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KAWASAKI DISEASE

CLINICAL GUIDELINES, EVIDENCE-BASED

2026

CONTENT

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Clinical guideline revision scheduled for 2031

List of abbreviations

AKA	coronary artery aneurysm
ALT	alanine aminotransferase
ASK	acetylsalicylic acid
in/in	intravenous
INFLUENCE	intravenous immunoglobulin
GGT	gamma-glutamyltransferase
GCS	glucocorticosteroids
DNA	deoxyribonucleic acid
ECG	electrocardiogram
Echo KG	echocardiography
ZAK	complete blood count
IM	myocardial infarction
KA	coronary arteries
CT	computed tomography
KTA	computed tomography angiography
LV	left ventricle
MRI	magnetic resonance imaging
LMH	low molecular weight heparin
NSAIDs	nonsteroidal anti-inflammatory drugs
OCT	optical coherence tomography
RCA/Phono	right coronary artery
POAC (DOAC)	direct oral anticoagulants
PPT (BSA)	body surface area
p/w	subcutaneously
RCD	randomized controlled trial
CRB	C-reactive protein
TNF-α	tumor necrosis factor alpha
PRK	fractional blood flow reserve
HC	Kawasaki disease
PCI	percutaneous coronary intervention
ESR	erythrocyte sedimentation rate
AHA	American Heart Association - American Heart Association
AoV	aortic valve
AV	atrioventricular
BNP	B-type natriuretic peptide
CABG	coronary artery bypass grafting
CD25	soluble interleukin-2 receptor α

DOAC	direct oral anticoagulants
IVUS	intravascular ultrasound examination
LAD	anterior descending branch of the left coronary artery
LMCA	left main coronary artery
LV	left ventricle
MIS-C	multisystem inflammatory syndrome in children
NSTE-ACS	acute coronary syndrome without ST segment elevation
NFAT	nuclear factor of activated T cells
PLAX	parasternal long axis
PSAX	parasternal short axis
PV	pulmonary valve
RAISE	RCT of the effectiveness of immunoglobulin with corticosteroids in chronic hepatitis C
RV	right ventricle
RVOT	right ventricular outflow tract
TNF	tumor necrosis factor
SAX	short axis
STEMI	acute coronary syndrome with ST segment elevation
WBC	leukocytes

FOREWORD BY THE MULTIDISCIPLINARY WORKING GROUP.

This clinical guideline (hereinafter referred to as the GD) was developed in accordance with the Methodology for the Development and Implementation of Medical Standards for Medical and Rehabilitation Care on the Basis of Evidence-Based Medicine, approved by the Order of the Ministry of Health of Ukraine dated September 28, 2012 No. 751 "On the Creation and Implementation of Medical and Technological Documents for the Standardization of Medical and Rehabilitation Care in the System of the Ministry of Health of Ukraine", registered with the Ministry of Justice of Ukraine on November 29, 2012 under No. 2001/22313 (as amended) and adapted for the healthcare system of Ukraine on the basis of ***Update on Diagnosis and Management of Kawasaki Disease: A Scientific Statement From the American Heart Association, 2024 https://www.ahajournals.org/doi/10.1161/CIR.0000000000001295,*** *that was chosen working group, as an example of best practice in providing medical care to patients with Kawasaki disease (hereinafter referred to as "KD"), and is based on evidence-based medicine data regarding the effectiveness and safety of medical interventions, pharmacotherapy, and organizational principles of its provision.*

The document for the creation of this guideline was selected based on objective evaluation criteria using the international guideline appraisal and evaluation questionnaire AGREE II in order to select the prototype of the best methodological quality.

Adaptation of the CN involves introducing into the unchanged text of the original Guidelines the comments of the working group, which reflect the possibility of implementing certain provisions of the CN in the real conditions of the Ukrainian healthcare system, the availability of medical interventions, the presence of registration in Ukraine of medicinal products specified in the CN, and compliance with the regulatory framework for the organization of medical care.

It should be noted that the use of some medicinal products (hereinafter referred to as medicinal products) that have demonstrated sufficient efficacy in international clinical trials and are used to treat children with CD may be restricted in Ukraine due to the lack of indications for the treatment of CD or the presence of restrictions on their use in children in the instructions for their medical use approved by the Ministry of Health (hereinafter referred to as the Ministry of Health).

According to Article 441 of the Law of Ukraine "Fundamentals of Ukrainian Legislation on Healthcare", unregistered medicinal products or registered medicinal products for indications not specified in the instructions for medical use or the summary of product characteristics may be used in the interests of curing a person only upon receipt of the written consent of the patient or his legal representative and informing the patient or his legal representative about the goals, methods, side effects, possible risks and expected results of treatment.

The proposed CQ should not be considered as a standard of medical treatment. Compliance with the provisions of the CQ does not guarantee successful treatment in every specific case, it cannot be considered as a guide that includes all necessary treatment methods or, conversely, excludes others. The final decision regarding the choice of a specific clinical procedure or treatment plan should be made by the physician, taking into account the clinical condition of the patient and the possibilities of carrying out diagnostic and treatment measures in the healthcare facility. The physician is also responsible for checking the rules and regulations applicable to medicinal products and medical devices in force at the time of prescribing such medical technologies.

The main goal of the Kawasaki Disease Clinical Practice Guideline is to assist the physician and patient in making rational decisions in various clinical situations, and also to provide information support for improving the quality of clinical practice based on evidence of the effectiveness of certain medical approaches, medications, and organizational resources for medical care.

AHA SCIENTIFIC STATEMENT

Update on Diagnosis and Management of Kawasaki Disease: A Scientific Statement From the American Heart Association 2024

Introduction

Kawasaki disease (KD)— is an acute febrile disease that affects predominantly in children under 5 years of age and is the leading cause of acquired heart disease in children in developed countries. Without treatment, about 25% of patients develop coronary artery dilation (CA) or coronary artery aneurysms (CAAs) [1].

The incidence of CD in the United States is 18 to 25 cases per 100,000 children under 5 years of age; in Northeast Asian countries, including Japan, South Korea, China, and Taiwan, the rate is 10 to 30 times higher [1,2]. The pathogenesis of CD remains unknown, and diagnosis is based on established clinical criteria [1].

This update highlights key aspects of coronary artery disease and summarizes current clinical evidence published since the 2017 American Heart Association (AHA) scientific statement on diagnosis, cardiac imaging in acute coronary artery disease, and long-term management [1]. Although diagnostic criteria have not changed since the previous statement, early diagnosis of coronary artery disease remains critical to reducing the risk of developing ACA. Criteria have been published to identify patients at high risk of ACA in North America who may benefit from more intensive treatment early in the disease course [3]. Advances in cardiovascular imaging have improved the ability to detect CA stenoses in patients with coronary artery disease, but gaps in knowledge remain regarding the optimal frequency of serial monitoring and the best technique for detecting the risk of induced myocardial ischemia [4–7].

New data have improved understanding of the safety and dosing of a number of anti-inflammatory drugs used in CD. Some studies suggest that increasing initial anti-inflammatory therapy in high-risk patients may improve outcomes in coronary artery disease [8–10].

Large cohort studies and international registries have provided new information on clinical outcomes and risk factors for cardiovascular complications, in particular, it was found that children with transient dilation of the CA or small ACA (CA Z-score <5) have a minimal risk of adverse cardiovascular events, and most of them undergo remodeling to normal internal lumen [11–14].

However, there remains a significant gap in the transition of patients with HC to adult care, as well as in the management of women with HC and giant aneurysms who are receiving long-term anticoagulation therapy and planning to

pregnancy. The document also discusses promising areas of research in the field of diagnostics and treatment of patients with CD.

Diagnostics

CD remains a clinical diagnosis characterized by fever, unilateral lymphadenopathy, rash, bilateral non-exudative conjunctival injection, swelling and erythema of the hands and feet, and oropharyngeal changes, including a strawberry tongue and reddened lips [1]. The diagnostic algorithm for complete or incomplete CD, taking into account confirmatory laboratory signs, is presented in Figure 1.

If ≥4 major clinical features are present, the diagnosis of CD can be made as early as the fourth day of fever [1]. Experienced clinicians can make the diagnosis as early as the third day of fever [1,15]. When evaluating infants and children suspected of having CD, consideration should be given to other childhood febrile illnesses that have similar clinical presentations. However, some symptoms, including oral ulcers, exudative pharyngitis, exudative or unilateral conjunctivitis, and vesicular rash, are not characteristic of CD.

Working group comment:*the working group considers it appropriate to provide information on the differential diagnosis of Kawasaki disease with other febrile illnesses in children and multisystem inflammatory syndrome in children (MIS-C) in COVID-19 in the appendix to the Clinical Guideline.*

Shock syndrome of KD is a rare but severe form of the disease in which patients present with vasodilatory shock, hypotension, and impaired perfusion, with or without myocardial dysfunction [16]. Because there is no pathognomonic test for KD, KD itself and the associated shock syndrome can be difficult to distinguish clinically from other hyperinflammatory conditions.

For example, in 2020, with the emergence of SARS-CoV-2 and the subsequent recognition of multisystem inflammatory syndrome in children (MIS-C), this new condition became part of the differential diagnosis of CD [17–19]. Although MIS-C and CD share clinical similarities, it has become increasingly clear during the COVID-19 pandemic that they are two distinct diseases. Some clinical features (including severe gastrointestinal symptoms—abdominal pain, vomiting, diarrhea, headache), laboratory findings (e.g., thrombocytopenia, lymphopenia, elevated troponin or BNP—B-type natriuretic peptide), and cardiac findings (decreased left ventricular systolic function, pericardial effusion) are more typical of MIS-C [17–22].

In contrast, rash, conjunctival injection, oral mucosal changes, and CA involvement are more common in patients with CD. Since 2022, the incidence of MIS-C has decreased significantly, likely due to widespread immune development.

to SARS-CoV-2 or a reduction in the ability of newer virus variants to cause MIS-C [23]. Machine learning algorithms have been developed to improve the differentiation between HC and MIS-C and may help clinicians distinguish between these diseases [24].

It is extremely important to diagnose HC within 10 days of the onset of fever. — preferably on day 4–5 of illness in patients with complete CD and as early as possible (but no later than 10 days) in suspected incomplete CD. Treatment initiated within 10 days of fever onset is clearly associated with a reduced risk of dilatation or ACA. Identification of patients at high risk of ACA at the time of diagnosis allows for increased initial anti-inflammatory therapy, which may improve treatment outcomes. Although identifying all children with CD who are at risk of ACA in a multiethnic population remains a challenge, some criteria have been published for North America. These include age <6 months and a Z-score of CA ≥2.5 on initial echocardiography [25, 26]. Children under 1 year of age are at higher risk of ACA compared with older children. This is supported by the prevalence of ACA in patients aged 6–12 months (40%) and <6 months (68%) [27]. Studies have shown that infants <6 months of age are at particularly high risk of developing ACA, with nearly 50% having a CA Z-score ≥2.5 at the time of initial echocardiography [25, 26]. In a study by Son et al. [3], risk assessment criteria for a North American population were established, which included: age <6 months, Asian descent, CA Z-score >2 at initial echocardiography, and C-reactive protein

> 13 mg/dL (each parameter is scored 1 point, except for CA, which is scored 2 points). A score of ≥3 reliably predicts the development of ACA within 8 weeks of the acute phase of the disease. Although this scale emphasizes the increased risk in children <6 months of age, in Japan the criterion for high risk is considered to be age <12 months.

Identifying patients at high risk of developing AKA is important, as recent evidence suggests that such patients may benefit from intensification of initial anti-inflammatory therapy, as discussed in more detail in the section on the treatment of UC.

Key provisions:

1. The diagnosis of UC remains a clinical diagnosis for which there is no pathognomonic diagnostic test.

2. If ≥4 main clinical signs are present, the diagnosis of full-blown UC is made can be established on the 4th day of fever.

3. The diagnostic criteria for incomplete form of CD remain unchanged, however, clinicians are advised to make the diagnosis as early as possible to prevent CA dilation and the development of aneurysms.

4. MIS-C should be included in the differential diagnosis of HC, although from 2022

The incidence of this syndrome has decreased significantly over the years.

5. Although identifying all children with CD who are at risk
Although the development of ACA in multiethnic populations remains challenging, a significant body of data suggests that a right CA or left anterior descending coronary artery Z-score ≥2.5 at diagnosis and age <6 months are markers of high risk across racial and ethnic groups; such patients should be considered for intensified initial therapy.

CARDIAC VISUALIZATION IN THE ACUTE PHASE OF CHD

Echocardiography (Echo CG)

Echocardiography is the main imaging modality in CHD. It is noninvasive, has high spatial and temporal resolution, and provides rapid visualization of proximal CA abnormalities. Imaging standards for echocardiography during patient preparation, technical standards for CA assessment, and quantification of echocardiographic findings are listed in Table 1. The most common locations of ACA are the proximal left anterior descending branch and the proximal right CA; the posterior descending branch is the least commonly affected [1, 28]. The left main CA rarely has ACA in the absence of aneurysms in the anterior descending or circumflex arteries. CA lumen dimensions are normalized to body surface area using Z-scores. The 2017 AHA guideline introduced a Z-score-based classification of ACA [1]. The 2020 Guidelines of the Japanese Society of Cardiology also adopted the classification of ACA using Z-scores [29, 30]. The routine use of CA Z-scores has provided a certain level of standardization in the quantification of CA size, but challenges still remain. Even a small error in measuring CA diameter can translate into a significant difference in Z-score, which can alter the classification of CA, especially in young children. Accurate anthropometric measurements (body weight and height) are necessary to correctly calculate body surface area and avoid errors in determining Z-scores, which can lead to over- or underestimation of arterial size.

Several systems for calculating Z-scores for CA have been published to date [30–34], but no single standard Z-score system for CA has been established, which accounts for the variability in their use across studies. Studies have shown that when comparing different Z-score systems, the classification of the level of risk of CA damage may change. [35–37] Thus, for reliable monitoring of the condition of patients with CH, it is important that the medical institution uses the same Z-score formula for consecutive assessments over time.

Working group comment:*determining the risk category for damage The calculation of CA and ACA formations based on Z-scores in Ukraine is carried out using the Dallaire & Dahdah calculator, which can be found at the link: (http://www.parameterz.com/refs/dallaire-jase-2011 Accurate measurements of a child's weight and height are critical to avoid over- or underestimation of the CA Z-score.*

The risk stratification of CAD adopted in the 2017 AHA guideline [1] and in the updated 2024 AHA guideline were based on formulas proposed in studies by the National Heart, Lung, and Blood Institute's (NHLBI) Pediatric Heart Network [32].

