NOVEDADES EN LA ENFERMEDAD DE KAWASAKI

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Hospital de Sabadell, Parc Taulí

Un poco de historia...

1960s	Descripción EK Tomisaku Kawasaki
1970s	Japón 10 casos muerte por infarto de miocardio
1980s	cateterismo cardíaco, ecocardiografía --- aneurismas
1985	IVIG, reducción de aneurismas
1990s	No todos los pacientes responden a IVIG

Cuál es la causa de la EK?
Qué otros tratamientos utilizar?
Qué pasará con los pacientes que sobreviven?

Novedades

1. Etiopatogenia
   - Búsqueda del agente etiológico
   - Susceptibilidad Genética
2. Tratamiento
3. Evolución a largo plazo

Novedades en la etiopatogenia

"Teoría de la infección en paciente genéticamente predispuesto"

Datos a favor de la infección

- A favor de la infección:
  - Manifestaciones clínicas y analíticas
  - Edad: 6m-5a
  - Epidemias, predominio invierno-primavera

- Pero en 50 años de investigación, todavía no se ha identificado el agente causal

Table 1 | **Aetiological agents postulated for Kawasaki disease**

Postulated agent	Proposed pathogenesis	Current status	Refs
Mercury	Direct toxic effect	Lack of supporting evidence	98
Rickettsia-like agent	Infection of macrophages and/endothelial cells	Lack of supporting evidence	36
Propriobacterium acnes	Infection of macrophages and/endothelial cells	Lack of supporting evidence	35
Rug shampoo	Aerosolization of mites or a direct toxic effect	Lack of supporting evidence	37–39
Leptospira spp.	Infection of endothelial cells	Lack of supporting evidence	99
Streptococcus sanguis	Infection or toxin effect	Lack of supporting evidence	100
Retrovirus	Infection of lymphocytes	Lack of supporting evidence	40–43
Epstein–Barr virus or cytomegalovirus	Infection of various cell types	Lack of supporting evidence	101,102
Toxic shock syndrome toxin 1 (TSST1)	Superantigen-induced immune response	Not confirmed by follow-up studies	44–46
Bacterial toxin other than TSST1	Superantigen-induced immune response	Lack of supporting evidence; still under investigation	72–74
Coronavirus NL-63	None	Not confirmed by follow-up studies	47–49
Human bocavirus	None	Reported by one group; currently unconfirmed	50
Previously unrecognized persistent RNA virus	Infection of targeted cells with antigen-driven immune response; cytoplasmic inclusion bodies are formed and can persist	Under investigation	17–22, 87

"Teoría de la infección en paciente genéticamente predispuesto"

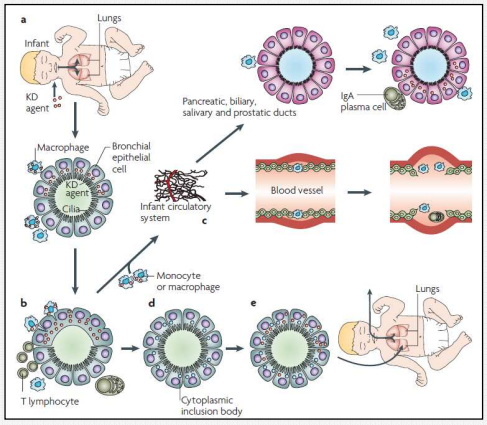
Datos a favor de la infección

- Teoría del super-antígeno/ toxina bacteriana
  - Descamación (escarlatina, SST)
  - Expansión selectiva de familias Vβ del receptor de células T
  - Citoquinas en sangre periférica

- No es específico de la respuesta a un superantígeno
- No se ha podido comprobar

"Teoría de la infección en paciente genéticamente predispuesto"
Datos a favor de la infección

- Estudios recientes
  - Células plasmáticas IgA en tejidos inflamados (arterias, TRS, riñón…)
  - La presencia de lf B IgA y lf T CD8 sugieren la respuesta inmune a un patógeno intracelular (virus) con puerta de entrada respiratoria

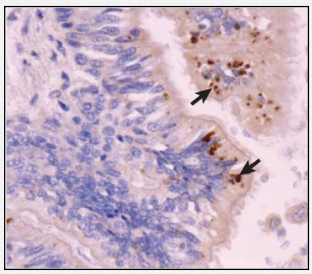


- *El agente EK se inhala e infecta las células epiteliales bronquiales ciliadas*
- *Macrófagos fagocitan al agente y activan respuesta inmune*
- *Las cel. Bronquiales son infiltradas por Mϕ, lfT i cel plasmáticas IgA*
- *Ag es trasladado a sangre periférica y tejidos diana*
- *En las cél bronquiales queda los cuerpos de inclusión citoplasmáticos*

Rowley AH, Baker SC, Orenstein JM, Shulman ST. Searching for the cause of Kawasaki disease—cytoplasmic inclusion bodies provide new insight. Nature Reviews Microbiology 2008; 6: 394-401.

