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Clinical Guidelines

Mucocutaneous lymphonodular syndrome [Kawasaki] (Kawasaki syndrome/disease) in children

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Keywords

- Vascular aneurysms
- Arteritis
- Kawasaki disease
- Vasculitis
- Intravenous immunoglobulin
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- Kawasaki syndrome
- Systemic disease
- Mucocutaneous lymphonodular syndrome.
- Vascular stenoses

Abbreviations List

CABG - aortocoronary artery bypass grafting ALT - alanine aminotransferase
AST - aspartate aminotransferase.
APTT - Activated partial thromboplastin time
GABHS - β-hemolytic group A streptococcus (Streptococcus pyogenes)
IVIG - intravenous human immunoglobulin
GCS - glucocorticosteroids
UTI - urinary tract infections
CT - computerized tomography
INR - international normalized ratio
MRI - magnetic resonance imaging
PCT - procalcitonin
KS - Kawasaki syndrome.
ESR - Erythrocyte sedimentation rate CRP - C-reactive protein
FC - functional class
TNF-alpha - Tumor Necrosis Factor-alpha
CHF - chronic heart failure
ECG - electrocardiography
EchoCG - echocardiographic examination
AHA - American Heart Association
AAP - American Academy of Pediatrics
EULAR - European League against Rheumatism.
PReS - Paediatric Rheumatology European Society

Terms and definitions

New and narrowly defined terms are not used in these clinical guidelines.

1. Summary

1.1 Definition

Mucocutaneous lymphonodular syndrome (Kawasaki syndrome/disease) is an acute systemic disease characterized by predominant involvement of medium and small arteries (arteritis), development of destructive-proliferative vasculitis. Sometimes the aorta and other large arteries may become involved. Kawasaki syndrome is most common in infants and young children.

Kawasaki syndrome (KS) is one of the diagnoses that should definitely be considered as a cause of febrile fever in children. KS in children, being a relatively rare pathology, can cause the development of coronary artery aneurysms and stenoses, especially in case of late diagnosis and untimely and/or inadequate treatment. Thus, KS is one of the causes of acquired cardiovascular disease.

Coronary artery lesions, which are a risk factor for death and myocardial infarction at a young age, can be prevented in the vast majority of patients with timely (up to day 10 of the disease) treatment with large doses of intravenous human immunoglobulin (IVIG) in combination with acetylsalicylic acid.

1.2 Etiology and pathogenesis

The etiology of Kawasaki syndrome has not been definitively established to date. The authors of most of the numerous epidemiologic and immunologic studies tend to agree that an infectious agent (presumably a virus) is the most likely causative factor [1]. In addition, autoimmune mechanisms and genetic predisposition may be important factors in the development of Kawasaki syndrome [2,3,4]. To date, there is evidence for 6 genetic loci associated with this disease [5].

1.3 Epidemiology

KS was first described by T. Kawasaki in 1967 in Japan; there, as well as in Asian countries, this pathology is the most frequent, indicating the presence of genetic predisposition. In Japan, the incidence is 137.7 per 100,000 children in 2002 and 218.6 in 2008 [6], in the United States - 9 - 19 [7], in Taiwan - 69 [6] [8], in the UK it is 8 per 100,000 child population [9].

Approximately 90-95% of cases are children under 10 years of age, with up to 85-90% of cases occurring in patients younger than 5 years of age. Infants 9-11 months of age are the most commonly affected.

The peak of morbidity occurs in the winter-spring period [10].

In Russia, KS is diagnosed more often, but often at a late stage, as a result of which treatment is prescribed untimely and not always adequately [10,11]. According to an epidemiological study conducted in the Irkutsk region from 2005 to 2009, the average incidence rate was 2.7 per 100,000 children from 0-17 years of age and 6.6 among children under 5 years of age; however, the authors admit that these figures may be underestimated [12].

1.4 ICD-10 coding

M30.3 - Mucocutaneous lymphonodular syndrome [Kawasaki]

1.5 Examples of diagnoses

- *Kawasaki syndrome, complete form.*
- *Kawasaki disease, complete form dated 11.2014. Dilated cardiomyopathy syndrome. Aneurysms of the left and right coronary arteries. Chronic heart failure (CHF) IIa, functional class (FC) II according to Ross.*
- *Kawasaki disease, incomplete form dated 05.2013. Right coronary artery occlusion. CHF I, NYHA class I.*

1.5 Classfication

Paediatric Rheumatology European Society (PReS) and European League against Rheumatism (EULAR) in 2006 adopted the following classification of vasculitis in children: [13].

I. Vasculitides of predominantly large vessels

- Takayasu's arteritis (non-specific aortoarteritis).

II. Vasculitides predominantly of the middle vessels

- Polyarteritis nodosa in children
- Cutaneous polyarteritis
- ***Kawasaki disease***

III. Vasculitides predominantly of small vessels

Granulomatous:

- Wegener's granulomatosis
- Charge-Strauss syndrome

Nongranulomatous:

- Microscopic polyangiitis

- Schenlein-Henoch purpura.
- Hypocomplementemic urticarial vasculitis

IV. Other vasculitites

- Behcet's disease
- Secondary vasculitides from infections (including hepatitis B-associated polyarteritis nodosa), tumors, and drugs, including hypersensitivity vasculitis
- Vasculitis associated with connective tissue diseases
- Isolated vasculitides of the central nervous system
- Cogan's syndrome
- Unclassifiable vasculitides

Cardiovascular disorders resulting from KS are classified according to the size of aneurysms and the severity of cardiovascular manifestations [14]

A. Classification of coronary artery aneurysm size in the acute phase

- *small aneurysms or dilatations* (vessel inner diameter ≤4mm);

In children ≥5 years of age: the internal diameter of the measured segment differs from the internal diameter of the adjacent segment by a factor of less than 1.5.

- *medium-sized aneurysms*: Aneurysms with an internal diameter of >4 mm to <8 mm;

In children ≥5 years of age: the inner diameter of the measured segment differs from the inner diameter of the adjacent segment by a factor of 1.5-4

- *giant aneurysms*: aneurysms with an internal diameter ≥8 mm

In children ≥5 years of age: the inner diameter of the measured segment differs from the inner diameter of the adjacent segment by a factor of more than 4

B. According to the degree of severity of manifestations of cardiovascular disorders in KS, groups from I to V are distinguished.

