KAWASAKI DISEASE-TREATMENT

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To the uninitiated, the diagnosis of KD may seem like an enigma. There seems to be more of “art” than “science” in arriving at a diagnosis. **KD remains purely a clinical diagnosis** and is a delight for the hardcore clinician.

It cannot be overemphasized that the diagnosis rests on the recognition of a typical temporal sequence of a constellation of clinical features, with none of the features taken individually being of any diagnostic significance whatsoever.

Kawasaki Disease – An Indian Perspective

SURJIT SINGH AND TOMISAKU KAWASAKI

INDIAN PEDIATRICS

Why identify KD?

Untreated 20% to 25 % incidence of coronary artery aneurysms.

Commonest cause of MI in children

Incidence of MI-1.9%(39% in those with persistent aneurysms).

Majority of MI within 1 year of onset,mortality 20%

Goals of Therapy

Control of the acute inflammation

+ **prevent long-term sequelae** and, **most importantly, coronary artery abnormalities**.

How to treat?

Intravenous immunoglobulin (IVIG) + high-dose aspirin have traditionally been the cornerstones of Kawasaki disease management, *although the role of high dose aspirin has been called into question.*

IVIg treatment of KD is one of the most cost effective medical therapies available,leading to short and long term savings.

IVIg

IVIG prevents the development of coronary aneurysms in a dose-dependent fashion.

A single dose of 2 g per kg is administered over 12 hours.

Start with a slow infusion rate, increase rate after the first few hours.

Available brands: Immunorel (Reliance), Intas, Plasmagen, Gamma Safe(Halsted)

Potential Mechanisms of Intravenous Immunoglobulin

- Provides antibodies against infectious agent
- Provides antibodies against circulating toxin
- Provides anti-idiotypic antibodies
- Blockades Fc receptors
- Accelerates clearance of activated complement fragments

- IVIg reduces the incidence of CAA to 1-5%
- IVIG also improves myocardial function in KD patients having myocarditis
- Usually very prompt defervescence, but irritability may persist for days.

S/E:

- Infusion reactions -fever, rash, nausea, and hypotension—

managed by slowing the rate of infusion and treating with an antiallergic.

Headache up to 72 hours after the infusion is common

Anemia

Timing of IVIG therapy

Therapy should be instituted **within the first 10 days** of illness and, if possible, within 7 days of illness.

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However, this 10 days watershed zone was arbitarily fixed and so .....

if a patient presents late with persistent fever, aneurysms, or inflammation , DONOT HESITATE to administer IVIG.

Late diagnosis are often complicated by aneurysms at diagnosis and requires augmentation of therapy (Infliximab/ Steroids)

ASPIRIN

Anti-inflammatory regimens using medium dose (30 mg/kg/day) have been recommended during the acute phase of the illness.

However some centres would favour initiation with 3-5 mg/kg/day.

- In cases of aspirin sensitivity, another antiplatelet agent, such as dipyridamole, should be considered.

- Risks : transaminitis , transient hearing loss, and, rarely, Reye syndrome.

NOT to be used for associated arthritis

No defervescence by 48 hours of completion of IVIG or disease recrudescence within 2 weeks: IVIG nonresponders

- 10- 15 % fails to respond to 1st dose IVIg
- Increased risk of developing coronary artery aneurysms

0PTIONS??

- 2 nd dose IVIg 2gm/kg
- Pulse methyl-prednisolone 30 mg/kg/dose for 1-3days
- **Infliximab**

IVIg nonresponders

Others---

Cyclophosphamide

Cyclosporin

Doxycycline

Ulinastatin

Anakinra

Cases with persistent active disease unresponsive to conventional therapy

2ND Dose IV Ig

Failure rate — 30%

INFLIXIMAB – preferred treatment mode in most centers

Single infusion of 10 mg/kg

After the infliximab infusion, majority of patients had a **rapid decrease in their temperature within 24 hours** and had rapid improvement in their inflammatory markers .

Screening tests for tuberculosis (chest x-ray, Tuberculin test, QuantiFERON-TB Gold test) not necessary prior to IFX.

Plasmapheresis

A **dramatic response** to plasmapheresis has been reported.

Best to **reserve when ALL available medical interventions fail**, including multiple doses of IVIG, intravenous methylprednisolone, and TNF inhibition

When to use IVIG+ STEROIDS ??

1. Suspected IVIG resistance according to risk scores.
2. Coronary aneurysms at diagnosis
3. Complicated by macrophage activation syndrome
4. Pre emptively for therapy intensification in infantile KD

KD in Infants

- Diagnose (The Trickiest part) : 50-70% can have incomplete/ atypical presentations.
- Consequently late diagnosis and higher incidence of aneurysms at diagnosis.

