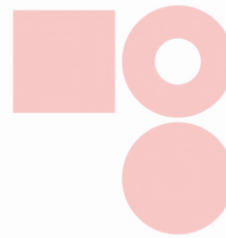


Obrigada por ver esta apresentação

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18º CONGRESSO
NACIONAL
DE PEDIATRIA

25 — 27 out 2017
Centro de Congressos
Alfândega do Porto

DOENÇA DE KAWASAKI: O QUE HÁ DE NOVO?



Mariana Rodrigues

A. H. Pediatria

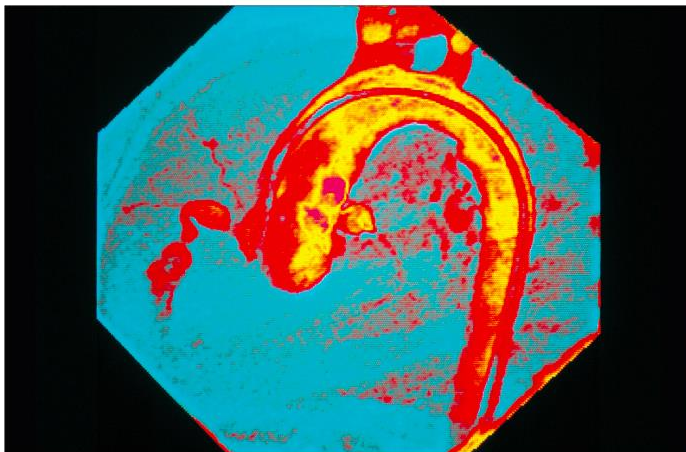
Unidade de Reumatologia Pediátrica

Centro Hospitalar São João

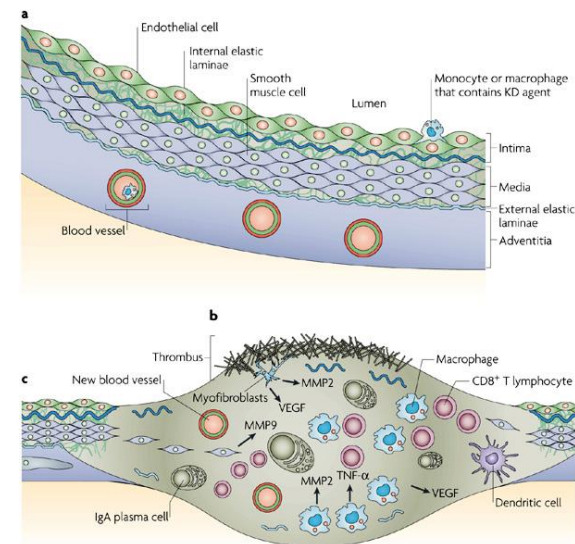
Faculdade de Medicina da Universidade do Porto

INTRODUÇÃO

- A D. Kawasaki afeta 5-10/100000 crianças < 5 anos (Europa)
 - Os **aneurismas das artérias coronárias** (AAC) ocorrem em 15–25% dos pacientes não tratados
 - Causa mais comum de doença cardíaca adquirida em idade pediátrica em países desenvolvidos
 - Importante causa potencial de doença cardiovascular a longo prazo na vida adulta



Abnormal coronary arteries in Kawasaki disease



EPIDEMIOLOGIA

- É a segunda vasculite mais frequente da infância, afetando artérias de médio e pequeno calibre
- 85% das crianças têm < 5 anos, pico incidência 18–24 meses
 - Extremos etários → maior risco de formação de AAC
- Predomínio sexo masculino ($\approx 1.5:1$), ↑risco em crianças asiáticas, sazonalidade, epidemias ocasionais
- Incidência no Japão: 138/100000 crianças <5 anos, EUA 17.1/100000, UK 8.1/100000, Portugal 6.48/100000
- Os dados epidemiológicos sugerem um *trigger* ambiental / infeccioso comum, assim como uma base genética de susceptibilidade

ESTUDOS GENÉTICOS

- ↑risco em crianças asiáticas → persiste quando migram
- ↑ risco relativo em irmãos de crianças afetadas

McCordle et al. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease - AHA Guidelines. Circulation, 2017

Table 2. Genes Implicated in Susceptibility to KD With Replication in Independent Cohorts

Gene	Chromosome Location	Genetic Methods	Validation Populations	Potential Significance	Reference and Year
<i>FCGR2A</i>	1q23	GWAS	European descent, Taiwanese, Koreans, Han Chinese	Low-affinity receptor for Fc fragment of IgG; risk allele has lower binding affinity	Khor et al ⁶¹ 2011
<i>CASP3</i>	4q34-35	Linkage analysis Candidate gene study	Japanese, Taiwanese, Koreans, Chinese, Euro-Americans	Mediates apoptosis in immune cells and cardiomyocytes Risk allele decreases gene transcription	Onouchi et al ⁶² 2010
<i>HLA class II</i>	6p21.3	GWAS	Japanese, Taiwanese, Koreans	Activation marker for immune cells; antigen presentation	Onouchi et al ⁶³ 2012
<i>BLK</i>	8p23-22	GWAS	Japanese, Taiwanese, Koreans	B-cell receptor signal transduction	Onouchi et al ⁶³ 2012
<i>IPTKC</i>	19q13.2	Linkage analysis TDT	Japanese, Taiwanese, Koreans, Chinese, Euro-Americans	Negative regulator of calcineurin-NFAT signaling pathway; risk allele increases signaling	Onouchi et al ⁶⁴ 2008
<i>CD40</i>	20q12-13.2	GWAS	Japanese, Taiwanese, Koreans	Risk alleles associated with increased translation	Onouchi et al ⁶³ 2012

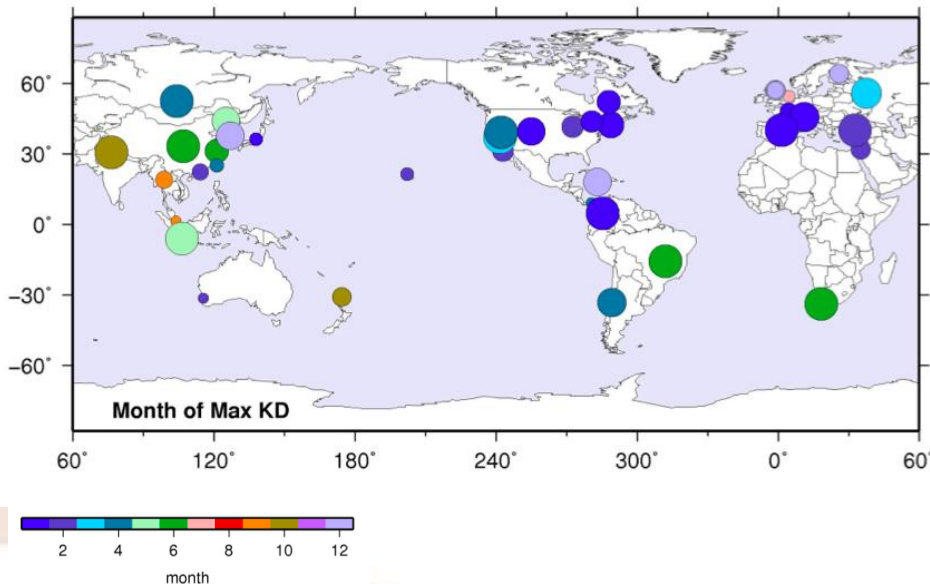
BLK indicates B-cell lymphoid kinase; CASP3, caspase 3; FCGR, Fcγ receptor; GWAS, genome-wide association study; HLA, human leukocyte antigen; IgG, immunoglobulin G; IPTKC, inositol 1,4,5-trisphosphate kinase-C; KD, Kawasaki disease; NFAT, nuclear factor of activated T cells; and TDT, transmission disequilibrium test.

CAUSAS AMBIENTAIS / INFECIOSAS

- Sazonalidade e picos epidêmicos
- Frequentemente precedida por sintomas respiratórios ou GIs
- ~50% dos casos em irmãos geralmente ocorrem com ~10 dias de diferença
- Mas nunca foi identificado consistentemente um agente...

KD Seasonality

Strength indicated by circle size and month of max/min indicated by color



Adenovirus

Herpes virus

Mycoplasma

Streptococcus

Staphylococcus

Propionobacterium acnes

Ehrlichia

Rickettsia

EBV

Retrovirus

Coronavirus

V sarampo

Chlamydia pneumoniae

Bartonella

Coxiella

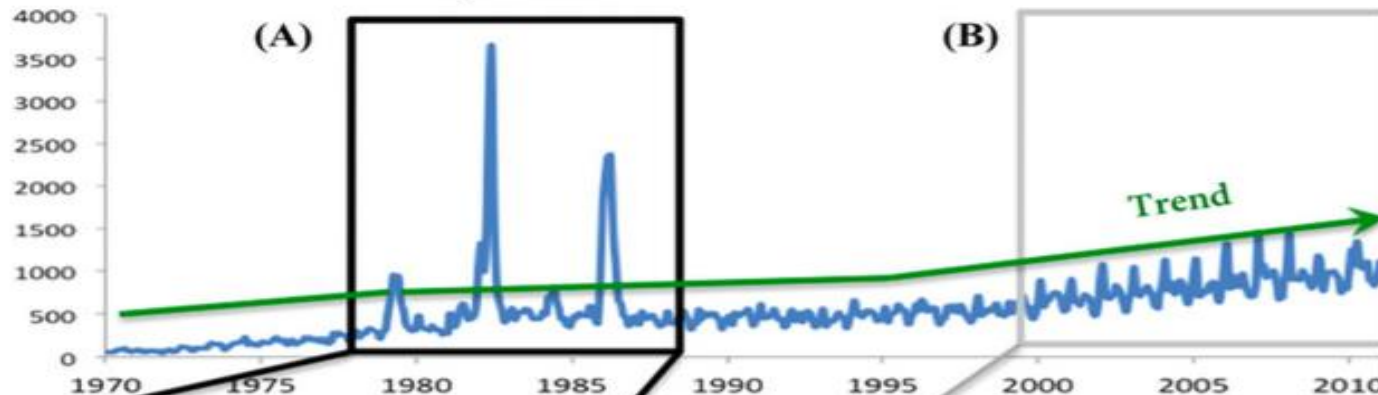
Mercúrio

Ácaros pó doméstico

Champô de carpetes

PONTO COMUM?

Epidemics

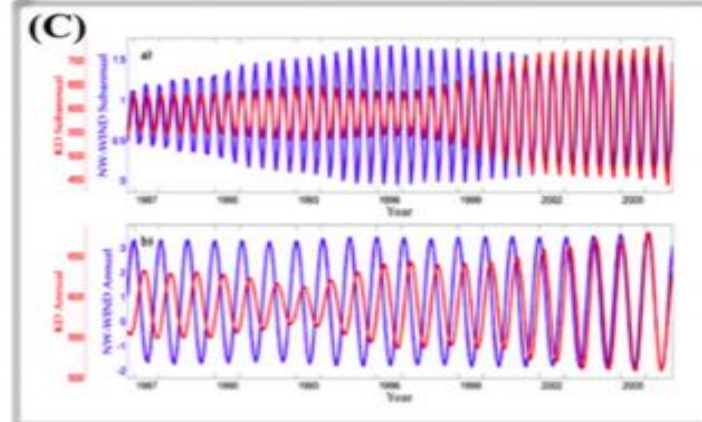


**DANGER
SIGNALS**

Agentes de
poluição?

