Current recommendations for the pharmacologic therapy in Kawasaki syndrome and management of its cardiovascular complications

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Abstract. – Kawasaki syndrome is a potentially life-threatening disease of early childhood that untreated holds a risk of severe coronary involvement. Its diagnosis is made via a list of clinical signs because etiology and pathophysiology are still unknown and no specific laboratory tool is available. Appropriate therapy with intravenous immunoglobulins and aspirin reduces the incidence of coronary abnormalities to less than 5%. Immunoglobulins have been shown to be highly effective in reducing disease symptoms or their severity and chiefly in reducing the rate of coronary artery aneurysm development. Aspirin is firstly used in high dose for its anti-inflammatory properties and then in low dose for its anti-thrombotic effects. Timely diagnosis and precociously administered treatment are two crucial points in the definition of prognosis for Kawasaki syndrome. In this review heart complications are discussed and therapeutic options stratified according to both severity of coronary involvement and grading of cardiovascular risk.

Key Words: Kawasaki syndrome, Cardiovascular complications.

Introduction

Kawasaki syndrome (KS) or muco-cutaneous-lymph node syndrome is an acute systemic vasculitis of unknown etiology that involves the walls of medium- and small-sized muscular arteries throughout the body in the pediatric age, which was firstly described by Tomisaku Kawasaki in 1967. At that time, he reported 50 children from 1961-1967 who presented with a distinctive clinical illness characterized by fever and skin rash, which was then thought to be a benign childhood disease: several years later, fatalities occurred in Japan among children with KS younger than 2 years when they had apparently recovered. Post-mortem examinations revealed complete thrombotic occlusion of coronary artery aneurysms with myocardial infarction as the immediate cause of death. This syndrome has now surpassed rheumatic fever as the leading cause of acquired heart disease in the developed countries among children younger than 5 years¹. Although its etiology is largely unknown, epidemiological findings suggest that genetic factors play a role in the pathogenesis of KS: although KS has been reported all over the world, it is overexpressed among Asian populations, especially in children of Japanese ancestry. KS results 10 times more prevalent in Japan, if compared with other nations, especially for infants with less than 2 years. The proportions of KS Japanese patients with cardiac sequels (such as dilation or stenosis of coronary arteries, myocardial infarction and valvular lesions) 1 month or more after onset were analyzed using nationwide survey protocols: the prevalence of heart abnormalities was particularly high in males, infants younger than 1 year and children older than 5 years of age². In the natural history of the disease three phases occur: we can distinguish an acute phase (in the first 2 weeks of illness), a subacute phase (including the 3rd and 4th week of illness) and a phase of convalescence (lasting from the 5th to the 8th week since the onset). The original guidelines for the diagnosis of KS were created by a committee that was appointed by the Japanese Ministry of Health in 1970. In the acute phase KS usually starts with more than 5 days of high fever followed by at least 4 of 5 main clinical features: non-exudative conjunctival injection, polymorphous skin rash, reddening/fissuring of lips and oral mucosa, abnormalities in-
volving extremities of limbs and perineum and cervical lymphadenitis (Table I). In the absence of specific diagnostic tests, pathognomonic features or evidence-based diagnostic algorithms, KS diagnosis remains basically clinical\(^3\). Laboratory findings are frequently helpful in confirming the correct diagnostic suggestion: inflammatory markers as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum amyloid-A (SAA) are markedly elevated; neutrophil leukocytosis (with toxic granulations and left shift), mild-to-moderate normochromic anemia (with haemoglobin levels < 2 SD for age), hypoalbuminemia (< 3.5 g/dl), hyponatremia (< 135 mEq/L), elevated serum transaminases and sterile pyuria are typical of KS. In the subacute phase the vast majority of patients displays skin desquamation starting in the subungual regions of the fingers and spreading to palms and soles in combination with the increase of platelet count, sometimes exceeding 1.000.000/mm\(^3\). In some patients arthralgias or arthritides can appear in the subacute phase. Incomplete and atypical forms of KS (with other vasculitic features as abdominal pain, pneumonia, seizures, meningitis, urethritis, hepatitis and gallbladder distention, parotitis, uveitis, etc.) are more common in young infants with less than 1 year of age\(^4\). Characteristics suggesting disease other than KS include exudative conjunctivitis, exudative pharyngitis, bullous, vesicular or exfoliating rash and generalized adenopathy. There is a great number of pathologic conditions mimicking KS which require to be considered attentively in the differential diagnosis as staphylococcal scalded skin syndrome, toxic shock syndrome, Stevens-Johnson syndrome, scarlet fever, measles, Epstein-Barr virus infection, Cytomegalovirus infection, tick-borne diseases, juvenile rheumatoid arthritis, reaction to drugs and mercury hypersensitivity (acrodynia).

