The Fever Files: Updates in Kawasaki Disease Management

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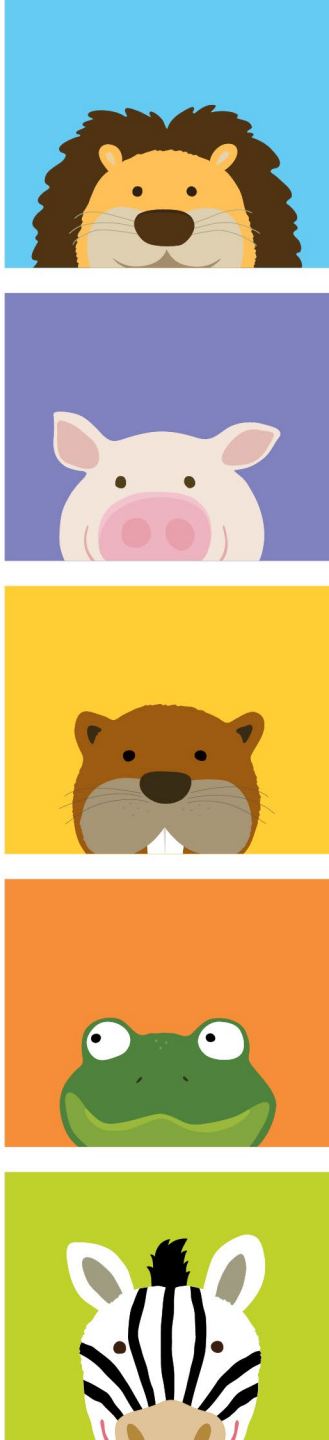
Disclosures

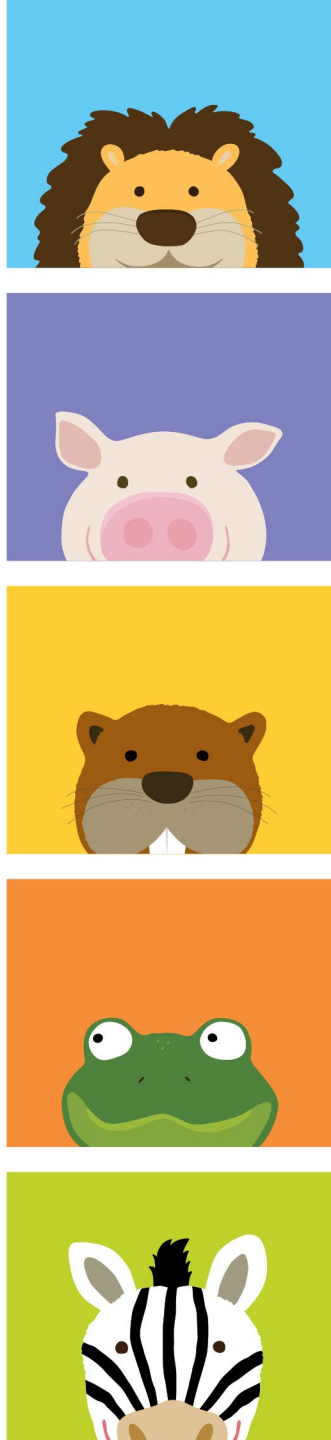
The planner(s) and speaker(s) have indicated that there are no relevant financial relationships with any ineligible companies to disclose.



Learning Objectives

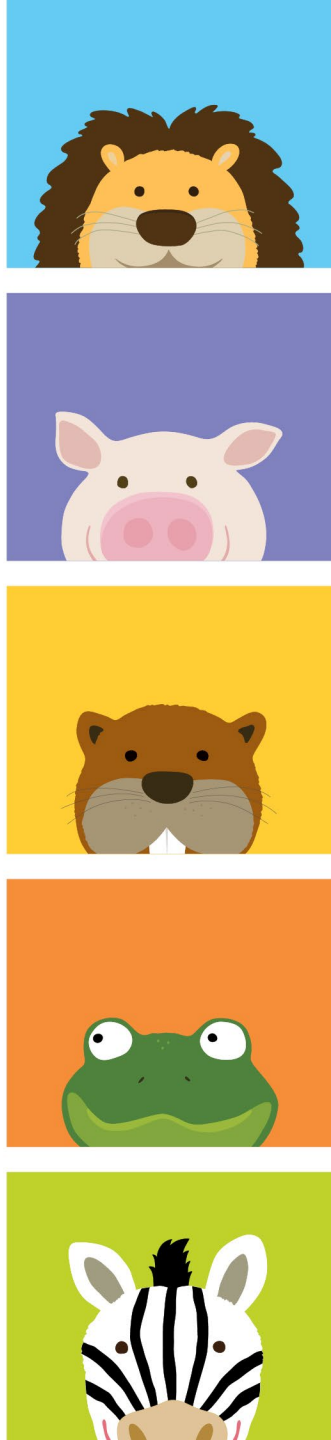
At the end of this session, learners should be able to:

1. Identify risk stratification criteria for diagnosis of Kawasaki disease
2. Outline aspirin dosing for patients with Kawasaki disease
3. Compare anti-inflammatory therapies for IVIG-resistant disease



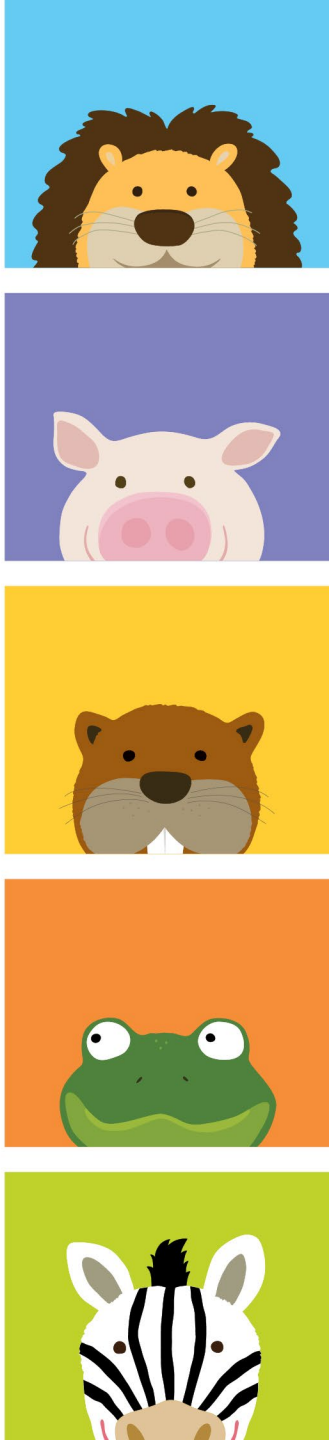
Outline

1. Background
2. Diagnosis
3. Anti-inflammatory Therapies
4. Antiplatelet Therapies
5. Anticoagulation



Abbreviation Key

- AAT: alpha-1 antitrypsin
- AC: anticoagulation
- ACH: Advocate Children's Hospital
- ACR: American College of Rheumatology
- ADP: adenosine diphosphate
- AHA: American Heart Association
- ALT: alanine aminotransferase
- CAA: coronary artery aneurysm
- CABG: coronary artery bypass graft
- CBC: complete blood count
- CMP: comprehensive metabolic panel
- CMV: cytomegalovirus
- CNS: central nervous system
- CRP: C-reactive protein
- DAPT: dual antiplatelet therapy
- DOAC: direct oral anticoagulant
- EBV: Epstein-Barr virus
- ESR: erythrocyte sedimentation rate
- GI: gastrointestinal
- IL-10: interleukin 10
- INR: international normalized ratio
- IVIG: intravenous immunoglobulin
- KD: Kawasaki disease
- LFT: liver function test
- LMWH: low molecular weight heparin
- MIS-C: multisystem inflammatory syndrome in children
- RPP: respiratory pathogen panel
- TNFα: tumor necrosis factor alpha
- TTE: trans-thoracic echocardiogram
- VKA: vitamin K antagonist
- VTE: venous thromboembolism
- WBC: white blood cell



Background

1946

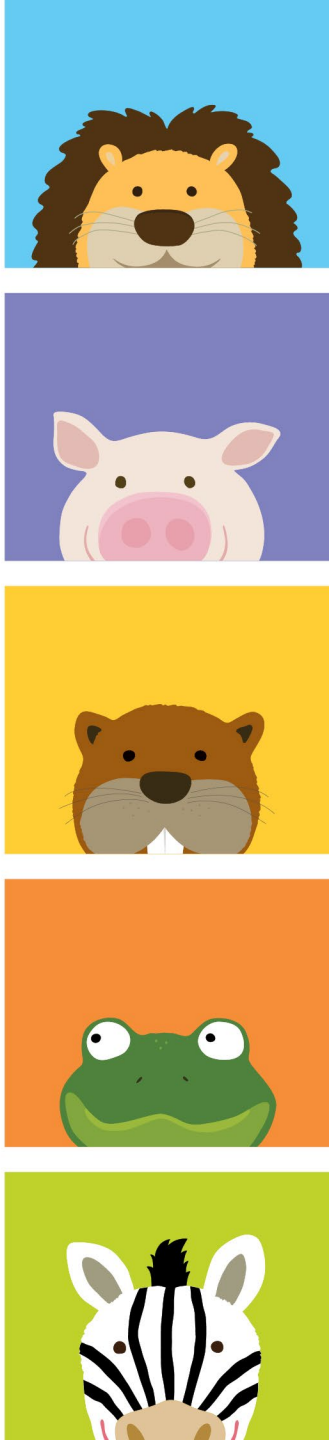
4-year-old boy with persistent fever is diagnosed with “second measles”

1961

Japanese pediatrician Dr. Tomisaku Kawasaki encounters his first patient with acute vasculitis

1967

Dr. Kawasaki publishes paper describing 50 patients with same vasculitis



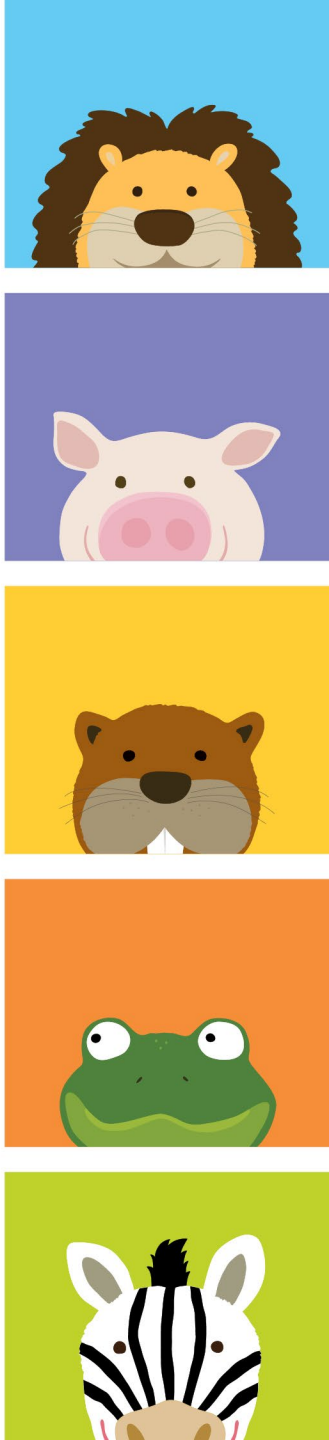
Rajasekaran et al. *Cureus.* 2022;14(8):e28358
Burns JC. *Int J Rheum Dis.* 2018;21(1):13-15

Background

Pediatric acute febrile mucocutaneous lymph node syndrome with characteristic desquamation of fingers and toes: my clinical observation of fifty cases*

TOMISAKU KAWASAKI, MD

Originally published in Japanese but later translated to other languages as cases were identified around the world



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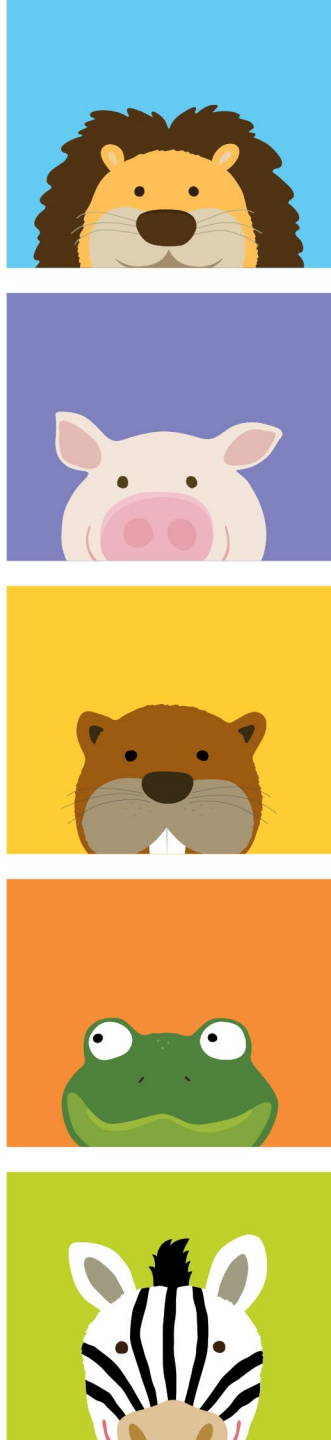
Epidemiology

Leading cause of acquired heart disease in developed nations

25 cases per 100,000 children in the United States

Highest prevalence in:

- Children < 5 years of age
- Males (1.5x to 1.7x)
- Asian descent
- Winter and spring months



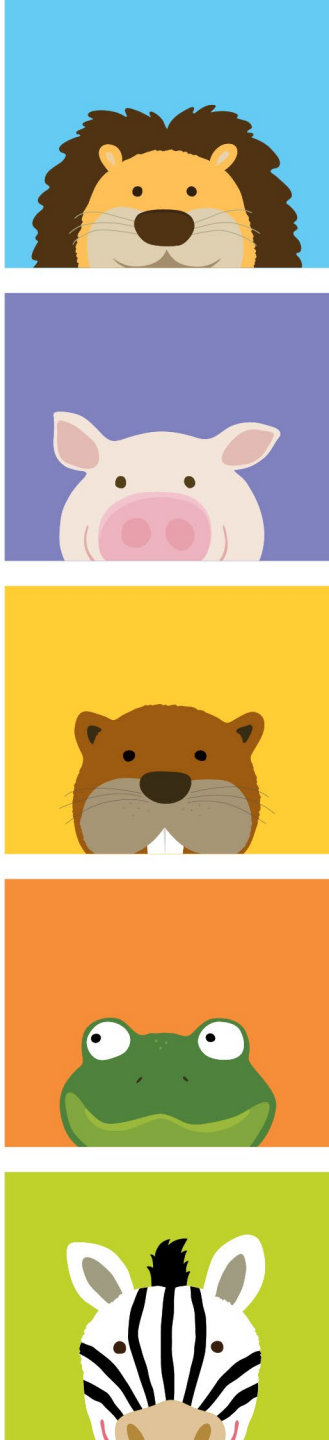
McCrindle et al. *Circulation.* 2017;135(17):e927-e999

Diagnosis

CRASH & BURN

- **C**onjunctivitis
- **R**ash
- **A**denopathy
- **S**trawberry tongue
- **H**ands and feet swelling
- **BURN:** ≥ 5 days of fever

- Clinical features occurring at **any point during course of fever** should be counted towards diagnosis, even if resolved at time of physical examination
- Detailed history with caregivers is important for accurate diagnosis
- Other reported symptoms may include irritability, abdominal pain, diarrhea, and vomiting