Microorganismos?

Seasonality



Rodó *et al*; Environment
and climate in Kawasaki
disease; Ann. N.Y.
Acad. Sci. (2016)

Figure 1. Monthly evolution of the composite series of Kawasaki disease clinical cases for all of Japan between 1970 and 2011. Note three interesting features of this time series, namely (A) the three large epidemics, (B) the decadal changes in trends in the 1980s and mainly after the year 2000, and (C) the amplification of seasonal fluctuations toward the present. (A) Time-averaged sea-level pressure (hPa) and surface winds (m/s) before and after March/May 1979 (a–c), May 1982 (d–f), and March 1986 (g–i) epidemics, respectively. Monthly atmospheric variables were averaged for the subsequent summer (June–July–August– (JJA) 1979 in a, JJA 1982 in d, and JJA 1986 in g), when winds from the south typically blow across Japan, and for the rising phase of the epidemics, from September to the last month before the peak (September 1978–March 1979 in Aa, September 1981–April 1982 in Ad, and September 1985–February 1986 in Ag), when winds blew from the northwest. Red/blue colored areas depict increases/decreases in KD incidence (per million inhabitants) by prefecture between the preceding September and the KD peak (April 1979 minus September 1978 in a, May 1982 minus September 1981 in d, and March 1986 minus September 1985 in g). (C) Coherence in subseasonal winds developing over Japan and the variability in KD incidence at the same timescale (a) and for the annual components (b). Wind intensity (blue) and KD (red) are composited for all prefectures in Japan. Partly adapted from Ref. 38.

FISIOPATOLOGIA | INFLAMOSSOMA

Alphonse MP et al. J Immunol. 2016

- ITPKC *Inositol-Triphosphate 3-Kinase C*
 - Regulador da mobilização do Ca^{2+} em resposta a sinais extracelulares
 - Ativação do inflamossoma NLRP3
 - ↑ IL-1 β e IL-18
- Níveis aumentados de IL-1 β e IL-18 na fase aguda

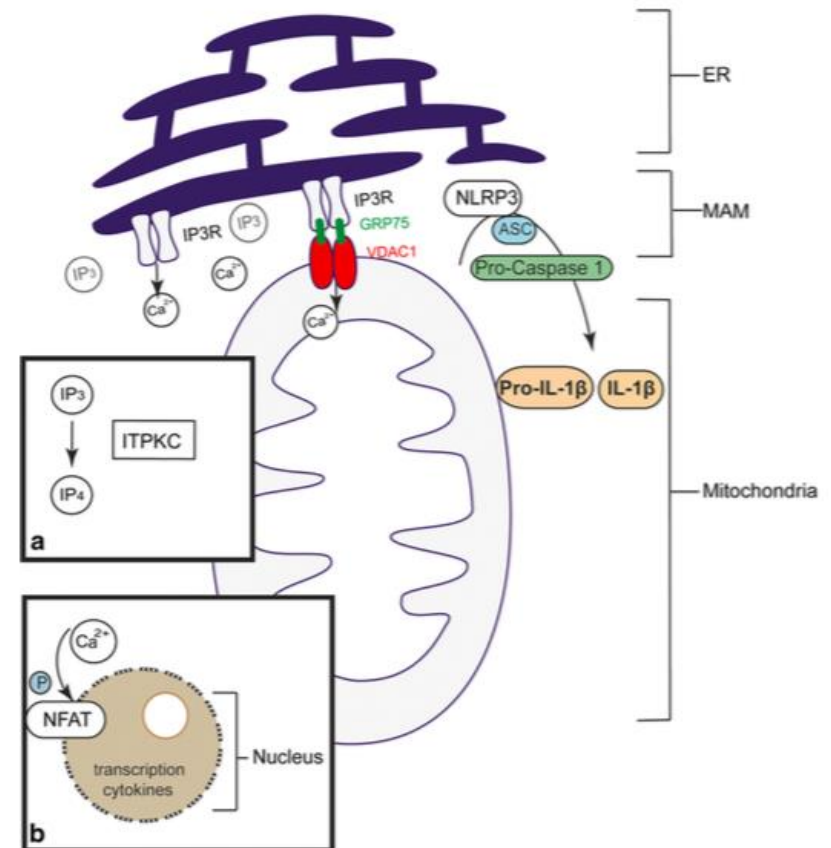


Fig. 1 The role of IP3 and ITPKC in calcium signaling. (a) ITPKC phosphorylates IP3 to IP4 and modulates the abundance of IP3 and influences the calcium signaling. (b) Nuclear factor of activated T cells (NFAT) are regulated by calcium signaling and enter the nucleus when dephosphorylated, there it activates cytokine transcription namely IL-2, IFN γ in T cells and Pro-IL1, IL-10, Pro-IL18 in macrophages. *Footnote:* Inositol triphosphate receptor (IP3R) forms a bridge between the endoplasmic reticulum (ER) and mitochondria creating a site of contact between the ER and mitochondria called the mitochondria-associated ER membrane (MAM). NLRP3 is an inflammasome that forms at or close to the MAM upon cellular activation and ER stress

and plays a pivotal role (by activating caspase-1) in the cleavage of pro-IL1 β into IL1 β and its subsequent secretion. The ER releases calcium into the cytosol and into mitochondria through (a.o.) the IP3R, which is a calcium channel, to which IP3 as an agonist binds to induce calcium release. IP3R binds via glucose-regulated protein 75 (GRP75) with the mitochondrial voltage-dependent anion channel 1 (VDAC1) which may cause mitochondrial stress and leakage off reactive oxygen species (ROS), both important for inflammasome activation. Macrophages activate via their Toll-like receptors (TLRs) or G-protein coupled receptors several signaling pathways, that result in IP3 formation, NF- κ B activation, and/or ER stress.

- Alvo terapêutico
 - Anti IL-1

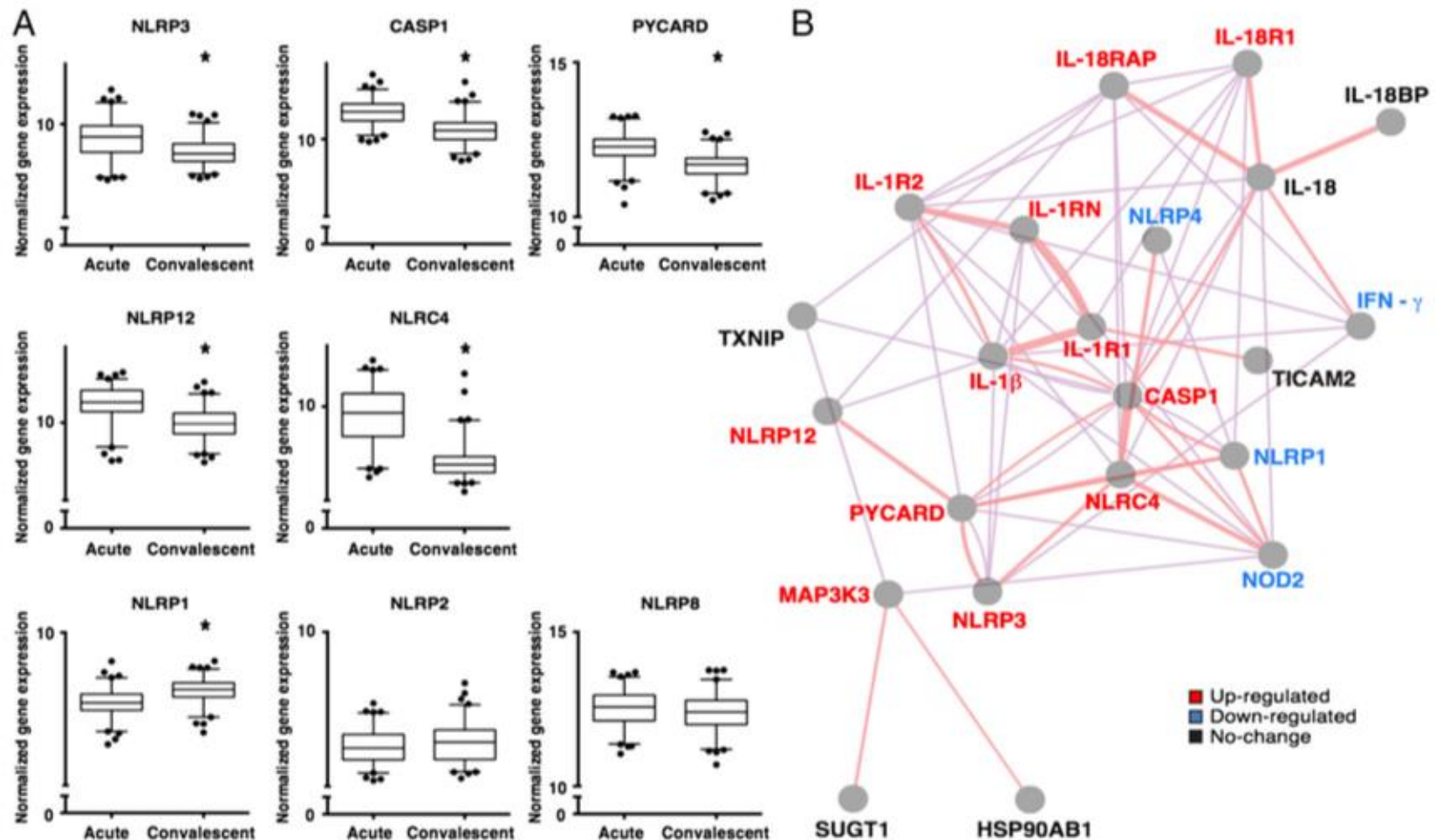


FIGURE 4. Increased expression of NLRP3 inflammasome-associated genes during acute KD. **(A)** Gene expression profile of inflammasome-associated genes from serial samples from children with KD ($n = 171$) during acute and convalescent phases of disease. The box plots show the median (thick black line) within the box (25th and 75th percentiles) whose whiskers represent the 3rd and 97th percentiles. $*p < 0.0001$. **(B)** GeneMANIA functional association gene network for inflammasome-associated genes. The physical interaction and coexpression between genes are expressed as pink and purple lines, respectively; the thicker the line, the stronger the association. Gene names denoted in red, blue, and black are upregulated, downregulated, or unchanged, respectively, during acute phase of KD.