Determination of severity group - based on electrocardiography (Echo-CG) and selective angiography or other methods:

I. No coronary artery dilatations: patients without coronary artery dilatations, including during the acute phase of the disease;

II. Transient dilatation of the coronary arteries during the acute phase of the disease: patients with mild and transient dilatations that usually disappear within 30 days of their onset;

III. Regression: patients who still have coronary artery aneurysms meeting the criteria for dilatation or more severe changes at day 30 after their onset despite complete disappearance of changes in the bilateral coronary artery systems within the first year after their onset, and patients whose coronary artery changes do not meet the criteria for inclusion in Group V;

IV. Persistent coronary artery aneurysms: patients with single or bilateral coronary artery aneurysms detected by coronary angiography in the second year after acute MI or later and patients with coronary artery changes that do not meet the criteria for inclusion in group V;

V. Coronary artery stenosis: patients with coronary artery stenosis confirmed by coronary angiography:

(a) Patients without signs/symptoms of ischemia confirmed by laboratory tests or other methods;

(b) Patients with signs/symptoms of ischemia confirmed by laboratory tests or other methods;

Other clinical symptoms or signs:

- If patients have moderate to severe heart valve disease, heart failure, severe arrhythmias or other cardiovascular disease, these conditions should be taken into account when assessing SC severity.

1.6 Clinical presentation

The clinical manifestations of the disease are characterized by three successive stages:

- acute febrile stage lasting 1-2 weeks (sometimes up to 4-5 weeks),
- subacute stage - 3-5 weeks,
- recovery - in 6-10 weeks from the onset of the disease. The most characteristic manifestations of Kawasaki syndrome are presented in Table. 1.

Table 1 - Stages of Kawasaki syndrome [15]

Stage	Characterization	Duration
Acute febrile	Fever and symptoms of acute inflammation (conjunctival injection, erythema of the oral mucosa, erythema and edema) of hands and feet, rash, cervical lymphoadenopathy), myocarditis, pericardial effusion	1-2 weeks or more until fever disappears

Subacute	Resolution of fever, possible persistence of conjunctival injection, peeling of fingers and toes, thrombocytosis, arteritis of coronary arteries, increased risk of sudden death.	From the 2nd or 3rd week.
Recovery	All clinical symptoms of the disease are resolved, the stage lasts until normalization ESR	6-8 weeks after the onset of the disease

Classical clinical manifestations of KS allow diagnosis in typical cases as early as day 3-8 of the disease. Late diagnosis in selected children is due to the fact that fever and symptoms of KS are combined with other manifestations. Thus, in a series of 198 observations of KS, vomiting was noted in 44% of patients, diarrhea in 26%, abdominal pain in 18%, cough in 28%, rhinitis in 19%, and arthralgia in 15% of patients. One or more gastrointestinal symptom was reported in 61% of patients and respiratory symptoms in 35% [16]. The onset of KS with cholestasis with jaundice has been described, in 5% the disease manifested with symptoms of acute abdomen [17,18]. Severe myocarditis was observed in 0.16%, and tachyarrhythmia was observed in 0.09% [14]. Some children show signs of aseptic meningitis, in which the cerebrospinal fluid (CSF) shows a lymphocytic pleocytosis of 25-100 in 1 μL, normal glucose and protein levels, and less commonly, strokes may develop. Rare manifestations of SC also include testicular edema, hemophagocytic syndrome, and pleural effusion.

Often tonsillitis, symptoms of pneumonia, or urinary tract infection (UTI) are identified at the onset of KS. In such cases, especially with an incomplete picture of KS, fever is mistaken for a symptom of bacterial infection. But the persistence of fever after prescribing an antibiotic to a child with signs of UTI or pneumonia allows you to doubt the diagnosis. Thus, initial empirical antibiotic therapy delays the diagnosis of KS by no more than 2-3 days.

Arterial changes - not necessarily only of the coronary arteries - in the acute period have the character of perivasculitis or vasculitis of capillaries, arterioles and venules, as well as inflammation of the intima of medium and large arteries. But it is the lesion of coronary arteries that is the most characteristic and important diagnostic sign of KS. Detection of aneurysms, especially in the incomplete form of KS, allows to establish the diagnosis of KS with a high degree of probability, but in this case we have to state the fact of untimely diagnosis. It is therefore necessary to strive for the earliest possible diagnosis in order to make timely prescriptions of specific therapy to prevent the development of aneurysms, the formation of which occurs between the first and sixth week from the onset of the disease.

In case of early (within the first 10 days of the disease) therapy with VBIH, the risk of coronary artery lesions decreases more than 5 times [15].

In the acute period, manifestations of KS from the cardiovascular system may include: myocarditis, pericarditis, endocarditis, lesions of the valve apparatus and coronary arteries (increased echogenicity and thickening of the arterial walls, irregularity of the internal contour).

In the subacute period arterial dilation - aneurysms, thrombosis, medium-sized arterial stenosis, panvasculitis and edema of the vascular wall can already be observed; myocarditis is less obvious.

In the future, inflammatory phenomena in the vessels decrease, small dilations undergo reverse development, but part of the aneurysm remains, threatening thrombosis and myocardial infarction.

In 2.2% of patients with KS, aneurysms detected by angiography not only in the coronary arteries but also in the subclavian artery, axillary arteries, internal thoracic artery, renal artery, superior mesenteric artery, common iliac artery, internal iliac artery, and femoral artery were giant in size and multiple in nature [19]. Aneurysmal dilatation of peripheral vessels can sometimes be palpated.

One diagnostic problem is that the manifestations of KS occur sequentially, so that early ones, such as rash, may not be recorded by the physician. And the most frequently detected sign - flaking skin on the palms and feet - is detected in the later, subacute stage, when there may already be complications from the heart.

In addition to the classical form, KS can occur as an "incomplete form", more often in children of the first months of life [20]. According to the observations of the National Scientific and Practical Center for Children's Health, atypical KS is noted in 20% of patients [10]. Usually there are not 4, but only 2-3 signs in addition to fever: for example, scleritis and skin hyperemia with swelling over the interphalangeal joints of the hands. The diagnosis of KS in these cases is difficult, sometimes it becomes obvious with the appearance of additional symptoms, in others the diagnosis is helped by the exclusion of other causes of persistent fever. In some cases with incomplete clinical picture of KS , EchoCG revealed changes in the walls and diameter of coronary arteries, which made the diagnosis of KS very likely [21]. These changes and later developing aneurysms of coronary arteris (CAA) are almost pathognomonic for KS, as non-KS arterial aneurysms are infrequent in children (in the aorta in coarctation, intracranial vessels in Marfan syndrome, and in bacterial arterial emboli, polyarteritis nodosa, or aortoarteritis, which have a different clinical presentation).

Unusual onset of KS with a picture of pharyngeal abscess (fever, soreness when turning the head, trismus) with hypoechogenic (native CT density 20-30 units) lens-shaped, non-contrast-accumulating accumulation in the pharyngeal region on CT. The absence of pus

at the opening of the swelling on the posterior pharyngeal wall and the persistence of fever despite antibiotic therapy, mild scleritis and the effect of administration of 2 g/kg of IVIG, as well as peeling of the skin of the palmar surface of the fingers allow to confirm the diagnosis of KS[22].

2. Diagnostics

Criteria for the diagnosis of Kawasaki syndrome [13,23]:

1. Fever, often up to 40 C˚ or higher, lasting at least 5 days and the presence of at least four of the following five signs:

2. Changes in the mucous membranes, especially of the oral cavity and respiratory tract, dry, cracked lips; "strawberry"/raspberry tongue, hyperemia of the lips and oropharynx.

