La maladie de Kawasaki
Toujours un sujet d'actualité ?

Damien Bonnet

Unité médico-chirurgicale de Cardiologie Congénitale et Pédiatrique
Hôpital Universitaire Necker Enfants malades – APHP, Université Paris Descartes, Sorbonne Paris Cité
IcarP Cardiology, Institut Hospitalo-Universitaire IMAGINE

Centre de Référence Maladies Rares
Malformations Cardiaques Congénitales Complexes-M3C
Centre de Référence Maladies Rares
Maladies Cardiaques Héréditaires- CARDIOGEN

Kawasaki disease : Key points 1

1. Kawasaki disease (KD) is an acute, self-limited febrile illness of unknown cause that predominantly affects children <5 years of age.

2. KD is now **the most common cause of acquired heart disease in children in developed countries**.

3. In the **absence of pathognomonic tests**, the diagnosis continues to rest on the **identification of principal clinical findings** and the exclusion of other clinically similar entities with known causes.

Kawasaki disease : Key points 2

1. **Timely initiation of treatment with intravenous immunoglobulin** (IVIG) **has reduced the incidence of coronary artery aneurysms** defined from absolute luminal dimensions from 25% to ≈4%. Ongoing studies with **additional therapies have not substantially** reduced this residual risk.

2. **The long-term prognosis is determined by the initial and current level of coronary artery involvement.** Certain subsets of patients are at risk for myocardial ischemia from coronary artery thrombosis and stenoses.

3. Medical management of such patients hinges on judicious use of thromboprophylaxis and vigilance to identify evolving stenoses. Invasive revascularization procedures might be required for selected patients.

Key points: epidemiology

- The estimated incidence in North America is ≈ 25 cases per 100 000 children <5 years of age per year.
- The highest relative risk is in Asian children, especially of Japanese ancestry.
- The ratio of males to females is ≈ 1.5:1.
- KD affects predominantly, but not exclusively young children.
- It is most common in winter and early spring in Europe and North America.
- In Japan, the recurrence rate is ≈ 3%, and the relative risk in siblings is 10-fold higher.
- The case fatality rate is <0.1% in Japan.
- Coronary artery aneurysms from KD account for 5% of acute coronary syndromes (ACS) in adults <40 years of age.

Pathology of Kawasaki disease

- KD vasculopathy primarily involves muscular arteries and is characterized by 3 linked processes:

  (1)necrotizing arteritis;

  (2) subacute/chronic vasculitis;

  (3) luminal myofibroblastic proliferation (LMP).

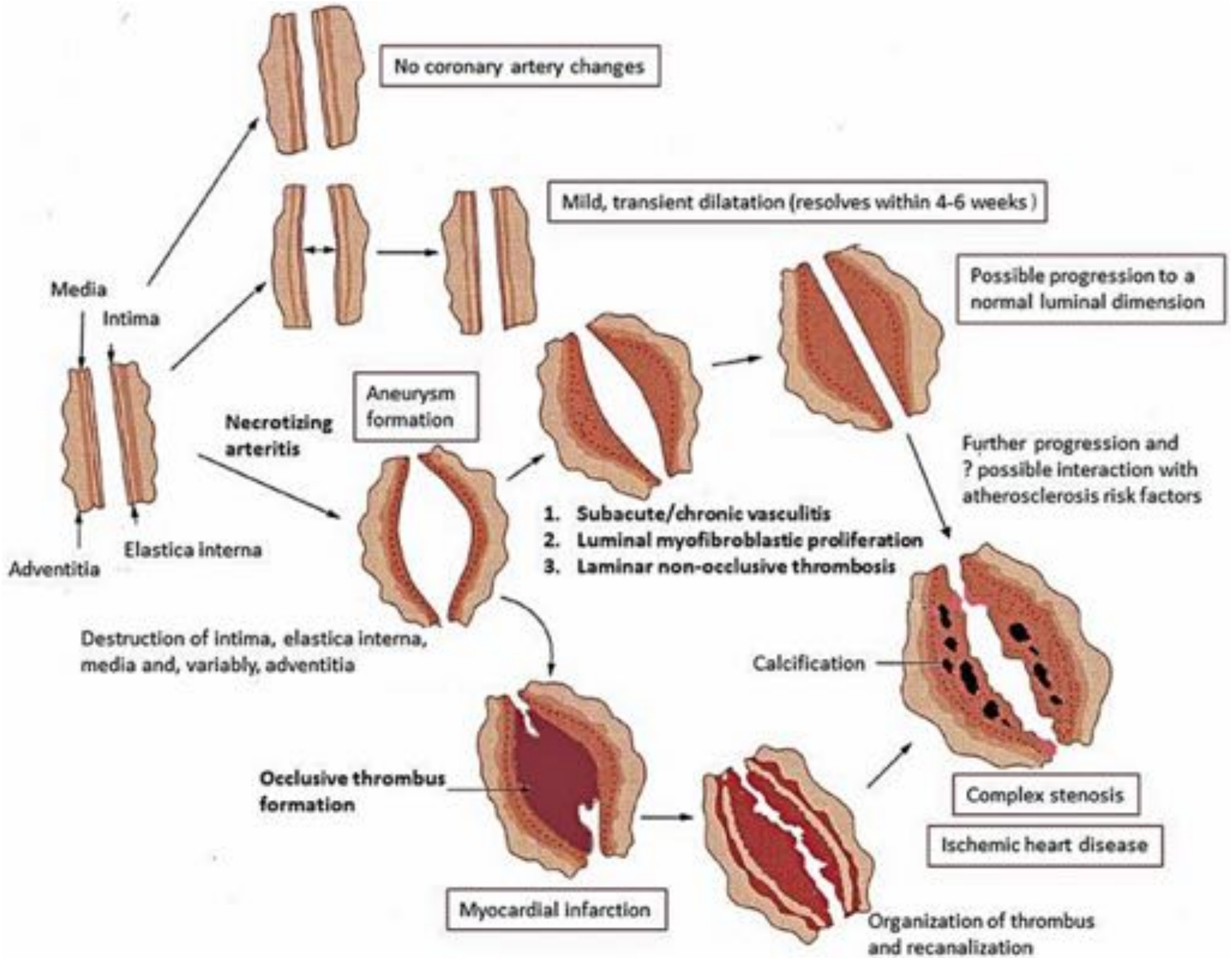
- Large or giant coronary artery aneurysms ≥ 8 mm in diameter or with a Z score ≥ 10 do not “resolve", “regress,” or “remodel.” They rarely rupture and virtually always contain thrombi (the oldest of which may calcify) that can become occlusive.

- Aneurysms with markedly damaged but partially preserved media may develop decreases in lumen diameter over time as the result of LMP or thrombus and can become progressively stenotic.

- Atherosclerotic features are not characteristic of KD vasculopathy even in late deaths or transplants.

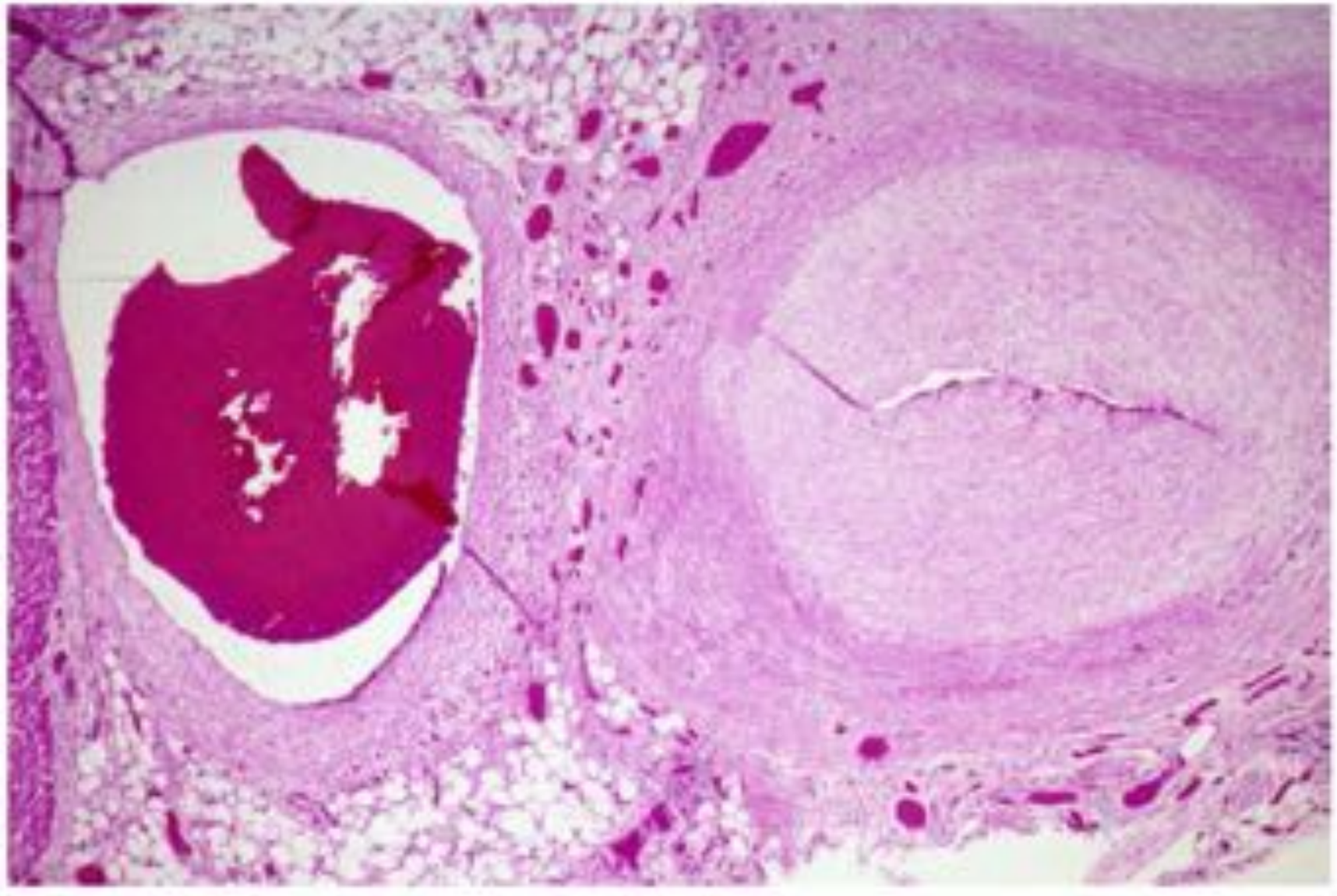
- Pericarditis and myocarditis result from subacute/chronic inflammation, which is usually concentrated around coronary arteries.