FISIOPATOLOGIA | INFLAMMOSSOMA e IL-1

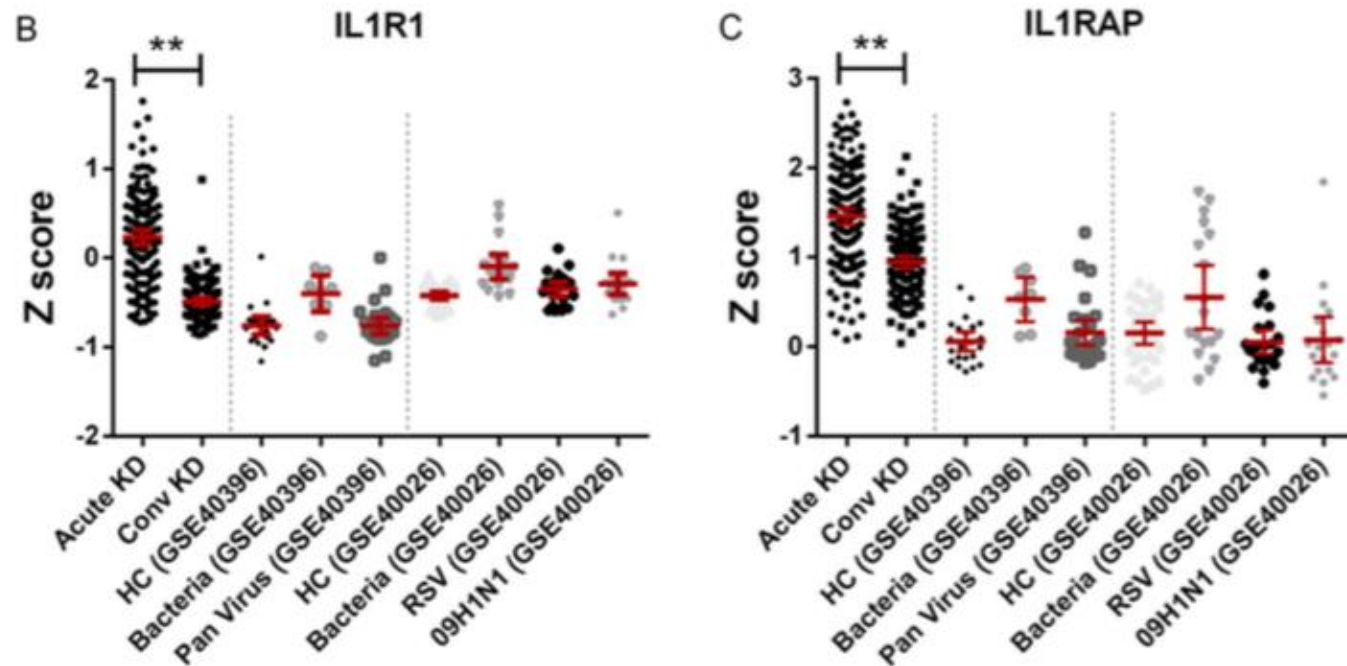


Figure 5 IL1 signaling pathway was the key upregulated pathway in acute KD. (A) Transcripts involved in IL1 signaling pathways were more abundant in acute KD; DATs between acute and convalescent KD samples are highlighted in red. (B, C) IL1R1 and IL1RAP were differentially expressed only in acute vs. convalescent KD but not in other diseases. ** P value <0.01 .

DIAGNÓSTICO

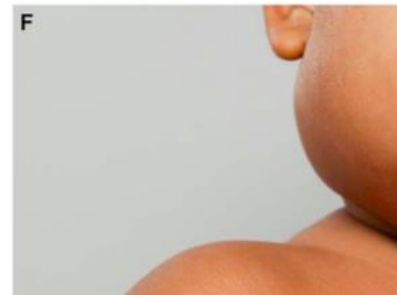
Table 3. Diagnosis of Classic KD

Classic KD is diagnosed in the presence of fever for at least 5 d (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. 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 d of fever, although experienced clinicians who have treated many patients with KD may establish the diagnosis with 3 d of fever in rare cases (Figure 2):

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

McCrindle et al. Circulation, 2017

- A duração da febre é sobretudo de importância histórica
- Na presença de ≥ 4 critérios clínicos, particularmente se rubor e edema das extremidades, o diagnóstico pode ser estabelecido com 4 dias de febre



OUTRAS MANIFESTAÇÕES CLÍNICAS

Other clinical findings may include the following:
Cardiovascular
Myocarditis, pericarditis, valvular regurgitation, shock
Coronary artery abnormalities
Aneurysms of medium-sized noncoronary arteries
Peripheral gangrene
Aortic root enlargement
Respiratory
Peribronchial and interstitial infiltrates on CXR
Pulmonary nodules
Musculoskeletal
Arthritis, arthralgia (pleocytosis of synovial fluid)
Gastrointestinal
Diarrhea, vomiting, abdominal pain
Hepatitis, jaundice
Gallbladder hydrops
Pancreatitis

Nervous system
Extreme irritability
Aseptic meningitis (pleocytosis of cerebrospinal fluid)
Facial nerve palsy
Sensorineural hearing loss
Genitourinary
Urethritis/meatitis, hydrocele
Other
Desquamating rash in groin
Retropharyngeal phlegmon
Anterior uveitis by slit lamp examination
Erythema and induration at BCG inoculation site

McCrindle et al. *Circulation*, 2017



QUANDO É QUE SE INICIA A DILATAÇÃO CORONÁRIA?

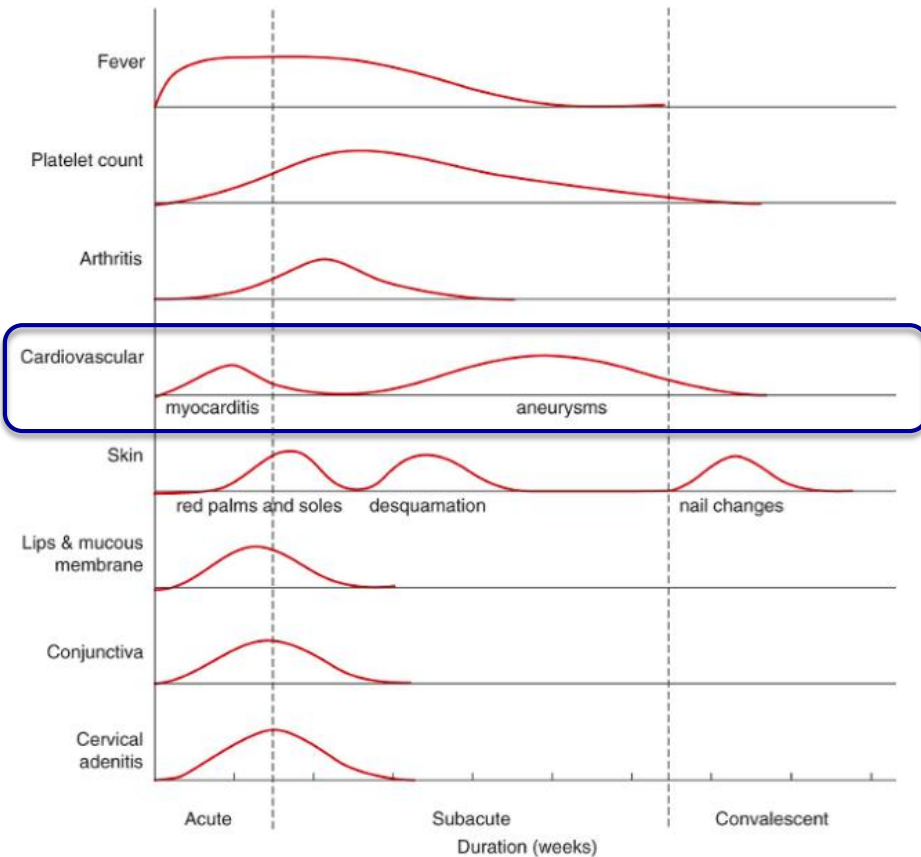


Table 1. Pretreatment Maximum Coronary Artery Z-Score and Day of Examination for Patients With KD

Day	No. patients	preZmax				
		>1.5	1.5–2.0	2.0–2.5	2.5–3.0	>3.0
2	13	9	2	1	1	0
3	49	29	5	8	3	4
4	110	70	14	12	3	11
5	121	83	14	11	9	4
6	72	47	10	5	5	5
7	27	16	3	3	2	3
8	7	5	0	0	1	1
9	3	2	0	0	0	1
10	3	0	0	0	1	2
11	1	1	0	0	0	0
12	1	0	1	0	0	0
13	1	1	0	0	0	0
15	1	1	0	0	0	0
20	1	1	0	0	0	0
Total	410	265	49	40	25	31

KD, Kawasaki disease; preZmax, pretreatment maximum coronary artery Z-score.

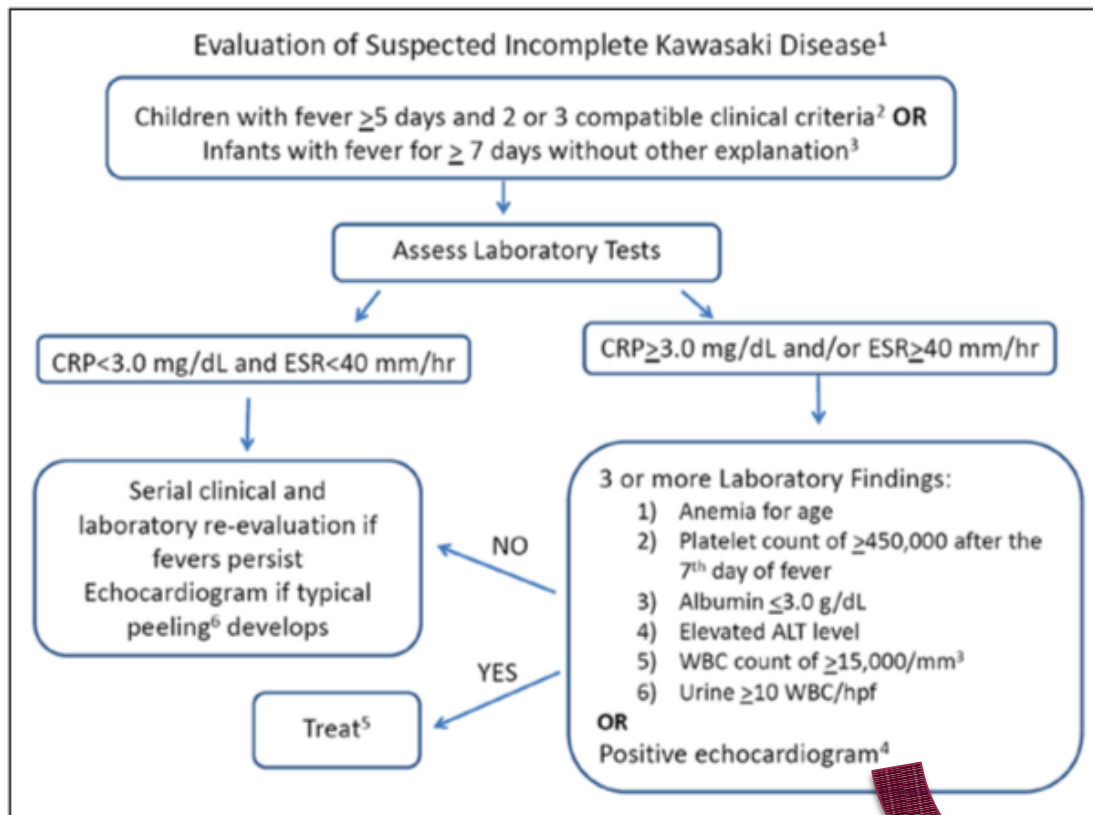
Fuse S et al. *Circ J*. 2017

- A dilatação das coronárias pode começar antes do 5º dia de doença, aumentando gradualmente até ao 10º dia.
- Z score máximo ≥ 2 (pré-tx) tem elevado VPP
→ marcador de dilatação coronária em fases precoces

Textbook of Pediatric Rheumatology, 7ª edição

Conclusions—In a North American center, baseline zMax ≥ 2.0 in children with Kawasaki disease demonstrated high predictive utility for later development of CAA. Future studies should validate the utility of our findings. (*J Am Heart Assoc*. 2017;6:e005378. DOI: 10.1161/JAHA.116.005378.)

