

Jornada de Reumatología Pediátrica

REUMATOLOGÍA PARA TODOS LOS PÚBLICOS

16 de mayo de 2018

Hospital General de Villalba



Hospital General de Villalba



CASO CLÍNICO

Dra. María de la Parte
Cardiología infantil

Caso clínico

FIEBRE 48h

ADENOPATÍA CERVICAL

IRRITABILIDAD

Caso clínico

Analítica:

- Leucocitos: 11,420/ul (Nt 8,400 uL), Hb 9,4 g/dl.
- GPT **68** UI/L, GOT **60** UI/L, albúmina **2,6** g/dl.
- PCR: **30,80** mg/dl.
- VSG: **57 mm/h**
- Sistemático de orina: normal. Sedimento: ligera piuria.
- Serologías, cultivo sangre y orina pendiente

Evolución planta I

- JC: Adenitis cervical
- Ingresa con Amoxicilina-Clavulánico 100 mg/kg/día IV
- 3er día, persiste **fiebre**.

Aparece...

Conjuntivitis no purulenta, fisuración labios, edemas en pies y exantema con descamación en área genital.

ProBNP 2520 pg/ml.

**Enfermedad de
Kawasaki**

Evolución planta II

- Tratamiento día +5:
 - IGIV 2 g/kg
 - AAS a dosis antiinflamatorias (80 mg/kg/día)


- Ecocardiograma (día +6):
 - Ectasias coronarias múltiples.
 - Resto normal.

Evolución planta III

- **Reaparece fiebre**

- Segunda dosis de IgG a 2 g/kg

- **Reaparece fiebre**

 ¿Corticoides VS Infliximab?

Ciclo de megabolos de CC IV (30 mg/kg) + pauta de mantenimiento CC VO.

- **Desaparece la fiebre (día +10)**

Evolución día +14

- Clínica:
 - Descamación de manos y pies
 - Aparición nuevo exantema
 - Regresión adenopatía
- Analítica:
 - Trombocitosis: $1,467 \times 10$
 - GOT 100, GPT 75
 - VSG 22 mm/h
 - Descenso ProBNP (343 pg/ml)
 - Descenso PCR (1,1 mg/dl)
 - Troponinas negativas

Evolución cardiaca día +14

- ECG: ESV
- Derrame pericárdico leve
- Insuficiencia tricúspide leve
- Función biventricular normal
- Dilatación coronaria **progresiva**
- Se inicia anticoagulación con Clexane 1 mg/kg/dosis sc

TRASLADO A
HOSPITAL LA PAZ

ENFERMEDAD
DE
KAWASAKI

Circulation

Circulation. 2017;135:00–00.

Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease

**A Scientific Statement for Health Professionals From the American Heart
Association**

España: Estudio KAWA-RACE

- ✓ Multicéntrico nacional
- ✓ Prospectivo y retrospectivo (2011-2016; n: 625)
- ✓ Factores epidemiológicos, clínicos, analíticos y microbiológicos:
 - Respuesta tratamiento
 - Riesgo desarrollo aneurismas

Documento de Consenso Nacional sobre diagnóstico, tratamiento y seguimiento cardiológico de la enfermedad de Kawasaki (pendiente publicación)



*Sociedad Española de Cardiología
Pediátrica y Cardiopatías Congénitas*



**SOCIEDAD ESPAÑOLA DE
REUMATOLOGÍA PEDIÁTRICA**

Introducción

- Vasculitis aguda autolimitada vasos pequeño y mediano calibre.
- Causa más común enfermedad cardíaca adquirida en niños en países desarrollados.
- Segunda causa de vasculitis en la infancia.
- Afectación coronaria: 25% no tratados; 4% tratados
- 85% **menores 5 años** (pico incidencia **18-24 meses**)
- Ratio ♂:♀ **1,5-2,1:1**
- Invierno-primavera

Hipótesis etiológica

- “Respuesta **inmune patológica** y estereotipada ante uno o varios **factores ambientales o infecciosos** en individuos **genéticamente predispuestos**”

Patogenia

Inflamación sistémica

- Hepatitis
- Neumonitis intersticial
- Afectación GI (abdominalgia, vómitos, diarrea, hidrops vesícula biliar...)
- Meningitis aséptica
- Cardíacas: miocarditis, pericarditis, valvulopatía
- Piuria estéril
- Pancreatitis
- Linfadenopatía
- Artritis