3. Changes in the skin of hands, feet, (including dense edema, redness of palms and soles, often - bright erythema over small joints of hands and feet) in the early phase, as well as generalized or localized peeling in the groin areas and on the pads of fingers and toes on 14-21 days from the onset of the disease.

4. Ocular changes, primarily bilateral injection of scleral and conjunctival vessels, without lacrimation or corneal ulceration; examination in transmitted light may reveal anterior uveitis.

5. Increased size of lymph nodes (in 50% of cases), especially cervical lymph nodes, more often there is a single painful node with a diameter of more than 1.5 cm.

6. A rash that appears in the first few days of the disease and subsides after a week; the rash is more often diffuse, polymorphic - maculopapular, urticarial, scarlet-like or even rash-like without vesicles or crusts.

- *Kawasaki syndrome is much more common than recognized. When fever is*
- *more than 5 days, this diagnosis should be considered*

In addition to the above symptoms, it is also recommended to consider the possibility of Kawasaki syndrome in a child if the following signs and symptoms are present [24]:

1. Cardiovascular system: auscultation (heart murmur, gallop rhythm), ECG changes (prolongation of PR/QT intervals, abnormal Q wave, low voltages of the QRS complex, ST and T-segment changes, arrhythmias), cardiomegaly on chest X-ray, EchoCG (fluid in the pericardial cavity, coronary aneurysms), peripheral arterial aneurysms (e.g., axillary), chest pain (angina pectoris), or myocardial infarction.

2. Gastrointestinal tract: diarrhea, vomiting, abdominal pain, gallbladder dropsy, paralytic ileus, mild jaundice of the skin, slight transient elevation of serum transaminases.

3. Blood: Leukocytosis with a left shift, thrombocytosis (up to 1-1.2 million), accelerated SLE, increased SRB levels, hypoalbuminemia, increased α2-globulin levels, slight increase in erythrocyte count and hemoglobin levels

4. Urine: proteinuria, sterile leukocyturia.

5. Skin: hyperemia and crusting at the VCG vaccine injection site, small pustules, transverse furrows on fingernails.

6. Respiratory organs: cough, rhinorrhea, pulmonary shading on chest X-ray

7. Joints: pain, swelling

8. Neurological: pleocytosis in cerebrospinal fluid (with predominance of mononuclei with normal protein and carbohydrate levels), seizures, loss of consciousness, facial nerve palsy, limb paralysis

The importance of detecting scleritis to suggest KS when other symptoms are scarce or unusual should be emphasized. The detection of dilation or at least changes in the coronary artery walls on ultrasound allows to confirm the diagnosis of KS in the presence of only 2 signs out of 6.

2.1 Complaints and history

The most significant sign of KS is persistent fever, which starts, as a rule, suddenly, reaching 40˚C and above, resistant to antipyretics. Its "diagnostic minimum" is 5 days, but it usually lasts much longer, sometimes for a month. Against a background of fever for the first 10 days, symptoms related to the main criteria for the diagnosis of the disease (typical signs of SC) usually appear: rash, dry and chapped hyperemic lips, hyperemia and injected sclerae, dense edema and redness of the palms and soles.

The characteristic clinical sign for infants is redness and thickening of the VCG injection site (this sign was not listed as mandatory because there is no mass VCG vaccination in the United States).

(Strength of recommendation 1; level of evidence C)

In the subacute stage - flaking of the skin on the tips of the fingers and toes.

Parents (legal representatives) should be carefully questioned for anamnestic data on typical and/or probable manifestations of KS.

2.2 Physical examination

A standardized examination of the child should be performed. Be sure to pay attention to the typical signs of KS.

Clinically, tachycardia, arrhythmia (due to the involvement of the conduction system of the heart, up to the development of life-threatening arrhythmias), heart murmurs can be heard due to damage to the valve apparatus (mitral, aortic, tricuspid insufficiency, usually reversible without the formation of valve defects), the possible development of heart failure.

One of the diagnostic challenges is that the manifestations of KS occur sequentially, so that early manifestations, such as a rash, may not be recorded by the physician. And the most frequently detected sign - flaking skin on the palms and feet, is detected at a later, subacute stage, when there may already be complications from the heart.

2.3 Laboratory diagnostics

- The following laboratory tests are recommended (American Heart Association (AHA) and American Academy of Pediatrics (AAP)), especially in patients with probable incomplete Kawasaki syndrome [23,25]:
  - C-reactive protein
  - TBC with evaluation of ESR and leukocytic formula
  - Urinalysis (middle portion)
  - Serum alanine aminotransferase level (ALT>50 U/L)
  - Serum albumin level

(Strength of recommendation 1; level of evidence C)

Comments: *Laboratory signs in favor of KS:*

- *Elevation of CRP ≥3 mg/dL or ESR≥40 mm/h)*
- *Leukocytosis ≥15,000/μL*
- *Normochromic normocytic anemia*
- *Platelet count in the general blood count ≥450,000/μL after day 7 of illness*
- *Sterile leukocyturia (≥10 leukocytes per field of view)*
- *Serum albumin level ≤3 g/dL*

Leukocytosis (more than 15-20x10^9/l) with neutrophilia is typical for KS. Hypochromic anemia and increasing thrombocytosis (more than 1000x10^9/L) may be detected in week 2, ESR is usually elevated. Thrombocytosis is accompanied by hypercoagulability threatening thrombosis.

Some children have elevated levels of C-reactive protein (CRP) and show sterile leukocyturia and proteinuria, but none of these tests are pathognomonic. Laboratory parameters return to normal in 6-8 weeks. The data on procalcitonin (PCT) are somewhat different: its level in the first days of the disease is high (3 or more ng/mL), but quickly, already by the 2nd week of the disease normalizes.

- A *coagulogram* study is also recommended [10, 23, 25].

  (Strength of recommendation 1; level of evidence C)

- If the diagnosis is unclear, it is recommended to assess the following:
  - blood cultures,
  - urine cultures,
  - smears from the pharynx (and/or rapid test) for β- hemolytic streptococcus group A (GABHS, *Streptococcus pyogenes*),
  - Determine antistreptolysin O (ASLO),
  - PCT,
  - autoantibodies to neutrophils [6].

  (Strength of recommendation 1; level of evidence C)

2.4 Instrumental diagnostics

- In patients with unclear febrile fever ≥5 days, an Echo-CG with coronary assessment is recommended [10,25].

(Strength of recommendation 1; level of evidence C)

Comment: *In KS, the following are usually visualized: fluid in the pericardial cavity, aneurysms and dilatation of coronary vessels, coronary artery wall thickening, irregular contours, coronary artery thrombosis with subsequent development of myocardial infarction. In coronary artery thrombosis, there are: impaired global and local systolic function of the heart ventricles due to myocardial ischemia, decreased pumping function of the heart and other hemodynamic parameters leading to the development of circulatory failure.*

- In patients with suspected KS, an electrocardiogram (ECG) is recommended [23,25,10].
  (Strength of recommendation 1; level of evidence C)
  Comment: *ECG changes: in the acute phase, these include increased PR interval, decreased QRS complex voltages, flattened T, and ST segment changes.. Ischemic changes occur later, in the subacute phase, as a result of thrombosis of coronary artery aneurysms.*

- When indicated (suspected myocardial infarction or myocardial ischemia), studies of levels are recommended for:
  - Creatine kinase;
  - Myocardial fraction of creatine kinase;
  - Myocardial troponin T and I [15,14].