KAWASAKI INCOMPLETO



McCrindle et al. Circulation, 2017

- Mais frequente em lactentes → elevado risco de AAC
- Importante manter elevado índice de suspeição
- Se dúvida → consultar um perito

- **Considerar outras causas**

- *Faringite exsudativa*
- *Conjuntivite exsudativa*
- *Úlceras orais*
- *Exantema bolhoso ou vesicular*
- *Adenomegalias generalizadas*
- *Esplenomegalia*
- *Exantema petequial extenso (SAM?)*

- **Achados ecocardiograma**

- DA ou CD com Z score ≥ 2.5
- Presença aneurisma coronário
- Presença de ≥ 3 achados:
 - ↓função VE, insuficiência mitral, DA ou CD com Z score 2.0 – 2.5

KAWASAKI DISEASE SHOCK SYNDROME

Kanegaye JT, Wilder MS, Molkara D, et al. Recognition of a Kawasaki disease shock syndrome. *Pediatrics*. 2009;123:e783-e789.

- Uma parte dos doentes com DK apresentam-se com instabilidade hemodinâmica, necessitando de volemização, fármacos vasoativos e admissão em UCI
 - Hipotensão sistólica para a idade; diminuição da TAS base em $\geq 20\%$; sinais clínicos de hipoperfusão (taquicardia, TPC prolongado, extremidades frias, pulsos filiformes, oliguria ou afundamento do estado de consciência sem outra causa)
- Até 40% destes doentes não têm diagnóstico de DK na admissão
- Este subgrupo apresenta um curso clínico mais grave, com maior probabilidade de resistência à IGIV e desenvolvimento de complicações coronárias
- Tipicamente crianças mais velhas, febre + prolongada, ↑↑ marcadores inflamatórios, hipoalbuminemia, disfunção miocárdica, BNP mais elevado, trombocitopenia
- Maior risco de Síndrome de Ativação Macrofágica

BIOMARCADORES CANDIDATOS

Kimura Y et al. Sci Rep. 2017

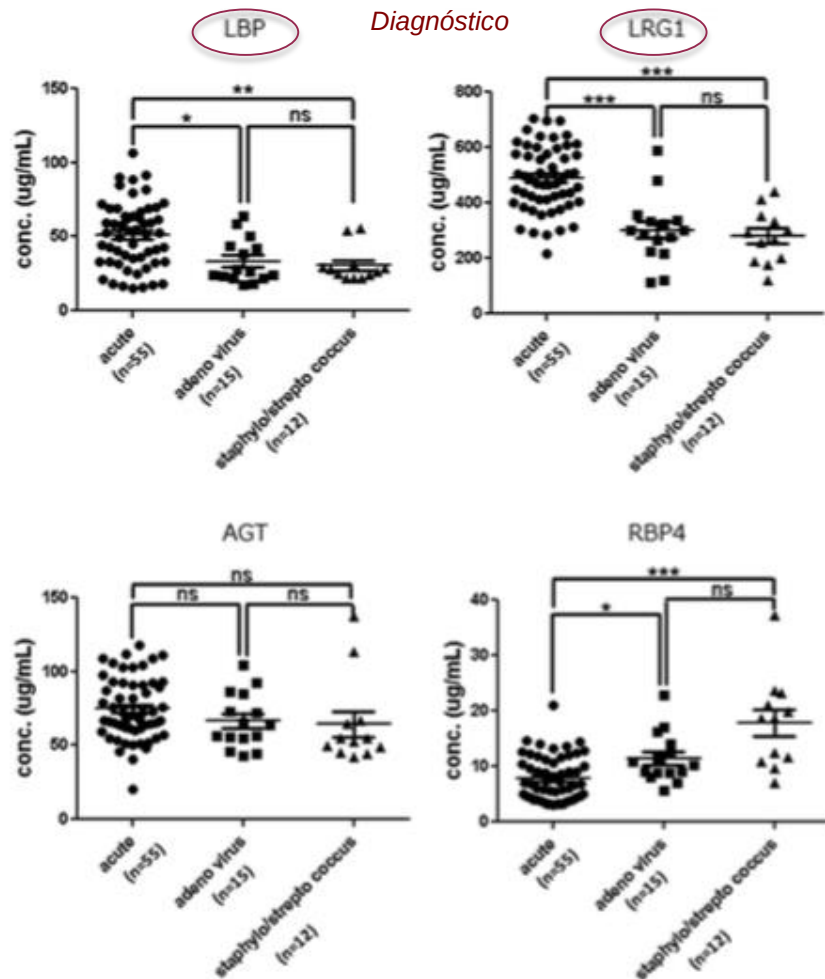


Figure 4. Verification of candidate proteins for KD diagnostic biomarkers by microarray ELISAs. Expression levels of the four candidate biomarkers were evaluated in the acute phase of KD and other infections that mimic KD, such as human adenovirus, *Staphylococcus*, and *Streptococcus* species. The serum concentrations of three proteins (LBP, LRG1, and RBP4) differed significantly in the acute phase of KD in comparison with these infections. The sera used in this experiment are described in Tables S1 and S3. The horizontal lines and error bars indicate means and SEMs, respectively. P values were used to evaluate the significance of differences between the acute phase of KD and these infections: *** $p < 0.001$; ** $p < 0.01$; * $p < 0.1$; ns: non-significant.

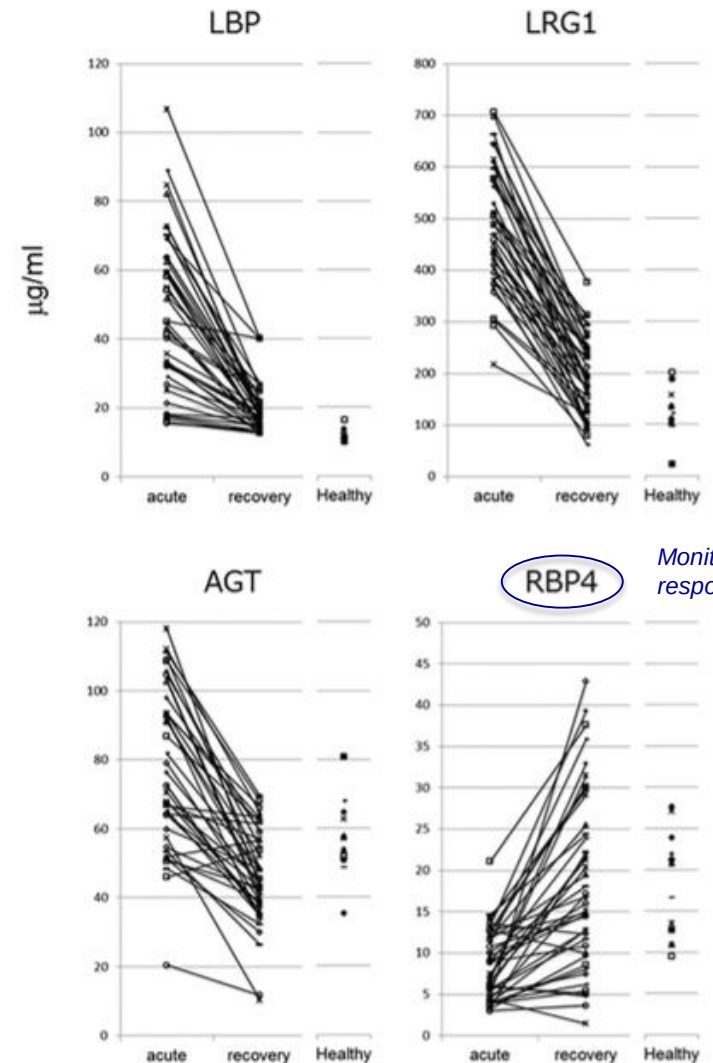


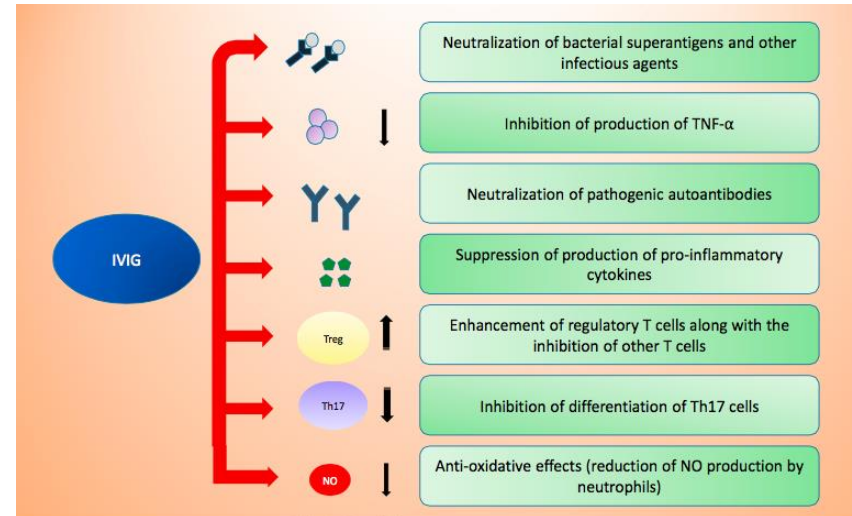
Figure 3. Changes in protein levels between acute and recovery phase sera from KD patients measured by microarray ELISA. Expression levels of each protein in the paired sera obtained during the acute and recovery phases from 42 KD patients and in the sera from 13 healthy subjects as measured by microarray ELISA. The solid line indicates the paired sera from each patient.