Natural history of coronary artery abnormalities

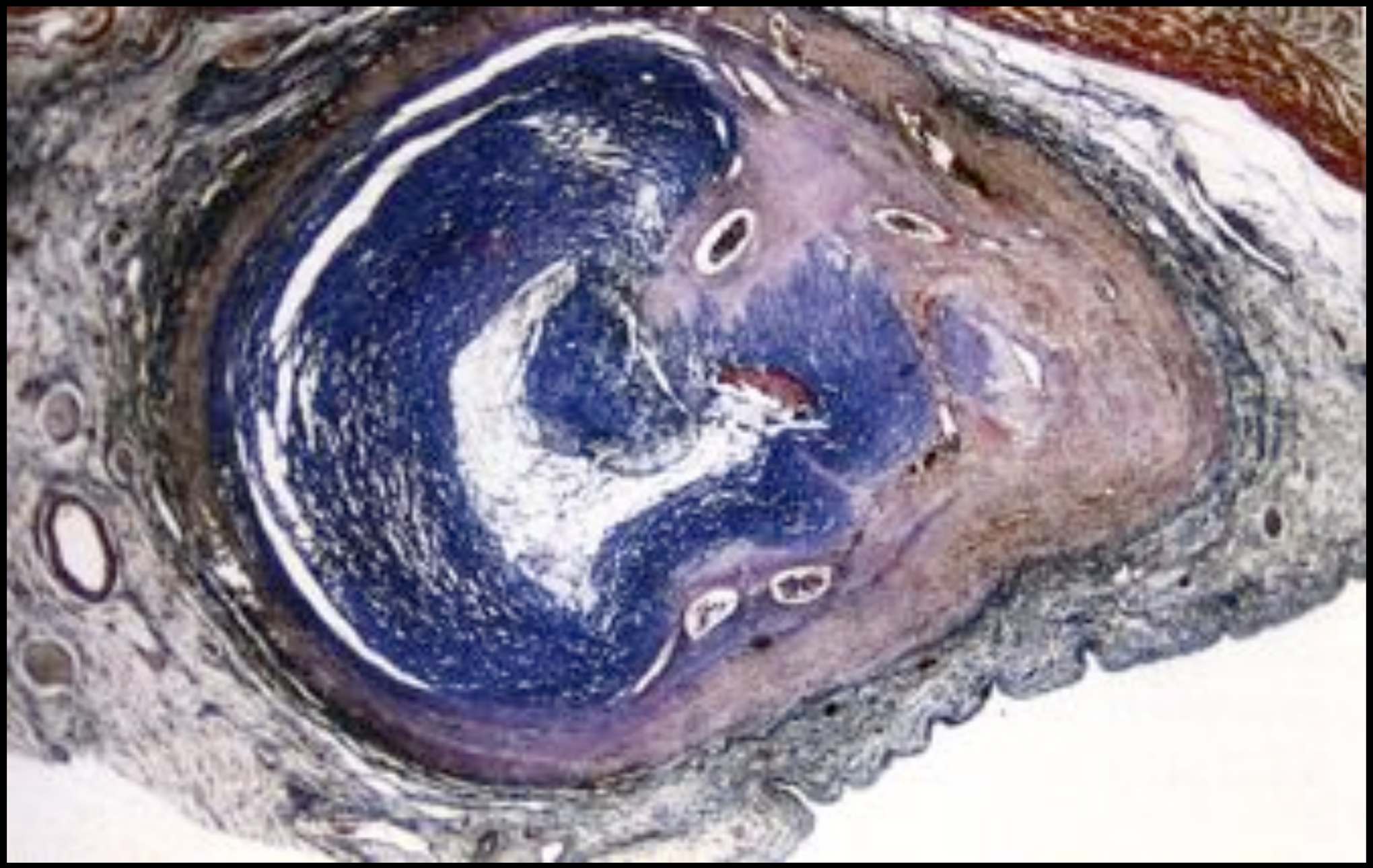


Brian W. McCrindle et al. Circulation. 2017;135:e927-e999

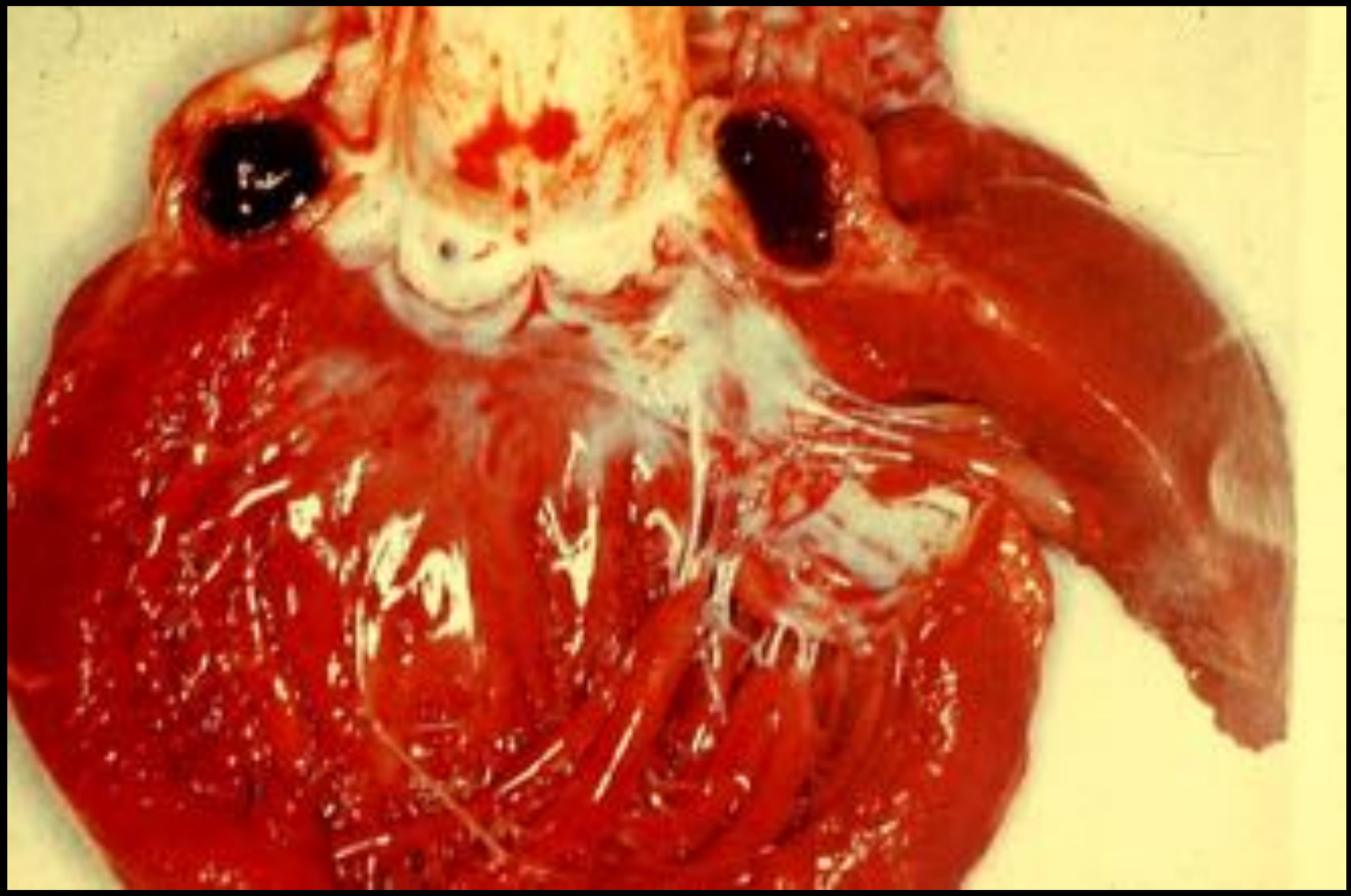
Epicardial coronary artery (right) and epicardial vein (left) from a 19-month-old child who died 10 months after Kawasaki disease onset.



Brian W. McCrindle et al. Circulation. 2017;135:e927-e999



Luminal myofibroblastic proliferation



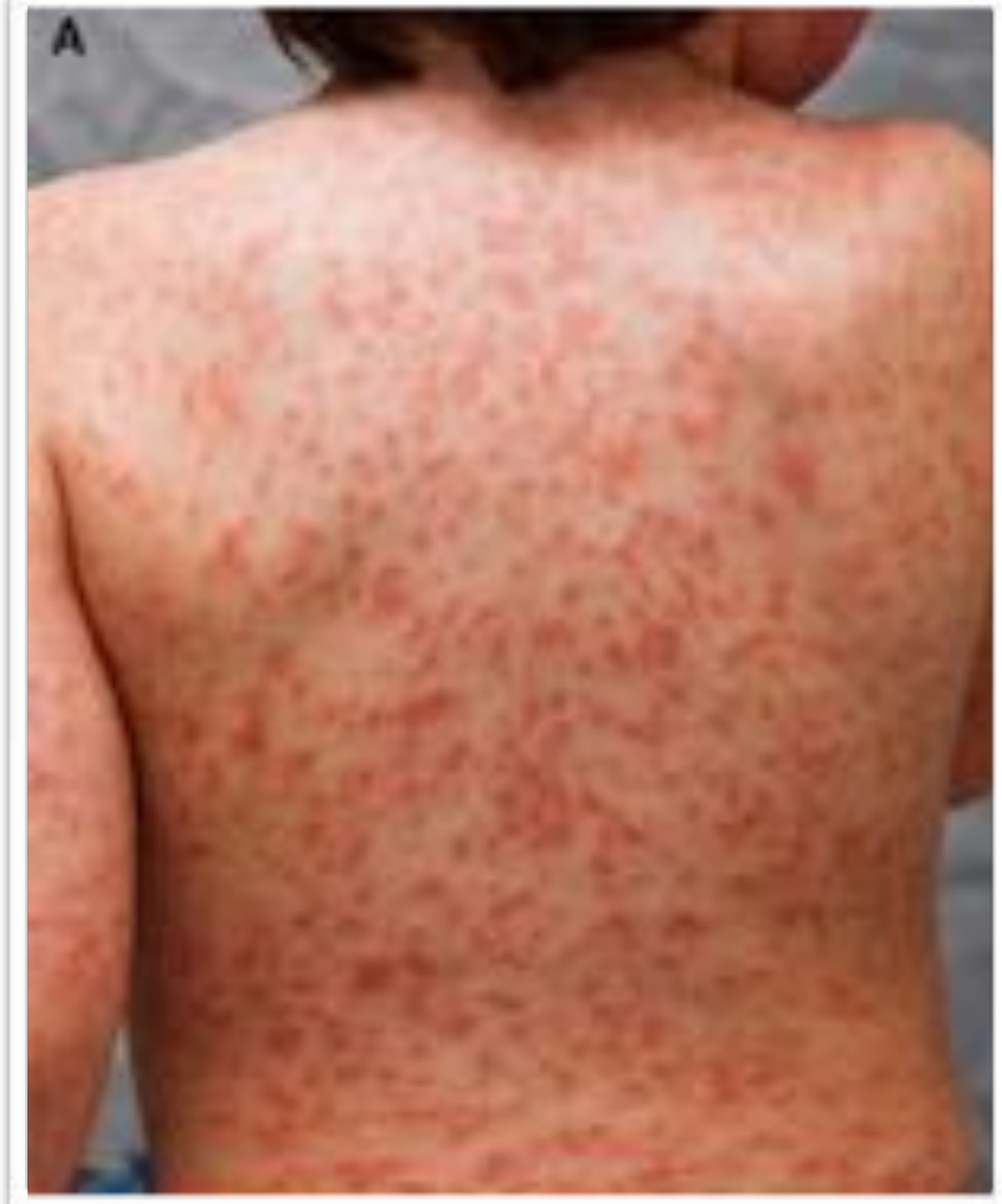
Thrombosis of giant coronary artery aneurysms in Kawasaki disease

Clinical criteria for the diagnosis of Kawasaki disease

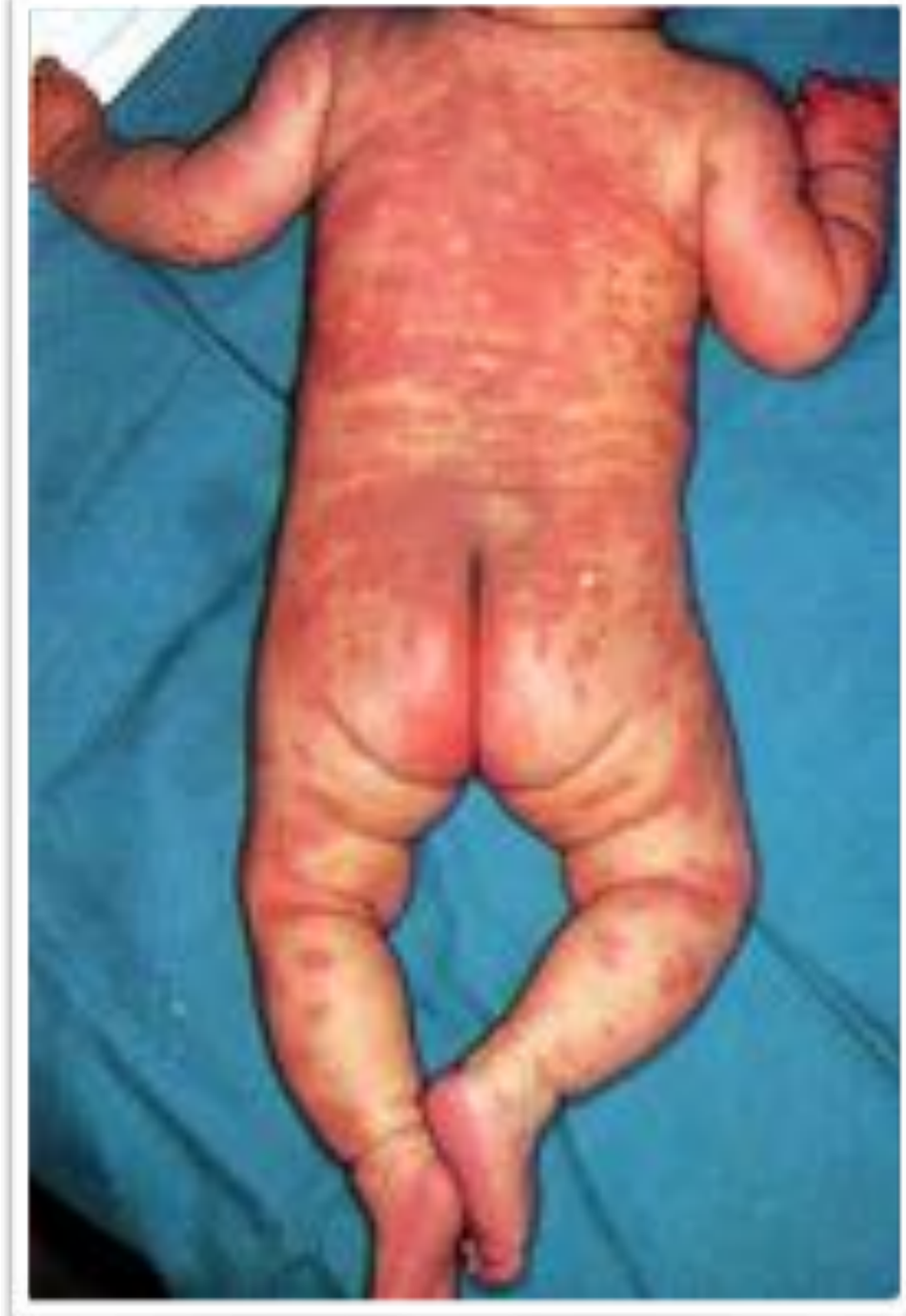
Classic KD is diagnosed in the presence of **fever for at least 5 days** (the day of fever onset is taken to be the first day of fever) together **with at least 4 of the 5** following principal clinical features:

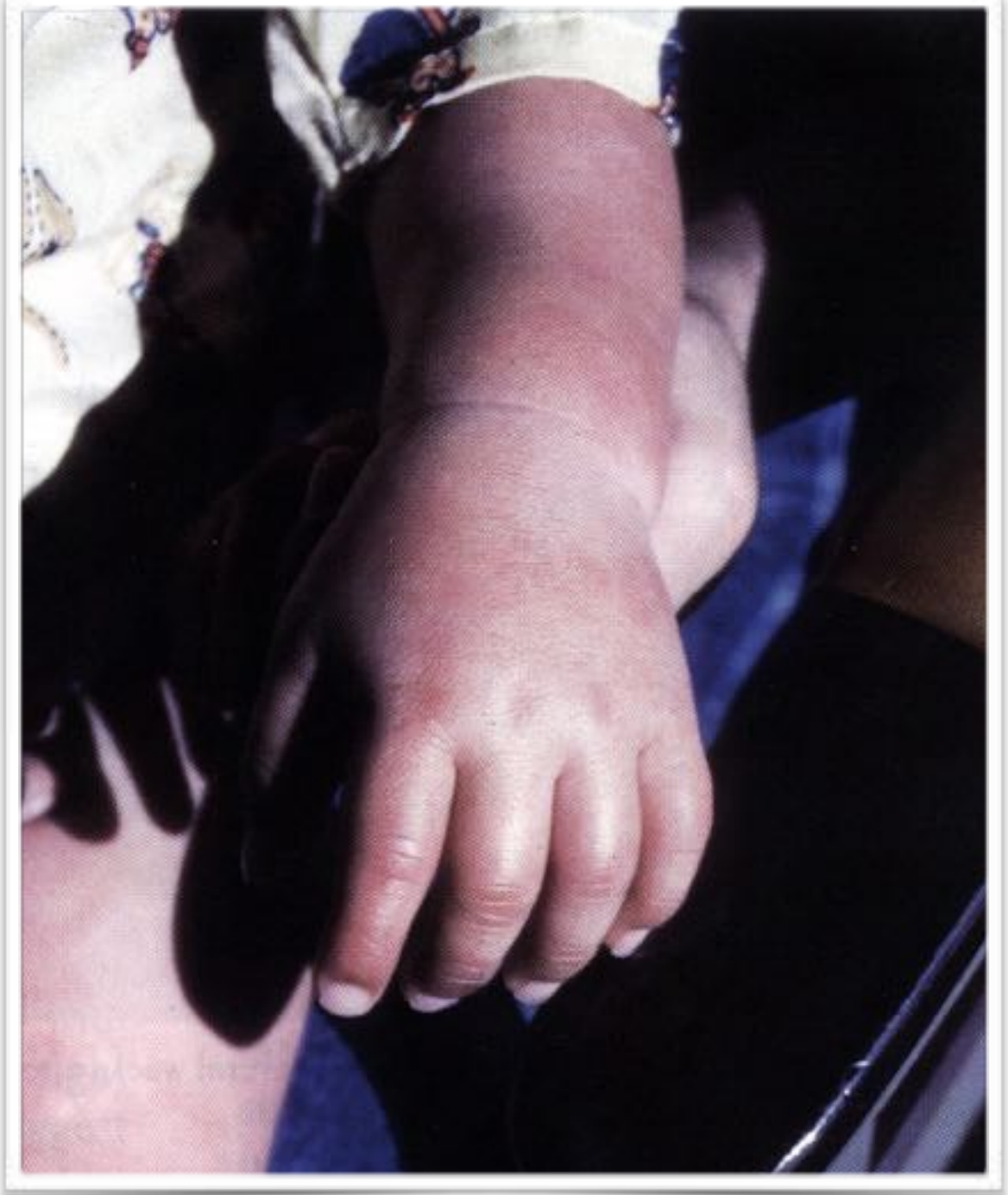
1. Erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa
2. Bilateral bulbar conjunctival injection without exudate
3. Rash: maculopapular, diffuse erythroderma, or erythema multiforme-like
4. Erythema and edema of the hands and feet in acute phase and/or periungual desquamation in subacute phase
5. Cervical lymphadenopathy (≥1.5 cm diameter), usually unilateral

Clinical features of classic Kawasaki disease.