Diagnóstico EK COMPLETO

CRITERIOS CLÍNICOS

Apoyan:

- Marcadores de inflamación elevados (PCR/VSG)
- Hiponatremia
- Hipoalbuminemia
- Hipertransaminasemia
- Piuria estéril
- En la segunda semana: trombocitosis

NT-proB-NP

AHA SCIENTIFIC STATEMENT

Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease

**A Scientific Statement for Health Professionals From the American Heart
Association**

- Marcador afectación miocárdica
- Elevado en algunos pacientes
- No suficiente capacidad para diferenciar EK
- Valores de corte no establecidos

Criterios EK COMPLETO

- FIEBRE durante **5 días** Y **4** de 5 criterios principales
- FIEBRE durante **4 días** Y ≥ 4 criterios principales especialmente **eritema, edema o hinchazón** de manos y pies

No todos los criterios tienen que estar presente a la vez

Presencia anomalías coronarias: confirma diagnóstico

Exclusión de otras enfermedades con hallazgos similares

Crterios principales

1. Alteraciones labios y/o mucosa oral



3. Exantema maculo-papular, eritrodermia difusa



2. Inyección conjuntival no supurativa



5- Adenopatía cervical



4- Cambios en extremidades

Crterios principales

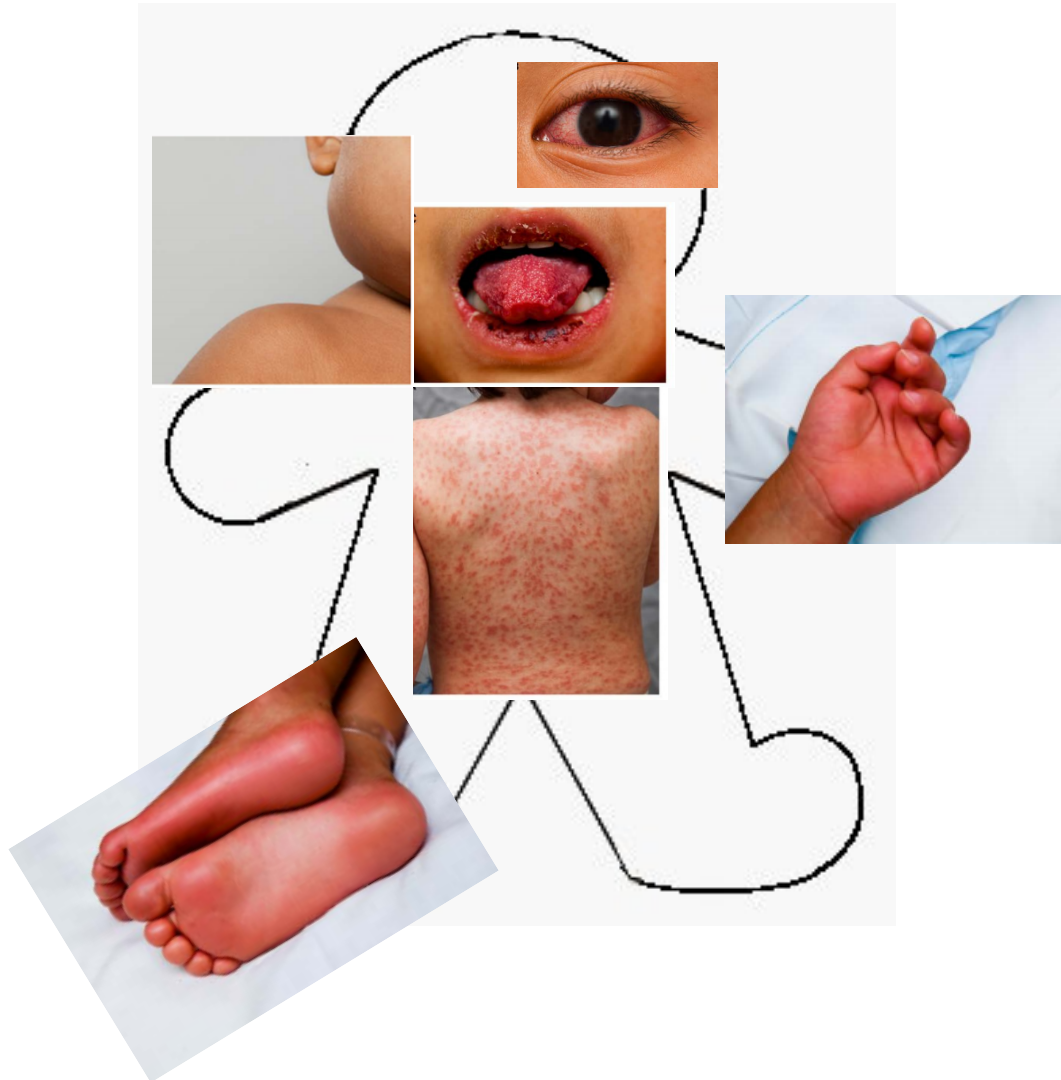
1

2

3

4

5



Inyección conjuntival bulbar no supurativa

- Típicamente deja libre el limbo corneal
- Ocasionalmente hemorragia subconjuntival y queratitis punteada



Alteraciones de los labios y/o mucosas orales

- Eritema, fisuras, sangrado en los labios
- Lengua aframbuesada con papilas prominentes
- Eritema de mucosa oral o faríngea sin exudados ni ulceraciones



Exantema

- Puede ser urticariforme o micropustuloso
- Sin vesículas/bullas, Petequias ni costras
- Característico: región perineal con descamación precoz.



Linfadenopatía cervical

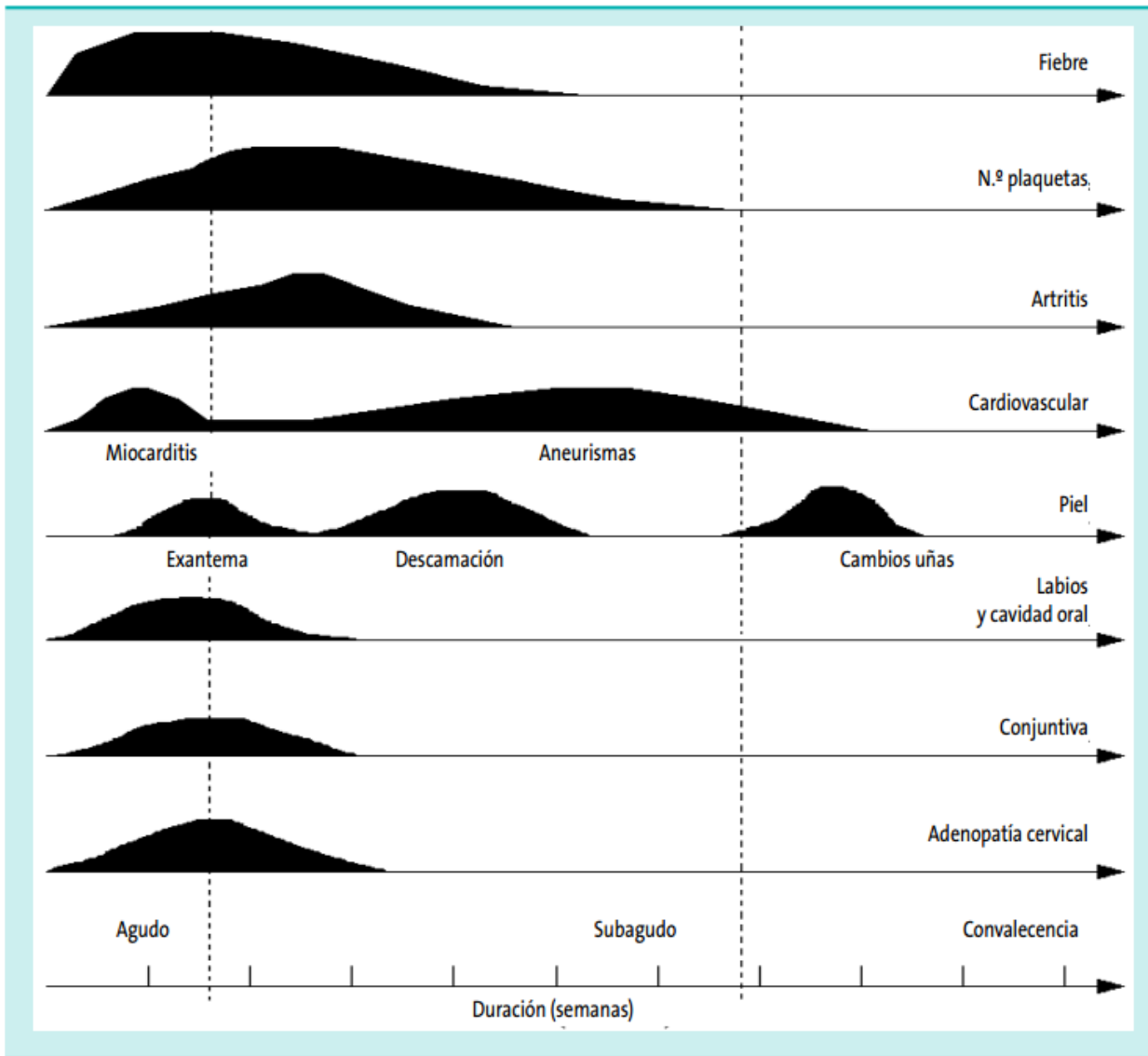
- $\geq 1,5$ cm de diámetro
- Generalmente unilateral
- Puede asociar edema retro/parafaríngeo