Monitorização
resposta à tx

TRATAMENTO INICIAL | IGIV

IMUNOGLOBULINA HUMANA EV

- 2 g/kg em perfusão única – ao diagnóstico
 - Reduz o aparecimento de AAC de 25% para 5%, reduz a duração da fase aguda
- >10 dias: se evidência de inflamação sistêmica (febre e PCR >30 mg/L ou Z score coronário >2.5)
- Complicação emergente: anemia hemolítica Coombs +, especialmente em indivíduos grupo AB (A, B); mais frequente após retratamento com IGIV



Agarwal et al, 2016

TRATAMENTO INICIAL | AAS

ÁCIDO ACETILSALICÍLICO | sem evidência na redução de AAC

- 80-120 vs 30-50 mg/kg/dia (4 id) na fase aguda → 3-5 mg/Kg após 48-72h de apirexia
 - Meta-análises não mostram diferença na incidência de AAC, com ↑ efeitos laterais
- Alta dose vs baixa dose (*Dallaire et al, 2017*) → sem diferença
- Dose moderada vs baixa dose (*Kuo et al, 2015*) → sem diferença
- Dose baixa vs moderada vs elevada (*Kim et al, 2016*) → maior risco de AAC nas doses moderadas e elevadas mas... sem randomização! Viés por indicação
- Cuidado – o uso de ibuprofeno (e outros AINEs que interferem no ciclo da COX) pode antagonizar o efeito anti-trombótico do AAS





RESISTÊNCIA À IGIV | ELEVADO RISCO DE AAC

- A resistência ao tratamento com IGIV é o maior fator de risco para o desenvolvimento de AAC
- Como identificar *a priori* quais as crianças que não vão responder?
- Scores de risco desenvolvidos na pop. japonesa → na pop. Europeia/EUA com elevada especificidade mas baixa sensibilidade para prever resistência à IGIV

Table 3 Scoring systems for predicting IVIG resistance

EGAMI ⁴⁹	KOBAYASHI ⁴⁷	SANO ⁵⁰
≤4 days of illness (1 point)	Na ≤133 (2 points)	Total bilirubin ≥0.9 mg/dl (1 point)
ALT >100 U/L (1 point)	≤4 days of illness (2 points)	AST ≥200 U/L (1 point)
≤300 ×10 ⁹ /L platelets (1 point)	ALT ≥ 100 U/L (1 point)	CRP ≥7 mg/dL (1 point)
CRP ≥8 mg/dL (1 point)	≤300×10 ⁹ /L platelets (1 point)	
Age ≤6 months (2 points)	CRP ≥10 mg/dL (1 point)	
	Age ≤12 months (1 point)	
	≥80% neutrophils (2 points)	
High risk ≥3 points	≥5 points	≥2 points
<i>Test performance in Japanese vs non-Japanese</i>		
Japanese cases		
Sensitivity (%)	86	77
Specificity (%)	67	86
Non-Japanese cases ⁵¹		
Sensitivity (%)	33	40
Specificity (%)	87	85

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; IVIG, intravenous immunoglobulin.

TRATAMENTO | Papel da corticoterapia

- Resistência à IGIV ocorre em até 20% dos casos
- Os corticosteróides são eficazes no tratamento de outras vasculites
 - Estudos retrospectivos antigos sugeriram uma associação com aumento do risco de AAC → viés de seleção !

VOLUME 63 • FEBRUARY 1979 • NUMBER 2

Pediatrics

ARTICLES

Kawasaki Disease: Effect of Treatment on Coronary Artery Involvement

Hirohisa Kato, M.D., Sigeyuki Koike, M.D., and Takashi Yokoyama, M.D.

INCIDENCE OF CORONARY ANEURYSM IN GROUPS TREATED WITH FIVE DIFFERENT PROTOCOLS

Protocol	Incidence of Coronary Aneurysm	
	No.	%
1. Prednisolone	11/17	64.7
2. Prednisolone plus warfarin	2/7	28.6
3. Prednisolone plus aspirin	0/7	0
4. Aspirin	4/36	11
5. Antibiotic only	5/25	20

TRATAMENTO | Papel da corticoterapia

Wardle AJ, Connolly GM, Seager MJ, Tulloh RMR.

Corticosteroids for the treatment of Kawasaki disease in children.

Cochrane Database of Systematic Reviews 2017, Issue 1. Art. No.: CD011188.

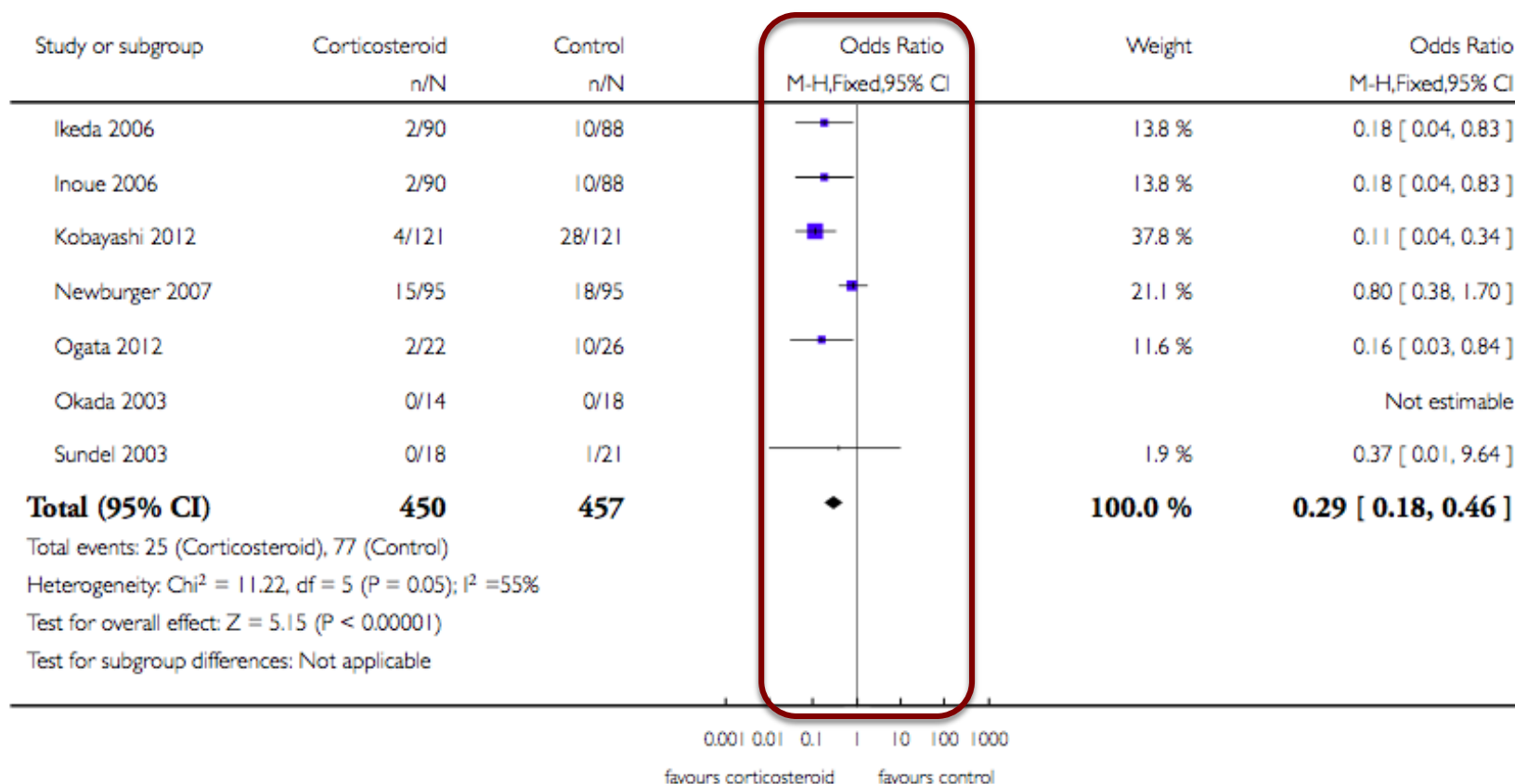
DOI: 10.1002/14651858.CD011188.pub2.

Analysis 1.1. Comparison 1 Corticosteroids vs no corticosteroid use, Outcome 1 Incidence of coronary artery abnormalities.

Review: Corticosteroids for the treatment of Kawasaki disease in children

Comparison: 1 Corticosteroids vs no corticosteroid use

Outcome: 1 Incidence of coronary artery abnormalities



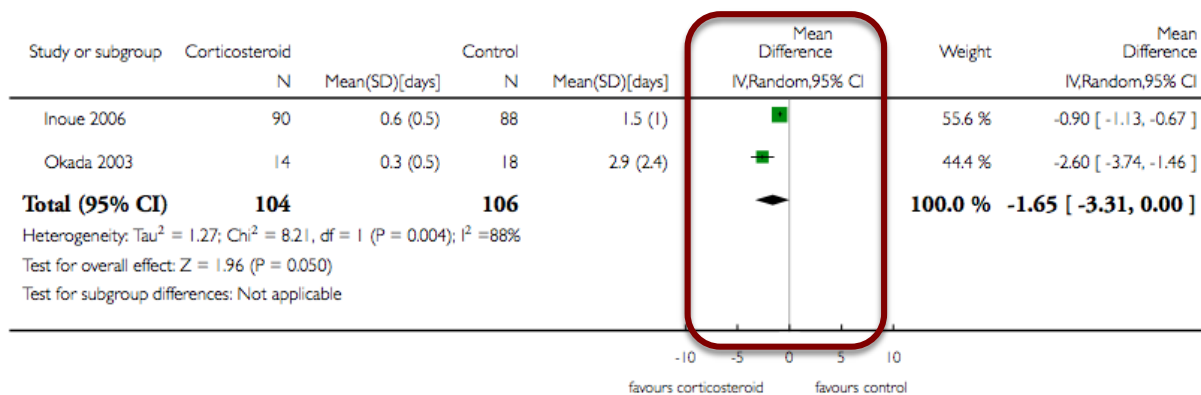
TRATAMENTO | Papel da corticoterapia

Analysis 1.4. Comparison 1 Corticosteroids vs no corticosteroid use, Outcome 4 Duration of clinical symptoms: fever, rash.

Review: Corticosteroids for the treatment of Kawasaki disease in children

Comparison: 1 Corticosteroids vs no corticosteroid use

Outcome: 4 Duration of clinical symptoms: fever, rash

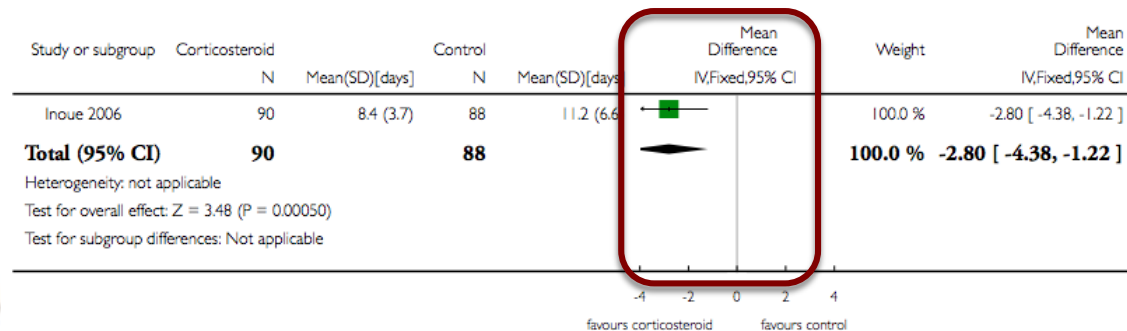


Analysis 1.5. Comparison 1 Corticosteroids vs no corticosteroid use, Outcome 5 Time for laboratory parameters to normalise: CRP, ESR.