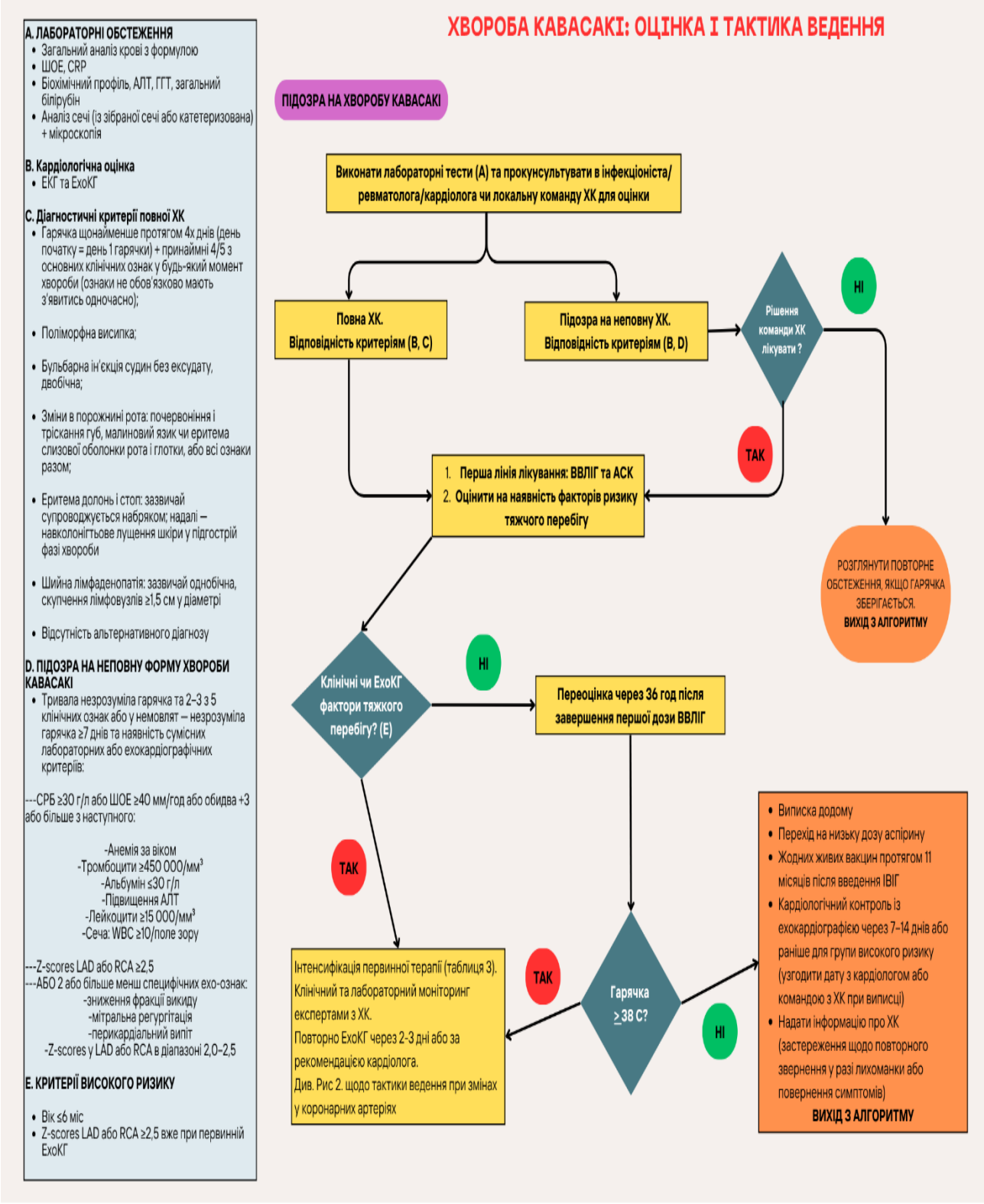
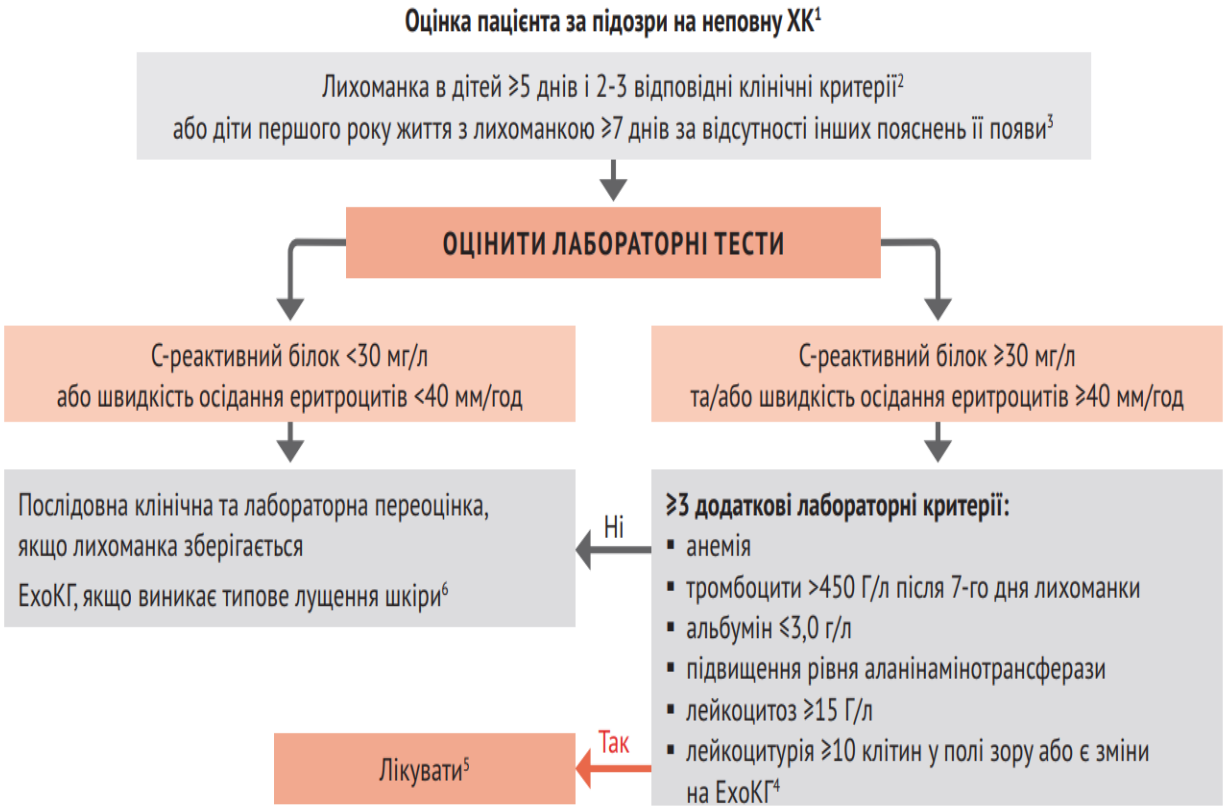


Figure 1. Diagnostic algorithm for the diagnosis and management of Kawasaki disease

Working group comment: *the working group considers it appropriate to provide information on the algorithm of actions in case of suspected incomplete HC.*

Algorithm of actions for incomplete Kawasaki disease



1A UC expert should always be consulted if necessary. 2 Clinical features of UC are listed in Table
3. Clinical features not typical of CD include exudative conjunctivitis, exudative pharyngitis, oral ulceration, bullous or vesicular rash, generalized lymphadenopathy, or splenomegaly. If these features are present, alternative diagnoses should be considered. 3 Children younger than 6 months may have prolonged fever without other criteria for CD. These children are at particularly high risk for coronary vascular anomalies.
4 Echocardiogram results are considered positive if one of the following 3 conditions is present: Z-scores (standardized score) >2.5 for the left anterior descending artery or right CA; CA aneurysms are present; or >3 of the following are present: decreased left ventricular function, mitral regurgitation, pericardial effusion, or Z-scores for the right or left anterior descending CA or right CA are 2-2.5.
5 If the EchoCG results are "positive", treatment should be carried out until the 10th day from the onset of fever or after 10 days if fever and signs of systemic inflammation (C-reactive protein, erythrocyte sedimentation rate) persist.
6 Peeling that begins below the nail bed of the fingers and toes is typical.

Echocardiography should not delay initiation of therapy, and normal echocardiography does not exclude the diagnosis of CD [1, 38]. In the presence of pathological changes, echocardiography is a useful adjunct to confirm the diagnosis. Normal echocardiography early in the first week of illness does not exclude the possibility of later development of AKA. Repeat echocardiography should be performed during hospitalization and before discharge in patients with high-risk clinical features or resistance to intravenous immunoglobulin (IVIG), defined as persistent or recurrent fever ≥36 hours after completion of the initial IVIG infusion. Body temperature, clinical status, and laboratory values should be closely monitored during hospitalization. In the event of a re-elevation of fever within a week of discharge

Table 1. Echocardiography imaging standards for patients with CD

Patient preparation	**Technical aspects of the assessment coronary arteries**	**High quality rating**	**Quantitative assessment**
Equipment 1. Usage sensor with maximum possible frequency 2. Dynamic recording video or digital digital cine	Left main coronary artery (LMCA): imaging techniques 1. Short axis at the level of the aortic valve (PSAX — *parasternal short axis* on a level AoV) 2. Parasternal long section of the left ventricle with an upper tangential slope (PLAX — *parasternal long axis of the left ventricle*) 3. Subcostal long axial section of the ventricles (*subcostal ventricular long axis*)	Availability aneurysm or thrombosis KA	CA damage by Z-scores (normalized to body surface area – BSA) 1. No lesion: Z-score <2 in all segments 2. Dilation only: Z-score from 2 to <2.5 3. Small aneurysm: Z-score ≥2.5 to <5 4. Medium aneurysm: Z-score ≥5 to <10 and absolute size <8 mm 5. Large or giant aneurysm: Z-score ≥10 or absolute size ≥8 mm It is advisable to repeat Echo CG more frequently in the acute phase in patients with CA lesions until their size stabilizes or before discharge - especially in patients with high-risk factors (age <6 months or baseline Z-score ≥2.5).
Sedation should be considered in the following cases: 1. Children aged <3 years 2. Non-contact or excited children who are not cooperative under examination time	Front descending branch left coronary artery (LAD): 1. Short axis at the level of the aortic valve (AoV) and the left ventricle (LV); distal part LAD	Violation regionally y short-lived myocardial infarction	Ventricular function 1. LV ejection fraction or measurement in M-mode (decrease systolic LV functions turns out approximately 20% of patients at the time of presentation and

	passes in front of the pulmonary valve (PV) 2. Parasternal long slice of the left ventricle with an upper tangential inclination (PLAX)		is associated with CA damage [33]. 2. End-diastolic volume or LV dimensions 3. End-systolic volume or LV dimensions 4. Diastolic function LV/RP 5. LV deformity
	Circumferential branch of the left coronary artery: 1. Short axis at the level of the aortic valve (PSAX) 2. Apical four-chamber view (apical 4-chamber) — lower view in the left atrioventricular groove		Availability or degree atrioventricular regurgitation
	Right coronary artery (RCA), proximal segment: 1. Short axis at the level of the aortic valve (PSAX) 2. Parasternal long slice of the left ventricle with a lower tangential slope (PLAX) 3. Subcostal coronal section in the right ventricular outflow tract (RVOT) region 4. Subcostal short-axis section at the level of the atrioventricular groove (SAX)		Availability and dimensions pericardial effusion
	PCA, middle segment: 1. Parasternal long slice of the left ventricle with a lower tangential slope (PLAX) 2. Apical four-chamber view (apical 4-chamber) 3. Subcostal long axial section of the left ventricle 4. Subcostal short-axis section at the level of the atrioventricular groove (SAX)		Aortic root dimensions (in more than 10% of patients with the disease Kawasaki observed Z-score aortic root >2)
	PCA, distal segment: 1. Apical four-chamber view (apical 4-chamber), lower view 2. Subcostal long axial section of the atria, lower view		
	Posterior descending artery: 1. Apical 4-chamber view, inferior view 2. Subcostal long axial section of the atria, lower view 3. Parasternal long slice with lower tangential inclination (PLAX) 4. Section in the plane of the posterior interventricular sulcus		

An echocardiogram should be performed urgently if there is no clear alternative diagnosis.

In patients without CAD at the time of admission, echocardiography should be repeated within 1–2 weeks after discharge, as a small proportion of patients may develop CAD during this period, and early detection allows for timely initiation of additional anti-inflammatory therapy. In patients who respond to anti-inflammatory therapy and have normal echocardiography at diagnosis and 1–2 weeks after discharge, the likelihood of developing CAD is extremely low.

A recent study showed that in this category of patients, 98.6% had normal echocardiographic results at 4–6 weeks of illness, suggesting that further cardiac surveillance could be discontinued unless new clinical indications arise [39]. The few patients (1.4%) who showed signs of new CAD within 4–6 weeks of follow-up after initially normal echocardiographic results all had CAD Z-scores <5, and the CAD changes were transient and normalized during the first year of follow-up. In patients at risk level 2 (CAD Z-score 2 to 2.5), follow-up is recommended 1–2 weeks after discharge and a repeat visit in 4–6 weeks if echocardiographic results, clinical status, or laboratory parameters remain abnormal after 1–2 weeks (Table 2). However, patients in whom CAD was not adequately visualized or in whom inflammatory changes have not regressed should be reexamined sooner than 4–6 weeks. In patients with a CA Z-score ≥2.5, it is advisable to repeat echocardiography at least twice a week during hospitalization until dilation resolves or aneurysm progression stops (Figure 2).

The maximum CA Z-score achieved during the course of the disease is the most reliable prognostic indicator and determines the AHA risk stratification and subsequent patient management (Table 2). Patients with a CA Z-score ≥2.5 should also have a pre-discharge echocardiogram and a follow-up echocardiogram within a week of discharge. The presence of CA dilation does not confirm or exclude structural damage to the arterial wall, whereas a documented anatomical aneurysm indicates morphological damage [40]. The Z-score alone does not determine the nature of the coronary artery damage.

Other echocardiographic investigations are listed in Table 1. Myocardial dysfunction with reduced ejection fraction is present in approximately 20% of patients at diagnosis and is associated with dilatation of the coronary arteries or aortic arch [41]. Deformation imaging techniques, including both ventricular and atrial deformation, are increasingly being used in CHD; however, the clinical utility and prognostic impact of these parameters are not yet fully established [42].

Key provisions:

1. Echocardiography remains the primary non-invasive imaging modality for assessment of CAs, and the accuracy of measuring their size is crucial for patients with CD.

2 Institutions should use the same formula to calculate Z-scores over time for the same patient; using different formulas may alter the classification of risk for CAD.

3. Accurate measurements of patient weight and height are critical for avoiding over- or underestimation of the Z-score of the CA.

4. The ACA classification defined in the 2017 AHA guideline is useful from an epidemiological point of view. However, the Z-score alone does not allow us to assess the nature of the damage to the wall of the coronary artery.

TREATMENT OF KAWASAKI DISEASE

Treatment of UC begins with identifying patients at standard and high risk at diagnosis. Patients at standard risk can receive therapy with intravenous immunoglobulin (IVIG) and aspirin. Patients at high risk may benefit from intensification of treatment with IVIG and additional anti-inflammatory therapy to reduce the risk of AKA. This section discusses: initial therapy for acute phase UC, treatment in the event of resistance to IVIG, intensification of initial therapy in high-risk patients, and additional approaches to the treatment of patients with refractory UC.

Working group comment:*international nonproprietary name of the medicinal product Aspirin is acetylsalicylic acid (ASA).*

According to the instructions for medical use, the drug with the international non-proprietary name acetylsalicylic acid is prescribed to patients over 18 years of age. The use of acetylsalicylic acid in children under 16 years of age may cause severe adverse reactions (including Reye's syndrome).

Initial therapy for acute UC

Intravenous human immunoglobulin (IVIG) at a dose of 2 g/kg body weight, administered over 8–12 hours, remains the standard of care for patients with acute phase CR to reduce inflammation. The duration of infusion may vary depending on the brand of IVIG used in a particular healthcare facility. Patients with persistent or recurrent fever lasting ≥36 hours after the completion of the initial IVIG infusion are defined as IVIG-resistant. IVIG is generally well tolerated. Hemolytic anemia is a dose-dependent complication of IVIG administration and occurs more frequently in patients with blood groups A, B, or AB [43, 44]. Recent data suggest that patients with

In obese patients, it is advisable to calculate the dose of IVIg based on lean body mass to reduce the risk of hemolytic anemia [44]. Another potential complication is aseptic meningitis, which is usually transient and without sequelae. All live vaccines, including measles, mumps, rubella, and varicella, should be postponed for 11 months after IVIg administration, as passively administered antibodies may reduce the efficacy of these live vaccines. It should be noted that the erythrocyte sedimentation rate (ESR) increases after IVIg infusion, so this indicator is not a reliable marker of active inflammation after infusion.

In the acute phase of Kawasaki disease, ASA is prescribed, but its antiplatelet effect may be inhibited by concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs). ASA is traditionally used in moderate (30–50 mg/kg/day) or high (80–100 mg/kg/day) doses as anti-inflammatory and antipyretic therapy until body temperature normalizes within 48–72 hours. After that, low doses of ASA (3–5 mg/kg/day once a day) are used to provide antiplatelet effect after fever subsides and continue to be taken for up to 6–8 weeks from the onset of the disease [1].

However, increasing evidence suggests that the use of moderate or high doses of ASA in the acute phase of the disease is not associated with improved outcomes in CA. Several retrospective cohort studies have found no difference in the incidence of ACA between patients receiving moderate or high doses of ASA [45, 46]. Two retrospective non-randomized cohort studies also found no difference in the incidence of ACA between patients receiving high or low doses of ASA in the acute phase [47, 48]. Furthermore, one retrospective study in Japan demonstrated that treatment without ASA in the acute phase of CC resulted in similar rates of ACA and resistance to IVLIG compared with medium-dose therapy [49]. Two meta-analyses have confirmed the absence of statistically significant differences in the incidence of AKA, resistance to IVLI, or length of hospital stay with different doses of ASA [50, 51]. A multicenter prospective open-label RCT is currently underway to compare the efficacy of moderate- and low-dose ASA in combination with IVLI in the acute phase of chronic hepatitis C [52].

In case of allergy or resistance to ASA, clopidogrel or dipyridamole may be used as an alternative therapy [1, 53]. Dual antiplatelet therapy (e.g., ASA plus clopidogrel) may be considered in patients with a coronary artery Z score ≥5, but this use is largely extrapolated from the experience of adult patients with atherosclerosis after coronary artery stenting in the context of myocardial infarction [54]. Future data should clarify the optimal dosing of ASA in the acute phase of CHD, as well as

the need for randomized controlled trials (RCTs) of dual antiplatelet therapy in patients with a coronary artery Z score ≥5.

