reduce the risk of CAL occurrence from 15-20% to 3%-5% [13, 14]. Medications are currently the main treatment options for KD and its complications, among which the
preferred treatment option IVIG combined with oral Asp has been widely used, and GC is used as a complementary treatment for IVIG non-response and KD combined with CAA.

Current studies suggest that KD pathogenesis may be involved with pathogenic infections, environmental factors, immune dysregulation, and genetic predisposition, but definitive conclusions are still deficient, making individualized treatment for different etiologies particularly important [15, 16]. Studies on the dosage, duration, and timing of drug treatment for KD have been inconsistently reported in many countries. The Kawasaki Disease Treatment Center in Shaanxi, China, the Shaanxi Clinical Medical Research Center for Pediatric Internal Diseases, the Children's Hospital of Shaanxi Provincial People's Hospital, the Pediatric Capacity Building Committee of the National Society for Research on Maternal and Child Health, and the General Pediatrics (General Practice) Group of the Pediatricians Branch of the Chinese Medical Association, including 100 The Kawasaki disease expert consensus group, including more than 100 scholars. They discussed the mechanism, treatment dose, course, optimal timing, and safety of IVIG, Asp, and GC for KD through several online video conferences, and finally formed three consensuses [17-19], all of which were published in the Chinese Journal of Contemporary Pediatrics. The consensus aims to provide a basis for the standardized clinical management of KD in China, ultimately achieving effective prevention of complications and sequelae in children with Kawasaki disease and reducing the risk of cardiovascular events and death in children with Kawasaki disease [20].

**Methods**

These consensuses are for children under 18 years old with all types of initial and retreatment KD, except those with a history of allergy to IVIG, GC, or Asp, or with drug contraindications [17]. The population of use includes all pediatric rheumatologists and pediatric cardiovascular physicians and all general practitioners. All these consensus items have been registered on the International Practice Guideline Registrable Platform (http://www.guidelines-registry.cn) under the registration numbers IPGRP-2021CN183, IPGRP-2021CN183, and IPGRP-2021CN321, respectively.

English databases for consensus search include UpToDate, BMJ Clinical Evidence, National Guideline Clearinghouse, Joanna Briggs Institute Library, Cochrane Library, and PubMed. Cochrane library PubMed, etc.; Chinese databases include China Biomedical Literature Service, China Knowledge Network, Wanfang database, etc. All literature searches ended on February 28, 2022. Nearly 200 papers were finally included, including 7 guidelines, 9 expert consensus and standards, 2 BMJ Best Practice, 12 UpToDate, 41 Meta-analyses and systematic reviews, 18 randomized controlled trials, and 102 observational studies.

The development of these consensuses is based on the current research progress and relevant research data on the drug treatment of KD in children at home and abroad, as well as with reference to domestic and international guidelines and experience in the diagnosis and treatment of KD, and was developed after many thorough discussions. The consensus follows the following principles:

(1) Participation of professionals from multiple centers, including pediatric specialty physicians, pediatric cardiovascular physicians, and experts in the field of evidence-based medicine.
(2) Using the Grading of Recommendations Assessment, Development and Evaluation of Evidence (GRADE) method, the GRADE manual was used as a guide to determine the level of recommendation for a clinical issue in this consensus based on the credibility level of the literature or information (see Table 1 for the rubric) (see Table 2 for the grading criteria).

1 Chinese expert consensus on IVIG for KD [17]

1.1 Mechanism of IVIG for the treatment of KD

The main objectives of treatment in the acute phase of KD are to control and terminate the inflammatory response, reduce the incidence of coronary artery damage, and prevent coronary thrombosis [23]. IVIG is an immunoglobulin preparation isolated from the blood of healthy people, of which IgG is the most abundant immunoglobulin, accounting for more than 95%. The IgG molecule is hydrolyzed to obtain a crystallizable fragment with an important role (Fragment crystallizable (Fc), IgG Fc can bind to harmful complement components in the body and block their deposition in target tissues, thus avoiding immune damage, while IgG Fc can bind to Fc receptors and regulate immune function by activating intrinsic immunity [24, 25]. Although the therapeutic regimen of IVIG applied to Kawasaki disease has been gradually refined and matured, its specific mechanism has not been elucidated in detail, and it is currently believed that IVIG treatment of Kawasaki disease may be through the following pathways:

(1) modulates macrophage activity by inhibiting autoantibodies that bind to Fc receptors; inhibits endothelial cell activation, adhesion molecule expression, and secretion of soluble mediators; neutralizes antibodies to cytokines, chemokines, and activated complement proteins that activate inhibitory Fc receptors on macrophages [26]; and blocks the transport of adhesion molecules critical for inflammatory cells to vascular endothelial cells; produces anti-liposomes to reduce inflammation and attenuate endothelial cell injury [26].

(2) Immunoglobulins stimulate an adaptive immune response that can bind to bacteria or viruses and their toxins, and interact with unique type determinant clusters on pathogenic autoantibodies (and autoantibody-producing B cells), allowing direct neutralization of pathogens and thus their clearance; IVIG may also affect the number and function of regulatory T cells that help control inflammation [27].

(3) IVIG can also bind to the Fc receptor, but FcRN is not directly involved in the regulation of immune cell activation, ut acts as a protective receptor by preventing the catabolism of immunoglobulins.

(4) Human immunoglobulins have regulatory effects on lymphocytes, monocytes, and macrophages. Multiple classes of antibodies in human immunoglobulins can provide passive immunity to the organism in the short term, and all have an enhancing effect on the immune status of the organism. Analysis of serum cytokine levels in children with Kawasaki disease treated with IG revealed that the levels of gamma interferons (interferons-γ, INF-γ) and L-10 decreased rapidly, and in contrast, IVIG treatment enhanced the expression of the Treg transcription factor FoxP3. in IVIG, IgG monomers accounted for more than 95%, with the remainder being dimeric or multimeric IgG. clinically Often large doses of IVIG are more effective
in treatment, suggesting a better anti-inflammatory effect of IgG dimers or multimers. The specific mechanism is unclear, and it is speculated that the IgG dimer structure may enhance the binding ability of Fc to Fc receptors, thus effectively inhibiting the activation of intrinsic immune cells and reducing autoimmune damage [28].

Table 1 Recommended intensity grading [21] [1]

<table>
<thead>
<tr>
<th>Grade</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strongly recommended 1</td>
<td>Effective measures that are clinically accepted and supported by curative cases</td>
</tr>
<tr>
<td></td>
<td>Treatment with conflicting effectiveness and usefulness</td>
</tr>
<tr>
<td>Weak recommendation 2</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 [22] [2]