- Hence, primary therapy needs to be intensified in majority with steroids or Infliximab

Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study). LANCET 2012

Patients with severe Kawasaki disease were randomly assigned by a minimisation method to receive either intravenous immunoglobulin (2 g/kg for 24 h and aspirin 30 mg/kg per day) or intravenous immunoglobulin plus prednisolone (the same intravenous immunoglobulin regimen as the intravenous immunoglobulin group plus **prednisolone 2 mg/kg per day given over 15 days after concentrations of C-reactive protein normalised.**

Interpretation

Addition of prednisolone to the standard regimen of intravenous immunoglobulin improves coronary artery outcomes in patients with severe Kawasaki disease in Japan.

Kobayashi Risk Score(2006) -

identifies patients with Kawasaki syndrome at high risk of being resistant to intravenous immunoglobulin

Sodium <133 mmol/L
Days of illness at initial treatment < 4
Aspartate aminotransferase > 100 IU/L
Percentage of neutrophils > 80%
C-reactive protein >10 mg/dL
Age < 12 months
Platelet count < 300000

Although there is no conclusive body of evidence defining the best second and third-line therapies for Kawasaki patients, Infliximab and steroids are currently the two agents that have been most studied.

Anticoagulation in KD

1. Giant aneurysm, multiple or complex aneurysms, presence of thrombus
2. Associated stenosis
3. Peripheral gangrene

Initiate with LMW heparin followed by oral warfarin to maintain INR of 2-2.5

For arterial thrombosis/ peripheral gangrene- **thrombolytics** have been tried in addition to anticoagulation

ROLE OF THE PEDIATRIC CARDIOLOGIST

- Catheter intervention with angioplasty, rotoablation, and stenting and surgical intervention with internal mammary artery bypass grafts and cardiac transplantation reserved for patients with severe coronary artery damage and ischemia.

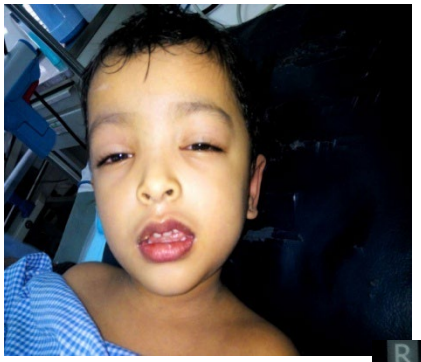
TREATING ASSOCIATED COMPLICATIONS

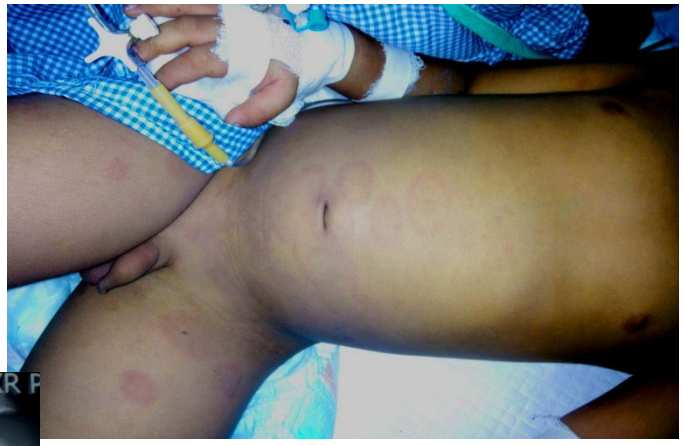
Arthritis- 5-10% develop a reactive arthritis.

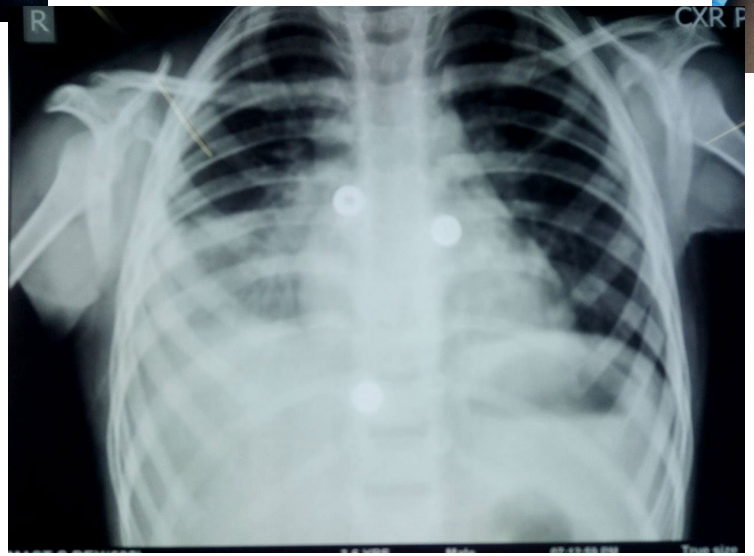
Tm- NSAID/ steroids

FAILURE TO RESPOND????