Working group comment:*according to the instructions for medical use, the drug with the international non-proprietary name clopidogrel is prescribed to patients over 18 years of age, the drug with the international non-proprietary name dipyridamole is not recommended for children under 12 years of age.*

Table 2. Long-term treatment, thromboprophylaxis, and drug therapy for Kawasaki disease

Classes fication I equal risk in	Description coronary x arteries	Frequency observations after stabilization of the spacecraft in patient or normalization sizes at discharge: medical history; physical examination; ECG; Echocardiography	Diagnoses ka induced oh myocardium flax ischemia* (stressful tests)	Extended coronary visualization I	Antitrom bocitary therapy	Anticoagulation ulyantana therapy	Consultation tion with questions physical activity and
1 (Z-rating <2)	Absence damage KA in any which moment	1–2 weeks (consider possibility observation after 4–6 weeks, if visualization KA suboptimal or laboratory inflammatory markers are abnormal because 1–2 weeks); possible termination observation between 4 weeks and 1 year	Not shown	Not shown	Low ASA dose for 6 weeks, then to stop	Not shown	Consultation tion during each visit
2 (Z-rating 2–2.5)	If observes only expansion – it disappears for 6 weeks - 1 year	1–2 weeks (consider visit after 6 weeks if abnormal to decide stored through 1-2 weeks); 1 year; possible termination observation after 1 year, if symptoms disappear; spend reviews every 2–5 years, if the disease stored	Not shown	Not shown	Low ASA dose within 6 weeks; if KA normal through 6 weeks, then to stop	Not shown	Consultation tion during each visit

3 (Z-rating 2.5–<5)	3.1 Small aneurysm, current or persistent and	If during 1 week observed progressive expansion, then recommended thorough observation 1. once a week until the CA stabilizes; 6 weeks; 6 months; 12 months; annually	Examined every 3–5 years	Consider coronary KTA in 1 year as basic; can consider every 3–5 years	Low ASA dose	Not exposed	Consultation tion during each visit
	3.2 Small aneurysm, regressed to only expansion or to norms	Within 1 week; 6 weeks; 1 year; 5 years, possible cessation observation by conditions, what is stress-test and coronary CTA is normal	Examined every 5 years	Consider coronary AND through 1 year as base indicator; can consider, if there is induced ischemia	Reception low doses of ASA I will continue. they go to normal x sizes	Not shown	Consultation tion during each visit
4† (Z-rating 5–<10 and absolutely tny size <8 mm)	4.1: Average aneurysm, current or persistent and	Within 1 week (if progressive expansion, then recommended thorough observation 1 time per week to stabilization of the spacecraft); 6 weeks; 3 months; 6 months; 12 months; annually	Examined every 2–5 years	Consider coronary KTA in 1 year as base level; can consider every 2–5 years	Low ASA dose plus clopidogrel l	Not shown	Consultation tion during everyone; to consider limitation activity; self-restricted ntion
	4.2: Average aneurysm, regressed to small aneurysms	Within 1 week; 6 weeks; 6 months; 12 months; annually	Examined every 3–5 years	Consider coronary KTA in 1 year as base level; can to consider every 3–5 years	Low ASA dose	Not shown	Consultation tion during each visit
	4.3: Average aneurysm, regressed to norms or only expansion	Within 1 week; 6 weeks; 6 months; 12 months; every 2 years	Examined every 4–5 years	Coronary KTA in 1 year is possible consider as a weekend indicator, if available induced ischemia	Low ASA dose	Not shown	Consultation tion during each visit
5† (Z-rating ≥10 or	5.1: Big or gigantic aneurysm, current or	Within 1 week (if the extension progresses, recommended thorough observation 1 time	Examined every 6–12 months.	Consider possibility carrying out initial coronary KTA	Low ASA dose; double antithrombus ocytic therapy with	Warfarin, LMWH or PLA	Consult tation during each visit; limitation

absolutely tny size > 8 mm)	persistent and	on week to stabilization of the spacecraft); 6 weeks; 3 months; 6 months; 9 months; 12 months, then every 6–12 months		within 2–6 miss.; can to consider every 1–5 years, or carrying out invasive coronary angiography	clopidogrel lem can be considered		activity; self-restricted ntion
	5.2: Big or gigantic aneurysm, regressed to average aneurysms	Within 1 week (if the extension progresses, then recommended thorough observation 1 time per week to stabilization of the spacecraft); 6 weeks; 3 months; 6 months; 9 months; 12 months, then every 6–12 months	Examined every 2–5 years	Consider coronary KTA in 1 year as basic and repeat and every 2–5 years	Low ASA dose; double antithrombus ocytic therapy with clopidogrel lem can be considered	Can to consider version applied no warfarin, LMWH or DOAC‡	Consult tation during each visit; limitation activity; self-restricted ntion
	5.3: Big or gigantic aneurysm, regressed to small aneurysms	Within 1 week (if the extension, progresses then recommended thorough observation 1 time per week to stabilization of the spacecraft); 6 weeks; 3 months; 6 months; 9 months; 12 months, then annually	Examined every 3–5 years	Consider coronary KTA in 1 year as basic and repeat every 3–5 years	Low ASA dose; double antithrombus ocytic therapy with clopidogrel lem can be considered	Not shown	Consult tation during each visit; limitation activity; self-restricted ntion
	5.4: Big or gigantic aneurysm, regressed to norms or only dilations	During 1 week (if dilation, progresses then recommended thorough observation 1 time per week to stabilization of the spacecraft); 6 weeks; 3 months; 6 months; 9 months; 12 months, then every 1–2 years	Examined every 3–5 years	Consider coronary KTA in 1 year as base indicator, and repeat and every 3–5 years	Low ASA dose	Not shown	Consult tation during each visit; limitation activity; self-restricted ntion

CTA - CT angiography; DOAC - direct oral anticoagulant; and LMWH - low molecular weight heparin.
* If symptoms are present, stress testing may be performed earlier.
†Beta-blockers and statins may be considered.
‡Anticoagulation therapy may be considered in patients at risk of thrombosis (risk level 5.2). Lumbar narrowing may be associated with thrombosis, in which case anticoagulant therapy is warranted. When the trade-offs between thrombosis and bleeding risks are difficult to balance, consultation with a cardiac specialist may be helpful in developing a thromboprophylaxis regimen.

Treatment of resistance to IVLIG

Resistance to IVLIG is defined as persistent or recurrent fever lasting ≥36 hours after completion of the first IVLIG infusion [1]. Such

patients are at increased risk of developing AKA compared to those who responded to IVLIG treatment.

Various anti-inflammatory strategies with varying degrees of evidence have been studied for the treatment of resistance to IVLIG, including glucocorticosteroids (GCS), tumor necrosis factor alpha inhibitors (infliximab and etanercept), interleukin-1 inhibitors (anakinra), and cyclosporine (see Table 3).

Working group comment: *medicines with international The generic names of infliximab, etanercept, cyclosporine, and anakinra do not have indications for the treatment of CD in their instructions for medical use.*

Glucocorticosteroids

In Japan, risk scores for resistance to IVIG have been developed [55], but these scores have not demonstrated adequate predictive efficacy in North American cohorts [56]. In Japanese patients using the Kobayashi risk score, the RAISE (Randomized Controlled Trial to Assess Immunoglobulin Plus Steroid Efficacy for Kawasaki Disease; https://www.umin.ac.jp/ctr ; identifier: UMIN000000940) showed that the combination of IVLIG with prednisolone at a dose of 2 mg/kg per day for 5 days with subsequent gradual dose reduction orally resulted in a significantly lower incidence of CA lesions than IVLIG monotherapy (4 patients [3%] vs. 28 patients [23%]; risk difference 0.20; 95% CI: 0.12–0.28; P<0.0001) [57]. A follow-up study from RAISE, which included 724 patients with CD who were at high risk of resistance to IVLI according to the Kobayashi scale, also demonstrated that IVLI therapy in combination with prednisolone reduced the incidence of IVLI resistance and reduced the incidence of CA to 5.9% according to American Heart Association (AHA) criteria and to 3.8% according to Japanese criteria [58]. Although the results of the RAISE study are convincing, they have not yet been confirmed in non-Japanese populations.

Infliximab and etanercept

The KIDCARE trial (Kawasaki Disease Comparative Effectiveness; https://www.clinicaltrials.gov; identifier: NCT03065244) compared the efficacy of infliximab (10 mg/kg intravenously), a monoclonal antibody to tumor necrosis factor alpha (TNF-α), with re-infusion of IVLIG in patients refractory to initial IVLIG. The results of this trial showed that infliximab resulted in faster resolution of fever, reduced need for additional therapy, less severe anemia, and shorter length of hospital stay compared with re-infusion of IVLIG [59]. Since patients who had undergone initial intensive care were not included in the study,

therapy for AKA, statistical power to detect differences in clinical outcomes from AKA was limited.

Etanercept, a soluble TNF-α receptor antagonist, was studied as an adjunctive therapy to IVLIG in a multicenter, double-blind, randomized, placebo-controlled trial to evaluate its efficacy in reducing the incidence of IVLIG resistance [60]. Although the primary analysis did not show a significant difference in IVLIG resistance between the etanercept and placebo groups, a secondary analysis found a lower rate of IVLIG resistance in the etanercept group among children older than 1 year. In addition, patients with baseline CA dilation had less progression of this lesion.

Anakinra

Genes involved in the interleukin-1 signaling pathway are highly upregulated in patients with UC in the acute phase of the disease, and interleukin-1 blockers have been considered as potential therapies for this condition [61]. An open-label phase II study in 16 patients with IVIG-resistant UC demonstrated that anakinra, a recombinant interleukin-1β receptor antagonist, at doses of 2 to 6 mg/kg/day subcutaneously was well tolerated and associated with resolution of fever [62].

Cyclosporine

Cyclosporine is a selective T-cell inhibitor that blocks the calcium-dependent calcineurin–NFAT signaling pathway (*nuclear factor of activated T cells. nuclear factor of activated T cells*), is also being studied as a treatment option for CD. Polymorphisms in genes related to calcium pathways and calcium channels are risk factors for CD susceptibility, highlighting the importance of the calcineurin–NFAT pathway[63]. In the placebo-controlled RCT KAICA (*Kawasaki Disease Study to Assess the Efficacy of Immunoglobulin Plus Cyclosporine A*; identifier: JMA-ILA00174) Japanese patients with high risk of resistance to IVLIG according to the Kobayashi scale were randomly assigned to receive either IVLIG in combination with cyclosporine (5 mg/kg daily for 5 days) or IVLIG alone [64]. Although the cyclosporine group had a higher incidence of treatment resistance, the incidence of CA at week 2 was lower in the IVLIG + cyclosporine group compared with the IVLIG alone group. However, this difference was not maintained at weeks 1 and 4. The incidence of adverse events did not differ between groups. However, the cyclosporine group had a higher incidence of relapse requiring additional therapy. In North America, a longer course of cyclosporine is usually used (Table 3). During treatment with cyclosporine, oral administration of magnesium (e.g., in the form of magnesium protein complex) is important to prevent hypomagnesemia. The brand name should also be considered.

cyclosporine, as absorption may vary significantly between generic forms of the drug.

Figure 2. Management of progressive coronary artery aneurysms in chronic coronary artery disease in the acute phase(Addendum to the items indicated in the orange block on**Figure 1).**

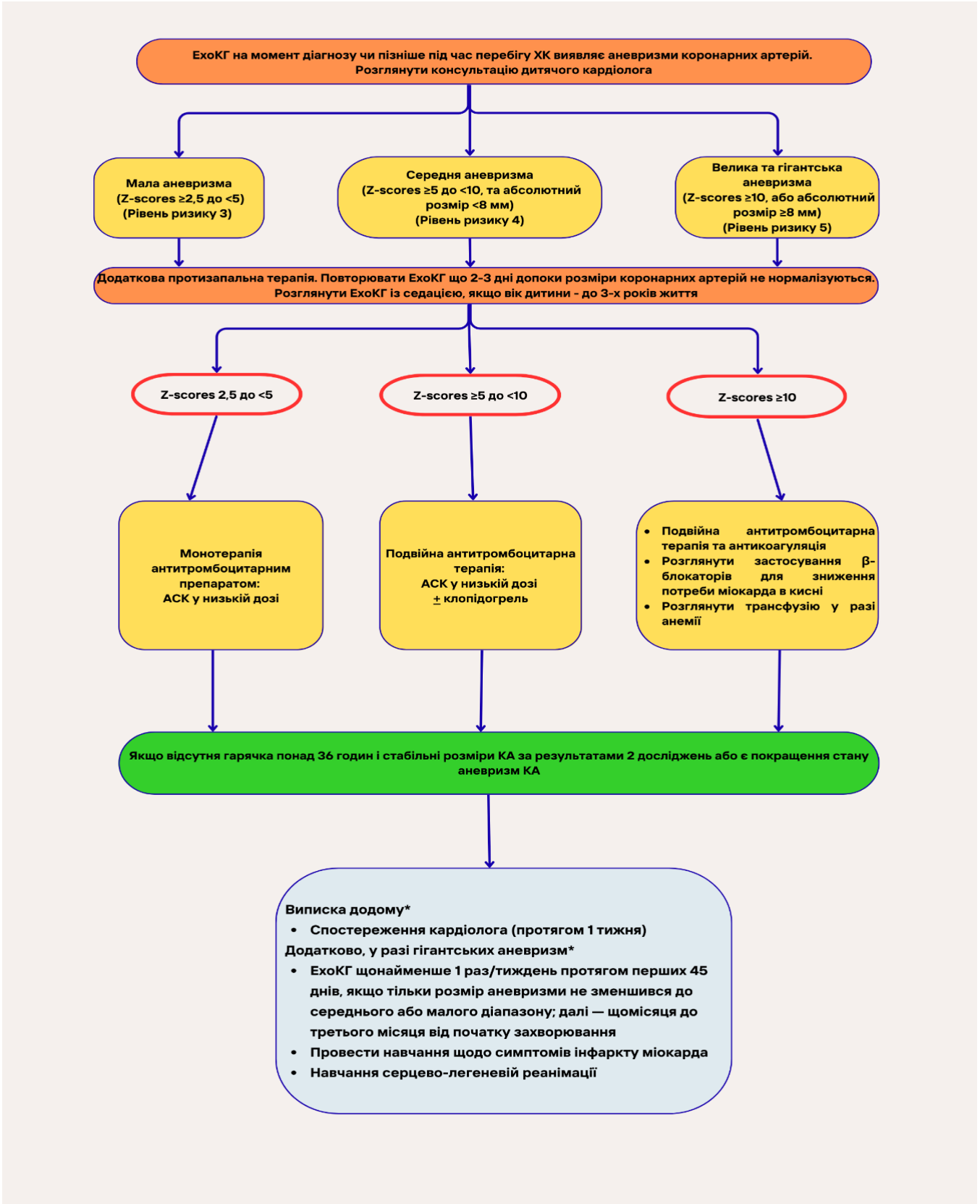

ЕхоКГ на момент діагнозу чи пізніше під час перебігу ХК виявляє аневризми коронарних артерій. Розглянути консультацію дитячого кардіолога
Мала аневризма (Z-scores ≥2,5 до <5) (Рівень ризику 3)
Середня аневризма (Z-scores ≥5 до <10, та абсолютний розмір <8 мм) (Рівень ризику 4)
Велика та гігантська аневризма (Z-scores ≥10, або абсолютний розмір ≥8 мм) (Рівень ризику 5)
Додаткова протизапальна терапія. Повторювати ЕхоКГ що 2-3 дні допоки розміри коронарних артерій не нормалізуються. Розглянути ЕхоКГ із седацією, якщо вік дитини - до 3-х років життя
Z-scores 2,5 до <5
Z-scores ≥5 до <10
Z-scores ≥10
Монотерапія антитромбоцитарним препаратом: АСК у низькій дозі
Подвійна антитромбоцитарна терапія: АСК у низькій дозі ± клопідогрель
Подвійна антитромбоцитарна терапія та антикоагуляція
Розглянути застосування β-блокаторів для зниження потреби міокарда в кисні
Розглянути трансфузію у разі анемії
Якщо відсутня гарячка понад 36 годин і стабільні розміри КА за результатами 2 досліджень або є покращення стану аневризм КА
Виписка додому*
Спостереження кардіолога (протягом 1 тижня)
Додатково, у разі гігантських аневризм*
ЕхоКГ щонайменше 1 раз/тиждень протягом перших 45 днів, якщо тільки розмір аневризми не зменшився до середнього або малого діапазону; далі — щомісяця до третього місяця від початку захворювання
Провести навчання щодо симптомів інфаркту міокарда
Навчання серцево-легеневій реанімації

Table 3.Initial therapy, treatment intensification in patients with resistance to IVLIG or high risk in HC, as well as additional therapy options for refractory disease

Medicinal means	Description	Dose	Additional medical fastening
Initial treatment			
INFLUENCE	Mixture polyclonal their immunoglobe lazy	IV, 2 g/kg over 8–12 hours; consider slower administration for shock in HC or myocardial dysfunction; in obese patients consider dosage with taking into account lean body mass	The risk of developing hemolytic anemia in patients with obesity, if not ideal lean body mass is used
ASK	Acetylsalicylic acid tsylvan acid	Oral, 30–50 mg/kg/day*, every 6 hours; oral 3–5 mg/kg/day after fever subsides within 48–72 hours; * (used in many centers, although a prospective study is currently underway to determine the optimal dosage)	Should not be prescribed together with NSAIDs, as efficacy is reduced; for patients who cannot use aspirin, for example, with glucose-6-phosphate dehydrogenase deficiency phosphate dehydrogenase or acute flu-like illness, can use alternative class antiplatelet drugs.
Intensification of treatment in patients with resistance to IVLIG or high risk for HC			
Prednisolone	Corticosteroids roids in accordance to protocol RAISE	IV, 2 mg/kg/day, divided every 8 hours for 5 days (maximum 60 mg/day) during hospitalization; then oral prednisolone 2 mg/kg/day divided every 8 hours; slow dose reduction for 15 days (maximum 30 mg/ dose) after normalization of CRP levels	Famotidine is used to prevent stomach ulcers.
Methylprednisolone ash	Corticosteroids roids in accordance with north-east Erican we	IV, 2 mg/kg/day, divided every 12 hours for 5 days (maximum 60 mg/day) during hospitalization; then oral prednisone 2 mg/kg/day, divided every 12 hours; after CRP <1 g/L GCS	Famotidine is used to prevent stomach ulcers.

	research pits	gradually reduced over 2–4 weeks, reducing the dose by half every 5 days ***Working group comment:****on the moment of development of this CN medicinal product with an international non-proprietary name* *Prednisone in dosage form for oral administration is not registered in Ukraine.*	
Infliximab	Monoclone flax antibody against TNFα	IV, 10 mg/kg, administered over 2 hours	
Etanercept	Soluble receptor, What is connected with TNFα and TNFβ	Subcutaneous, 0.8 mg/kg once weekly × 3 doses	
Additional treatment for refractory disease			
Cyclospores n	Inhibitor calcineurin-NFAT way	Oral, 5 mg/kg/day, divided every 12 hours; monitor serum level 2 hours after third dose (target level 300–600 ng/mL); begin gradual dose reduction (10% every 3 days), then normalization of body temperature, clinical improvement, and decrease in CRP level ≤1.0 g/l or after 10 days of therapy, whichever comes later	You should use Neoral (not generic) cyclosporine) through Absorption variability; supplemental magnesium-protein complex (133 mg) should be taken once daily while taking cyclosporine for prevention of hypomagnesemia; should not be combined with statins, as both drugs are metabolized by the enzyme system cytochrome P450, which may increase the risk of side effects
Anakinra	Recombinant tny antagonist receptor interleukin y-1β	IV or SC, 10 mg/kg/day (IV is preferred) divided every 12 hours compared to subcutaneous) during hospitalization; gradual dose reduction in preparation for discharge (5 mg/kg per day	

		within 1 day, then the drug is discontinued)	
Second dose **INFLUENCE**		IV, 2 g/kg, administered over 8–12 hours	Increased risk hemolytic anemia in patients with blood groups A, B and AB
Cyclophosphine **copper**	Alkylating agents block replication DNA	IV, 10 mg/kg/day in 1 or 2 divided doses	Sufficient is needed hydration; rheumatologist consultation recommended

**Used in many centers, although a prospective study is currently underway for determining the optimal dosage.*

Working group comment:*in the Table3 the trade name of the medicinal product with the international non-proprietary name cyclosporine - Neoral is used, in accordance with the text of the prototype. The medicinal product with the international non-proprietary name cyclophosphamide, according to the instructions for its medical use, has no indications for the treatment of HC. Magnesium citrate - a protein complex containing 133 mg of magnesium is not registered in Ukraine as a medicinal product.*

Intensification of initial therapy in high-risk patients Intensification of initial therapy (dual therapy) may be beneficial for patients with high-risk UC disease (**baseline AKA Z-score** ≥2.5, babies**age <6 months**, or are in the high-risk category according to the Son score). In 18% of infants <6 months of age with normal echocardiography at diagnosis, within 8 weeks of diagnosis, the Z-score increased to ≥2.5, despite timely treatment with IVLI [25]. These findings were confirmed in a large cohort of patients in Latin America: in which infants <6 months of age who received IVLI within the first 10 days of illness were 5 times more likely to develop a Z-score ≥2.5 than those aged <6 months who received IVLI within the first 10 days of illness.
> 6 months [26]. Treatment strategies for children with AKA in the acute phase of the disease are shown in Fig. 3. These treatments include: corticosteroids, tumor necrosis factor alpha inhibitors (e.g., infliximab and etanercept), interleukin-1 inhibitors (e.g., anakinra), and cyclosporine (Table 3) [60, 64–67]. Although short-term safety and pharmacokinetic data are available in patients with CD, allowing for more precise dosing regimens, the efficacy of these approaches has not yet been confirmed by RCTs.