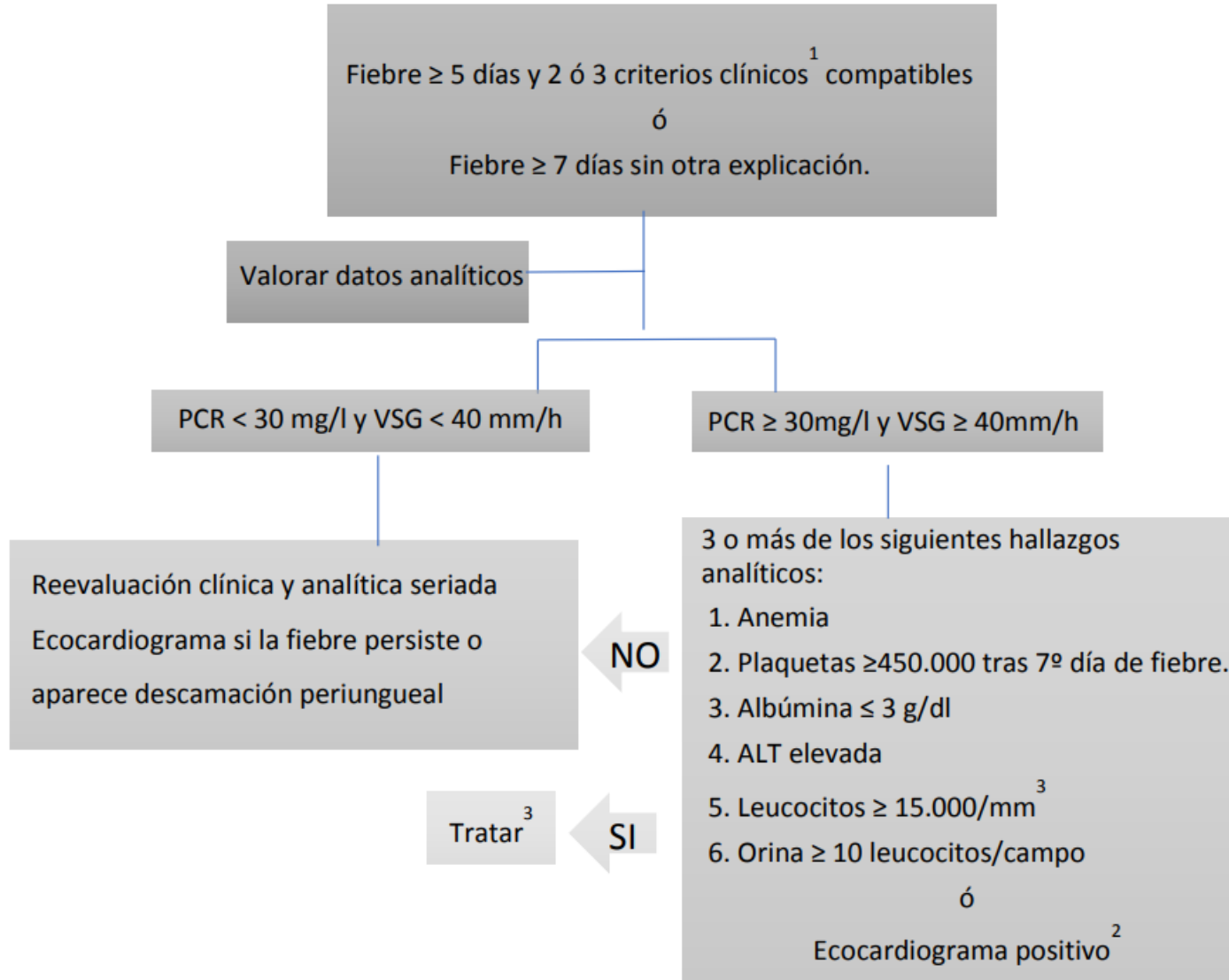
Cambios en las extremidades

- Fase aguda: Eritema y edema
- Fase subaguda: Descamación ungueal
- A veces la induración es dolorosa
- En 1-2 meses pueden aparecer líneas de Beau (uñas)





Crterios EK incompleto



No EK...