<table>
<thead>
<tr>
<th>Rank</th>
<th>Explanation</th>
<th>Examples*</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Further research is very unlikely to change our confidence in the estimate of effect</td>
<td>Randomized trials without serious limitations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Well-performed observational studies with very large effects (or other qualifying factors)</td>
</tr>
<tr>
<td>Moderate</td>
<td>Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate</td>
<td>Randomized trials with serious limitations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Well-performed observational studies yielding large effects</td>
</tr>
<tr>
<td>Low</td>
<td>Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate</td>
<td>Randomized trials with very serious limitations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Observational studies without special strengths or important limitations</td>
</tr>
<tr>
<td>Very low</td>
<td>Any estimate of effect is very uncertain</td>
<td>Randomized trials with very serious limitations and inconsistent results</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Observational studies with serious limitations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unsystematic clinical observations (e.g. case series or case reports)</td>
</tr>
<tr>
<td>Items</td>
<td>Recommendations</td>
<td>Recommendation strength and evidence level</td>
</tr>
<tr>
<td>-----------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Timing of IVIG</td>
<td>The best time is 5-10 d after the onset of the disease, and the best within 7 d</td>
<td>1A</td>
</tr>
<tr>
<td>IVIG application</td>
<td>The use within 5 d after onset may lead to an increased incidence of IVIG resistance (1B); in severe cases, such as combined hypertension, shock, hemodynamically unstable myocarditis, paralytic intestinal obstruction, etc. should still be applied promptly (1A)</td>
<td>1B;1A</td>
</tr>
<tr>
<td></td>
<td>Children with an onset of more than 10 d, excluding other causes of persistent fever with elevated ESR or CRP, or elevated inflammatory markers combined with CAL, still need to be treated with sub-IVIG</td>
<td></td>
</tr>
<tr>
<td>IVIG application</td>
<td>A single dose of IVIG (2g/kg) is usually administered intravenously by drip over 12-24 hours. The recommended initial infusion rate is 0.01mL/(kg.min) [5% IVIG 30mg/(kg.h)] for 15-30min, then increase the dose to 0.02mL/(kg.min), if well tolerated, adjust to 0.04mL/(kg.min), and finally adjust to the maximum rate of 0.08mL/(kg.min)</td>
<td>1B</td>
</tr>
<tr>
<td>IVIG protocol</td>
<td>Complete Kawasaki disease, incomplete Kawasaki disease, recurrent Kawasaki disease: IVIG dose is 2g/kg, single intravenous infusion in 12–24h, with oral aspirin</td>
<td>1A</td>
</tr>
<tr>
<td></td>
<td>Non-responsive Kawasaki disease (IVIG-resistant Kawasaki disease): early reapplication of IVIG at a dose of 2g/kg, single intravenous infusion over 12 to 24h is recommended. For those who still have a fever, glucocorticoids can be used in combination with IVIG</td>
<td>1B</td>
</tr>
<tr>
<td>IVIG Application</td>
<td>Infants and children with fluid restriction need to avoid low concentration preparations</td>
<td>1A</td>
</tr>
<tr>
<td>Safety</td>
<td>Infants and children with cardiovascular disease should be careful to avoid IVIG with high sodium content</td>
<td>1B</td>
</tr>
<tr>
<td></td>
<td>Preparations using maltose or glucose as stabilizers are not recommended for use in patients with diabetes and risk of renal injury</td>
<td>1B</td>
</tr>
<tr>
<td></td>
<td>Amino acid-containing preparations need to be used with caution in patients with specific genetic metabolic abnormalities</td>
<td>1B</td>
</tr>
<tr>
<td>IVIG adverse reaction</td>
<td>Headache is a common adverse reaction, usually occurring during or 2-3d after infusion, and mild cases can be treated with NSAIDs for pain relief</td>
<td>1A</td>
</tr>
<tr>
<td></td>
<td>Transient asymptomatic neutropenia after IVIG treatment usually occurs 2-4 d after infusion and recovers within 2 weeks, generally, no treatment is needed, but some scholars believe</td>
<td>2B</td>
</tr>
</tbody>
</table>
that it can be prevented by glucocorticoids

1gG subclass deficiency and high 1gM syndrome are not contraindications to IVIG. For patients who have had severe allergic reactions, anti-IgA antibodies can be detected, and if the anti-IgA antibody titer is high (>1/1000), 1gG replacement therapy should be applied with caution.

Renal impairment is firstly manifested by elevated blood urea nitrogen or creatinine, followed by oliguria and renal failure, which peaks 5-7 d after high-dose infusion. In patients with existing renal impairment, IVIG should be infused slowly, and hydrated appropriately, and IVIG products containing sucrose should be avoided.

The estimated incidence of thrombotic events ranges from 1% to 16.9%, with risk factors including first high-dose IVIG, previous/current thrombosis, previous atherosclerotic disease, hyperviscosity syndrome, hereditary hypercoagulability, rapid infusion rate, pre-hydration, a rate less than 50 mg/(kg. h), hypotonic IVIG products (3% to 6%) and prophylactic use of aspirin or Low-molecular-weight heparin and other measures to reduce the incidence of thrombosis in high-risk patients, and patients with thrombotic complications need to receive antithrombotic therapy.