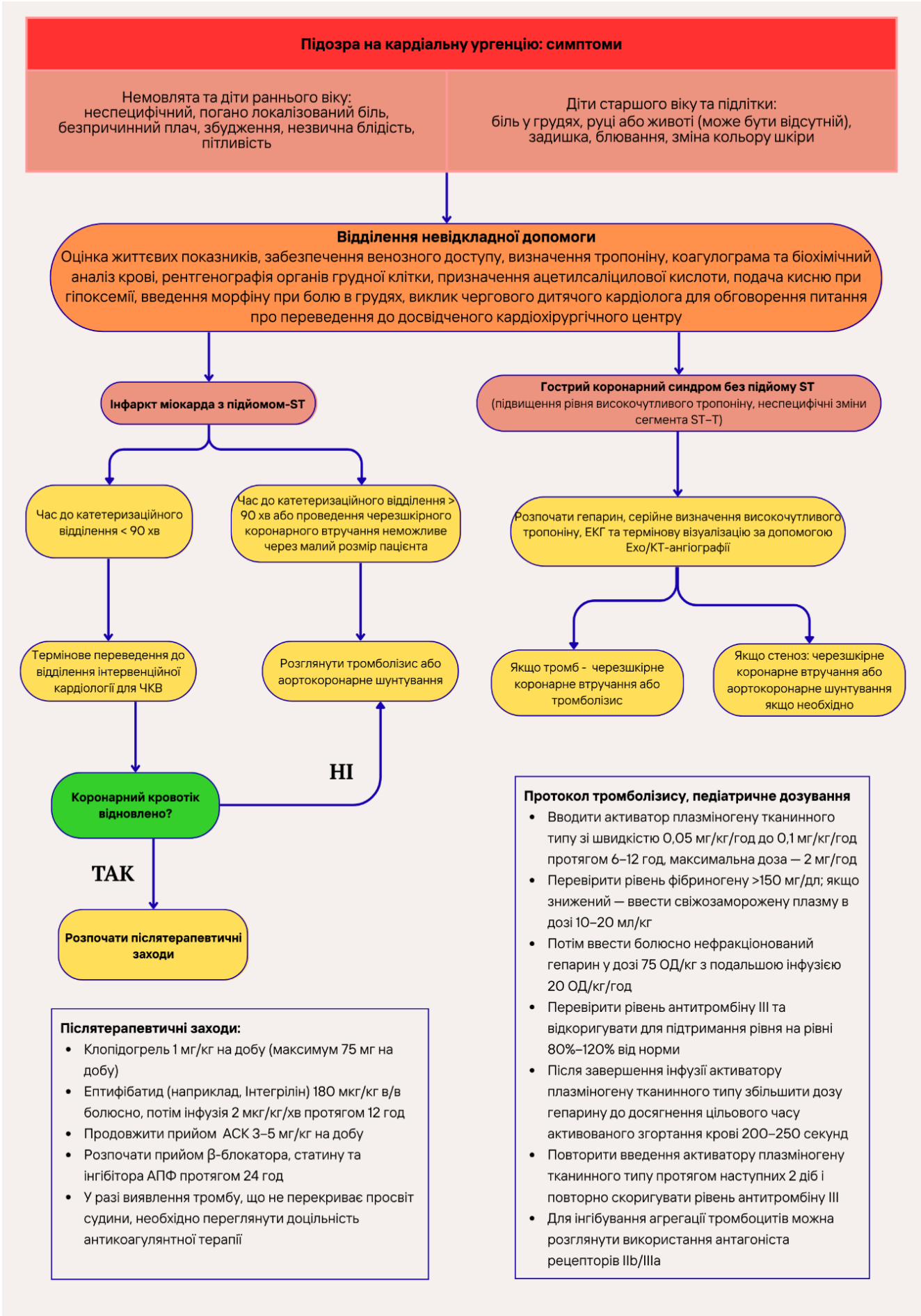
Working group comment:*inIn 2021, the results of a study by Japanese authors were published, evaluating risk models for CD to predict AKA in the Japanese population. The Son score had insufficient sensitivity and good specificity in a Japanese cohort of CD patients (Koichi Miyata, Masaru Miura,*

Tetsuji Kaneko et all. Evaluation of a Kawasaki Disease Risk Model for Predicting Coronary Artery Aneurysms in a Japanese Population: An Analysis of Post RAIS. J Pediatr. 2021 Oct:237:96-101.e3. doi: 10.1016/j.jpeds.2021.06.022. Epub 2021 Jun 18. DOI: 10.1016/j.jpeds.2021.06.022. In 2024, the results of Italian researchers (a single-center study) were published. The Son score showed an association with AKA at one- and two-month follow-up, but not at six-month follow-up. The authors concluded that in the European population, the Son score should be validated in larger European samples and the observation time should be increased to 8 weeks (Adriano La Vecchia, Rita Stracquadaino, Lucia Mauri. Risk factors and scores for prediction of coronary artery aneurysms in Kawasaki disease: a European monocentric study. BMC Pediatr. 2024 Feb 23;24:139. doi: 10.1186/ s12887-024-04623- 3

Corticosteroids and infliximab

Several retrospective studies have compared the progression of ACA in patients treated with IVLI alone with those treated with dual therapy (IVLI plus corticosteroids or infliximab). Among a group of patients with HC and a Zscore ≥2.5 on baseline echocardiography treated at three different centers with different approaches to ACA therapy, those treated with infliximab or corticosteroids in addition to IVLI had less progression of ACA size (increased Z-score > 1 standard deviation unit) compared to those who received only IUIG [10]. In addition, two other retrospective studies of infliximab (10 mg/kg) or methylprednisolone followed by oral prednisolone in combination with IVLIG demonstrated that intensification of primary therapy was associated with a higher likelihood of AKA regression in patients with AKA who had a Z-score ≥2.5 at diagnosis [68,69]. Given the retrospective nature of the studies and the small number of patients, these results should be interpreted with caution; larger prospective randomized trials are needed.

Figure 3. Management scheme for patients with Kawasaki disease and acute myocardial infarction*Adapted fromBrogan et al. [83]. © 2020 The Authors. Published on behalf of the BMJ Group. This article is open access and is licensed under the Creative Commons Attribution-NonCommercial License, which permits use, distribution, and reproduction in any format, provided the original source is properly cited and the use is non-commercial.* ***Abbreviation:*** *CT – computed tomography, ASA – acetylsalicylic acid, ACE – angiotensin converting enzyme CABG – coronary artery bypass grafting; IV – intravenous; NSTE-ACS – non-ST segment elevation acute coronary syndrome; PCI – percutaneous coronary intervention; tPA – tissue activator plasminogen.*


Підозра на кардіальну ургенцію: симптоми
Немовлята та діти раннього віку: неспецифічний, погано локалізований біль, безпричинний плач, збудження, незвична блідість, пітливість
Діти старшого віку та підлітки: біль у грудях, руці або животі (може бути відсутній), задишка, блювання, зміна кольору шкіри
Відділення невідкладної допомоги
Оцінка життєвих показників, забезпечення венозного доступу, визначення тропоніну, коагулограма та біохімічний аналіз крові, рентгенографія органів грудної клітки, призначення ацетилсаліцилової кислоти, подача кисню при гіпоксемії, введення морфіну при болю в грудях, виклик чергового дитячого кардіолога для обговорення питання про переведення до досвідченого кардіохірургічного центру
Інфаркт міокарда з підйомом-ST
Гострий коронарний синдром без підйому ST
(підвищення рівня високочутливого тропоніну, неспецифічні зміни сегмента ST–T)
Час до катетеризаційного відділення < 90 хв
Час до катетеризаційного відділення > 90 хв або проведення черезшкірного коронарного втручання неможливе через малий розмір пацієнта
Розпочати гепарин, серійне визначення високочутливого тропоніну, ЕКГ та термінову візуалізацію за допомогою Ехо/КТ-ангіографії
Термінове переведення до відділення інтервенційної кардіології для ЧКВ
Розглянути тромболізис або аортокоронарне шунтування
Якщо тромб - черезшкірне коронарне втручання або тромболізис
Якщо стеноз: черезшкірне коронарне втручання або аортокоронарне шунтування якщо необхідно
НІ
Коронарний кровотік відновлено?
ТАК
Розпочати післятерапевтичні заходи
Післятерапевтичні заходи:
• Клопідогрель 1 мг/кг на добу (максимум 75 мг на добу)
• Ептифібатид (наприклад, Інтегрілін) 180 мкг/кг в/в болюсно, потім інфузія 2 мкг/кг/хв протягом 12 год
• Продовжити прийом АСК 3–5 мг/кг на добу
• Розпочати прийом β-блокатора, статину та інгібітора АПФ протягом 24 год
• У разі виявлення тромбу, що не перекриває просвіт судини, необхідно переглянути доцільність антикоагулянтної терапії
Протокол тромболізису, педіатричне дозування
• Вводити активатор плазміногену тканинного типу зі швидкістю 0,05 мг/кг/год до 0,1 мг/кг/год протягом 6–12 год, максимальна доза — 2 мг/год
• Перевірити рівень фібриногену >150 мг/дл; якщо знижений — ввести свіжозаморожену плазму в дозі 10–20 мл/кг
• Потім ввести болюсно нефракціонований гепарин у дозі 75 ОД/кг з подальшою інфузією 20 ОД/кг/год
• Перевірити рівень антитромбіну III та відкоригувати для підтримання рівня на рівні 80%–120% від норми
• Після завершення інфузії активатору плазміногену тканинного типу збільшити дозу гепарину до досягнення цільового часу активованого згортання крові 200–250 секунд
• Повторити введення активатору плазміногену тканинного типу протягом наступних 2 діб і повторно скоригувати рівень антитромбіну III
• Для інгібування агрегації тромбоцитів можна розглянути використання антагоніста рецепторів IIb/IIIa

Working group comment:*according to the instructions for medical use of a medicinal product with the international non-proprietary name eptifibatide – the safety and effectiveness of its administration to children have not been studied.*

Figure 3 shows the trade name of the medicinal product with the international non-proprietary name eptifibatide - Integrilin, according to the information provided in the prototype.

Anakinra

A phase I/IIa dose-escalation study of anakinra (2–11 mg/kg/day) in 22 patients with acute phase HC and AKA demonstrated that both intravenous and subcutaneous administration of anakinra are safe in infants and children [66]. Intravenous administration every 8–12 hours during hospitalization for acute phase HC may provide sustained blood concentrations and avoid frequent subcutaneous injections. Although anakinra is well tolerated and is considered a potential treatment option for patients with AKA, there are currently no data on its efficacy in patients with coronary artery disease.

Cyclosporine

Cyclosporine was used in patients with AKA, which is appropriate because gene expression studies in post-mortem KA tissues from patients with CD have revealed increased transcription associated with cytotoxic T cells, the activity of which can be inhibited by cyclosporine [70].

Shock in Kawasaki disease

HC accompanied by hypotension, inadequate perfusion, or myocardial dysfunction is described as shock syndrome in HC. This form is characterized by a higher frequency of elevated CRP, hypoalbuminemia, and thrombocytopenia compared with HC without shock [16,71,72].

Hemodynamic instability usually improves rapidly after the administration of IVLI. Given the increased risk of IVLI resistance and CA damage, it is appropriate to consider intensifying the initial IVLI therapy by adding a second anti-inflammatory agent.

Working group comment:*the members of the working group consider it appropriate to provide to the CN information on the symptoms and laboratory signs of another severe rare complication of CD - hemophagocytic lymphohistiocytosis (one of the varieties of macrophage activation syndrome).*

Clinical and laboratory features of hemophagocytic lymphohistiocytosis (HLH)

(Table adapted from Henter JI. Hemophagocytic Lymphohistiocytosis. N Engl J Med. 2025 Feb 6;392(6):584-598. doi: 10.1056/NEJMra2314005. PMID: 39908433)

	Sign	*Threshold value*
1.	*Fever*	*≥38.5°C*
2.	*Splenomegaly*	*≥2 cm below the costal margin*
3.	*Cytopenia*	*≥2 of the following cell lines*
	Hemoglobin	*<90 g/l (in newborns <100 g/l)*
	Platelets	*<100 × 10^9/l*
	Neutrophils	*<10^9/l*
4.	*Hypofibrinogenemia or hypertriglyceridemia*	*Fibrinogen≤1.5 g/l or triglycerides ≥3.0 mmol/l*
5.	*Hyperferritinemia*	*≥500 µg/L*
6.	*Hemophagocytosis*	*Bone marrow, other tissues*
7.	*Increased level soluble CD25‡*	*≥2400 U/ml*

The HLH-2004 diagnostic criteria were revised in 2024 by the Histiocytosis Society. According to the HLH-2004 criteria, at least five of the eight criteria must be met to make the diagnosis. In the revised criteria, natural killer (NK) cell activity has been removed, and five of the seven remaining criteria must be met to make the diagnosis.

HLH – hemophagocytic lymphohistiocytosis

‡ Soluble CD25 is also known as soluble interleukin-2 receptor α

ADDITIONAL THERAPY FOR AKA

Cyclophosphamide

In patients with giant aneurysms that continue to progress despite IVIG and other adjunctive NSAIDs, cyclophosphamide, an alkylating agent that blocks DNA replication and is used in patients with CD who are refractory to multiple prior therapies, may be considered. [73] It is usually administered in collaboration with pediatric rheumatologists. Patients should be adequately hydrated during cyclophosphamide therapy.

Statins

Statins have pleiotropic, antioxidant, and anti-inflammatory properties that contribute to the maintenance of endothelial cell homeostasis and block endothelial to mesenchymal transformation, a process that may play a role in the pathogenesis of acute phase CR. In a Phase I/IIa study of atorvastatin in children aged 2 years and older with acute CR and a Z-score ≥2.5, 34 patients were treated for up to 6 weeks in a dose-escalation study with atorvastatin from 0.125 to 0.75 mg/kg/day [74]. Atorvastatin was well tolerated

all patients, and 18 of them received treatment at the highest dose without any side effects. Gene expression profiling showed that cultured endothelial cells incubated with serum from patients with CD who received IVLIG, infliximab, and atorvastatin demonstrated improved endothelial function and reduced inflammatory markers compared with the control group (IVLIG + infliximab without statins) [75]. However, to date, no RCT has tested whether the use of statins in the acute phase of CD improves clinical outcomes, so this remains a promising area for further research.

Working group comment:*medicinal product with international non-proprietary use The drug called atorvastatin, according to the instructions for its medical use, is not prescribed to children under 10 years of age.*

Anticoagulant therapy for coronary artery aneurysms

Patients with large ACAs are at risk of CA luminal thrombosis in both the acute and chronic phases of the disease. Such patients are traditionally prescribed antiplatelet therapy (usually ASA at a dose of 81 mg daily or dual antiplatelet therapy - ASA + clopidogrel) and anticoagulant therapy - warfarin or low molecular weight heparin (LMWH).

Working group comment:*according to the instructions for medical The use, safety and efficacy of the medicinal product with the international non-proprietary name enoxaparin (low molecular weight heparin) in children have not been established.*

In this update, compared to the 2017 AHA Guidelines, anticoagulation therapy may be considered in patients with large or giant aneurysms that have regressed to medium-sized aneurysms and may be at risk for thrombosis (risk level 5.2). Lumbar reduction may be associated with thrombosis, in which case anticoagulation therapy is indicated. The increased risk of bleeding with anticoagulation therapy, particularly with triple therapy, should be weighed clinically, and consultation with a specialist in the treatment of CHD may be helpful in developing a thromboprophylaxis regimen.