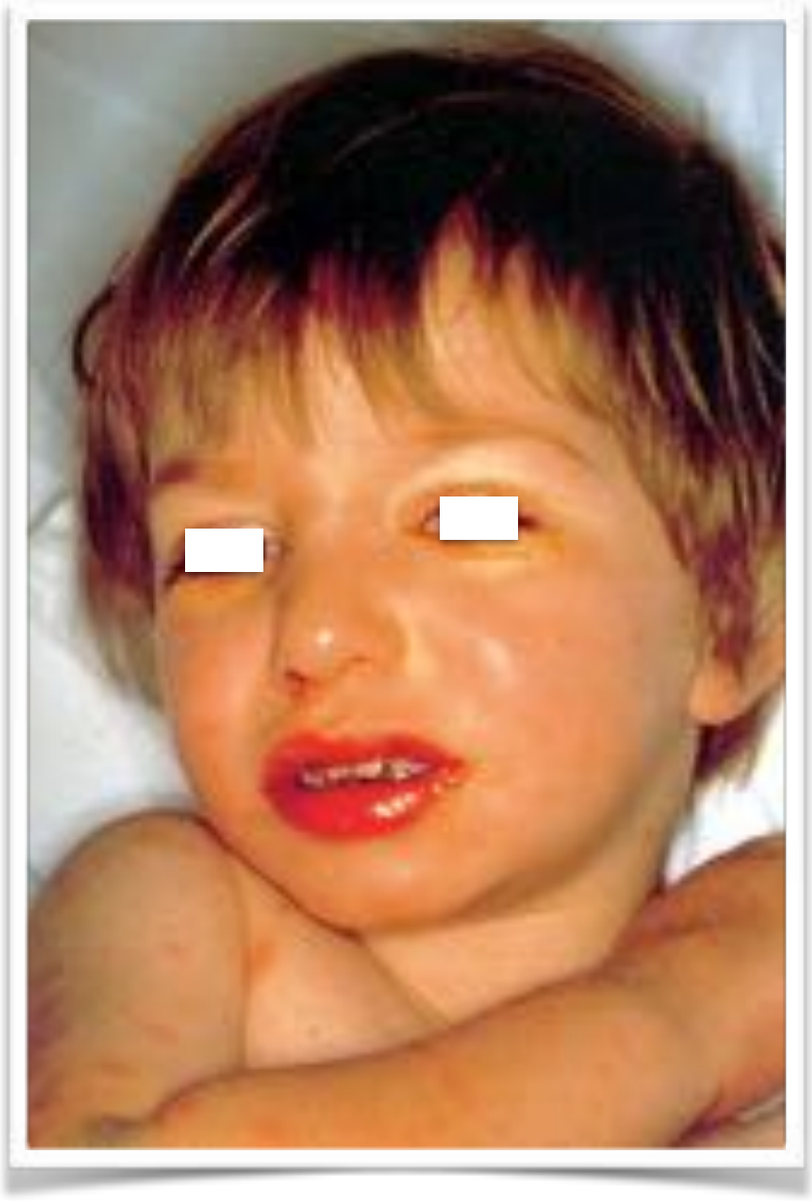


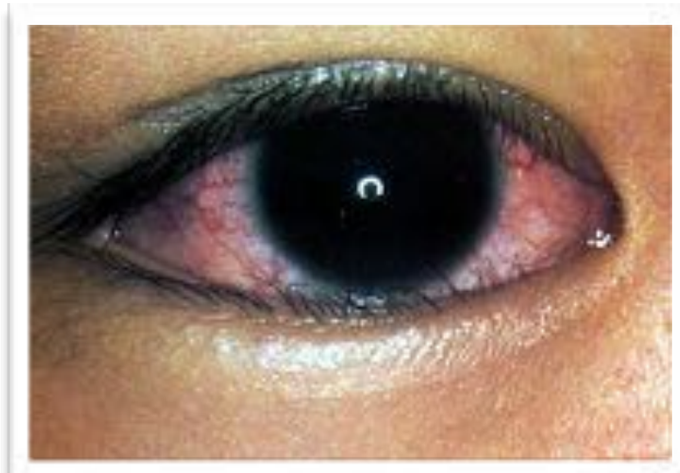
Clinical features of classic Kawasaki disease.



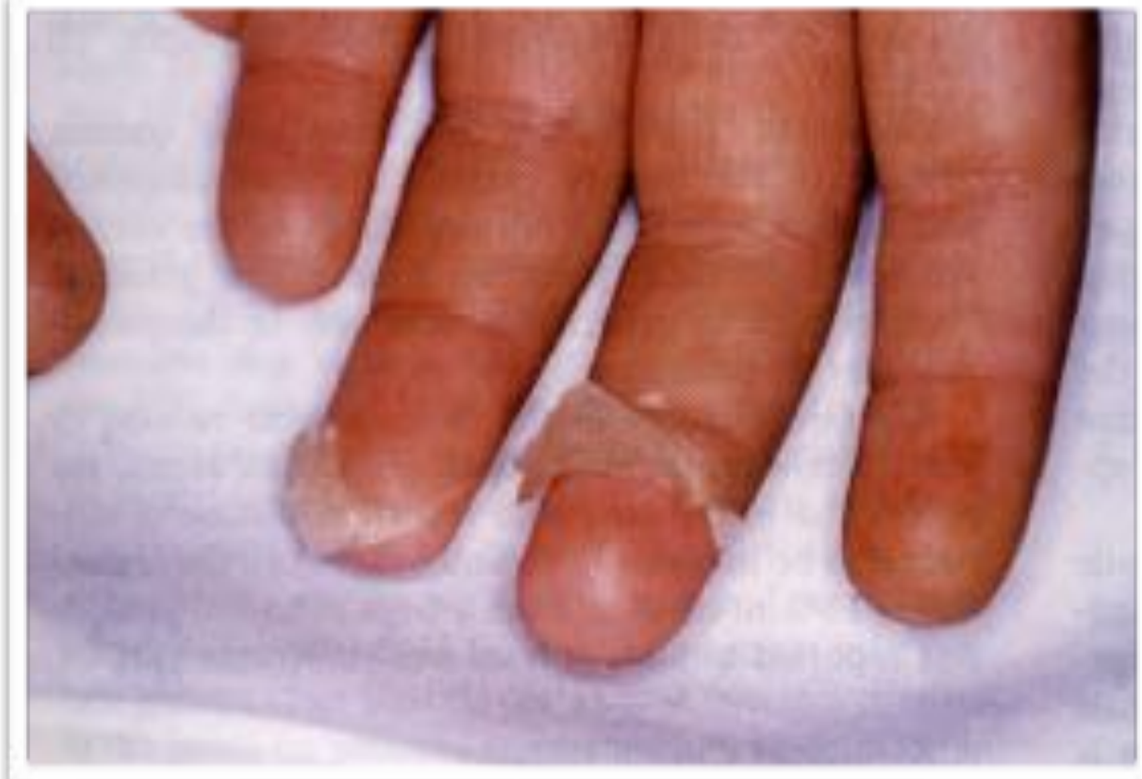


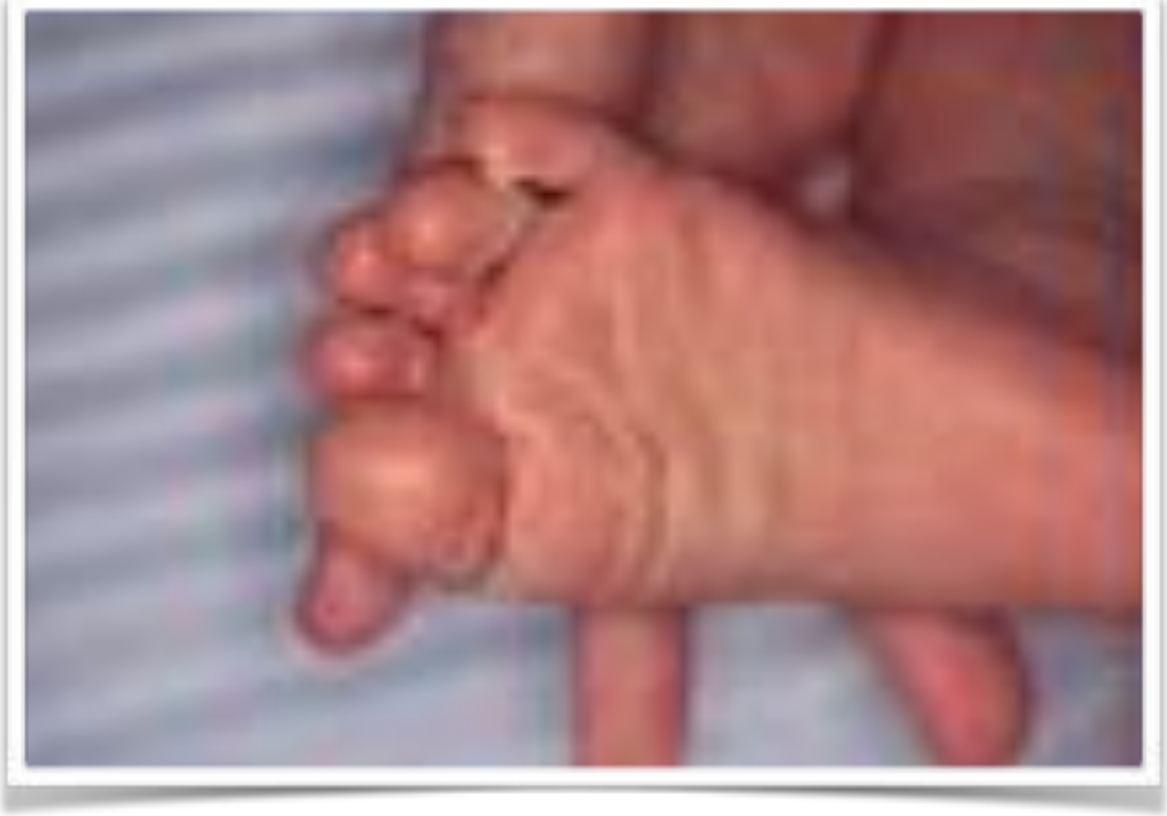
Clinical features of classic Kawasaki disease.

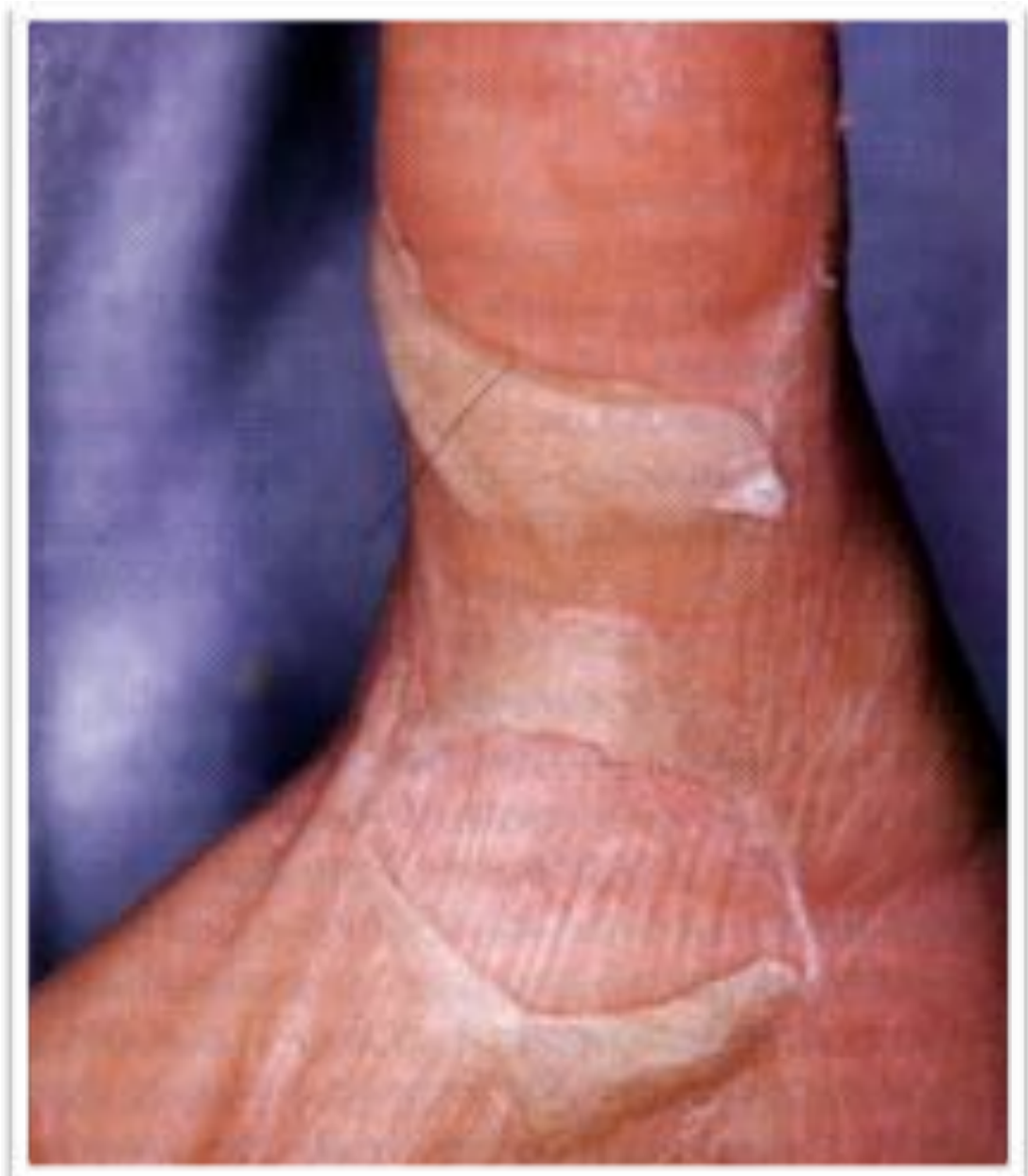




Clinical features of classic Kawasaki disease.