Review: Corticosteroids for the treatment of Kawasaki disease in children

Comparison: 1 Corticosteroids vs no corticosteroid use

Outcome: 5 Time for laboratory parameters to normalise: CRP, ESR



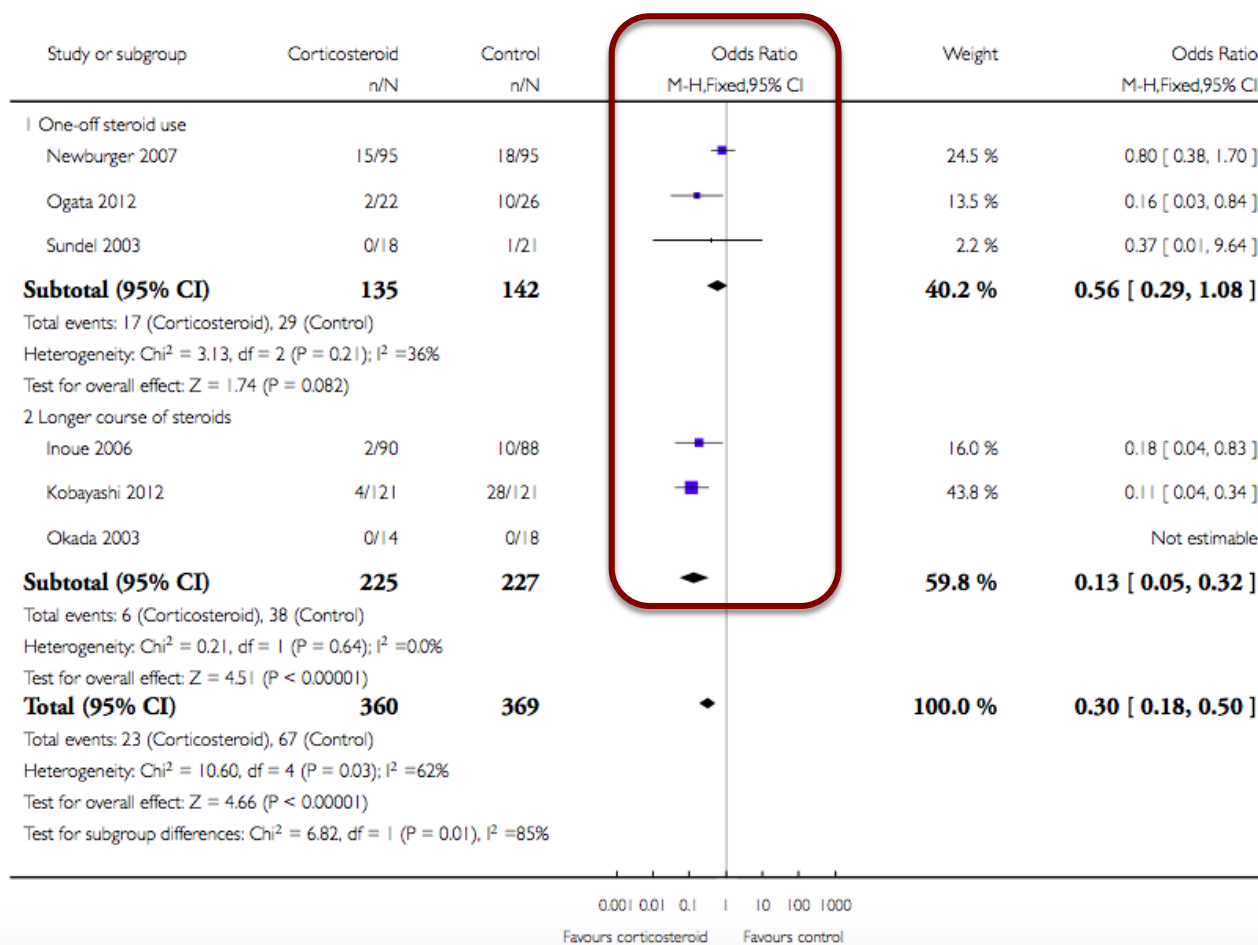
TRATAMIENTO | Pulso único VS Curso prolongado

Analysis 2.1. Comparison 2 Subgroup: One-off steroid use vs longer course of steroids, Outcome 1 Coronary artery abnormalities.

Review: Corticosteroids for the treatment of Kawasaki disease in children

Comparison: 2 Subgroup: One-off steroid use vs longer course of steroids

Outcome: 1 Coronary artery abnormalities



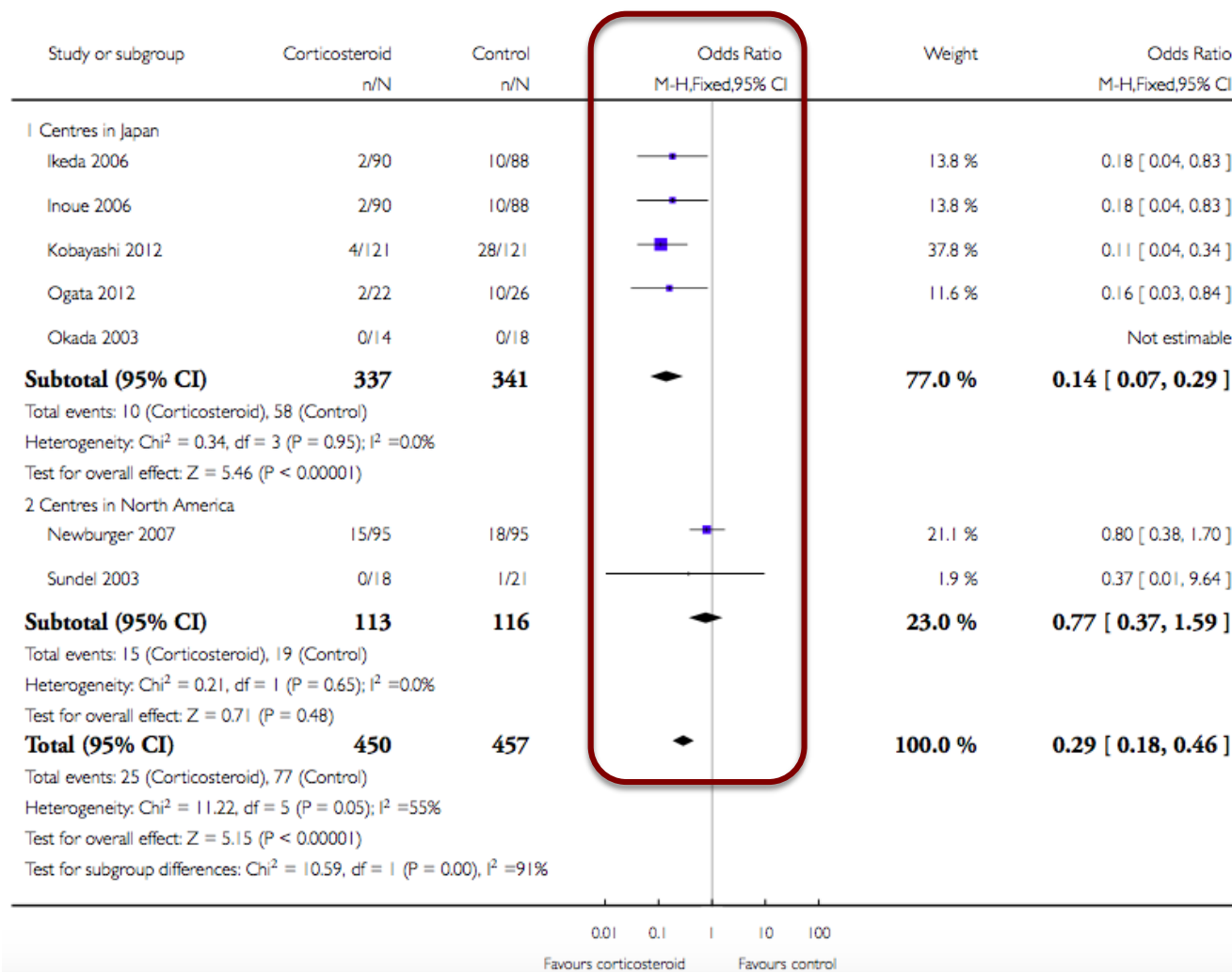
TRATAMENTO | Japão VS EUA

Analysis 3.1. Comparison 3 Subgroup: Geography, Outcome 1 Coronary artery abnormalities.

Review: Corticosteroids for the treatment of Kawasaki disease in children

Comparison: 3 Subgroup: Geography

Outcome: 1 Coronary artery abnormalities



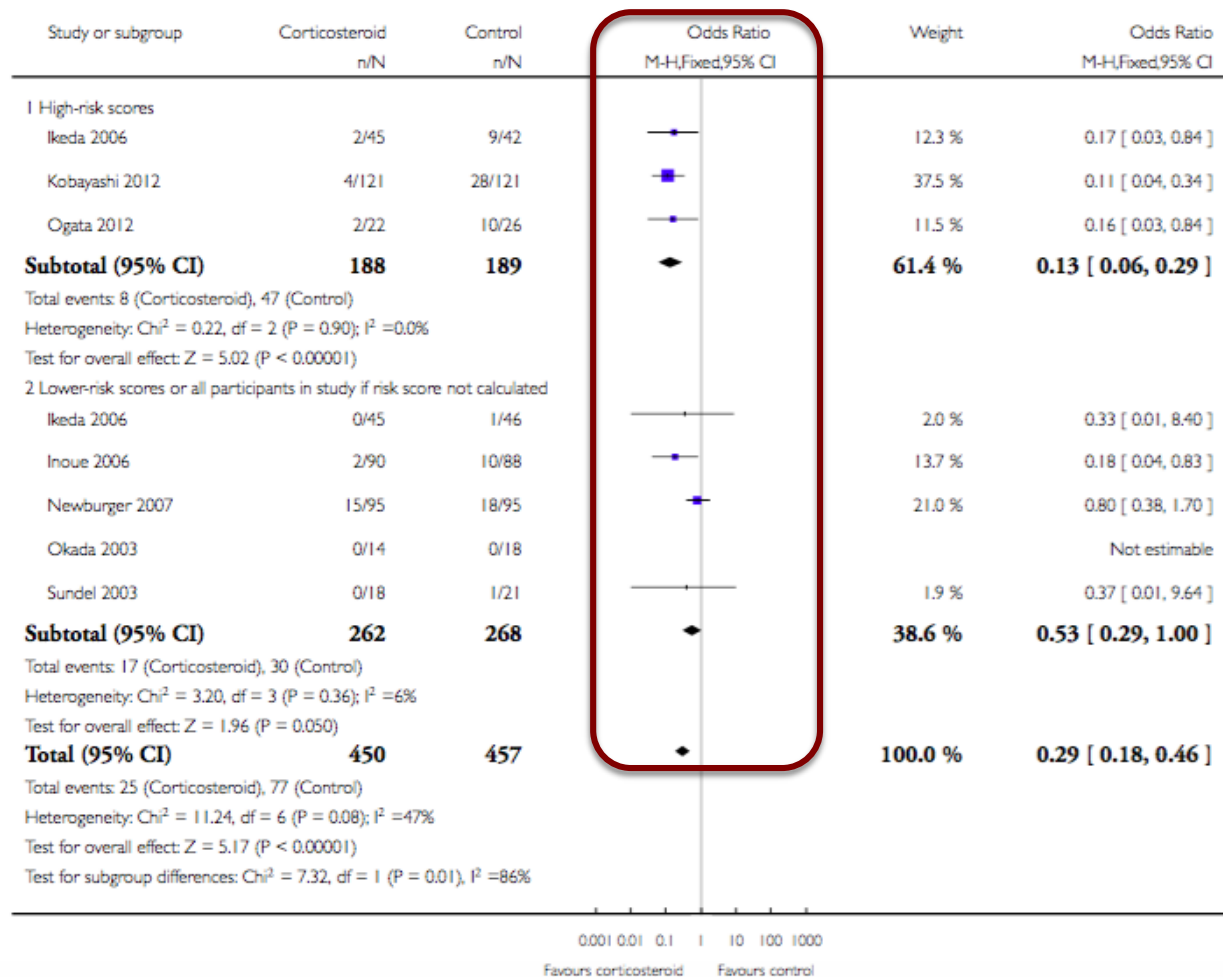
TRATAMENTO | Alto risco VS Baixo risco / todos

Analysis 4.1. Comparison 4 Subgroup: High-risk scores vs lower-risk scores or all participants if risk score not calculated in study, Outcome 1 Coronary artery abnormalities.