"Teoría de la infección en paciente genéticamente predispuesto"
Datos a favor de la infección

- Por ME han identificado cuerpos de inclusión citoplasmáticos:
  - Agregados de proteínas virales y ácidos nucleídos
  - RNA
  - "Nuevo" virus RNA ???



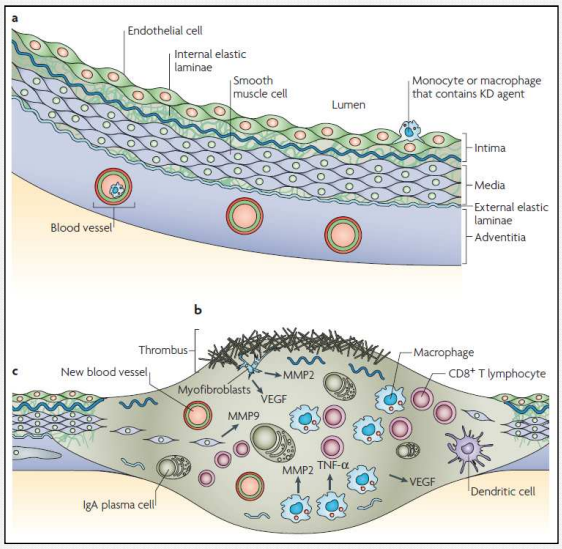
Futuro: Posibilidad de secuenciación y bioinformática para identificar el posible agente causal

Rowley AH. Kawasaki Disease: Novel insights into etiology and genetic susceptibility. Annu Rev Med 2011.62

"Teoría de la infección en paciente genéticamente predispuesto"

Datos a favor de la infección

- Mecanismo por el que se producirían los aneurismas

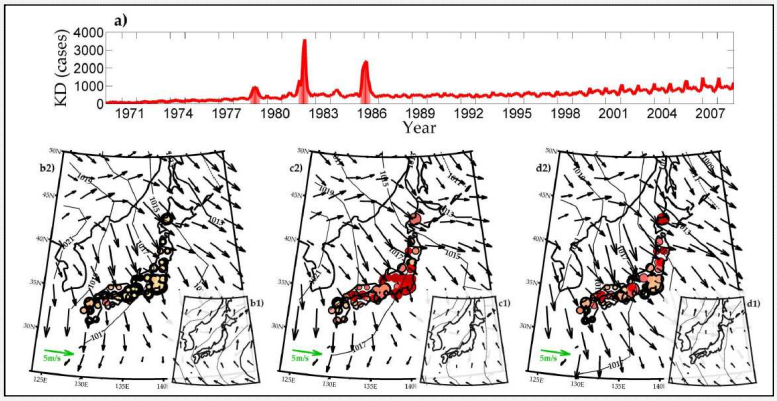


- *Monocitos y Mϕ circulantes (con el agente EK) se adhieren a las cél endoteliales y a través de vasa vasorum penetran a la adventicia*
- *Activa más monocitos y Mϕ – estos segregan VEFG, MMP, TNF, citoquinas*
- *Activación de lf T CD8+ y cel B IgA*

"Teoría de la infección en paciente genéticamente predispuesto"

Datos a favor de la infección

- Teoría de la transmisión por vientos troposféricos



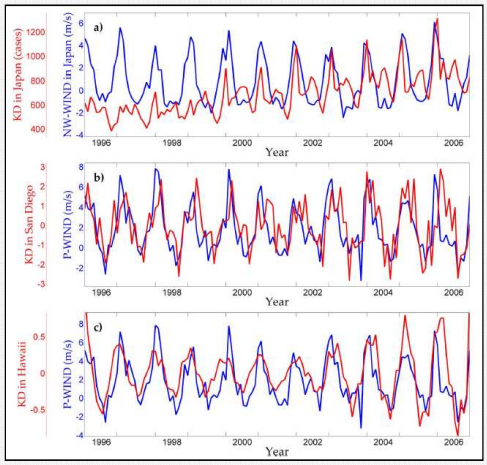
Vientos del noroeste relacionados con alta incidencia de EK en Japón

Medidas atmosféricas y oceanográficas, que relacionan los patrones de pressión con el viento de superfície a capas troposféricas

Rodó X, Ballester J, Cayan D, Melish M, Nakamura Y, Uehara R, Burns J. Association of Kawasaki disease with tropospheric wind patterns. Sci Rep. 2011. 1, 152

"Teoría de la infección en paciente genéticamente predispuesto"
Datos a favor de la infección

- Teoría de la transmisión por vientos troposféricos



Estacionalidad (Nov-Mar)
EK y vientos de superficie

Rodó X, Ballester J, Cayan D, Melish M, Nakamura Y, Uehara R, Burns J. Association of Kawasaki disease with tropospheric wind patterns. Sci Rep. 2011. 1, 152