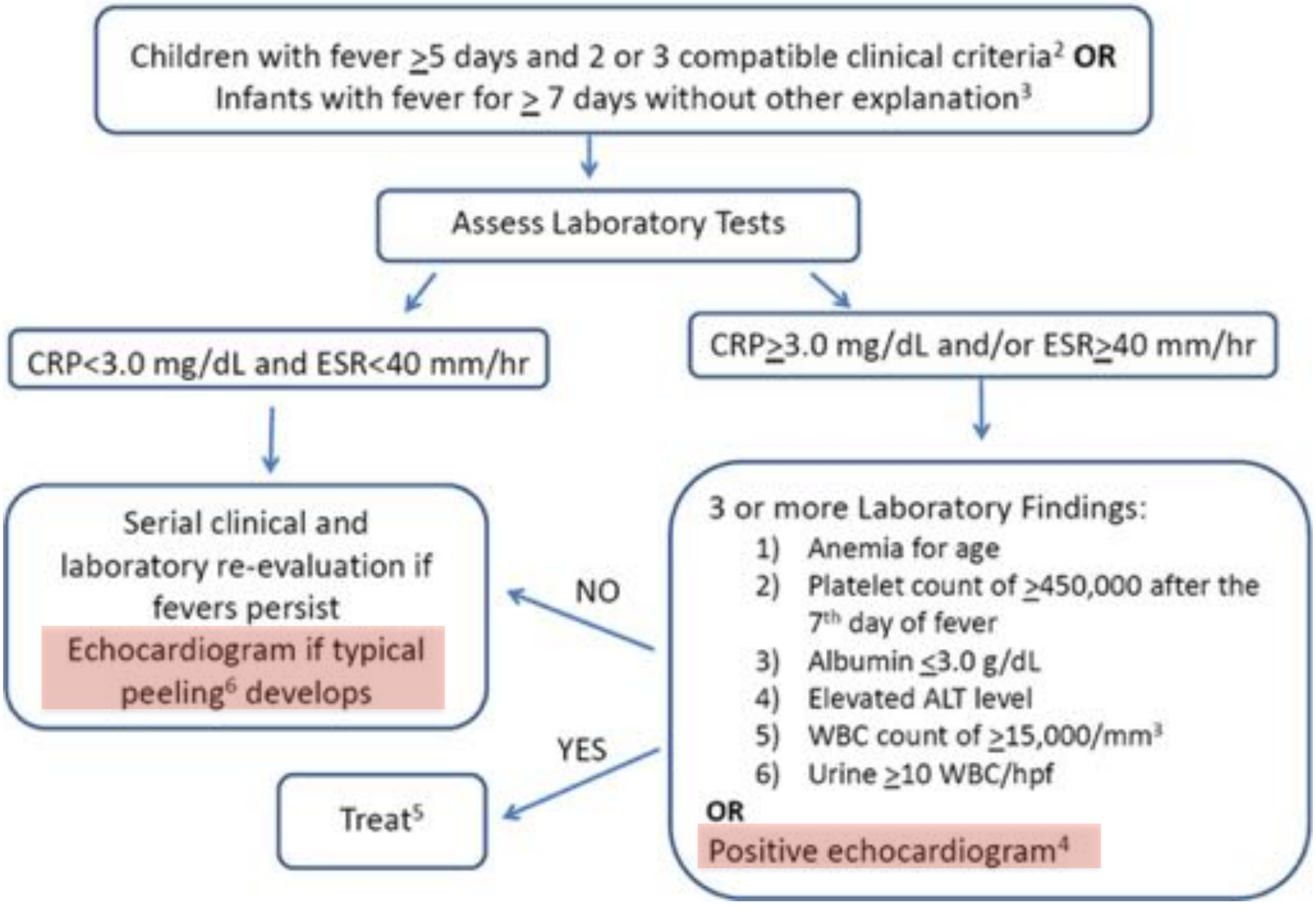




Clinical criteria for the diagnosis of Kawasaki disease

In the presence of ≥4 principal clinical features, particularly when redness and swelling of the hands and feet are present, the diagnosis of KD can be made with 4 days of fever, although experienced clinicians who have treated many patients with KD may establish the diagnosis with 3 days of fever in rare cases

Evaluation of suspected incomplete Kawasaki disease



Brian W. McCrindle et al. Circulation. 2017;135:e927-e999

Differential diagnoses in suspected Kawasaki disease

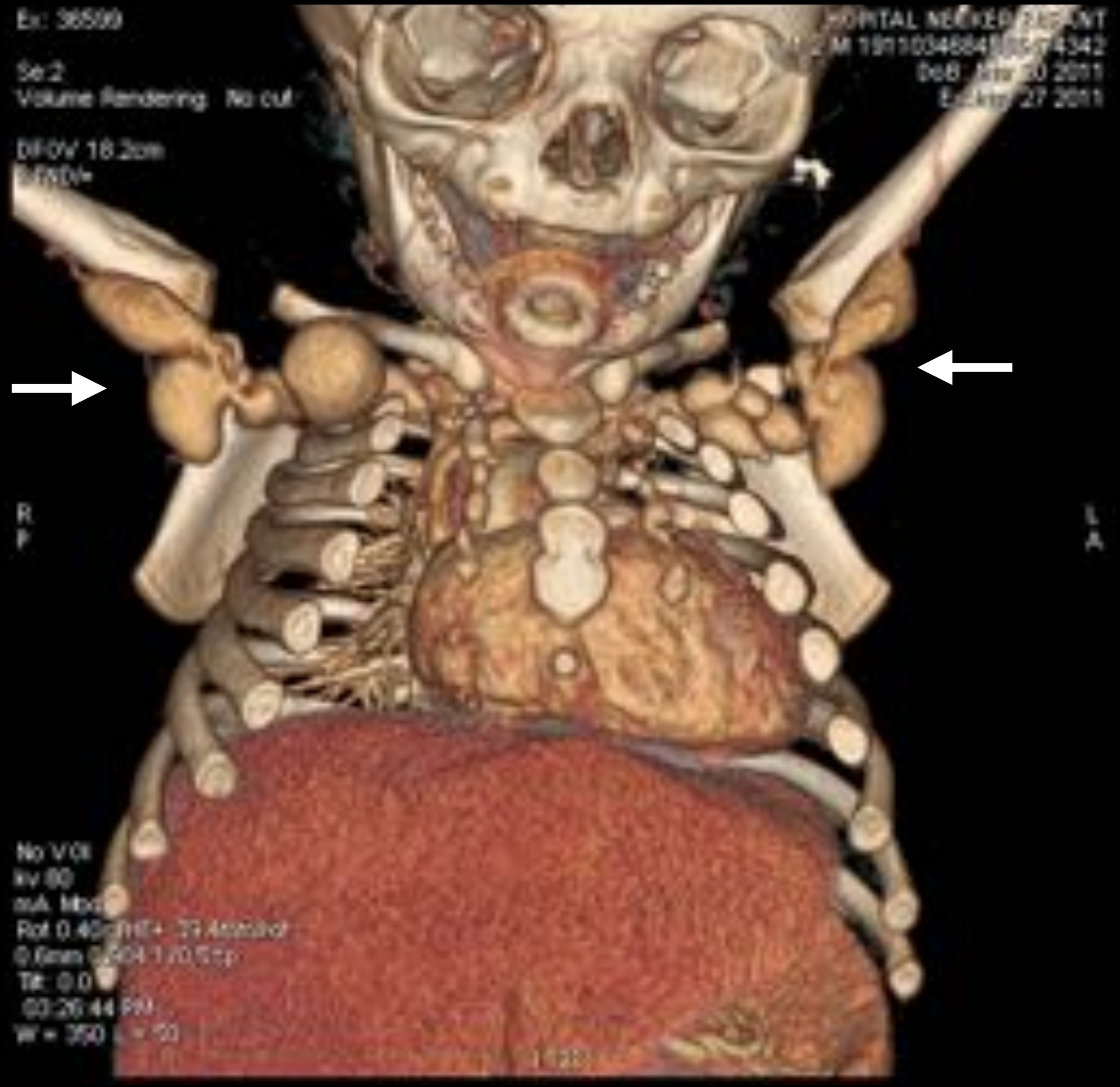
- Measles
- Other viral infections (eg, adenovirus, enterovirus)
- Staphylococcal and streptococcal toxin-mediated diseases (eg, scarlet fever and toxic shock syndrome)
- Drug hypersensitivity reactions, including Stevens Johnson syndrome
- Systemic onset juvenile idiopathic arthritis

When to consider Kawasaki disease in certain infants or children

- Infants <6 months old with prolonged fever and irritability
- Infants with prolonged fever and unexplained aseptic meningitis
- Infants or children with prolonged fever and unexplained or culture-negative shock
- Infants or children with prolonged fever and cervical lymphadenitis unresponsive to antibiotic therapy
- Infants or children with prolonged fever and retropharyngeal or parapharyngeal phlegmon unresponsive to antibiotic therapy

Cardiac involvement in Kawasaki disease

- Cardiovascular collapse : rare
- Myocardial dysfunction : frequent but rarely overt
- Valvar abnormalities
  - Mitral valve regurgitation is frequently observed
  - Aortic regurgitation is rare but aortic root dilatation is not uncommon during acute phase


Ex: 36509
Ser 2
Volume Rendering No cut
Diff OV 16.2cm
R
P
L
A
No VOI
kv 80
Tilt: 0.0
03:26:44 PM
W = 350

Z-Score Classification in Kawasaki disease

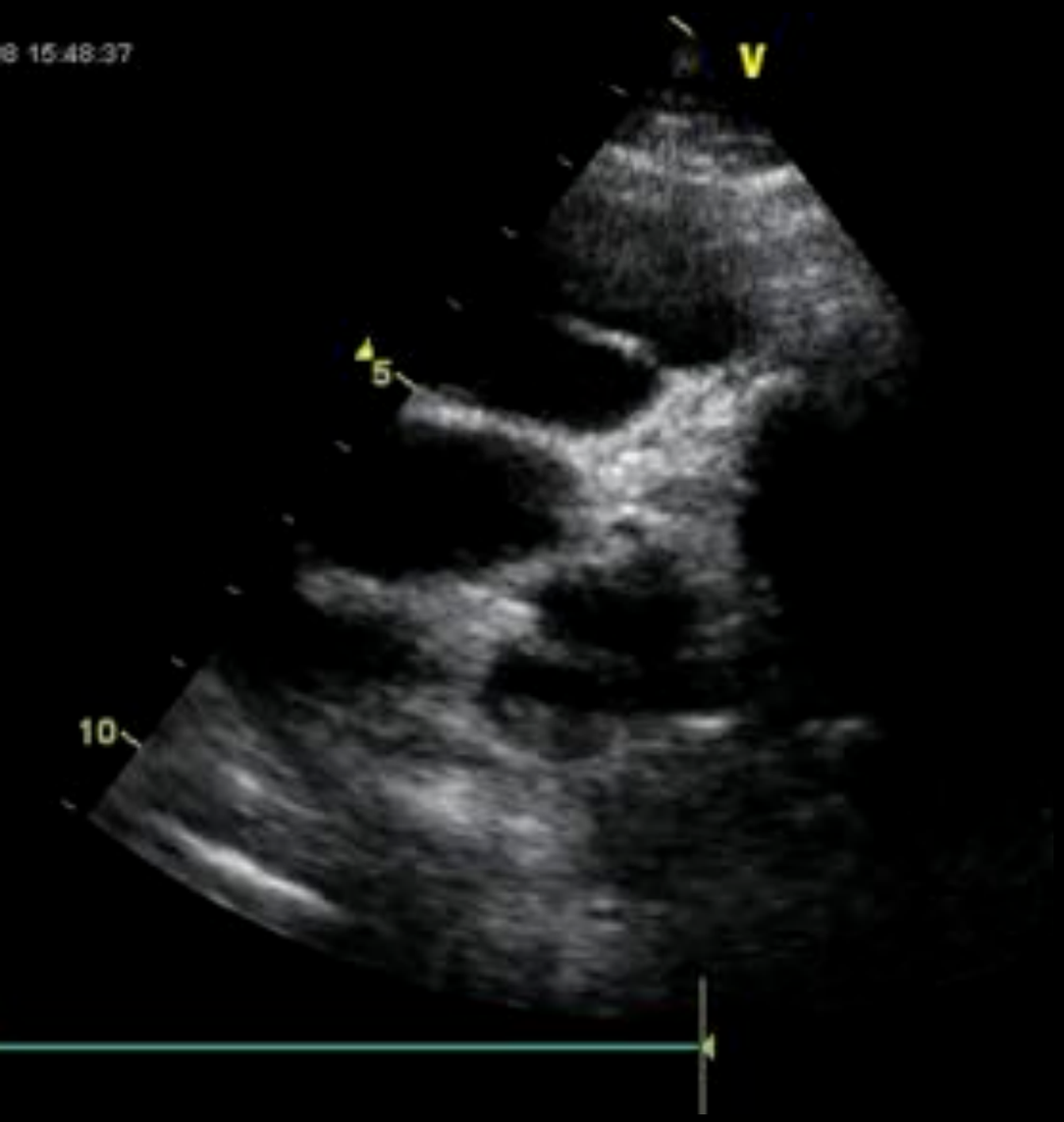
1. No involvement: Always <2

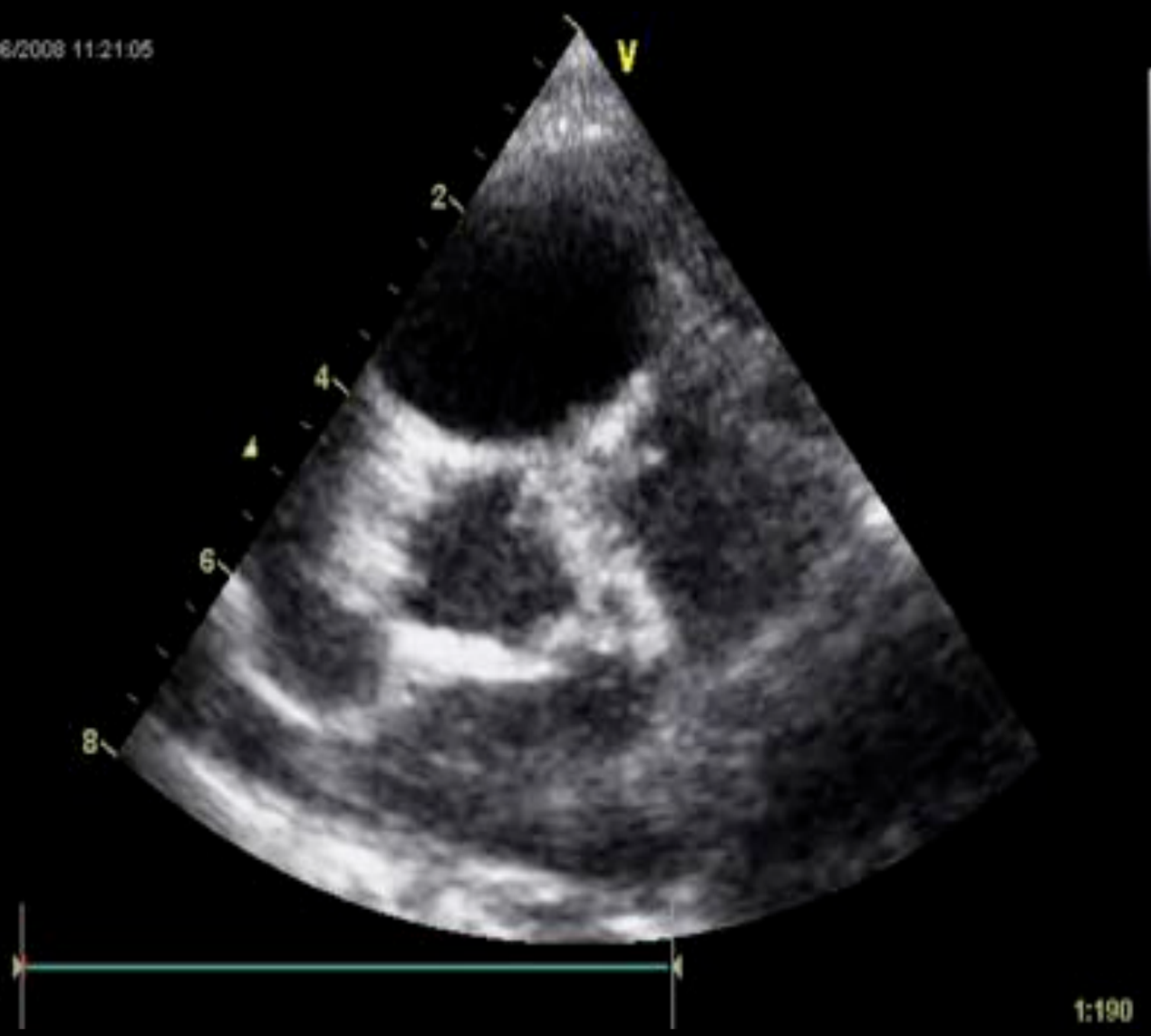
2. Dilation only: 2 to <2.5; or if initially <2, a decrease in Z score during follow-up ≥ 1