A prospective registry study showed that warfarin and LMWH are equivalent in preventing thrombosis in large ACAs after HC [76]. Despite adequate clinical efficacy, both approaches have tolerability issues, particularly bleeding complications and ease of administration are concerns. Warfarin is difficult to treat in many children, with international normalized ratios in the target range.

range in only two-thirds of cases, and twice-daily LMWH injections can be difficult [77]. Direct oral anticoagulants (DOACs) are a potential alternative for thromboprophylaxis. They are characterized by low rates of clinically significant bleeding and thrombosis, convenient dosing (once or twice daily orally, depending on body weight), and minimal laboratory monitoring. [78,79] In addition, they have few drug and food interactions, making them attractive for use in pediatrics. In the international 3-month RCT ENNOBLE-ATE (Edoxaban for Prevention of Blood Vessels Being Blocked by Clots in Children at Risk Because of Cardiac Disease; NCT03395639), edoxaban was found to cause treatment-emergent adverse events in 46.8% of patients (51 of 109), compared with 41.4% (24 of 58) in the standard anticoagulant treatment group [78]. In the one-year apixaban study SAXOPHONE (*Safety of Apixaban on Pediatric Heart Disease on the Prevention of Embolism*; NCT02981472) in children with cardiac disease, apixaban was shown to be safe and well tolerated, with no thromboembolic events in patients with HC (HC was 14% of the 192 study participants) [80]. For severe bleeding in patients receiving DOACs, reversal agents such as prothrombin concentrates and the antidote andexanet alfa are available [81]. Further data on the safety and efficacy of DOACs in patients with HC may be obtained from post-marketing surveillance and require additional studies.

Working group comment:*according to the instructions for medical use of medicines with international non-proprietary names edoxaban, apixaban (direct oral anticoagulants)—The effectiveness and safety of their use in children (under 18 years of age) have not been established.*

At the time of development of this Clinical Guideline, the medicinal product with the international non-proprietary name andexanet alfa was not registered in Ukraine.

Key provisions:

1. Intensification of primary therapy by adding anti-inflammatory therapy (dual therapy) may be beneficial for patients with CD who are at high risk.
2. Patients with large ACAs require a combination of antiplatelet and anticoagulant therapy.
3. Newer POACs are not as dependent on vitamin K as warfarin, and do not require regular therapeutic monitoring, typical of warfarin or LMWH.
4. New POACs may be a more convenient and safer alternative compared to warfarin or LMWH.

5. To confirm the safety and efficacy of DOACs in patients with Further research is needed on HC.

TACTICS FOR MYOCARDIAL INFARCTION

The risk of myocardial infarction (MI) in patients with CHD and ACA is highest within the first 2–3 months after disease onset [82]. Although the risk of MI decreases after 2 years from disease onset, patients with large or giant ACA remain at constant risk of ischemia throughout their lives [1, 82–85]. Acute MI is a medical emergency [11, 82, 86, 87]. Its management is divided according to the presence of ST-segment elevation: ST-segment elevation MI (STEMI): results from sudden complete occlusion of a segment of the coronary artery, resulting in transmural ischemia with myocardial damage or necrosis [54]. Non-ST-segment elevation acute coronary syndrome (NSTE-ACS): includes chest pain, elevated troponin levels, and nonspecific ST-segment and T-wave changes on the ECG. This condition indicates a mismatch between myocardial oxygen demand and blood flow, which causes damage to the heart muscle, but without the extensive necrosis characteristic of STEMI [54].

Working group comment:*treatment of acute coronary syndrome in Ukraine is carried out in accordance with industry standards in the field of healthcare.*

The treatment of children with CHD who experience first-time ischemia requires an urgent and coordinated response from a multidisciplinary cardiology team, including: interventional cardiologists (pediatric and adult), cardiologists, and cardiac surgeons — both pediatric and adult [29, 54, 82, 83].

The symptoms of acute coronary syndrome in patients with CHD may differ from the classic manifestations of MI in adults with atherosclerosis [82, 83]. In infants and young children, symptoms are often nonspecific: poorly localized pain, incomprehensible crying, restlessness, unusual pallor, sweating [82, 83]. In older children, the following may be observed: pain in the chest, arm, or abdomen, shortness of breath, vomiting, and skin discoloration [82, 83]. Treatment strategies presented in**Rice.3**, extrapolated from adult guidelines for coronary revascularization and expert consensus [54, 82, 83].

If a patient with STEMI is transported to a cardiac catheterization laboratory within 90 minutes of an experienced interventional cardiologist, percutaneous coronary intervention (PCI) can be performed. If intervention is not possible, medical thrombolytic therapy is recommended. This is especially important in very young children, as there are no appropriate catheter sizes for performing PCI in infants for acute MI [29]. NSTE-ACS (non-ST-segment elevation MI) can progress to STEMI, especially in the first months after the onset of CHD. Antiplatelet and anticoagulant therapy are prescribed after acute MI.

Anticoagulant therapy. β-blockers, statins, angiotensin-converting enzyme (ACE) inhibitors may also be considered [29, 54].

Key provisions:

1. The risk of MI in patients with HC and ACA is highest during the first 2–3 months after the onset of the disease.

2. Acute coronary syndrome in patients with CH may manifest different from the classic symptoms of MI in adults with atherosclerosis.

3. Medical institutions that monitor patients with COPD and giant AKAs, should have a multidisciplinary cardiology team and an approved protocol for responding to serious cardiovascular complications.

LONG-TERM MANAGEMENT OF PATIENTS WITH CHD

Long-term management of patients with CHD depends on the extent of CA involvement, taking into account the maximum Z-score achieved during the acute phase of the disease. Patients are stratified by risk based on the maximum CA size and the associated Z-score. The main goals of long-term follow-up are to prevent thrombosis and MI, and to provide advice on optimal cardiovascular health. CA dilation usually occurs early in the acute phase of CHD, with maximum CA size achieved by the second or third week of illness. In some patients, the increase in CA diameter may persist for up to 6 weeks after illness, and in particularly severe cases (rarely) for more than 2 months.

Patients with persistent AKA, defined as a Z-score ≥2.5 after 6 weeks, are considered to have long-term arterial damage [1, 29]. However, the level of risk for adverse cardiac events and the need for further follow-up are variable and should be determined based on current scientific evidence. Since the publication of the 2017 AHA Guidelines, a number of studies have been conducted to assess the risk of adverse cardiac events and regression of AKA.

Several recent studies have shown that in patients with small ACAs, the internal lumen of the CA usually normalizes over time, and the risk of adverse cardiac events is almost zero. In a large registry study of 1651 patients, normalization of the CA diameter was recorded in 99 ± 4% of patients with small ACAs and in 92 ± 1% of patients with medium ACAs during 10 years of follow-up. In addition, no adverse cardiac events occurred in patients with a maximum Z-score of CA <10 [14]. In a 2018 Japanese multicenter retrospective cohort study involving 1006 patients, the 10-year coronary event-free survival was: for patients with small ACAs — 100% in boys and girls, for medium ACAs — 94% in boys and 100% in girls [12]. A large number of other smaller studies in different populations have demonstrated similar results, including regression of small and medium ACAs.

in most patients and with extremely rare cardiac complications [11]. These data suggest that in patients with small ACAs, the frequency of visits and examinations can be reasonably reduced (Table 2) [14].

Visualization monitoring

Imaging monitoring of CHD should be individualized based on the presence and extent of CA involvement, from maximal to current CA involvement, and the rate of CA size change and ventricular function. Transthoracic echocardiography remains the primary imaging modality for monitoring CHD, especially in childhood. However, it is less reliable in older children due to poor acoustic window quality. Its sensitivity for detecting distal CAD is lower than that of computed tomography angiography (CTA) [88]. Transesophageal echocardiography may be used in adolescents and adults with CHD if visualization through transthoracic acoustic windows is poor (e.g., obesity or pulmonary artifacts).

Enhanced coronary imaging using coronary CTA, cardiac magnetic resonance imaging (MRI), or invasive coronary angiography are important tools for surveillance in HC.

Coronary CT angiography

Coronary CTA allows visualization of all segments of the coronary tree, reliably assessing ACA, thrombosis, and detecting CA stenoses (≥50%) in patients with CHD [89, 90]. CTA has a higher spatial resolution than cardiac MRI for detecting distal CA lesions and thrombi, although it is associated with radiation exposure. Modern dose-reduction technologies and dual-source CT scanners have reduced radiation exposure to <1 mSv in some studies [89]. β-blockers may be required to reduce heart rate before gated CTA. Transthoracic echocardiography and CTA show a high level of concordance in the assessment of proximal CA segments, particularly in the measurement of aneurysms [91].

There are currently no normal values for CTA in children, so clinical practice often applies Z-scores calculated from echocardiography to proximal CTA results. Although this approach is not ideal, studies have shown excellent agreement in proximal CA measurements even in small cohort studies, and high reliability of CTA results for coronary aneurysms, both between studies and within a single study in CHD. [91]

Coronary CTA in the distal coronary vessels usually shows smaller sizes than transthoracic echocardiography, but coronary CTA better detects distal coronary artery segments than transthoracic echocardiography [91,92].

Coronary CTA is also used in patients with symptoms of acute MI. The fractional flow reserve (FFR) method calculated from CTA data is a physiological modeling method that simulates coronary blood flow obtained from coronary artery CTA and is used in adults with coronary artery disease to assess stenoses [93]. This is an active area of research, and future work on CT-based FFR in patients with CHD may help identify stenoses that require intervention. For patients with ACA, long-term monitoring using coronary CTA is appropriate and informative.

Calcification in ACA occurs late in the course of CHD, and significant calcification may complicate measurement of CA on coronary CTA. Tsuji et al. [94] reported that the incidence of aneurysmal calcification was: 10% at 10 years, 38% at 20 years, and 72% at 30 years after the initial episode of CHD in patients with persistent aneurysms. Kahn et al. [95] evaluated patients with CHD with CT to determine the calcium index and demonstrated that only patients with persistent coronary lesions had calcified segments.

Coronary artery calcium index assessment is useful in adult patients with unknown coronary artery disease after childhood coronary artery disease to screen for calcification as a marker of ACA.

In these patients, further follow-up with coronary CTA is necessary for further evaluation of ACA. Given the current technology in reducing the radiation dose and time of CTA, this method can be used in patients with progressive giant ACA during hospitalization and immediately before discharge, for short-term assessment of aneurysm size. Coronary CTA can also be useful 1 year after diagnosis as a baseline study for further dynamic follow-up of patients with ACA, especially in cases of: large or giant aneurysms, presence of distal ACA, limited visualization on echocardiography due to suboptimal echocardiographic windows) (Table 2). In addition, CTA can be used for long-term follow-up: in case of suspected progressive stenosis, to confirm thrombus formation detected on echocardiography, in case of suspected acute coronary syndrome during clinical observation, according to Table 2.

Cardio MRI

Cardiac MRI allows visualization of the coronary arteries, assessment of ventricular function, and myocardial status without the use of ionizing radiation. Limitations and

Features in children: Visualization of the coronary arteries in children can be difficult due to high heart rates and small vessel diameters. MRI imaging requires sedation in children under 8 years of age.

In adults, ferumoxytol-enhanced coronary MR angiography has been used and correlates well with invasive catheter angiography for the diagnosis of CA stenosis [96, 97]. Matsumoto et al. [98] demonstrated that 3D turbo-spleen imaging of the CA vessel wall was equivalent to standard 2D dual inversion-reconstruction turbo-spleen echocardiography in a small cohort of patients with CH.

Working group comment:*at the time of development of this Clinical Guideline The drug with the international non-proprietary name ferumoxytol is not registered in Ukraine.*

The 2020 MRI Society Expert Statement on Acquired Childhood Heart Diseases suggests a comprehensive MRI imaging protocol for patients with CHD to assess the walls and lumen of the coronary arteries, detect myocardial inflammation (T2-weighted imaging), detect fibrosis (T1-weighted imaging and late enhancement with gadolinium-enhancing paramagnetic contrast agents, and assess at rest and with exercise. [5]. In the recovery phase after CHD, patients demonstrate a decrease in circular and longitudinal strain on cardiac MRI, even after normalization of systolic function on standard imaging, regardless of the presence of ACA [99]. Myocardial fibrosis is an ischemic disease that occurs in a small number of patients with severe ACA and is not necessarily limited to areas of reduced perfusion [100].

Patients who have experienced shock syndrome in chronic heart failure, especially those with myocardial dysfunction, may be at higher risk of developing myocardial fibrosis in the long term, and are therefore recommended to undergo cardiac MRI later in life [101]. Decreased myocardial perfusion reserve on cardiac MRI has been found in patients with chronic heart failure with persistent and even regressing ACA on follow-up [102]. Stress testing with cardiac MRI imaging can be performed using: inotropic agents (dobutamine), coronary vasodilators (adenosine, dipyridamole, or regadenoson). Cardiac MRI imaging with adenosine reveals induced perfusion defects in chronic heart failure patients with ACA [100]. Regadenoson, a more selective and hemodynamically safe vasodilator, shows promise in children with CHD and ACA and may help identify patients who require revascularization [103]. However, the relationship between cardiac MRI findings and clinical outcomes in patients with CHD remains a subject of further investigation.

Working group comment:*at the time of development of this Clinical Guideline The drug with the international non-proprietary name ragadenoson is not available in Ukraine.*

registered. The safety and efficacy of the medicinal product with the international non-proprietary name dobutamine in children have not been established.

The medicinal product with the international non-proprietary name adenosine, according to the instructions for its medical use, is not for use in children.

Invasive imaging of the CA

Invasive coronary angiography allows detailed assessment of coronary anatomy, including stenoses, collaterals, and the anatomy of peripheral arteries and the internal mammary artery. It is usually performed in patients who are scheduled for percutaneous coronary revascularization (e.g., in acute myocardial infarction, angina, or a positive stress test for induced ischemia) or in cases where noninvasive imaging modalities (CT, MRI) are insufficiently informative for clinical decision-making.

PRK is a method of assessing the pressure difference between the proximal and distal stenotic artery during invasive coronary angiography. It is a widely used tool for assessing CA lesions and determining the need for percutaneous coronary intervention. [54]. According to the American College of Cardiology / AHA / Society for Cardiovascular Angiography & Interventions Guidelines (2021), percutaneous revascularization is not recommended if PRK >0.8 in atherosclerotic disease, as this indicates adequate blood flow in the CA [54]. The use of PRK in patients with CH is under active investigation, and its clinical role is not yet defined [104, 105].

Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) are important adjuncts to coronary angiography, providing higher spatial resolution (IVUS: 100–150 μm, OCT: 10 μm, coronary angiography: 300 μm) and more detailed assessment of lesions compared with angiography alone. IVUS has been used for the past 30 years in patients with coronary artery disease to: differentiate atheroma, thrombus, or myointimal proliferation; and guide PCI in patients with acute coronary syndrome or stable angina [106, 107]. However, the impact of IVUS on long-term outcomes in patients with coronary artery disease remains unclear. OCT is used in patients with coronary artery disease to visualize structural changes in the coronary artery wall [56]. This technique requires the removal of blood from the lumen to obtain a high-quality image, which limits its use. The role of OCT in CD remains an area of active research [108]. Both methods are invasive and not suitable for routine monitoring of CD patients, but may be useful in selected clinical situations.

Assessment of induced myocardial ischemia

Patients with ACA are at increased risk of CA stenosis and obstruction. The highest risk is seen in patients with ACA and Z-scores ≥10, especially those with Z-scores ≥20, and those with complex anatomy (e.g., multi-branch involvement with multiple aneurysms). In patients with Z-scores ≥10, the cumulative incidence of >50% lumen narrowing was 20±3%, CA thrombosis was 18±2%, and major adverse cardiovascular events was 14±2% over a 10-year follow-up [14]. Accordingly, periodic surveillance for induced myocardial ischemia is mandatory in patients with ACA Z-scores ≥10, regardless of the presence or absence of potential symptoms suggestive of ischemia, with the frequency of examination consistent with the severity of the maximally achieved and current ACA size (Table 2).

The choice of imaging modality for the assessment of induced myocardial ischemia depends on: patient age, center experience in performing the examination, and the need to minimize cumulative radiation exposure. Clinical experience in the performance and interpretation of the appropriate techniques should also be considered when selecting a modality for the assessment of induced myocardial ischemia. Because exercise stress echocardiography does not involve radiation, it is recommended for routine monitoring of induced myocardial ischemia in asymptomatic children, compared with positron emission tomography (PET) or radionuclide methods. The use of cardiac stress MRI is a useful, radiation-free alternative for the assessment of ischemia in children who are too young for exercise.

Stress echocardiography

Exercise stress echocardiography is considered a more physiological method than pharmacological stress testing. In a single-center study, this method was used in 53 patients with CHD and ACA and allowed: to detect myocardial ischemia in a subgroup of high-risk patients (AHA risk level 4 or 5) and to confirm the absence of ischemia in patients with lower risk levels [109]. Pharmacological stress testing with dobutamine is used in children with CHD who are unable to exercise. The degree of left ventricular wall contractility detected by dobutamine stress echocardiography is independently associated with reduced event-free survival at 15 years [110]. Exercise stress echocardiography can be safely used in children older than 7 years as a screening tool for the assessment of induced myocardial ischemia [109].

Transition of patients with HC to adult care The transition of children with HC to the adult-serving health care system is critical to providing care for this growing population.

patient population. A key element of a successful transition is a structured intervention that includes: transition planning, direct transfer, and patient integration into the new system of medical care. The recommended approach is the “Six Core Elements” — six basic components of transition, supported by many medical academies [111].

Medical teams managing patients with complicated CHD and ACA should establish a formal transition program to adult care to ensure a smooth transition with continuity of care as these children become adults. Pediatric cardiologists who see these patients should identify an adult cardiologist in their community who is experienced in managing patients with CHD and willing to continue their care and follow-up into adulthood. The long-term prognosis and potential interventions for adult patients with ACA who may be associated with acute coronary syndrome, heart failure, or arrhythmia require further investigation [87, 112].