  (Strength of recommendation 1; level of evidence B)

2.5 Differential diagnosis

A number of diseases with exanthema and joint changes have similar manifestations to SC. It's toxic shock syndromes and "scalded skin," juvenile rheumatoid arthritis, Stevens-Johnson syndrome, and a number of exanthemal infections.

- *There is no skin desquamation in measles on the hands or feet.*
- *Infectious mononucleosis caused by Epstein-Barr virus in 10-15% of cases is accompanied by maculo-papular rash, but fever usually lasts less than a week, and laboratory data help to distinguish this condition from KS.*

- *Adenovirus infection is characterized by pronounced manifestations of nasopharyngitis, fever lasting about 5 days, while such a symptom as "raspberry tongue" is not characteristic.*
- *Inoculation of the conjunctivae is not common in scarlet fever.*
- *Stevens-Johnson syndrome (possible causative agent - Mycoplasma pneumoniae) differs from KS by the presence of sequentially transforming rashes: macules - papules - vesicles and bullae, urethral elements or erythema with ulceration and necrosis.*
- *Systemic juvenile idiopathic arthritis may debut with prolonged (2 weeks or more) hectic fever, generalized lymphadenopathy, and a patchy pink volatile rash in the absence of arthritis. It, like polyarteritis nodosa, should be thought of in patients with suspected KS who have been treated with an adequate dose of IVIG without effect.*

3. Therapy

3.1 Conservative treatment

- Infusion of intravenous normal human immunoglobulin *,** against the background of antiaggregant therapy with acetylsalicylic acid *,** as the main method of KS treatment is recommended. Both manifest and
  "incomplete" cases are subject to treatment, as the latter, according to a number of observations, are more likely to lead to changes in the coronary arteries [25].
  (Strength of recommendation 1; level of evidence A)
  Comment: *The effect of IVIG is manifested by a decrease in temperature within 48-72 h and has prophylactic value in the development of coronary artery anomalies. If the fever is controlled, the patient is left with a maintenance dose of acetylsalicylic acid and Echo-CG is repeated at the 2nd and 6th week of the disease. the conducted studies suggest that the development of coronary artery lesions depends on the dose of IVIG and does not depend on the dose of acetylsalicylic acid [15].*
  Some patients may be resistant to IVIG therapy, usually due to their genetic characteristics [26,28].
  Resistance to IVIG (16.6% of patients) [14] is possible in children if the following factors are present:

- ✓ *Age less than 1 year old;*
- ✓ *Early diagnosis with initiation of therapy on or before day 4 of illness;*
- ✓ *Significant elevation of CRP (≥8-10 mg/dL);*
- ✓ *Elevated ALT and AST levels;*
- ✓ *Platelet count in the TBC ≤300,000/mm^3;*
- ✓ *Band form and stab form formula shift*
- ✓ *Decreased serum sodium level ≤133 mmol/L and low serum albumin level.*

- Intravenous immunoglobulin is recommended to be administered by prolonged (8-24 h) infusion at a dose of 2 g/kg body weight immediately after diagnosis, preferably during the first 7-10 days of the disease (the most optimal period to prevent cardiovascular complications) [10,15,14,22,25,26,27].
  (Strength of recommendation 1; level of evidence A)

- If a patient with KS for any reason did not receive IVIG therapy in the first few days of the disease, an immediate infusion of intravenous immunoglobulin at a dose of 2 g/kg body weight is recommended immediately after confirmation of the diagnosis[10,15,14,22,26,27].
  (Strength of recommendation 2; level of evidence B)

- If the patient does not respond to initial therapy with IVIG with a drop in fever within 48 hours or an exacerbation occurs within 2 weeks, it is recommended to repeat IVIG administration at the same dose [26].
  (Strength of recommendation 2; level of evidence B)

- Antibiotic drug therapy is not recommended because it is not effective in treating Kawasaki syndrome.
  (Strength of recommendation 2; level of evidence B)

- Acetylsalicylic acid (*ATX code: B01AC06)* has been recommended for use in KS as both anti-inflammatory (high-dose) and antiaggregant (low-dose) agents [10,15,14,22,25,26,27].
  (Strength of recommendation 2; level of evidence C).
  Comment: *in the acute stage of the disease is prescribed in a dosage of 30-100 mg/kg/day in 4 doses (in different countries different dosages are accepted: in Japan 30-50mg/kg/day, in the USA - higher doses): 80-100 mg/kg/day). After the termination*

of fever (in most cases after the administration of IVIG) in 48-72 h the dose is reduced to 3-5 mg/kg/day in one administration and continued until the level of acute inflammatory markers and platelet count normalizes, if no coronary artery aneurysms were detected by EchoCG within 6-8 weeks from the onset of the disease. If aneurysms <8 mm without thrombosis are detected, continue until changes are resolved by repeat Echo-CG and ECG (follow-up every 6 months). In case of coronary artery aneurysms ≥ 8 mm and/or the presence of thrombosis, the drug administration at a dose of 2-5 mg/kg per day (in combination with warfarin, ATX code B01AA03, under control of the international normalized ratio - INR) is continued for life [14,15].

- Tumor necrosis factor-alpha (TNF-alpha) blockers. Since during the acute stage of SC there is activation of T cells with TNF-alpha production responsible for the classic symptoms of systemic inflammatory response, it may be advisable to consider TNF-alpha blockers in the initial therapy, which are administered together with or even instead of IVIG as first-line drugs [29,30].

  (Strength of recommendation 2; level of evidence C).

  Comment: *There are publications of several cases of effective use of infliximab*[*, **] *(Use of the drug in children off label - outside the indications registered in the drug's instructions, with the permission of the Local Ethical Committee of the medical organization, in the presence of signed informed consent of the legal representative and the child over the age of 14 years) in case of resistance to conventional therapy with IVIG [29,30].*

  The effect of cyclosporine has been described in case of refractoriness to IVIG (Use of the drug in children off label - outside the indications registered in the instructions of the drug, with the permission of the Local Ethical Committee of the medical organization, in the presence of signed informed consent of the legal representative and the child over 14 years of age), methotrexate, cyclophosphamide, plasmapheresis [31,32,27,33].

- The widespread use of glucocorticosteroids (GCS) in addition to IVIG is not recommended, although some studies indicate some reduction in the incidence of aneurysm development with combined therapy [10,27,33].

(Strength of recommendation 1; level of evidence B).

- It has been recommended that consideration be given to the possible administration of GCS in patients who do not respond to repeat IVIG [10,27,33].