"Teoría de la infección en paciente genéticamente predispuesto"
Datos a favor de la predisposición genética

- A favor de la predisposición genética:
  - Prevalencia elevada en Asia (Japón)
  - Mayor riesgo en hermanos e hijos de pacientes con EK

- Durante décadas se ha intentado buscar los genes que conferirían una susceptibilidad a padecer EK
  - estudios con pocos números de casos
  - no permitían confirmar los hallazgos en otras cohortes

"Teoría de la infección en paciente genéticamente predispuesto"
Datos a favor de la predisposición genética

- En los últimos años estudios "Genome-wide"

1. Población Japón
   - Estudio de GW en hermanos con EK y padres sanos
   - Identifica 10 loci que parecen asociados a susceptibilidad para padecer EK

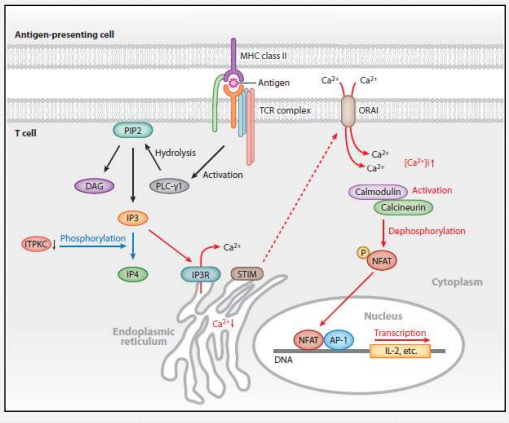
Onouchi Y, Tamari M, Takahashi A et al. A genome-wide linkage analysis of Kawasaki disease: evidence for linkage to chromosome 12. J Hum Genet. 2007. 52:179

2. Población caucásica
   - Identifica 8 loci asociados a susceptibilidad para EK

Burgner D, Davila S, Breunis WB et al. A genome-wide association study identifies novel and functionally related susceptibility loci for Kawasaki disease. PLoS Genet. 2009 5: e1000319

"Teoría de la infección en paciente genéticamente predispuesto"
Datos a favor de la predisposición genética

– SNPs *1,4,5-triphosphate 3-kinase C* (***ITPKC***)



- La actividad reducida de *ITPKC* en EK produciría una aumento de la activación de lf T y una respuesta inflamatoria exagerada
- Asociado a susceptibilidad de EK y formación de aneurismas en la población japonesa y en una cohorte US

Onouchi Y, Gunji T, Burns JC et al 2008. ITPKC functional polymorphism associated with kawasaki disease susceptibility and formation of coronary artery aneurysms. Nat. Genet. 40: 35-42

"Teoría de la infección en paciente genéticamente predispuesto"
Datos a favor de la predisposición genética

Genome-wide association study identifies *FCGR2A* as a susceptibility locus for Kawasaki disease

Chiea Chuen Khor[1–3,73], Sonia Davila[2,4,73], Willemijn B Breunis[5,6,73], Yi-Ching Lee[7], Chisato Shimizu[8,9], Victoria J Wright[10], Rae S M Yeung[11–13], Dennis E K Tan[4], Kar Seng Sim[4], Jie Jin Wang[14,15], Tien Yin Wong[14,16,17], Junxiong Pang[1,18], Paul Mitchell[14], Rolando Cimaz[19,20], Nagib Dahdah[21], Yiu-Fai Cheung[22], Guo-Ying Huang[23], Wanling Yang[22], In-Sook Park[24], Jong-Keuk Lee[25], Jer-Yuarn Wu[7], Michael Levin[10,74], Jane C Burns[8,9,74], David Burgner[26,27,74], Taco W Kuijpers[5,6,74], Martin L Hibberd[1,3,74], Hong Kong–Shanghai Kawasaki Disease Genetics Consortium[72], Korean Kawasaki Disease Genetics Consortium[72], Taiwan Kawasaki Disease Genetics Consortium[72], International Kawasaki Disease Genetics Consortium[72], US Kawasaki Disease Genetics Consortium[72] & Blue Mountains Eye Study[72]

- GWAS
  - 2173 pacientes con EK
  - 9383 controles
- Identifica
  - Locus nuevo *FCGR2A*
  - Confirma asociación *ITPKC*

Futuro en etiopatogenia

1. Definir las proteínas y ácidos nucleídos en los cuerpos de inclusión citoplasmáticos de EK
   a. Identificación del agente etiológico. Posibilidad de:
      - Test diagnóstico
      - Mejorar tratamiento
      - Vacuna
2. Definir los genes que confieren susceptibilidad a padecer EK y un mayor riesgo de desarrollar aneurismas coronarios
   a. Prevención y nuevas terapias génicas

Novedades en el tratamiento

No todos los pacientes responden a IVIG...