- Faringitis exudativa
- Úlceras orales
- Exantema vesicular o bulloso
- Adenopatías generalizadas
- Leucopenia con linfocitosis
- Esplenomegalia
- VSG, PCR y plaquetas normales después del 7º día

Diagnóstico diferencial

Infecciones	Adenovirus Sarampón Parvovirus Herpesvirus Escarlatina Mononucleosis infecciosa
Reacciones inmunitarias	Síndrome de Steven-Johnson Síndrome del shock tóxico
Enfermedades reumáticas	AIJ PAN LES Fiebre reumática

Afectación cardiológica

- Mayor causa de morbimortalidad
- **Inflamación** pericardio, miocardio y endocardio (incluyendo válvulas) y arterias coronarias

Afectación cardiovascular

- Shock cardiogénico
- Disfunción miocárdica
- Disfunción valvular
- Dilatación de raíz aórtica
- Alteraciones coronarias

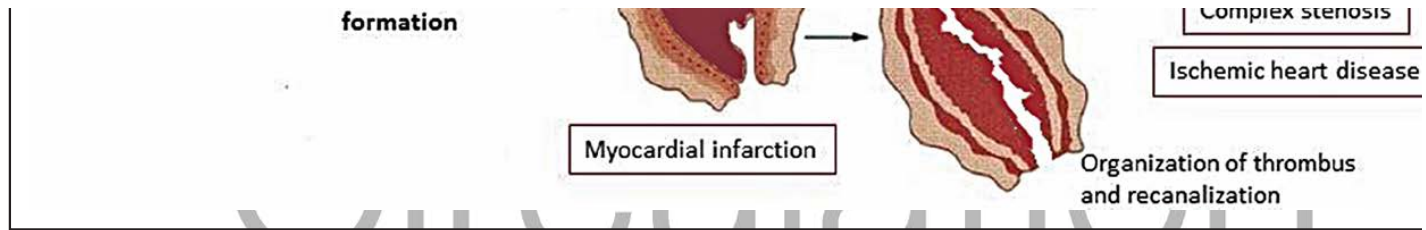


Figure 4. Natural history of coronary artery abnormalities.

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

Coronary Artery Abnormalities

Prevalence

The original descriptions of KD did not recognize the presence of coronary artery abnormalities until it was observed that 1% to 2% of patients died suddenly of cardiac complications.²⁵⁹ An angiographic study of 1100 patients showed coronary artery lesions in 24%, with aneurysms in 8% and a number of patients with stenoses and occlusions.²⁶⁰ The early reports of the prevalence of abnormalities vary widely given the lack of uniformity in the timing of angiography and the definition of abnormalities, and they predate echocardiography and treatment with IVIG. The clinical trial of 4-day IVIG treatment with strict entry criteria (classic KD presenting within 10 days of fever onset) and using the 1984 Japanese Ministry of Health criteria (based on absolute luminal dimensions) noted a prevalence of coronary artery abnormalities of 23% in the ASA-only group versus 8% in the IVIG-plus-ASA group at 2 weeks, with a lower prevalence at 7 weeks.¹⁷⁶ A similar subsequent trial of a

single high dose of IVIG showed coronary artery abnormalities, again using Japanese Ministry of Health criteria, at 2 weeks in 9.1% of those treated with 4 treatment versus 4.6% in those treated with 1 IVIG (further reduced to 2.4% when those with artery abnormalities at presentation were excluded). Using a cut point of a Z score of 2.5 together with Japanese Ministry of Health criteria, a further single-dose methylprednisolone in addition to 1 IVIG showed a prevalence of coronary artery abnormalities of 30% in both groups at 1 week.¹⁷⁶ The inclusion of dilation into the definition results in a higher prevalence of coronary artery abnormalities. The prevalence of dilation is further increased if one includes those patients whose coronary artery Z score is below the cut point for abnormality (<2) but does not increase significantly during follow-up.^{129,130}

These studies define the prevalence of coronary artery abnormalities in homogenous populations; however, some patients in clinical populations may have

Hallazgos ECG

Cambios PR, ST, QT, T, Q...