**Therapeutical Approach in Kawasaki Syndrome**

A combination of a single dose of intravenous immunoglobulins (2 grams/kg of body weight infused over a period of 10-12 hours) and aspirin at high doses (30 to 100 mg/kg/day in four divided doses) are recommended when KS diagnosis is made during the first 10 days of illness. KS therapy is schematized in the Table II. Treatment with intravenous immunoglobulins is directed at reducing the inflammation in the vessel walls involved by the disease, mostly in the coronary artery walls, and at preventing coronary artery thrombosis. High-dose aspirin is administered to reduce fever and KS inflammatory signs. The efficacy of intravenous immunoglobulins is dose-dependent: a randomized-controlled trial has demonstrated that a single infusion of 2 g/kg infused in a time of 10 hours has a higher efficacy than a 4-day-infusion of 400 mg/kg/day\(^5\). There is no evidence that immunoglobulin treatment on day 4 of fever or earlier has greater efficacy in preventing cardiac complications than treatment on days 5 to 9. The mechanism of action of intravenous immunoglobulins is unknown, though it might include neutralization of hypothetic infectious agents, inhibition of endothelial cell functions, non-specific anti-inflammatory effects by the down-regulation of proinflammatory cytokines as tumour necrosis factor-\(\alpha\) (TNF-\(\alpha\)) and interferon-gamma, blockage of Fc-receptors on macrophages, suppression of T and B cells and blockage of complement cascade. Aspirin inhibits prostaglandin synthesis and has been the first drug used in children with KS. High doses are used only during the acute inflammatory phase and vary across countries: 30-50

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**Table I.** Criteria for the diagnosis of Kawasaki syndrome.

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<thead>
<tr>
<th>Fever persisting at least for 5 days (or more) plus at least 4 of the following 5 clinical main signs:</th>
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<tbody>
<tr>
<td>Bilateral bulbar conjunctival injection without exudate</td>
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<tr>
<td>Polymorphous skin rash</td>
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<tr>
<td>Changes in lips (reddened, dry or cracked) and oral cavity (strawberry tongue, diffuse oral and pharyngeal hyperemia)</td>
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<tr>
<td>Changes in the extremities and in the perineum (erythema of palms or soles, inducative edema of hands or feet, desquamation of perineal skin)</td>
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<tr>
<td>Acute cervical lymph node enlargement (with a diameter superior than 15 mm)</td>
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**Table II.** Standard treatment for Kawasaki syndrome.

| Intravenous immunoglobulins: | 2 g/kg of body weight (infused over a period of 10-12 hours) |
| Aspirin: | 30-100 mg/kg orally, daily divided into 4 doses, until the normalization of inflammatory parameters |
| Subsequent antiplatelet treatment with aspirin: | 3-5 mg/kg orally, once daily for 6-8 weeks (starting in the subacute phase of the disease) or continued indefinitely if coronary abnormalities are observed |
mg/kg/day in the United Kingdom and 80-100 mg/kg/day in Japan and in the United States. Low-dose aspirin in the subacute phase inhibits platelet aggregation and is aimed at the reduction of the thrombotic risk which is higher in patients showing coronary artery dilations. However, the occurrence of coronary abnormalities is not influenced by the association intravenous immunoglobulins-aspirin, if compared with intravenous immunoglobulins alone. It is not known the correct timing of high-dose aspirin administration and some physicians use low-dose aspirin even during the acute phase of illness: there are no clinical trials to confirm this therapeutic strategy or the effectiveness of the association of high-dose aspirin with intravenous immunoglobulins. Aspirin dose can be reduced to the single daily dose of 3-5 mg/kg after having obtained the complete normalization of the inflammatory markers, specifically CRP. This antiaggregating dosage is continued for 6 to 8 weeks after the onset of illness, but it should be continued indefinitely over time in those children who have developed coronary abnormalities. Coronary thrombosis can be prevented using other antiplatelet agents, depending on the severity of coronary involvement, though no perspective data exist to guide clinicians in choosing the optimal therapy and recommendations are based on the empirical stratification of the cardiovascular risk, published by a committee of the American Heart Association (Table III).

