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Review article

French national diagnostic and care protocol for Kawasaki disease

Protocole national de diagnostic et de soins maladie de Kawasaki

C. Galeotti[a,*], F. Bajolle[b], A. Belot[c], S. Biscardi[d], E. Bosdure[e], E. Bourrat[f], R. Cimaz[g], R. Darbon[h], P. Dusser[a], O. Fain[i], V. Hentgen[j], V. Lambert[k], A. Lefevre-Utile[l], C. Marsaud[a], U. Meinzer[f], L. Morin[m], M. Piram[n], O. Richer[o], J.-L. Stephan[p], D. Urbina[q], I. Kone-Paut[a], collaborators1

[a] *Service de rhumatologie pédiatrique, centre de référence des maladies auto-inflammatoires rares et des amyloses, CHU de Bicêtre, 78, rue du Général-Leclerc, 94275 Le Kremlin-Bicêtre, France*
[b] *M3C-Necker-Enfants–Malades, hôpital Necker-Enfants–Malades, université de Paris Cité, Paris, France*
[c] *Service de néphrologie, rhumatologie et dermatologie pédiatriques, centre de référence des rhumatismes inflammatoires et maladies auto-immunes systémiques rares de l'enfant (RAISE), hôpital Femme-Mère–Enfant, hospices civils de Lyon, Lyon, France*
[d] *Service des urgences pédiatriques, centre hospitalier intercommunal de Créteil, Créteil, France*
[e] *Service de spécialités pédiatriques et médecine infantile, CHU Timone-Enfants, 13385 Marseille cedex 5, France*
[f] *Service de pédiatrie générale, maladies infectieuses et médecine interne, centre de référence des rhumatismes inflammatoires et maladies auto-immunes systémiques rares de l'enfant, hôpital universitaire Robert-Debré, université hospital, Assistance publique–Hôpitaux de Paris, 75019 Paris, France*
[g] *Pediatric Rheumatology Unit, Gaetano Pini Hospital, Department of Clinical Sciences and Community Health, Research Centre for Adult and Pediatric Rheumatic Diseases, Università degli Studi di Milano, Milan, Italy*
[h] *Association France vascularites, Blaisy-Bas, France*
[i] *Service de médecine interne, hôpital Saint-Antoine, Sorbonne université, AP–HP, 75012 Paris, France*
[j] *Service de pédiatrie, centre de référence des maladies auto-inflammatoires et de l'amylose (CEREMAIA), centre hospitalier de Versailles, Le Chesnay, France*
[k] *Service de radiologie pédiatrique, Institut mutualiste Montsouris, CHU de Bicêtre, Le Kremlin-Bicêtre, France*
[l] *Service de pédiatrie générale et des urgences pédiatriques, hôpital Jean-Verdier, Assistance publique–Hôpitaux de Paris (AP–HP), Bondy, France*
[m] *Service de réanimation pédiatrique et néonatale, DMU 3 santé de l'enfant et adolescent, hôpital Bicêtre, université Paris-Saclay, AP–HP, Le Kremlin-Bicêtre, France*
[n] *Division of Dermatology, Department of Pediatrics, Centre Hospitalier Universitaire Sainte Justine, Université de Montréal, Montréal, Quebec, Canada*
[o] *Service des urgences pédiatriques, hôpital universitaire de Pellegrin, Bordeaux, France*
[p] *Service de pédiatrie, CHU Saint-Étienne, Saint-Étienne, France*
[q] *Service d'accueil des urgences pédiatriques, hôpital Nord, AP–HM, 13005 Marseille, France*

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ABSTRACT

Kawasaki disease (KD) is an acute vasculitis with a particular tropism for the coronary arteries. KD mainly affects male children between 6 months and 5 years of age. The diagnosis is clinical, based on the international American Heart Association criteria. It should be systematically considered in children with a fever, either of 5 days or more, or of 3 days if all other criteria are present. It is important to note that most children present with marked irritability and may have digestive signs. Although the biological inflammatory response is not specific, it is of great value for the diagnosis. Because of the difficulty of recognising incomplete or atypical forms of KD, and the need for urgent treatment,

Abbreviations: ACS, acute coronary syndrome; AHA, American Heart Association; ANSM, French National Agency for the safety of medicines and health products; ARF, acute renal failure; BCG, Bacillus Calmette-Guérin; CPK, creatinine phospho-kinase; CRP, C-reactive protein; CT, computed tomography; CVRF, cardiovascular risk factor; ECG, electrocardiogram; EMS, emergency medical services; ENT, ear, nose, throat; ESR, erythrocyte sedimentation rate; FAI^{2}R, Rare Autoimmune and Autoinflammatory Diseases Network; HAS, French Supreme Health Authority; HDL, high density lipoprotein; ICU, intensive care unit; IFX, infliximab; IgA, immunoglobulin A; IVIG, intravenous immunoglobulin; IL, interleukin; INR, International normalized ratio; KD, Kawasaki disease; KDSS, Kawasaki disease shock syndrome; LMWH, low molecular weight heparin; LVTD, left ventricle telediastolic; LVTS, left ventricle telesystolic; MA, marketing authorisation; MAS, macrophage activation syndrome; MISC, multisystem inflammatory syndrome in children; MMR, measles, mumps, rubella; MRI, magnetic resonance imaging; NDCP, national diagnostic and care protocol; NSAID, non-steroidal anti-inflammatory drug; PET, positron emission tomography; PIMS, paediatric inflammatory multisystem syndrome; SHARE, single hub and access point for paediatrics rheumatology in Europe; SIADH, syndrome of inappropriate antidiuretic hormone secretion; tPA, tissue plasminogen activator; TNF, tumor necrosis factor; TPE, therapeutic patient education; TSS, toxic shock syndrome; VIA, anterior interventricular; VKA, vitamin K antagonist; VZV, varicella-zoster virus.

* Corresponding author.
E-mail address: caroline.galeotti@aphp.fr (C. Galeotti).
[1] R. Basmaci, L. De Pontual, S. Di Filippo, E. Grimprel, C. Labreze, M. Luypaert, T. Mehaigneire, E. Merlin, R. Mouy, K. Retornaz, H. Reumaux, S. Tellier, B. Terrier, T.A. Tran.

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the child should be referred to a paediatric hospital as soon as the diagnosis is suspected. In the event of signs of heart failure (pallor, tachycardia, polypnea, sweating, hepatomegaly, unstable blood pressure), medical transfer to an intensive care unit (ICU) is essential. The standard treatment is an infusion of IVIG combined with aspirin (before 10 days of fever, and for a minimum of 6 weeks), which reduces the risk of coronary aneurysms. In case of coronary involvement, antiplatelet therapy can be maintained for life. In case of a giant aneurysm, anticoagulant treatment is added to the antiplatelet agent. The prognosis of KD is generally good and most children recover without sequelae. The prognosis in children with initial coronary involvement depends on the progression of the cardiac anomalies, which are monitored during careful specialised cardiological follow-up.

Mots clés :
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Diagnostic
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Suivi

RÉSUMÉ

La maladie de Kawasaki (MK) est une vascularite aiguë ayant un tropisme particulier pour les artères coronaires. La MK touche préférentiellement les enfants âgés de 6 mois à 5 ans, avec une prédominance masculine. Le diagnostic est clinique, basé sur les critères internationaux de l'American Heart Association, et doit être posé systématiquement chez les enfants présentant une fièvre depuis 5 jours ou plus, ou depuis 3 jours si tous les critères sont présents. Il est important de noter que la plupart des enfants présentent une irritabilité marquée et parfois des signes digestifs. Une inflammation biologique marquée, bien que non spécifique, est d'une grande valeur pour le diagnostic. En raison des difficultés à reconnaître la MK dans les formes incomplètes ou atypiques, et de l'urgence du traitement, l'enfant doit être référé à un hôpital pédiatrique dès que le diagnostic est simplement suspecté. En cas de signes d'insuffisance cardiaque (pâleur, tachycardie, polypnée, sueurs, hépatomégalie, instabilité tensionnelle), un transfert en soins intensifs est indispensable. Le traitement de référence repose sur les IgIV associée à l'aspirine, (avant 10 jours de fièvre, et pour une durée minimale de 6 semaines), ce qui réduit le risque d'anévrisme coronarien. En cas d'atteinte coronarienne, les antiagrégants peuvent être maintenus à vie. En cas d'anévrisme géant, les anticoagulants sont ajoutés aux antiagrégants. Le pronostic de la MK est généralement bon, la majorité des enfants se rétablissant sans séquelles. En cas d'atteinte coronarienne initiale, le pronostic dépend de l'évolution de l'atteinte cardiaque telle qu'elle est définie au cours d'un suivi cardiologique rapproché.

1. Summary for the attending physician

Kawasaki disease (KD) is an acute vasculitis of the medium and to a lesser degree the small vessels, with a particular tropism for the coronary arteries. KD is the leading cause of acquired heart disease in children in the developed countries.

KD is potentially serious because it may damage the coronary arteries, which is more frequent when diagnosis and treatment are delayed. Early treatment with IVIG (within 10 days after the onset of fever) reduces the risk of coronary aneurysms to 5%, compared to a rate of 15–25% without early treatment.

KD usually mainly affects male children who are between 6 months and 5 years of age (sex ratio male/female: 1.5/1). The prevalence varies according to ethnic group. The incidence in Japanese and North East Asian populations is 10–60 times higher than that in Western populations.

Although the pathophysiology of KD is still unknown, it is generally accepted that one or more infectious agents possibly induce an inappropriate inflammatory response in genetically predisposed individuals.

The diagnosis is clinical and should be systematically suspected in children presenting with a fever of 5 days or more (and of 3 days if all clinical signs are present). It is important to note that most children present with marked general signs (irritability) and may have digestive symptoms (anorexia, diarrhoea, abdominal pain). Although the biological inflammatory response (leukocytosis and elevated C-reactive protein [CRP]) is not specific, it is of great value for the diagnosis.

The diagnosis is sometime difficult. According to international criteria, it is made in the event of persistent fever associated with at least 4 of the following clinical criteria of mucocutaneous inflammation:

- polymorphic skin rash (most often morbilliform, scarlatiniform or urticarial);
- bilateral acute non-purulent conjunctival hyperaemia;
- enanthema of the lips and entire oral cavity: dry, cracked lips, raspberry tongue (with desquamation of the filiform papillae, with a red, shiny surface), stomatitis, pharyngeal erythema;
- involvement of the extremities: erythema, oedema, desquamation (late sign);
- cervical lymphadenopathy, one of which is larger than 1.5 cm.

The signs of KD do not appear simu7ltaneously, and some of them may have disappeared if the patient is seen 1 to 2 weeks after the onset of fever. In this case, it is very important to review the initial signs and symptoms with parents and possibly previously consulted doctors because they are highly important for the diagnosis.

Certain children may present with incomplete (not meeting all criteria), or atypical (with rarer signs) forms, particularly when KD occurs before the age of 1 or after 5 years old. Additional biological signs and cardiac ultrasound help make the diagnosis in these cases.

The prognosis of KD is generally good and most children recover without sequelae. The prognosis in children with initial coronary involvement depends on the progression of cardiac lesions that are monitored during regular specialised cardiological follow-up.

Due to the difficulty of identifying incomplete or atypical forms of KD and the urgency of treatment, a child should be referred

to a paediatric hospital as soon as the diagnosis is suspected. In the presence of signs of heart failure (pallor, tachycardia, polypnea, sweating, hepatomegaly, blood pressure instability), the child must be transferred to an ICU (see Orphanet Emergency form[1]).

The first-line treatment is an infusion of polyvalent immunoglobulin IVIG combined with aspirin for at least 6 weeks. Although the vaccination schedule must be adapted when patients receive IVIG (https://www.infovac.fr/), vaccines are not contraindicated.

In case of coronary involvement, antiplatelet therapy can be maintained for life. In case of a giant aneurysm, anticoagulant treatment is added to the antiplatelet agent.

Children can lead a normal life. Physical activity and sports are recommended. The adaptation of certain sports practices is only relevant in patients who require prolonged cardiological monitoring.

2. Kawasaki disease: the essentials in 25 points

1. The diagnosis of KD is mainly clinical. The international criteria are an important aid to diagnosis.
2. Not all mucocutaneous signs of KD are present at diagnosis and should therefore also be looked for retrospectively during the examination.
3. Unexplained prolonged fever in an infant with a biological inflammatory reponse should suggest KD.
4. Although it is not part of the international criteria, irritability, erythema of the perineum and inflammation of the BCG scar are helpful in the diagnosis of KD.
5. KD may present misleadingly as a retropharyngeal or paratracheal pseudo adenophlegmon.
6. Viral co-infection and/or lymphocytic meningitis in a patient does not justify reconsidering the diagnosis of Kawasaki.
7. If there are any clinical signs suggesting a diagnosis of KD, inpatient treatment should be begun very rapidly because of the risk of early cardiac complications.
8. In the presence of signs of circulatory failure (pallor, dyspnoea, tachycardia, hepatomegaly, blood pressure instability), the patient should be transferred to an ICU, after first contacting emergency medical services (EMS) if necessary (see Orphanet's Emergency form[1]).
9. Indicators of severe forms at the outset are: age less than 1 year, the presence of shock, a major inflammatory syndrome and/or macrophage activation syndrome (MAS), the presence of early coronary dilatation/aneurysm. These patients should first receive corticosteroids in combination with IVIG.
10. Cardiac ultrasound is necessary to detect complications, particularly coronary aneurysms. It should not delay the start of treatment. A normal cardiac ultrasound does not exclude the diagnosis.
11. Coronary measurements should be related to body surface area and expressed as a Z-score for a comparison over time.
12. The standard of care for KD is a single intravenous infusion of polyvalent immunoglobulins (IVIG) at a dose of 2 g/kg in combination with aspirin.
13. Aspirin is continued at an antiplatelet dose of 3–5 mg/kg/day until at least 6 weeks after the onset of disease.
14. Treatment with IVIG should be started as soon as KD is diagnosed between 4 and 10 days after the onset of fever. It reduces the risk of coronary aneurysms from 25 to 5%.
15. After 10 days, an additional IVIG treatment is justified if fever and/or inflammatory biological response (high CRP) persist.
16. Resistance is defined as persistent or recurrent fever more than 36 hours after the end of IVIG infusion. Therapy must be intensified because this event is associated with a risk of cardiac complications.
17. Delayed initiation of IVIG or the presence of an indicator of a severe form of the disease at the outset are risks of resistance to IVIG treatment. These situations should be discussed with an expert centre for immediate treatment intensification.
18. Predictive scores for IVIG resistance have not been validated except in Asian populations. However, a positive Kobayashi score can be considered to be a risk of resistance in all populations. The Kawanet IVIG resistance prediction score can be used for all non-Asian populations.
19. Treatment intensification includes a second IVIG infusion, corticosteroids, infliximab or anakinra.
20. Cardiological follow-up of patients with uncomplicated KD should include a total of 3 cardiac ultrasounds: at diagnosis, 1–2 weeks and 4–6 weeks after the onset of fever.
21. Patients with coronary anomalies and with a Z-score > 2.5 require more frequent monitoring until luminal dimensions have stopped increasing.
22. A giant aneurysm is defined as a coronary diameter ≥ 8 mm or a Z-score ≥ 10. These patients require anticoagulant therapy with vitamin K antagonists (VKA) or heparin combined with antiplatelet therapy.
23. Education about VKAs must be provided and validated before the patient returns home, to limit the treatment-related complications as much as possible.
24. Children can lead a normal life. Physical activity and sports are recommended.
25. Adaptation of the practice of sports is only relevant in patients who require prolonged cardiological monitoring.