- Inflamación miocárdica clínica o subclínica
- Afectación coronaria



Evaluación fase aguda

ECOCARDIOGRAMA

- TC
- RM
- Coronariografía
- ETE

No indicadas de rutina

TRATAMIENTO

FASE AGUDA

INMUNOGLOBULINA



ÁCIDO ACETIL
SALICÍLICO

FASE AGUDA

INMUNOGLOBULINA IV

- Mecanismo de acción? ... “Efecto antiinflamatorio generalizado”
- Único en reducción de síntomas y desarrollo aneurismas coronarios
- Infusión única IGIV 2 g/kg, 10-12 horas.
- Primeros **10 días** de la enfermedad
- Razonable más allá del día 10 y existe fiebre sin foco o aneurismas coronarios junto con aumento de RFA (VSG/PCR)
- La VSG se afectada por el tratamiento con IgG

FASE AGUDA

A PESAR DEL TRATAMIENTO PRECOZ CON IGIV...

- 20% Dilatación coronaria transitoria en segmentos proximales (ACD/TCI)
- 5% Aneurismas coronarios
- 1% Aneurismas coronarios gigantes

FASE AGUDA

- **ÁCIDO ACETIL SALICÍLICO**

- Actividad antiinflamatoria y antiplaquetaria
- No influye en prevención desarrollo aneurismas coronarios
- Dosis antiinflamatoria al inicio:
 - 80-100 mg/kg/día, cada 6-8 horas (EEUU)
 - 30-50 mg/kg/día (Japón y Europa occidental)

30-50 mg/kg/día, cada 6 horas, VO

FASE AGUDA

- **ÁCIDO ACETIL SALICÍLICO**

- Disminuir a dosis antiagregante (3-5 mg/kg/día, dosis única VO)
 - Cuando lleve 48-72 h afebril.
 - Hasta comprobar no afectación coronaria (6-8 semanas desde el inicio), normalización de plaquetas y descenso de RFA.
 - Niños con aneurismas: continuar hasta su resolución.
 - Evitar el uso concomitante con AINEs

Tratamiento coadyuvante

- Corticoides
- Infliximab
- Etanercept
- Ciclosporina
- Anakinra
- Ciclofosfamida
- Plasmaféresis

Resistencia a IgG

”Persistencia de fiebre más allá de las 36 horas desde el final de la infusión de IgG”

- 10-20% de los niños
- Mecanismo desconocido, factores genéticos?
- Mayor riesgo de afectación coronaria
- No datos concluyentes sobre la elección del fármaco
- Mayoría expertos recomiendan **segunda dosis de IgG**

Resistencia a IgG

recommendations for primary adjunctive treatment with etanercept await publication of the results of this clinical trial. The potential advantage of etanercept might be the shorter half-life if secondary infections are of concern. However, the soluble receptor only binds to circulating and not cell-bound TNF- α , which could reduce the anti-inflammatory effect.

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 (Class III; Level of Evidence B).**

of IVIG is poorly understood. It is likely that HLA factors, such as polymorphisms in the Fc gamma receptors, play a role in both the response and resistance to IVIG.^{61,202,203}

Risk Scores for Predicting Nonresponse to IVIG

Approximately 10% to 20% of patients with KD have persistent or recurrent fever after primary therapy plus ASA.^{204,205} Many studies have shown that patients who are resistant to initial IVIG are at increased risk of developing coronary artery abnormalities.^{171,206} Scoring systems have been constructed to identify patients likely to be resistant to IVIG and who may benefit from more aggressive initial therapy. In 2006, these groups devised scoring systems to predict response to IVIG.^{187,189,208,209} However, currently

Prevención de trombosis

- AAS (3-5 mg/kg/día) hasta comprobar que no haya afectación coronaria (4-6 semanas)
- Pacientes con aneurismas coronarios rápidamente progresivos o gigantes: añadir **anticoagulación** con HBPM, warfarina o acenocumarol
- **Triple terapia** (segundo antiagregante): pacientes con aneurismas gigantes e historia reciente de trombosis coronaria.