  (Strength of recommendation 2; level of evidence C).

  Commnet: *the most common is intravenous methylprednisolone*[*, **] *at a dose of 30 mg/kg for 40 min once a day for 2-3 days. There is a scheme of pulse therapy with methylprednisolone (ATX code H02AB04) at 600 mg/m*^{2} *twice a day for 3 days or taking prednisolone*[*, **] *(code ATX H02AB06) for 6 weeks at a dose of 2 mg/kg/day [10,27,33].*

- The following drugs are recommended for thrombosis prophylaxis by indication (Table 2) [adapted from 15].

Table 2 - Drugs to prevent thrombosis.

Acetylsalicylic acid[*, **]	In the acute stage 30-100 mg/kg in 4 doses; 48-72 h later. After cessation of fever 3-5 mg/kg/day.
Warfarin[*, **]	0.05-0.12 mg/kg (US: 0.05-0.035 mg/kg) with control of INR (1.6-2.5).
Unfractionated heparin (sodium heparin[*, **]) i/v	The saturation dose is 50 units/kg. Maintenance dose - 20 units/kg (with control of APPT: 60-85 sec. - 1.5-2 times higher than the initial level)
Low-molecular-weight heparin s/c (in acute situation with the clinic of myocardial ischemia - may be administered intravenously)	For example, enoxaparin[*, **] Children <1 year old: Treatment - 3 mg/kg/day, in 2 doses 12 hours apart Prophylaxis - 1.5 mg/kg/day. Children >1 year of age and adolescents: Treatment - 2 mg/kg/day. In 2 doses with an interval of 12 hours The prophylactic dose is 1 mg/kg/day.
Clopidogrel[*, **]	1 mg/kg/day in one administration

- Thrombolytic therapy for coronary artery aneurysm occlusion in KS has been recommended for:
  - Lysis of clots in coronary arteries in patients with myocardial infarction (within the first 12 hours);
  - Lysis of coronary artery clots resulting from KS.

  (Strength of recommendation 1; level of evidence B)

- Recommended use of the following drugs: urokinase (Use of the drug in children off label - outside the indications registered in the instructions of the medicinal product, with the permission of the Local Ethics Committee of the medical organization, in the presence of signed informed consent of the legal representative and the child over 14 years of age), alteplase[*, **] i/v [14,15]:

  (Strength of recommendation 1; level of evidence C)

3.2 Surgical treatment

- It has been recommended to consider aorto-coronary artery bypass grafting (CABG) in patients with severe occlusion of major branches of coronary arteries, especially in the central portion, or in gradually progressive disorders with proven myocardial ischemia and decreased myocardial viability in the affected area [14].

  (Strength of recommendation 1; level of evidence C).

  Comment: *Myocardial viability should be assessed comprehensively, taking into account the presence/absence of angina symptoms, exercise ECG data, myocardial thallium scintigraphy, two-dimensional Echo-CG, left ventriculography (local mobility of the myocardial wall) and others.*

- It is recommended to consult a cardiac surgeon (based on the lesions detected by coronary angiography) in case of:
  - severe occlusions in the left main coronary artery;
  - severe multi-vessel occlusions (2 or 3 vessels);
  - severe occlusions in the proximal part of the anterior descending branch of the anterior coronary artery;
  - loss of collaterals [14].

  (Strength of recommendation 1; level of evidence C).

  Comment*: The following conditions should also be considered when selecting a therapy strategy:*
  - *if the patient has a second or third myocardial infarction due to the presence of chronic infarct foci: in this situation, surgery may be indicated, for example, to treat lesions limited to the right coronary artery.*

- *lesions associated with recanalization of an occluded coronary artery or formation of collateral vessels. In this situation, the approach to surgical intervention must be extremely cautious. Surgical intervention is performed only in patients with severe myocardial ischemia.*
- *the need for ACBG should be particularly carefully weighed in young children, due to the long-term functioning of the shunt. Young children whose condition can be controlled with drug therapy should be managed conservatively. They should be adequately monitored with periodic coronary angiography. This tactic is assumed in order to delay ACBG as much as possible so that the child can grow up. Nevertheless, patients with severe changes undergo surgical intervention even at the age of 1-2 years.*
- *Results of left ventricular function testing. Preferably, patients with preserved left ventricular function should be treated surgically, although patients with localized myocardial hypokinesia may also be treated surgically. In patients with marked diffuse hypokinesia, the condition of the coronary arteries is necessarily determined. In rare cases, a heart transplant may be indicated.*

- In patients with severe mitral insufficiency resistant to drug therapy, valvuloplasty and valve replacement are recommended[14].
  (Strength of recommendation 1; level of evidence C).

- In rare cases, KS may be complicated by cardiac tamponade, left ventricular aneurysm, or occlusive disorders. In such situations, appropriate types of surgical interventions have been recommended[14].
  (Strength of recommendation 1; level of evidence C).

4. Rehabilitation

Should be aimed at maintaining cardiac function and improving patients' quality of life.

5. Prevention and follow-up

5.1 Prevention

There is no specific prophylaxis.

Prevention of cardiovascular abnormalities in most patients is early diagnosis and timely implementation of therapy with IVIG.

5.2 Follow-up of children

A child should be monitored by a pediatric cardiologist after KS. Currently, there is no clear consensus on the duration of follow-up, However, most specialists recognize that KS survivors have a high risk of cardiovascular complications, including the formation of stenoses and their progression during life.

Echo-CG should be performed regularly, every 6 months, until persistent disappearance of coronary aneurysms. Children with formed persistent aneurysms have a lifetime Echo-CG and ECG every 6 months. Coronarography and exercise testing are performed when indicated.

Because KS may be a risk factor for atherosclerosis, patients should be educated about the need for an appropriate lifestyle (diet with restriction of saturated fats and fatty acids and "fast" carbohydrates, body weight control, smoking cessation, etc.) [14].

5.3 Peculiarities of vaccination

- Vaccination with inactivated vaccines is recommended for all patients only after the acute manifestations of KS have resolved; live viral vaccines (measles, mumps, rubella, poliomyelitis and varicella) can be administered no earlier than 3-6 months after immunoglobulin administration [27,33]. **(Strength of recommendation 2; level of evidence C)**

- Patients older than 6 months of age, who are long-term administered acetylsalicylic acid, should be vaccinated only with inactivated influenza vaccine due to the risk of Reye's syndrome on the background of influenza disease, in addition, it is recommended to vaccinate against varicella due to the fact that "wild" types of *Varicella zoster* may also be a more common cause of Reye's syndrome in these patients. Influenza and varicella vaccination should be administered 3-6 months after completion of a course of IVIG [14,34,35].