3. Introduction [1–19]

3.1. Pathophysiology

The aetiology of KD is poorly understood. The very young age of onset, the disparities in incidence between countries, associated with migration studies in the USA and the UK, which show that children of Asian origin have a higher incidence than Caucasian children, suggest a genetic predisposition to the disease. Moreover, genetic polymorphisms in certain genes such as *ITPKC, CASP3, FCGR2A, BLK, ORAI*, and *CD40* have been found to be associated with KD and its complications. However, genetics do not fully explain the epidemiology of this disease. Familial forms are rare (2% in siblings, 1% with parents). Some countries report seasonal peaks of disease incidence in winter (Japan, Canada), spring (Taiwan), summer (Korea), autumn (India, Costa Rica) or none (Hawaii). Others describe discordant links with rainfall (rainy season in Costa Rica and Japan or during the driest months in India) or associations with variations in wind direction in the tropospheric layer suggesting that the aetiological agent of KD is airborne. Although many infectious triggers have been described, none are constant or universal. Nevertheless, this hypothesis is consistent with clinical observations that up to 60% of children have digestive (abdominal pain, diarrhoea, vomiting) and/or respiratory symptoms early in the course of the disease. Work on a mouse model suggests that inappropriate activation of innate immunity may play a role, with excessive secretion of pro-inflammatory cytokines such as interleukin 1 (IL-1) and tumour necrosis factor (TNF). Endothelial damage (vasculitis) occurs due to primary activation of innate immunity with monocyte and macrophage infiltration and

[1] https://www.orpha.net/data/patho/Emg/Int/fr/Kawasaki_FR_fr_EMG_ORPHA2331.pdf.

secondary activation of adaptive immunity, involving cytotoxic T cells and IgA due to increased digestive permeability. These findings suggest that the origin of KD is probably multifactorial, triggered by an environmental stimulus, possibly infectious, which induces an inflammatory cascade in genetically predisposed subjects.

3.2. Epidemiology

KD mainly affects children under 5 years of age with a peak incidence between the age of 9 and 11 months. Occurrence after the age of 5 is rare. KD is rarely described in young adults. The disease occurs more frequently in boys and is more severe than in girls (sex ratio = 1.5). KD is an acute disease, with less than 5% of recurrence and low mortality < 0.1%. Deaths usually occur within 15–45 days after the onset of fever and always in association with cardiac complications.

KD is found worldwide but is much more common in Asia, particularly Japan. Its estimated annual incidence (per 100,000 children < 5 years) is 360 in Japan, 220 in South Korea, 20 in North America, 10 in Oceania and 5–15 in Western Europe. The incidence remains poorly known in Africa, South America, Eastern Europe and the Near and Middle East. Epidemiological surveys in the last few years seem to show an unexplained increase in incidence in Asia and Australia, while it has remained stable in North America and Europe. The proportion of incomplete forms also seems to be increasing, and the frequency of cardiac complications is decreasing in Asia while they are stable or increasing in Europe.

4. Objectives of the French national diagnostic and care protocol

The objective of this national diagnosis and care protocol (NDCP) is to provide healthcare professionals with a description of the current optimal diagnostic and therapeutic management and the care pathway for patients with KD. The goal of this NDCP is to optimise and harmonise the management and follow-up protocols for this rare disease throughout the country. It also identifies pharmaceuticals used for an indication that is not included in the marketing authorization as well as specialties, products, or services necessary for patient care but not usually covered or reimbursed.

This NDCP can be used as a reference by the general practitioner, the physician appointed by the patient's national health insurance plan) in consultation with the physician specialised in KD, in particular to draft the treatment protocol with the consulting physician and the patient, in case of a request for exemption from co-payment for an off-list disability.

However, the NDCP cannot take into consideration all specific cases, comorbidities or complications, therapeutic specificities or all hospital care protocols. It does not claim to cover all possible management approaches or to replace the physician's individual responsibility to his patient. Nevertheless, this protocol describes the reference standard of care for a patient with KD. It will be updated according to new validated data. This NDCP has been drafted according to the "Method for drafting a national protocol for the diagnosis and care of rare diseases" published by the Haute Autorité de santé in 2012 (methodological guide available on the HAS website: www.has-sante.fr).

5. Diagnosis and initial assessment [1–171]

5.1. Objectives

- Establish the diagnosis of KD in a timely manner after eliminating differential diagnoses.
- Recognise the different forms of the disease: complete, incomplete or atypical KD.
- Assess the severity of damage, particularly cardiological, and establish a prognosis.
- Announce the diagnosis and present the different aspects of management.
- Establish therapeutic indications.

5.2. Professionals involved (and coordination arrangements)

Any doctor may be confronted with a patient presenting with a combination of clinical signs suggesting KD. Thus, the patient's initial clinical assessment may be performed by the general practitioner, the emergency room physician or the paediatrician. If the results suggest a diagnosis of KD, the child should be referred to a hospital for further treatment. The receiving hospital must perform and have access to a cardio-paediatric evaluation (either because of the presence of or proximity of a cardio-paediatric team (see Orphanet Emergency sheet[1]).

In typical forms of KD without risk factors or immediate severity criteria, treatment may be managed in the local hospital. Management may require the expertise of specialised hospital units (paediatric rheumatology, paediatric infectious diseases and paediatric cardiology team).

The expertise of a specialised paediatric centre is required from the outset to perform the necessary tests and provide optimal treatment to any child with KD and clinical or ultrasound severity criteria or with risk factors (defined in section 5.8). This centre should have a multidisciplinary team: paediatric cardiology, paediatric rheumatology/infectious diseases and nearby paediatric intensive care units.

More rarely, the diagnosis of KD is made retrospectively by the discovery of a coronary anomaly on cardiac ultrasound performed for another reason. Consultation with a specialist is required in this case.

5.3. Circumstances of discovery/suspected diagnosis

The typical presentation is an otherwise healthy young infant or child under 5 years old (most affected children are between 6 months and 5 years old, but KD has been diagnosed in patients up to the age of 40).

The initial symptoms are persistent fever that is often high and spiking, and a marked change in general condition, refusing food, diffuse pain and irritability/inconsolability.

Digestive signs are frequent at this stage (60% of cases) and may be relatively mild with anorexia, abdominal pain, meteorism or diarrhoea, but can occasionally be more severe with signs of peritonitis.

Mucocutaneous inflammation develops either simultaneously or sequentially and includes a generalised, usually maculopapular rash, red eyes without conjunctival discharge, redness and dryness of the lips and the entire oral cavity.

Changes may occur in the hands and feet such as redness and diffuse swelling.

The cervical lymph node syndrome may associate several adenopathies but is usually limited to a single, large, unilateral lymphadenopathy > 1.5 cm. Nevertheless, lymphadenopathy may be misleading and suggests a purulent collection (cervical lymphadenitis initially suspected to be a pyogenic para or retropharyngeal abscess). Lymphadenopathy may be absent in very young infants (< 12 months).

Table 1
Diagnostic criteria for KD [102].

Fever	Duration of 5 days or more
And presence of 4 of the following 5 criteria	
1. Conjunctival hyperaemia	Bilateral, bulbar, non-suppurated
2. Lymphadenopathy	Cervical, often > 1.5 cm usually unilateral
3. Skin rash	Polymorphic, without vesicles or crusts
4. Changes in the lips or oral mucosa	Cracked lips; raspberry tongue; or diffuse oropharyngeal erythema
5. Changing the extremities	Initial stage (up to 10 days of fever): erythema, oedema of hands and feet Convalescent stage (after 10 days of fever): scaling of the skin on the fingertips in a glove-like pattern

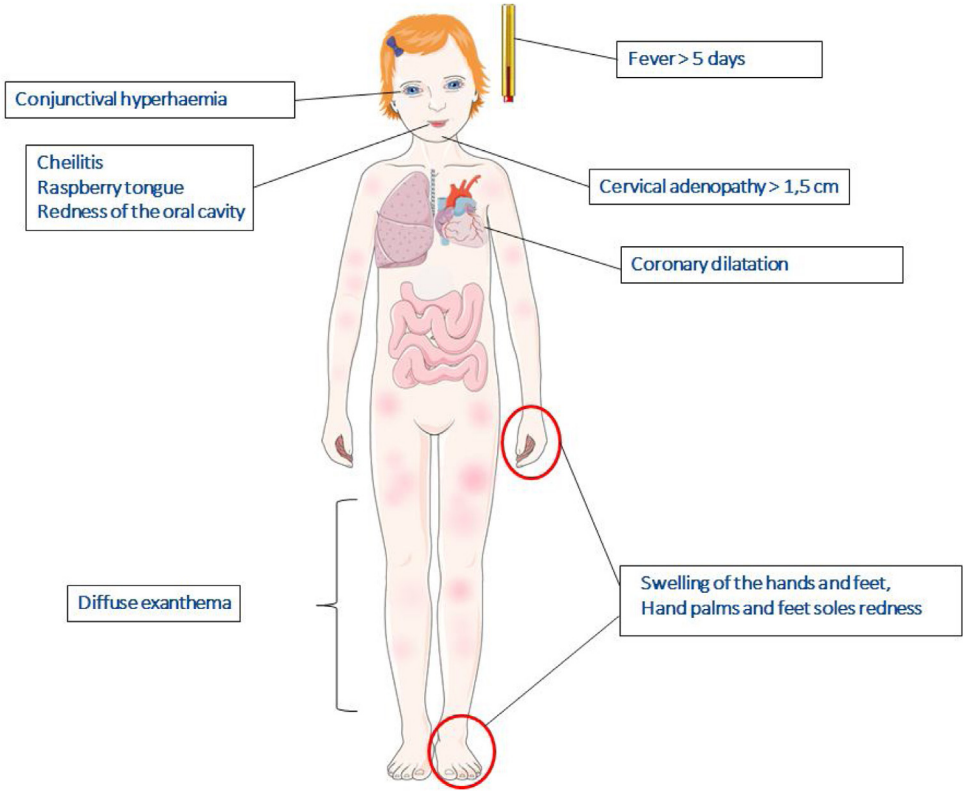

Fig. 1. Diagnostic criteria for KD.

5.4. Confirmation of diagnosis/differential diagnosis

5.4.1. International diagnostic criteria and other common signs

Confirmation of the diagnosis is difficult because it is based on clinical and biological criteria only, which may be supported by the presence of coronary dilatations/aneurysms. Because the treatment of KD is urgent, a mere suspicion of the diagnosis is enough to begin treatment as long as other causes have been reasonably excluded.

5.4.2. Diagnostic criteria

The list of diagnostic criteria is presented in Table 1. Particular attention should be paid to the detailed description of these criteria.

Complete KD corresponds to a fever that has lasted at least 5 days (or only 3 days if all other criteria are met) and the presence of least 4 of the 5 criteria mentioned in Table 1 (American Heart Association [AHA] 2017 criteria, SHARE 2019).

Thus, the diagnosis can be suspected in any infant presenting:

- with a febrile rash and a biological inflammatory response that has been present for more than 3 days (SHARE 2019);
- with a fever that has lasted at least 4 days and with 4 out of 5 of the major criteria, including redness and oedema of the extremities (AHA 2017);
- after only 3 days of fever, by an experienced clinician (AHA 2017);
- or in the case of an isolated fever associated with an inflammatory syndrome that has lasted more than 7 days (AHA 2017).

5.4.3. Other signs suggesting KD

Other signs may be present during acute KD that can help make the diagnosis when all the main criteria are not present. Although there are many signs (see Figs. 1 and 2), these four, in particular, are pertinent:

- irritability: a child who is grumpy, in pain and inconsolable, even in the parent's arms;
- marked rash in the perineal area with early scaling (Fig. 3);
- BCG site reaction: local inflammatory reactivation at the BCG inoculation site (especially in younger children who were vaccinated less than 2 years before);
- brown or white banded discolouration of the nails (chromonychia/leukonychia).

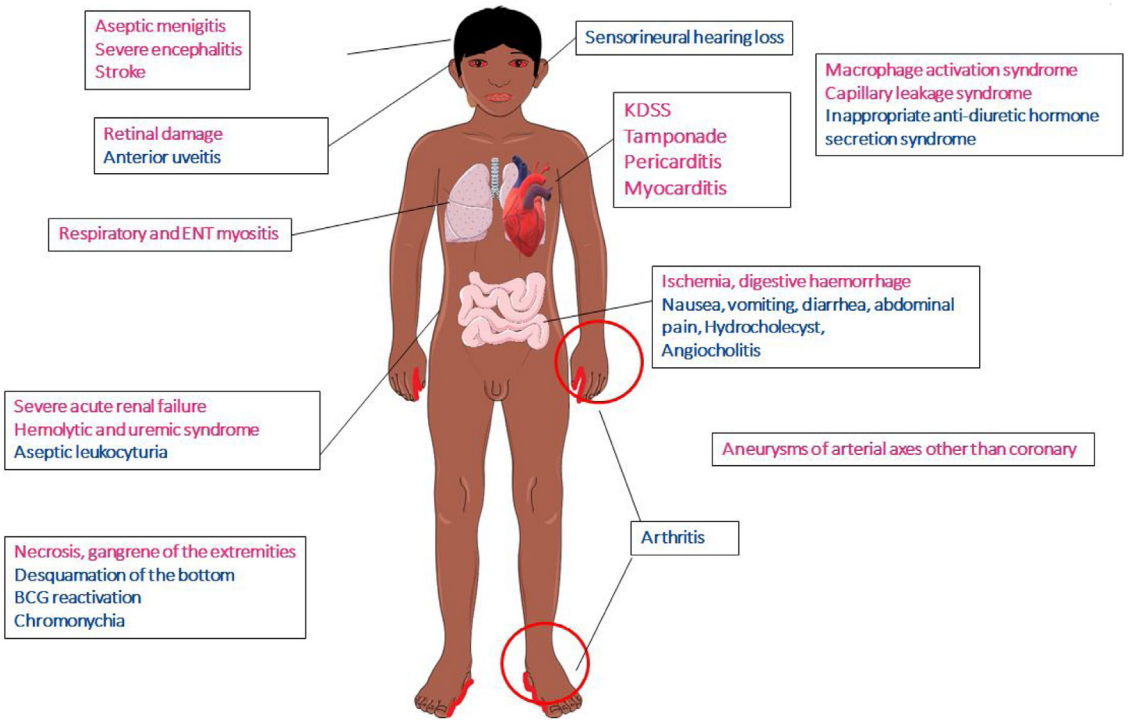

Fig. 2. Other manifestations of KD (pink: severe complications).

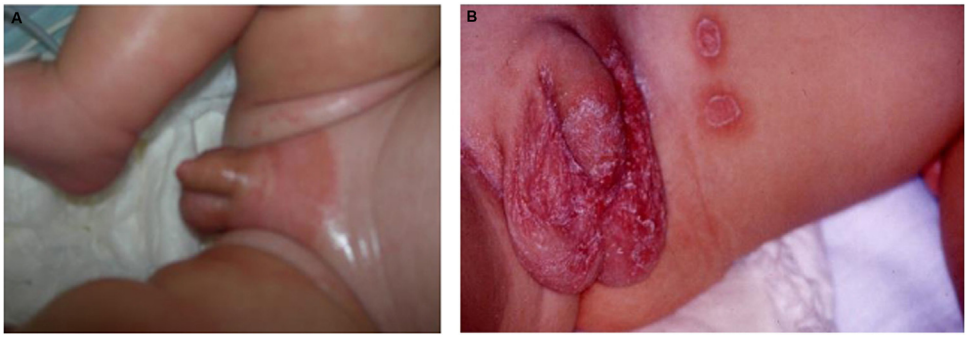

Fig. 3. Perineal damage. A. Perineal exanthema. B. Perineal desquamation.

5.4.4. Diagnosis in the absence of sufficient criteria

Unfortunately, not all affected children are identified with the diagnostic criteria. The diagnosis can be made if a coronary aneurysm is detected on echocardiography. However, a normal cardiac ultrasound does not exclude a diagnosis of KD.

In addition to echocardiography (see specific chapter), blood test results showing marked inflammation help guide the diagnosis, in particular:

- leucocytosis with polynucleosis;
- thrombocytosis after the 10th day of fever (more rarely thrombocytopenia);
- inflammatory anaemia;
- hypoalbuminemia;
- transaminase elevation, hyperbilirubinemia (rare);
- elevated CRP and erythrocyte sedimentation rate (ESR).