Pregnant women with CHD and giant aneurysms who are receiving anticoagulant therapy are at particularly high risk and should be managed by obstetricians and gynecologists who are specialized in high obstetric risk, in collaboration with a cardiologist knowledgeable in CHD. Further research is needed to optimize the management of these patients.

Key provisions:

1. Long-term follow-up is necessary for patients with AKA, especially in cases of large or giant aneurysms 1 year after the onset of HC. This may include low-dose CT angiography, MRI with ferumoxytol, or invasive angiography depending on the complexity of the lesion, clinical status, and resources of the medical institution.

2. Modern CT angiography with reduced radiation dose can be used as a basic method for monitoring patients with CH and ACA, as well as for detecting coronary artery stenoses.

3. Cardio-MRI with enhanced visualization of the coronary arteries allows examination patients with HC and ACA without irradiation. At the same time, cardiac MRI is better suited for assessing myocardial function and perfusion changes under stress to detect induced ischemia.

4. Stress Echocardiography can be used to assess induced ischemia myocardial infarction in patients with HC and AKA.

5. Invasive coronary angiography provides the most detailed imaging of coronary artery anatomy, but its use should be carefully weighed against the risk of invasive procedure, patient clinical status, and facility resources. The method is indicated in patients with myocardial ischemia and for revascularization.

6. Medical teams managing children with HC and AKA should create a structured program for their transition to the adult health care system, ensuring continuity of care as children reach adulthood.

PROSPECTIVE DIRECTIONS

Over the past 50 years, significant progress has been made in the diagnosis, treatment, and long-term management of children with CD. This update summarizes current evidence on several clinically important aspects. Despite these advances, significant gaps in knowledge remain, including: pathogenesis, diagnostic tests, emergency treatment in the acute phase, and long-term follow-up.

Future revisions of the diagnostic criteria for CD will need to be considered in the light of the large body of published and evidence-based clinical data. Risk scores for predicting resistance to IVLI and the development of AKA have been developed based on data from diverse populations and may improve outcomes by allowing targeted adjunctive therapy in high-risk patients. Iterative improvements in diagnostic testing and algorithms, including the potential for artificial intelligence, are needed, as well as risk stratification for both AKA and adverse cardiac events in patients with AKA.

Ultrafast ultrasound imaging is a new technology capable of capturing images with a frame rate 100 times higher than conventional echocardiography.

One of its new clinical applications is ultrafast Doppler angiography of the coronary artery, a technology that allows for anatomical and hemodynamic analysis of coronary blood flow and appears promising for diagnosis in patients with CHD. [113] Imaging-based monitoring and newer techniques for assessing inflammation and vessel wall characteristics (optical tomography) have shown potential to improve understanding of vascular biology and the response of vessel wall inflammation to therapy, but require further investigation and validation.

Larger studies are needed to confirm these findings and examine their impact on clinical outcomes and long-term prognosis. Large international studies continue to provide fundamental outcome data, including compelling recent data that confirm that small ACAs in the vast majority of cases regress and are not associated with a risk of late cardiac complications, but the burden of ACA and its associated long-term cardiac consequences remains.

RCTs that directly compare acute intensification of therapy with the use of anti-inflammatory agents in high-risk patients may result in a reduction in the incidence of AKA and less progression of AKA in patients with AKA at the time of diagnosis. Use of statin therapy in acute

Phase 1 HC in patients with acute ACA has shown promising results, but requires further long-term study in patients with persistent ACA. Additional data have accumulated showing a clear advantage of anticoagulant therapy in combination with antiplatelet therapy in patients with HC and large ACA, but optimal thromboprophylaxis, including the new oral anticoagulants DOACs and evidence-based criteria for initiating anticoagulant therapy remain insufficient. Establishing the efficacy of easier-to-use DOACs (compared to warfarin or LMWH) has the potential to improve both cardiac outcomes and quality of life in patients with large ACA. Evidence of the safety and efficacy of DOACs in HC will be obtained from postmarketing surveillance. Further evidence-based criteria for the timing and types of coronary interventions in patients with large ACA and ischemia are urgently needed.

Formal transition programs and teams for adult patients with HC and AKA should be established to ensure continuity of patient care and treatment.

References

1. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, Baker AL, Jackson MA, Takahashi M, Shah PB, et al; on behalf of the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Council on Epidemiology and Prevention. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation*. 2017;135:e927–e999. doi: 10.1161/CIR.0000000000000484

2. Maddox RA, Person MK, Kennedy JL, Leung J, Abrams JY, Haberling DL, Schonberger LB, Belay ED. Kawasaki disease and Kawasaki disease shock syndrome hospitalization rates in the United States, 2006-2018. Pediatr Infect Dis J. 2021;40:284–288. doi: 10.1097/INF.0000000000002982

3. Son MBF, Gauvreau K, Tremoulet AH, Lo M, Baker AL, de Ferranti S, Dedeoglu F, Sundel RP, Friedman KG, Burns JC, et al. Risk model development and validation for prediction of coronary artery aneurysms in Kawasaki disease in a North American population. J Am Heart Assoc. 2019;8:e011319. doi: 10.1161/JAHA.118.011319

4. Tsuda E, Tsujii N, Hayama Y. Stenotic lesions and the maximum diameter of coronary artery aneurysms in Kawasaki disease. J Pediatr. 2018;194:165–170.e2. doi: 10.1016/j.jpeds.2017.09.077

5. Dorfman AL, Geva T, Samyn MM, Greil G, Krishnamurthy R, Messroghli D, Festa P, Secinaro A, Soriano B, Taylor A, et al. SCMR expert consensus statement for cardiovascular magnetic resonance of acquired and nonstructural pediatric heart disease. J Cardiovasc Magn Reson. 2022; 24:44. doi: 10.1186/s12968-022-00873-1

6. Jones PN, Romanowicz J, Browne L, Malone LJ. Imaging evaluation of Kawasaki disease. Curr Cardiol Rep. 2022;24:1487–1494. doi: 10.1007/s11886-022-01768-4

7. van Stijn D, Planken RN, Groenink M, Streekstra GJ, Kuijpers TW, Kuipers IM. Coronary artery assessment in Kawasaki disease with dual-source CT angiography to uncover vascular pathology. Eur Radiol. 2020;30:432–441. doi: 10.1007/s00330-019-06367-6

8. Miyata K, Bainto EV, Sun X, Jain S, Dummer KB, Burns JC, Tremoulet AH. Infliximab for intensification of primary therapy for patients with Kawasaki disease and coronary artery aneurysms at diagnosis. Arch Dis Child. 2023;108:833–838. doi: 10.1136/archdischild-2023-325639

9. Ae R, Abrams JY, Maddox RA, Schonberger LB, Nakamura Y, Kuwabara M, Makino N, Matsubara Y, Kosami K, Sasahara T, et al. Corticosteroids added to initial intravenous immunoglobulin treatment for the prevention of coronary artery abnormalities in high-risk patients with Kawasaki disease. J Am Heart Assoc. 2020;9:e015308. doi: 10.1161/JAHA.119.015308

10. Dionne A, Burns JC, Dahdah N, Tremoulet AH, Gauvreau K, de Ferranti SD, Baker AL, Son MB, Gould P, Fournier A, et al. Treatment intensification in patients with Kawasaki disease and coronary aneurysm at diagnosis. Pediatrics. 2019;143:e20183341. doi: 10.1542/peds.2018-3341

11. Friedman KG, Gauvreau K, Hamaoka-Okamoto A, Tang A, Berry E, Tremoulet AH, Mahavadi VS, Baker A, deFerranti SD, Fulton DR, et al. Coronary artery aneurysms in Kawasaki disease: risk factors for progressive disease and adverse cardiac events in the US population. J Am Heart Assoc. 2016;5:e003289. doi: 10.1161/JAHA.116.003289

12. Miura M, Kobayashi T, Kaneko T, Ayusawa M, Fukazawa R, Fukushima N, Fuse S, Hamaoka K, Hirono K, Kato T, et al; The Z-score Project 2nd Stage Study Group. Association of severity of coronary artery aneurysms in patients with Kawasaki disease and risk of later coronary events. JAMA Pediatr. 2018;172:e180030. doi: 10.1001/jamapediatrics.2018.0030

13. Kato T, Miura M, Kobayashi T, Kaneko T, Fukushima N, Suda K, Maeda J, Shimoyama S, Shiono J, Hirono K, et al; The Z-score Project 2nd Stage Study Group. Analysis of coronary arteries

aneurysm regression in patients with Kawasaki disease by aneurysm severity: factors associated with regression. J Am Heart Assoc. 2023;12:e022417. doi: 10.1161/JAHA.121.022417

14. McCrindle BW, Manlhiot C, Newburger JW, Harahsheh AS, Giglia TM, Dallaire F, Friedman K, Low T, Runeckles K, Mathew M, et al; International Kawasaki Disease Registry. Medium-term complications associated with coronary artery aneurysms after Kawasaki disease: a study from the International Kawasaki Disease Registry. J Am Heart Assoc. 2020;9:e016440. doi: 10.1161/JAHA.119.016440

15. Kobayashi T, Ayusawa M, Suzuki H, Abe J, Ito S, Kato T, Kamada M, Shiono J, Suda K, Tsuchiya K, et al. Revision of diagnostic guidelines for Kawasaki disease (6th revised edition). Pediatr Int. 2020;62:1135–1138. doi: 10.1111/ped.14326

16. Gamez-Gonzalez LB, Moribe-Quintero I, Cisneros-Castolo M, Varela-Ortiz J, Munoz-Ramirez M, Garrido-Garcia M, Yamazaki-Nakashimada M. Kawasaki disease shock syndrome: unique and severe subtype of Kawasaki disease. Pediatr Int. 2018;60:781–790. doi: 10.1111/ped.13614

17. Jone PN, John A, Oster ME, Allen K, Tremoulet AH, Saarel EV, Lambert LM, Miyamoto SD, de Ferranti SD; on behalf of the American Heart Association Leadership Committee and Congenital Cardiac Defects Committee of the Council on Lifelong Congenital Heart Disease and Heart Health in the Young; Council on Hypertension, and Council on Peripheral Vascular Disease. SARS-CoV-2 infection and associated cardiovascular manifestations and complications in children and young adults: a scientific statement from the American Heart Association. Circulation. 2022;145:e1037–e1052. doi: 10.1161/CIR.0000000000001064

18. Godfred-Cato S, Abrams JY, Balachandran N, Jaggi P, Jones K, Rostad CA, Lu AT, Fan L, Jabbar A, Anderson EJ, et al. Distinguishing multisystem inflammatory syndrome in children from COVID-19, Kawasaki disease and toxic shock syndrome. Pediatr Infect Dis J. 2022;41:315–323. doi: 10.1097/inf.0000000000003449

19. Harahsheh AS, Shah S, Dallaire F, Manlhiot C, Khoury M, Lee S, Fabi M, Mauriello D, Tierney ESS, Sabati AA, et al; International Kawasaki Disease Registry. Kawasaki disease in the time of COVID-19 and MIS-C: the International Kawasaki Disease Registry. Can J Cardiol. 2023;40:58–72. doi: 10.1016/j.cjca.2023.06.001

20. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, Ramnarayan P, Fraisse A, Miller O, Davies P, et al; PIMS-TS Study Group and EUCLIDS and PERFORM Consortia. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA. 2020;324:259–269. doi: 10.1001/jama.2020.10369

21. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, Newburger JW, Kleinman LC, Heidemann SM, Martin AA, et al; Overcoming CI and Team CC-R. Multisystem inflammatory syndrome in US children and adolescents. N Engl J Med. 2020;383:334–346. doi: 10.1056/nejmoa2021680

22. Fridman MD, Tsoukas P, Jeewa A, Yeung RSM, Gamulka BD, McCrindle BW. Differentiation of COVID-19-associated multisystem inflammatory syndrome from Kawasaki disease with the use of cardiac biomarkers. Can J Cardiol. 2023;39:815–823. doi: 10.1016/j.cjca.2022.11.012

23. McCrindle BW, Harahsheh AS, Handoko R, Raghuveer G, Portman MA, Khoury M, Newburger JW, Lee S, Jain SS, Khare M, et al; International Kawasaki Disease Registry. SARS-CoV-2 variants and multisystem inflammatory syndrome in children. N Engl J Med. 2023;388:1624–1626. doi: 10.1056/NEJMc2215074

24. Lam JY, Shimizu C, Tremoulet AH, Bainto E, Roberts SC, Sivilay N, Gardiner MA, Kanegaye JT, Hogan AH, Salazar JC, et al; Pediatric Emergency Medicine Kawasaki Disease Research GROUP; CHARMS Study Group. A machine-learning algorithm for diagnosis of multisystem inflammatory syndrome in children and Kawasaki disease in the USA: a retrospective model

development and validation study. Lancet Digit Health. 2022;4:e717–e726. doi: 10.1016/s2589-7500(22)00149-2

25. Salgado AP, Ashouri N, Berry EK, Sun X, Jain S, Burns JC, Tremoulet AH. High risk of coronary artery aneurysms in infants younger than 6 months of age with Kawasaki disease. J Pediatr. 2017;185:112–116.e1. doi: 10.1016/j.jpeds.2017.03.025

26. Moreno E, Garcia SD, Bainto E, Salgado AP, Parish A, Rosellini BD, Ulloa-Gutierrez R, Garrido-Garcia LM, Duenas L, Estripeaut D, et al; The REKAMLATINA-2 Study Group Investigators. Presentation and outcomes of Kawasaki disease in Latin American infants younger than 6 months of age: a multinational multicenter study of the REKAMLATINA network. Front Pediatr. 2020;8:384. doi: 10.3389/fped.2020.00384

27. Cameron SA, Carr M, Pahl E, DeMarais N, Shulman ST, Rowley AH. Coronary artery aneurysms are more severe in infants than in older children with Kawasaki disease. Arch Dis Child. 2019;104:451–455. doi: 10.1136/archdischild-2018-314967

28. Tsuda E, Tsujii N, Kimura K, Suzuki A. Distribution of Kawasaki disease coronary artery aneurysms and the relationship to coronary artery diameter. Pediatr Cardiol. 2017;38:932–940. doi: 10.1007/s00246-017-1599-4

29. Fukazawa R, Kobayashi J, Ayusawa M, Hamada H, Miura M, Mitani Y, Tsuda E, Nakajima H, Matsuura H, Ikeda K, et al; on behalf of the Japanese Circulation Society Joint Working Group. JCS/JSCS 2020 guideline on diagnosis and management of cardiovascular sequelae in Kawasaki disease. Circ J. 2020;84:1348–1407. doi: 10.1253/circj.cj-19-1094

30. Kobayashi T, Fuse S, Sakamoto N, Mikami M, Ogawa S, Hamaoka K, Arakaki Y, Nakamura T, Nagasawa H, Kato T, et al; Z Score Project Investigators. A new Z score curve of the coronary arterial internal diameter using the lambda-mu-sigma method in a pediatric population. J Am Soc Echocardiogr. 2016;29:794–801.e29. doi: 10.1016/j.echo.2016.03.017

31. Dallaire F, Dahdah N. New equations and a critical appraisal of coronary artery Z scores in healthy children. J Am Soc Echocardiogr. 2011;24:60–74. doi: 10.1016/j.echo.2010.10.004

32. McCrindle BW, Li JS, Minich LL, Colan SD, Atz AM, Takahashi M, Vetter VL, Gersony WM, Mitchell PD, Newburger JW; Pediatric Heart Network Investigators. Coronary artery involvement in children with Kawasaki disease: risk factors from analysis of serial normalized measurements. Circulation. 2007;116:174–179. doi: 10.1161/CIRCULATIONAHA.107.690875

33. Lopez L, Colan S, Stylianou M, Granger S, Trachtenberg F, Frommelt P, Pearson G, Camarda J, Cnota J, Cohen M, et al; Pediatric Heart Network Investigators. Relationship of echocardiographic Z scores adjusted for body surface area to age, sex, race, and ethnicity: the Pediatric Heart Network normal echocardiogram database. Circ Cardiovasc Imaging. 2017;10:e006979. doi: 10.1161/CIRCIMAGING.117.006979

34. Olivieri L, Arling B, Friberg M, Sable C. Coronary artery Z score regression equations and calculators derived from a large heterogeneous population of children undergoing echocardiography. J Am Soc Echocardiogr. 2009;22:159–164. doi: 10.1016/j.echo.2008.11.003

35. Lopez L, Frommelt PC, Colan SD, Trachtenberg FL, Gongwer R, Stylianou M, Bhat A, Burns KM, Cohen MS, Dragulescu A, et al; Pediatric Heart Network Investigators. Pediatric heart network echocardiographic Z scores: comparison with other published models. J Am Soc Echocardiogr. 2021;34:185–192. doi: 10.1016/j.echo.2020.09.019

36. Lorenzoni RP, Elkins N, Quezada M, Silver EJ, Mahgerefteh J, Hsu DT, Choueiter NF. Impact of Z score system on the management of coronary artery lesions in Kawasaki disease. Cardiol Young. 2022;32:952–959. doi: 10.1017/S1047951121003437

37. Robinson DL, Ware AL, Sauer MC, Williams RV, Ou Z, Presson AP, Tani LY, Minich LL, Truong DT. Implications of changing Z-score models for coronary artery dimensions in Kawasaki disease. Pediatr Cardiol. 2021;42:432–441. doi: 10.1007/s00246-020-02501-0

38. Gorelik M, Chung SA, Ardalan K, Binstadt BA, Friedman K, Hayward K, Imundo LF, Lapidus SK, Kim S, Son MB, et al. 2021 American College of Rheumatology/Vasculitis Foundation guideline for the management of Kawasaki disease. Arthritis Care Res (Hoboken). 2022;74:538–548. doi: 10.1002/acr.24838