3. Small aneurysm: ≥ 2.5 to <5

4. Medium aneurysm: ≥ 5 to <10, and absolute dimension <8 mm

5. Large or giant aneurysm: ≥ 10, or absolute dimension ≥ 8 mm

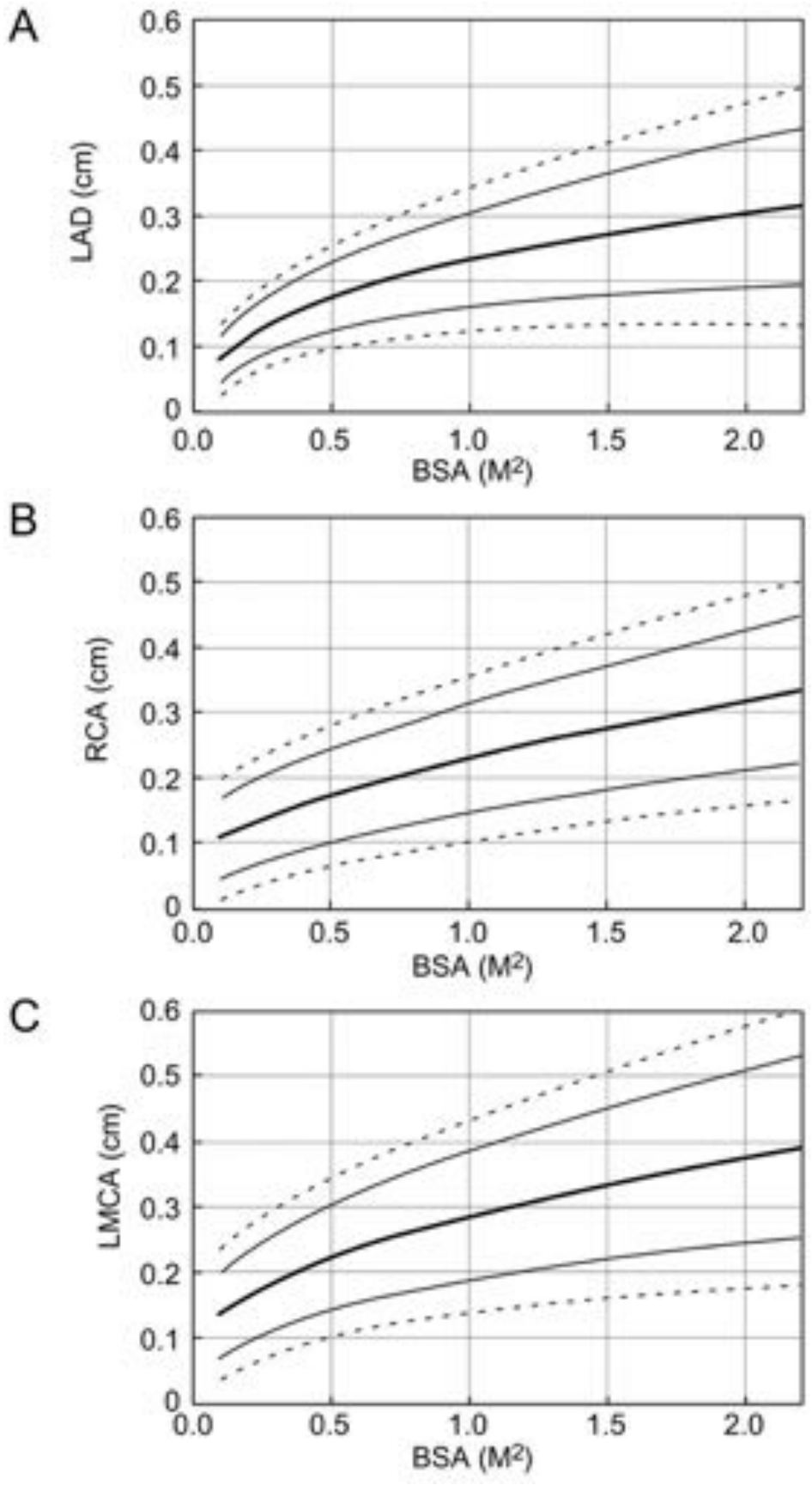

8 15:48:37
V
5
10


24/06/2008 11:21:05
V
2
4
6
8
1:190

Echo criteria for the diagnosis of Kawasaki disease

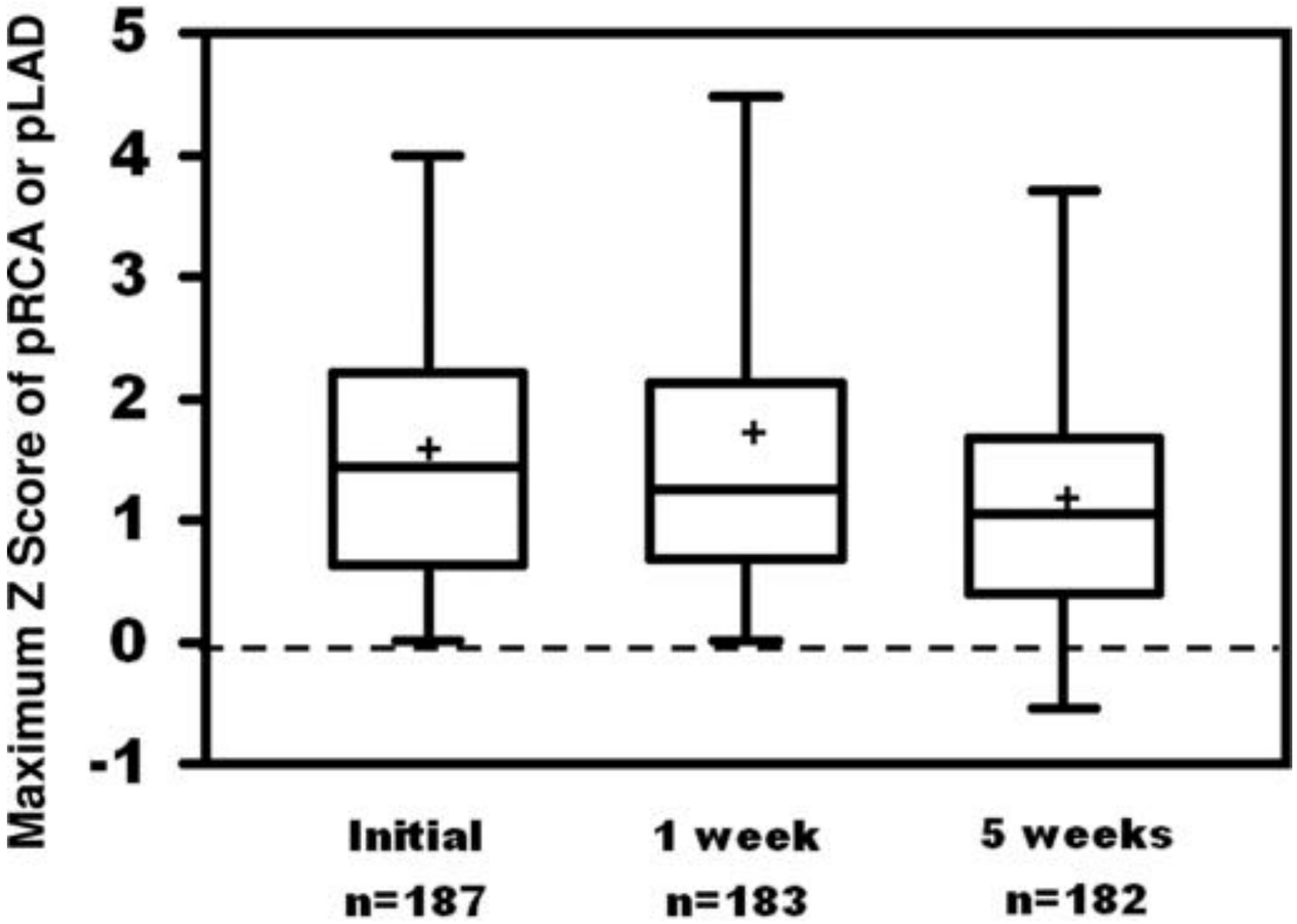
- The z score for the anterior interventricular or right coronary artery is >2.5,
- Coronary arteries meet Japanese Ministry of Health and Welfare criteria for aneurysms,
- or there are >3 other suggestive features, including
  - perivascular brightness,
  - lack of tapering,
  - decreased left ventricular function,
  - mitral regurgitation,
  - pericardial effusion,
  - or z scores for the anterior interventricular and right coronary arteries between 2 and 2.5.

Mean and prediction limits for 2 and 3 SDs for size of (A) LAD, (B) proximal RCA, and (C) LMCA according to body



Jane W. Newburger et al. Circulation. 2004;110:2747-2771

Maximum z score of either the pLAD or pRCA branch diameters according to time from randomization



A maximal z score > 2.5 at any time was noted in 26% of patients

74% of patients never had any coronary artery dilatation

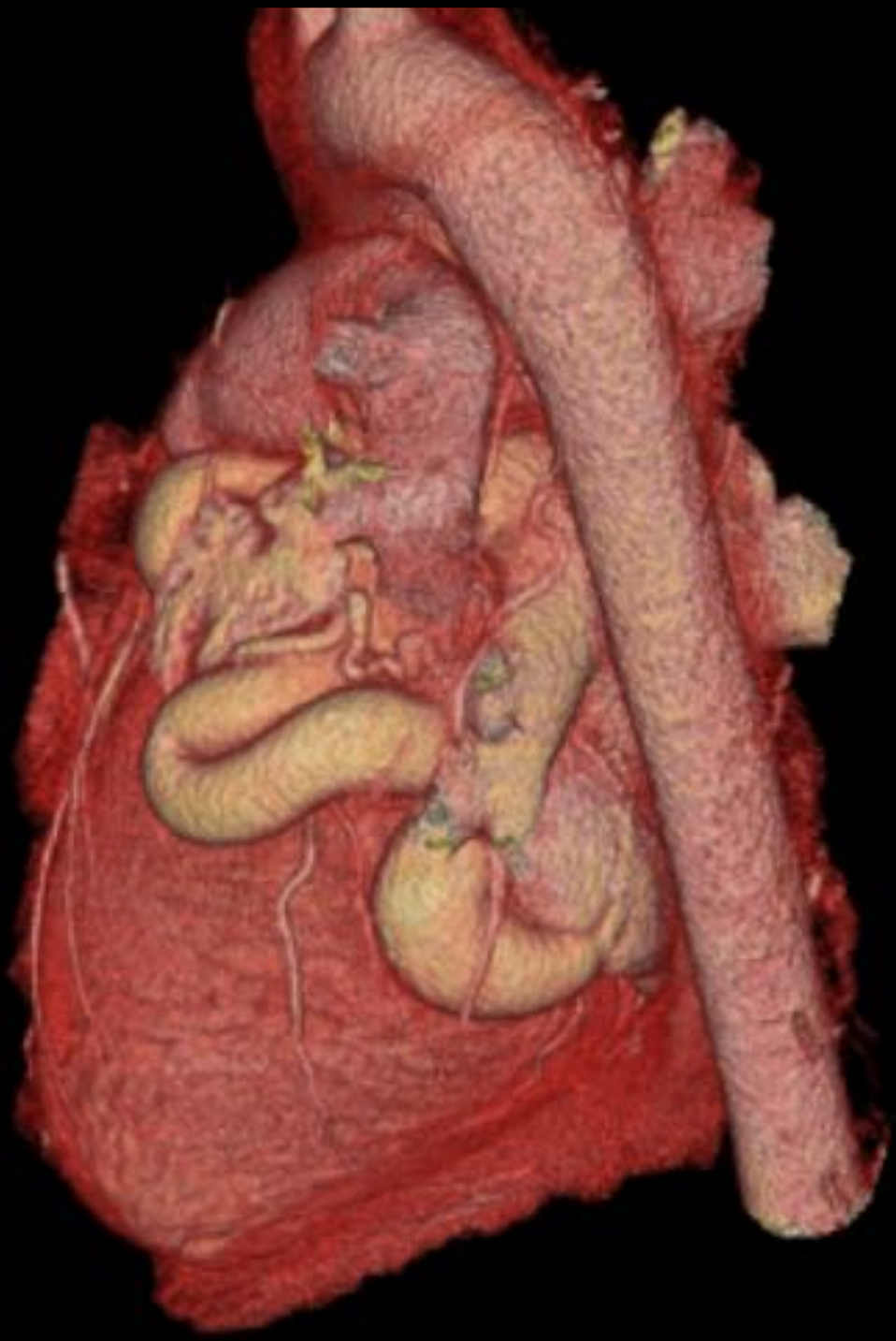
Brian W. McCrindle et al. Circulation. 2007;116:174-179

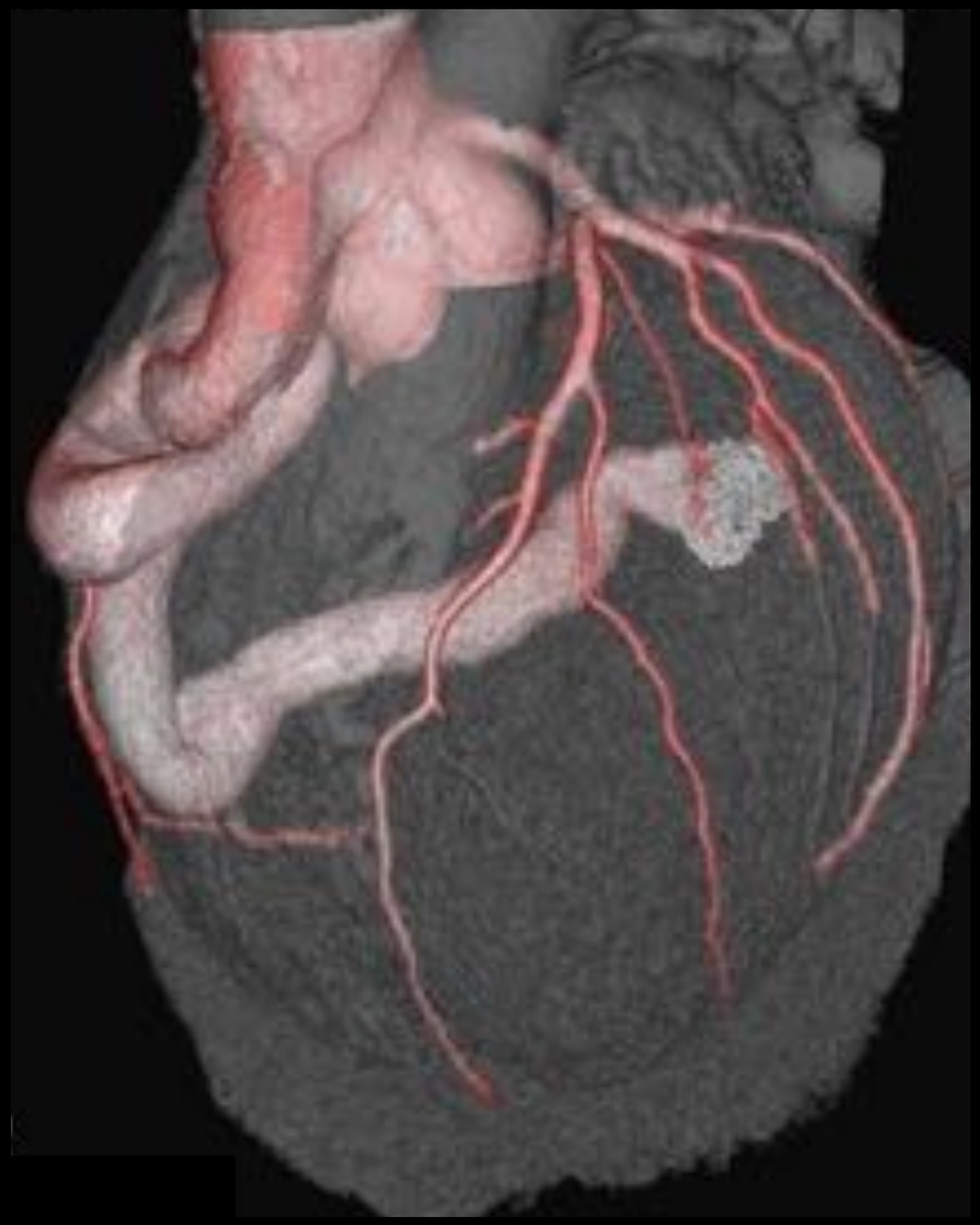
La dilatation coronaire est-elle pathognomonique ?