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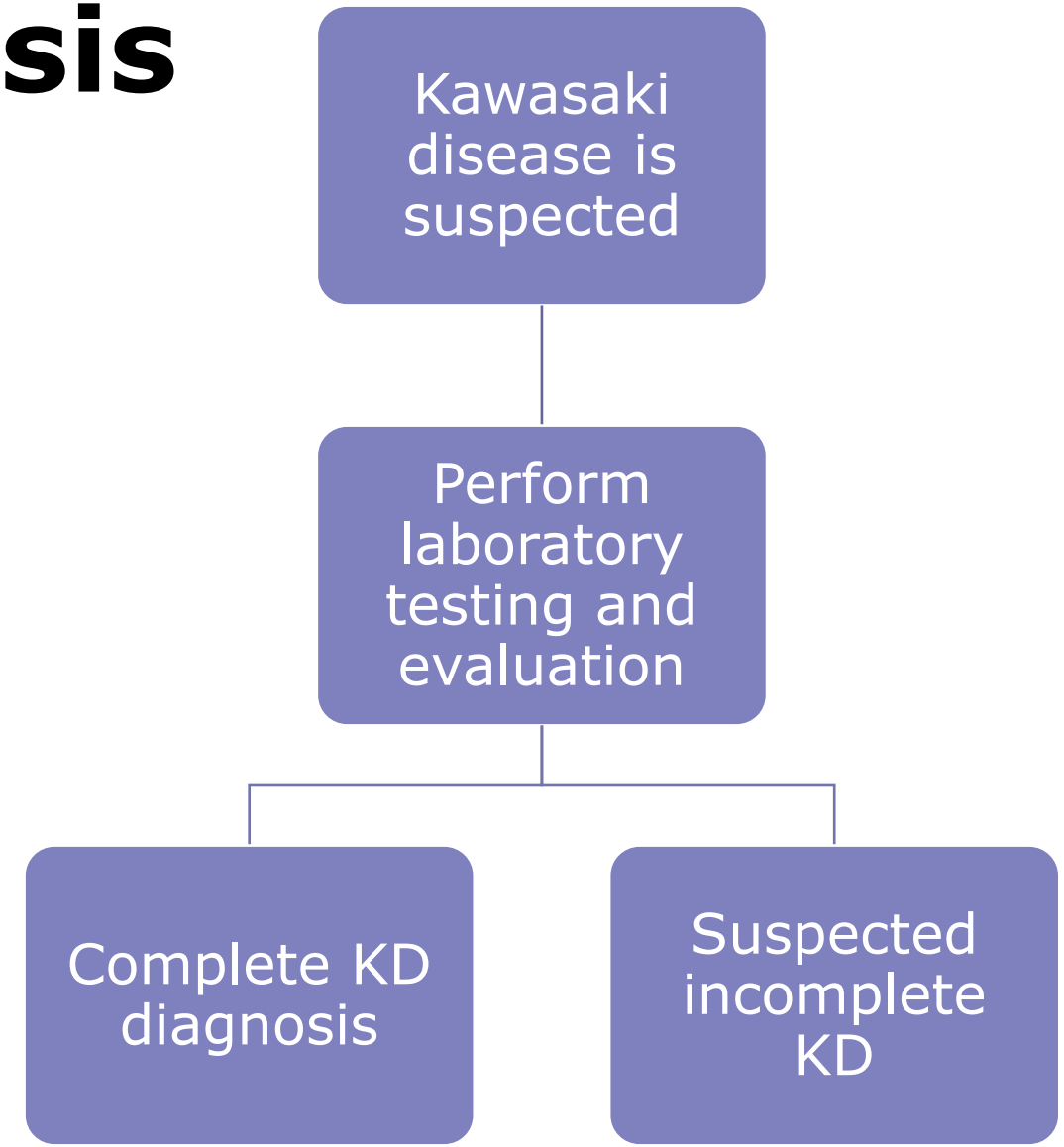
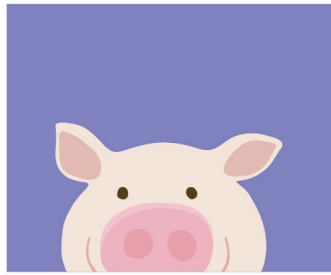
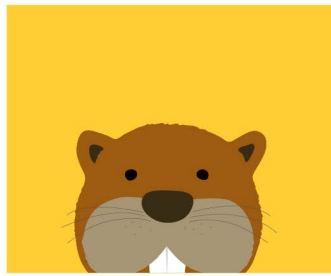
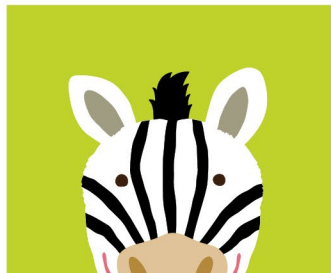
Diagnosis



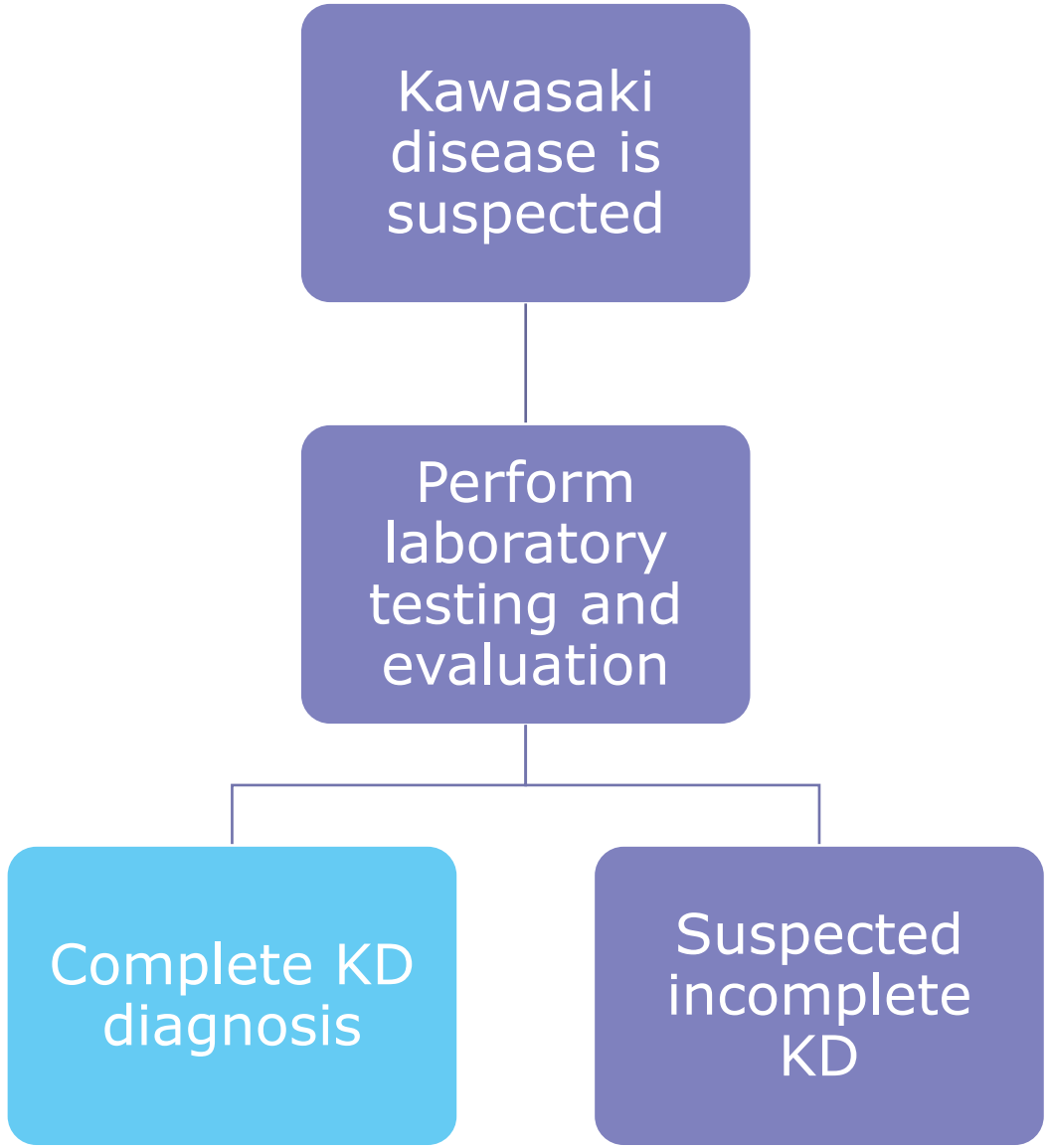


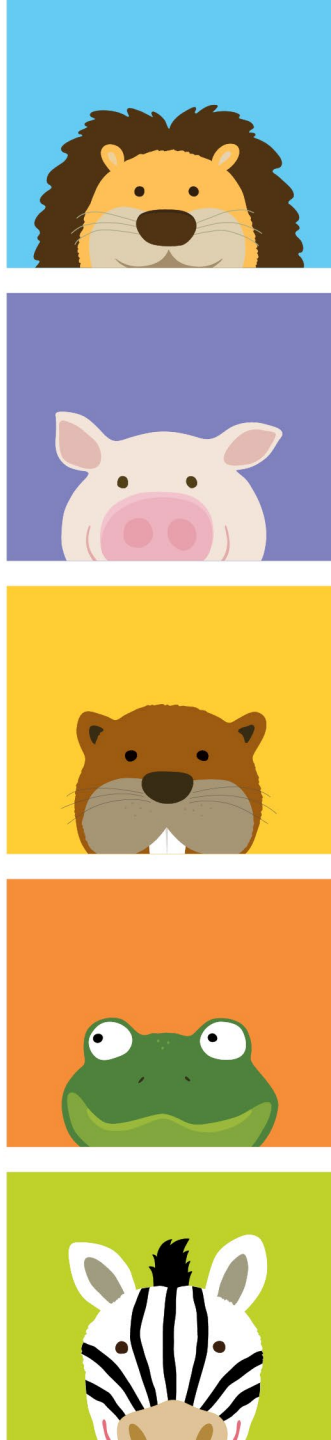
Jone et al. *Circulation.* 2024;150(23):e481-e500

Diagnosis

Complete KD diagnosis

- Fever > 4 days
- 4 to 5 clinical features





Diagnosis

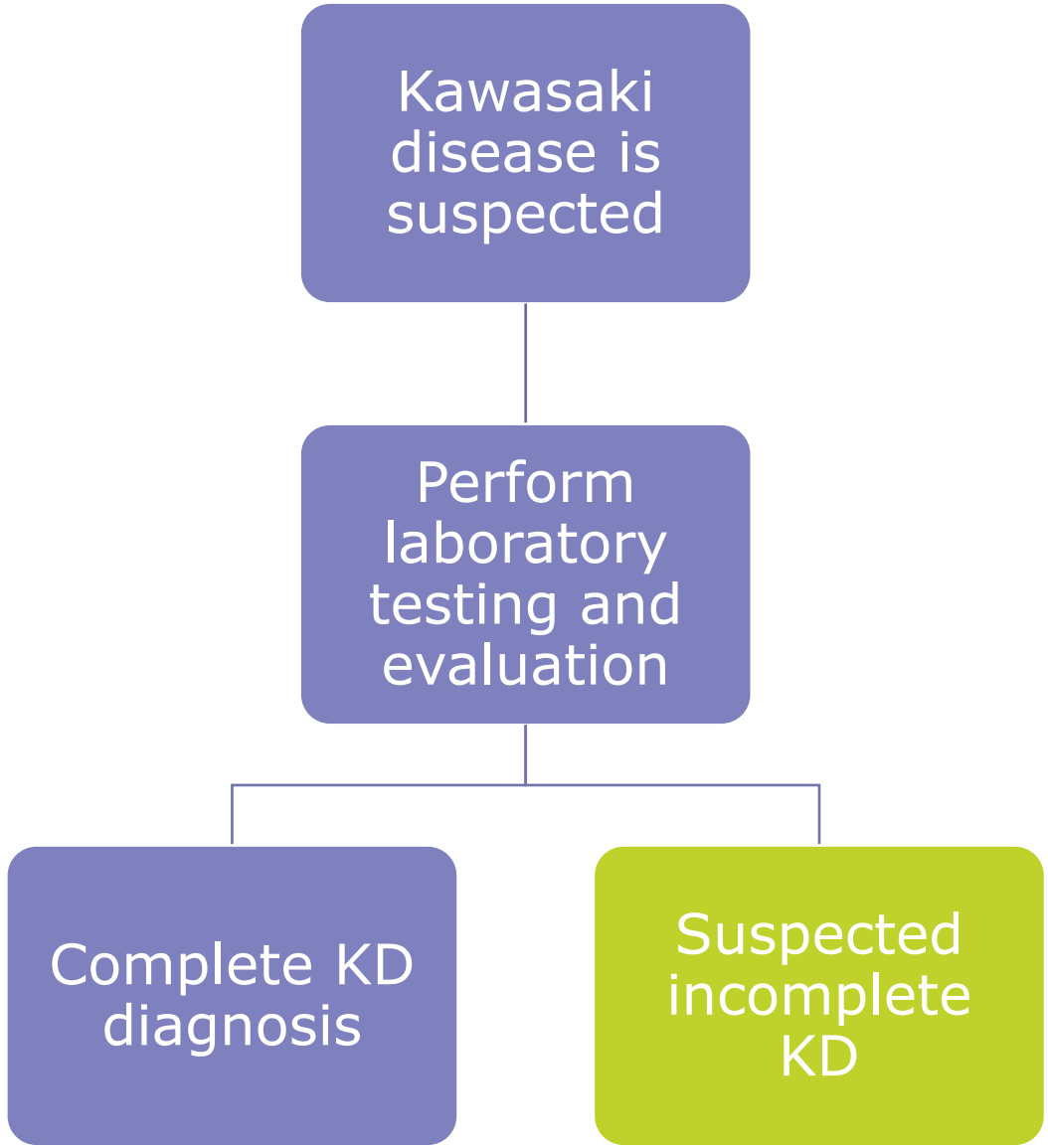
Suspected incomplete KD

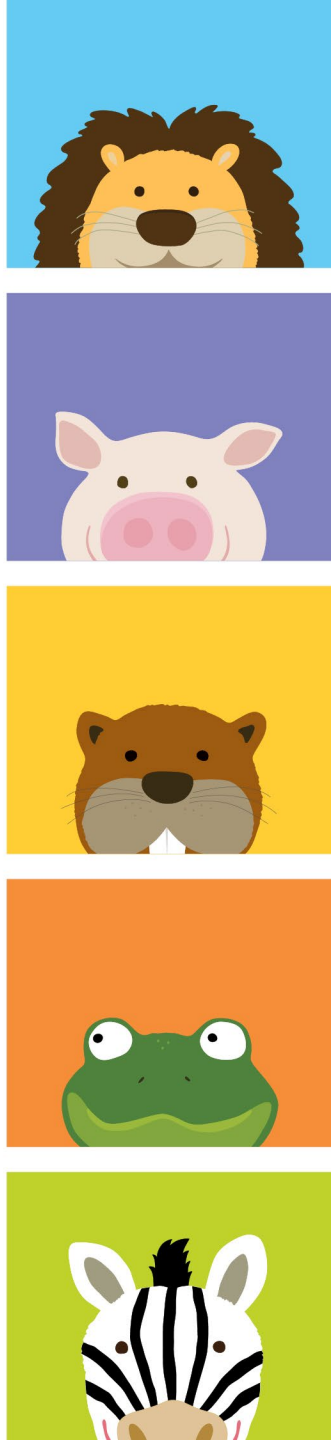
- Prolonged unexplained fever with 2 to 3 clinical features
- Infant with unexplained fever for 7 days

+

At least 1 of the following:

- Elevated CRP or ESR with 3 laboratory findings
- Z-score > 2.5
- At least 3 other suggestive cardiac features