Review: Corticosteroids for the treatment of Kawasaki disease in children

Comparison: 4 Subgroup: High-risk scores vs lower-risk scores or all participants if risk score not calculated in study

Outcome: 1 Coronary artery abnormalities



TRATAMENTO | Papel da corticoterapia

- Parece haver benefício global do uso de corticoterapia na D. Kawasaki com redução da incidência de AAC, do tempo de febre e de exantema
 - Cursos mais prolongados (2-3 semanas) são melhores do que pulso único
 - Maior benefício na população japonesa ? – confundidor com o tipo de corticoterapia
 - Maior benefício no subgrupo de doentes de alto risco...
 - mas como selecionar estes doentes na nossa população?



TRATAMENTO | Recomendações para o uso de corticóides

- **Resistência à IGIV** → persistência de febre e/ou inflamação persistente ≥ 36 h após tratamento com IGIV 2 g/kg
- **Características de doença grave** – na ausência de scores de risco validados, sugere-se
 - < 12 meses (< 24 meses?); características de hemofagocitose e/ou choque; marcadores de inflamação grave: PCR persistentemente elevada após IGIV, disfunção hepática, hipoalbuminemia, hiponatremia, anemia, ausência de trombocitose
- Presença de **envolvimento coronário** ou **aneurismas periféricos** na apresentação
 - Coronárias hiperrefringentes ou dilatadas (*Z score* >2.0) ou manifestações extra-coronárias sugestivas (ex: insuficiência mitral, derrame pericárdico, disfunção VE...)

TRATAMENTO | Regime de corticoterapia

- Prednisolona EV 2 mg/kg (equivalente) até apirexia → P.O. até normalização da PCR → desmame durante 2-3 semanas
 - *Não utilizar VS para monitorização da doença, uma vez que aumenta após administração de IGIV*
- Pulsos de metilprednisolona EV (30 mg/kg) reservados para casos selecionados (ex: SAM, choque)



TRATAMENTO | Resistência à IGIV

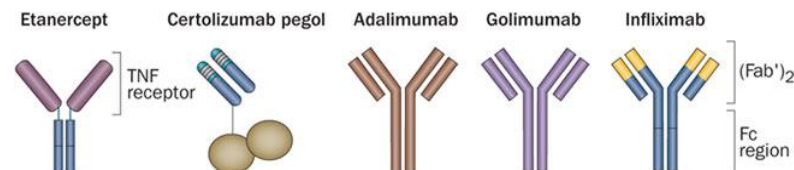
Table 6. Treatment Options for IVIG-Resistant KD Patients

Agent	Description	Dose	References
Most frequently administered			
IVIG: Second infusion	Pooled polyclonal IG	2 g/kg IV	211
IVIG + prednisolone	IVIG + steroid	IVIG: 2 g/kg IV + prednisolone 2 mg·kg ⁻¹ ·d ⁻¹ IV divided every 8 h until afebrile, then prednisone orally until CRP normalized, then taper over 2–3 wk	212
Infliximab	Monoclonal antibody against TNF- α	Single infusion: 5 mg/kg IV given over 2 h	194, 213, 214
Alternative treatments			
Cyclosporine	Inhibitor of calcineurin-NFAT pathway	IV: 3 mg·kg ⁻¹ ·d ⁻¹ divided every 12 h PO: 4–8 mg·kg ⁻¹ ·d ⁻¹ divided every 12 h Adjust dose to achieve trough 50–150 ng/mL; 2-h peak level 300–600 ng/mL	215, 216
Anakinra	Recombinant IL-1 β receptor antagonist	2–6 mg·kg ⁻¹ ·d ⁻¹ given by subcutaneous injection	217, 218
Cyclophosphamide	Alkylating agent blocks DNA replication	2 mg·kg ⁻¹ ·d ⁻¹ IV	219
Plasma exchange	Replaces plasma with albumin	Not applicable	220

IVIG resistance is defined as persistent or recrudescence fever at least 36 hours and <7 days after completion of first IVIG infusion. The top 3 treatments have been most commonly used, although no comparative effectiveness trial has been performed. Pulsed high-dose steroid treatment is not recommended. The alternative treatments have been used in a limited number of patients with KD.

CRP indicates C-reactive protein; IG, immunoglobulin; IL, interleukin; IV, intravenous; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; NFAT, nuclear factor of activated T cells; PO, by mouth; and TNF, tumor necrosis factor.

TRATAMENTO | OUTRAS OPÇÕES



- **ANTI-TNF**

- Infliximab é aquele com maior experiência reportada na literatura (5-6 mg/kg em 1-2 doses)
- Tremoulet *et al*, 2014 | IGIV+AAS vs IGIV+AAS+IFX como tratamento inicial num grupo de 196 doentes não selecionados → ↓ duração da febre, ↓ marcadores inflamatórios, ↓ Z score da DA mas não ↓ resistência à IGIV ou incidência de AAC (underpowered)
- Menos experiência com etanercept mas parece ser seguro e bem tolerado (0.8 mg/kg)

- **CICLOSPORINA** (inibidor da calcineurina)

- Infiltrados de céls T CD₈⁺ na parede arterial
- Estudos genéticos → ativação das vias NFAT-calcineurina dependentes de cálcio
- Quando doente apirético e PCR <10 mg/L (ou após 2 semanas) → diminuir 10% a cada 3 dias → suspender quando 1 mg/kg/dia

TRATAMENTO | OUTRAS OPÇÕES

- ANTI-IL₁

- Anakinra (antagonista recetor IL-1)
- Canakinumab, rilonacept

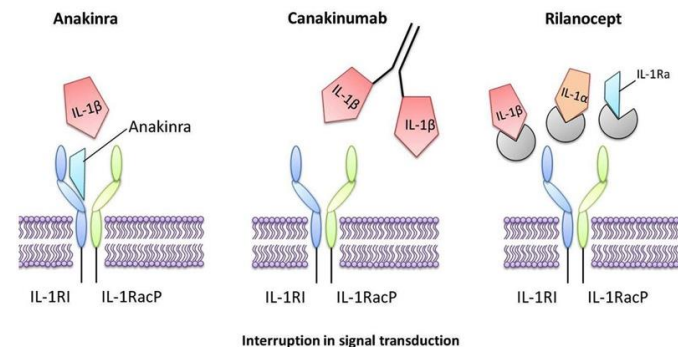


TABLE 2 | Clinical trials of IL-1 blockade enrolling KD patients conducted in Western Europe and in USA (Burns et al., 2016).

Name	Type of trial	IL-1 blockade/Doses	Population KD patients	Objective	Time
Kawakinra trial (Europe) (Eudract Number: 2014-002715-41)	Phase IIa, multi-centered trial	Anakinra: 2 mg/kg/day Dose can be increased by 2 mg/kg/24 h if persistent or recrudescence fever (max 6mg/kg/d)	Children: 8 months (≥ 10 kg)–18 years Screened: 4th–13th day of fever	Primary end points Efficacy and safety of anakinra Secondary objectives Effects of anakinra on coronary artery Disease activity and inflammation biomarkers	14 days of treatment
Anakid trial (USA) (clinicaltrials.gov#NCT02179853)	Phase I/IIa study: Two-centered and dose escalation trial	Anakinra: 2, 4 or 8 mg/kg Persistent or recrudescence fever after ≥ 36 h and < 7 days following the end of intravenous immunoglobulin (IVIg) infusion	Children (≥ 8 -M -old) with acute KD and with coronary artery (Z-score ≥ 3.0 in the RCA or LAD) abnormalities	Safety, tolerability, and pharmacokinetics of anakinra	2–6 weeks
Canakinumab trial (Europe)	Phase II trial: Two-arm, multi-centered and carried out in seven European countries	Canakinumab: 6 mg/kg IV Group 1: Complete fever resolution Canakinumab (1 or 2 SC injections) at 4 and 8 weeks Depending on the clinical and CRP course Group 2 Fever remains after 48–72 h of canakinumab IVIg	Naïve KD patients or IVIg-resistant KD patient	The presence or absence of fever will be looked-for.	

IVIg, intravenous immunoglobulin; RCA: right coronary artery; LAD, left anterior descending coronary artery; SC, subcutaneous.

Estabelecer diagnóstico de D. Kawasaki

Não

- IGIV 2 g/kg em perfusão única
- AAS 30-50 mg/kg/dia, 4 id
- Obter ecocardiograma e ECG assim que possível, mas não atrasar a instituição de terapêutica

Defervescência: apirexia após 36h, melhoria clínica e analítica (PCR)

- AAS 3-5 mg/kg e manter durante 6 - 8 semanas

Se primeiro ecocardiograma normal e PCR normal em 1 semana com boa evolução clínica

Características de alto risco?

- Resistência à IGIV
- Doença grave: <12 meses, marcadores de inflamação severa (PCR persistentemente elevada após IGIV, disfunção hepática, hipoalbuminemia, hiponatremia, anemia, ausência de trombocitose)
- Choque ou evolução para SAM
- Atingimento coronário ou aneurismas periféricos ao diagnóstico

Se dúvida: contactar um perito

Sim

- IGIV e AAS (= baixo risco) +
- Metilprednisolona 0.8 mg/kg EV 2 id até PCR normalizar → prednisolona 2 mg/kg/dia PO e desmame em 2-3 semanas
- Obter ecocardiograma e ECG assim que possível, mas não atrasar a instituição de terapêutica

Sem defervescência após 36h, ou recrudescência da doença

Repetir ecocardiograma às 2 e 6 semanas

**Sem defervescência após 36h,
ou recrudescência da doença**

Transferir o doente para hospital central; considerar

- Corticoterapia como acima, se ainda não utilizada
- Repetir 2ª dose de IGIV 2 g/kg
 - Cuidado com hemólise no tipo AB
- Infliximab 6 mg/kg (1 – 2 doses)
- Anakinra 2 mg/kg/dia (até 6 mg/kg/dia)

- Ciclosporina
- Ciclofosfamida
- Plasmaferese ...