On dit d'un signe clinique ou d'un symptôme qu'il est **pathognomonique** lorsqu'il est **caractéristique d'une seule maladie donnée** et qu'il **permet d'en établir le diagnostic certain**.

Les dilatations coronaires malformatives

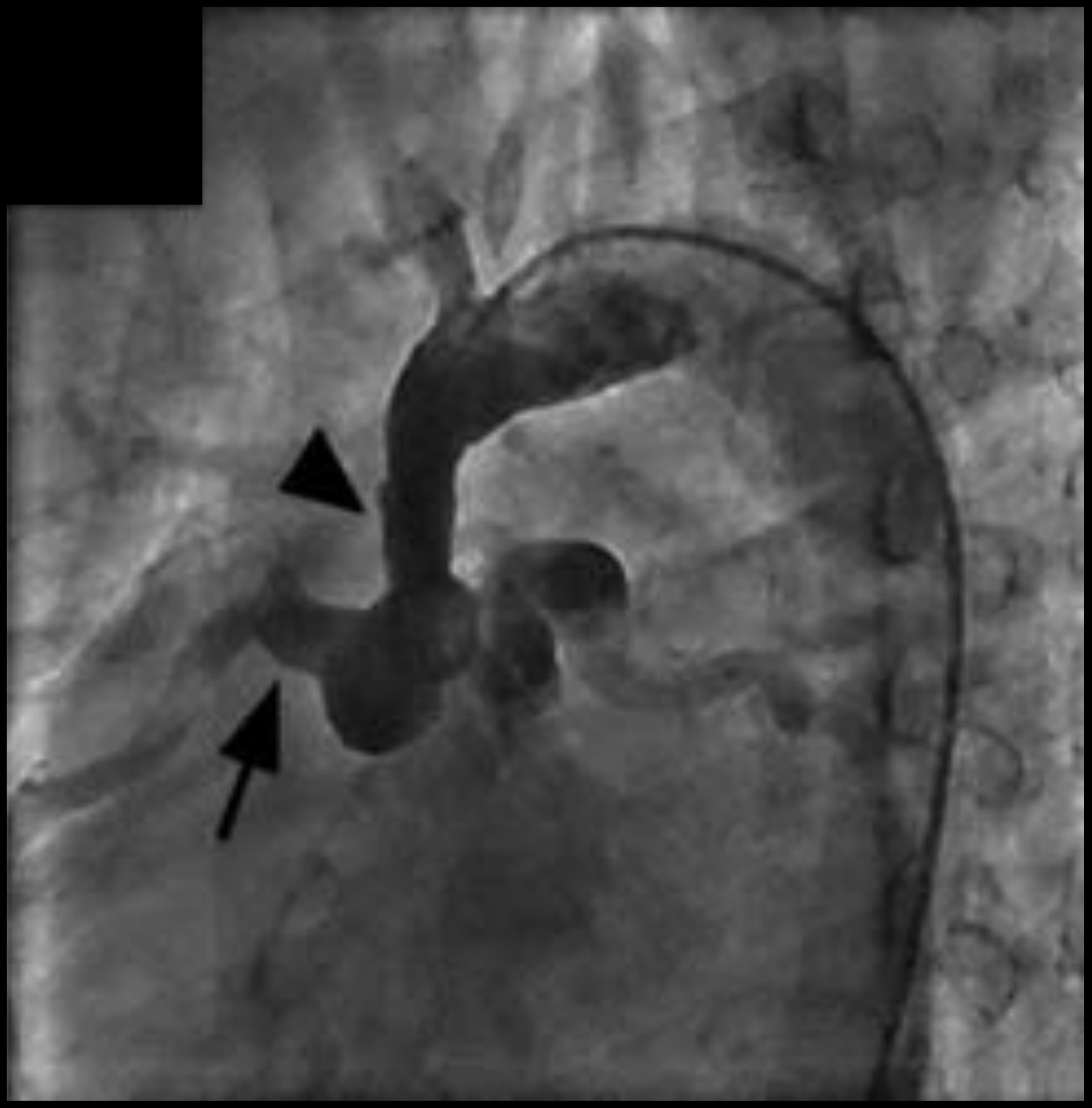
Fistules coronaro-camérales



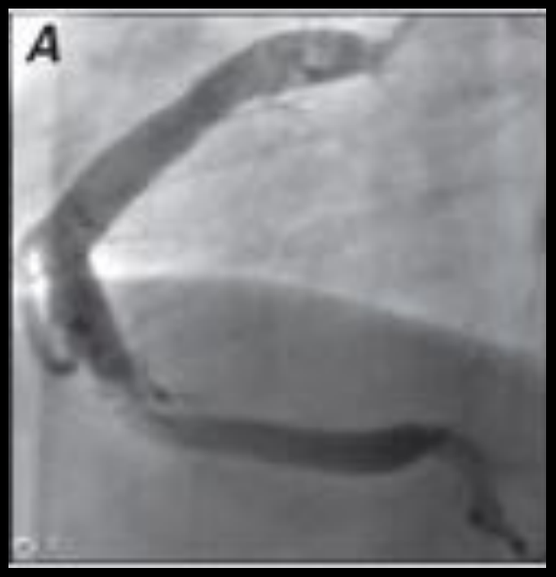


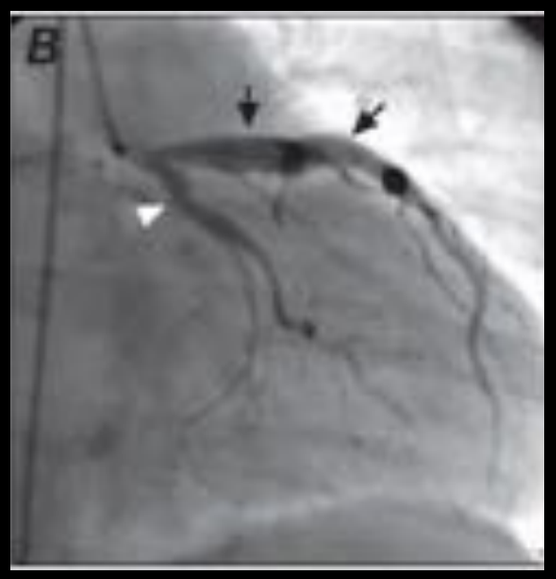
Les dilatations coronaires des syndromes