Pediatr Infect Dis J. 2001 Jun;20(6):635-7.

Response of refractory Kawasaki disease to pulse steroid and cyclosporin A therapy.

Raman V, Kim J, Sharkey A, Chatila T.

Division of Cardiology, Immunology and Rheumatology, St. Louis Children's Hospital, MO, USA.

Case Report

Infliximab as a Novel Therapy for Refractory Kawasaki Disease

JENNIFER E. WEISS, B. ANNE EBERHARD, DEVYANI CHOWDHURY, and BETH S. GOTTLIEB

The Journal of Rheumatology 2004; 31:4

ardio

eurismas

Letters to the Editor

Efficacy of infliximab in long-lasting refractory Kawasaki disease

Nihon Rinsho Meneki Gakkai Kaishi. 1995 Jun;18(3):282-8.

[Coronary arteritis of Kawasaki disease unresponsive to high-dose intravenous gammaglobulin successfully treated with plasmapheresis].

[Article in Japanese]

Mori M, Tomono N, Yokota S.

Department of Pediatrics, Yokohama City University School of Medicine.

Yonsei Med J. 2002 Aug;43(4):527-32.

A case of intravenous immunoglobulin-resistant Kawasaki disease treated with methotrexate.

Lee MS, An SY, Jang GC, Kim DS.

Department of Pediatrics, Yonsei University College of Medicine, C.P.O. Box 8044, Seoul 120-752, Korea. drmslee@freechal.com

J Pediatr. 2000 Nov;137(5):723-6.

Treatment of severe complicated Kawasaki disease with oral prednisolone and aspirin.

Dale RC, Saleem MA, Daw S, Dillon MJ.

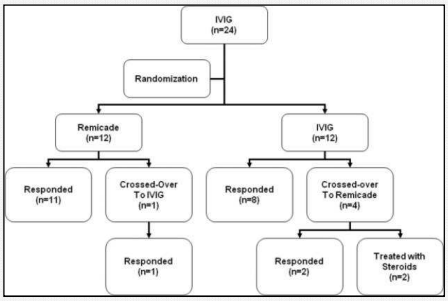
Great Ormond Street Hospital for Children, London, England.

Estudios con infliximab

Infliximab treatment of intravenous immunoglobulin-resistant Kawasaki disease

Jane C. Burns, M.D.[1], Brookie M. Best, Pharm.D., M.A.S.[1,2], Asuncion Mejias, M.D.[3], Lynn Mahony, M.D.[3], David E. Fixler, M.D.[3], Hasan S. Jafri, M.D.[3], Marian E. Melish, M.D.[4], Mary Anne Jackson, M.D.[5], Basim I. Asmar, M.D.[6], David J. Lang, M.D.[7], James D. Connor, M.D.[1], Edmund V. Capparelli, Pharm.D.[1], Monica L. Keen, B.S.[8], Khalid Mamun, B.S.[8], Gregory F. Keenan, M.D.[8], and Octavio Ramilo, M.D.[3]
SD and WFB
J Pediatr. 2008 December ; 153(6): 833–838. doi:10.1016/j.jpeds.2008.06.011.

Estudio multicéntrico prospectivo randomizado



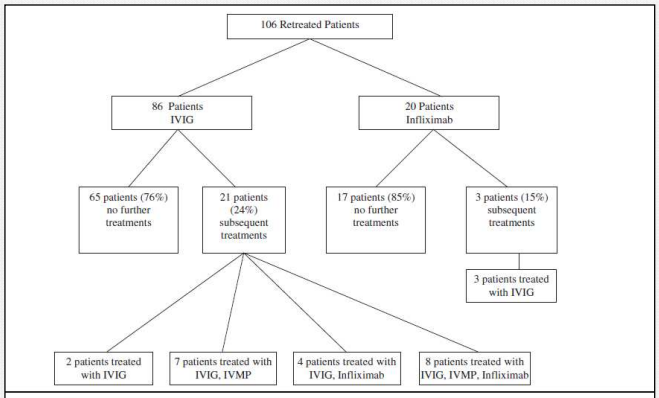
- Infliximab es seguro y bien tolerado en pacientes con EK (no se observaron EA atribuibles a ninguno de los grupos terapéuticos)
- Estudio de farmacocinética de infliximab. Similar independiente de la edad
- No muestra suficiente para valorar efectividad
- Puerta abierta de infliximab como tratamiento para EK resistente a IVIG

Estudios con infliximab

Infliximab for Intravenous Immunoglobulin Resistance in Kawasaki Disease: A Retrospective Study

Mary Beth Son, MD, Kimberlee Gauvreau, ScD, Jane C. Burns, MD, Elena Corinaldesi, MD, Adriana H. Tremoulet, MD, MAS, Virginia E. Watson, MD, Annette Baker, RN, MSN, PNP, David R. Fulton, MD, Robert P. Sundel, MD, and Jane W. Newburger, MD, MPH
J Pediatr 2011;158:644-9,

Estudio dos centros retrospectivo, comparando:
- **duración de fiebre**
- **tamaño de AC**



Therapeutic regimens for patients with KD requiring re-treatment after receiving IVIG (2 g/kg) as primary therapy.