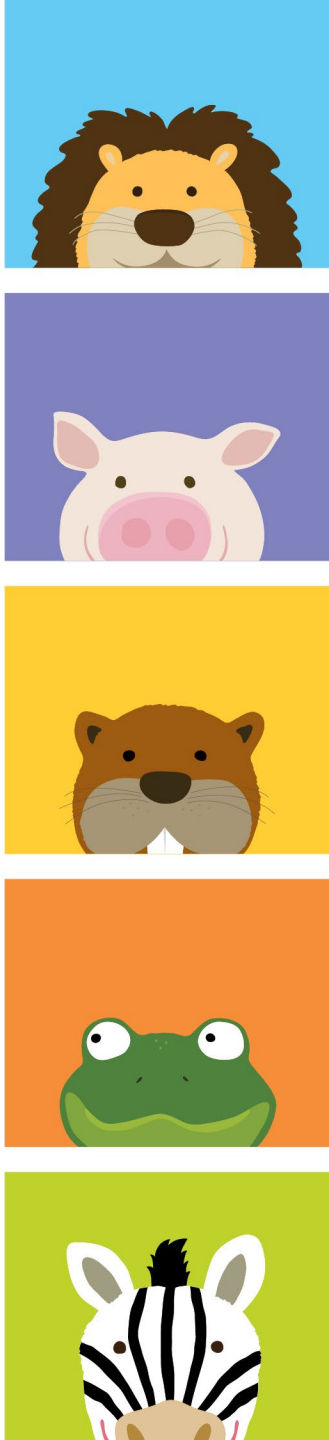


Jone et al. *Circulation.* 2024;150(23):e481-e500

Diagnosis

Initial laboratory evaluation should include CBC with differential, CMP, CRP, ESR, and urinalysis

CBC	CMP	Urinalysis	Inflammatory Markers
• Anemia for age • Platelets > 450,000/mm3 after day 7 of fever • WBC > 15,000/mm3	• Albumin < 3 g/dL • ALT > 55 units/L	• WBC > 10/hpf • Absence of bacterial growth on culture	• CRP ≥ 30 g/dL • ESR ≥ 40 mm/hr

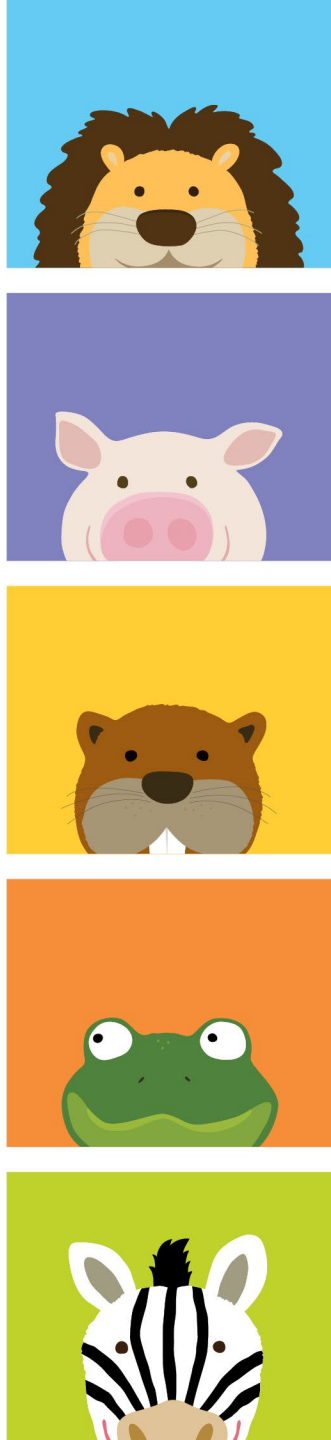


McCrindle et al. *Circulation.* 2017;135(17):e927-e999

Diagnosis

Echocardiogram is performed to establish Z-scores for coronary arteries and determine course of management

< 2	2 to < 2.5	≥ 2.5 to < 5	≥ 5 to < 10	≥ 10
• No involvement	• Dilation only	• Small aneurysm	• Medium aneurysm	• Large or giant aneurysm



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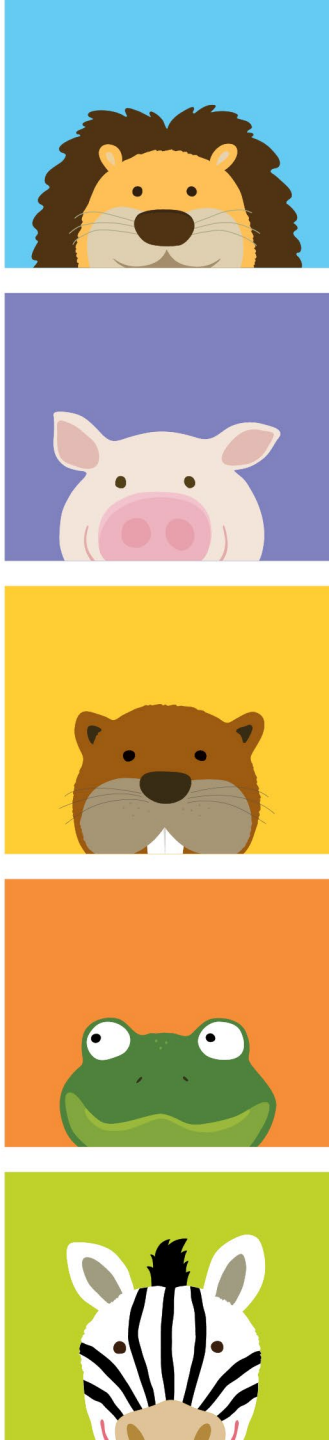
Diagnosis

Other infectious and rheumatologic processes should be ruled out to accurately diagnose Kawasaki disease

Infectious Conditions	Autoimmune Conditions

• Viral infections
  ○ Measles
  ○ EBV
  ○ CMV
  ○ Adenovirus
  ○ Enterovirus
• Staphylococcal and streptococcal toxin-mediated infections
• Rickettsial infections
• Leptospirosis
	• MIS-C
	• Drug hypersensitivity reactions
	• Systemic onset juvenile idiopathic arthritis



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Assessment Question #1

- TK is a 4-year-old male presenting to the emergency department with 5 days of fever. His mother reports that over the past 5 days, he has experienced symptoms such as red eyes and swollen hands and feet. She also mentions that he has appeared congested with a runny nose. Upon physical examination, there is no evidence of conjunctival injection, but the swelling and erythema of the hands and feet has persisted. He also appears to have strawberry tongue and cervical lymphadenopathy. Which of the following symptoms is not associated with Kawasaki disease?

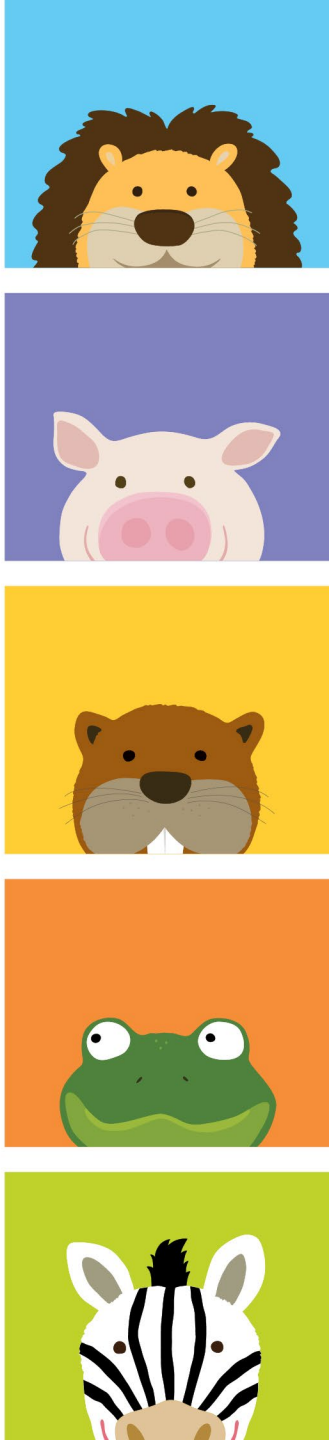
A. Conjunctivitis

B. Rhinorrhea

C. Adenopathy

D. Strawberry tongue

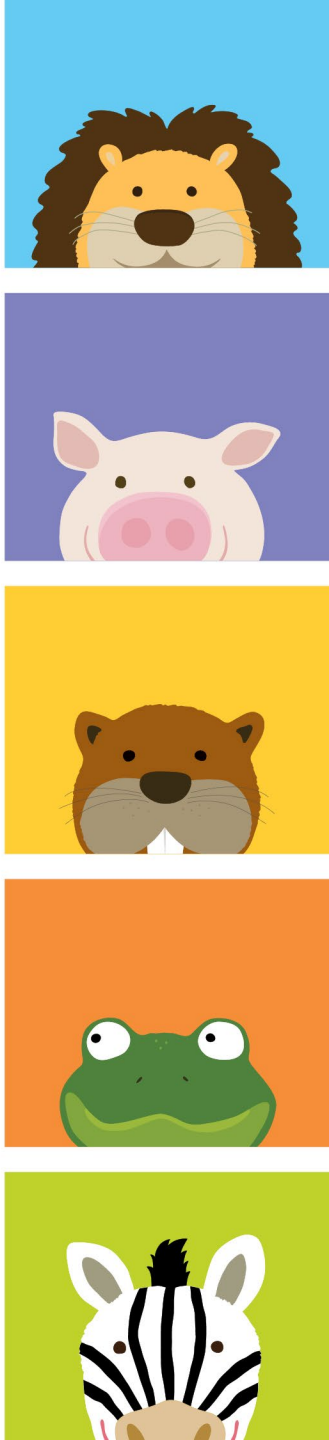
E. Hands and feet swelling



Management

KD diagnosis → IVIG + Aspirin

Z-score > 2.5 (or age < 6 months)	Z-score > 5	Z-score > 10
Methylprednisolone	Clopidogrel	Anticoagulation



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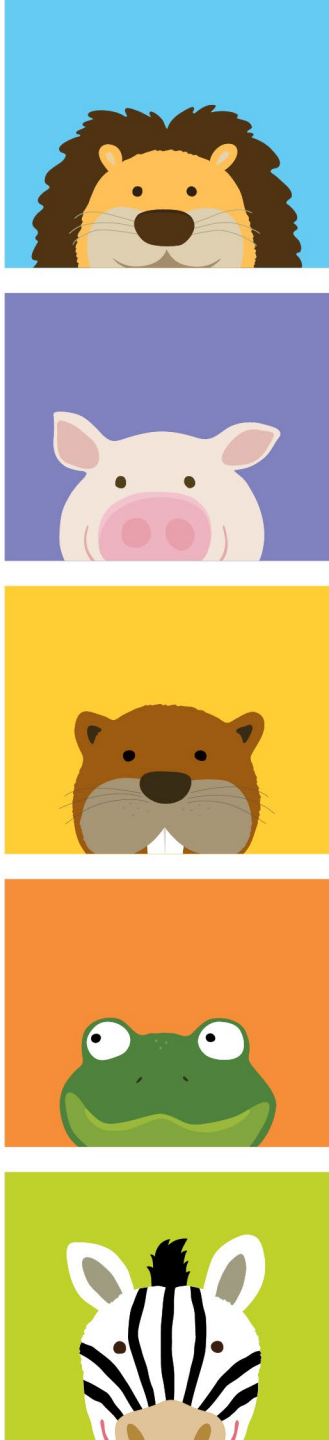
IVIG

Intravenous immunoglobulin (IVIG or IVIg) is polyclonal pooled donor immunoglobulin used as the mainstay of therapy for Kawasaki disease

Mechanism	• Not entirely known but may involve increased IL-10 secretion and activation of regulatory T-cells
Dosing	• 2 g/kg IV over 8 to 12 hours within 10 days of fever onset • Increase infusion rate by intervals as tolerated up to 4 mg/kg/min
Adverse Effects	• Infusion-related reactions • Coombs-positive hemolytic anemia • Aseptic meningitis • Hypersensitivity reactions
Considerations	• Routine premedication is recommended with medications such as acetaminophen, diphenhydramine, and famotidine • Rescue medications should be available for potential hypersensitivity reactions • Order instructions to slow or stop infusion based on infusion-related reactions • Defer live vaccines for 11 months following administration



McCrindle et al. *Circulation.* 2017;135(17):e927-e999

IVIG

Several formulations of IVIG are available but no clinical evidence exists to support use of any specific brand for treatment of KD

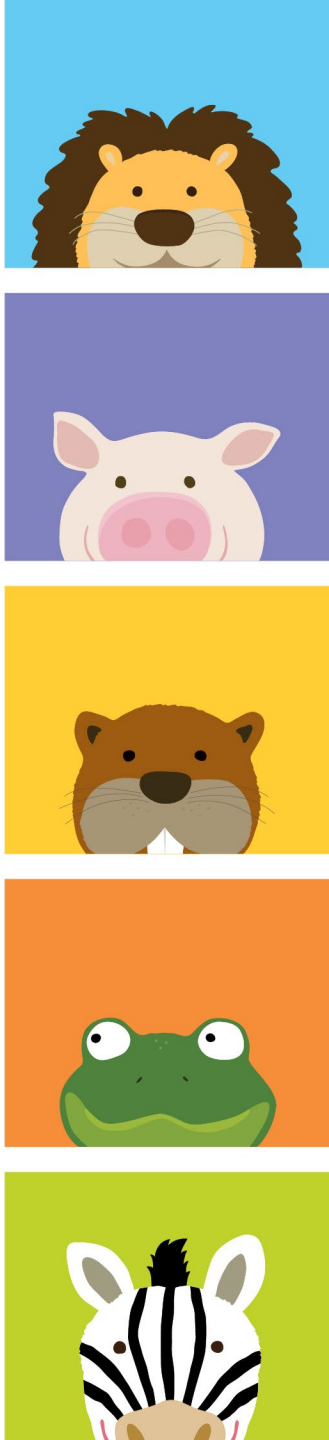
- Incidence of hemolytic anemia may be related to levels of ABO antibodies present in different formulations

Gamunex-C™ is the formulary product for Advocate Health

- Gammagard S/D™ is restricted to use in patients with documented IgA deficiency or history of reaction to other IVIG products

Other immune globulin formulations are designed for intramuscular or subcutaneous administration

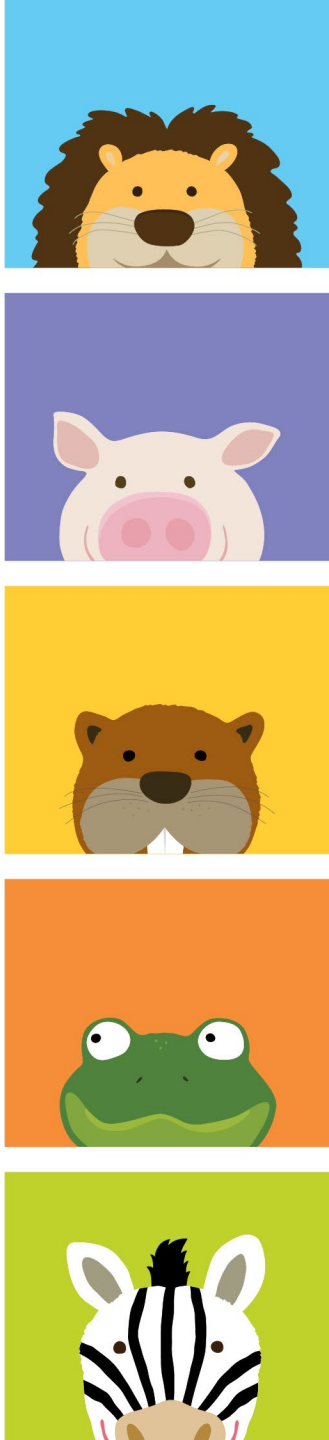
- These products are not used for Kawasaki disease



Jone et al. *Circulation.* 2024;150(23):e481-e500

Newburger et al. 1991

A Single Intravenous Infusion of Gamma Globulin as Compared with Four Infusions in the Treatment of Acute Kawasaki Syndrome	
Purpose	To assess if therapy with a single, very high dose of gamma-globulin would be at least as effective as the standard multidose regimen
Study Design	Prospective, randomized, open-label, blinded-endpoints trial
Population	Multicenter; pediatric patients (N=549) with acute Kawasaki disease
Intervention	Single-dose IVIG + aspirin (n=273) vs multidose IVIG + aspirin (n=276) • Single-dose regimen: IVIG 2 g/kg once • Multidose regimen: IVIG 400 mg/kg q24h for 4 days • Aspirin 100 mg/kg daily through day 14 then 3 to 5 mg/kg daily
Outcomes	Incidence of coronary artery abnormalities, body temperature, duration of fever, inflammatory markers, IgG levels, adverse events