5.4.5. The clinical signs of KD in detail

5.4.5.1. Fever. Fever is the main diagnostic feature of KD. It is usually high (39–40 °C), often spikes, is usually without chills and is not very responsive to antipyretics. It may improve spontaneously after 7 days, which is not necessarily a sign of disease remission. It is usually associated with irritability, anorexia, and sometimes abdominal pain.

In infants under 6 months old, prolonged fever is often the only visible sign and irritability has important diagnostic value in these cases.

If not treated appropriately, the fever can last for more than 15 days.

5.4.5.2. Mucocutaneous involvement. Skin involvement is an initial sign and is often concomitant with fever. Various types of rash are possible, but it is usually diffuse, maculopapular (Fig. 4), morbilliform, erythematous or urticarial and more rarely psoriasiform or target-like. The presence of bullae and vesicles is not typical of KD and other diagnoses should be considered.

Mucosal involvement is present in 99% of complete forms and 77% of incomplete forms and includes a non-exudative redness of the entire oral cavity and pharynx. The lips are dry with radial cracks (Fig. 4). Deep fissures may sometimes cause bleeding and crusting. The tongue is frazzled with protruding fungiform papillae. Ocular involvement is seen as red eyes in the bulbar conjunctiva (Fig. 4), with an avascular area (white border) around the iris and with no discharge (which is distinct from infectious conjunctivitis). The

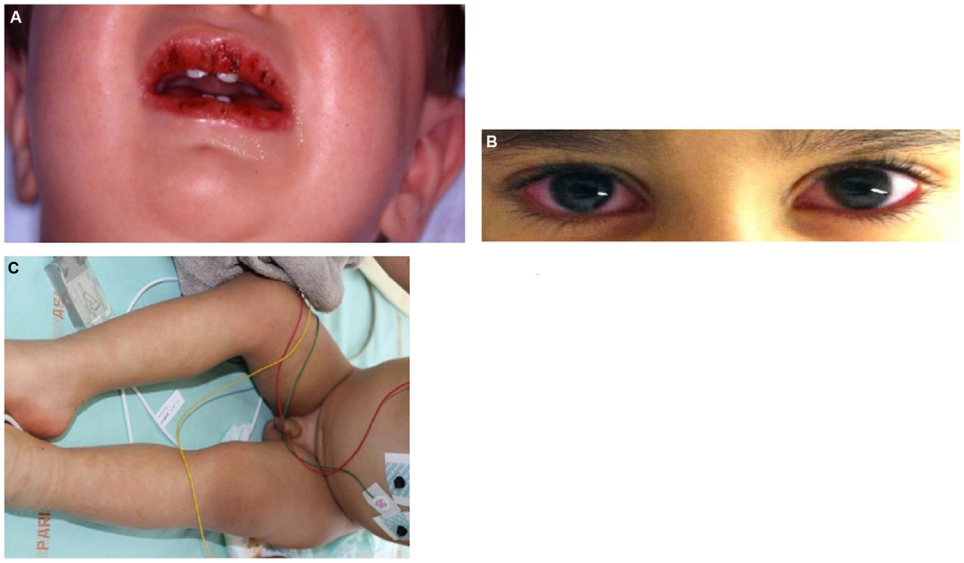

Fig. 4. Mucocutaneous involvement. A. Erythema and dryness of the lips. B. Eye redness. C. Generalized maculopapular exanthema.

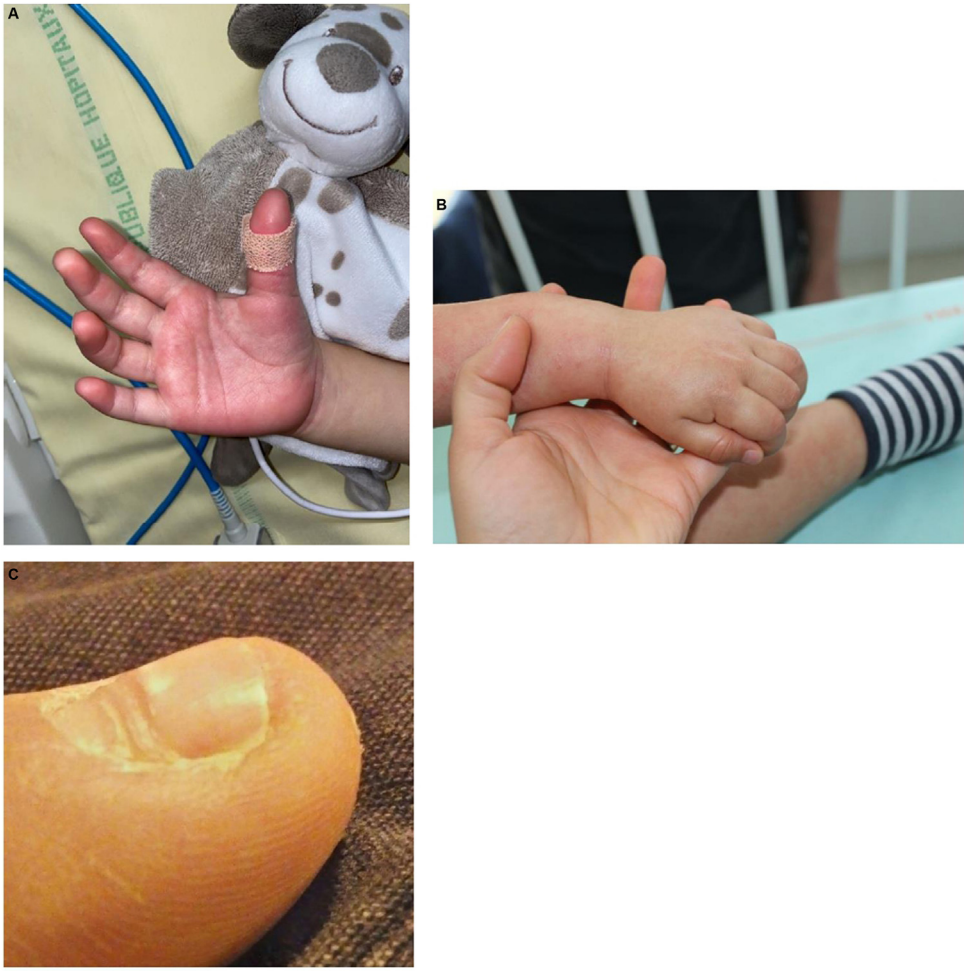

Fig. 5. Involvement of extremities. A. Erythema of the palm. B. Oedema of the extremities. C. Beau's line.

development of a rash, red eyes and red lips may be misdiagnosed as an allergy to antibiotics.

5.4.5.3. Involvement of the extremities. During the first 10 days of fever, the hands and feet may be swollen and red (Fig. 5) and the nails may be discoloured brown (chromonychia). After this phase, the skin peels away from the nails like a glove and one to two months later, Beau's lines may appear (Fig. 5) in the nails. These deep ridges indicate a defect in collagen synthesis during the inflammatory phase. Onychomadesis (nail loss) may also occur.

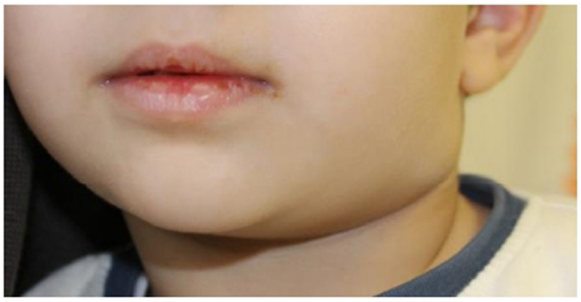

Fig. 6. Cervical lymphadenopathy with "pseudo-adenophlegmon" appearance.

The child must be carefully examined to identify these signs, and the parents should be closely questioned because the clinical features may occur successively and then disappear. Analysis of pictures taken by the parents in the days before the medical consultation is often very informative.

5.4.5.4. Lymph node involvement. A large cervical lymphadenopathy > 1.5 cm is the least common criterion found in complete forms of KD (55%) although it has strong diagnostic value. In these cases, the diagnosis of KD may be delayed and mistaken for adenophlegmon or a retropharyngeal septic abscess (Fig. 6).

5.4.5.5. Cardiac involvement. Except for shock or specific cardiac involvement, the classic presentation of KD has no cardiological features.

Tachycardia is common and mainly related to fever.

Tachycardia associated with hepatomegaly with hepato-jugular reflux and a galloping sound on auscultation are all signs of myocardial dysfunction. The presence of pericardial friction or signs of tamponade are very rare. The perception or accentuation of a cardiac systolic and/or diastolic murmur may indicate valve dysfunction, in particular mitral and less frequency aortic insufficiency. Symptoms of myocardial ischaemia secondary to coronary aneurysms may occur both during the acute phase and over the long term. These symptoms are misleading in infants and young children: feeding difficulties, vomiting, tiredness during feedings, unexplained crying, unusual restlessness or malaise. The older child may report chest pain.

5.4.6. Differential diagnoses

The differential diagnoses are listed for information only (Table 2). They should be investigated on a case-by-case basis and should not delay the rapid initiation of treatment for KD. Viral and bacterial co-infections are common and should not be ruled out.

Measles shares many clinical features with KD and should be considered a differential diagnosis in any unvaccinated infant or child. Measles usually occurs in the winter and spring, when many respiratory viruses are circulating. It starts with significant oculonasal discharge and a posterior cervical lymphadenopathy. A localised endobuccal enanthema (Koplick's sign) helps confirm the diagnosis in 50% of cases. A generalised maculopapular purpuric rash then develops and ends with a fine generalised peeling.

Detection of an adenovirus from a nasopharyngeal specimen of a patient with suspected KD is particularly challenging because these diseases have similar clinical features. Adenoviruses (particularly of the C species) can persist in the tonsils and adenoids which can confuse the diagnosis in patients with fever. KD is unlikely in a patient with fever, pharyngitis, conjunctivitis with discharge and an adenovirus-positive nasopharyngeal specimen on PCR (polymerase chain reaction). Even so, a diagnosis of KD should always be considered if adenovirus is detected in a patient with conjunctivitis. Other diagnostic features of KD that are not usually found in adenovirus infections include erythema and swelling of the hands and feet, a raspberry tongue and a scaly rash.

Scarlet fever usually presents in children over 3 and is associated with high fever, pharyngeal pain and erythematous angina due to group A haemolytic streptococcus. There is a satellite cervical lymph node and a patchy rash that is rough to the touch. It can affect the whole body, particularly the flexural folds, but does not affect the mouth, the palms and the soles of the feet. The tongue follows a 3-phase cycle: initially sandy with a white coating that peels from the edges to the centre and finally turns raspberry red. The diagnosis of KD should be reconsidered in children with certain clinical features of KD who receive a rapid test or positive culture for group A streptococcus but do not improve after 24–48 hours of appropriate antibiotic therapy (streptococcal carriers).

Stevens-Johnson syndrome is an epidermal necrolysis that occurs about 1–3 weeks after an inducing drug, and rarely after a vaccination. It starts with fever and headache, cough, malaise and keratoconjunctivitis. Small blisters appear first on the face and then on the rest of the body and develop into bullae.

Toxic shock syndrome (TSS) is an acute illness caused by toxins from bacteria, usually staphylococcus (predominant in children) and streptococcus. Its symptoms are fever, hypotension due to capillary leakage, multivisceral failure and a generalised erythrodermic rash that peels after 2–3 weeks. Other possible signs are general weakness, headache, chills, odynophagia, abdominal pain and watery diarrhoea with oedema of the extremities. With mucosal involvement raspberry tongue, conjunctivitis and vaginitis may be present. Biological abnormalities include leukocytosis, anaemia, thrombocytopenia and signs of disseminated intravascular coagulation (hypo fibrinaemia), hypoalbuminemia, hyponatremia, rhabdomyolysis and renal failure. TSS usually occurs in younger and older patients (< 5 years old and > 50 years old) but has been observed with staphylococcus in adolescent girls from hygienic tampons and other intrauterine devices. Streptococcal TSS can complicate viral infections such as chickenpox or deep skin wounds. The patient is treated by restoring blood volume by vascular filling, avoiding the inducing agent and antibiotic therapy with antitoxin effect.

Multisystemic inflammatory syndrome (PIMS or MIS-C) is an inflammatory condition that has been reported since the first wave of the COVID-19 pandemic in 2020 (Belot et al., Euro Surveill. 2020). PIMS occurs a few weeks after SARS-CoV2 infection, (often asymptomatic) and shares many features with KD. It is a post-infection syndrome that may be related to a super antigen effect. An immunological signature of the disease is found in more than 75% of cases (Vb21.3 lymphocyte expansion). The anti-SARS-Cov2 serology is usually IgG positive. PIMS usually begins with a fever associated with marked digestive signs and clear biological inflammation. The characteristics of PIMS that distinguish it from KD are shown in Table 3.

Cardiac involvement during PIMS usually involves left ventricular failure, which makes it similar to Kawasaki shock syndrome. However, coronary involvement in PIMS is much rarer and less severe than in KD. Left ventricular failure is prominent in most cases (pallor, dyspnoea, hepatomegaly, blood pressure instability, and tachycardia) and requires continuous monitoring or resuscitation. Ocular redness and rash are present in half of the cases but lymphadenopathy and involvement of the extremities are much less common (10–25%).

Inflammation is usually somewhat more marked in PIMS than in KD, which is reflected by more marked increases in CRP, fibrinogen and ferritin levels. In practice, it is impossible to determine a relevant threshold because of the significant inflammation in both entities. Thrombocytopenia is common in PIMS, but is only present in KD during associated macrophage activation. Increased NT-proBNP (a marker of myocardial overload) is common in PIMS.

Table 2
Main differential diagnoses of KD.

Viral causes	Measles
	Adenovirus
	Parvovirus
	Enterovirus
	Epstein Barr virus
Bacterial causes	Scarlet fever
	Infectious adenitis
	Leptospirosis
	Brucellosis
	Rickettsioses, borrelioses
Toxic causes	Staphylococcal scaled skin syndrome (SSSS)
	Toxic shock syndrome
Hypersensitivity reactions	Stevens-Johnson syndrome
	Drug hypersensitivity reactions
Systemic inflammatory diseases	Juvenile arthritis in its systemic form (Still's disease)
	SARS-CoV-2 related paediatric multisystemic inflammatory syndrome (PIMS or MIS-C)

KD: Kawasaki disease.

Table 3
Characteristics of PIMS that distinguish it from KD.

	PIMS/MIS-C	Kawasaki
Median age	5–10 years (January 2022)	1–5 years
Initial digestive signs	+++	+
Conjunctival hyperaemia	+	++
Exanthema	+	++
Lymphadenopathy	±	++
Modification of the extremities	±	++
Coronary artery disease	–	++
Left ventricular dysfunction	++	±
Biology		
Thrombocytopenia	+++	±
Polynucleosis	+	+++
Lymphopenia	+++	+

KD: Kawasaki disease; PIMS/MIS-C: SARS-CoV-2 related paediatric multisystemic inflammatory syndrome.

Table 4
Considering KD in the differential diagnosis of certain infants or children.

Consider KD in the differential diagnosis in
Infants under 6 months with prolonged fever and irritability
Infants with prolonged fever and unexplained aseptic meningitis
Infants or children with prolonged fever or unexplained shock with negative bacterial cultures
Infants or children with prolonged fever and cervical lymphadenitis that does not respond to antibiotics
Infants or children with prolonged fever and retropharyngeal or paratracheal phlegmon that does not respond to antibiotics

KD: Kawasaki disease.

Treatment of PIMS is based on a combination of IVIG with corticosteroids or anti-IL-1 biotherapy. The response to IVIG alone is usually partial and transient.

Systemic-type juvenile idiopathic arthritis (or Still's disease) shares clinical signs with KD including a fever that lasts more than 5 days, maculopapular rash, lymphadenopathy and changes in the extremities that are more consistent with arthritis. In some patients, the onset of Still's disease includes all KD criteria including coronary dilatations (Lefèvre-Utile A, et al., Joint Bone Spine 2014).

5.4.6.1. Common diagnostic pitfalls. A diagnosis of KD must be considered and not be missed in certain clinical situations (see Table 4) such as extreme age and/or atypical manifestations. The diagnosis is all the more important in these cases as they are often associated with an increased risk of developing coronary aneurysms. A specialised centre should be contacted if the diagnosis is suspected but remains uncertain.