**Prognosis in Kawasaki Syndrome**

Prognosis in KS strictly depends on the cardiac involvement and is of lifetime significance: coronary artery aneurysms develop in 20-40% of untreated children and may lead to rupture in adulthood, ischemic heart disease and myocardial infarction. Due to the fact that KS is a generalized systemic vasculitis involving blood vessels throughout the body, aneurysms might be demonstrated in other extra-parenchymal muscular arteries such as the celiac, mesenteric, femoral, renal, axillary and brachial arteries, with the exception of central nervous system arteries. The major sequels of KS are related to the cardiovascular district which might be interested in all its structures: pericardium, myocardium, endocardium and above all coronary arteries. Myocardial disease during the acute phase is commonly reported: inflammation has been documented in 50-70% of autoptic descriptions. Its clinical findings are tachycardia, gallop rhythm and congestive heart failure in cases of disturbed ventricular function. The electrocardiogram may show arrhythmias, prolongation of PR, decreased QRS voltage and T-wave flattening. Echocardiography is useful in detecting left ventricular dilation or reduced systolic function. In the acute phase the severity of myocardial involvement is unrelated to the development of coronary artery abnormalities during sub-acute or chronic phases. Myocardial mechanics improves rapidly after pharmacological therapy. Intravenous immunoglobulins combined with aspirin have given substantial results in the prevention of coronary artery dilatation and the reduction of severity of coronary aneurysms. Perspective controlled clinical trials have showed that the infusion of intravenous immunoglobulins during the first week to 10 days of illness reduces the incidence of coronary aneurism from 23 to 9% after the first month and up to 4% after two months. A host of retrospective observations has proved the low incidence of coronary abnormalities when KS is promptly diagnosed with therapy instituted within the first 10 days of illness. Immunoglobulins should be also administered to children presenting after the 10th day of illness without other explanation or significant elevation of ESR, CRP and SAA. Treatment with intravenous immunoglobulins should not be started in children in whom KS diagnosis was missed earlier or if it occurred retrospectively without evidence of persisting laboratory signs of inflammation.

**Table III.** Anti-thrombotic treatment related to the severity of coronary artery involvement in patients with Kawasaki syndrome.

<table>
<thead>
<tr>
<th>Mild coronary involvement</th>
<th>Low-dose aspirin</th>
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<tr>
<td>Mild-to-moderate coronary involvement</td>
<td>Combination of aspirin with dipyridamole</td>
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<tr>
<td>Coronary aneurysm in rapid expansion</td>
<td>Combination of heparin with aspirin</td>
</tr>
<tr>
<td>Giant aneurysm</td>
<td>Combination of aspirin with warfarin</td>
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Management of Unresponding and Recurrent Kawasaki Syndrome

Clinical efficacy of intravenous immunoglobulins is proved by the deverfescence within 12-24 hours. Approximately 10% of patients with KS fail to respond after the first infusion of immunoglobulins with an increasing risk of developing coronary artery abnormalities: this has been observed mostly in infants with incomplete or atypical forms of KS. In the refractory cases of KS there are no documented treatment guidelines. Most experts in the field of KS recommend re-treatment with intravenous immunoglobulins (at the same dosage of 2 g/kg of body weight) which can be repeated for a total of three infusions. Corticosteroids have also been used to treat patients who have failed to respond to the standard therapy: studies of steroids as initial treatment for KS or as treatment of patients with persistent or recrudescent fever despite treatment with intravenous immunoglobulins have shown that they reduce fever, although their effects on coronary artery abnormalities are still uncertain. The most commonly used steroid regime is intravenous pulse methylprednisolone (30 mg/kg of body weight administered once daily in a time of 2-3 hours for 1 to 3 days). The use of biological agents directed against proinflammatory cytokines as TNF-α has recently been suggested by the American Heart Association: infliximab, the chimeric monoclonal antibody IgG1, comprising 75% human and 25% murine sequences, acts by blocking the molecular system that drives the immune response through TNF-α and has been approved for the treatment of moderate-to-severe Crohn’s disease refractory to conventional therapy. Infliximab, at a dose of 5 mg/kg, can reverse the clinical signs of KS unresponsive to intravenous immunoglobulins and methylprednisolone, although its effectiveness in reducing the prevalence of coronary artery aneurysms is still unproven. Further studies seem to be necessary with a major number of cases treated to confirm infliximab efficacy and safety. Because controlled data are lacking, other treatments including plasmapheresis or cytotoxic agents such as cyclosporine or cyclophosphamide for patients with refractory KS remain of doubtful usefulness. The recurrence rate of KS is low: 1-3% in the Japanese and 1% in the Caucasian population. Clinical criteria for diagnosing recurrent KS are the same as in the classic form and it is of outstanding priority to not underestimate this possibility, due to the increased risk of coronary artery involvement than in the primary disease. The recurrence of skin peeling in patients who have previously suffered from KS appears relatively common in the case of other viral feverish diseases: thus the only presence of skin peeling is not a diagnostic feature to confirm the recurrence of KS. After using intravenous immunoglobulins, the administration of live viral vaccines (such as the ones for measles and chickenpox) should be deferred of about 11 months, though there are differences between Japan and United States suggestions related to the interval before vaccination. In patients who need long-term therapy with aspirin the annual vaccination against influenza virus is recommended to reduce the risk of Reye syndrome.