Estudios con infliximab

Infliximab for Intravenous Immunoglobulin Resistance in Kawasaki Disease: A Retrospective Study

Mary Beth Son, MD, Kimberlee Gauvreau, ScD, Jane C. Burns, MD, Elena Corinaldesi, MD, Adriana H. Tremoulet, MD, MAS, Virginia E. Watson, MD, Annette Baker, RN, MSN, PNP, David R. Fulton, MD, Robert P. Sundel, MD, and Jane W. Newburger, MD, MPH

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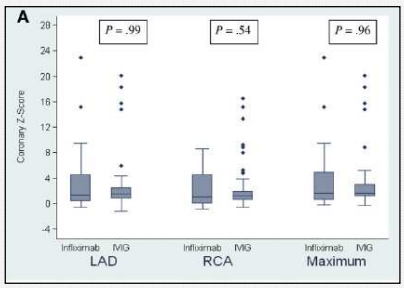
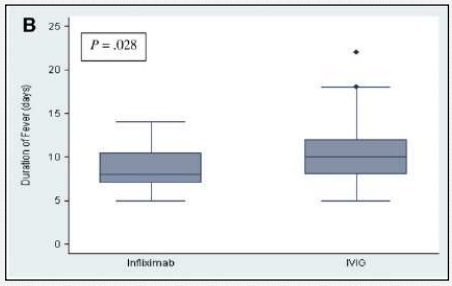




La estrategia de administrar infliximab, comparado con IVIG, como primer re-tratamiento:
- se asoció a menos días de fiebre y estancia hospitalaria
- no mejoró la afectación coronaria

Estudios con infliximab

- Estudio de dos centros, randomizado, doble ciego, placebo control.
- 200 pacientes- randomizados a:
  - IVIG + INF
  - IVIG + placebo
- Objetivos:
  1. Porcentaje de pacientes que persisten con fiebre 24h después de IVIG
  2. Nº días de fiebre, valores hemoglobina, marcadores inflamación, z score AC
- Determinar si añadiendo infliximab al tratamiento con IVIG puede reducir el % de pacientes resistentes al tratamiento.

Corticoides

- **Corticoides como terapia inicial (+IVIG)**

Table 1 Summary of patients receiving corticosteroids in initial treatment

	Study	Patient characteristics					Aspirin	IVIG		Corticosteroid		
		Total patients	Therapy group	Sex (male %)	Age (year)	Therapy day	mg/kg per day	g/kg per dose	No. of doses	Drug preparation	Dosage (mg/kg per day)	Duration of therapy (days)
2007	Newburger et al. [17]	199	101	62	2.9	10	80–100	2	1	IVMP	30	1
2006	Inoue et al. [8]	178	90	57.3	4.5	9	30	1	2	Pred	2	3
	Okada et al. [21]	32	14	56.3	2.8	9	30	1	2	Pred	2	3
	Sundel et al. [25]	39	18	69		10	20–25	2	1	IVMP	30	1
2009	Okada et al. [20]	94	62	77.4	2.8	6	30	2	1	IVMP	30	1
	Jibiki et al. [10]	92	46	48.9	2.3	7	30	0.4 or 0.5	4–5	Dex	0.3	3
	Shinohara et al. 1 [22]	212	170	–	–	9	30	0	0	Pred	2	Defervescence
	Shinohara et al. 2 [22]	87	62	–	–	9	30	0.2 or 0.4	5	Pred	2	Defervescence

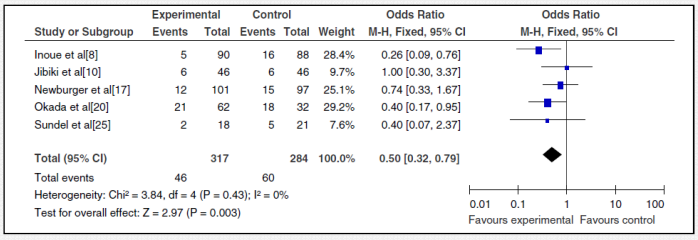
IVMP intravenous methylprednisone, *Pred* prednisolone

Inoue: combinación IVIG+pred mejoró el curso clínico y pronóstico de AC sin EA
Newb: no muestra ventajas el añadir MP al trat clásico (similar hospit, retratamiento y EA)