5.4.6.1.1. Atypical age. Delays in diagnosis are common in children less than a year old (especially under 6 months) and over 5 years old and/or adolescents who appear to develop coronary anomalies more frequently.

5.4.6.1.2. Meningitis. Irritability with cerebrospinal fluid (CSF) pleocytosis and negative cultures in an infant with prolonged fever suggests aseptic meningitis and may hide the diagnosis of KD, even though it is an integral part of the systemic inflammation response associated with KD.

5.4.6.1.3. Cervical adenitis or retropharyngeal abscess. Patients that present with large adenopathies as the first clinical sign may be misdiagnosed and treated for bacterial adenitis and/or retropharyngeal phlegmon.

5.4.6.1.4. Gastrointestinal symptoms. Gastrointestinal symptoms suggest viral gastroenteritis, bacterial pancolitis, lower respiratory infection (base lung disease or pleurisy) or, more rarely, surgical abdomen (peritonitis).

5.4.6.1.5. KD and shock syndrome. KD presents as initial cardiogenic shock in about 2–7% of cases. These cases may be mistakenly diagnosed as septic or toxic (staphylococcal or streptococcal) shock and may be secondary to fulminating myocarditis, ruptured giant aneurysms with haemopericardium or myocardial infarction due to coronary thrombosis. Nevertheless, shock does not usually occur with these latter two complications. It appears to be secondary to major inflammation with endogenous discharge (cytokine release) resulting in vasodilatory shock with a drop in peripheral vascular resistance and hypovolaemia, to cardiogenic shock with myocardial dysfunction secondary to myocarditis, with or without ischaemia, and/or to capillary leakage (equivalent to toxin shock). Blood markers of heart failure and/or ischaemia will be elevated and there is often a major biological inflammatory syndrome. Treatment may include inotropes, vasopressors and/or filling. The presence of marked biological inflammation and any mucocutaneous signs

help in the diagnosis, but these may be missed. Thus, these elements should be systematically looked for so that immunomodulatory treatment may be implemented, as it is essential in addition to inotropic drugs, especially because of the increased coronary risk.

5.5. Description of cardiac disorders and their evolution

Cardiac complications play a major role in the morbidity and mortality associated with acute and long term KD. The inflammatory process during the acute phase can affect all cardiac tissues: pericardium, myocardium and the endocardium including valves, but mainly results in diffuse vasculitis with a more specific tropism for the coronary arteries. The long-term prognosis is determined by the complications of any coronary aneurysms.

5.5.1. Vascular damage

Although aneurysms may develop in all the arterial territories, the strong predilection of KD for the coronary arteries may result in life-threatening cardiac complications.

Coronary aneurysms, the most common cardiac complications, occur during the acute phase of KD in 15–25% of children who are left untreated. Aneurysms develop due to progressive damage to all three layers of the vessel wall. The earliest damage (7–9 days after the onset of symptoms) occurs in the endothelium with endothelial cell dissociation and subendothelial oedema related to an accumulation of mononuclear cells. The inflammation then spreads to the media from the vascular lumen on one hand and the adventitia on the other, rupturing the internal elastic lamina and destroying the media so the aneurysm is formed. Later, active remodelling occurs. Fibrosis then stenosis progressively develop due to intimal proliferation and neoangiogenesis. Even after regression of the aneurysm, the vascular wall remains stiffer than a healthy wall, with intimal thickening and endothelial dysfunction. The response to vasodilatators is altered. These characteristics are similar to those observed in early atheromatous lesions of adult atherosclerosis. These aneurysms usually involve the proximal segments of the coronary arteries. It is important to determine their size because this determines their progression and the prognosis of KD. In particular, a distinction is made between giant aneurysms with a diameter $\geq$ 8 mm, non-giant aneurysms (small and medium), and simple coronary dilatation.

Predictive factors for coronary damage have been identified (SHARE 2019):

- children under one year old;
- KD shock syndrome (KDSS);
- major inflammation and stigmata of macrophage activation;
- initial coronary or peripheral aneurysms;
- high risk score such as a Kobayashi score $\geq$ 5, in addition to being refractory to IVIG treatment.

5.5.2. Myocardial dysfunction

Myocarditis is common but usually asymptomatic (without detectable myocardial dysfunction or clinical cardiological symptoms). It should be systematically investigated during diagnostic and follow-up investigations. Although myocardial dysfunction is rare in KD, it must be considered because it can be the initial sign of shock (KDSS) requiring admission to an intensive care unit. Myocardial damage occurs before coronary damage and independently from ischaemia. Heart failure, when present, may be due to the myocardial depressant effect of circulatory substances such as pro-inflammatory cytokines, and more rarely to cellular necrosis.

5.5.3. Pericarditis

Pericarditis may be isolated or associated with KD-related vasculitis and myocarditis. In combination with other signs, it can help make the diagnosis of KD. The presence and severity of pericardial effusion should be noted. Large pericardial effusions resulting in haemodynamic abnormalities are very rare (Fig. 4).

5.5.4. Valvular dysfunctions

Mitral insufficiency is present in 25% of patients during the acute phase. It is usually minimal to moderate and regressive. Valve damage is a result of pancarditis with endocardial damage and is correlated to biological inflammatory markers. Aortic insufficiency is extremely rare (1% of patients) and occurs early in the acute phase. It is usually associated with aortic root dilatation, which is reported in about 10% of patients during the acute phase, as well as coronary dilatation.

5.5.5. Vascular damage

5.5.5.1. Coronary arteries. The distinction between giant and non-giant aneurysms is important because of the different natural histories of these entities. While non-giant aneurysms usually regress, several studies have shown that giant aneurysms do not regress completely and tend towards stenosis. Thus, the progression of these different coronary lesions is correlated with their initial anatomy.

Aneurysms, and especially giant aneurysms are a high cardiovascular risk, with thrombosis and intra-luminal rupture leading to acute myocardial ischaemia or tamponade. Aneurysm rupture is very rare and usually occurs in the early months of the disease, during the acute phase when they may expand rapidly. Occlusive thrombosis of a coronary aneurysm may develop during the acute phase of KD and cause myocardial infarction or sudden death. The factors that favour thrombosis include: thrombocytosis and increased platelet adhesion, inflammation and endothelial dysfunction, and abnormal flow conditions in areas of high dilation (vortex effect). The estimated mortality rate of KD in Japan is 0.015% and these deaths are related to cardiac damage. Peak mortality occurs between 15 and 45 days after the onset of fever, when coronary vasculitis, thrombocytosis and hypercoagulability are at their peaks.

Complete regression of coronary lesions only occurs in dilatations and small or medium aneurysms during the first two years after the initial presentation. Although the wall is permanently injured, giant aneurysms may decrease in size, persist, or normalise to the size of the coronary lumen. They may progress to stenosis or complete obstruction of the coronary artery. The risk of persistent aneurysms and the occurrence of cardiac events are correlated to the presence of giant aneurysms.

If aneurysms are complicated by the formation of occlusive thrombus (which may persist or recanalise), multiple mural thrombi or myofibroblastic luminal proliferations, these lesions may progress to coronary stenosis or remodelling may occur, with normalisation of the size of the vessel lumen but with a persistently abnormal arterial wall. These stenoses may result in an acute coronary syndrome (ACS) in the short, medium or long term (5% of ACS in patients under the age of 45 are secondary to sequelae of known or unknown KD). To prevent these complications, giant coronary aneurysms are an indication for lifelong anti-aggregation therapy combined with curative anticoagulation with VKA if they persist. Morbidity and mortality mainly occur in patients with giant aneurysms with a maximum risk of infarction during the first 2 years after KD.

One study in a large American cohort of patients with coronary aneurysms of all sizes described 75% regression after 2 years. Two Japanese studies reported that more than 50% of patients with giant aneurysms developed late coronary complications such as stenosis, calcifications or myocardial infarction. Finally, a recent French series from M3C-Necker followed 46 patients with giant aneurysms for 20 years and showed that at the one-year imaging follow-up

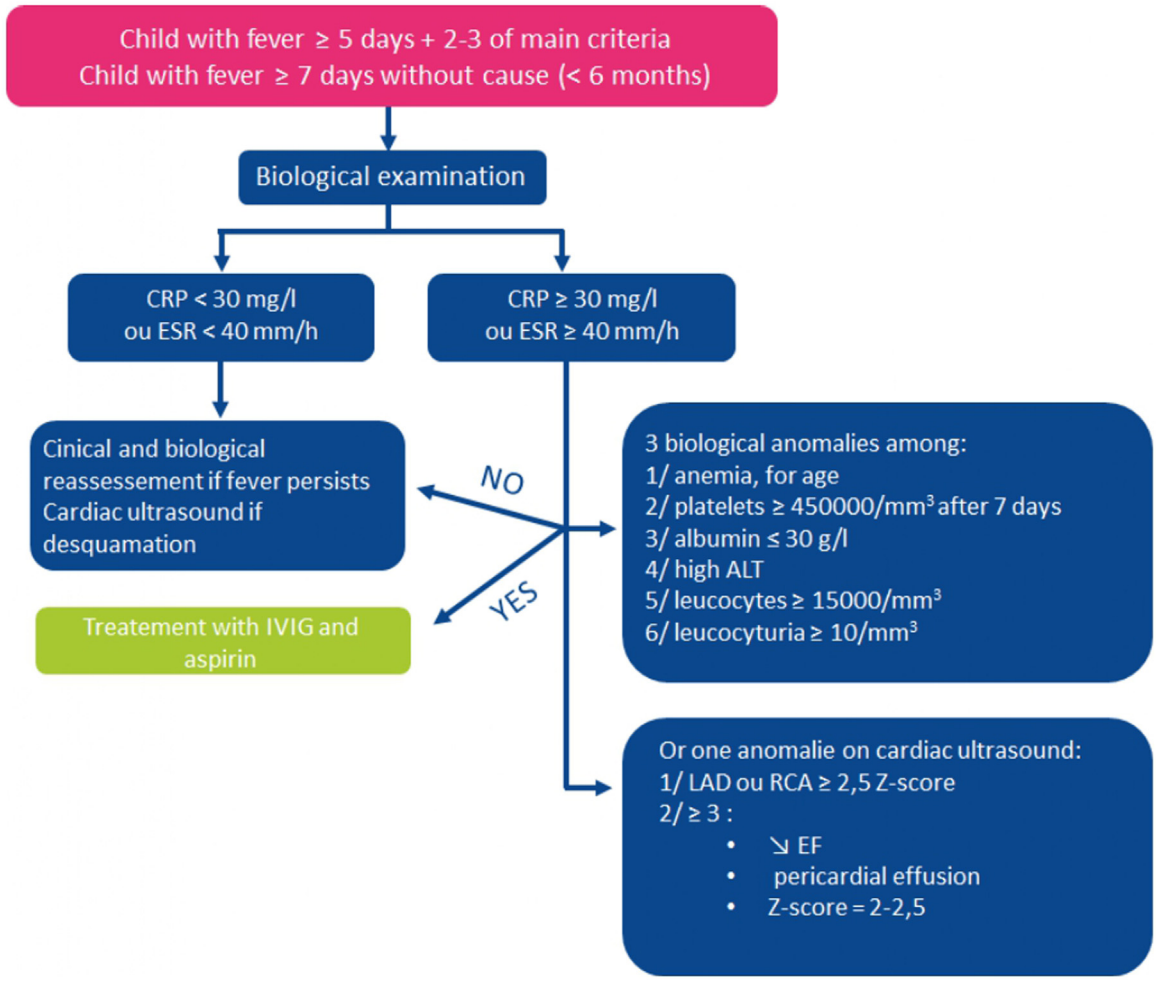

Fig. 7. Proposed flowchart (adapted from AHA 2017) for diagnostic support for atypical or incomplete KD, when criteria for complete KD are not met.

giant aneurysms persisted in 25% of patients, non-giant aneurysms in 25% while the aneurysms had disappeared in 50%. This shows that after one year of follow-up, 25% of patients treated with VKAs will need to continue this treatment on a long-term basis.

Today, the survival rate after a 30-year follow-up of patients with giant aneurysms is 90% with a worse prognosis in patients with bilateral coronary involvement. Bypass surgery is performed in 50% of these patients. In a study by Tsuda et al. in 245 patients with aneurysms ≥ 8 mm, 23% of patients had myocardial infarction (i.e., 57 patients) after a median delay of 8 months (18 days–35 years) and 70% of these occurred within 2 years after diagnosis. The 30-year survival rate was found to be lower in patients presenting with bilateral disease initially (87%) than with unilateral disease (96%). The 30-year cardiac event-free survival rate in this population (defined as death, myocardial infarction, percutaneous or bypass surgery, syncope, or ventricular tachycardia) was only 36% (59% in those with unilateral disease and 21% in bilateral disease).

5.5.5.2. Other arteries. Some patients with severely damaged coronary arteries may develop aneurysms in other medium-sized arteries that rarely cause thrombosis or rupture. The most common arterial sites are the axillary, subclavian, brachial, femoral, iliac, splanchnic and mesenteric arteries, most often at their bifurcation. The course of these vasculitides is probably similar to that of the coronary arteries, i.e., thrombosis and stenosis, but they are rarely symptomatic due to the development of collaterals.

5.6. Description of other rarer complications (renal damage, cholangitis, intestinal damage, pleural damage, neurological damage, etc.)

Incomplete KD cases have a fever that lasts more than 5 days but are associated with fewer than 4 major diagnostic criteria, while atypical KD have less common clinical signs that are not included in the traditional diagnostic criteria. These signs may or may not be associated with a complete picture of KD. Many articles mix these two entities, leading to confusion and misunderstanding of the disease forms.

5.6.1. Atypical forms

The overall incidence of atypical forms is unknown, although they appear to be more common in infants under 6 months and children over 5 years of age. Very few studies have specifically described and grouped together the atypical presentations of KD. They are frequently the subject of case reports or short series. It is useful to be aware of these forms because the presence of atypical features can influence the clinician in two ways. In case of a complete form of KD, atypical features are distracting and more easily cause differential diagnoses, resulting in a delay in treatment. On the other hand, in the presence of signs of incomplete KD, atypical signs suggesting KD (Fig. 7) help make a diagnosis with greater certainty.

5.6.2. Other KD manifestations

This section will describe the various clinical, biological and radiological signs that are not included in the American Heart Association (AHA) diagnostic criteria, with emphasis on their epidemiology, when known, and their impact on diagnosis and treatment (Fig. 7).

5.6.2.1. Nephrological complications. Kidney damage has been discussed in several publications with large populations.

Sterile pyuria is the most frequent disorder, affecting 30–80% of patients. The origin may be tubulointerstitial or urological and, unlike a urinary infection, cytology shows mainly mononuclear cells. It should be systematically investigated in incomplete forms of KD to improve the diagnostic sensitivity.

Acute renal failure (ARF) occurs in 0–28% of children and it seems to be more frequent in infants. The frequency of this entity is a subject of debate among authors due to the absence of a common definition. The severity varies and metabolic abnormalities are inconsistent. ARF is generally asymptomatic but clinical signs may include oliguria, oedema and hypertension. A renal biopsy is only indicated in atypical forms with metabolic repercussions or progressive disease and is discussed on a case-by-case basis. The pathophysiology of ARF is classified into three co-existing forms: pre-renal, intrinsic and post-renal. The intrinsic form is the most common, involving parenchymal damage, usually with tubulointerstitial nephritis, and characterised by sterile pyuria associated with low molecular weight proteinuria of moderate flow. In rare cases, tubular involvement may be a complication of fever-induced rhabdomyolysis and KD myositis. Glomerular disease is less frequent and more worrying, and is often an indication for renal biopsy. Glomerular disease should be suspected in the presence of albumin proteinuria of variable flow, total haematuria without clots and extracellular hyperhydration (oedema, arterial hypertension). It usually presents as a nephritic syndrome induced by transient hypocomplementemia secondary to the administration of polyclonal IVIG. Nephrotic syndromes are less frequent and should mainly be investigated for haemolytic uraemic syndrome or immune complex disease. Pre-renal ARF is rare and is usually not isolated. In these cases, acute functional renal failure occurs due to organ hypoperfusion, and cardiac failure should be investigated. Involvement of a stenotic or aneurysmal renal artery is extremely rare. The causes of post-renal ARF are described in the paragraph on urological damage.