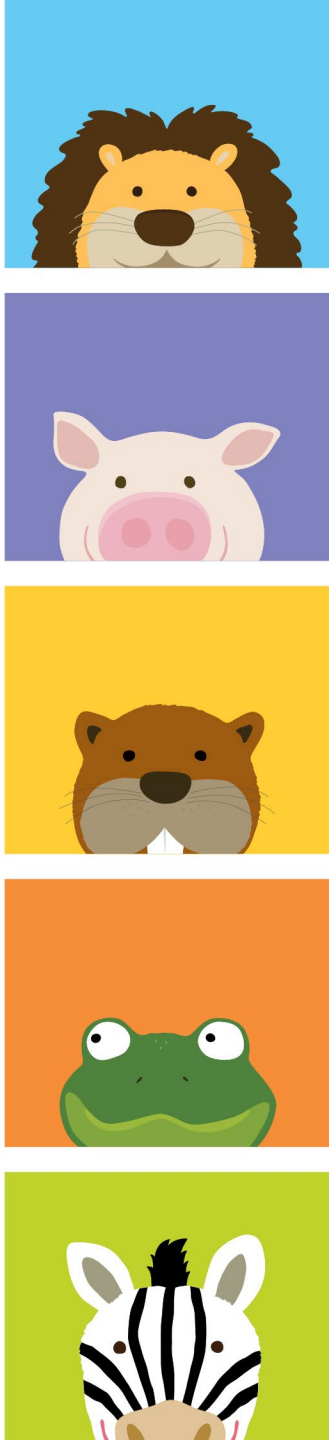


Newburger et al. *N Engl J Med.* 1991;324(23):1633-1639

Newburger et al. 1991

Outcomes	Multidose (n=276)	Single-dose (n=273)	p-value
Coronary artery abnormalities (including at baseline)			
At 2 weeks, n (%)	24 (9.1)	12 (4.6)	0.045
At 7 weeks, n (%)	19 (7.2)	10 (3.9)	0.099
Coronary artery abnormalities (excluding at baseline)			
At 2 weeks, n (%)	14 (5.6)	6 (2.4)	0.067
At 7 weeks, n (%)	10 (4)	6 (2.4)	0.307
Albumin at day 4, mean ± SE	27.8 ± 0.4	29.1 ± 0.3	0.002
Albumin at week 2, mean ± SE	37.2 ± 0.3	38.3 ± 0.3	0.004
AAT at week 2, mean ± SE	1.96 ± 0.04	1.83 ± 0.03	0.007
CRP at week 2, mean ± SE	-1.46 ± 0.08	-1.70 ± 0.07	0.017

- Patients treated with single-dose regimen had lower mean temperatures while hospitalized and a shorter mean duration of fever
- Lower IgG levels on day 4 were associated with a higher prevalence of coronary lesions and with a greater degree of systemic inflammation



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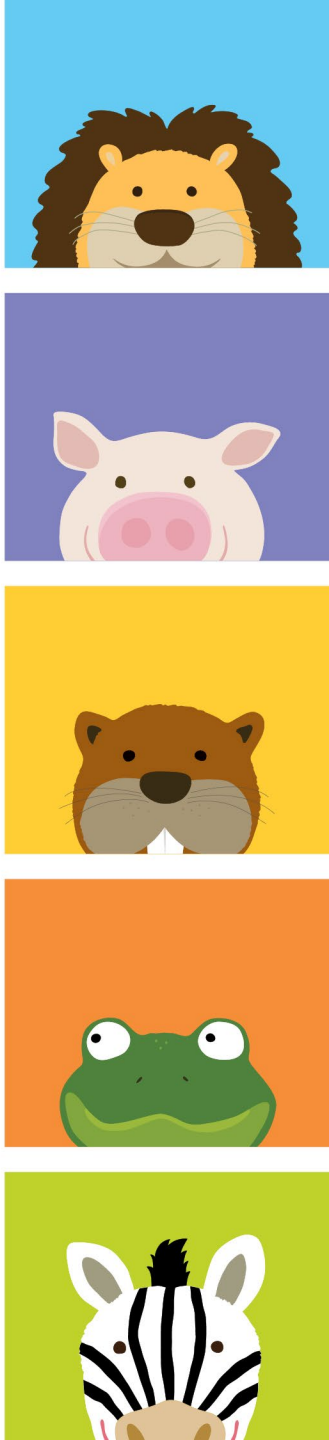
Goals of Therapy

- Resolution of fever within 36 hours of completing IVIG infusion
- Reduction of inflammation and arterial damage
- Prevention of coronary artery thrombosis



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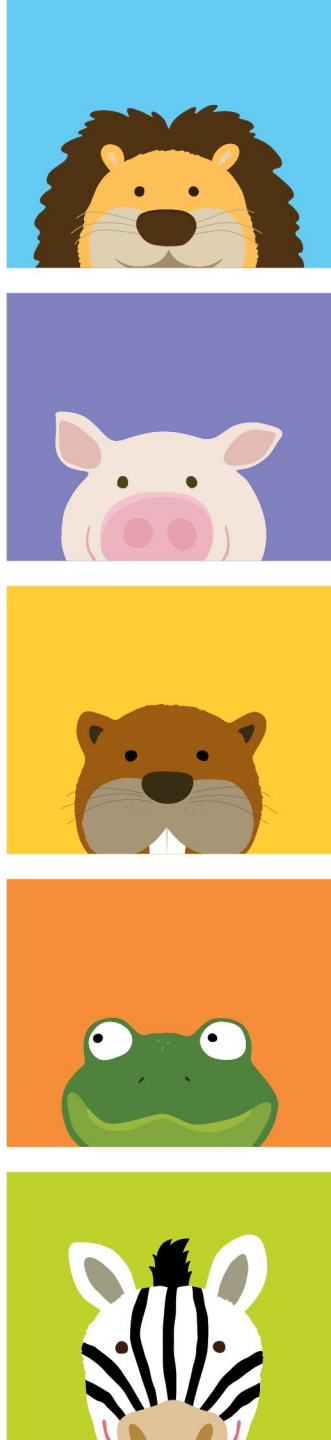
Refractory Management

Several anti-inflammatory therapies are available for Kawasaki disease that is refractory to initial IVIG infusion

- Repeat IVIG
- Infliximab
- Cyclosporine
- Anakinra
- Cyclophosphamide
- Etanercept

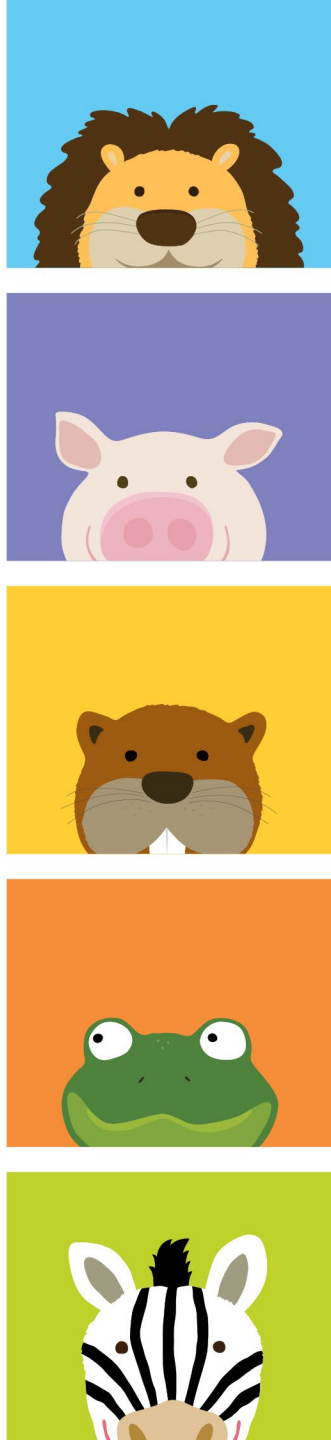


Jone et al. *Circulation.* 2024;150(23):e481-e500

Infliximab

Infliximab is a chimeric monoclonal antibody used as first-line therapy for IVIG-resistant Kawasaki disease

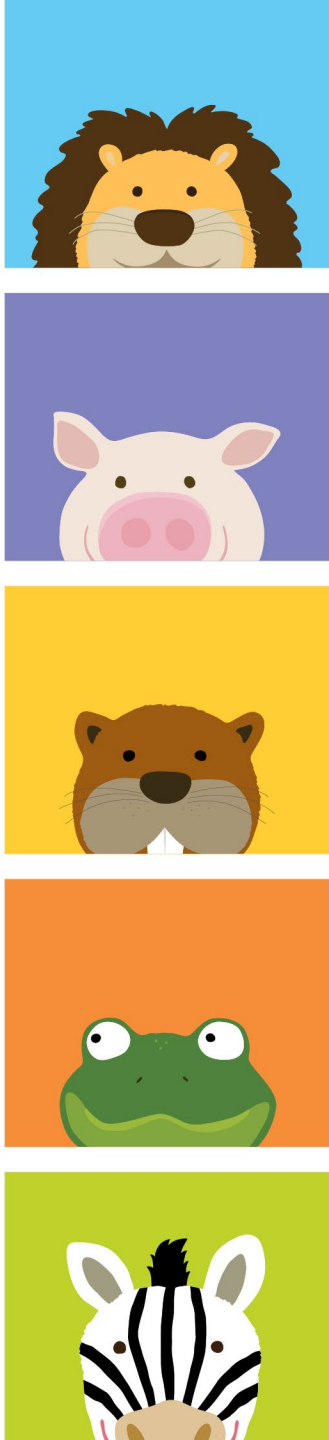
Mechanism	• Inhibits activity of TNFα to reduce proinflammatory cytokines, leukocyte migration, and acute phase reactants
Dosing	• 10 mg/kg IV over 2 hours • Higher dose preferred for refractory Kawasaki disease
Adverse Effects	• Infusion-related reactions • Autoantibody development • Dermatologic reactions • Hepatotoxicity • Hypersensitivity reactions • Tuberculosis or hepatitis B reactivation
Considerations	• Premedication may be considered with medications such as acetaminophen, diphenhydramine, and famotidine • Rescue medications should be available for potential hypersensitivity reactions • Tuberculosis screening is not required for single-dose therapy



Jone et al. *Circulation.* 2024;150(23):e481-e500
Gorelik et al. *Arthritis Care Res (Hoboken).* 2022;74(4):538-548

KIDCARE 2021

Infliximab versus Second Intravenous Immunoglobulin for Treatment of Resistant Kawasaki Disease in the USA	
Purpose	To compare infliximab with a second infusion of IVIG for treatment of resistant Kawasaki disease
Study Design	Randomized comparative analysis
Population	Multicenter; pediatric patients (N=103) with IVIG-resistant disease
Intervention	Infliximab (n=54) vs repeat IVIG (n=49) • Infliximab 10 mg/kg over 2 hours without premedication • IVIG 2 g/kg over 8 to 12 hours • Crossover for patients with fever 24 hours to 7 days after completion
Outcomes	Fever resolution at 24 hours, fever duration, hospital LOS, inflammatory markers, Z-scores

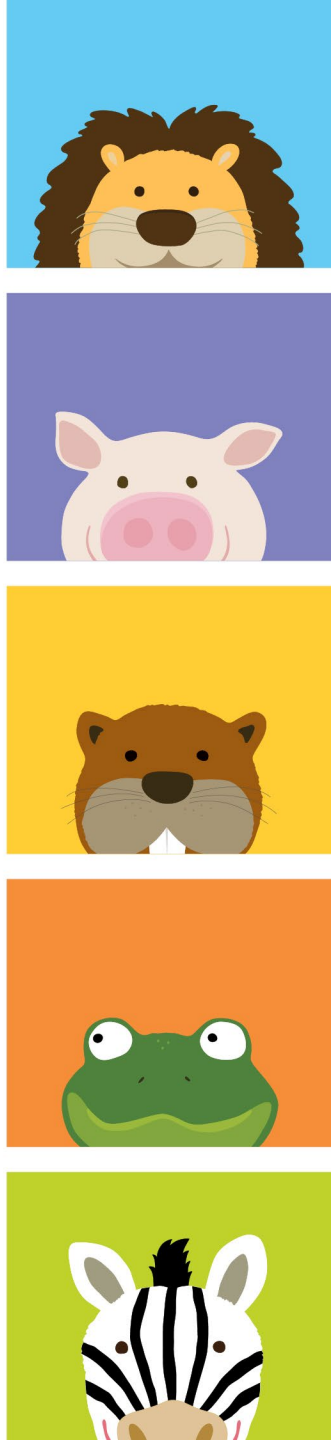


Burns et al. *Lancet Child Adolesc Health.* 2021;5(12):852-861

KIDCARE 2021

Outcomes	Infliximab (n=54)	Repeat IVIG (n=49)	p-value
Fever resolution at 24 hours, n (%)	40 (77)	25 (51)	0.0076
Fever days, mean ± SD	1.5 ± 1.4	2.5 ± 2.5	0.014
Crossover treatment for fever beyond 24 hours, n (%)	9 (17)	22 (45)	0.0024
Hospital days, mean ± SD	3.2 ± 2.1	4.5 ± 2.5	0.0005

- Hemoglobin drop of 2 g/dL seen in 19/58 (33%) who received IVIG as first or second treatment and 3/43 (7%) who received infliximab only (p=0.0028)
- No difference between groups for inflammatory markers or Z-scores
- Infliximab was associated with a shorter duration of fever, reduced need for additional therapy, less severe anemia, and shorter hospitalization compared with repeat IVIG



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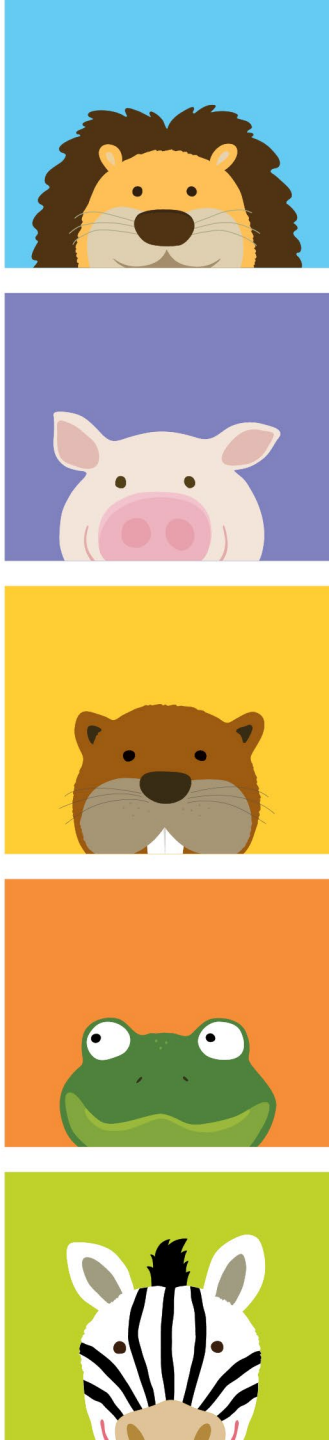
Refractory Management

Agent	Mechanism	Dosing	Duration
Cyclosporine	Calcineurin-NFAT pathway inhibitor	5 mg/kg/day PO divided q12h	10 days or until afebrile, clinically improving, and CRP < 1 mg/dL
Anakinra	Recombinant IL-1b receptor antagonist	10 mg/kg/day IV or SC divided q12h	While hospitalized; wean prior to discharge
Cyclophosphamide	Alkylating agent	10 mg/kg/day IV	1 to 2 doses
Etanercept	Soluble receptor inhibitor of TNF-a and TNF-B	0.8 mg/kg SC weekly	3 weeks

No specific agent is recommended for cases that are refractory to both IVIG and infliximab



Jone et al. *Circulation.* 2024;150(23):e481-e500

Assessment Question #2

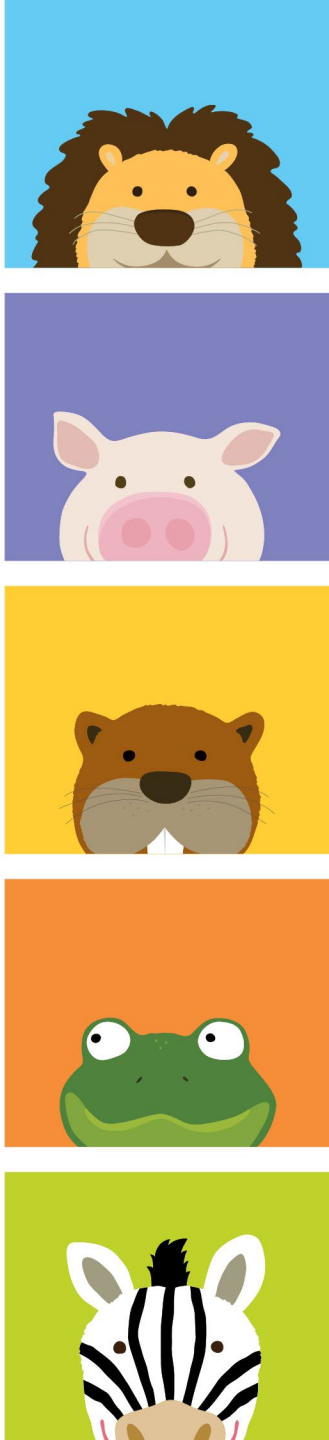
- TK is a 4-year-old male diagnosed with complete Kawasaki disease. He has been treated with IVIG 2 g/kg over 8 hours. It has now been 48 hours since the infusion completed. The nurse reports that he appears irritable, and his temperature is 101.2 F. What is the best course of action based on guideline recommendations?