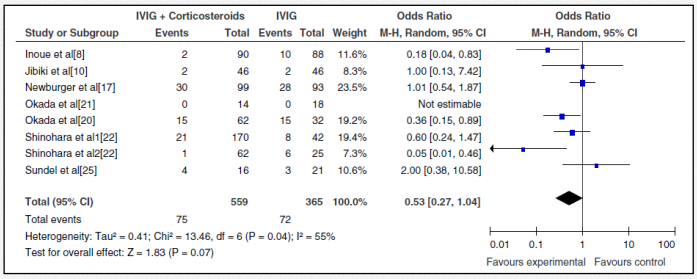
Zhu B, Hai-tao L et al. A meta-analysis on the effect of corticosterois therapy in Kawasaki disease. Eur J Pediatr 2011

Corticoides

- **Corticoides como terapia inicial (+IVIG)**



Respuesta al tratamiento



Incidencia aneurismas

Zhu B, Hai-tao L et al. A meta-analysis on the effect of corticosterois therapy in Kawasaki disease. Eur J Pediatr 2011

Corticoides

Eur J Pediatr (2009) 168:181–185
DOI 10.1007/s00431-008-0727-9

ORIGINAL PAPER

Pulse methylprednisolone with gammaglobulin as an initial treatment for acute Kawasaki disease

Keiko Okada · Junichi Hara · Ichiro Maki · Kazunori Miki · Kouji Matsuzaki · Taro Matsuoka · Takehisa Yamamoto · Toshinori Nishigaki · Syunji Kurotobi · Tetsuya Sano · For the Osaka Kawasaki Disease Study Group

MP + IVIG	IVIG	
n 62 (high risk KD)	n 32 (high risk historical)	
66% response	44% response	p= 0.048
24.2% C lesions	46.9% C lesions	p= 0.025
3.2% CAA	25% CAA	p= 0.02

Corticoides

- **Cortidoides como terapia de rescate**

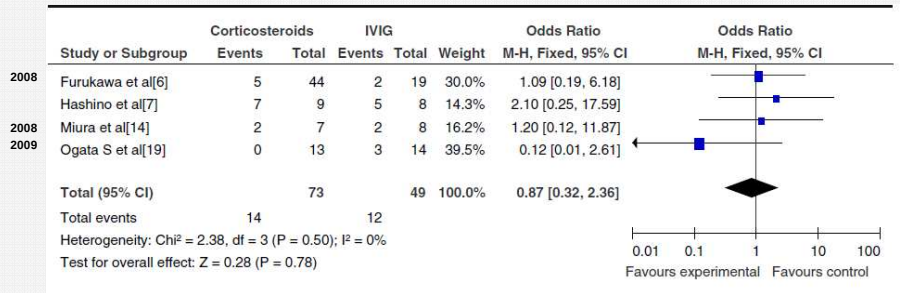


Fig. 2 The incidence of coronary artery lesions following failure of primary treatment and after secondary treatment. Secondary treatment consisted of either corticosteroids or a second round of IVIG

Ogata: diferencias significativas en duración de fiebre y costes médicos, pero no en CAA

Zhu B, Hai-tao L et al. A meta-analysis on the effect of corticosterois therapy in Kawasaki disease. Eur J Pediatr 2011

Novedades respecto al pronóstico a largo plazo

Recomendaciones de seguimiento de pacientes con EK

Risk Level	Pharmacological Therapy	Physical Activity	Follow-Up and Diagnostic Testing	Invasive Testing
I (no coronary artery changes at any stage of illness)	None beyond 1st 6–8 weeks	No restrictions beyond 1st 6–8 weeks	Cardiovascular risk assessment, counseling at 5-y intervals	None recommended
II (transient coronary artery ectasia disappears within 1st 6–8 weeks)	None beyond 1st 6–8 weeks	No restrictions beyond 1st 6–8 weeks	Cardiovascular risk assessment, counseling at 3- to 5-y intervals	None recommended
III (1 small-medium coronary artery aneurysm/major coronary artery)	Low-dose aspirin (3–5 mg/kg aspirin per day), at least until aneurysm regression documented	For patients <11 y old, no restriction beyond 1st 6–8 weeks; patients 11–20 y old, physical activity guided by biennial stress test, evaluation of myocardial perfusion scan; contact or high-impact sports discouraged for patients taking antiplatelet agents	Annual cardiology follow-up with echocardiogram + ECG, combined with cardiovascular risk assessment, counseling; biennial stress test/evaluation of myocardial perfusion scan	Angiography, if noninvasive test suggests ischemia
IV (≥1 large or giant coronary artery aneurysm, ormultiple or complex aneurysms in same coronary artery, without obstruction)	Long-term antiplatelet therapy and warfarin (target INR 2.0–2.5) or low-molecular-weight heparin (target: antifactor Xa level 0.5–1.0 U/mL) should be combined in giant aneurysms	Contact or high-impact sports should be avoided because of risk of bleeding; other physical activity recommendations guided by stress test/evaluation of myocardial perfusion scan outcome	Biannual follow-up with echocardiogram + ECG; annual stress test/evaluation of myocardial perfusion scan	1st angiography at 6–12 mo or sooner if clinically indicated; repeated angiography if noninvasive test, clinical, or laboratory findings suggest ischemia; elective repeat angiography under some circumstances (see text)
V (coronary artery obstruction)	Long-term low-dose aspirin; warfarin or low-molecular-weight heparin if giant aneurysm persists; consider use of β-blockers to reduce myocardial O_2 consumption	Contact or high-impact sports should be avoided because of risk of bleeding; other physical activity recommendations guided by stress test/myocardial perfusion scan outcome	Biannual follow-up with echocardiogram and ECG; annual stress test/evaluation of myocardial perfusion scan	Angiography recommended to address therapeutic options

Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Statement for Health Professionals From the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association

Jane W. Newburger, Masato Takahashi, Michael A. Gerber, Michael H. Gewitz, Lloyd Y. Tani, Jane C. Burns, Stanford T. Shulman, Ann F. Bolger, Patricia Ferrieri, Robert S. Baltimore, Walter R. Wilson, Larry M. Baddour, Matthew E. Levison, Thomas J. Pallasch, Donald A. Falace and Kathryn A. Taubert

Pediatrics 2004;114;1708-1733
DOI: 10.1542/peds.2004-2182

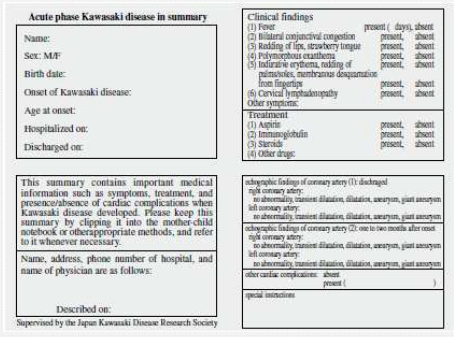
Recomendaciones de seguimiento de pacientes con EK

Severity	Pathophysiology	Diagnosis / clinical course	Treatment	Daily life/exercise management*
I No dilatation	There is no evidence whether or not a history of Kawasaki disease is a factor associated with arteriosclerotic lesion.	Follow up patients for 5 years. Evaluate at 30 days, 60 days, 6 months, 1 year, and 5 year after onset with ECG, echocardiography, and, if necessary, chest X-ray. It is desirable that patients be evaluated with exercise ECG at the final examination.	Basically, no treatment is required during the remote phase. Patients with no coronary aneurysms after the acute phase may discontinue antiplatelet drugs such as aspirin.	No restriction is placed on daily life or exercise. Management Table: "No management needed" for children ≥5 years after onset. Consult with parents (or patients) to determine further management. Lifetime prevention of lifestyle-related diseases is important. Junior and senior high school students should be educated on lifestyle-related diseases (blood lipid measurement, education on smoking cessation, and prevention of obesity).
II Transient dilatation during the acute phase	During the acute phase, histopathologically vasculitis develops in the outer layer of the tunica media and then expands to the intima in coronary arteries. Echocardiography reveals diffuse dilatation of coronary arteries, but these changes subside within 30 days after onset.			
III Regression	In many cases regression may occur 1 to 2 years after onset, particularly in small or medium aneurysms. In the segment with regression, decrease in coronary diastolic function, abnormal function of vascular endothelium, and substantial intimal hyperplasia have been reported.	Basically, follow patients annually with ECG, echocardiography, and chest X-ray up to entry into elementary school (age of 6, 7), and then with the same methods and exercise ECG in 4th grade (age 9, 10), at entry into junior high school (age 12, 13), and entry into senior high school (age 15, 16). Follow patients who had coronary aneurysms with a large internal diameter during the acute phase with an appropriate combination of imaging techniques**.		No restriction is placed on daily life or exercise. Follow the recommendations for Categories I and II.
IV Remaining coronary aneurysms	Aneurysms remaining during the convalescence phase or later are considered sequelae. Histopathologically, progression of inflammation leads to rupture of the internal elastic band, causing panargiitis. The internal and external elastic bands are broken into fragments and ruptured by arterial pressure to form aneurysms. Patients with giant aneurysms must be observed carefully for myocardial ischemia, since in such patients myocardial ischemia may develop even if no significant stenotic lesions are present.	Patients must be followed with exercise ECG and an appropriate combination of imaging techniques.** It is desirable that patients who had coronary aneurysms with a large internal diameter during the acute phase be evaluated with stress myocardial scintigraphy every 2 to 5 years to monitor for progression to stenotic lesions.	Continue treatment with antiplatelet agents such as aspirin. Anticoagulant therapy may be needed in patients with giant coronary aneurysms or thrombi in coronary aneurysms. CABG may be indicated for patients with giant coronary aneurysms not accompanied by significant stenotic lesions when myocardial ischemia has occurred.	No restriction is placed on daily life or exercise. Management Table: "E-allowed". Patients with giant aneurysms: Instruct as "D-prohibited" in the Management Table. In the second year after onset or later, "E-prohibited" is possible when no changes are noted.
V-a Coronary stenotic lesions (no findings of ischemia)	Thrombotic occlusion of medium or giant aneurysms may develop during the relatively early stage after onset. Sudden death may occur, though two-thirds patients with occlusion are asymptomatic. Patients often show improvement of myocardial ischemia due to the development of recanalized vessels and collateral flow after occlusion. Development/progression of regional stenosis during the remote phase is more prevalent in the left coronary artery than in the right coronary artery. The segments with greatest prevalence are the proximal segment or the main trunk of the left anterior descending artery. The risk of progression to stenosis/occlusion is higher in larger aneurysms. Stenosis may develop during long-term follow up.	Patients must be followed for life, and physicians must design the tailor-made management plan for individual patients. Follow-up examination must include exercise ECG and an appropriate combination of imaging techniques**. Although schedule may differ among individuals, patients are generally evaluated every 3 to 6 months.	Continue treatment with antiplatelet drugs such as aspirin. Use Ca-blockers, nitrates, β-blockers, ACE inhibitors, and angiotensin receptor II blockers to prevent ischemic attacks and heart failure.	No restriction is placed on daily life or exercise. Management Table: "E-allowed" for patients other than those with giant aneurysms. Explain the importance of drug treatment and ensure adherence, as well as symptoms which may occur and actions to be taken when ischemia develops. Patients must be followed at least annually until regression of aneurysms is documented.
V-b Coronary stenotic lesions (with findings of ischemia)			Follow the instructions for drug treatment in Category V-a. Consider CABG or appropriate PCI technique when exercise ECG or stress myocardial scintigraphy reveals ischemia.	Exercise should be restricted. Categorize in "D" or higher category based on patient condition. School sport club activities should be "prohibited". Select the most appropriate category from "A" to "D" on the basis of findings of exercise testing and evaluation of severity of myocardial ischemia. Educate patients well about the importance of drug treatment.