(Strength of recommendation 2; level of evidence C)

5.4 Monitoring of patients with KS

- It has been recommended to follow the general principles of monitoring of patients with KS [10,15,14,25,28]:
  - It is recommended that all patients with KS have an Echo-CG at diagnosis and 6-8 weeks after the first manifestations of the disease;
  - In the absence of changes in the diagnostic (primary) Echo-CG, an additional repeat study on day 10-14 is recommended;
  - In patients with aneurysms detected on Echo-CG and in children with persistent laboratory signs of disease activity, weekly follow-up Echo-CG studies are recommended;
  - In patients with persisting aneurysms according to Echo-CG data, long-term administration of acetylsalicylic acid at a dose of 3-5 mg/kg/day is recommended. Acetylsalicylic acid can be discontinued if the aneurysm disappears;
  - Patients with complaints of pain or discomfort in the chest area and/or palpitations, as well as all patients with stenosis and giant arterial aneurysms are recommended to perform daily (Holter) ECG monitoring to exclude arrhythmias and ischemic disorders.
  - Depending on the size of the aneurysm according to the Echo-CG data, it is recommended to perform further control studies of the heart and coronary vessels every 6-12 months.
  - The principles of management of patients with KS depending on the phase and severity of the disease are presented in Appendix D1.

(Strength of recommendation 1; level of evidence C)

6. Additional information affecting the course and outcome of the disease/syndrome

6.1 Complications

In addition to coronary artery lesions and their thrombosis with myocardial infarction and heart rhythm disturbances, gallbladder dropsy, hepatitis, pancreatitis, myositis, pericarditis and myocarditis, and sensorineural deafness are observed with varying frequency in KS. Aneurysm formation can lead to peripheral gangrene.

6.2 Outcomes and prognosis

Prognostically unfavorable is the persistence of fever for more than 16 days, relapse after 2 days of normal temperature, cardiomegaly, cardiac rhythm disturbances (except for atrioventricular blockade of the 1st degree). The prognosis is worse in boys and children of both sexes under 1 year of age. Thrombocytopenia, low hematocrit and albumin levels at disease onset are also unfavorable signs [10].

The prognosis of KS when treated is favorable, lethality is less than 1%, relapses are rare (1-3%), more often within a year after the first episode and in children with cardiac pathology. The main danger is associated with coronary aneurysms - thrombosis of aneurysms, especially giant aneurysms, KS is fraught with myocardial infarction, as well as infarction can develop due to the progression of coronary artery stenosis.

Criteria for assessing the quality of medical care

Table 1 - Organizational and technical conditions of medical care.

Type of medical care	specialized, including high-tech medical care
Age group	children
Conditions of medical care	inpatient, day care
Form of medical care	urgent, routine

Table 2 - Criteria for the quality of medical care assessment

No.	**Quality criteria**	**Strength of recommendation**	**Level of credibility of recommendations**
1	Intravenous therapy was performed with normal human immunoglobulin	1	A
2	Echocardiography was performed	1	C
3	Electrocardiography was performed	1	C

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Appendix A1. Composition of the working group

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Appendix A2. Methodology for the development of clinical guidelines

The target audience for these clinical guidelines is:

1. Pediatricians
2. General family practitioners (family medicine)
3. Pediatric cardiologists
4. Cardiac surgeons
5. Rheumatologists
6. Medical students, interns, residents;

The principles that are key to high quality and reliable clinical guidelines were followed in the development of the clinical guideline.

Methods used to collect/select evidence

Search of electronic databases.

Description of methods used to collect/select evidence

The evidence base for the publication is publications included in the Cochrane Library, EMBASE and MEDLINE databases. The depth of the search was 5 years.

Methods used to assess the quality and strength of evidence

Expert consensus.

Significance assessment according to the rating scheme (Table 1).

Table P1 - Rating scheme to assess the strength of the recommendation

Degree of credibility of the recommendations	Risk/benefit ratio	Methodological quality of available evidence	Explanation of the application of the recommendations
1A Strong recommendation based on high quality evidence	The benefits clearly prevail over risks and costs, or vice versa	Reliable consistent evidence based on well-performed RCTs or incontrovertible evidence presented in some other form. Further research is unlikely to change our confidence in assessing the benefit-risk ratio.	A strong recommendation that can be used in the majority of cases in the majority of patients without any modifications or exceptions

1B **Strong recommendation based on moderate quality evidence**	The benefits clearly prevail over risks and costs, or vice versa	Evidence based on RCTs performed with some limitations (inconsistent results, methodological errors, indirect or randomized, etc.) or other strong grounds. Further research (if any) is likely to have an impact on our confidence in the benefit-risk assessment and may change it.	A strong recommendation that can be applied in most cases
1C **Strong recommendation based on low quality evidence**	The benefits are likely to prevail over the possible risks and costs, or vice versa	Evidence based on observational studies, haphazard clinical experience, results of RCTs performed with significant flaws. Any estimate of the effect is regarded as uncertain.	Relatively strong recommendation, subject to change when receiving higher-quality evidence
2A **Weak recommendation based on high quality evidence**	The benefits are comparable to the possible risks and costs	Robust evidence based on well-performed RCTs or supported by other hard data. Further research is unlikely to change our confidence in assessing the benefit-risk ratio.	Weak recommendation. Choosing the best tactics will depend on clinical situation(s), patient or social preferences.
2B **Weak recommendation based on moderate quality evidence**	The benefits are comparable to the risks and complications, but there is uncertainty in this assessment.	Evidence based on the results of RCTs performed with significant limitations (contradictory results, methodological flaws, circumstantial or accidental), or strong evidence presented in some other form. Further research (if any) is likely to influence and may change our confidence in our assessment of the benefit-risk ratio.	Weak recommendation. Alternative tactics may be the best choice for some patients in certain situations.
2C **Weak recommendation based on low quality evidence**	Ambiguity in assessing the balance of benefits, risks and complications; benefits can be weighed against possible risks and complications.	Evidence based on observational studies, haphazard clinical experience or RCTs with significant flaws. Any estimate of the effect is regarded as uncertain.	Very weak recommendation; alternative approaches could be used equally.

Methods used to collect/select evidence

- Reviews of published meta-analyses;
- Systematic reviews with evidence tables.

Description of the methods used to analyze the evidence

In order to eliminate the influence of subjective factor and minimize potential errors, each study was evaluated independently by at least two independent members of the working group. Any differences in assessment were discussed by the full group as a whole. If consensus could not be reached, an independent expert was engaged.

Methods used to formulate the recommendations

Expert consensus.

Method of validation of recommendations

- External peer review
- Internal peer review

Description of the method of validation of recommendations

The recommendations presented in the preliminary version have been peer-reviewed by independent experts who have determined that the evidence underlying these recommendations is understandable.

These guidelines have been shared with pediatricians who have indicated that they are easy to understand and important as a working tool for daily practice.

All comments received from experts were carefully systematized and discussed by the chairman and members of the working group and, if necessary, amendments were made to the clinical guidelines.

Economic analysis

No cost analysis was performed and pharmacoeconomics publications were not analyzed.

Consultation and expert assessment

The latest revisions to these recommendations were presented for discussion in a preliminary version at the meeting of the working group, PUR Executive Committee and members of the specialized commission in February 2015.