Several studies have described abnormalities on renal imaging with no directly associated biological or clinical abnormality. An incidental finding of nephromegaly may occur and although isolated and transient, it may be associated with parenchymal inflammation and distant renal scarring.

Renal involvement is common during acute KD. It is most often transient, with no repercussions. Otherwise, certain less frequent complications must be investigated, and a renal biopsy and specific treatment may be discussed.

5.6.2.2. Urological and genital complications. Urogenital involvement is much less frequent than renal or abdominal involvement. However, KD vasculitis may affect the entire urinary tract resulting in priapism, meatitis, urethritis or cystitis. Signs are dysuria and sterile pyuria with possible ARF in case of obstruction.

Testicular complications have been reported in about ten cases of acute KD. Possible mechanisms include capillary leakage, hypoalbuminemia and vasculitis. They present as hydrocele or orchitis with painful, inflamed testicles that may require surgical exploration.

5.6.2.3. Digestive complications. A distinction must be made in KD between digestive complications with clinical signs, which are frequent, and pseudo-surgical presentations, which are less frequent. Indeed, at least one abdominal sign (pain, diarrhoea, nausea, vomiting, jaundice, cessation of watery sounds, abdominal distension) is present in about 35% of patients. They are secondary to classic KD mechanisms, as well as to the possible presence of mesenteric lymphadenitis, which is underestimated. Surgical or pseudosurgical complications are more severe and occur in 2–5% of cases. They are due to inflammatory and ischaemic involvement and may present as occlusion, haemorrhage or even digestive perforation. Patients with digestive injury are younger, with a more severe biological inflammatory syndrome. Treatment in these cases seems to have been delayed, with more resistance to IVIG and an increased risk of coronary complications. The need for surgery due to severe vasculitis is associated with a risk of mortality.

5.6.2.4. Hepatobiliary and pancreatic complications. Abdominal complications that do not involve the digestive tract must be discussed separately because they are highly specific.

The most unique clinical sign is hydrops of the gallbladder, characterised by thickening of the gallbladder wall with or without distension of the gallbladder and bile ducts. There is no concomitant gallstone and biological abnormalities and jaundice are rare. This common finding affects 21–36% of children who undergo hepatobiliary ultrasound. No prospective studies have been performed to determine the incidence in all patients. For certain authors, this entity is a risk factor of treatment resistance and acute coronary involvement, but not of a remote aneurysm. Although a risk of rupture has been described, most cases have a favourable outcome.

Biological liver test anomalies, mainly cytolysis and cholestasis, occur in up to 45% of children. Jaundice is less common. In less than 5% of cases, cytolysis may be greater than five times normal and constitute acute hepatitis. KD is the second most frequent cause of acute cholestatic hepatitis in children after hepatotropic viruses.

There are very few descriptions of pancreatic involvement. It is usually limited to biological disturbances with few or no symptoms. Its impact on the prognosis of KD is not known.

Thus, hepatobiliary abnormalities are common in KD and should be investigated to support the diagnosis.

5.6.2.5. Neurological complications. The most frequent neurological complication is aseptic meningitis. The incidence varies in the literature from 4 to 40%. It is a mixed or lymphocyte-predominant meningitis with normal or slightly elevated CSF protein and lowered CSF glucose levels. It may be associated with a higher incidence of coronary anomalies during acute KD. This frequent complication should not be confused with a rare but well-known iatrogenic complication. Indeed, meningitis symptoms may follow IVIG treatment in about 1% of children.

Extra-meningeal central neurological involvement affects only 1.1 to 3.7% of children and presents mainly as encephalitis with disorders of consciousness and behaviour, usually without convulsions. Although this event is often mentioned, there are very few published reports. There are rare descriptions of stroke. They may be ischaemic, are mainly located in the middle cerebral artery territory in these cases, and occur during early KD. There are numerous causes, including migrating thrombus complicating heart failure, inflammatory stenosis or IVIG-induced hyperviscosity. Some strokes are haemorrhagic and occur following an arterial aneurysm rupture far from the stroke.

Although cranial nerve involvement is often described, its incidence has not been clearly assessed. It mainly involves facial paralysis, which may be bilateral, although the other cranial pairs may also be affected. There are no descriptions of involvement of other nerves or nerve roots in KD.

Of all the neurological complications, aseptic meningitis has the greatest diagnostic sensitivity for KD and may be looked for when

the diagnosis is uncertain or is suggested. However, it should not change the management strategy.

5.6.2.6. Ophthalmological complications. Although bilateral conjunctival hyperaemia is the major ophthalmological complication of KD, other signs exist.

Uveitis is the most common. Contiguous to the conjunctiva, anterior uveitis occurs in 29–36% of cases and is usually bilateral, while intermediate uveitis only occurs in 5% of cases. These signs have no prognostic value and progress well under treatment.

Retinal and papillary involvement are more severe and much less common. They are characterised by exudative vasculitis or papilledema, which may result in arterial occlusion and retinal detachment. There is a high risk of functional injury in these cases, requiring more intensive treatment. Finally, one case of orbital myositis with neighbouring cellulitis and another of "punctate" or "disciform" keratitis has been described.

5.6.2.7. Ear, nose, throat (ENT) complications. Seemingly, infectious complications can confuse the clinician and lead to a delay in diagnosis. In particular, retro- or para-pharyngeal abscesses and otitis media have been found to have estimated incidences of 16 and 15% respectively. Uni- or bilateral parotitis has also been reported, but this is rare. The other salivary glands do not seem to be affected.

Particular attention should be paid to hearing impairment. Indeed, sensorineural deafness is underestimated because it often goes undetected, even though it may result in sequelae. Deafness was found to affect up to 3 to 6% of children in the few published series on this topic. Although the pathophysiology is not well understood, both the labyrinth and the auditory nerve seem to be involved. The presence of this complication during the acute phase probably partly explains the child's inconsolability and neurosensory hyperesthesia. Moreover, because recovery may be incomplete, it could be the cause of learning difficulties noted in these children during follow-up.

5.6.2.8. Musculoskeletal and joint complications. The tropism of KD for the heart muscle is well known and described in a specific paragraph. Other muscles, especially the proximal groups, can be affected. Clinical symptoms include muscle pain and weakness, with inconsistently elevated creatinine phospho-kinase (CPK) levels. If the respiratory or ENT muscles are affected, an increase in treatment should be discussed.

The joints are involved in 11% of children with mono or oligo (i.e., less than 5 joints) joint involvement in 67% of cases, usually the large joints. Joint fluid puncture shows inflammation with predominantly neutrophils and no germs. Certain atypical locations have been described, in particular in the cervical spine. Patients with joint involvement usually have more inflammation with an increased risk of remote coronary aneurysms but a good response to IVIG. If joint involvement continues after the acute phase, Still's disease should be discussed.

5.6.2.9. Respiratory disease. Clinical respiratory signs (cough, dyspnoea) are found in fewer than 2% of patients during early KD while subclinical radiological abnormalities are found in 15% of cases. This mainly includes bronchial syndromes or interstitial ground glass images. It is sometimes difficult to distinguish KD from a differential diagnosis, a triggering factor or an infectious complication. Thus, some infections may be found and should be investigated. On the other hand, KD should also be considered in the presence of antibiotic-resistant pneumonia. The most frequent symptomatic respiratory diseases in KD are alveolar pneumonitis and pleural effusions, which may be exudative with a predominance of neutrophils, haemorrhagic and/or aerated, and finally empyemas, parenchymal nodules and interstitial pneumopathies.

Table 5
Complementary tests required for the diagnosis and screening of complications.

First-line tests	Complete blood count
	CRP and/or ESR
	Blood ionogram, urea, creatinine
	Transaminases, γGT, bilirubin
	Albumin levels
	Urine cytobacteriological examination
	Blood cultures
	ECG and cardiac ultrasound
Tests to be discussed	Viral serology
	Streptotest (in case of angina)
	Serum bank (before IVIG)
	Abdominal ultrasound
	Lumbar puncture
	Joint puncture (in case of doubt about septic arthritis)
	Triglyceridemia, ferritinemia, haemostasis (in case of doubt about MAS)

CRP: C-reactive protein; ECG: electrocardiogram; ESR: erythrocyte sedimentation rate; IVIG: intravenous immunoglobulins; MAS: macrophage activation syndrome.

5.6.2.10. Endocrine damage. Hyponatremia is sometimes reported in early KD. It was linked to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) in two studies and has an estimated incidence of 9%. It usually resolves spontaneously. No other types of endocrine involvement have been described in KD.

5.6.2.11. Severe haematological disease. Macrophage activation syndrome (MAS) complicates 1–2% of patients during acute KD or sometimes later. Although it may be mild, bone marrow haemophagocytosis is frequent in the absence of clinical and biological MAS. MAS should be suspected in the presence of hepatosplenomegaly based on characteristic biological signs (see chapter 5.6). This complication may be life-threatening and is related to the intensity of the inflammation. It regresses with immunomodulatory treatment, but more aggressive treatment is recommended including the combination of IVIG and corticosteroid therapy and even ciclosporin or targeted biotherapy.

5.7. Complementary examinations necessary for the diagnosis and screening of complications

The diagnosis of KD is essentially clinical. Nevertheless, certain paraclinical examinations can help make the diagnosis in case of atypical KD or an uncertain diagnosis (Table 5). These tests can help:

- support the diagnosis;
- exclude differential diagnoses;
- detect complications;
- define predictive scores for IVIG resistance.

5.7.1. Biological tests

Certain tests should be performed as soon as a diagnosis of KD is suspected: blood count with platelet count, CRP and/or ESR to look for an inflammatory response, liver tests (transaminases, γGT, bilirubin), albumin and urine cytobacteriological examination.

5.7.1.1. C-reactive protein and sedimentation rate. Although elevated CRP (≥ 30 mg/L) and ESR (≥ 40 mm/h) levels are nearly always found during acute KD, the two results may be discordant. CRP levels are the most relevant marker of inflammation in KD. They increase during the first hours of inflammation and may be used to follow the progression of this event because they normalise within 10 days to 3 weeks after inflammation has resolved.

On the other hand, the ESR normalises more slowly after inflammation has resolved and is increased by IVIG. Thus, it is uninterpretable during follow-up and to monitor the response to treatment.

5.7.1.2. Blood count. A complete blood count shows leucocytosis with neutrophilia. The biological inflammatory response is usually associated with a normocytic/microcytic normochromic anaemia.

Thrombocytosis does not develop until the 2nd week of disease, with an average level of 700,000/mm^3. Blood platelet kinetics are well known during KD, with a normal (sometimes low) level in the early phase that gradually increases after the first week to reach a peak during the 3rd week and normalise between the 4th and 6th week of symptoms. In some cases, thrombocytopenia may be a sign of disseminated intravascular coagulation or MAS and is a risk factor for the development of coronary anomalies.

The absence of an inflammatory syndrome, leukopenia and/or lymphocytic hyperleukocytosis are arguments supporting infection rather than KD.

5.7.1.3. Liver function tests and albumin levels. Mild to moderately elevated serum transaminases occur in 40 to 60% of patients and may be associated with hyperbilirubinemia (10%). Hypoalbuminemia is common and associated with more severe and prolonged acute illness.

5.7.1.4. Urine analysis. Urinalysis shows sterile pyuria in 30–80% of children, with cytological analysis showing a predominance of mononuclear cells. This finding is not specific for KD.

5.7.1.5. Other biological tests.

5.7.1.5.1. Lumbar puncture. Aseptic meningitis is found in about 30% of children who undergo a spinal tap, presenting as pleiocytosis with a predominance of mononuclear cells (lymphocytes or monocytes); normoglycorrhachia and normoproteinorrhachia.

5.7.1.5.2. Arthrocentesis. Arthrocentesis in patients with arthritis generally reveals a purulent but aseptic (gram stain and negative cultures) and inflammatory fluid (white blood cells between 125,000 and 300,000 per mm^3). This test should not be performed unless there is a doubt about septic arthritis.

5.7.1.5.3. Cardiac markers. Since the COVID-19 pandemic, troponin and NT-proBNP assays have been performed for a differential diagnosis of multisystemic inflammatory syndrome (PIMS/MISC).

The sensitivity and specificity of these assays are not known because they were not previously part of the routine initial work-up for suspected KD.

Troponin, a marker of myocardial injury, can be normal or low in subclinical myocarditis and very high in severe myocarditis or myocardial ischaemia (post-coronary thrombosis).

NT-proBNP, a marker of myocardial fibre stretch, may be increased in cases of severe myocarditis, but is mainly a marker of heart failure, suggesting a diagnosis of associated shock, as in KDSS, or the differential diagnosis of PIMS/MISC. The assays of these two markers seem to be of value, but further studies are needed.

5.7.2. Additional tests

5.7.2.1. Electrocardiogram. A standard 12-lead electrocardiogram (ECG) is recommended during acute KD, to search for myocardial ischaemia or necrosis complicating a coronary occlusion, even if coronary aneurysms are not visible on echocardiography. In the presence of coronary damage, the ECG should be repeated. During acute KD, the ECG may also show rhythm abnormalities such as sinus dysfunction or conduction disturbances with a prolonged PR interval. Nonspecific ST-segment and T-wave abnormalities or diffuse micro-voltage may indicate myocardial and/or pericardial inflammation. Severe ventricular arrhythmias may be present in rare cases of ventricular dysfunction secondary to myocarditis or ischaemia.

Changes in electrocardiographic findings reinforce suspected coronary thrombosis.

5.7.2.2. Two-dimensional ultrasound with Doppler. Cardiac ultrasound is the main imaging modality for cardiac assessment in KD because it is non-invasive with good sensitivity/specificity for detecting abnormalities in the proximal segments of the coronary arteries. It is also needed to detect other complications (see Appendix 2).

An initial echocardiography should be prescribed as soon as the diagnosis is suspected, and may be performed during the first week of illness. However, treatment should not be delayed if the test is unavailable or if it is initially normal, as this does not rule out a diagnosis of KD. The paediatric cardiologist may be consulted before treatment is started in case of incomplete KD. Indeed, an abnormal echocardiogram can confirm the diagnosis and treatment can be rapidly begun.

In addition to standard anatomical and physiological images, echocardiography in patients with suspected KD should focus on a quantitative assessment of coronary artery diameters including: common coronary trunk, anterior interventricular artery, circumflex artery and right coronary artery. The coronary assessment should include: the name of the affected vessel, size, number and location of aneurysms, presence or absence of intraluminal thrombus and morphology of any saccular or fusiform aneurysms. The presence of simple dilatation with no loss of parallelism of the coronary margins, irregularity of the vascular lumen or hyperechogenicity of the vessel walls may indicate early coronary involvement. Assessment of left ventricular function should include two-dimensional analysis of regional myocardial wall kinetics and M-Mode measurement of end-diastolic and telesystolic diameters as well as shortening and ejection fractions. Aortic root dilatation should also be looked for as well as possible pericardial effusion. Pulsed and colour Doppler can be used to identify and assess the severity of valve leaks, particularly mitral and aortic.

Coronary measurements should be related to the body surface area and expressed as a Z-score to assess initial coronary risk and allow comparison over time. Thus, the child's height and weight should be recorded in the emergency department and forwarded to the paediatric cardiologist performing the echocardiography.

Aneurysms are classified according to the measurement of their internal diameter on echocardiography and normalised according to the Z-score (which expresses the deviation from the mean value normalised by body surface area, in standard deviation), see Table 6.

Follow-up in patients with progressive coronary aneurysms should include regular echocardiograms to monitor:

- increased luminal dimensions and therefore thrombotic risk;
- the presence of thrombosis or signs of ventricular dysfunction.

Recommendations to this effect were issued by the AHA in 2017 and are summarised in Table 7.