Heart Complications in Kawasaki Syndrome

Coronary artery aneurysms are the major risk associated with KS and echocardiographic examination, focused on the coronary arteries, including quantitative assessment of the internal vessel diameters, remains a critical part of the diagnostic course of all patients with a suspected KS. Coronary artery abnormalities might develop in 20-40% of untreated patients or in patients treated with only aspirin, with differences depending on the ultrasound assessment of coronary involvement. When a coronary artery is dilated without a segmental aneurysm and the internal diameter of this segment measures 1.5 times than an adjacent segment it is defined as ectasia. The Japanese Ministry of Health criteria classify coronary arteries as “abnormal” if the internal lumen diameter is greater than 3 mm in children with less than 5 years or greater than 4 mm in children aged more than 5 years. Care must be taken in making the diagnosis of ectatic coronary arteries because of normal variability in coronary artery distribution and dominance. Aneurysms are classified as saccular if axial and lateral diameters are nearly equal or as fusiform if symmetric dilation with gradual proximal and distal tapering are seen. In the last American Heart Association statement coronary aneurysms were classified as “small” (when the internal lumen diameter is inferior than 5 mm), “medium” (when the internal diameter is 5 to 8 mm) or “giant” (when the internal diameter is superior than 8 mm).
diagnostic evaluation of patients with suspected KS should be focused on visualizing the left main coronary artery, the right coronary artery and the left circumflex coronary artery. This study should include the quantitative assessment of their internal diameters, should be aimed at diagnosing the presence of ectasia, the number and the location of eventual aneurysms and the finding of intraluminal thrombi. In patients correctly treated with intravenous immunoglobulins the incidence of coronary abnormalities is inferior than 5%. Ten years ago de Zorzi et al. showed the importance of coronary vessel measurements adjusted for body surface to avoid underestimating the true prevalence of coronary involvement in KS in comparison with normal children: in particular, a z score 2.5 (i.e. a coronary dimension that is 2.5 SDs above the mean for body surface area) in proximal right coronary artery or left anterior descending coronary artery would be expected to occur in 0.6% of the population without KS. Frequent sites of coronary aneurysms are the proximal left anterior descending coronary artery, the proximal right coronary artery and the left main coronary artery. Cardiac ultrasound studies need to be performed serially at the time of the diagnosis, at 2 weeks and at 6 to 8 weeks after the onset of KS and should be supervised by an experienced pediatric echocardiographer. The indication of stricter echocardiographic evaluations should be given by the pediatric cardiologist. Because detailed echocardiographic imaging is compromised if children are overweight, other non-invasive or invasive cardiac tests can be required for more specific evaluations such as heart magnetic resonance imaging, trans-esophageal echocardiography, coronary angiography and intravascular ultrasound. In patients without coronary artery changes on echocardiography at any phase of KS no antiplatelet therapy is needed beyond the initial 6 to 8 weeks after the onset of illness. Periodic assessment of children having passed KS is strongly suggested to control the known cardiovascular risk factors at least every 2 years, because these patients seem to be prone to a higher cardiovascular risk profile with high blood pressure and greater adiposity compared with control children. Coronary artery lesions resulting from KS tend to diminish over time, although fibrous intimal thickening and reduced vascular reactivity might persist: various research articles suggest the constant presence of subclinical abnormalities of the endothelial function also in those patients without coronary artery dilations at any phase of illness.