A. Repeat IVIG 2 g/kg over 8 to 12 hours

B. Give infliximab 10 mg/kg IV over 2 hours

C. Give cyclophosphamide 10 mg/kg IV

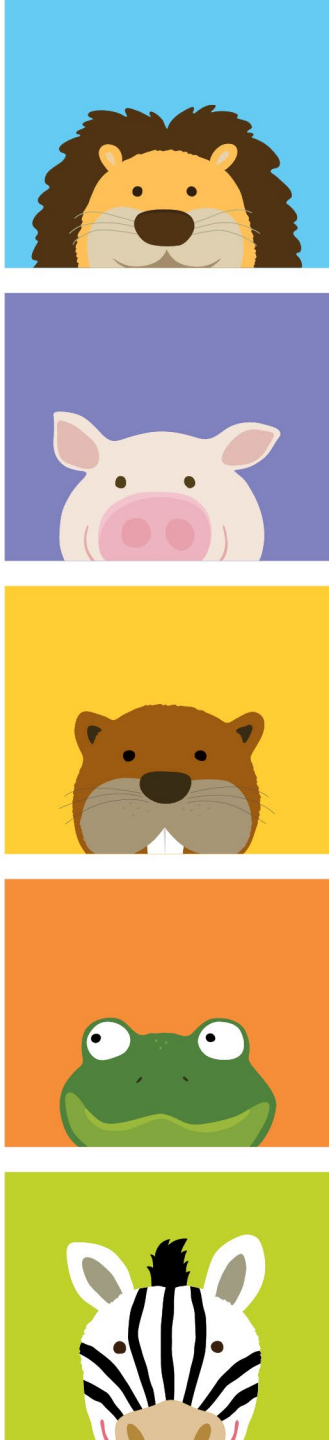
D. Wait until 72 hours after infusion for fever resolution



Management

KD diagnosis → IVIG + Aspirin

Z-score > 2.5 (or age < 6 months)	Z-score > 5	Z-score > 10
Methylprednisolone	Clopidogrel	Anticoagulation

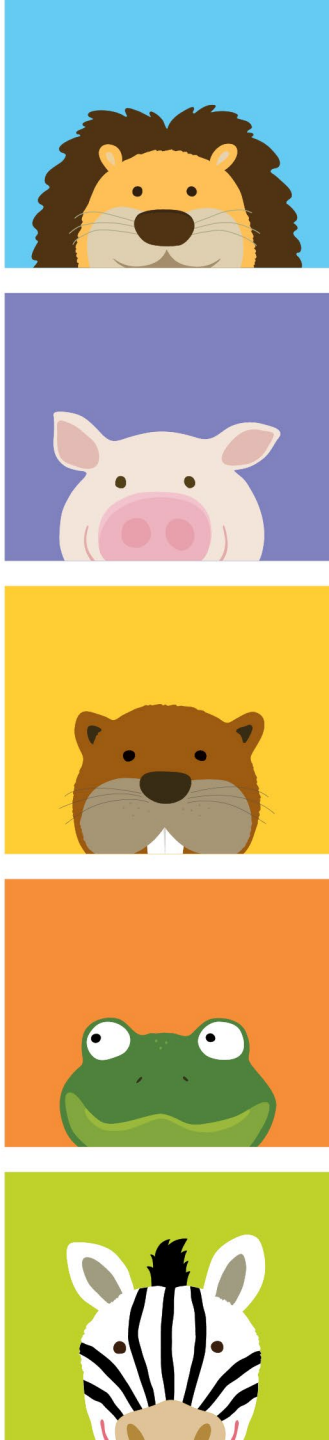


McCrindle et al. *Circulation.* 2017;135(17):e927-e999

Aspirin

Aspirin is started in all patients diagnosed with Kawasaki disease to prevent thrombosis of coronary artery aneurysms

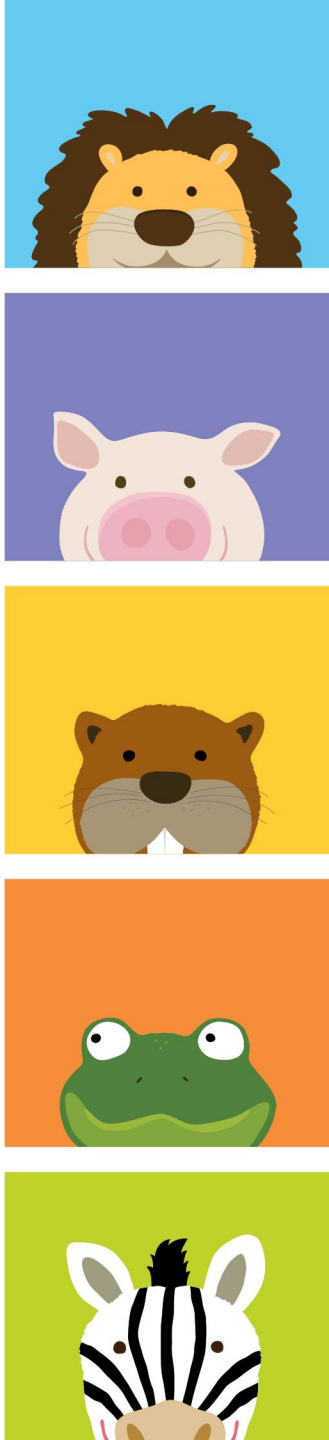
Mechanism	• Irreversible inhibition of COX-1 and COX-2 to reduce formation of prostaglandins, including platelet activator thromboxane A2
Dosing	• 3 to 5 mg/kg PO daily (maximum dose 81 mg) • Standard-dose aspirin (30 to 50 mg/kg/day) can be considered in acute febrile phase but has not demonstrated benefit for coronary artery aneurysms
Adverse Effects	• Reye's syndrome • GI bleeding • Anemia • LFT elevations
Considerations	• Incidence of Reye's syndrome is very low • Doses should be rounded to fractions of 81 mg tablet for administration • NSAIDs compete with aspirin for COX-1 and COX-2 binding which may decrease antiplatelet efficacy



Jone et al. *Circulation.* 2024;150(23):e481-e500
Gorelik et al. *Arthritis Care Res (Hoboken).* 2022;74(4):538-548

Kim et al. 2017

Medium- or Higher-Dose Acetylsalicylic Acid for Acute Kawasaki Disease and Patient Outcomes	
Purpose	To investigate the effect of medium- or higher-dose aspirin for treating acute-phase Kawasaki disease to prevent coronary artery aneurysm
Study Design	Retrospective cohort study
Population	Multicenter; pediatric patients (N=8456) with acute Kawasaki disease
Intervention	Medium- or higher-dose (n=7947) vs low-dose aspirin (n=509) • Medium or higher-dose regimen: ≥ 30 mg/kg/day • Low-dose regimen: 3 to 5 mg/kg/day • IVIG 2 g/kg once
Outcomes	Incidence of coronary artery aneurysms, IVIG resistance, duration of fever

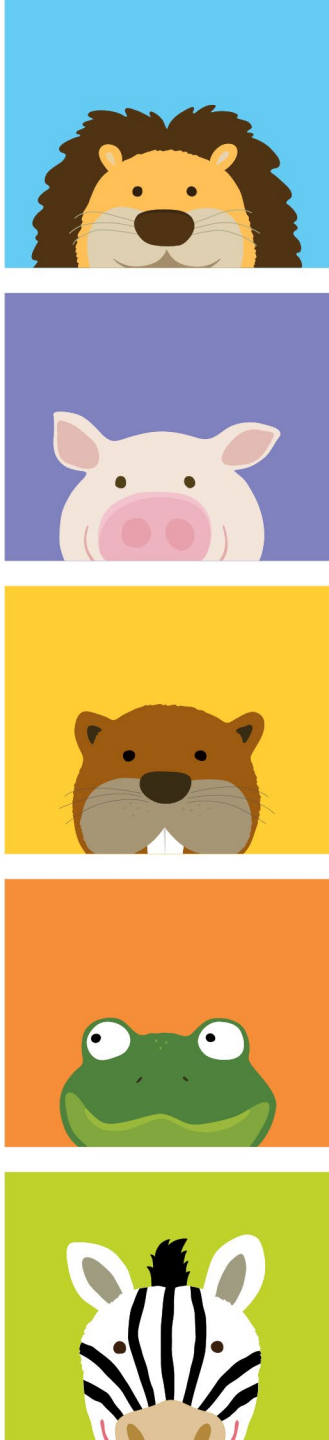


Kim et al. *J Pediatr.* 2017;184:125-129.e1

Kim et al. 2017

Outcomes	HD group (n=7947)	LD group (n=509)	p-value
Unresponsive to IVIG, n (%)	838 (10.5)	86 (16.9)	< 0.001
Duration of fever, days, mean ± SD	5.7 ± 2.2	6.1 ± 1.9	0.001
Based on Z-score			
CAA, n (%)	1968 (24.8)	93 (18.3)	< 0.001
Giant aneurysm, n (%)	54 (0.7)	3 (0.6)	0.810
Based on Japanese criteria			
CAA, n (%)	1507 (19.0)	53 (10.4)	< 0.001
Giant aneurysm, n (%)	17 (0.2)	0 (0)	0.296

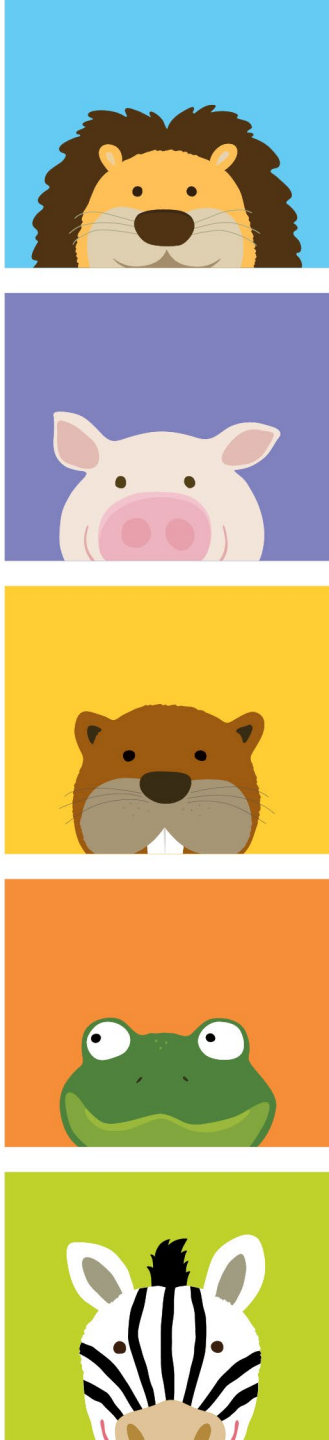
- Improved IVIG responsiveness and fever resolution in higher-dose group but increased rate of coronary artery aneurysms compared to low-dose group
- Results do not support use of high-dose aspirin for acute phase of Kawasaki disease



Kim et al. *J Pediatr.* 2017;184:125-129.e1

Hayashi et al. 2024

Initial Intravenous Immunoglobulin Therapy without Aspirin for Acute Kawasaki Disease	
Purpose	To clarify the necessity of aspirin administration combined with IVIG therapy in the treatment of acute Kawasaki disease
Study Design	Retrospective cohort study
Population	Multicenter; pediatric patients (N=735) with Kawasaki disease hospitalized between days 4 and 10 of illness
Intervention	High-dose aspirin (n=333) vs no routine aspirin (n=402) with IVIG • High-dose regimen: 30 to 50 mg/kg/day • No routine aspirin: Patients with coronary artery lesions or pericardial effusion were started on 3 to 5 mg/kg/day • IVIG 2 g/kg once
Outcomes	Incidence of coronary artery lesions, IVIG responsiveness

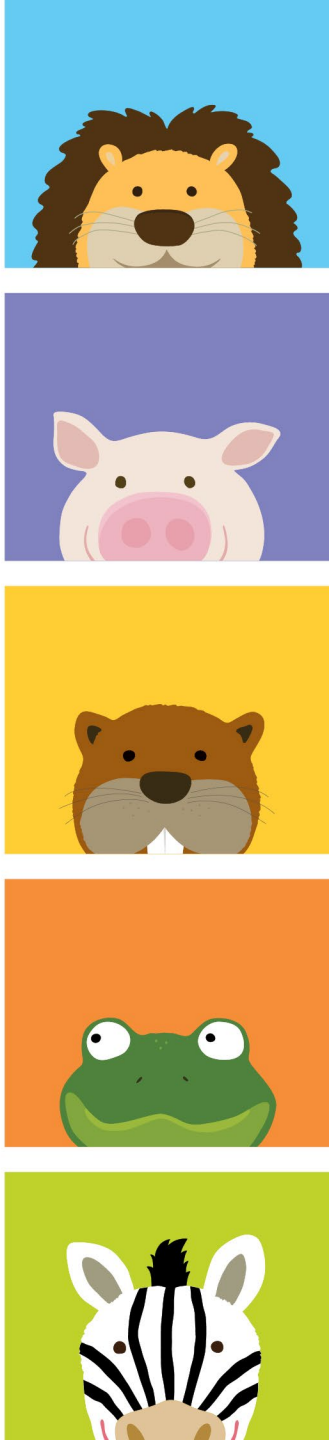


Hayashi et al. *BMJ Paediatr Open.* 2024;8(1):e002312

Hayashi et al. 2024

Outcomes	Unadjusted RR (95% CI)	p-value	Adjusted RR (95% CI)	p-value
Development of coronary artery lesions within 1 month				
High-dose aspirin	Reference	N/A	Reference	N/A
No routine aspirin	1.27 (0.97-1.67)	0.08	1.12 (0.83-1.51)	0.46
IVIG unresponsiveness				
High-dose aspirin	Reference	N/A	Reference	N/A
No routine aspirin	1.04 (0.92-1.19)	0.50	1.09 (0.92-1.29)	0.30