1.2. Summary of expert consensus recommendations for the use of IVIG in Kawasaki disease [17] all recommendationals are summarised in table 3

3 Chinese expert consensus on GC for the treatment of KD [15]

3.1 Mechanism of action of GC for the treatment of KD

Vascular endothelial injury is a key link in the pathogenesis of KD. Neutrophils, CD8+ T lymphocytes, and mononuclear macrophages accumulate in the coronary artery mesothelium during the acute phase of KD, causing vascular endothelial injury is a key link in the pathogenesis of KD. Disruption of the vascular barrier releases cytokines and adhesion molecules that diffuse into the vessel wall, leading to vessel wall edema, elastic fiber fracture, and destruction of the elastic layer, causing vascular remodeling leading to
coronary artery dilation or CAA. GC can reduce the transcription of inflammatory mediators and decrease the level of fever and inflammation in KD patients, thus reducing the incidence of coronary artery damage and future cardiovascular sequelae [37, 38].

3.2 Indications for KD treatment

Indications for GC application for KD include (1) IVIG unresponsive KD remedial therapy; (2) children with combined CAA or peripheral hemangioma with persistently elevated inflammatory markers; (3) KDSS; (4) KD combined with macrophage activation syndrome (MAS); (5) children at high risk of IVIG unresponsiveness, including children with an age of onset less than 0.5 years, high levels of inflammatory markers, and a Kobayashi warning score greater than or equal to 5 (Table), or children with high-risk KD as judged by the IVIG high-risk warning score at each hospital [39, 40].

Table 4 Kobayashi score of high-risk Kawasaki disease [41]

<table>
<thead>
<tr>
<th>indicator</th>
<th>critical value</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum sodium levels</td>
<td>≤133 mmol/L</td>
<td>2</td>
</tr>
<tr>
<td>Aspartate transaminase</td>
<td>≥100 IU/L</td>
<td>2</td>
</tr>
<tr>
<td>Start time of treatment</td>
<td>Day 4 or earlier</td>
<td>2</td>
</tr>
<tr>
<td>Percentage of neutrophils</td>
<td>≥80%</td>
<td>2</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>≥100 mg/L</td>
<td>1</td>
</tr>
<tr>
<td>blood platelet count</td>
<td>≤300×10⁹/L</td>
<td>1</td>
</tr>
<tr>
<td>age</td>
<td>≤12</td>
<td>1</td>
</tr>
</tbody>
</table>

3.3 Types and methods of adaptation of GC application in KD

The type of GC treatment for KD patients is methylprednisolone intravenous shock followed by oral prednisone sequential therapy [38].

4 Dose and course of GC applied to KD

4.1 First-line treatment for children with combined CAA or peripheral hemangioma with Kobayashi warning score of IVIG non-responsive KD or persistently elevated inflammatory index

Recommendation: prednisone [1 to 2 mg/(kg.d)], morning dose, total dose <60 mg/d or methylprednisolone [1 to 2 mg/(kg.d)], intravenous drip, 1 to 2 times daily, with dose reduction starting after temperature and CRP normalization and tapering off over 15 d [1 to 2 mg/(kg.d)], 5 d; 0.5 to 1 mg/(kg.d), 5 d. 0.25 to 0.5 mg/(kg.d), 5d] [42-46]. (1A)

4.2 Second-line treatment of IVIG non-responsive KD

Optional 2nd dose infusion of IVIG combined with prednisone (methylprednisolone) (1A)
**Recommendation:** prednisone [1-2 mg/(kg.d)], morning dose, total dose <60 mg/d or methylprednisolone [1-2 mg/(kg.d)], intravenous drip, 1-2 times daily, start to reduce the dose after the body temperature and CRP are normalized, and gradually stop within 15 d [1-2 mg/(kg.d)], 5 d; 0.5 -1 mg/(kg.d), 5 d. 0.25 to 0.5 mg/(kg.d), 5d] [42-46]. (1A)

4.3 First-line treatment of KDSS

**Recommendation:** methylprednisolone 10-30 mg/(kg.d) for 1 to 3 d with 2 to 3 h of each intravenous infusion. Heparin anticoagulation [10 U/(kg.d) of heparin concurrently 2 h before the start of methylprednisolone] for 24 h is recommended, or low-molecular heparin anticoagulation with coagulation, echocardiography and blood pressure monitoring [47-50]. (2A)