Management of Coronary Artery Abnormalities

In patients with coronary artery changes long-term antiplatelet therapy with aspirin should be administered with the aim of reducing the risk of thrombosis or myocardial ischemia: serial stress tests, such as echo stress test – a specific ultrasound examination performed during exercise or under infusion of drugs – are mandatory in the management of these patients to assess the existence and functional consequences of coronary artery abnormalities in children with KS and determine the need for coronary angiography, transcatheter interventions or coronary bypass surgery. In patients with acute coronary occlusion due to acute thrombosis a thrombolytic treatment must be promptly started. Catheter interventions should be considered in patients presenting with ischemic symptoms or without ischemic symptoms but with reversible ischemia on stress test and patients without ischemia but with stenosis greater than 75% in the descending coronary artery. Stent placement has resulted useful in older children with mild calcifications and in children with giant aneurysms. Patients who develop large coronary artery aneurysms may benefit from a new pharmacologic agent, named abciximab, a glycoprotein IIb/IIIa receptor inhibitor that has been shown to prevent thrombotic complications and promote vascular remodelling. In the Primary Children's Medical Center of Salt Lake City standard therapy for KS in patients with large aneurysms has been compared with abciximab in addition to standard therapy. Abciximab was administered intravenously at a dose of 0.25 mg/kg, followed by the infusion of 0.125 µg/kg/minute for 12 hours. The resolution of coronary artery aneurysms occurred in 68% (13 of 19) of aneurysms in the group treated with abciximab at a short-term follow-up. The indication for coronary by-pass should be considered when there are severe occlusions of the main trunk of the left coronary artery, of more than one major coronary artery or in the proximal segment of the descending coronary artery. Cardiac transplantation is only indicated for a small number of patients with KS presenting with severe myocardial dysfunction or severe coronary arterial lesions, for whom in-
terventional catheterization or coronary artery by-pass procedures are not feasible. The angiographic resolution of coronary aneurysms has been observed 1 to 2 years after the onset of the disease in 50 to 67% of vessels: factors positively associated with the possibility of aneurysm regression include initial size, age at onset inferior than 1 year, morphology and location. Coronary abnormalities persist in the long-term in the remaining 33-50% cases: these patients had probably presented coronary artery aneurysms larger than 5 mm or multi-vessel involvement. Clinical experience with KS has permitted the stratification of patients according to their relative risk of myocardial ischemia. There are five risk-categories (Table IV): this stratification is useful for the management of patient with KS in order to establish the frequency of clinical follow-up and the timing of instrumental controls. The risk level for a patient with coronary artery involvement may change over time because of the changes in the coronary artery morphology.

In conclusion, children without known cardiac sequel during the first month of KS appear to return to their previous state of health without signs of cardiac impairment, but research studies suggest subclinical abnormalities of endothelial function and abnormal myocardial flow reserve many years after the onset of KS. Even patients with aneurysms regressed over time are managed controversially because structural and functional coronary artery abnormalities persist over time.

A host of questions related to KS still remain to be answered: the expanding knowledge about its pathogenesis will probably permit in the near future to define the best long-term surveillance modalities in all patients with a history of KS.

Table IV. Cardiovascular risk stratification for patients with Kawasaki syndrome.

<table>
<thead>
<tr>
<th>Risk level</th>
<th>Therapy</th>
<th>Physical activity</th>
<th>Follow-up</th>
<th>Invasive testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (No coronary artery changes)</td>
<td>None beyond first 6-8 weeks</td>
<td>No restrictions beyond first 6-8 weeks</td>
<td>Counseling at 5-year-intervals</td>
<td>None</td>
</tr>
<tr>
<td>II (Transient coronary artery ectasia)</td>
<td>None beyond first 6-8 weeks</td>
<td>No restrictions beyond first 6-8 weeks</td>
<td>Counseling at 3- to 5-year-intervals</td>
<td>None</td>
</tr>
<tr>
<td>III (One small-medium coronary artery aneurysm)</td>
<td>Low-dose aspirin at least until aneurysm regression is documented</td>
<td>For patients &lt; 11 years: no restriction; for patients of 11-20 years: physical activity must be guided by stress test and myocardial perfusion scan; discouraged contact or high-impact sports</td>
<td>Annual echocardiogramm + ECG; biannual stress test and myocardial perfusion scan</td>
<td>Angiography, if non invasive tests suggest ischemia</td>
</tr>
<tr>
<td>IV (≥1 large or giant coronary artery aneurysm or multiple aneurysms without obstruction)</td>
<td>Long term antiplatelet therapy and warfarin or low-molecular-weight heparin</td>
<td>Contact or high-impact sports should be avoided because of risk of bleeding; other physical activity recommendations must be guided by stress test and myocardial perfusion scan</td>
<td>Biannual echocardiogramm + ECG; annual stress test and myocardial perfusion scan</td>
<td>Angiography at 6-12 months after the disease</td>
</tr>
<tr>
<td>V (coronary artery obstruction)</td>
<td>Long term low-dose aspirin, warfarin or low-molecular-weight heparin if giant aneurysms persist</td>
<td>Contact or high-impact sports should be avoided because of risk of bleeding; other physical activity recommendations must be guided by stress test and myocardial perfusion scan</td>
<td>Biannual echocardiogramm + ECG; annual stress test and myocardial perfusion scan</td>
<td>Angiography is recommended to address the best personalized therapeutic options</td>
</tr>
</tbody>
</table>
References


27) Han RK, Silverman ED, Newman A, McCrindle BW. Management and outcome of persistent or recur-