Sténose supra-valvulaire aortique



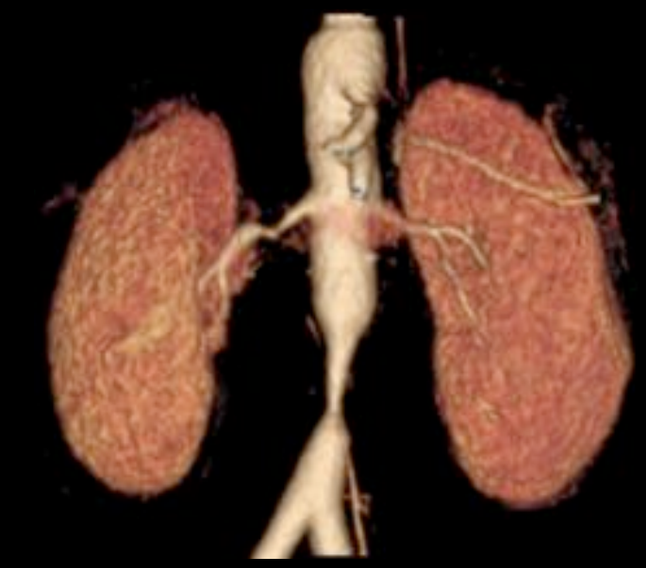
Syndrome de Noonan

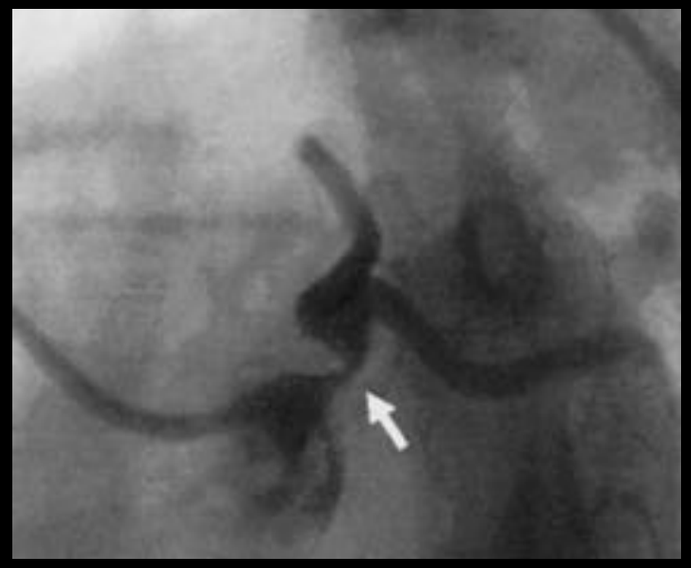


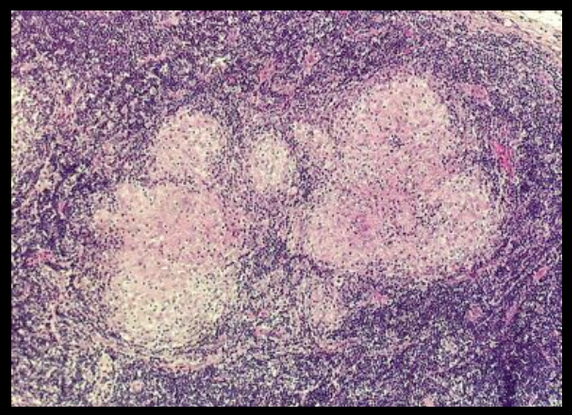


Les dilatations coronaires des vascularites inflammatoires de l'enfant

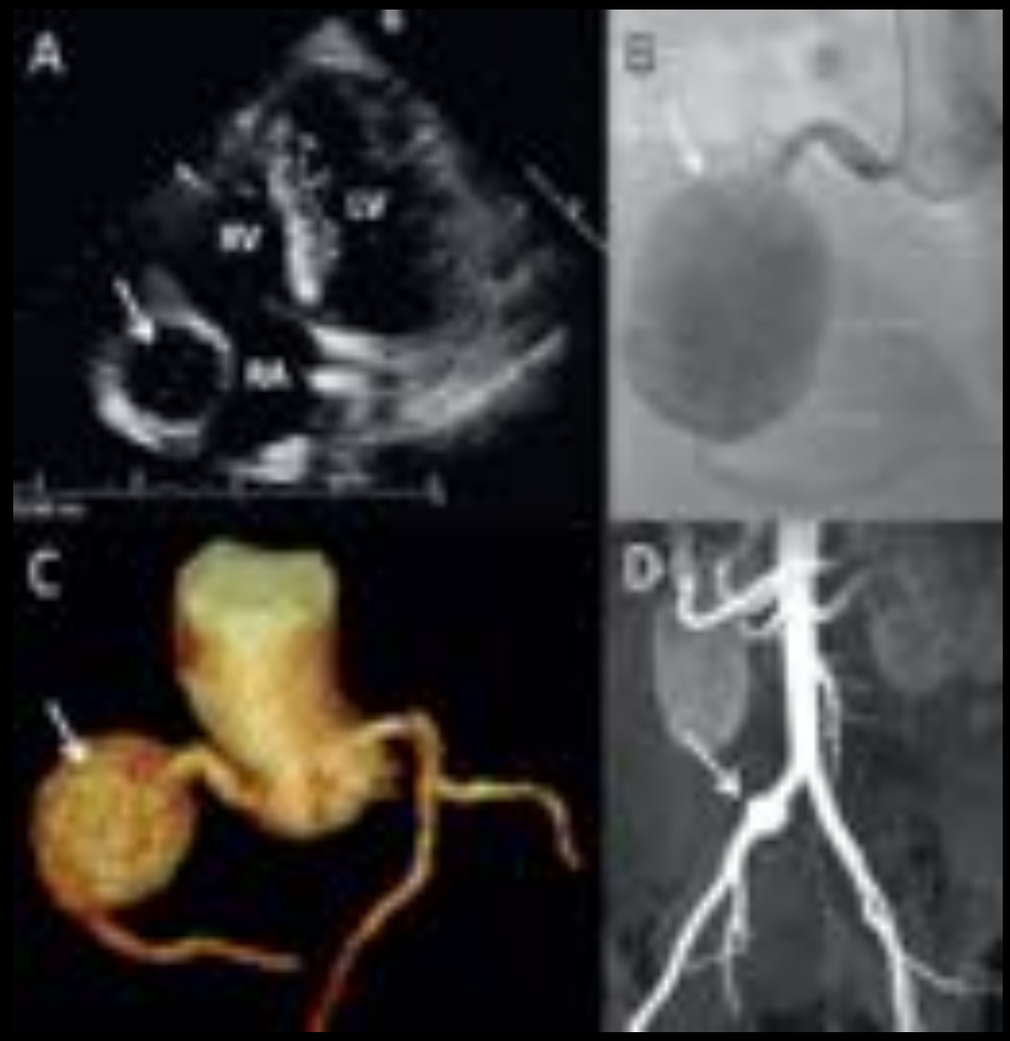
Takayasu

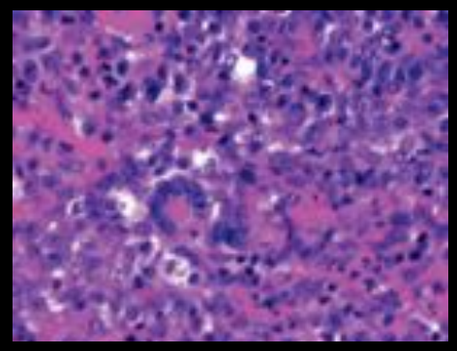






Périartérite Noueuse

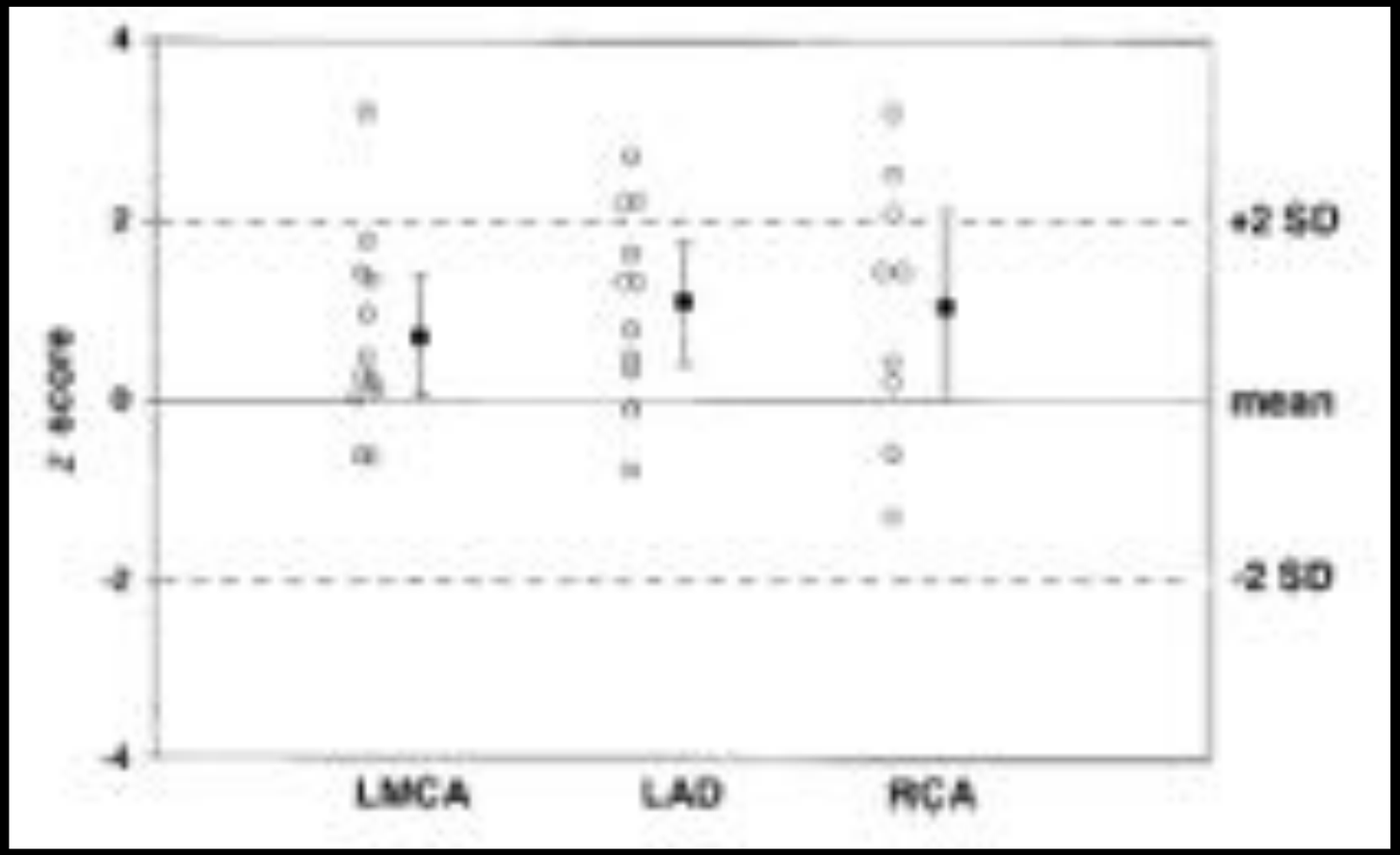


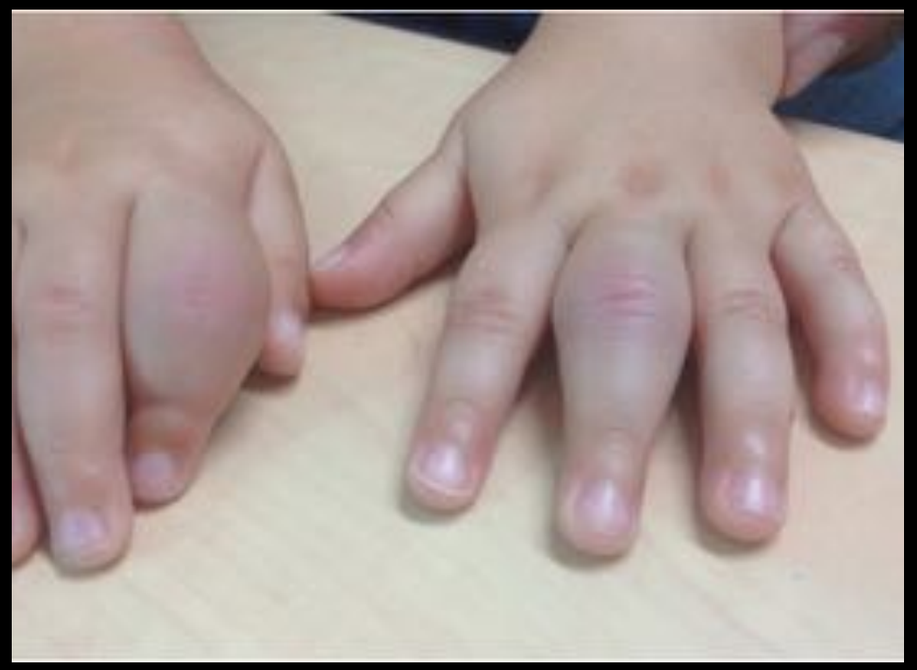


Ebesberger U et al. Images in Cardioloyg 2013

Les dilatations coronaires des vasculaires inflammatoires de l'enfant

Systemic onset Juvenile Idiopathic Arthritis
Maladie de Still





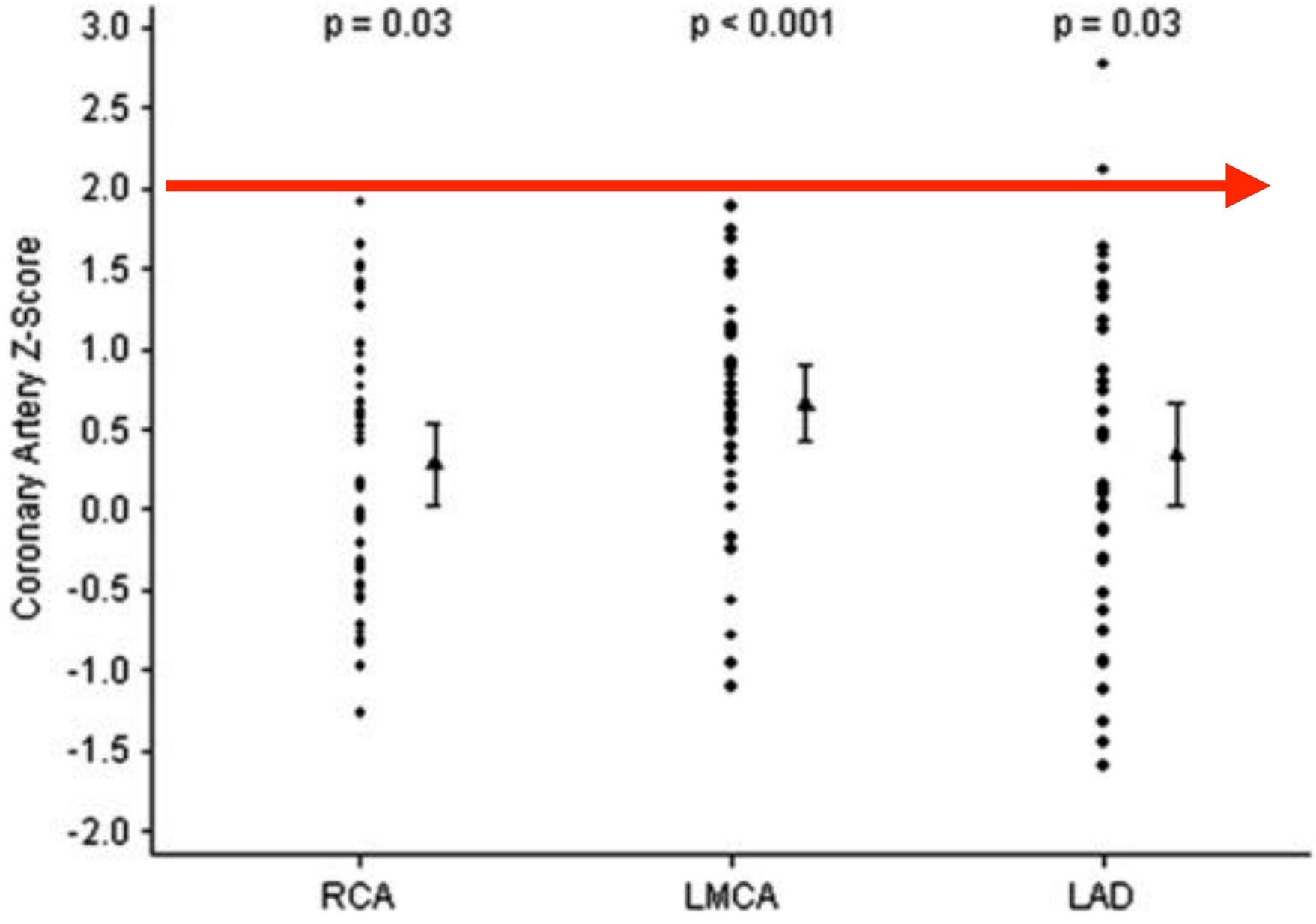
Bindstadt BA et al. Pediatrics 2005;116:e89-e93

Maladies infectieuses et dilatation coronaires
Kawasaki like ?

- Cytomégalovirus
- Herpes Virus
- Boccavirus
- Epstein-Barr virus
- Rickettsies

Dilatation coronaire chez l'enfant fébrile sans syndrome de Kawasaki

Coronary artery z scores for 43 patients with febrile illnesses other than Kawasaki disease



Juan-Carlos G. Muniz et al. Circ Cardiovasc Imaging. 2013;6:239-244

Recommendations for Cardiovascular Assessment for Diagnosis and Monitoring During the Acute Illness

1. **Echocardiography** should be performed when the diagnosis of KD is considered, but unavailability or technical limitations **should not delay treatment.**

2. Coronary arteries should be imaged, and **quantitative assessment of luminal dimensions**, normalized as Z scores adjusted for body surface, should be performed.

3. **For uncomplicated patients**, echocardiography should be repeated both within 1 to 2 weeks and 4 to 6 weeks after treatment.

4. **For patients with important and evolving coronary artery abnormalities** (Z score > 2.5) detected during the acute illness, more frequent echocardiography (**at least twice per week**) should be performed until luminal dimensions have stopped progressing to determine the risk for and presence of thrombosis.

5. To detect coronary artery thrombosis, it may be reasonable to perform echocardiography for **patients with expanding large or giant aneurysms twice per week while dimensions are expanding rapidly and at least once weekly in the first 45 days of illness, and then monthly until the third month after illness onset,** because the failure to escalate thromboprophylaxis in time with the rapid expansion of aneurysms is a primary cause of morbidity and mortality.

Recommendations for Initial Treatment With IVIG and ASA

1. Patients with 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 illness onset** but as soon as possible after diagnosis.

2. It is reasonable to administer IVIG to children presenting **after the 10th day** of illness (ie, in whom the diagnosis was missed earlier) if they have either **persistent fever** without other explanation **or coronary artery abnormalities together with ongoing systemic inflammation**, as manifested by elevation of ESR or CRP (CRP > 3.0 mg/dL).

3. **Administration** of moderate- (30–50 mg/kg/d) to high-dose (80–100 mg/kg/d) **ASA** is reasonable **until the patient is afebrile**, although there is no evidence that it reduces coronary artery aneurysms.

4. **IVIG** generally should **not** be administered to patients **beyond the tenth day of illness in the absence of fever, significant elevation of inflammatory markers, or coronary artery abnormalities**.

5. The **ESR** is accelerated by IVIG therapy and therefore **should not be used to assess response to IVIG therapy**. A persistently high ESR alone should not be interpreted as a sign of IVIG resistance.

Recommendations for Adjunctive Therapies for Primary Treatment

1. Single-dose pulse **methylprednisolone** should not be administered with IVIG as routine primary therapy for patients with KD.

2. Administration of a longer course of corticosteroids (eg, tapering over 2–3 weeks), together with IVIG 2 g/kg and ASA, may be considered for treatment of high-risk patients with acute KD, when such high risk can be identified in patients before initiation of treatment

Recommendations for Adjunctive Therapies for Primary Treatment

Approximately 10% to 20% of patients with KD have persistent or recurrent fever after primary therapy with IVIG plus ASA.

Many studies have shown that patients who are resistant to initial IVIG are at increased risk of developing coronary artery abnormalities.

Thus, scoring systems have been constructed to identify patients likely to be resistant to IVIG and who may benefit from more aggressive initial therapy.

Recommendations for Adjunctive Therapies for Primary Treatment

1. It is reasonable to administer **a second dose of IVIG (2 g/kg) to patients with persistent or recrudescent fever at least 36 hours after the end of the first IVIG infusion** .

2. Administration of **high-dose pulse steroids usually methylprednisolone** 20–30 mg/kg intravenously for 3 days, with or without a subsequent course and taper of oral prednisone) **may be considered as an alternative to a second infusion of IVIG** or for retreatment of patients with KD who have had recurrent or recrudescent fever after additional IVIG .

3. Administration of a longer (eg, 2–3 weeks) tapering course of prednisolone or prednisone, together with IVIG 2 g/kg and ASA, may be considered in the retreatment of patients with KD who have had recurrent or recrudescent fever after initial IVIG treatment.

4. Administration of **infliximab** (5 mg/kg) **may be considered as an alternative to a second infusion of IVIG or corticosteroids for IVIG-resistant patients**.

5. Administration of **cyclosporine** may be considered **in patients with refractory KD** in whom a second IVIG infusion, infliximab, or a course of steroids has failed.

6. Administration of **immunomodulatory monoclonal antibody therapy** (except TNF-α blockers), cytotoxic agents, or (rarely) plasma exchange may be considered **in highly refractory patients** who have failed to respond to a second infusion of IVIG, an extended course of steroids, or infliximab.

Recommendations for Prevention of Thrombosis
During the Acute Illness

1. **Low-dose ASA** (3–5 mg/kg/d) should be administered to patients without evidence of coronary artery changes **until 4 to 6 weeks after onset of illness**.

2. For patients with **rapidly expanding coronary artery aneurysms or a maximum Z score of ≥ 10**, **systemic anticoagulation** with LMWH or warfarin (international normalized ratio target 2.0–3.0) in addition to low-dose ASA is reasonable.

3. For patients at increased risk of thrombosis, for example, with large or giant aneurysms (≥ 8 mm or Z score ≥ 10) and a recent history of coronary artery thrombosis, “triple therapy” with ASA, a second antiplatelet agent, and anticoagulation with warfarin or LMWH may be considered.

4. Ibuprofen and other nonsteroidal antiinflammatory drugs with known or potential involvement of cyclooxygenase pathway may be harmful in patients taking ASA for its antiplatelet effects.