Tratamiento de trombosis

- Basados guías adultos
- Trombos mayor tamaño
 - Trombolisis mediante cateterismo
 - Agentes trombolíticos (tPA) + AAS + Heparina

Estratificación de riesgo

1 on May 29, 2017

converted to Z scores adjusted for BSA as the Diagnosis section. The risk stratification on the patient's maximal Z score at any time p any branch. The risk stratification is further n the maximal Z score in any branch at the time assessment (Table 8). This allows clinicians t rate different risk levels based on the past a coronary artery involvement, with changes in thrombosis and stenosis. Coronary artery ir based on Z scores from echocardiographic a: of luminal dimensions is classified into 5 cat outlined in the section Diagnosis, Echocar Classification of Coronary Artery Abnormalitie rent guidelines diverge from previous guideli primarily classified coronary artery involvem on absolute dimensions, with little to no adju body size.

Although the risk stratification scheme prin on maximal and current coronary artery Z scor from echocardiography, other features of th arteries and other noncoronary artery cardiac tions could also influence decisions regarding fication (Table 9). These additional features r be derived from other imaging modalities.

Según el grado de afectación coronaria

Seguimiento a largo plazo

A partir de la **6^a-8^a semana**

1. Prevenir trombosis
 2. Prevenir isquemia miocárdica
 3. Optimizar salud cardiovascular
- Tromboprofilaxis
 - Pruebas para detección de isquemia miocárdica
 - Estatinas
 - Seguimiento psicosocial, reproductivo.
 - Transición cardiología adultos

	persists					
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	Precaution: contraception, 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, 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	Precaution: contraception, 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	Precaution: contraception, 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	Precaution: contraception, 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	Precaution: contraception, 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	Precaution: contraception, 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	Precaution: contraception, 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	Precaution: contraception, pregnancy

Yellow indicates a Class IIa recommendation (it is reasonable to perform); orange indicates a Class IIb recommendation (may be considered).

*To include history and physical examination, echocardiography, and electrocardiography.

†May include stress echocardiography, stress electrocardiography, stress with magnetic resonance perfusion imaging, and stress with nuclear perfusion imaging.

‡General healthy lifestyle counseling should be provided at every visit (may be performed by primary care provider).

§Restrictions for contact apply to patients on anticoagulation or dual antiplatelet therapy; self-limit refers to allowing patients to participate in reasonable activities without coercion or pressure to perform or overexert (self, parents, coaches).

to normal or dilation only					be co
5.1: Large and giant aneurysm, current or persistent	Continue	Reasonably indicated	May be considered in addition to anticoagulation	May be considered	Empirical be co
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 be co
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 be co
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 be co

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).

weeks after the onset of fever. Until this point, patients should be managed in accordance with the recommendations in the Acute Treatment section.

No Involvement (Z Score Always <2)

Frequency of cardiology assessment (to include history and physical examination, echocardiography, electrocardiography):

- 1. It is reasonable to discharge patients from cardiology care at 4 to 6 weeks after KD onset, although ongoing follow-up to 12 months may be considered. Ongoing cardiology follow-up is not indicated. Patients and families should be advised to remember that having had KD is part of the patient's**

permanent medical history (Class of Evidence C).

Type and frequency of additional cardiology a (other cardiology testing):

- 1. It is reasonable that no additional c assessment be performed (Class IIa Evidence C)**

Cardiovascular risk factor assessment and ma

- 1. It is reasonable to provide general c regarding healthy lifestyle and ac motion at every visit; this may be pr the primary care provider (Class IIa Evidence C).**
- 2. It is reasonable to assess blood pres ing lipid profile, body mass index (**

Transición vida adulta

- Sin lesiones coronarias: **NO** precisa seguimiento
- Con lesiones coronarias, transitorias o persistentes: seguimiento de por vida
- Recomendado entre los 18-21 años (EEUU)
- Coordinación (evitar “lapsos”)
- Iniciar a los 12 años educación de enfermedad

Mayo 2018

- Asintomático
- Riesgo 5.1: Aneurismas gigantes persistentes
- AAS 4 mg/kg/día + ACO (Sintrom)

Conclusiones

- ✓ Objetivo principal: prevenir afectación coronaria
- ✓ Ante sospecha iniciar tratamiento empírico.
- ✓ Falta de consenso en casos de resistencia a tratamiento.
- ✓ Asegurar transición y seguimiento óptimo en cardiología de adultos.

FIN