Guidelines for Diagnosis and Management of Cardiovascular Sequelae in Kawasaki Disease (JCS 2008)
– Digest Version –
JCS Joint Working Group

Pacientes con EK sin lesión coronaria o transitoria

- Son la mayoría de pacientes!
- Intentar de alguna manera (coste médico y psicológico/beneficio) mantener "atados" al sistema de salud:
  - Visitas (+/- exploraciones) periódicas
  - Registros
  - Informe o tarjeta resumen



Acute phase Kawasaki disease in summary

Name:
Sex: M/F
Birth date:
Onset of Kawasaki disease:
Age at onset:
Hospitalized on:
Discharged on:

Clinical findings
(1) Fever present (days), absent
(2) Bilateral conjunctival congestion present, absent
(3) Rudding of lips, strawberry tongue present, absent
(4) Polymorphous exanthema present, absent
(5) Indurative erythema, rudding of palms/soles, membranous desquamation from fingertips present, absent
(6) Cervical lymphadenopathy present, absent
Other symptoms:

Treatment
(1) Aspirin present, absent
(2) Immunoglobulin present, absent
(3) Steroids present, absent
(4) Other drugs:

This summary contains important medical information such as symptoms, treatment, and presence/absence of cardiac complications when Kawasaki disease developed. Please keep this summary by clipping it into the mother-child notebook or otherappropriate methods, and refer to it whenever necessary.

Name, address, phone number of hospital, and name of physician are as follows:

Described on:

echographic findings of coronary artery (1): discharged
right coronary artery:
no abnormality, transient dilatation, dilatation, aneurysm, giant aneurysm
left coronary artery:
no abnormality, transient dilatation, dilatation, aneurysm, giant aneurysm
echographic findings of coronary artery (2): one to two months after onset
right coronary artery:
no abnormality, transient dilatation, dilatation, aneurysm, giant aneurysm
left coronary artery:
no abnormality, transient dilatation, dilatation, aneurysm, giant aneurysm
other cardiac complications: absent
present ( )
special instructions

Supervised by the Japan Kawasaki Disease Research Society

- Prevención de riesgo coronario:
  - Lesión vascular de la EK es diferente a la de la aterosclerosis por otras causa

Novedades en la Enfermedad de Kawasaki

- **Todavía no conocemos la causa de la EK**
  - Aunque parece que cada vez estamos más cerca
- **Porqué algunos pacientes no responden a IVIG y qué tratamiento deberían recibir?**
  - Estudios en marcha
- **Qué pasará con los pacientes con EK que no tienen lesiones cardíacas?**
  - Próximos años