Long term assessment and counseling algorithm

Risk Level	Frequency of Cardiology Assessment*	Assessment for Inducible Myocardial Ischemia†	Type and Frequency of Additional Cardiology Assessment	Cardiovascular Risk Factor Assessment and Management‡	Physical Activity Counseling§	Reproductive Counseling
1: No involvement	May discharge between 4 wk and 12 mo	None	None	Assess at 1 y	Promotion counseling at every visit	Age-appropriate counseling without modification
2: Dilation only	May discharge after 1 y if normal; assess every 2–5 y if persists	None	None	Assess at 1 y	Promotion counseling at every visit	Age-appropriate counseling without modification
3.1: Small aneurysm, current or persistent	Assess at 6 mo, then yearly	Assess every 2–3 y	May consider every 3–5 y	Assess at 1 y	Promotion counseling at every visit; restrict contact	Precautions for contraception and pregnancy
3.2: Small aneurysm, regressed to normal or dilation only	Assess every 1–3 y (may omit echocardiography)	Assess every 3–5 y	May consider if there is inducible ischemia	Assess at 1 y, then every 2 y	Promotion counseling at every visit	Age-appropriate counseling without modification

Long term assessment and counseling algorithm

Risk Level	Frequency of Cardiology Assessment*	Assessment for Inducible Myocardial Ischemia†	Type and Frequency of Additional Cardiology Assessment	Cardiovascular Risk Factor Assessment and Management‡	Physical Activity Counseling§	Reproductive Counseling
5.1: Large or giant aneurysm, current or persistent	Assess at 3, 6, 9, and 12 mo, then every 3–6 mo	Assess every 6–12 mo	Baseline within 2–6 mo; may consider every 1–5 y	Assess every 6–12 mo	Promotion counseling at every visit; restrict contact; self-limit	Precautions for contraception and pregnancy
5.2: Large or giant aneurysms, regressed to medium aneurysm	Assess every 6–12 mo	Assess yearly	May consider every 2–5 y	Assess yearly	Promotion counseling at every visit; restrict contact; self-limit	Precautions for contraception and pregnancy
5.3: Large or giant aneurysm, regressed to small aneurysm	Assess every 6–12 mo	Assess every 1–2 y	May consider every 2–5 y	Assess yearly	Promotion counseling at every visit; restrict contact; self-limit	Precautions for contraception and pregnancy
5.4: Large or giant aneurysm, regressed to normal or dilation only	Assess every 1–2 y (may omit echocardiography)	Assess every 2–3 y	May consider every 2–5 y	Assess every 2 y	Promotion counseling at every visit; restrict contact; self-limit	Precautions for contraception and pregnancy

Long term thromboprophylaxy

Risk Level	Low-Dose ASA	Anticoagulation (Warfarin or LMWH)	Dual Antiplatelet Therapy (ASA+Clopidogrel)	β-Blocker	Statin
1: No involvement	6–8 wk then discontinue	Not indicated	Not indicated	Not indicated	Not indicated
2: Dilation only	Continuation after 6–8 wk is reasonable	Not indicated	Not indicated	Not indicated	Not indicated
3.1: Small aneurysm, current or persistent	Continue	May be considered	May be considered as an alternative to anticoagulation	Not indicated	Empirical therapy may be considered
3.2: Small aneurysm, regressed to normal or dilation only	Continue, but discontinuation may also be considered	Not indicated	Not indicated	Not indicated	Empirical therapy may be considered
4.1: Medium aneurysm, current or persistent	Continue	May be considered	May be considered as an alternative to anticoagulation	Not indicated	Empirical therapy may be considered
4.2: Medium aneurysm, regressed to small aneurysm	Continue	Not indicated	May be considered	Not indicated	Empirical therapy may be considered
4.3: Medium aneurysm, regressed to normal or dilation only	Continue	Not indicated	May be considered	Not indicated	Empirical therapy may be considered

Long term thromboprophylaxy

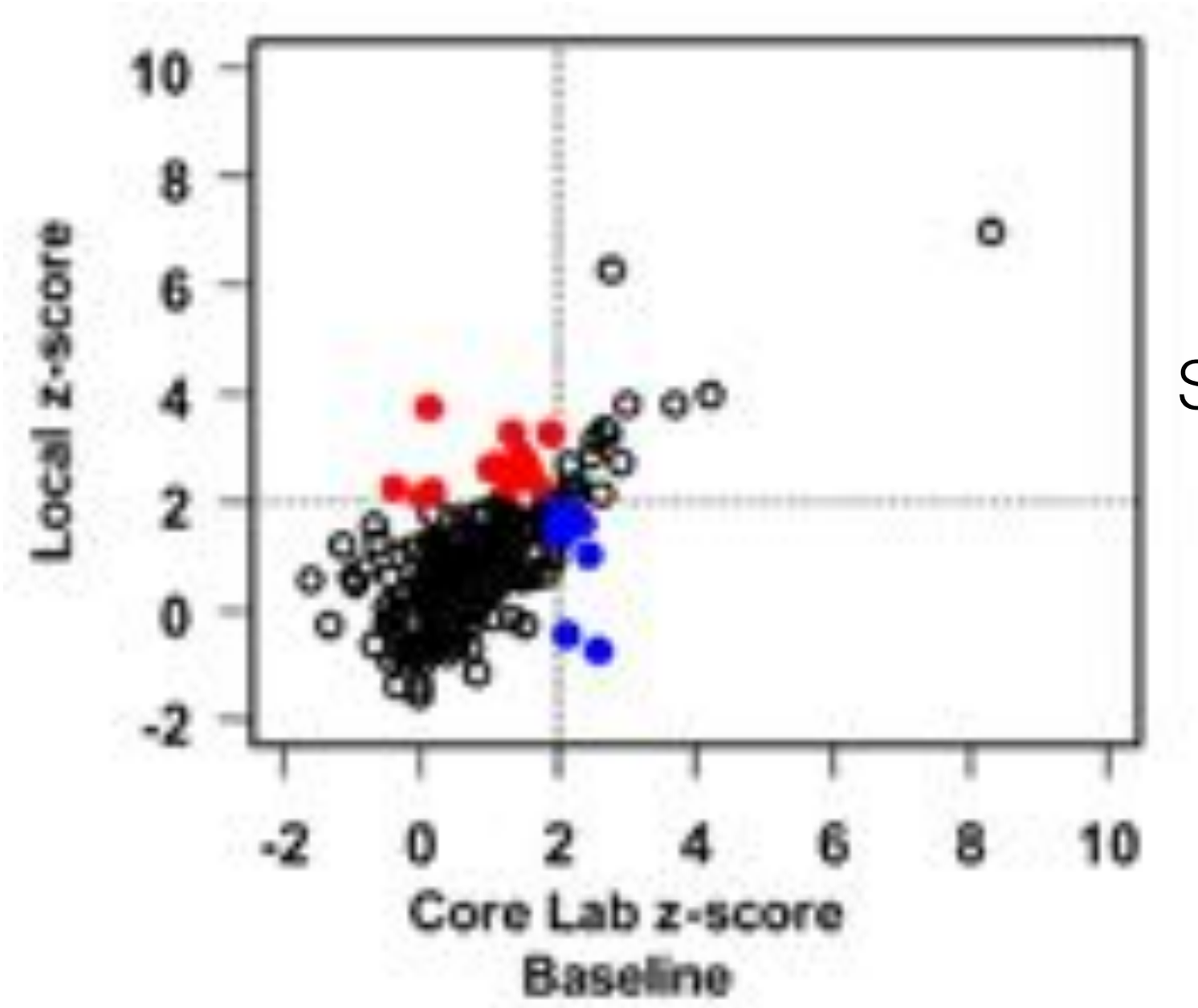
Risk Level	Low-Dose ASA	Anticoagulation (Warfarin or LMWH)	Dual Antiplatelet Therapy (ASA+Clopidogrel)	β-Blocker	Statin
5.1: Large and giant aneurysm, current or persistent	Continue	Reasonably indicated	May be considered in addition to anticoagulation	May be considered	Empirical therapy may be considered
5.2: Large or giant aneurysm, regressed to medium aneurysm	Continue	Reasonably indicated	May be considered as an alternative to anticoagulation	May be considered	Empirical therapy may be considered
5.3: Large or giant aneurysm, regressed to small aneurysm	Continue	May be considered	May be considered as an alternative to anticoagulation	May be considered	Empirical therapy may be considered
5.4: Large or giant aneurysm, regressed to normal or dilation only	Continue	Not indicated	May be considered as an alternative to anticoagulation	Not indicated	Empirical therapy may be considered

M3C

Merci

La sensibilité est l'estimation de la probabilité d'avoir un signe positif quand on est malade
Sensibilité = 1 = Aucun faux négatif
ou
L'atteinte coronaire est constante dans la maladie de Kawasaki.

Discordant evaluations between local lab and core-lab



Sensitivity (63%) was lower than specificity (90%)

Margossian R et al. J Am Soc Echocardiogr 2011;24:53-9

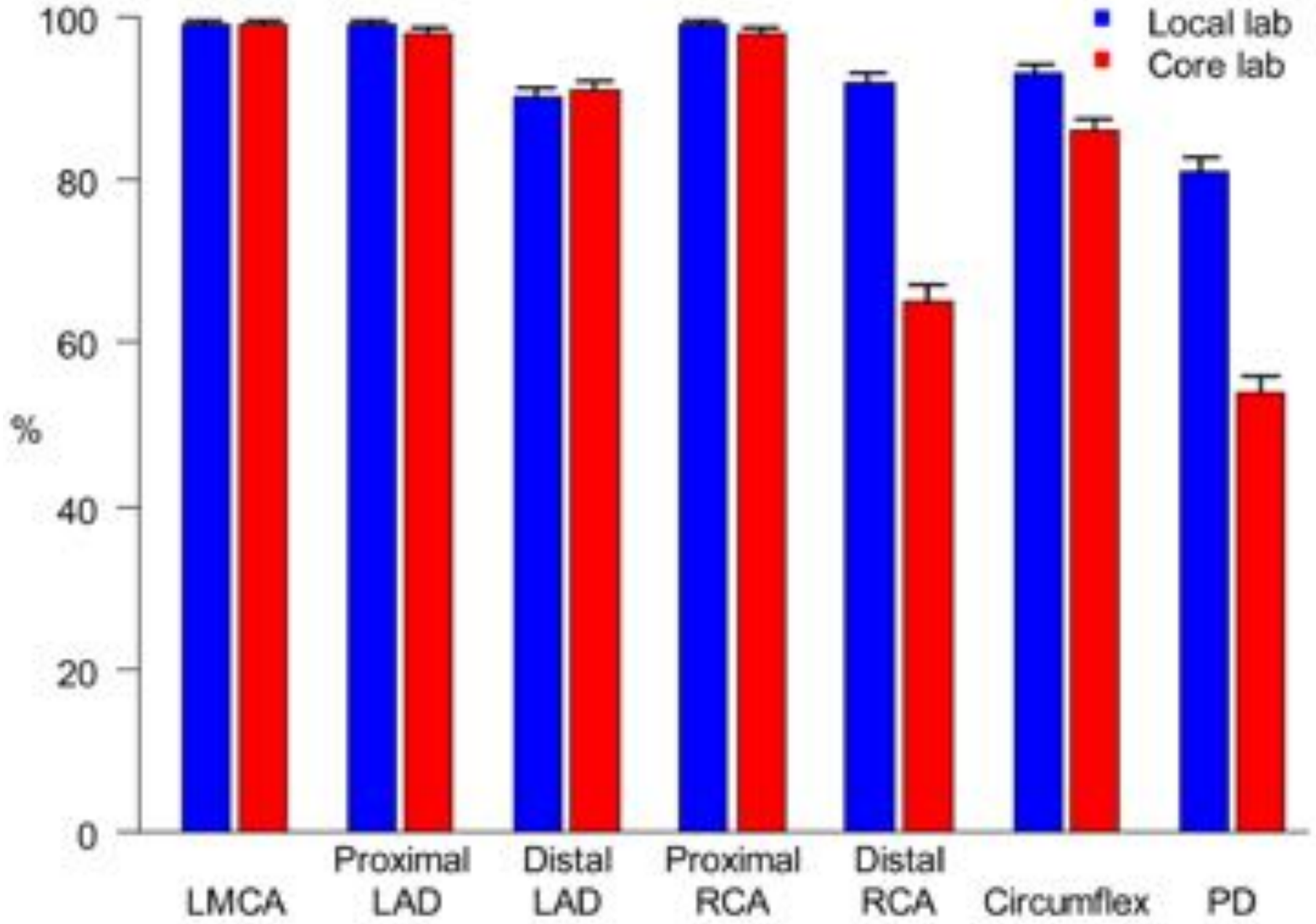


Figure 2.
Bar graph of visualization rates ± one standard error of coronary artery segment by the core laboratory and by local center assessment. LAD: left anterior descending; LMCA: left main coronary artery; PD: posterior descending; RCA: right coronary artery.

Risk factors for coronary artery involvement

Study	n	CAI%	↓Age	Fever	iKD	rKD	Male	↑ESR	↑WBC	↑N	Plt	↑CRP	↑ALT	↓Het	↓Albumin
Asai *et al.* [6]	102	14.7	Yes	Yes				Yes	Yes			No		No	
Ishihara *et al.* [20]	130	23.8	Yes	Yes			No	No	Yes		No			Yes	Yes
Koren *et al.* [21]	163	15.0	No	Yes			No	No	No		No			No	
Nakano *et al.* [22]	78	20.5	No				No		No		No	Yes		No	No
Nakano *et al.* [23]	22	36.4								Yes					Yes
Ichida *et al.* [25]	110	22.7	Yes	Yes			No	Yes	No		High			No	
Daniels *et al.* [26]	77	12	No	Yes			No	No	No		No			Yes	
Harada *et al.* [4]	258	13.2	Yes				Yes		Yes		Low	Yes		Yes	Yes
Lu *et al.* [27]	70	21							Yes			Yes			
Beiser *et al.* [5]	760	4.3								Yes	Low				
Mori *et al.* [28] * &	193	12.2	No	No			No		No	No	No	Yes			No
Morikawa *et al.* [29] #	451	6.9		Yes					Yes	Yes		Yes		Yes	Yes
Nomura *et al.* [30]	125	15.2							No			No	Yes		
Honkanen *et al.* [32]	344	28.5	Yes	Yes			Yes	No	No		No			Yes	Yes
Belay *et al.* [13]	2,798	12.9	Yes				Yes								
Durongpisitkul *et al.* [34]	432	14.5		Yes		Yes	Yes			Yes					
Kim *et al.* [35]	285	6.7	No	Yes	Yes	Yes	No		No	Yes	No	Yes		No	No
McCrindle *et al.* [2]	190	26	Yes	Yes											Yes
Chaiyarak *et al.* [33]	96	28.9						No							
Kim *et al.* [36]	475	33.5	No	Yes	Yes	Yes		No	No	No	No	No		No	Yes
Kaneko *et al* [37] &	43	14.0	No	No		No	No		No			No			No
Chen *et al.* [38] @	8,330							Yes	No	Yes	High			No	Yes
Tremoulet *et al.* [39]	380	31.6						Yes	Yes						
Caballero-Mora [40]	76	15.7						No	No		No	Yes	No	No	No
Weng *et al.* [41]	216	37.5	No			Yes	No		No	Yes	Low	No	No	No	
Zhang *et al.* [8]	553	63.3	Yes	No	Yes		No	No	No		No	No	No	No	Yes

Ghelani SJ et al. Diagnostics 2013;3:232-43

La spécificité est l’estimation de la probabilité d’avoir un signe négatif (S-) quand on est non malade (M-)
Spécificité = 1 = Aucun faux positif
ou
La dilatation coronaire ne s’observe que dans la maladie de Kawasaki.

Conclusions

- La dilatation coronaire n’est pas pathognomonique de la maladie de Kawasaki

- Son absence n’exclut pas le diagnostic

- Elle peut être observée dans une grande variété de pathologies malformatives, inflammatoires ou infectieuses bien plus rarement que dans la maladie de Kawasaki

- Les seuils diagnostiques (z-score > 2.0) doivent être utilisés car leur sensibilité chez un enfant fébrile reste correcte

- Le suivi coronaire est un élément indispensable en cas de maladie de Kawasaki confirmée