An associated Infection / Infectious Mimic







FAILURE TO RESPOND????

- **Incomplete, atypical kawasaki disease or evolving systemic juvenile idiopathic arthritis.** Cases Journal 2009
- **Failure to distinguish systemic-onset juvenile idiopathic arthritis from incomplete Kawasaki disease in an infant.** J Paediatr Child Health. 2007
- **Incomplete Kawasaki syndrome followed by systemic onset-juvenile idiopathic arthritis mimicking Kawasaki syndrome.** Rheumatology International 2010

FAILURE TO RESPOND????

Macrophage Activation Syndrome in Kawasaki Disease

MAS may rarely complicate the course of KD; prompt treatment with **pulse methylprednisolone** result in favourable outcome .

KD with coronary artery aneurysm at presentation

PEDIATRICS®

Article

Treatment Intensification in Patients With Kawasaki Disease and Coronary Aneurysm at Diagnosis

Audrey Dionne, Jane C. Burns, Nagib Dahdah, Adriana H. Tremoulet, Kimberlee Gauvreau, Sarah D. de Ferranti, Annette L. Baker, Mary Beth Son, Patrick Gould, Anne Fournier, Jane W. Newburger and Kevin G. Friedman

Pediatrics June 2019, 143 (6) e20183341; DOI: https://doi.org/10.1542/peds.2018-3341

CONCLUSIONS: Among a high-risk group of patients with Kawasaki disease with CAA on baseline echocardiography, those treated with corticosteroids or infliximab in addition to IVIg had less progression in CAA size compared with those treated with IVIg alone.

Repeat echocardiography at 2 and 6 weeks

If aneurysm +/- thrombus at presentation, more frequent (every 1 to 2 days for 10 to 14 days)

Fate of Aneurysms

50-70% will regress over a period of 1-2 years

Unresolved ones persist and develop stenosis and / thrombosis

Risk Stratification

Allows for INDIVIDUALISATION of patients—

- sorts out those who are at greatest risk of Myocardial Infarction

RISK STRATIFICATION

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 initial 6–8 weeks	No restrictions beyond initial 6–8 weeks	Cardiovascular risk assessment and counseling at 5-year intervals	None recommended
II (transient coronary artery ectasia that disappears within initial 6–8 weeks)	None beyond initial 6–8 weeks	No restrictions beyond initial 6–8 weeks	Cardiovascular risk assessment and counseling at 3- to 5-year intervals	None recommended
III (small to medium solitary coronary artery aneurysm)	Low-dose aspirin (3–5 mg/kg aspirin per day), at least until aneurysm regression is documented.	For patients in first decade of life, no restriction beyond initial 6–8 weeks. For second decade, physical activity guided by stress testing every other year. Contact or high-impact sports discouraged for patients on anti-platelet agents.	Annual cardiology follow-up with echocardiogram and ECG, combined with cardiovascular risk assessment and counseling. Stress testing with radioisotope perfusion scan or stress echocardiogram every other year.	Angiography, if non-invasive test suggests ischemia
IVa (one or more large or giant coronary artery aneurysms), or IVb (multiple or complex aneurysms, without obstruction)	Long-term anti-platelet therapy and warfarin (target: INR 2.0–2.5) or LMW heparin (target: antifactor Xa level 0.5–1.0 unit/mL) should be combined in giant aneurysms.	Contact or high-impact sports, isometrics, and weight training should be avoided because of the risk of bleeding. Other physical activity recommendations guided by outcome of stress testing or myocardial perfusion scan.	Biannual follow-up with echocardiogram + ECG. Annual pharmacological or exercise stress testing.	Initial angiography at 6–12 months. Repeated angiography if non-invasive test, clinical or laboratory findings suggest ischemia. Elective repeated angiography under some circumstances (see text)
V (coronary artery obstruction)	Long-term low-dose aspirin. Warfarin or LMW heparin if giant aneurysm persists. Use of β-blockers should be considered to reduce myocardial oxygen consumption	Contact or high-impact sports, isometrics, and weight training should be avoided because of the risk of bleeding. Other physical activity recommendations guided by outcome of stress testing or myocardial perfusion scan.	Biannual follow-up with echocardiogram and ECG. Annual pharmacological or exercise stress testing.	Angiography is recommended to address therapeutic options.

IF IN DOUBT- TREAT

The consequences of failure to treat a child appropriately with KD are so important that, error on the side of premature or unnecessary therapy is preferable to delayed or missed therapy for a child for whom the diagnosis is uncertain.

Textbook of Pediatric Rheumatology: Cassidy, Petty

- Vessels show histological and functional abnormalities at the sites of healed aneurysms, and vascular reactivity to endogenous vasodilators is abnormal in children who have had KD, regardless of whether they have detectable coronary artery abnormalities.
- **LIFELONG FOLLOW UP is required.**