39. de Ferranti SD, Gauvreau K, Friedman KG, Tang A, Baker AL, Fulton DR, Tremoulet. AH, Burns JC, Newburger JW. Association of initially normal coronary arteries with normal findings on follow-up echocardiography in patients with Kawasaki disease. JAMA Pediatr. 2018;172:e183310. doi: 10.1001/jamapediatrics.2018.3310

40. Shimizu C, Oharaseki T, Takahashi K, Kottek A, Franco A, Burns JC. The role of TGF-beta and myofibroblasts in the arteritis of Kawasaki disease. Hum Pathol. 2013;44:189–198. doi: 10.1016/j.humpath.2012.05.004

41. Printz BF, Sleeper LA, Newburger JW, Minich LL, Bradley T, Cohen MS, Frank D, Li JS, Margossian R, Shirali G, et al; Pediatric Heart Network Investigators. Noncoronary cardiac abnormalities are associated with coronary artery dilation and with laboratory inflammatory markers in acute Kawasaki disease. J Am Coll Cardiol. 2011;57:86–92. doi: 10.1016/j.jacc.2010.08.619

42. Sanchez AA, Sexson Tejtel SK, Almeida-Jones ME, Feagin DK Jr, Altman CA, Pignatelli RH. Comprehensive left ventricular myocardial deformation assessment in children with Kawasaki disease. Congenital Heart Dis. 2019;14:1024–1031. doi: 10.1111/chd.12787

43. Bruggeman CW, Nagelkerke SQ, Lau W, Manlhiot C, de Haas M, van Bruggen R, McCrindle BW, Yeung RSM, Kuijpers TW. Treatment-associated hemolysis in Kawasaki disease: association with blood-group antibody titers in IVIg products. Blood Adv. 2020;4:3416–3426. doi: 10.1182/bloodadvances.2020002253

44. Van Anh KY, Shah S, Tremoulet AH. Hemolysis from intravenous immunoglobulin in obese patients with Kawasaki disease. Front Pediatr. 2020;8:146. doi: 10.3389/fped.2020.00146

45. Suzuki T, Michihata N, Hashimoto Y, Yoshikawa T, Saito K, Matsui H, Fushimi K, Yasunaga H. Association between aspirin dose and outcomes in patients with acute Kawasaki disease: a nationwide retrospective cohort study in Japan. Eur J Pediatr. 2024;183:415–424. doi: 10.1007/s00431-023-05302-8

46. Kim GB, Yu JJ, Yoon KL, Jeong SI, Song YH, Han JW, Hong YM, Joo CU. Medium- or higher-dose acetylsalicylic acid for acute Kawasaki disease and patient outcomes. J Pediatr. 2017;184:125–129.e1. doi: 10.1016/j.jpeds.2016.12.019

47. Dallaire F, Fortier-Morissette Z, Blais S, Dhanrajani A, Basodan D, Renaud C, Mathew M, De Souza AM, Dionne A, Blanchard J, et al. Aspirin dose and prevention of coronary abnormalities in Kawasaki disease. Pediatrics. 2017;139:e20170098. doi: 10.1542/peds.2017-0098

48. Amarilyo G, Koren Y, Brik Simon D, Bar-Meir M, Bahat H, Helou MH, Mendelson A, Hezkelo N, Chodick G, Berkun Y, et al. High-dose aspirin for Kawasaki disease: outdated myth or effective aid? Clin Exp Rheumatol. 2017;35:209–212.

49. Hayashi K, Miyakoshi C, Hoshino S, Kobayashi N, Nakajima R, Sagawa H, Hayashiya T, Suzuki A, Aota C, Nishijima S, et al. Initial intravenous immunoglobulin therapy without aspirin for acute Kawasaki disease: a retrospective cohort study with a Bayesian inference. BMJ Paediatrics Open. 2024;8:e002312. doi: 10.1136/bmjpo-2023-002312

50. Huang YH, Hsin YC, Wang LJ, Feng WL, Guo MM, Chang LS, Tu YK, Kuo HC. Treatment of Kawasaki disease: a network meta-analysis of four dosage regimens of aspirin combined with recommended intravenous immunoglobulin. Front Pharmacol. 2021;12:725126. doi: 10.3389/fphar.2021.725126

51. Jia X, Du X, Bie S, Li X, Bao Y, Jiang M. What dose of aspirin should be used in the initial treatment of Kawasaki disease? A meta-analysis. Rheumatology (Oxford). 2020;59:1826–1833. doi: 10.1093/rheumatology/keaa050

52. Wu Y, Hu L, Xie X, Li W, Wang Y, Zhang L, Huang P, Li F, Li J, Xia S, et al. Different dose aspirin plus immunoglobulin (DAPI) for prevention of coronary artery abnormalities in Kawasaki disease: study protocol for a multi-center, prospective, randomized, open-label, blinded end-point, non-inferiority trial. Am Heart J. 2024;273:1–9. doi: 10.1016/j.ahj.2024.03.010

53. Mohanty S, Vaidyanathan B. Anti-platelet agents in pediatric cardiac practice. Ann Pediatr Cardiol. 2013;6:59–64. doi: 10.4103/0974-2069.107236

54. Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, Bischoff JM, Bittl. JA, Cohen MG, DiMaio JM, Don CW, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145:e18–e114. doi: 10.1161/CIR.0000000000001039

55. Kobayashi T, Inoue Y, Takeuchi K, Okada Y, Tamura K, Tomomasa T, Kobayashi T, Morikawa A. Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. Circulation. 2006;113:2606–2612. doi: 10.1161/CIRCULATIONAHA.105.592865

56. Sleeper LA, Minich LL, McCrindle BM, Li JS, Mason W, Colan SD, Atz AM, Printz BF, Baker A, Vetter VL, et al; Pediatric Heart Network Investigators. Evaluation of Kawasaki disease risk scoring systems for intravenous immunoglobulin resistance. J Pediatr. 2011;158:831–835.e3. doi: 10.1016/j.jpeds.2010.10.031

57. Kobayashi T, Saji T, Otani T, Takeuchi K, Nakamura T, Arakawa H, Kato T, Hara T, Hamaoka K, Ogawa S, et al; RAISE study group investigators. Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomized, open-label, blinded-endpoints trial. Lancet. 2012;379:1613–1620. doi: 10.1016/S0140-6736(11)61930-2

58. Miyata K, Kaneko T, Morikawa Y, Sakakibara H, Matsushima T, Misawa M, Takahashi T, Nakazawa M, Tamame T, Tsuchihashi T, et al; Post RAISE Group. Efficacy and safety of intravenous immunoglobulin plus prednisolone therapy in patients with Kawasaki disease (Post RAISE): a multicenter, prospective cohort study. Lancet Child Adolesc Health. 2018;2:855–862. doi: 10.1016/S2352-4642(18)30293-1

59. Burns JC, Roberts SC, Tremoulet AH, He F, Printz BF, Ashouri N, Jain SS, Michalik. DE, Sharma K, Truong DT, et al; KIDCARE Multicenter Study Group. Infliximab versus second intravenous immunoglobulin for treatment of resistant Kawasaki disease in the USA (KIDCARE): a randomized, multicenter comparative effectiveness trial. Lancet Child Adolesc Health. 2021;5:852–861. doi: 10.1016/S2352-4642(21)00270-4

60. ortman MA, Dahdah NS, Slee A, Olson AK, Choueiter NF, Soriano BD, Buddhe S, Altman CA; EATAK Investigators. Etanercept with IVIg for acute Kawasaki disease: a randomized controlled trial. Pediatrics. 2019;143:e20183675. doi: 10.1542/peds.2018-3675

61. Hoang LT, Shimizu C, Ling L, Naim AN, Khor CC, Tremoulet AH, Wright V, Levin M, Hibberd ML, Burns JC. Global gene expression profiling identifies new therapeutic targets in acute Kawasaki disease. Genome Med. 2014;6:541. doi: 10.1186/s13073-014-0102-6

62. Kone-Paut I, Tellier S, Belot A, Brochard K, Guitton C, Marie I, Meinzer U, Cherqaoui B, Galeotti C, Boukhedouni N, et al. Phase II open label study of anakinra in intravenous immunoglobulin-resistant Kawasaki disease. Arthritis Rheumatol. 2021;73:151–161. doi: 10.1002/art.41481

63. Onouchi Y. The genetics of Kawasaki disease. Int J Rheum Dis. 2018;21:26–30. doi: 10.1111/1756-185X.13218

64. Hamada H, Suzuki H, Onouchi Y, Ebata R, Terai M, Fuse S, Okajima Y, Kurotobi S, Hirai K, Soga T, et al; KAICA Trial Investigators. Efficacy of primary treatment with immunoglobulin plus ciclosporin for prevention of coronary artery abnormalities in patients with Kawasaki disease

predicted to be at increased risk of non-response to intravenous immunoglobulin (KAICA): a randomized controlled, open-label, blinded-endpoints, phase 3 trial. Lancet. 2019;393:1128–1137. doi: 10.1016/S0140-6736(18)32003-8

65. Vande Casteele N, Oyamada J, Shimizu C, Best BM, Capparelli EV, Tremoulet AH, Burns JC. Infliximab pharmacokinetics are influenced by intravenous immunoglobulin administration in patients with Kawasaki disease. Clin Pharmacokinet. 2018;57:1593–1601. doi: 10.1007/s40262-018-0653-6

66. Yang J, Jain S, Capparelli EV, Best BM, Son MB, Baker A, Newburger JW, Franco A, Printz BF, He F, et al. Anakinra treatment in patients with acute Kawasaki disease with coronary artery aneurysms: a phase I/IIa trial. J Pediatr. 2022;243:173–180.e8. doi: 10.1016/j.jpeds.2021.12.035

67. Jone PN, Anderson MS, Mulvahill MJ, Heizer H, Glode MP, Dominguez SR. Infliximab plus intravenous immunoglobulin (IVIg) versus IVIg alone as initial therapy in children with Kawasaki disease presenting with coronary artery lesions: is dual therapy more effective? Pediatr Infect Dis J. 2018;37:976–980. doi: 10.1097/INF.0000000000001951

68. Miyata K, Bainto EV, Sun X, Jain S, Dummer KB, Burns JC, Tremoulet AH. Infliximab for intensification of primary therapy for patients with Kawasaki disease and coronary artery aneurysms at diagnosis. Arch Dis Child. 2023;108:833–838. doi: 10.1136/archdischild-2023-325639

69. Friedman KG, Gauvreau K, Baker A, Son MB, Sundel R, Dionne A, Giorgio T, De Ferranti S, Newburger JW. Primary adjunctive corticosteroid therapy is associated with improved outcomes for patients with Kawasaki disease with coronary artery aneurysms at diagnosis. Arch Dis Child. 2021;106:247–252. doi: 10.1136/archdischild-2020-319810

70. Rowley AH, Wylie KM, Kim KY, Pink AJ, Yang A, Reindel R, Baker SC, Shulman ST, Orenstein JM, Lingen MW, et al. The transcriptional profile of coronary arteritis in Kawasaki disease. BMC Genomics. 2015;16:1076. doi: 10.1186/s12864-015-2323-5

71. Kanegaye JT, Wilder MS, Molkara D, Frazer JR, Pancheri J, Tremoulet AH, Watson VE, Best BM, Burns JC. Recognition of a Kawasaki disease shock syndrome. Pediatrics. 2009;123:e783–e789. doi: 10.1542/peds.2008-1871

72. Lamrani L, Manlhiot C, Elias MD, Choueiter NF, Dionne A, Harahsheh AS, Portman MA, McCrindle BW, Dahdah N. Kawasaki disease shock syndrome vs classical Kawasaki disease: a meta-analysis and comparison with SARSCoV-2 multisystem inflammatory syndrome. Can J Cardiol. 2021;37:1619–1628. doi: 10.1016/j.cjca.2021.05.014

73. Halyabar O, Friedman KG, Sundel RP, Baker AL, Chang MH, Gould PW, Kawasaki disease with coronary artery aneurysms. Pediatr Rheumatol Online J. 2021;19:31. doi: 10.1186/s12969-021-00526-0

74. Tremoulet AH, Jain S, Jone PN, Best BM, Duxbury EH, Franco A, Printz B, Dominguez. SR, Heizer H, Anderson MS, et al. Phase I/IIa trial of atorvastatin in patients with acute Kawasaki disease with coronary artery aneurysm. J Pediatr. 2019;215:107–117.e12. doi: 10.1016/j.jpeds.2019.07.064

75. Shimizu C, Kim J, He M, Tremoulet AH, Hoffman HM, Shyy JY, Burns JC. RNA Sequencing reveals beneficial effects of atorvastatin on endothelial cells in acute Kawasaki disease. J Am Heart Assoc. 2022;11:e025408. doi: 10.1161/JAHA.122.025408

76. Manlhiot C, Newburger JW, Low T, Dahdah N, Mackie AS, Raghuveer G, Giglia TM, Dallaire F, Mathew M, Runeckles K, et al; International Kawasaki Disease Registry. Low-molecular weight heparin vs warfarin for thromboprophylaxis in children with coronary artery aneurysms after Kawasaki disease: a pragmatic registry trial. Can J Cardiol. 2020;36:1598–1607. doi: 10.1016/j.cjca.2020.01.016

77. Baker AL, Vanderpluym C, Gauvreau KA, Fulton DR, de Ferranti SD, Friedman KG, Murray JM, Brown LD, Almond CS, Evans-Langhorst M, et al. Safety and efficacy of warfarin therapy in Kawasaki disease. J Pediatr. 2017;189:61–65. doi: 10.1016/j.jpeds.2017.04.051

78. Portman MA, Jacobs JP, Newburger JW, Berger F, Grosso MA, Duggal A, Tao B, Goldenberg NA; ENNOBLE-ATE Trial Investigators. Edoxaban for thromboembolism prevention in pediatric patients with cardiac disease. J Am Coll Cardiol. 2022;80:2301–2310. doi: 10.1016/j.jacc.2022.09.031

79. Dummer KB, Miyata K, Shimizu C, Tremoulet AH, Gleason J, Gordon JB, Burns JC. DOACs in patients with giant coronary artery aneurysms after Kawasaki disease. JAMA Netw Open. 2023;6:e2343801. doi: 10.1001/jamanetworkopen.2023.43801

80. Payne RM, Burns KM, Glatz AC, Male C, Donti A, Brandao LR, Balling G, VanderPluym CJ, Bu'Lock F, Kochilas LK, et al. Apixaban for prevention of thromboembolism in pediatric heart disease. J Am Coll Cardiol. 2023;82:2296–2309. doi: 10.1016/j.jacc.2023.10.010

81. Kustos SA, Fasinu PS. Direct-acting oral anticoagulants and their reversal agents: an update. Medicines (Basel). 2019;6:103. doi: 10.3390/medicines6040103

82. Burns JC, El-Said H, Tremoulet AH, Friedman K, Gordon JB, Newburger JW. Management of myocardial infarction in children with giant coronary artery aneurysms after Kawasaki disease. J Pediatr. 2020;221:230–234. doi: 10.1016/j.jpeds.2020.02.033

83. Brogan P, Burns JC, Cornish J, Diwakar V, Eleftheriou D, Gordon JB, Gray HH, Johnson TW, Levin M, Malik I, et al; Kawasaki Disease Writing Group on behalf of the Royal College of Paediatrics and Child Health and the British Cardiovascular Society. Lifetime cardiovascular management of patients with previous Kawasaki disease. Heart. 2020;106:411–420. doi: 10.1136/heartjnl-2019-315925

84. Tsuda E, Hamaoka K, Suzuki H, Sakazaki H, Murakami Y, Nakagawa M, Takasugi H, Yoshibayashi M. A survey of the 3-decade outcome for patients with giant aneurysms caused by Kawasaki disease. Am Heart J. 2014;167:249–258. doi: 10.1016/j.ahj.2013.10.025

85. Jone PN, Tapia D, Davidson J, Fagan TE, Browne L, Ing RJ, Kay J. Successful treatment of myocardial infarction in an infant with Kawasaki disease. Semin Cardiothorac Vasc Anesth. 2015;19:255–259. doi: 10.1177/1089253215573328

86. Daniels LB, Tjajadi MS, Walford HH, Jimenez-Fernandez S, Trofimenko V, Fick DB Jr, Phan HA, Linz PE, Nayak K, Kahn AM, et al. Prevalence of Kawasaki disease in young adults with suspectedmyocardial ischemia.Circulation.2012;125:2447–2453.doi: 10.1161/CIRCULATIONAHA.111.082107

87. Gordon JB, Daniels LB, Kahn AM, Jimenez-Fernandez S, Vejar M, Numano F, Burns. JC. The spectrum of cardiovascular lesions requiring intervention in adults after Kawasaki disease. JACC Cardiovasc Interv. 2016;9:687–696. doi: 10.1016/j.jcin.2015.12.011

88. Capannari TE, Daniels SR, Meyer RA, Schwartz DC, Kaplan S. Sensitivity, specificity and predictive value of two-dimensional echocardiography in detecting coronary artery aneurysms in patients with Kawasaki disease. J Am Coll Cardiol. 1986;7:355–360. doi: 10.1016/s0735-1097(86)80505-8

89. Hill KD, Frush DP, Han BK, Abbott BG, Armstrong AK, DeKemp RA, Glatz AC, Greenberg SB, Herbert AS, Justino H, et al; Image Gently Alliance. Radiation safety in children with congenital and acquired heart disease: a scientific position statement on multimodality dose optimization from the image gently alliance. JACC Cardiovasc Imaging. 2017;10:797–818. doi: 10.1016/j.jcmg.2017.04.003