The draft recommendations were also reviewed by independent experts who were asked to comment on the clarity and accuracy of the interpretation of the evidence base underlying the recommendations.

Work group

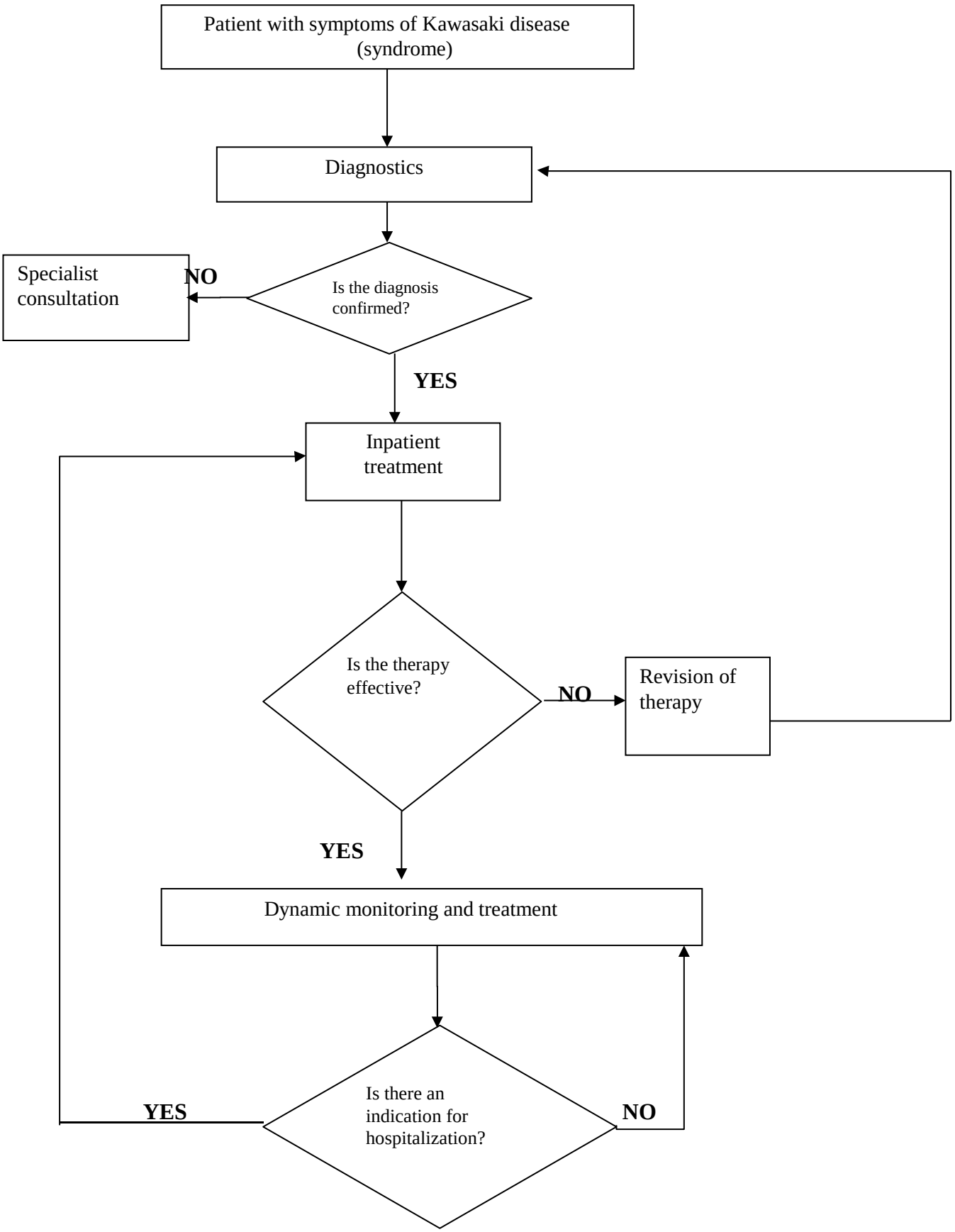
For final revision and quality control, the recommendations were re-analyzed by the members of the working group, who concluded that all comments and observations of the experts were taken into account and the risk of systematic error in the development of the recommendations was minimized.

These clinical guidelines will be updated at least once every three years. The decision to update will be made on the basis of proposals submitted by medical professional non-profit organizations, taking into account the results of comprehensive evaluation of medicinal products, medical devices, as well as the results of clinical approbation.

Appendix A3. Related documents

Medical care rendering procedures: Order of the Ministry of Health and Social Development of the Russian Federation of April 16, 2012 N 366n "On Approval of the Procedure for Pediatric Care”

Appendix B. Algorithms for patient management



Appendix C. Information for patients

Disease (Kawasaki syndrome) an acute disease in which medium and small arteries are affected (arteritis), with the development of destructive proliferative vasculitis. Sometimes the aorta and other large arteries may become involved. Kawasaki syndrome is most common in infants and young children.

Clear manifestations of the disease are persistent elevation of body temperature to high values (up to 40 °), usually at least 5 days (possibly up to 1 month). Along with fever during the first 10 days usually appear the following signs usually appear: rash, dry cracked bright red lips, bright "raspberry" tongue, reddening of the sclerae of the eyes with a pronounced vascular network, dense edema and redness of the palms of the hands and soles of the feet, subsequently replaced by peeling of the skin.

In young children (under 3 years of age), **redness and thickening of the VCG injection site may be seen.**

The main danger of Kawasaki disease is complications: the formation of irreversible changes in the vessels: dilation (aneurysms) or narrowing (stenoses), especially of the coronary arteries, which can lead to cardiovascular complications, up to myocardial infarction in childhood. Thus, Kawasaki disease is one of the causes of acquired cardiovascular disease.

The factors causing Kawasaki disease have not been precisely identified to date; a possible combination of genetic predisposition and exposure to certain viruses has been suggested. It is considered impossible to contract Kawasaki disease from another person.

How is Kawasaki disease diagnosed? It is not difficult to assume this disease in typical cases in the presence of characteristic manifestations. Due to the fact that the manifestations of the disease occur sequentially, and at the time of examination by a doctor, some signs may already disappear, always pay attention to the above changes in the skin and mucous membranes, remember them and be sure to report them to the pediatrician.

The doctor may prescribe a total blood count, a general urinalysis, and a cardiac ultrasound.

Treatment: Generally, children with Kawasaki disease in the acute and/or subacute stage require hospitalization. Most patients with Kawasaki disease are prescribed intravenous immunoglobulin and acetylsalicylic acid,

in individualized doses. These drugs can prevent cardiovascular complications in many children. If they are ineffective, the doctor will consider prescribing other groups of medications.

A record of Kawasaki disease in the past is not a contraindication for vaccination. Particularly relevant vaccinations for children taking acetylsalicylic acid are influenza and varicella vaccines. It is up to your doctor to decide when it is appropriate to vaccinate your child.