Reconsiderar diagnóstico

Repetir ecocardiograma às 2 e 6 semanas

Sem AAC

- Parar AAS às 6 - 8 semanas
- Seguimento até aos 12 meses e alta se bem

Table 8. Risk Classification of Coronary Artery Abnormalities During Follow-up

Classification	Description
1	No involvement at any timepoint (Z score always <2)
2	Dilation only (Z score 2 to <2.5)
3	Small aneurysm (Z score ≥2.5 to <5)
3.1	Current or persistent
3.2	Decreased to dilation only or normal luminal dimension
4	Medium aneurysm (Z score ≥5 to <10, and absolute dimension <8 mm)
4.1	Current or persistent
4.2	Decreased to small aneurysm
4.3	Decreased to dilation only or normal luminal dimension

5	Large and giant aneurysm (Z score ≥10, or absolute dimension ≥8 mm)
5.1	Current or persistent
5.2	Decreased to medium aneurysm
5.3	Decreased to small aneurysm
5.4	Decreased to dilation only or normal luminal dimension

McCrindle et al. Circulation, 2017

Table 11. Long-Term Thromboprophylaxis and Medical Therapy Algorithm

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
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

ASA indicates acetylsalicylic acid or aspirin; and LMWH, low-molecular-weight heparin. Green indicates a Class I recommendation (should be performed); yellow indicates a Class IIa recommendation (it is reasonable to perform); orange indicates a Class IIb recommendation (may be considered); and red indicates a Class III recommendation (should not be performed).

Table 10. 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
4.1: Medium aneurysm, current or persistent	Assess at 3, 6, and 12 mo, then yearly	Assess every 1–3 y	May consider every 2–5 y	Assess at 1 y	Promotion counseling at every visit; restrict contact; self-limit	Precautions for contraception and pregnancy
4.2: Medium aneurysm, regressed to small aneurysm	Assess yearly	Assess every 2–3 y	May consider every 3–5 y	Assess yearly	Promotion counseling at every visit; restrict contact; self-limit	Precautions for contraception and pregnancy
4.3: Medium aneurysm, regressed to normal or dilation only	Assess every 1–2 y (may omit echocardiography)	Assess every 2–4 y	May consider if there is inducible ischemia	Assess every 2 y	Promotion counseling at every visit; restrict contact; self-limit	Precautions for contraception and pregnancy
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

EVOLUÇÃO DO ENVOLVIMENTO CORONÁRIO

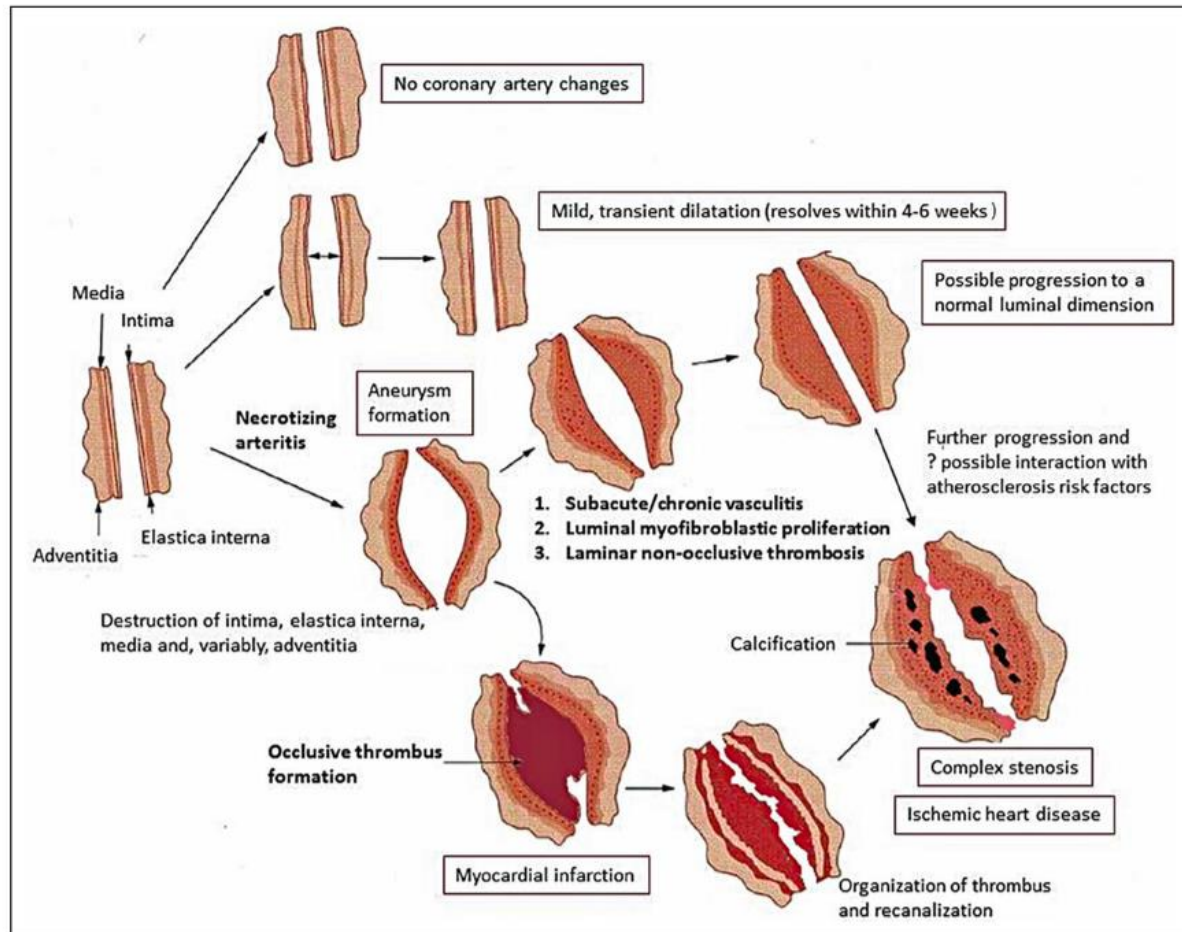


Figure 4. Natural history of coronary artery abnormalities.

Modified from Kato²⁵⁸ with permission from Elsevier. Copyright © 2004, Elsevier.

PROGNÓSTICO A LONGO PRAZO

- Amplamente determinado pelas sequelas cardíacas – risco de estenose e trombose
 - *British Paediatric Surveillance Unit* (1993): taxa de mortalidade 3.7%
 - Nakamura *et al* (2004): mortalidade nos homens com sequelas cardíacas 2.4 x superior
 - Aneurismas gigantes: taxa de sobrevida 30 anos de 88%; 16% desenvolveram EAM
- E no subgrupo de doentes que nunca apresentou AAC, ou em que estes regrediram?
 - Doença de Kawasaki foi descrita em 1967 → as crianças que tiveram DK nas décadas de 1960-1970 estão agora a entrar na meia idade

PROGNÓSTICO A LONGO PRAZO

Table 1 Methods for studying subclinical vascular changes in KD and their association with cardiovascular risk

	Abbreviations	Type of vascular structure or function measured	Association with increased cardiovascular risk
Carotid intima-media thickness	cIMT	Intima-media complex of the carotid artery	Increased carotid intima-media thickness
Flow-mediated dilatation	FMD	Endothelial function	Smaller percentage increase in the diameter of the brachial artery following cuff release after suprasystolic occlusion
Peripheral arterial tonometry	PAT	Endothelial function	Smaller pulse volume increase in the digital arteries following cuff release after suprasystolic brachial artery occlusion
Pulse wave velocity	PWV	Arterial stiffness	Increased pulse wave velocity

Chen et al. *Acta Paediatrica*, 2016

- Subgrupo com hx AAC → alterações vasculares estruturais persistentes, disfunção endotelial e ↑rigidez arterial; dados inconsistentes relativamente a diferenças entre regressão e não regressão dos AAC (estudos em pequenos grupos)
- Subgrupo sem hx AAC → cIMT semelhante, alguns dados apontam disfunção endotelial e ↑rigidez arterial.
- As implicações a longo prazo destes achados subclínicos não são claras, particularmente porque estas ferramentas foram desenvolvidas para estudar aterosclerose e não DK

CONCLUSÕES

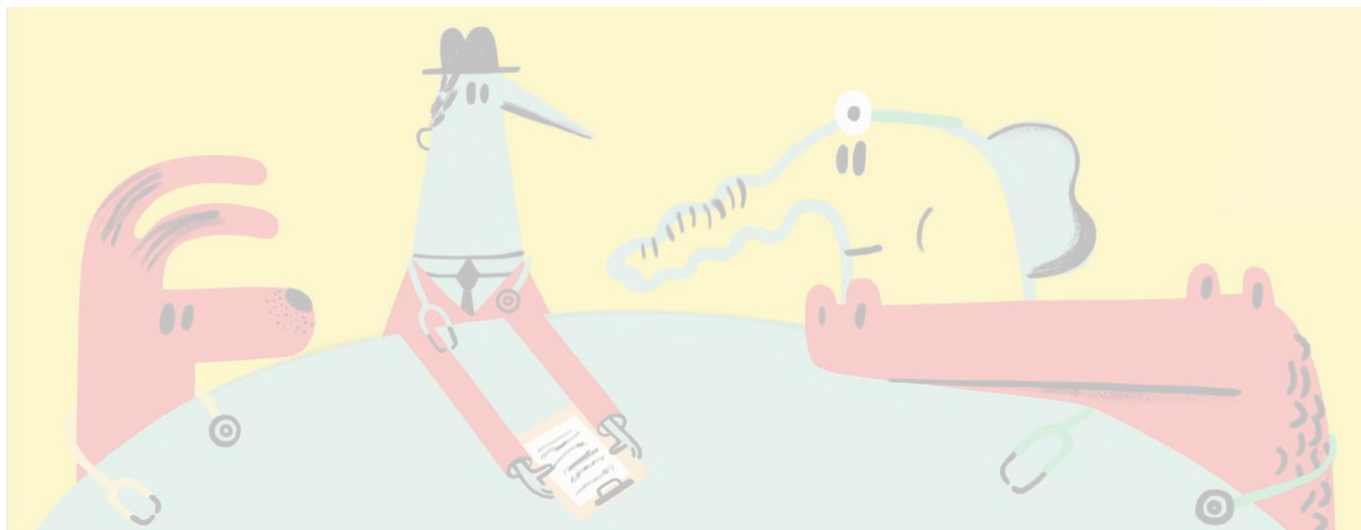
- A Doença de Kawasaki é a 2ª vasculite mais frequente da infância
- A ativação do inflamossoma NLRP3 parece ser fulcral na patofisiologia da DK
 - Papel promissor dos inibidores IL-1 → ensaios em curso; casos reportados de sucesso
- O diagnóstico pode ser difícil, especialmente nos casos incompletos, e assenta fundamentalmente numa avaliação clínica criteriosa e sequencial
 - Biomarcadores validados e amplamente disponíveis serão extremamente úteis
- A complicação mais temida são os aneurismas das artérias coronárias (AAC)
 - Resistência à IGIV é o maior fator de risco
 - Mais frequente nos extremos etários

CONCLUSÕES



- O tratamento inclui IGIV, AAS (não reduz AAC) e corticoterapia nos casos de alto risco
 - Não existem *scores* de risco validados
 - Julgamento clínico informado na seleção de doentes
- Nos casos resistentes à IGIV pode considerar-se
 - Corticoterapia
 - Repetir IGIV
 - Infliximab
 - Anakinra ?
 - ...
- O prognóstico depende fundamentalmente de um diagnóstico precoce e tratamento assertivo

- Resistência à IGIV
- Doença grave: <12 meses, marcadores de inflamação severa (PCR persistentemente elevada após IGIV, disfunção hepática, hipoalbuminemia, hiponatremia, anemia, ausência de trombocitose)
- Choque ou evolução para SAM
- Atingimento coronário ou aneurismas periféricos ao diagnóstico



OBRIGADA

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