90. Singhal M, Singh S, Gupta P, Sharma A, Khandelwal N, Burns JC. Computed tomography coronary angiography for evaluation of children with Kawasaki disease. Curr Probl Diagn Radiol. 2018;47:238–244. doi: 10.1067/j.cpradiol.2017.09.013

91. Gellis L, Castellanos DA, Oduor R, Gauvreau K, Dionne A, Newburger J, Friedman KG. Comparison of coronary artery measurements between echocardiograms and cardiac CT in Kawasaki

disease patients with aneurysms. J Cardiovasc Comput Tomogr. 2022;16:43–50. doi: 10.1016/j.jcct.2021.09.002

92. Singhal M, Pilania RK, Jindal AK, Gupta A, Sharma A, Guleria S, Johnson N, Maralakunte M, Vignesh P, Suri D, et al. Distal coronary artery abnormalities in Kawasaki disease: experience on CT coronary angiography in 176 children. Rheumatology (Oxford). 2023;62:815–823. doi: 10.1093/rheumatology/keac217

93. Rajiah P, Cummings KW, Williamson E, Young PM. CT fractional flow reserve: a practical guide to application, interpretation, and problem solving. Radiographics. 2022;42:340–358. doi: 10.1148/rg.210097

94. Tsujii N, Tsuda E, Kanzaki S, Ishizuka J, Nakashima K, Kurosaki K. Late wall thickening and calcification in patients after Kawasaki disease. J Pediatr. 2017;181:167–171.e2. doi: 10.1016/j.jpeds.2016.10.026

95. Kahn AM, Budoff MJ, Daniels LB, Oyamada J, Gordon JB, Burns JC Usefulness of calcium scoring as a screening examination in patients with a history of Kawasaki disease. Am J Cardiol. 2017;119:967–971. doi: 10.1016/j.amjcard.2016.11.055

96. Chin MS, Steigner M, Yin W, Kwong RY, Siedlecki AM. Intraluminal assessment of coronary arteries with ferumoxytol-enhanced magnetic resonance angiography. JACC Cardiovasc Imaging. 2018;11:505–508. doi: 10.1016/j.jcmg.2017.10.017

97. Dong Z, Si G, Zhu X, Li C, Hua R, Teng J, Zhang W, Xu L, Qian W, Liu B, et al. Diagnostic performance and safety of a novel ferumoxytol-enhanced coronary magnetic resonance angiography. Circ Cardiovasc Imaging. 2023;16:580–590. doi: 10.1161/CIRCIMAGING.123.015404

98. Matsumoto K, Yokota H, Yoda T, Ebata R, Mukai H, Masuda Y, Uno T. Reproducibility between three-dimensional turbo spin-echo and two-dimensional dual inversion recovery turbo spin-echo for coronary vessel wall imaging in Kawasaki disease. Sci Rep. 2022;12:6835. doi: 10.1038/s41598-022-10951-0

99. Bratis K, Hachmann P, Child N, Krasemann T, Hussain T, Mavrogeni S, Botnar R, Razavi R, Greil G. Cardiac magnetic resonance feature tracking in Kawasaki disease convalescence. Ann Pediatr Cardiol. 2017;10:18–25. doi: 10.4103/0974-2069.197046

100. Tacke CE, Romeih S, Kuipers IM, Spijkerboer AM, Groenink M, Kuijpers TW. Evaluation of cardiac function by magnetic resonance imaging during the follow-up of patients with Kawasaki disease. Circ Cardiovasc Imaging. 2013;6:67–73. doi: 10.1161/CIRCIMAGING.112.976969

101. Hoshino S, Shimizu C, Jain S, He F, Tremoulet AH, Burns JC. Biomarkers of inflammation and fibrosis in Kawasaki disease patients years after initial presentation with low ejection fraction. J Am Heart Assoc. 2020;9:e014569. doi: 10.1161/JAHA.119.014569

102. Mavrogeni S, Papadopoulos G, Hussain T, Chiribiri A, Botnar R, Greil GF. The emerging role of cardiovascular magnetic resonance in the evaluation of Kawasaki disease. Int J Cardiovasc Imaging. 2013;29:1787–1798. doi: 10.1007/s10554-013-0276-9

103. Doan TT, Wilkinson JC, Loar RW, Pednekar AS, Masand PM, Noel CV. Regadenoson stress perfusion cardiac magnetic resonance imaging in children with Kawasaki disease and coronary artery disease. Am J Cardiol. 2019;124:1125–1132. doi: 10.1016/j.amjcard.2019.06.033

104. Ogawa S, Ohkubo T, Fukazawa R, Kamisago M, Kuramochi Y, Uchikoba Y, Ikegami E, Watanabe M, Katsube Y. Estimation of myocardial hemodynamics before and after intervention in children with Kawasaki disease. J Am Coll Cardiol. 2004;43:653–661. doi: 10.1016/j.jacc.2003.10.032

105. Agrawal H, Qureshi AM. Cardiac catheterization in assessment and treatment of Kawasaki disease in children and adolescents. Children (Basel). 2019; 6:32. doi: 10.3390/children6020032

106. Sugimura T, Kato H, Inoue O, Fukuda T, Sato N, Ishii M, Takagi J, Akagi T, Maeno Y, Kawano T. Intravascular ultrasound of coronary arteries in children: assessment of the wall morphology and the lumen after Kawasaki disease. Circulation. 1994;89:258–265. doi: 10.1161/01.cir.89.1.258

107. Mitani Y, Ohashi H, Sawada H, Ikeyama Y, Hayakawa H, Takabayashi S, Maruyama K, Shimpo H, Komada Y. In vivo plaque composition and morphology in coronary artery lesions in adolescents and young adults long after Kawasaki disease: a virtual histology-intravascular ultrasound study. Circulation. 2009;119:2829–2836. doi: 10.1161/CIRCULATIONAHA.108.818609

108. Dionne A, Ibrahim R, Gebhard C, Bakloul M, Selly JB, Leye M, Dery J, Lapierre C, Girard P, Fournier A, et al. Coronary wall structural changes in patients with Kawasaki disease: new insights from optical coherence tomography (OCT). J Am Heart Assoc. 2015;4:e001939. doi: 10.1161/JAHA.115.001939

109. Tedla BA, Burns JC, Tremoulet AH, Shimizu C, Gordon JB, El-Said H, Golding F, Davis. CK, Dummer KB. Exercise stress echocardiography in Kawasaki disease patients with coronary aneurysms. Pediatr Cardiol. 2023;44:381–387. doi: 10.1007/s00246-022-03037-1

110. Noto N, Kamiyama H, Karasawa K, Ayusawa M, Sumitomo N, Okada T, Takahashi S. Long-term prognostic impact of dobutamine stress echocardiography in patients with Kawasaki disease and coronary artery lesions: a 15-year follow-up study. J Am Coll Cardiol. 2014;63:337–344. doi: 10.1016/j.jacc.2013.09.021

111. Dahdah N, Kung SC, Friedman KG, Marelli A, Gordon JB, Belay ED, Baker AL, Kazi DS, White PH, Tremoulet AH; on behalf of the American Heart Association Rheumatic Fever, Endocarditis, Kawasaki Disease Committee of the Council on Lifelong Congenital Heart Disease and Heart Health in the Young, and the Council on Arteriosclerosis, Thrombosis and Vascular Biology. Falling through the cracks: the current gap in the health care transition of patients with Kawasaki disease: a scientific statement from the American Heart Association. J Am Heart Assoc. 2021;10:e023310. doi: 10.1161/JAHA.121.023310

112. Mitani Y, Tsuda E, Kato H, Higaki T, Fujiwara M, Ogawa S, Satoh F, Nakamura Y, Takahashi K, Ayusawa M, et al. Emergence and characterization of acute coronary syndrome in adults after confirmed or missed history of Kawasaki disease in Japan: a Japanese nationwide survey. Front Pediatr. 2019;7:275. doi: 10.3389/fped.2019.00275

113. Maresca D, Correia M, Villemain O, Bize A, Sambin L, Tanter M, Ghaleh B, Pernot M. Noninvasive imaging of the coronary vasculature using ultrafast ultrasound. JACC Cardiovasc Imaging. 2018;11:798–808. doi: 10.1016/j.jcmg.2017.05.021

Addition

Differential diagnosis of Kawasaki disease with other diseases*

	Measles	Parvovirus infection	Scarlet fever	Infection, caused *Arcanobacterium haemolyticum*	Yersiniosis	Infection, caused by M. pneumoniae-associated mucositis (MPAM)	Idiopathic juvenile arthritis
Typical age	Any	7-10 years	> 7 years	10-30 years	Any	Any	< 16 years old
Fever	Above 38.3°C unanswered on antibiotics	Short-lived, usually subfebrile	Yes	Yes	Yes	Yes	Yes
Qatar upper respiratory ways	Bright expressed, exudative and	Possible, weakly expressed	Pharyngitis, typical purulent angina	Pharyngitis, typical purulent tonsillitis	Possible	Yes (100%)	Not characteristically
Rash	Spotted-papular, appearance – on 5- and day diseases I, characteristic phasedness	Generalized spotted, appears on background of disappearance fevers, typically on the face Possible "syndrome gloves and socks"	Generalized on the spotted dot wow, from the first days fever, necessarily on the face	Spotted, scarlet fever and rash (75%) from the first days fevers	Scarlatinopods BNA, papular, urticarial, Hemorrhagic Typical hyperemia face, neck, hands and feet	Minimal skin manifestations (31%)	Possible, spotted-papular, with any localization
Changes mucous oral cavities	Stains Koplika	Not typical	Pharyngitis, crimson tongue	Pharyngitis, raspberry tongue	Raspberry tongue	Bright hyperemia, soreness, chapped lips, aphthae and ulcers on the inside cheeks, tongue, gums	Not characteristically

Pharyngitis	Not characteristic	Not typical	Characteristic, from catarrhal about to purulent sore throat	Catarrhal (97-100%), purulent angina (70%)	Characteristic	Not typical	Not characteristic
Conjuncts vit	Double-sided, exudative and	Not typical	Not typical	Not typical	Possible	Typical (97%)	Not characteristic
Cervical lymphadenitis	Not characteristic	Not typical	Double-sided	Bilateral, 41-48%	Possible, additionally – others groups	Not typical	Not characteristic
Changes palms and stop	Not typical	Not typical	Peeling on 2-3 weeks	Peeling for 2-3 weeks	Erythema, peeling for 2-3 weeks	Possible	Not typical
Damage joints	Not typical	Possible arthritis and arthropathy after disappearance fevers	Possible as late complication	Not typical	Possible in 2-3%	Not typical	Characteristically
Diarrhea	Possible	Not typical	Not typical	Not typical	Characteristic	Not typical	Not typical
Changes in laboratory their indicators	Typical for viral infections	Typical for viral infections, possible anemia, thrombocytopenia	Leukocytosis with a shift formulas left ↑ ESR, ↑ SRB	Leukocytosis with by shifting the formula left ↑ ESR, ↑ CRP	Leukocytosis with by shifting the formula left ↑ ESR, ↑ CRP	Nonspecific	Leukocytosis with landslide formulas left ↑ ESR, ↑ CRP
Opportunities laboratory oh verifications	Virological not the same PCR research in the first 7 days diseases, serological research from 4 days ago	Virological, PCR, serological research for specification etiology	Selection pathogen from oropharynx - S. pyogenes, increase ASLO titer	Selection pathogen from oropharynx	Serological research (RA, RNGA, ELISA)	PCR and/or IgM to M. pneumoniae	

	appearances rashes Specification vaccination status						

* If criteria for complete or incomplete Kawasaki disease are present, priority should be given to initiating treatment rather than awaiting diagnostic results for other diseases

Differential diagnosis of MIS-c and HC (most distinctive features between the two conditions)

The criterion is whether **sign**	**Kawasaki disease**	**MIS-c (Multisystem Inflammatory Syndrome in Children). Multisystem inflammatory childhood syndrome**
Etiology	The exact cause is unknown. It is likely an immune response to an infectious or other trigger in genetically susceptible children.	Post-infectious hyperinflammatory state clearly associated with with a previous SARS-CoV-2 infection (develops 2–6 (up to 8) weeks after COVID-19). A link must be proven
Age	Mostly children under 5 years of age. Average age: children 2-3 years old, very rare in those older than 8 years. Highest incidence in children of East Asian origin	Average age 7–9 years. Highest incidence among children Latino and African Americans
Fever	≥4-5 days, usually >38–39°C, resistant to antipyretics	≥38°C ≥24 hours Often >39°C, often with chills
Conjunctivitis	Without exudate, bilateral. Classically, a limbal bright zone (absence of redness around the iris) is observed – up to 90% of cases	In about 40% of cases, limbal areas are involved
Oral changes cavities	Hyperemia of the oropharyngeal mucosa, dry, red and cracked lips, "Strawberry" tongue - very characteristic signs	Less common: lip lesions (20–30% of cases), “strawberry” tongue – rare (up to 4–5%)
Changes to limbs	Erythema and edema of the palms and feet in the acute phase; pain in the extremities. In the subacute phase, lamellar peeling of the skin on the tips of the fingers and toes.	Quite rare: Swelling or redness of the hands/feet is uncommon in MIS-s. Skin peeling is uncharacteristic
Lymphadenopathy iya	Usually unilateral – size of lymph node ≥1.5 cm (occurs in about 25–50% of patients with UC). Other groups of lymph nodes are not enlarged.	Cervical lymphadenopathy occurs in 4-5% of cases
Gastro-intestinal symptoms	In about 20% of cases (moderate abdominal pain, nausea, diarrhea, sometimes a rare clinical picture of acute abdomen)	Very common (50-90% of cases): abdominal pain (often severe), vomiting, diarrhea

Damage hearts	Hypotension/shock – very rare (≈2 –3% of cases, coronary shock syndrome). Heart failure – usually not, although minimal left ventricular dysfunction is possible. Myocarditis is possible but usually mild. Troponin is normal or slightly elevated, NT-proBNP often <1000 pg/mL. Systolic cardiac function is usually preserved (LVEF normal or slightly decreased)	Hypotension in almost all in severe cases. Shock often develops – most hospitalized MIS-C patients have signs of perfusion failure (cardiogenic or mixed genesis). Almost all patients: noted myocarditis/LV dysfunction of varying degrees. Often LVEF <55%, arrhythmias may be present (extrasystole, blockades). Troponin is elevated in most cases, NT-proBNP is very high (hundreds–thousands of pg/ml), which reflects severe heart damage
Coronary arteries	Without treatment, about 20-25% of patients develop aneurysms (sometimes giant). Aneurysms can persist, causing the risk of thrombosis, myocardial infarction in the long term	Dilatation or small aneurysms of the coronary arteries (10-15% of cases). Typically – transient, disappear within 1–3 months. Cases of giant aneurysms are casuistic. The risk of myocardial infarction is minimal
Laboratory markers inflammation	Elevated: CRP usually 30–100 mg/L. Marks of inflammation are pronounced, but rarely reach extreme values	Severely elevated: CRP often >100–200 mg/L. Elevated levels of inflammatory markers often greater than in UC
Leukocytes, differential	Leukocytosis with neutrophilia is characteristic. Lymphopenia is usually absent.	Often leukopenia or normal leukocytes on the background of lymphopenia
Platelets	Thrombocytosis after 7–10 days of illness (>450×10*9/L). May be normal in the acute period.	Thrombocytopenia is common. Thrombocytosis is not typical.
Coagulopathy (D-dimer)	Usually normal or moderately elevated. D-dimer values in UC rarely exceed 1000–2000 ng/mL.	Very high D-dimer is an almost constant sign of MIS-C (reflects hypercoagulability). Often >3000 ng/mL, sometimes >5000–8000 ng/mL
Ferritin	Moderate increase: usually <300–500 ng/ml, values >1000 ng/ml are uncharacteristic (if present, should be suspect macrophage activation syndrome)	Significant increase: often 500–1000 or more ng/ml, not infrequently > 2000 ng/ml in severe cases. Hyperferritinemia reflects massive activation of the immune system
Other flammable mediators	Clinically, incomplete MAS (macrophage activation syndrome) may develop in <2% of patients	Cytokine “storm”. Often there are signs of MAS-like

		hyperinflammation (very high ferritin, triglycerides, cytopenias)
PCR/serology SARS-CoV-2	Negative results (no connection with COVID-19). The presence of coronavirus infection is not typical; if a child with signs of HC tests positive for COVID-19, it is necessary to differentiate from MIS-c	Positive in most cases: ≥95% of patients have either a positive PCR or antigen or IgG antibodies to SARS-CoV-2 nucleocapsid (N) protein, or known recent contact
Treatment (first line)	IV infusion 2 g/kg IV (+ in the presence of risk factors, intensification of therapy)	IVIG 2 g/kg + glucocorticoids
Treatment (resistant cases)	If fever persists >36 hours – repeat dose of IVLIG 2 g/kg or pulse therapy with methylprednisolone, or infliximab 5 mg/kg IV (see the algorithm for treatment of chronic obstructive pulmonary disease)	If there is no response after 24–36 hours: re-administration of IVLI is not recommended. Instead, increase the dose of GCS or anakinra. Possible tocilizumab or infliximab
Forecast, consequences	With timely treatment, the prognosis is excellent. Mortality <0.1%. Fever and acute inflammatory manifestations resolve within 1–2 days after IVLIG. ACAs form in 3–5% (with treatment); most of them regress within 1–2 years, but lesions may remain (especially giant ones). Requires observation by a cardiologist (risk of thrombosis, coronary artery disease). Children without aneurysms recover completely without long-term consequences	The prognosis is generally favorable with appropriate treatment. Mortality rate ~1–2% (mostly from refractory shock or multiorgan failure). Cardiac function normalizes in > 80% of cases within 1–4 weeks; 10–20% may have mild residual changes (moderate LV dysfunction)