After suffering from Kawasaki disease, the patient should be observed by a pediatric cardiologist, it is very important to comply with the regime, diet, treatment, as well as diagnostic procedures prescribed by the doctor.

Appendix D1. Risk assessment and recommendations for the long-term management of children with KS

Severity	**Pathophysiology**	**Diagnostic measures depending on clinical course**	**Therapy**	**Physical activity, lifestyle**
I (no changes in the coronary arteries at any stage of the disease)	It is currently unproven whether or not KS without changes in coronary artery disease is or is not a risk factor for atherosclerosis.	Cardiovascular disease risk assessment, follow up for 5 years. Examination on day 30, day 60, at the 6th month, 1 year and 5 years after the onset of the disease (ECG, Echo-CG, If necessary, chest radiography. An exercise ECG at the last examination is recommended)	Not prescribed after the acute phase has resolved (after 6-8 weeks)	Physical activity - no restrictions. The possibility of sports is considered on an individual basis. Recommendations for a healthy lifestyle (see section 5.2)
II (transient coronary artery ectasia - up to 6-8 weeks from the onset of the disease)	During the acute phase, histopathologic vasculitis develops in the outer layer of the medial sheath and then spreads to the intima in the coronary arteries. Echo-CG reveals diffuse dilatation of the coronary arteries, but these changes disappear within 30 days of their appearance.			
III (Regression)	Most often, regression can occur within 1 to 2 years after onset, especially in the presence of small to medium diameter aneurysms. Segments with regression reveal: decreased coronary diastolic function, abnormal vascular endothelial function, and significant intimal hyperplasia. There are reports on the possibility of acute coronary syndrome in adults with a history of KS with regressed arterial lesions after the acute phase of the disease.	Observation and control every 3 months until the aneurysms disappear, then - annual observation by a cardiologist with Echo-CG and ECG, and, if necessary, chest X-ray until the age of 6 years, then - the same methods + ECG with exercise (as soon as the age of the child allows). Patients with coronary artery aneurysms with a large internal diameter in the acute phase of the disease should undergo appropriate imaging studies (CT or MRI angiography, MRI is preferable. due to the absence of radiation exposure)**	Low doses of acetylsalicylic acid (3-5 mg/kg/day) as needed (at least until documented disappearance of the aneurysm).	There are no restrictions after 8 weeks. It is not recommended to engage in traumatic sports while on antiaggregant therapy. Exemption from participation in athletic competition. Sports activities are prohibited. An exercise ECG should be performed as soon as the child's age (over 5 years of age) permits.

		When ischemia is detected during stress test a coronary angiography is indicated.		
Level IV (persistent coronary artery aneurysms)	Aneurysms persisting in the period of reconvalescence or later, considered as complications of KS. Histopathologically, progression of inflammation leads to damage to the inner elastic membrane, causing panangiitis. The outer and inner membranes are fragmented and destroyed by arterial pressure with the formation of aneurysms. A patient with giant aneurysms should be carefully evaluated for myocardial ischemia, as myocardial ischemia may develop in such patients even in the absence of significant stenotic changes in the arteries.	Cardiologist examination 2 times a year with Echo-CG and ECG; Annually - stress test; for visualization of coronary artery aneurysms - CT or MR angiography Assessment of myocardial perfusion. Patients who had coronary artery aneurysms with large internal diameter in the acute phase - myocardial scintigraphy with contrast every 2-5 years since the onset of myocardial ischemia. First angiography at 6-12 months from onset or later as indicated Repeat angiography if non-invasive tests, clinical or laboratory findings suggest ischemia; additionally repeat angiography if indicated.	Long-term therapy with acetylsalicylic acid, in patients with giant aneurysms or in the presence of thrombus in the coronary artery - in combination with anticoagulants: warfarin (target INR 2.0-2.5) or Low-molecular-weight heparin (target value of anti-Ha factor level: 0.5-1.0 U/mL). Coronary artery bypass grafting may be indicated in patients with giant aneurysms without significant stenoses in the presence of myocardial ischemia.	Eliminate contact and traumatic active games. Exemption from participation in athletic competition. Sports activities are prohibited. In patients with giant aneurysms, daily physical activity should be limited.

Level Va (coronary artery stenosis without signs of myocardial ischemia)	Clot occlusion of medium or giant coronary artery aneurysms may develop in the relatively early stages of the disease. May manifest with sudden death of the patient; however, 2/3 of patients have asymptomatic occlusions. Patients experience a reduction in myocardial ischemia due to vessel recanalization or collateralization of blood flow after occlusion.	Lifelong follow-up by a cardiologist according to an individualized scheme (once every 3-6 months). The following is performed: Echo-CG and ECG, including exercise ECG; Appropriate imaging modalities (Coronary angiography is recommended to guide therapy; consider the possibility	Long-term therapy with low-dose acetylsalicylic acid. Use of nitrates* to prevent ischemic attacks. Treatment of heart failure: calcium channel blockers*, β-blockers*,	Eliminate contact and traumatic sports. Exemption from participation in athletic competition. Sports activities are prohibited. Explain to the patient the importance and necessity of adherence
	The development/progression of regional stenosis in the remote period is more frequent in the left coronary artery than in the right one. Most common: in proximal segments in the main trunk of the left anterior descending artery. The larger the aneurysm, the higher the risk of progression to stenosis/occlusion. Stenoses may develop in the remote period.	periodic visualization of coronary artery aneurysms by CT or MR angiography for monitoring purposes)	Angiotensin-converting enzyme inhibitors*, angiotensin II receptor blockers* (see CR for diagnosis and treatment of children with chronic heart failure).	of patient's treatment regimen, assess adherence to treatment, talk about symptoms he or she may experience and the actions he or she should take to case of ischemia development.
Level V (coronary artery obstruction)			See recommendations for level Va. Consider coronary artery bypass grafting or coronary balloon angioplasty (percutaneous transluminal coronary angioplasty (PTCA)) if the ECG data from the physical activity or stress myocardiocentigraphy reveals myocardial ischemia.	Daily physical activity should be limited. Sports activities are prohibited. The level of physical activity is selected based on exercise test data and assessment of the severity of myocardial ischemia. Explain the importance of drug therapy to the patient.

* Use of the drug in children off label - outside the indications registered in the instructions of the medicinal product, with the permission of the Local Ethical Committee of the medical organization, in the presence of signed informed consent of the legal representative and the child over 14 years of age.

** Echo-CG, including stress-echo-CG, stress-myocardioscintigraphy, selective coronary angiography, intravascular ultrasound, MRI, MR angiography, multispiral computed tomography.

Appendix D2. Explanation of comments.

…* – a medicinal product included in the List of Vital and Essential Medicinal Products for Medical Use for 2016 (Order of the Government of the Russian Federation No. 2724-r dated 26.12.2015)

…** – a medicinal product included in the List of medicinal products for medical use, including medicinal products for medical use, prescribed by decision of medical commissions of medical organizations (Order of the Government of the Russian Federation dated 26.12.2015 N 2724-r)