4.4 First-line treatment of KD combined with MAS

**Recommendation:** methylprednisolone 10-30 mg/(kg.d) for 3 d, with each IV infusion for 2-3 h. Sequential prednisone orally [1-2 mg/(kg.d)] until complete control and remission of MAS with gradual dose reduction and discontinuation [51-53]. (2A)

4.5 GC is not recommended as a conventional first-line treatment for KD

Methylprednisolone or prednisone is not recommended as routine first-line therapy for KD (1A)

GC alone is unsafe and contraindicated as a first-line treatment for KD, as studies have shown that GC alone used as an initial treatment for KD can significantly increase coronary artery damage [37, 54].

5 Prevention of adverse reactions

During treatment with GC in children with KD, special attention should be paid to the prevention of Cushing's syndrome, infection, thrombosis, osteoporosis, aseptic necrosis of the femoral head, diabetes mellitus, hypertension, hormonal glaucoma, cataract, bradycardia, secondary adrenocortical insufficiency and growth retardation. For the prevention and treatment of osteoporosis, it is recommended to supplement vitamin D 600-800 U/d and calcium 1000-1200 mg/d during the application of GC. Various infections, such as tuberculosis, fungus, and chickenpox, should be fully excluded before high-dose methylprednisolone shock therapy, and blood pressure and blood glucose should be closely observed and tested to detect any of the above complications in time and deal with them actively. While applying CC, strive to minimize the adverse effects to improve the prognosis of children with KD.

6 Precautions

(1) Contraindicated: hypersensitivity to GC drugs, epilepsy, fractures, uncontrolled infections (e.g. chickenpox, fungal infections), active tuberculosis, etc.

(2) Caution: Cushing's syndrome, myasthenia gravis, hypertension, diabetes mellitus, intestinal disease or chronic malnutrition, infectious diseases, etc. must be combined with effective antibiotics.
(3) Other precautions: Prevent cross-allergy, those who are allergic to one GC drug may also be allergic to other GCs. (2) When using GC, adopt a low sodium, high potassium, high protein diet, supplement calcium and vitamin D, and add drugs to prevent peptic ulcer and bleeding and other adverse reactions. If there is infection, antibiotics should be applied at the same time to prevent the spread and aggravation of infection. The interaction between GC and other drugs should be noted, for example, excessive potassium loss can be caused when GC is combined with potassium-removing diuretics (e.g., thiazide or tab diuretics), and the incidence of gastrointestinal bleeding and ulcers increases when GC is combined with NSAIDs [38, 42, 55-57].

Conclusion

After more than thirty years of clinical validation, referring to half a century of domestic and international research results on KD, and combining the treatment experience of hundreds of pediatric KD clinicians and experts in China, three experts consensus standardized the usage of IVIG, Asp, and GC in pediatric KD pharmacotherapy, which has important clinical significance in effectively reducing the incidence of cardiovascular complications of KD and preventing cardiovascular sequelae caused by KD. Limitations of the consensus include the inclusion of relatively few high-quality randomized controlled studies, a small number of references, references to more foreign literature, and insufficient consideration of racial differences. Since the pathogenesis of KD is not fully understood, the protocols for drug treatment of KD are constantly being updated and researched. the consensus on drug treatment of KD will be constantly updated according to the latest research results at home and abroad, etc., and the doses and courses of treatment for other complications during various drug treatments, such as myocarditis, acute inflammatory response syndrome, macrophage activation syndrome and other diseases, will be supplemented and improved.

Declarations

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Author contribution
Ren Shuying is responsible for writing the manuscript, and Deng Fangming, Du Zhongdong, Yang Xiaodong, Xie Lijian, Wang Hong, and Jiao Fuyong are responsible for revision and verification.

**Statement of Conflict of Interest**

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**References**


42. [Consensus on the application of glucocorticoid from relative experts in pediatric rheumatoid diseases(part 1)]. J. Zhonghua Er Ke Za Zhi. 56(3), 166–173 (2018).https://doi.org/10.3760/cma.j.issn.0578-1310.2018.03.003