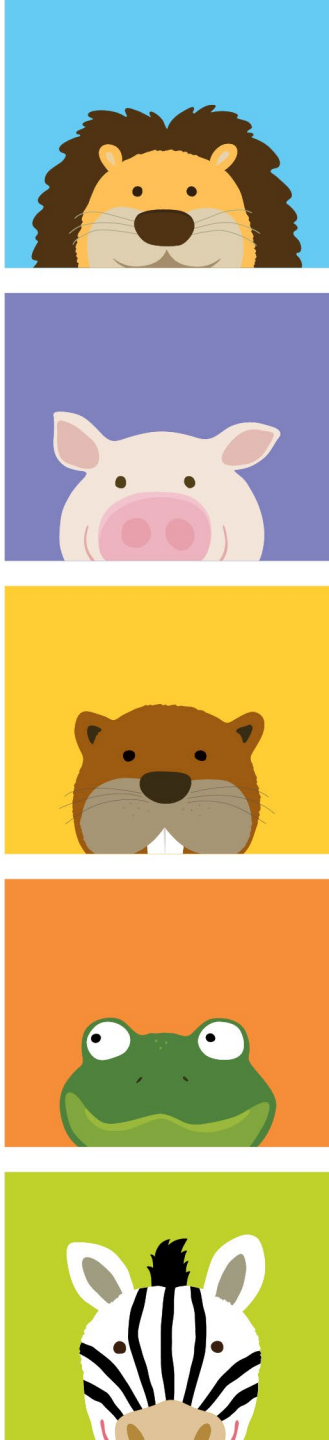
- Coronary artery lesions occurred in 12/333 (3.6%) for aspirin vs 15/402 (4%) for IVIG alone
- Non-responders to initial IVIG were similar between the two groups at 78/333 (23%) for aspirin vs 83/402 (22%) for IVIG alone
- Compared with high-dose aspirin treatment, treatment without aspirin in the acute phase was not associated with increased complications



Management

KD diagnosis → IVIG + Aspirin

Z-score ≥ 2.5 (or age < 6 months)	Z-score ≥ 5	Z-score ≥ 10
Methylprednisolone	Clopidogrel	Anticoagulation

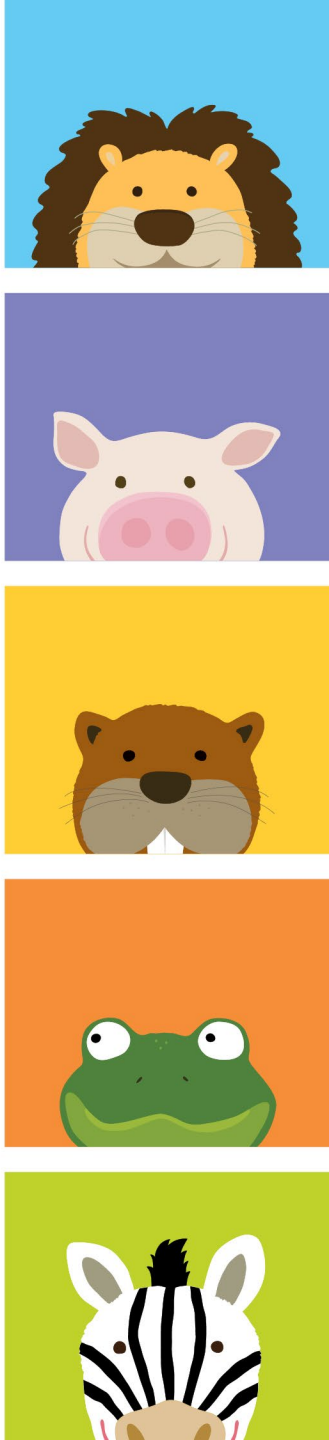


McCrindle et al. *Circulation.* 2017;135(17):e927-e999

Methylprednisolone

Methylprednisolone is used as part of initial anti-inflammatory therapy for patients < 6 months of age or Z-score ≥ 2.5

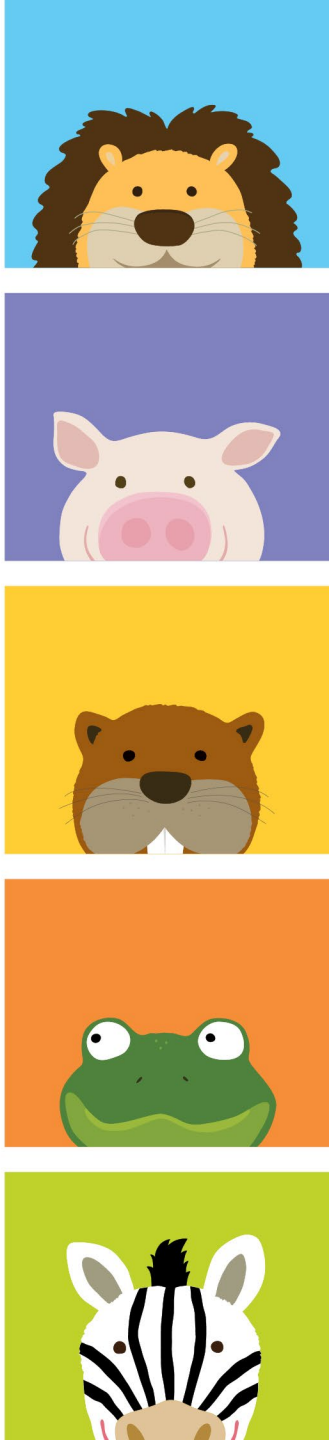
Mechanism	• Reduces inflammation by suppressing migration of leukocytes and reversing capillary permeability
Dosing	• 2 mg/kg/day IV (maximum dose 60 mg) with taper over 2 to 3 weeks
Adverse Effects	• Adrenal suppression • Bone growth inhibition • CNS disturbances • GI upset • Metabolic syndrome • Immunosuppression
Considerations	• Oral prednisolone can be used to taper when clinically improving or ready to discharge



McCrindle et al. *Circulation.* 2017;135(17):e927-e999

RAISE 2012

Efficacy of Immunoglobulin plus Prednisolone for Prevention of Coronary Artery Abnormalities in Severe Kawasaki Disease	
Purpose	To assess whether addition of prednisolone to IVIG with aspirin would reduce the incidence of coronary artery abnormalities in patients with severe Kawasaki disease
Study Design	Prospective, randomized, open-label, blinded-endpoints trial
Population	Multicenter; pediatric patients (N=248) with severe Kawasaki disease based on Kobayashi score
Intervention	Prednisolone plus IVIG with aspirin (n=125) or IVIG with aspirin (n=123) • Prednisolone 2 mg/kg/day for 15 days after CRP normalization • IVIG 2 g/kg once • Aspirin 30 mg/kg/day
Outcomes	Incidence of coronary artery abnormalities, adverse events

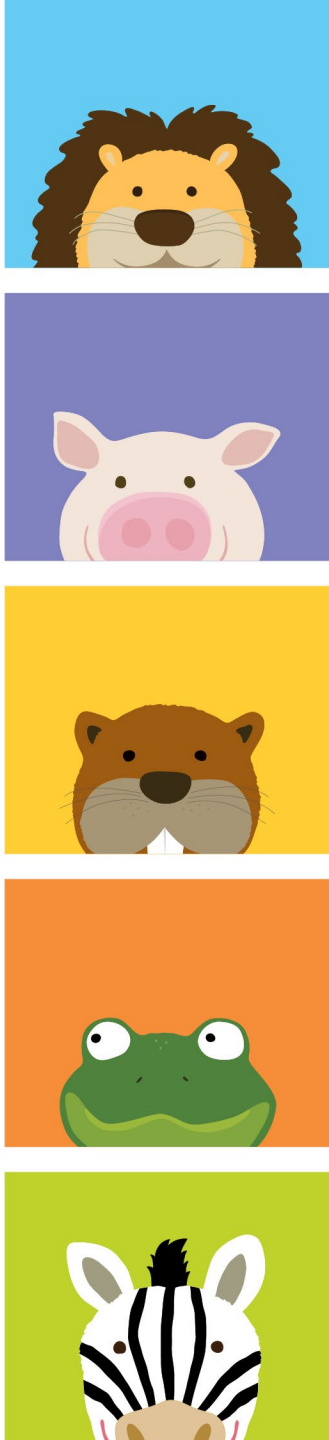


Kobayashi et al. *Lancet.* 2012;379(9826):1613-1620

RAISE 2012

Outcomes	IVIG + prednisolone (n=121)	IVIG monotherapy (n=121)	p-value
Coronary artery abnormality			
During study period, n (%)	4 (3)	28 (23)	< 0.0001
At week 4, n (%)	4 (3)	15 (13)	0.014
Fever days following enrollment, median (IQR)	1 (1-1)	2 (1-4)	< 0.0001
Additional therapy required, n (%)	16 (13)	48 (40)	< 0.0001
Non-response to primary treatment, n (%)	6 (5)	36 (30)	< 0.0001
Relapse, n (%)	13 (11)	15 (12)	0.84

- Addition of steroid significantly reduced coronary artery abnormalities, fever duration, and IVIG unresponsiveness
- Rates of adverse events were similar between groups



Kobayashi et al. *Lancet.* 2012;379(9826):1613-1620

RAISE 2012

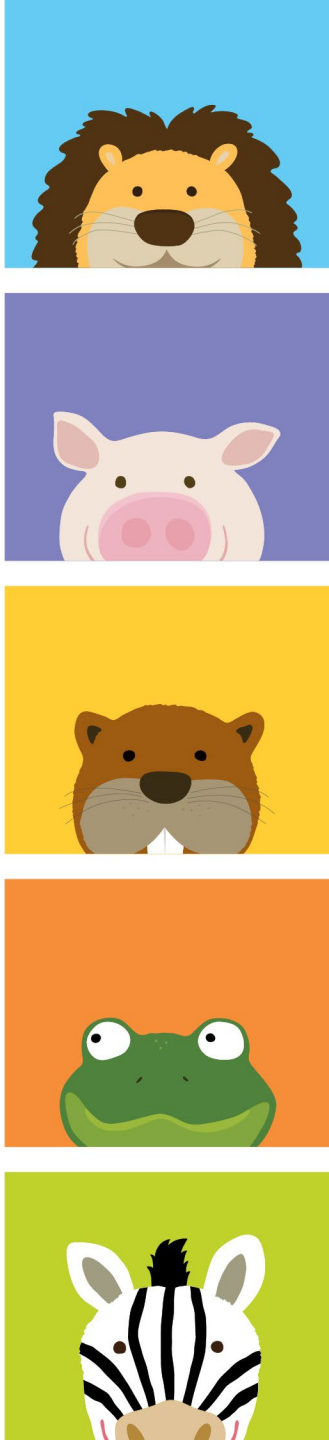
While RAISE showed substantial benefit for adding corticosteroids in patients with severe Kawasaki disease, the Kobayashi score is only accurate in Japanese populations

Benefits of adding corticosteroids have been extrapolated to other groups at high risk of developing coronary artery aneurysms using scoring tools designed for North American populations

Z-score > 2.5

or

Age < 6 months

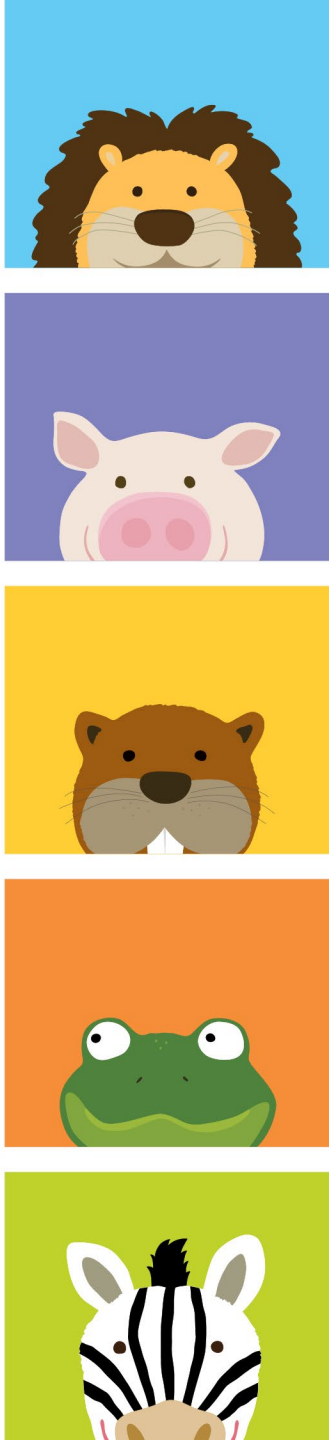


Kobayashi et al. *Lancet.* 2012;379(9826):1613-1620
Son et al. *J Am Heart Assoc.* 2019;8(11):e011319

Management

KD diagnosis → IVIG + Aspirin

Z-score > 2.5 (or age < 6 months)	Z-score > 5	Z-score > 10
Methylprednisolone	Clopidogrel	Anticoagulation

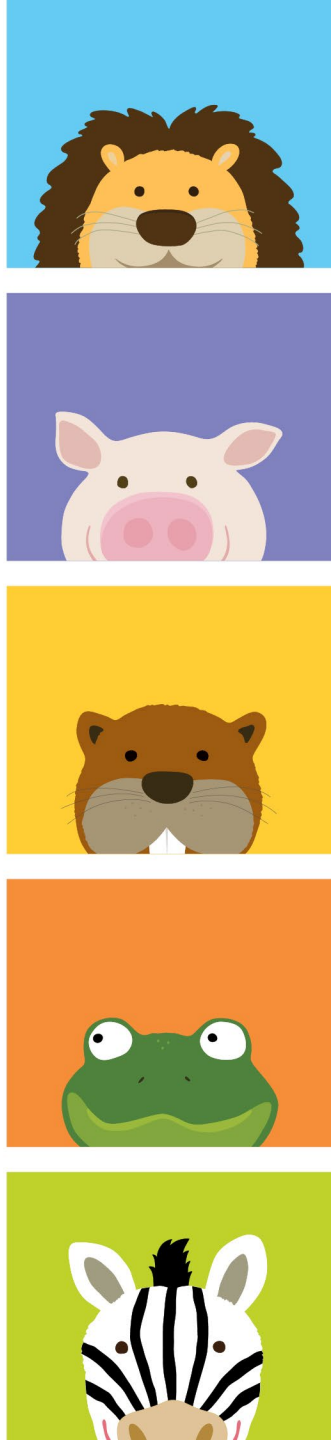


McCrindle et al. *Circulation.* 2017;135(17):e927-e999

Clopidogrel

Clopidogrel is added to aspirin as dual antiplatelet therapy in patients with Z-score ≥ 5

Mechanism	• Exhibits antiplatelet effects by irreversibly inhibiting P2Y12 component of ADP receptors on platelet surface
Dosing	• 0.2 to 1 mg/kg PO daily (maximum dose 1 mg/kg)
Adverse Effects	• Bleeding • Angioedema • Thrombotic thrombocytopenic purpura
Considerations	• Data for using clopidogrel is extrapolated from studies of adults with coronary artery and cerebrovascular disease • Compounded suspension can be used for providing doses smaller than commercially available 75 mg tablet