5.7.2.3. Other imaging modalities. Other imaging modalities, such as multi-slice coronary computed tomography (CT) imaging can visualise all types of KD lesions, whatever the age of the child. It can also be used to quantify the degree of thickening, which is not visible on coronary angiography, and detect parietal thrombi. Coronary angiography is an invasive examination that can be discussed. Although magnetic resonance imaging (MRI) angiography seems to be slightly less accurate than CT in detecting stenosis, it has the advantage of being without radiation.

These tests may be useful in assessing certain patients, but they are not routinely indicated for the diagnosis and management of

Table 6
Classification of coronary anomalies according to Z-score [1].

Z-score	Classification	
< 2	No coronary anomalies	
2 to < 2.5	Coronary dilatation	
≥ 2.5 to < 5	Small aneurysm	Coronary aneurysm
≥ 5 to < 10 and absolute size < 8 mm	Medium aneurysm	
≥ 10, or absolute dimension ≥ 8 mm	Giant aneurysm	

Table 7
AHA recommendations on echocardiographic monitoring of patients with KD and screening for coronary thrombosis.

Situations	Frequency of echocardiography
Uncomplicated patients	Repeat ultrasound within 1–2 weeks Then 4–6 weeks after treatment
Significant (Z-score > 2.5) and progressive coronary anomalies	Ultrasound 2×/week until luminal dimensions have stopped progressing
Patients with developing aneurysms at high risk of coronary thrombosis	2×/week as long as the size is rapidly increasing 1×/week in the first 45 days of illness 1×/month until the 3rd month after the start of the disease

AHA: American Heart Association; KD: Kawasaki disease.

acute disease. They may be useful in older children and adolescents when visualisation of the coronary arteries by transthoracic echocardiography is inadequate.

5.7.2.4. Imaging of other vascular axes. Patients with severe coronary artery disease may also develop aneurysms in other medium-sized arteries (axillary, subclavian, brachial, femoral, iliac, splanchnic and mesenteric), with rare cases of thrombosis or rupture at these sites. The physiopathology is probably similar to that of coronary artery disease, with a similar natural history leading to thrombosis and stenosis. However, clinical symptoms, signs and sequelae are often absent in childhood in these cases because of the development of collateral networks.

An MRI angiogram or thoracic-abdominal-pelvic angioscan is recommended in cases of KD with significantly refractory systemic inflammation (to look for diffuse systemic vasculitis) or severe coronary involvement.

5.8. Assessment of disease severity/extension/prognosis: risk factors of cardiac complications and non-response to treatment

5.8.1. Risk factors of cardiac complications

The risk factors of cardiac complications are usually related to delayed initiation of therapy or a non-response to IVIG therapy.

The main risk factors of coronary complications are:

- IVIG treatment after the 10th day of fever;
- IVIG resistance (fever 36 hours after completion of IVIG infusion);
- incomplete forms of KD;
- age < 1 year old;
- male gender;
- the severity of the inflammatory syndrome at diagnosis (hyperleukocytosis, anaemia, thrombocytosis, CRP).

Each day of delay in starting IVIG treatment in patients treated during the first 10 days of fever increases the risk of coronary complications by 18% [57].

5.8.2. Risk factors of non-response to initial IVIG treatment

Other scores predicting non-response to IVIG therapy are also available. Approximately 10–20% of patients with KD do not respond to IVIG therapy and are at risk of developing coronary complications. Early detection of these patients is essential to prescribe treatment with systemic corticosteroids or biotherapy in addition to IVIG. Although the sensitivity and specificity of several scores developed in the Japanese population such as the Kobayashi, Egami or Sano scores are good, (77–86%) and (67–86%), respectively, they lack sensitivity in North American, European and even other Asian populations.

The Kawanet study including 465 patients with KD from 65 French centres confirmed the poor sensitivity of these 3 scores in the multi-ethnic French population and proposed a new, more sensitive score that needs to be validated in other populations. The description of these 4 scores, as well as their sensitivities and specificities in the French population are reported in Table 8.

6. Therapeutic management [29,42,54,86,89,102,107,112,113,143,165,172–202]

6.1. Objectives

The treatment of KD is an emergency and the main objective is to resolve inflammation and prevent coronary damage. Treatment should be started early and the response to treatment should be assessed promptly to evaluate the need for second-line treatment.

The objectives are as follows:

- control systemic inflammation and fever;
- reduce acute coronary artery injury;
- prevent thrombosis in the coronary arteries.

6.2. Professionals involved (and coordination arrangements)

Initial treatment is based on international recommendations and is usually performed in a medical department (general paediatrics, paediatric rheumatology or paediatric emergencies), with the administration of polyvalent IVIG and aspirin. Any second-line treatment except for a second administration of intravenous immunoglobulins is decided during a multidisciplinary discussion including the expertise of the FAI^{2}R experts and reference centres, paediatric cardiologists and paediatricians with expertise in the management of KD.

6.3. Therapeutic management (pharmacological and other) in the initial phase

Several drugs mentioned in this French NDCP for the management of children are prescribed off-label.

Table 8
Description of 4 predictive scores of non-response to intravenous immunoglobulin and their performance in the French population according to the Kawanet database.

Score	Description	Predictive threshold for non-response	Go to (%)	Sp (%)
Egami (2006) [172]	Age ≤ 6 months (1 point) ALT ≥ 80 IU/L (2 points) Platelets ≤ 30.10^4 IU/L (1 point) CRP ≥ 80 mg/L (1 point) Started ≤ 4 days ago (1 point)	≥ 3 points out of 6	51	71
Sano (2007) [173]	Total bilirubin ≥ 0.9 mg/dL (1 point) AST ≥200 IU/L (2 points) CRP ≥ 70 mg/L (1 point)	≥ 2 out of 3 points	14	86
Kobayashi (2006) [174]	Natremia ≤ 133 mmol/L (2 points) AST ≥ 100 IU/L (2 points) Platelets ≤ 300,000 G/L (1 point) CRP ≥ 100 mg/L (1 point) Neutrophils ≥ 80 (2 points) Started ≤ 4 days ago (2 points) Age ≤ 12 months (1 point)	≥ 5 points out of 11	43	83
Kawanet (2020)	ALT ≥ 30 IU/L (1 point) Hepatomegaly (1 point) Lymphopenia < 2400/mm^3 (1 point) Processing time < 5 days (1 point)	≥ 2 points out of 4	77	60

ALT: alanine transaminase; AST: aspartate transaminase; CRP: C-reactive protein.

It should be remembered that the prescription of a drug is possible[2] in the absence of appropriate medicinal alternatives if the indication (or the conditions of use) has (have) been the subject of a temporary recommendation for use or if the prescriber considers it to be essential in light of scientific evidence to use this speciality to improve or stabilise the patient's clinical condition. In this case:

- the patient must be informed of the off-label nature of the prescription, "the absence of an appropriate medicinal alternative, the risks involved and the constraints and benefits likely to be provided by the medicinal product", and the conditions for reimbursement by the health insurance scheme;
- the words "Prescription without marketing authorisation" must appear on the prescription;
- the prescription must be justified in the patient's medical file;
- the French National Agency for the safety of medicines and health products (ANSM) may use the French NDCP to develop compassionate access in the off-label indication, if there is no suitable drug alternative[2].

The speciality may be covered or reimbursed by the health insurance scheme in an indication outside the marketing authorisation, by way of derogation and for a limited period of time, following the opinion of the HAS, provided that it has been the subject of prior compassionate access and that its use is essential to improve the patient's state of health or to prevent its deterioration[3].

Non-reimbursed procedures, products or services must also be indicated in the French NDCP. Non-reimbursed products or services may also be covered or reimbursed by the health insurance scheme, on an exceptional basis and for a limited period of time, following an opinion or recommendation from the HAS and consultation of the ANSM, if there is no appropriate alternative and provided that their use is essential to improve the patient's state of health or to prevent its deterioration[3].

The following recommendations are proposed by the AHA for the initial treatment of KD (first line treatment):

- patients who fulfil complete KD criteria and those who meet the algorithm criteria for incomplete KD should be treated with high-dose IVIG (2 g/kg given as a single intravenous infusion) within 10 days of disease onset, and ideally as soon as possible after diagnosis (class I; level of evidence A);
- it is reasonable to administer IVIG to children who present after day 10 of illness (late diagnosis) with persistent fever and no other explanation or coronary artery abnormalities with ongoing systemic inflammation, such as an elevated ESR or CRP (CRP > 30 mg/L) (class IIa; level of evidence B);
- moderate-dose aspirin (30–50 mg/kg/d) in four doses is offered until the patient is apyretic, although there is no evidence that this treatment reduces coronary artery aneurysms (class IIa; level of evidence C). Failing that, at a minimum, antiplatelet therapy at a dose of 3–5 mg/kg/d is offered for 6 weeks in the absence of complications;
- IVIG should generally not be given to patients beyond day 10 of the disease in the absence of fever, significant elevation of inflammatory markers or coronary artery abnormalities (class III; level of evidence C);
- the ERS is accelerated by IVIG therapy and should not be used to assess response to IVIG therapy. A persistently elevated ERS alone should not be interpreted as a sign of IVIG resistance (class III; level of evidence C).

6.3.1. *Identification of high-risk patients (see chapter 5.8)*

Patients at high risk of developing aneurysms may benefit from additional treatment at the outset with IVIG and aspirin. High risk criteria include: children under one year old, presenting with shock, a severe inflammatory syndrome, ± stigmata of MAS and/or with early coronary dilatations/aneurysms.

In these patients, the use of corticosteroids in combination with IVIG and aspirin has been shown to be more effective than IVIG alone in Japanese patients at risk of developing severe disease according to the Kobayashi criteria. The efficacy of this intensified therapy has not been demonstrated in the non-Asian population, but due to a clearly identified subgroup of patients at risk of IVIG resistance and severe complications, the latest SHARE guidelines indicate that additional corticosteroid therapy is needed in this group in addition to IVIG and aspirin.

The corticosteroid protocol has not been clearly defined but the following may be prescribed:

- methylprednisolone 0.8 mg/kg/12 h intravenous with electric syringe for 5–7 days or until CRP normalises, followed by oral

[2] Article L. 5121-12-1 of the Public Health Code.
[3] Article L. 162-17-2-1 of the Social Security Code (CSS).

prednisone or prednisolone 2 mg/kg/d decreasing over the 2nd and 3rd week then stopped, or;
- methylprednisolone bolus 10 to 30 mg/kg/24 h intravenous for 3 days (max 1 g/d) followed by oral prednisone or prednisolone at a dose of 2 mg/kg/d for 4 days or until CRP normalises then decreases over the 2nd and 3rd week then stopped.

6.3.2. Second-line treatments

Approximately 10 to 20% of patients develop recurrent or persistent fever at least 36 hours after the end of their IVIG infusion (resistant cases). Numerous studies have shown that patients who are resistant to initial IVIG are at increased risk of developing coronary anomalies.

There are no robust clinical trial data to guide the clinician in the choice of therapeutic agents in children with IVIG resistance, and no cost-effectiveness comparisons between different approaches have been reported. In this situation, participation in a clinical trial should be suggested when appropriate. These patients should be promptly referred to an expert centre.

6.3.2.1. Intravenous immunoglobulins. Re-treatment with IVIG 2 g/kg has not been tested in a randomised controlled trial, but retrospective series have suggested its efficacy (SHARE level 1A recommendations).

6.3.2.2. Corticosteroids. Steroids have also been used to treat patients who have not responded to initial KD treatment. Several small series and observational studies in children with KD with recurrent or persistent fever despite IVIG treatment have shown that steroid administration was associated with improved symptoms and an absence of significant progression of coronary artery anomalies.

6.3.2.3. Anti-TNF. Infliximab (IFX) is a chimeric monoclonal antibody used for the treatment of refractory KD. Three studies comparing IVIG as first line therapy vs. IVIG plus IFX showed a more rapid reduction in fever and a decrease in CRP as well as a shorter hospital stay. Only one of these studies (Japanese) showed that treatment helped prevent the development of coronary aneurysms. The use of IFX should be decided by an expert.

6.3.2.4. Anakinra. About 40 children have been treated with Anakinra to date, mostly published as clinical case reports. In a recent French trial, 2–6 mg/kg Anakinra was given for 14 days to 16 patients with KD in whom one or more courses of 2 g/kg IVIG had failed. Fever resolved in 75% of the 16 included patients within 48 hours after the last dose increase. Twelve of the sixteen patients had a Z-score max > 2 and 10/16 > 2.5. At day 45, 5/10 and 6/12 patients achieved a Z-score < 2.5 and < 2, respectively. Further clinical trials are ongoing.

6.3.2.5. Ciclosporin. Ciclosporin is a calcineurin inhibitor, and its administration has been used successfully in patients identified as IVIG resistant in a randomised study, IVIG versus IVIG plus 5 mg/kg ciclosporin for 5 days. Fourteen percent of patients who received IVIG plus ciclosporin developed aneurysms versus 31% in the group without ciclosporin.

6.3.2.6. Cytotoxics. Cytotoxic agents such as cyclophosphamide have been used in patients with particularly refractory KD. This treatment should be reserved for critical situations and after expert advice.

Box 1: Heparin prescription in children

When a loading dose is required, because immediate anticoagulation with IV unfractionated heparin at a dose of 75–100 IU/kg is desired, then the maintenance dose of unfractionated heparin is 500 IU/kg/day intravenous with electric syringe. Anti-Xa activity should be between 0.35 and 0.7 IU/mL.

However, the current recommendations mainly recommend the use of low molecular weight heparins (LMWH).

The usual doses of the main LMWH used in paediatrics are:

- enoxaparin 1.5 mg/kg/12 h or 150 IU/kg/12 h before 3 months old;
- enoxaparin 1.2 mg/kg/12 h or 120 IU/kg/12 h between 3 months and 2 years old;
- enoxaparin 1 mg/kg/12 h or 100 IU/kg/12 h from 2 years old;
- anti-Xa activity which should be between 0.5 and 1 IU/mL.

Heparin therapy is followed by oral anticoagulant treatment with VKA. The INR must be between 2 and 3.

Warfarin can be started with a first INR at D3, depending on the child's weight:

- < 20 kg: start with 2 mg/day;
- 20–30 kg: start with 3 mg/day;
- > 30 kg: start with 5 mg/day.

6.4. Management of cardiac complications

6.4.1. Management of cardiac complications during acute KD

IVIG treatment reduces the prevalence of coronary aneurysms, provides faster recovery from left ventricular dysfunction and prevents late endothelial dysfunction.

More intensive treatment combining IVIG and corticosteroids has been reported to increase the regression of coronary aneurysms from 68 to 91% (ref. abstract Friedmann 2016, JAHA).

Low-dose aspirin is then given as an antiplatelet drug (3 to 5 mg/kg/d or 50 mg/d before one year old and 100 mg/d after one year) for six weeks if there is no coronary involvement or dilatation alone that normalises within six weeks. If dilatation persists, aspirin should be continued until normalisation. If there is a small coronary aneurysm, antiplatelet treatment should be continued and may be discontinued if normalisation occurs. In the presence of aneurysms that are medium-sized (≥ 5 and < 10 mm) or larger, antiplatelet low-dose aspirin should be continued for life.

6.4.2. In cases of early giant coronary aneurysms

Urgent anticoagulant therapy is begun with hypocoagulant dose heparin (Box 1). An aneurysm that is ≥ 8 mm or with a Z-score ≥ 10 is defined as giant.

The patient's family must receive full information about VKAs that should be validated before returning home to limit the complications induced by this treatment as much as possible.

6.4.3. Treatment of acute myocardial dysfunction and shock (see chapter 9)

Although haemodynamic instability is usually rapidly controlled by the administration of inotropics, vasopressors (noradrenaline, adrenaline, dobutamine and dopamine) and diuretics, moderate left ventricular systolic dysfunction may persist.

6.4.4. Prevention of thrombosis in patients with coronary disease

All patients are promptly treated with a dose of antiplatelet aspirin, for a duration that is defined by the type and progression of coronary lesions (see Table 9).