McCrindle et al. *Circulation.* 2017;135(17):e927-e999

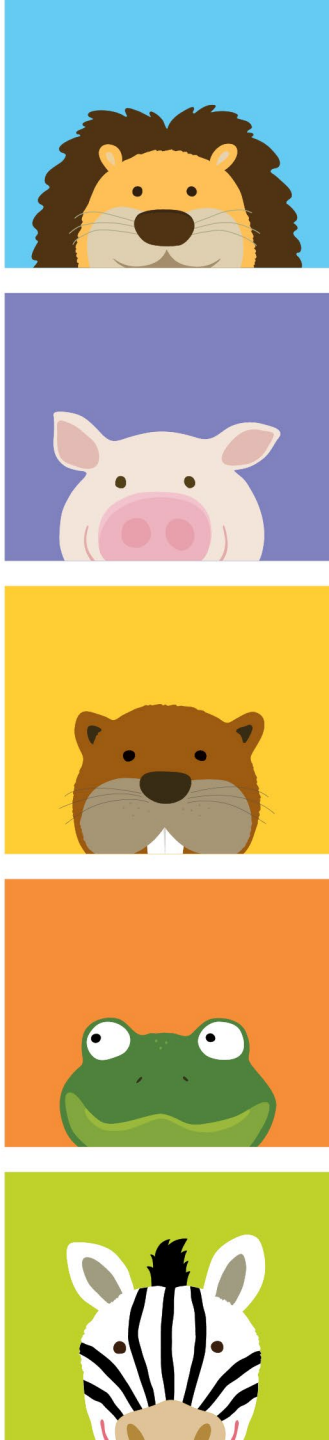
Management

KD diagnosis → IVIG + Aspirin

Z-score > 2.5 (or age < 6 months) → Methylprednisolone

Z-score > 5 → Clopidogrel

Z-score > 10 → Anticoagulation

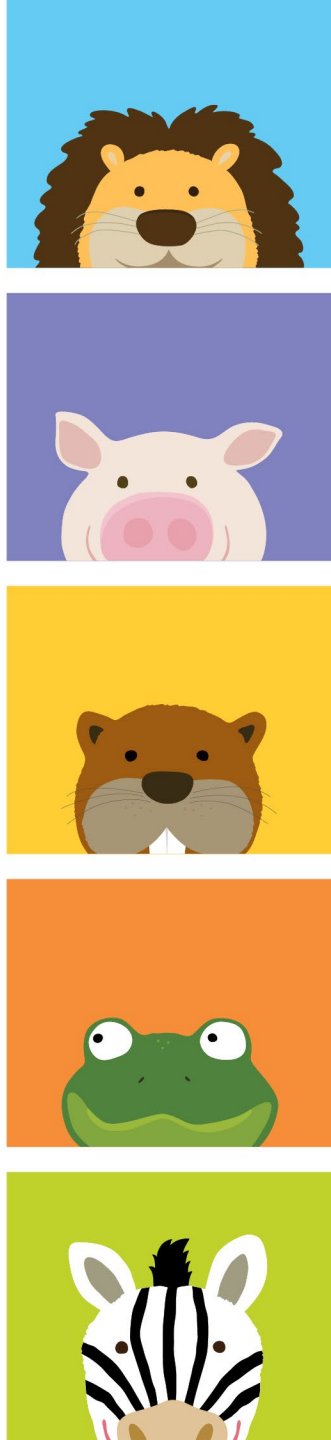


McCrindle et al. *Circulation.* 2017;135(17):e927-e999

Anticoagulation

According to current guidelines, anticoagulation with warfarin or LMWH should be initiated in patients with Z-score ≥ 10

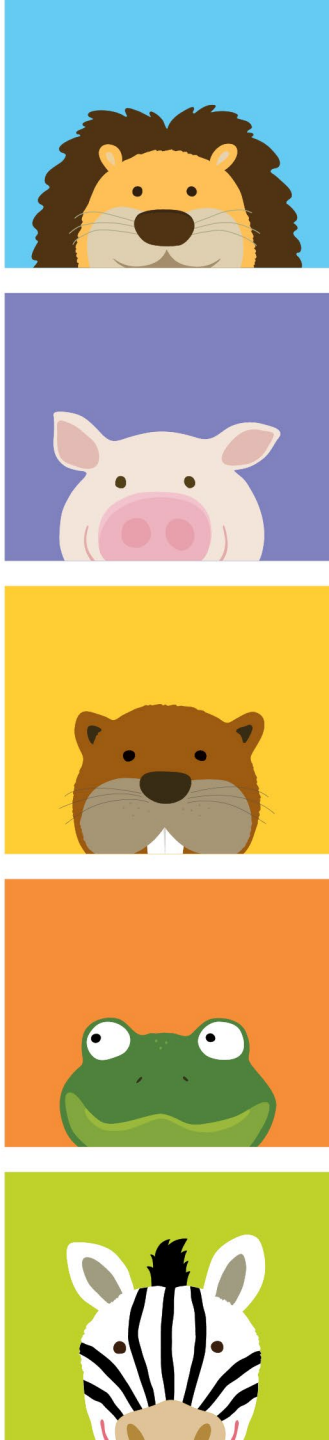
Mechanism	• Warfarin inhibits activity of VKORC to reduce production of clotting factors II, VII, IX, and X as well as protein C and S • Enoxaparin enhances inhibition of clotting factors by antithrombin III, particularly factor Xa	
Dosing	• Warfarin 0.2 mg/kg PO as loading dose then 0.1 mg/kg PO daily (INR goal 2-3) • Enoxaparin 1 mg/kg SC q12h or 1.5 mg/kg SC q12h if age < 2 months (anti-Xa goal 0.5-1)	
Adverse Effects	Warfarin • Bleeding • Decreased bone mineral density • Skin necrosis	Enoxaparin • Bleeding • Spinal or epidural hematoma • Heparin-induced thrombocytopenia
Considerations	• Warfarin has extensive drug-drug and drug-food interactions • Anti-Xa levels for enoxaparin should be drawn 4 to 6 hours after dose • DOACs have become an increasingly common alternative to warfarin or LMWH	



McCrindle et al. *Circulation.* 2017;135(17):e927-e999

Manlhiot et al. 2020

Low-Molecular-Weight Heparin vs Warfarin for Thromboprophylaxis in Children With Coronary Artery Aneurysms After Kawasaki Disease	
Purpose	To determine the effectiveness of anticoagulation for thromboprophylaxis in large CAAs
Study Design	Retrospective cohort study
Population	Single center; pediatric patients (N=383) with Kawasaki disease and large coronary aneurysms
Intervention	LMWH (n=114) vs warfarin (n=80) vs no anticoagulation (n=189) • 87% of patients received IVIG during acute phase • 96% of patients received aspirin and 23% received clopidogrel
Outcomes	Incidence of coronary artery thrombosis, recurrent thrombosis, severe bleeding complications

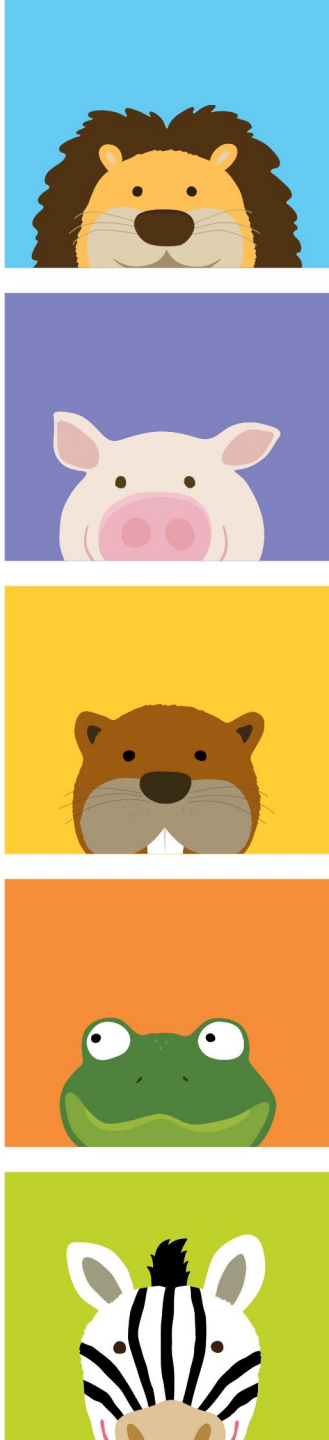


Manlhiot et al. *Can J Cardiol.* 2020;36(10):1598-1607

Manlhiot et al. 2020

Outcomes	HR (95% CI)	p-value
Coronary artery thrombosis		
LMWH	1.46 (0.42-5.12)	0.56
Warfarin	Reference	N/A
None	12.8 (5.0-32.81)	< 0.001
Recurrent thrombosis		
LMWH	2.85 (0.61-13.40)	0.18
Warfarin	Reference	
None	0.88 (0.14-5.62)	0.89
Major bleeding complications		
LMWH	2.05 (0.55-7.64)	0.28
Warfarin	Reference	

- Significant reduction in coronary artery thrombosis with warfarin compared to no anticoagulation
- No significant difference for secondary prevention of recurrent thrombosis
- No difference between warfarin and LMWH for major bleeding complications



Manlhiot et al. *Can J Cardiol.* 2020;36(10):1598-1607

Anticoagulation

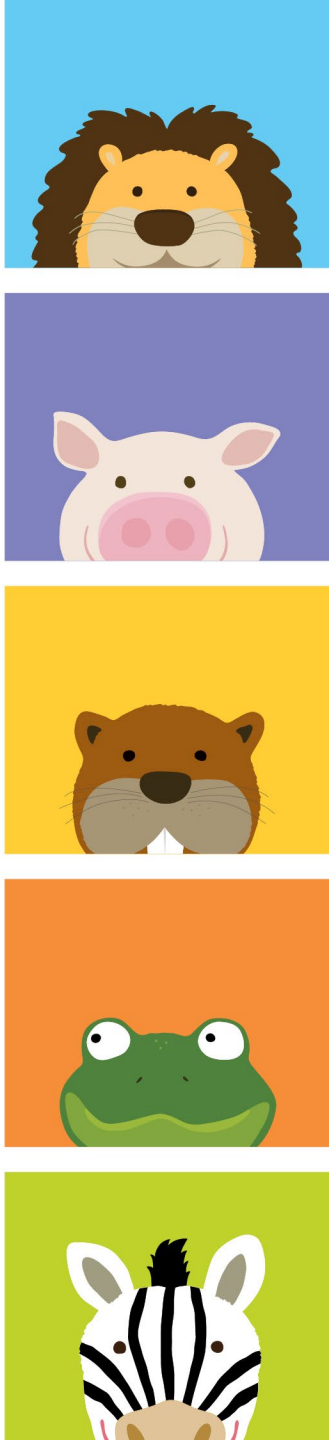
DOACs have been considered as alternative anticoagulation for Kawasaki disease

Further research is being conducted to establish safety and efficacy

- Reasonable option for patients unable to be anticoagulated with warfarin or LMWH

Commercially available dosage forms should be taken into consideration for ease of administration

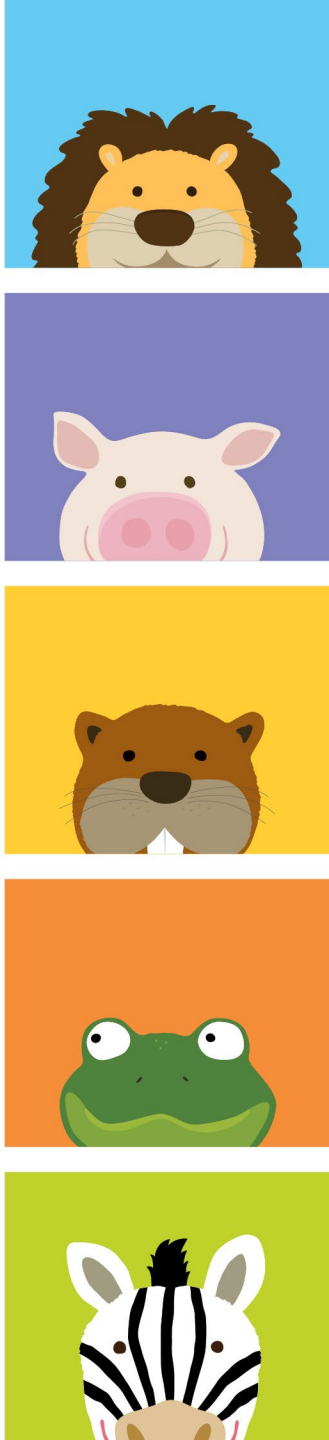
- Apixaban is available as oral tablets, soluble tablets, and sprinkle capsules
- Rivaroxaban is available as oral tablets and reconstituted suspension



Jone et al. *Circulation.* 2024;150(23):e481-e500

Dummer et al. 2023

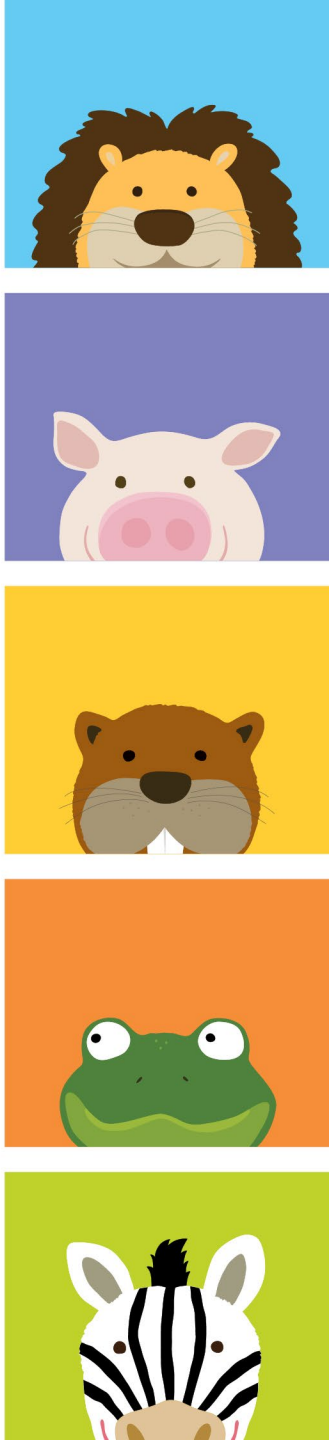
DOACs in Patients With Giant Coronary Artery Aneurysms After Kawasaki Disease	
Purpose	To describe outcomes of patients with giant coronary artery aneurysms after Kawasaki disease treated with direct oral anticoagulants
Study Design	Retrospective case series
Population	Single center; pediatric and adult patients (N=24) with Kawasaki disease and giant coronary artery aneurysms
Intervention	DOAC therapy as alternative thromboprophylaxis • 17 patients were treated with apixaban • 6 patients were treated with rivaroxaban • 1 patient was treated with dabigatran
Outcomes	Major adverse cardiovascular events, major bleeding events



Dummer et al. *JAMA Netw Open.* 2023;6(11):e2343801

Dummer et al. 2023

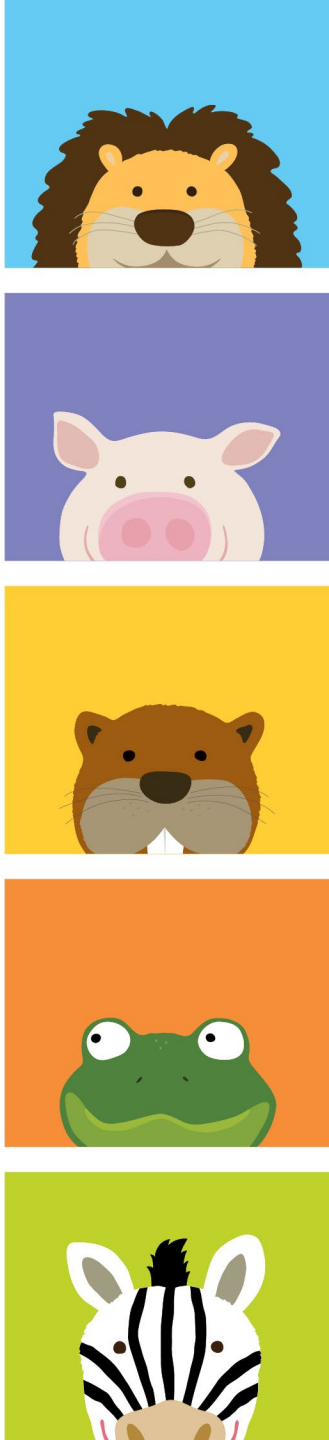
- Median observation period was 4.9 years with 138 total treatment-years observed
- Of 24 patients, 6 started DOAC therapy at age < 18 years
- No major bleeding events occurred during the observation period
- Major adverse cardiac events occurred in 3 patients
- Reasonable to consider DOAC as chronic treatment for adult and pediatric patients with Kawasaki disease and giant aneurysms



Dummer et al. *JAMA Netw Open.* 2023;6(11):e2343801

SAXOPHONE 2023

Apixaban for Prevention of Thromboembolism in Pediatric Heart Disease	
Purpose	To describe safety and efficacy of apixaban for thromboprophylaxis in children with heart disease
Study Design	Phase 2, open-label, randomized clinical trial
Population	Multicenter; pediatric patients (N=192) with congenital or acquired heart disease including Kawasaki disease (n=27)
Intervention	Apixaban (n=126) vs LMWH or warfarin (n=62) • Apixaban dosing was based on stratified weight categories • LMWH and warfarin dosing followed local guidelines
Outcomes	Thromboembolic events, bleeding events, pharmacokinetic exposures

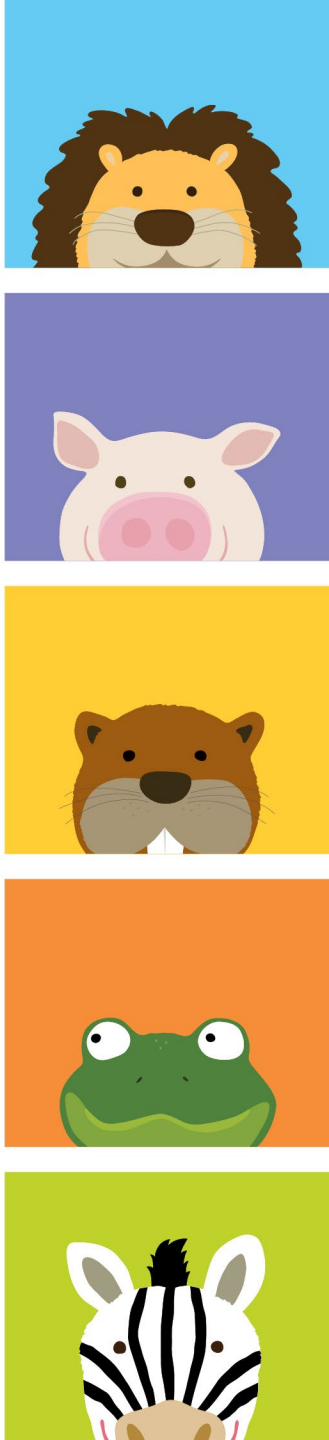


Payne et al. *J Am Coll Cardiol.* 2023;82(24):2296-2309

SAXOPHONE 2023

Weight Range	Apixaban Dose	Formulations Used
3 to < 4 kg	0.2 mg PO BID	0.1 mg capsule
4 to < 5 kg	0.3 mg PO BID	0.1 mg capsule
5 to < 6 kg	0.5 mg PO BID	0.5 mg tablet
6 to < 9 kg	1 mg PO BID	0.5 mg tablet
9 to < 12 kg	1.5 mg PO BID	0.5 mg tablet
12 to < 18 kg	2 mg PO BID	0.5 mg tablet or 0.4 mg/mL oral solution
18 to < 25 kg	3 mg PO BID	0.5 mg tablet or 0.4 mg/mL oral solution
25 to < 35 kg	4 mg PO BID	0.5 mg tablet or 0.4 mg/mL oral solution
≥ 35 kg	5 mg PO BID	0.5 mg tablet, 0.4 mg/mL oral solution, or 5 mg tablet

Oral solution was not used in patients < 5 years of age due to contents of propylene glycol

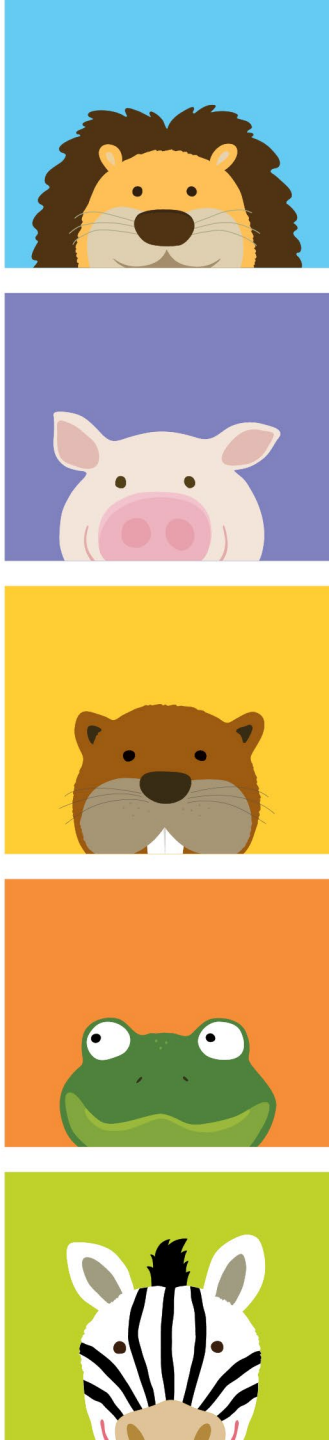


Payne et al. *J Am Coll Cardiol.* 2023;82(24):2296-2309

SAXOPHONE 2023

Outcomes	Apixaban (n=126)	VKA/LMWH (n=62)
Composite of major and clinically relevant non-major bleeding, incidence rate per 100 person-years	1.8	4
All bleeding, incidence rate per 100 person-years	100	58.2

- 1 apixaban participant (0.8%) and 3 with LMWH or warfarin (4.8%) had both major or clinically relevant nonmajor bleeding
- Apixaban incidence rate for all bleeding events was nearly twice the rate of SOC, driven by 12 participants with ≥4 minor bleeding events
- No thromboembolic events or deaths occurred in either arm
- Pediatric steady-state exposures were consistent with adult levels

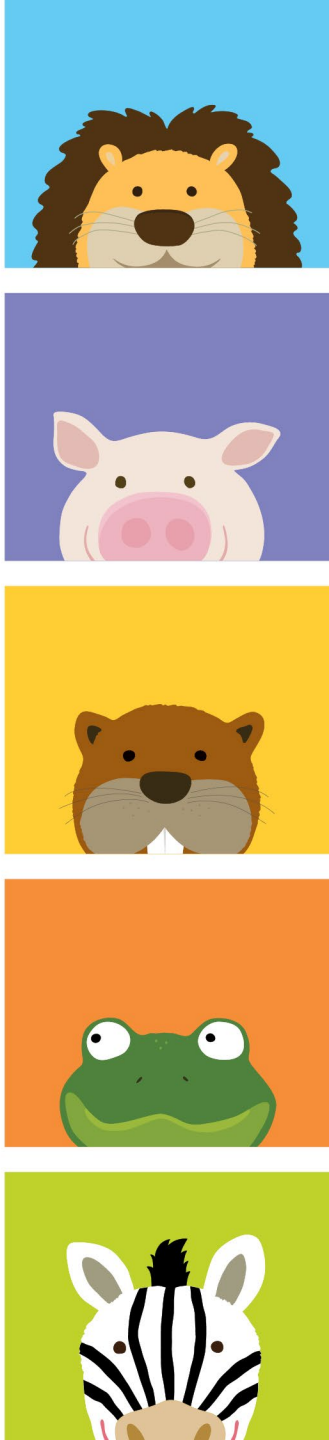


Payne et al. *J Am Coll Cardiol.* 2023;82(24):2296-2309

Anticoagulation

Rivaroxaban has not been studied in Kawasaki disease, but pediatric dosing exists for treatment and prevention of VTE associated with other conditions

Weight Range	Rivaroxaban Dose	Formulations Available
2.6 to < 3 kg	0.8 mg PO TID	1 mg/mL oral suspension
3 to < 4 kg	0.9 mg PO TID	1 mg/mL oral suspension
4 to < 5 kg	1.4 mg PO TID	1 mg/mL oral suspension
5 to < 7 kg	1.6 mg PO TID	1 mg/mL oral suspension
7 to < 8 kg	1.8 mg PO TID	1 mg/mL oral suspension
8 to < 9 kg	2.4 mg PO TID	1 mg/mL oral suspension
9 to < 10 kg	2.8 mg PO TID	1 mg/mL oral suspension
10 to < 12 kg	3 mg PO TID	1 mg/mL oral suspension
12 to < 30 kg	5 mg PO BID	1 mg/mL oral suspension
30 to < 50 kg	15 mg PO daily	1 mg/mL oral suspension or 15 mg tablet
≥ 50 kg	20 mg PO daily	1 mg/mL oral suspension or 20 mg tablet



Jone et al. *Circulation.* 2024;150(23):e481-e500

Assessment Question #3

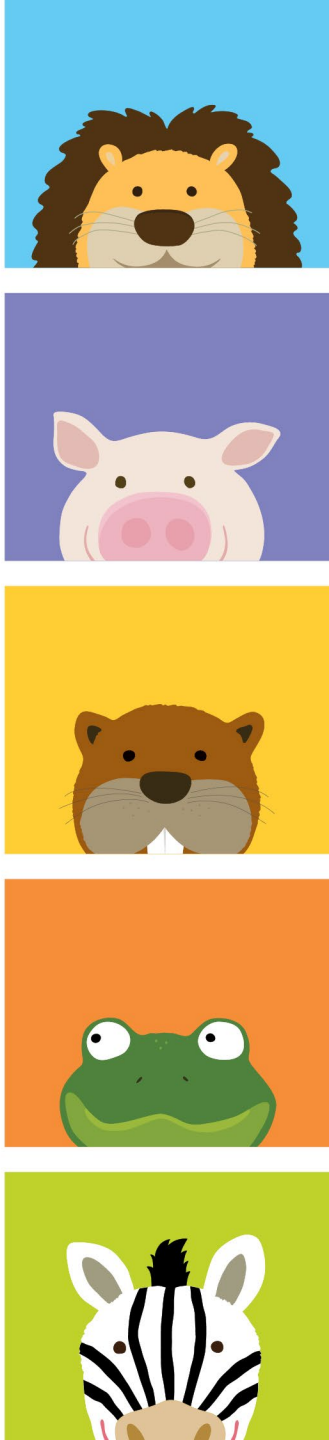
- TK is a 4-year-old male diagnosed with complete Kawasaki disease. He has defervesced following treatment with IVIG and infliximab. His maximum coronary artery Z-score is 2.3. What medication is most appropriate to start in this patient?

A. Warfarin 0.2 mg/kg PO once then 0.1 mg/kg PO daily

B. Aspirin 3 to 5 mg/kg PO daily

C. Enoxaparin 1 mg/kg SC q12h

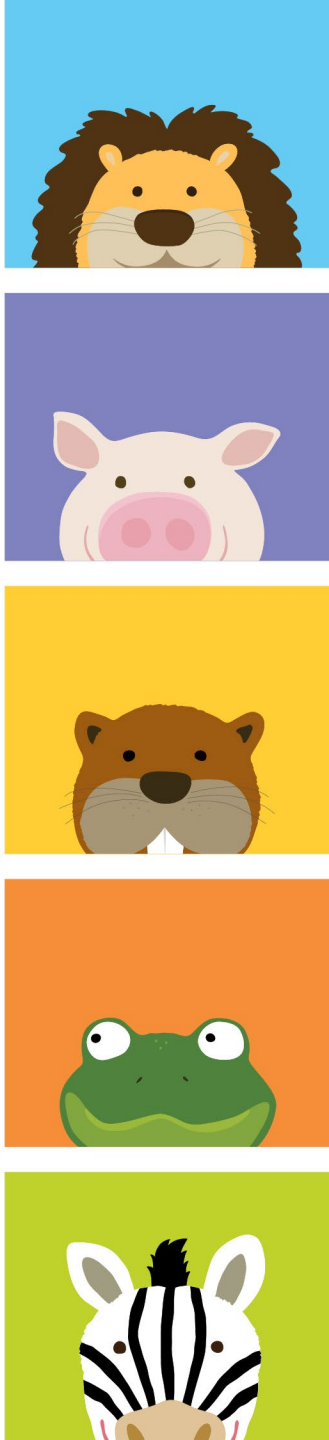
D. Clopidogrel 0.2 to 1 mg/kg PO daily



Maintenance Therapy

CAA Risk Level	Aspirin	Clopidogrel	Anticoagulation
1: No involvement	Discontinue after 4 to 6 weeks	Not indicated	Not indicated
2: Dilation only	Indicated until regression to normal	Not indicated	Not indicated
3.1: Small, current or persistent	Indicated	Not indicated	Not indicated
3.2: Small, regressed to normal	May be considered	Not indicated	Not indicated
4.1: Medium, current or persistent	Indicated	May be considered	Not indicated
4.2: Medium, regressed to small	Indicated	May be considered	Not indicated
4.3: Medium, regressed to normal	Reasonably indicated	May be considered	Not indicated
5.1: Large or giant, current or persistent	Indicated	May be considered	Reasonably indicated
5.2: Large or giant, regressed to medium	Indicated	Reasonably indicated	Not indicated
5.3: Large or giant, regressed to small	Indicated	Not indicated	Not indicated
5.4: Large or giant, regressed to normal	Reasonably indicated	Not indicated	Not indicated

Beta-blockers and statins have also been used as long-term therapy in patients with Kawasaki disease



McCrindle et al. *Circulation.* 2017;135(17):e927-e999

Conclusion

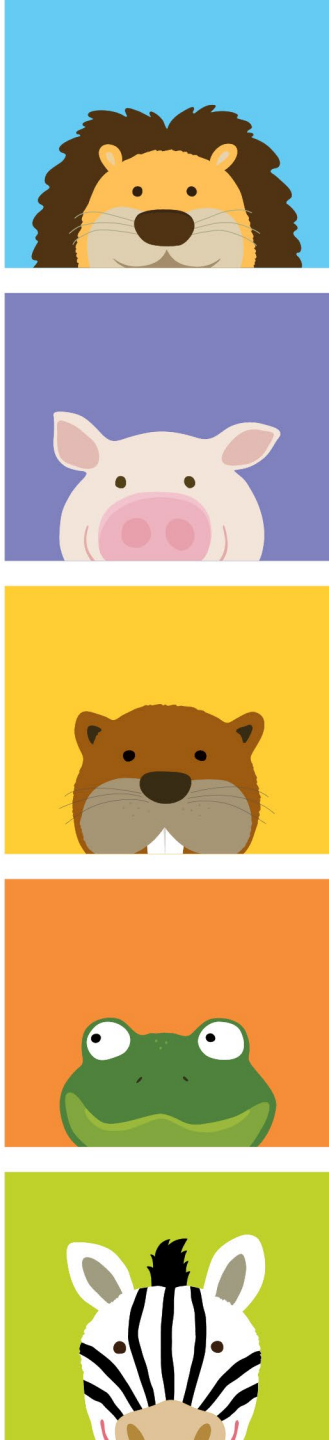
IVIG is the mainstay of therapy in acute phase of illness

Several options are available for IVIG-resistant disease with high-dose infliximab showing greatest efficacy

Low-dose aspirin should be started with IVIG in all patients

Steroids, clopidogrel, and anticoagulation may be added depending on severity of coronary artery abnormalities

Appropriate maintenance therapy is determined using risk stratification criteria



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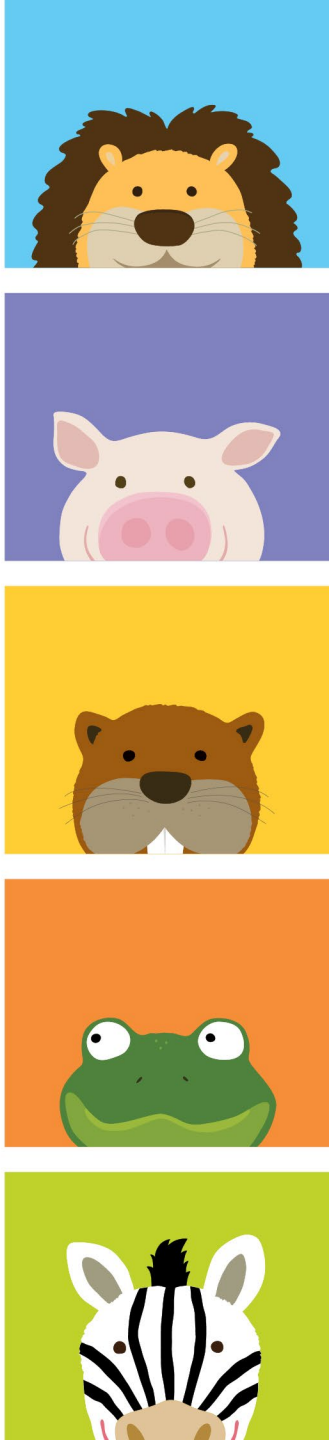

Questions?

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