Anticoagulation with heparin (LMWH) combined with antiplatelet aspirin is indicated for rapidly expanding coro-

Table 9
Planning the frequency and content of cardiological follow-up consultation according to risk.

Level of risk	Treatment	Therapeutic education and sport	Follow-up
1: no coronary anomaly	Aspirin 6 weeks	Education CVRF Normal physical activity	Stopping cardiological monitoring after the 6th week No further investigations
2: expansion only	Aspirin 6 weeks	Education CVRF Normal physical activity	If normalization of dilatation after 6 weeks, discontinue cardiological monitoring If dilation persists after 6 weeks, follow-up every 2–5 years
3.1: small, current or persistent aneurysm	Aspirin for life ± statin (recommendation IIb)	Education CVRF Normal physical activity	Consultation every year[a] Search every 2–3 years for inducible myocardial ischemia[b] Possible additional invasive tests every 3–5 years[c]
3.2: small aneurysm with complete regression or dilation only	Aspirin 1 year minimum and stop if normalisation ± statin (recommendation IIb)	Education CVRF Normal physical activity	Consultation every 1–3 years[a] Search every 3–5 years for inducible myocardial ischemia[b] Possible additional invasive tests if ischemia[c]
4.1: medium, current or persistent aneurysm	Aspirin for life ± double antiplatelet aggregation (recommendation IIb) ± statin (recommendation IIb)	Education CVRF Normal physical activity, competitive sports depending on stress tests No contact sport if double antiplatelet aggregation	Consultation every year[a] Search every 1–3 years for inducible myocardial ischemia[b] Possible additional invasive tests every 2–5 years[c]
4.2: medium aneurysm, which has regressed to a small aneurysm	Aspirin for life ± double antiplatelet aggregation (recommendation IIb) ± statin (recommendation IIb)	Education CVRF Normal physical activity, competitive sports depending on stress induction tests No contact sport if double antiplatelet aggregation	Consultation every year[a] Search every 2–3 years for inducible myocardial ischemia[b] Possible additional invasive tests every 3–5 years[c]
4.3: medium aneurysm with complete regression or dilation only	Aspirin for life ± double antiplatelet aggregation if inducible myocardial ischaemia (recommendation IIb) ± statin (recommendation IIb)	Education CVRF Normal physical activity, competitive sports depending on stress tests	Consultation every year[a] Search every 2–4 years for inducible myocardial ischaemia[b] Possible additional invasive tests if ischemia[c]
5.1: giant, current or persistent aneurysm	Aspirin for life VKA for INR 2–3 ± double antiplatelet aggregation if distal and extensive aneurysms or a history of coronary artery thrombosis (recommendation IIb) ± statin (recommendation IIb) ± beta-blocker (recommendation IIb)	Education CVRF Normal physical activity, competitive sports depending on stress tests No contact sports if double antiplatelet aggregation or anti-coagulation	Consultation every 6 months[a] Search every 6–12 months for inducible myocardial ischaemia[b] Additional invasive tests ([c]) during the first year and then possibly every 1–5 years
5.2: giant aneurysm that has regressed to a medium aneurysm	Aspirin for life ± double antiplatelet aggregation (recommendation IIb) ± statin (recommendation IIb) ± beta-blocker (recommendation IIb)	Education CVRF Normal physical activity, competitive sports depending on stress tests No contact sport if double antiplatelet aggregation	Consultation every year[a] Annual search for inducible myocardial ischaemia[b] Possible additional invasive tests every 2–5 years[c]
5.3: giant aneurysm that has regressed to a small aneurysm	Aspirin for life ± statin (recommendation IIb) ± beta-blocker (recommendation IIb)	Education CVRF Normal physical activity, competitive sports depending on stress tests	Consultation every year[a] Search every 1–2 years for inducible myocardial ischaemia[b] Possible additional invasive tests every 2–5 years[c]
5.4: giant aneurysm, fully regressed or dilated only	Aspirin for life ± statin (recommendation IIb)	Education CVRF Normal physical activity, competitive sports depending on stress tests	Consultation every year[a] Search every 2–3 years for inducible myocardial ischemia[b] Possible additional invasive tests every 2–5 years[c]

CVRF: cardiovascular risk factors.
[a] Consultation: ECG, echocardiography, stress test (as soon as feasible)
[b] May include stress ultrasound, stress MRI, PET scan and myocardial perfusion scan.
[c] Additional explorations with invasive angiography (coronary angiography) or coroscanner, MRI.

nary aneurysms, (class IIa recommendation). This may be switched to a VKA with a target INR of 2 to 3 if the Z-score is ≥ 10 or the absolute value ≥ 8 mm.

In patients at an increased risk of thrombosis, e.g., with a giant aneurysm and a recent history of coronary artery thrombosis, "triple therapy" with dual antiplatelet drugs (aspirin and clopidogrel) and a VKA or LMWH anticoagulant should be considered (class IIb recommendation).

Ibuprofen and other non-steroid anti-inflammatory drugs (NSAIDs) with potential action on the cyclooxygenase pathway may be harmful by interacting with and diminishing the aggregation inhibition of aspirin.

6.4.5. Treatment of coronary thrombosis

Sudden deterioration in ventricular function or ECG abnormalities should suggest coronary thrombosis and prompt troponin testing.

Thrombolytic therapy can be administered in confirmed thrombosis including a dose of tissue plasminogen activator (tPA) at 0.5 mg/kg/hr for 6 hrs in addition to low-dose aspirin and low-dose

heparin 10 U/kg/hr. Coagulation parameters should be carefully monitored to avoid bleeding events, by maintaining fibrinogen >10 g/L and platelets > 50,000/mm^3. After tPA administration, the heparin dose is increased in relation to the child's weight and the thrombus should be reassessed on ultrasound.

Coronary angiography should also be discussed to identify the thrombosis and possibly perform interventional revascularisation, if necessary. Revascularisation by catheterisation is an alternative to thrombolytic treatment in older patients.

Sudden infarct-related deaths may occur several years after KD in patients with sequelae from coronary stenosis. Beta-blockers should be prescribed for ischaemic sequelae and statins have been proposed as adjuvant therapy (class IIb recommendation).

Myocardial infarction may increase the incidence of ventricular tachycardia. Patients with severe myocardial damage should have extensive heart rhythm monitoring (Holter) to correctly assess the need for anti-arrhythmic therapy.

6.4.6. Catheterisation and surgery of the coronary arteries

6.4.6.1. Acute coronary syndromes (ACS). Acute coronary syndromes include ST+ ACS (with ST elevation on the electrocardiogram), ST− ACS and unstable angina. KD patients may have ST+ ACS following acute/subacute aneurysm thrombosis, residual giant aneurysm thrombosis or atherosclerotic plaque rupture in adulthood.

The best option in young patients during the acute or subacute phase of KD is systemic thrombolytic therapy or intravenous anti-aggregation. Angioplasty can be discussed but bypass surgery should not be considered.

Patients with KD may have ST-ACS or unstable angina due to non-occlusive thrombus or the progression of calcified stenosis. The appropriate treatment for thrombosis is thrombolytic therapy and more intensive anticoagulation. Revascularisation may be considered for calcified stenosis.

Patients with stable angina should undergo revascularisation if they have symptomatic common trunk involvement, impact on their lifestyle or high-risk factors for ischaemia. The first-line therapy is coronary artery bypass grafting, although angioplasty may be considered.

6.4.6.2. Coronary artery bypass surgery or angioplasty?. There are several arguments to support bypass surgery rather than angioplasty. Bypass surgery should be performed in patients with left main trunk involvement, multiple coronary involvement, left ventricular dysfunction or diabetes. The mammary arteries should be used because the length and diameter continue to grow with the child, unlike the saphenous vein.

Angioplasty is indicated in patients with single coronary artery involvement, multiple involvement but with easily treatable focal lesions, normal left ventricular function and without diabetes. Angioplasty is the first line treatment in older children and young adults. It may also be considered in patients with multiple comorbidities if bypass surgery is a high risk.

6.4.6.3. Heart transplantation. A small number of patients with severe irreversible myocardial dysfunction, severe ventricular arrhythmias, or severe coronary lesions that cannot be treated by catheterisation or bypass surgery following KD, have had a heart transplant. Transplantation may be required within weeks after the onset of disease or up to 20 years after the acute phase. It has been performed in both children and adults.

6.5. Therapeutic education and lifestyle adaptations

A therapeutic education programme for young patients with KD should be designed based on the definition of therapeutic patient education (TPE) proposed by the World Health Organisation. This includes an educational contract between the carer and the patient. A consent form is signed. The aim of TPE is to improve the patient's quality of life while providing quality care. It is organised into different educational sessions (initial and then reinforcement ± repeat). If the patient is on VKAs for life, he/she may also be enrolled in a TPE programme for children on VKAs.

The goal of the initial session is to:

- make the educational diagnosis. This involves assessing the skills and knowledge already acquired about the disease, establishing action objectives for care at home, and helping the patient achieve the goals by reconciling the constraints of daily life and the disease;
- provide patients with theoretical knowledge and information about the disease, monitoring, sports and puberty;
- give families the opportunity to meet and exchange with other families facing the same disease and treatment;
- assess the patient's quality of life.

The goal of reinforcement and/or recovery sessions is to:

- remind patients/families about the disease and signs of complications (tachycardia, malaise, myocardial infarction pain);
- share experiences among families, educational nurses and doctors;
- test knowledge in a playful way through collective educational games and follow-up the educational diagnosis;
- assess quality of life in a sequential manner.

All the elements of each TPE session must be recorded in a specific therapeutic education file that can be consulted by the patient and the medical team. A letter is systematically sent to the general practitioner.

Discussing the disease during these sessions with several families allows the team to evaluate the knowledge acquired in a playful and collective manner, while giving each family the skills to react to everyday situations. Thus, TPE provides comprehensive care to the patient by placing him or her in a psychosocial context. This "humanised" care takes into consideration the patient as a person and not an illness. The patient thus becomes an actor in his or her own care.

The child's lifestyle should be as normal as possible. There is no cardiological situation that should interfere with a child's life. Treatment should be optimal and as aggressive as necessary to allow the patient every chance to develop normally. Practicing sports is essential and the necessary measures should be taken to adapt to the child and prevent exclusion.

6.5.1. Why therapeutic education?

If coronary anomalies do not normalise, there is a risk of progression towards persistent aneurysmal dilatation, thrombosis or stenosis. In patients with persistent coronary anomalies, the incidence of stenosis, which is proportionally higher with the size of the aneurysm, continues to increase linearly over time. The risk of infarction is highest within one year after the onset of disease, but it may also occur in adulthood in cases of undiagnosed KD. In certain cases, although the anomalies normalise on coronary angiography, their "disappearance" involves myointimal proliferation that fills the aneurysm, resulting in normalisation of the luminal diameter but not the vessel itself. They therefore remain abnormal and at risk.

Thus, patients with coronary sequelae need to understand their disease and receive education about the prevention of cardiovascular risk factors.

6.5.2. Prevention of cardiovascular risk factors

Since 2011 patients with a coronary aneurysm are considered to have a high cardiovascular risk, and those with an aneurysm that has regressed, a moderate cardiovascular risk. Several studies have shown that high-density lipoprotein (HDL) levels decrease during acute KD, sometimes with increased triglycerides and decreased apolipoproteins. Low HDL levels may persist following acute KD, especially in patients with severe coronary artery disease. In addition, patients with KD may be at a higher risk of being overweight and obese, probably due to a lifestyle with less physical exercise. Thus, these patients should be educated to fight against cardiovascular risk factors and should be informed, in particular, that cocaine use can be extremely deleterious in patients with coronary artery disease.

6.6. Use of patient organisations

Patients and other participating healthcare professionals may be informed about patient organisations by their general practitioner, reference and/or expert centres, institutional websites or Orphanet (see list of useful links for health professionals and patients).

These associations help improve disease management by promoting cooperation among patients, patient associations and carers as well as medico-social and administrative institutions.

The France Vascularites Association, created in 2006, is a non-profit public-interest organisation, under the French law of 1901. It includes patients with vasculitis, their relatives and caregivers. It connects patients to limit their isolation as well as to share experiences and information. It can help improve the care pathway by working with different healthcare networks. The association provides information that has been validated by its scientific committee to doctors. It co-promotes medical research and organises charity events to support research.

Several specific actions are provided to help patients live with KD on a daily basis:

- the patients receive the association's telephone number and e-mail;
- information sessions (face-to-face or web-conference) are organised for patients with the help of specialists;
- patient group meetings are organised;
- courses are provided to understand the biological mechanism of vasculitis, to explain the medical vocabulary, to know how to interpret blood test results;
- connected tools are developed (self-monitoring sheets, educational games, etc.) to help patients have a better understanding of their disease;
- information pamphlets are drafted on vasculitis, treatment, schooling, different types of aid, etc.;
- therapeutic education is promoted for patients and caregivers in the region.

The association France Vascularites created a KD branch in 2017 to develop specific actions for this form of vasculitis, in particular:

- appointing specific KD referents (parents) to help and guide patients and their relatives;
- recording the day-to-day problems encountered by patients and their parents/relatives;
- publishing a diagnostic poster;
- organising information sessions and specific web conferences;
- providing information pamphlets for the general public, pupils and teachers;
- integrating paediatric TPE programmes;
- training expert parents.

6.7. Impact on daily life

In some cases, KD may progress to a disability or invalidity. In children, a disease is considered chronic after at least 6 months, and if it requires ongoing medical management, while taking into account the complexity and severity of the disease, the age of the child and the family environment.

A survey of 105 patients and their relatives performed by the patient association France Vascularites, reported on "secondary" symptoms of KD, that are more common in patients with severe or incomplete forms of the disease. These symptoms can result in frequent absences from school (47% of respondents). The most frequent secondary symptoms were headaches, extreme fatigue and/or loss of energy, irritability, joint pain, abdominal pain, increased sensitivity to infections, hyperactivity and loss of appetite[4].

An Individualised Reception Project can be created for children with cardiac sequelae, extreme fatigue and/or on AVK. This document specifies how different community services (nursery, school, college, high school, leisure centre), can be adapted to the child's or adolescent's needs. The Individualised Reception Project may be for school and extracurricular activities.

In certain complex cases, one of the two parents may have to stop working to manage the family (medical or paramedical appointments, schooling, etc.). Several financial aid programs can be applied to for this purpose. Support can also be obtained from the Departmental Center for Disabled Persons.

6.8. Post-treatment immunoglobulin vaccination

6.8.1. Inactivated (inert) vaccines

The vaccine response to inert vaccines is not influenced by the administration of polyvalent immunoglobulins. In the same way, KD per se does not modify vaccine tolerance or place the patient at a particular risk. Patients can (and should) therefore receive all inert vaccinations according to the vaccination schedule for the general population.

6.8.2. Live vaccines

Donor-derived antibodies contained in polyclonal immunoglobulin (IVIG) preparations may inactivate certain live virus vaccines and reduce their immunogenicity. These vaccines should therefore be delayed for different periods of time when the patient receives IVIG treatment. In France, the only risk of interference from IVIG is for the measles, mumps, rubella (MMR) and varicella (VZV) vaccines. The level of natural antibodies in IVIG preparations should not affect other live vaccines (e.g. yellow fever). The recommended delay between IVIG administration and these live vaccines depend on the total dose of immunoglobulin administered:

- 1 g/kg: 10 months between immunoglobulin and the MMR or VZV vaccines;
- 2 g/kg: 11 months between immunoglobulin and the MMR or VZV vaccines.

These recommended intervals are based on an estimated half-life of 30 days for passively acquired antibodies and an observed interference with the immune response to the measles vaccine of 5 months after a dose of 80 mg IgG/kg.

It is important to report the cases of KD to improve monitoring of the epidemiological progression, the effects of treatment and the understanding of its long-term outcome.

[4] https://www.association-vascularites.org/accueil/nos-actions/enquetes/questionnaire-symptomes-secondaires-maladie-de-kawasaki.

Contacts: Kawanet Registry: JIR Cohort: https://www.jircohorte.org/; francois.hofer@jircohorte.ch.

7. Follow-up [8,32,36,54,64,102,112,165,202]

The frequency and content of follow-up consultations are determined on a case-by-case basis taking into account the initial cardiac damage.

Any coronary damage is managed in relation to the disease progression and the presence or absence of myocardial ischaemia.

7.1. Objectives

The goal of follow-up is mainly to monitor anti-inflammatory treatment.

7.2. Aspirin

Because the doses and duration of aspirin therapy are low and reduced, the risk of anti-inflammatory-induced adverse effects is limited. However, Reye's syndrome, which may occur in children taking aspirin during chickenpox or influenza, has also been reported in patients receiving long-term aspirin after KD. Thus, a patient presenting with KD associated with influenza should be treated with IVIG without aspirin, and the use of another antipyretic and antiplatelet agent should be considered for at least two weeks.

7.3. Corticosteroids

There are numerous adverse effects associated with high doses of corticosteroids. The immediate effects include fluid retention (particularly when boluses of 15–30 mg/kg are used), with hypertension, rhythm disturbances (hypokalaemia) and a risk of heart failure as well as metabolic (hyperglycaemia), bone (aseptic osteonecrosis) and psychomotor excitement (more rarely slowing/depression). The effects observed after 10 days of treatment are excitement, hyperphagia and metabolic disorders (glucose intolerance, fat distribution variations, amyotrophy, osteopenia). The risk of infection should be systematically assessed, especially in the event of recurrent fever during treatment.

7.4. Biotherapies

Biotherapies increase the risk of infection. The risk of tuberculosis must be systematically assessed before starting biotherapy based on an interview (return from a high-risk area, contact with a sick person, known immunodepression) and a chest X-ray. The blood count and liver enzymes (transaminases, bilirubin, γGT) must be monitored with anakinra because of the risk of leukopenia and drug-induced hepatitis, respectively.

7.5. Professionals involved (and coordination arrangements)

If possible, follow-up should be coordinated by the doctor specialised in KD, usually a hospital paediatrician assisted by a paediatric cardiologist. The general practitioner or paediatrician can coordinate the care. Other specialists may be involved in patient follow-up including dermatologists, neurologists, vascular specialists and haematologists. Other health professionals may also play a role in treatment: therapeutic education professionals, dieticians, nurses, physiotherapists, occupational therapists, child psychologists, child psychiatrists, social workers, or specialists in complementary medicines (sophrology, hypnosis, meditation...).

Table 10
Myocardial ischemia risk level stratification scale.

Stratification of risk level	
Level 1	1. Not affected at any time (Z-score always < 2)
Level 2	2. Dilation only (Z-score 2 to < 2.5)
	3. Small aneurysm (Z-score ≥ 2.5 to < 5)
Level 3	3.1. Current or persistent
	3.2. Decrease to expansion only or normal lumen size
	4. Medium aneurysm (Z-score ≥ 5 to < 10, and absolute size < 8 mm)
Level 4	4.1. Current or persistent
	4.2. Decrease to a small aneurysm
	4.3. Decrease to expansion only or normal lumen size
	5. Large and giant aneurysm (Z-score ≥ 10, or absolute size ≥ 8 mm)
Level 5	5.1. Current or persistent
	5.2. Small to medium aneurysm
	5.3. Decrease to small aneurysm
	5.4. Decrease to expansion only

7.6. Frequency and content of paediatric consultations

All patients with KD should be reviewed by a paediatrician within 15 days after discharge from the hospital, then at 6 weeks and 3 months. If there are no complications, the patient may have an annual follow-up consultation either in the same department or by the attending physician who has been informed of the protocol.

The first three follow-up visits confirm the maintenance of clinical (absence of fever and other signs of KD) and biological (normalisation of CRP) remission. Anti-inflammatory drugs are also monitored, and decisions may be made to stop ongoing treatments. Secondary symptoms of KD may be detected (headaches, sleep disorders, fatigue or deafness). The child's overall development is assessed, vaccinations are performed, and the family is reassured during these consultations. The other consultations assess the child's overall development, repeat the vaccination schedule if necessary and may also often be used to reassure the family. Visits are more frequent in children with cardiac complications, with a cardiological consultation to decide on the treatment strategy and make any necessary adaptations to daily life.

Cardiological and paediatric follow-up visits are associated.

7.7. Monitoring cardiac complications

7.7.1. During acute disease

7.7.1.1. Risk stratification. Clinical experience with KD has shown that patients should be stratified according to the relative level of risk of myocardial ischaemia, whether it is due to coronary artery thrombosis or stenosis/occlusions. Long-term management of patients can then be individualised for the frequency of clinical follow-up and diagnostic tests, assessment and management of cardiovascular risk factors, medical therapy, thromboprophylaxis, physical activity and reproductive counselling.

A recent risk stratification scheme was based on the AHA guidelines published in 2017 to define a graded strategy for long-term follow-up depending on the appearance of the coronary arteries on echocardiography. This scheme first uses the patient's maximum Z-score at any time and in any branch, which is then modified by the maximum Z-score in a currently assessed branch. The scale has 5 risk levels and is presented in Table 10.

Although the risk stratification scheme is primarily based on peak coronary artery Z-scores derived from echocardiography, other coronary artery characteristics and non-coronary cardiac complications may influence decisions on risk (Table 11). These additional features may be obtained from other imaging modalities.

This stratification scheme can be used to individualise long-term patient management and determine the frequency of clinical follow-up and diagnostic tests, assessment and management of cardiovascular risk factors, medical therapy and thromboprophylaxis.

Table 11
Additional clinical features increasing the risk of myocardial ischemia.

Other additional clinical features that may increase the risk of long-term myocardial ischaemia [102]
Longer length and distal location of aneurysms increase the risk of flow stasis
Total number of aneurysms high
More branches affected
Presence of luminous irregularities
Abnormal characterisation of the vessel wall (calcification, luminal proliferation, myofibroblastic proliferation)
Presence of functional abnormalities (impaired vasodilation, impaired flow reserve)
Absence or poor quality of collateral vessels
Anterior revascularisation
Anterior coronary artery thrombosis
Anterior myocardial infarction
Presence of ventricular dysfunction

The frequency and content of follow-up consultations are summarised in Table 9.

7.7.1.2. Assessment of inducible ischemia in patients with coronary aneurysms [102]. In patients with coronary aneurysms, different pathological factors such as thrombosis and luminal myofibroblastic proliferation increase the risk of stenosis and obstructions. Periodic monitoring for inducible myocardial ischaemia is therefore recommended. The timing of the initial assessment and the frequency of subsequent tests depend on the severity of the maximal and current coronary artery anomalies.

The tests used to monitor inducible myocardial ischaemia should take into account the expertise of the institution, although physiological exercise stress tests are preferred to pharmacological stress tests, while minimising the cumulative radiation dose and risk to the patient.

7.7.1.3. Recommendations for screening for inducible ischaemia [203]. Stress echocardiography or cardiac MRI, stress scintigraphy or positron emission tomography (PET) can be used to assess inducible myocardial ischaemia. Electrocardiographic treadmill exercise tests should not be used alone.

7.7.1.4. Recommendations for the assessment of patients with inducible myocardial ischaemia. Patients with evidence of inducible ischaemia on examination and significant coronary stenosis or occlusion on advanced imaging should be managed by a specialised cardiology team with the expertise to perform coronary catheterisation and surgical interventions.

7.7.1.5. Role of advanced cardiovascular imaging and functional assessment. The long-term cardiovascular impact of KD may result in both distortion of coronary luminal geometry and changes in the structure and function of the endothelium and arterial wall as well as in the myocardium. Advanced imaging techniques can help characterise vascular remodelling, flow reserve, endothelial dysfunction and myocardial fibrosis, which can all influence the prognosis and risks in patients with significant coronary artery involvement.

In summary, risk stratification should be applied to patients with a history of KD and coronary anomalies who should be monitored for inducible ischaemia and receive long-term follow-up. Testing should include anatomical imaging of the coronary arteries as well as functional or pharmacological stress tests with ultrasound. Specialised long-term follow-up is recommended in these patients.

7.7.2. Long-term follow-up

7.7.2.1. Advice on physical activity and reproduction. In addition to the items listed in Table 9 and depending on the individual patient's situation, the practitioner may also provide information and advice on physical activity and reproductive counselling:

- physical activity: advice on physical activity can be freely provided at each visit. Participation in competitive sports or high-intensity activities should be determined in relation to test results for myocardial ischaemia or exercise-induced arrhythmia. In patients receiving anticoagulation or dual antiplatelet therapy, activities with a risk of body contact, trauma or injury should be restricted or modified;
- reproductive counselling: advice may be provided on age-appropriate contraception. Pregnancies should be supervised by a multidisciplinary team including a cardiologist and thromboprophylaxis should be modified during pregnancy and delivery.

7.7.2.2. Psychosocial follow-up. After KD, almost all children recover their basic functional health. Reports on general psychosocial well-being are reassuring and show that KD does not affect long-term quality of life in most patients. Similarly, KD has not been shown to have long-term effects on cognitive development or academic performance. Patients with a history of KD had similar or better physical and psychosocial health scores on questionnaires completed by their parents. The association between KD and behavioural problems has not been demonstrated. Several studies have suggested that parents continue to worry about their child's long-term health after KD, regardless of the condition of their child's coronary arteries. Healthcare providers need to accompany families throughout the disease. Acute KD is stressful for patients and families due to hospitalisation, medical procedures, and uncertainty about short- and long-term outcomes. Children with coronary aneurysms may have a severe chronic disease requiring continuous medical testing and treatment. Physical activity must be limited in the small group of patients on anticoagulation or with heart sequelae.

Caregivers must determine whether a psychologist or a social worker is needed on a case-by-case basis.

An Individualised Care Plan should be drafted for all patients with cardiovascular injury level 3 or greater to define the instructions for care and/or transfer to a specialised centre in case of symptoms of myocardial ischemia during school or other extracurricular activities.

8. Special presentation in adults [204,205]

KD rarely affects adults (43 cases in a French retrospective multicentre study between 1967 and 2015). In that study, KD was definite in 79% of cases and probable in 21% (according to Newburger 2004 criteria [112], Appendix 3). The mean age was 31 years ± 12 [18–68], the sex ratio (M/F) 1.2.

High fever and mucocutaneous signs were present in all patients, with more frequent involvement of the extremities and the mouth. Characteristic desquamation, cracked lips and conjunctival hyperemia were present in more than 70% of cases and lymphadenopathy in 56% of cases.

Cardiac involvement was detected in 44% of patients with pericarditis or myocarditis and coronary involvement (coronary vasculitis 23% and coronary aneurysms 19%), complicated in 4 cases by myocardial infarction due to lack of treatment because of a delay in diagnosis. Arthromyalgia was present in half the patients. Digestive or neurological disorders were noted. Vasculitis rarely affected the limbs (< 10%) or the digestive arteries. Clinical signs were similar to those in children although involvement of the extremities and arthritis were more frequent in adults.

The CRP was always very high > 100 mg/L.

Cardiac ultrasound was abnormal in 50% of cases (pericarditis, myocarditis, hypokinesia or coronary aneurysm). Although cardiac ultrasound can detect early hyperechoic lesions when performed by an expert, it cannot visualise all coronary arteries. Coronary CT scan show parietal inflammation as well as early lesions, and all coronary arteries can be visualised. Coronary angiography detects late lesions and aneurysms.

Treatment was similar to that in children but was often delayed because of a late diagnosis. Intravenous immunoglobulin was used in 73% of patients and resulted in apyrexia within 2 days. Aspirin was used alone or in combination with IVIG, at anti-aggregation (50%) or anti-inflammation (50%) doses, and corticoids in 16% of cases.

IVIG (one 2 g/kg/day course for 2 days) before day 10 (or even day 7) provides a clear benefit by significantly reducing coronary aneurysms which occur in 15–25% of patients in the absence of treatment and 5% when treatment with IVIG + aspirin is started before day 7.

The efficacy of other therapies discussed in children has not been demonstrated in adults because of limited number of cases. The therapeutic strategy is therefore based on the recommendations for children.

9. Special resuscitation forms [46,206]

During the acute phase, 2–7% of patients develop life-threatening complications requiring admission to an intensive care unit (ICU).

In a recent study by Cherqaoui et al. [46] of 48 patients with KD who were admitted to the ICU, the average length of stay was 7.9 days. Two children (3 months and 1.5 years old) died of myocardial infarction.

The main reason for admission to the ICU is cardiovascular dysfunction, most often secondary to KD shock syndrome (KDSS). Shock is defined as a life-threatening mismatch between tissue oxygen supply and demand. In KDSS, this shock is secondary to a decrease in systemic vascular resistance, i.e., a decrease in mean arterial pressure and therefore in organ perfusion, and leads to organ failure. Differentiating this shock from toxic shock syndrome can be difficult. Ultrasound showing the presence of mitral or tricuspid insufficiency, as well as anaemia and thrombocytosis are early signs suggesting KDSS.

Other causes of admission to the ICU, in descending order, were: the presence of a giant aneurysm and/or myocarditis (15%), neurological symptoms (13%), multiple organ dysfunction (8%), cardiorespiratory arrest (4%) and respiratory failure (2%). The initial diagnoses were toxic/septic shock (52%) and acute abdominal syndrome (25%). Incomplete forms of KD are more frequently found in ICU patients and many cases of cardiac arrest are reported following incomplete KD.

Coronary thrombosis secondary to vasculitis can be a cause of ICU admission, particularly in cases of myocardial infarction or cardiac arrest. Treatment is based on standard KD therapy with specific therapies discussed in section 6.4.5.

In case of myocarditis associated with KD, refer to chapter 5.4.2.

10. Transition [32,79,205]

A transition "passport" has been shown to be effective in the process of transition from paediatric to adult management. This includes a medical file containing a summary medical letter, and a copy of the various examinations required in the follow-up of KD with coronary and/or myocardial sequelae (ECG, stress test, cardiac ultrasound, coronary CT or coronary angiography, ischaemia test such as perfusion MRI or myocardial scintigraphy).

A summary of the TPE file must also be included so that the adult team that takes over from the paediatric team knows the patient's skills as well as his or her lifestyle and life goals (sports, studies, profession, desire for pregnancy, contraception, lifestyle habits and exposure to toxic substances).

Adult cardiologists can manage patients with cardiac sequelae of KD but their knowledge of this paediatric disease is still limited. Cardiopaediatricians should therefore provide a transition programme to improve management of these patients and avoid breaks in follow-up. Joint transition consultations between the paediatric cardiologist and the adult cardiologist are recommended.

The system should respect the general principles of transition with an emphasis on the prevention of coronary risk factors: prevention of smoking in adolescence, encouragement of physical activity, health and diet rules and adaptation of contraception.

Several studies in educational sciences have shown that certain elements of the TPE system are essential for successful transition of patients to adulthood. Integrating these elements optimises the transition for a young adult with KD with coronary sequelae to adult follow-up.

CeReMAIA transition booklet: BrochureTransition_CeReMAIA.pdf (fai2r.org).

FAI^{2}R Transition Tab: The Transition from Paediatrics to Adult Care – Fai2r.

Disclosure of interest

All participants in the development of the French NDCP filled out a declaration of interest. The declarations of interest are online and available on the website of the reference centre(s).

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Authors' contributions

CG, FB, AB, SB, EB, EB, RC, RD, PD, OF, VH, VL, ALU, CM, UM, MP, LM, OR, JLS, DU, IKP wrote the first draft of the manuscript and participated to writing. All authors participated to edition. All authors read and approved the final version of the manuscript.

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The French version is available free of charge on the following link: Haute Autorité de sauté – maladie de Kawasaki (has-sante.fr).

Prof. Rolando Cimaz passed away suddenly while this French NDCP was being finalised. His contribution to international paediatric rheumatology was exceptional and even though he was involved in all fields, he was especially interested in Kawasaki disease, published numerous studies on this topic. He was particularly attached to France and was a major contributor to the success of the SOFREMIP congresses. Grateful for all that he gave us, we dedicate this French NDCP to him, to which he contributed greatly.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.revmed.2023.06.002.

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