

PRESENTED BY Robert Wittler, MD

# *Kawasaki Update*

Diagnosis & Initial Treatment

**KU**  
WICHITA  
PEDIATRICS  
The University of Kansas

## Disclosure

- I have no relevant financial relationships with the manufacturers(s) of any commercial products(s) and/or provider of commercial services discussed in this CME activity
- Recommended treatment modalities for Kawasaki disease are FDA approved but they are not necessarily specifically approved for Kawasaki disease

# Guideline

- American Heart Association Scientific Statement
- Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease. *Circulation* 2017; 135:e927-e999
- [https://www.ahajournals.org/doi/full/10.1161/CIR.0000000000000484?url\\_ver=Z39.88-2003&rfr\\_id=ori%3Arid%3Acrossref.org&rfr\\_dat=cr\\_pub%3Dpubmed](https://www.ahajournals.org/doi/full/10.1161/CIR.0000000000000484?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed)

# Epidemiology

- Unknown cause
- Estimated incidence in North America is ~25 cases per 100,000 children <5 years of age per year
- Highest relative risk is in Asian children, especially of Japanese ancestry
- Ratio of males to females is ~1.5:1
- Affects predominantly, but not exclusively, young children

# Epidemiology

- Most common in the winter and early spring in North America
- Nonspecific symptoms are common in the 10 days before diagnosis
- In Japan, the recurrent rate is ~3%, and the relative risk in siblings is 10-fold higher
- Case fatality rate is <0.1% in Japan
- Coronary artery aneurysms from KD account for 5% of acute coronary syndromes in adults <40 years of age

# Pathology

- KD vasculopathy primarily involves muscular arteries and is characterized by 3 linked processes:
  1. necrotizing arteritis
    - neutrophilic process complete within 2 weeks after fever onset
    - the only self-limited process and progressively destroys the arterial wall into the adventitia, causing aneurysms
  2. subacute/chronic vasculitis
    - infiltration of lymphocytes, plasma cells, and eosinophils with fewer macrophages that begins in the first 2 weeks after fever onset but can continue for months to years in a small subset of patients and is closely linked to LMP
  3. luminal myofibroblastic process (LMP)
    - LMP is characterized by a unique medial smooth muscle cell-derived myofibroblastic process that begins in the first 2 weeks and persists for months to years, with the potential to cause progressive arterial stenosis

# Pathology

- Large or giant coronary aneurysms  $\geq 8$  mm in diameter or with a Z score  $\geq 10$  do not resolve, regress, or remodel
  - rarely rupture and virtually always contain thrombi that can become occlusive
- Aneurysms with markedly damaged but partially preserved media may develop decreases in lumen diameter over time as the result of LMP or thrombi and can become progressively stenotic
- Pericarditis and myocarditis result from subacute/chronic inflammation, which is usually concentrated around coronary arteries

# Classic KD Diagnosis

- Presence of fever for at least 5 days (the day of fever onset is taken to be the first day of fever) together with at least 4 of the 5 principal clinical features
  1. Erythema and cracking of the lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa
  2. Bilateral bulbar conjunctival injection (often spares the limbus) without exudate
  3. Rash: maculopapular, diffuse erythroderma, or erythema multiforme-like
  4. Erythema and edema of the hands and feet in the acute phase and/or periungual desquamation in the subacute phase (2-3 weeks after onset of fever and may extend to involve the palms and soles)
  5. Cervical lymphadenopathy ( $\geq 1.5$  cm diameter), usually unilateral

# KD Diagnosis

- In the presence of  $\geq 4$  principal features, particularly when redness and swelling of the hands and feet are present, the diagnosis may be made with only 4 days of fever
- Fever is typically high spiking ( $>39^{\circ}\text{C}$  to  $40^{\circ}\text{C}$ ) and remittent
  - lasts 1-3 weeks in the absence of appropriate therapy
- A careful history may reveal that  $\geq 1$  principal clinical features were present during the illness but resolved by the time of presentation
- Patients who lack full clinical criteria of classic KD are often evaluated for incomplete KD. If coronary artery abnormalities are detected, the diagnosis of KD is considered confirmed in most cases.
- Lab tests typically reveal normal or elevated white blood cell count with neutrophil predominance and elevated acute phase reactants such as C-reactive protein and ESR during the acute phase.
- In the second week after fever onset, thrombocytosis is common.

# KD Diagnosis

- In a child with clinical findings compatible with KD the detection of respiratory viruses such as RSV, metapneumovirus, coronaviruses, parainfluenza viruses, or influenza viruses
- The detection of adenovirus in a nasopharyngeal specimen from a patient with suspected KD poses a particular challenge, since the illnesses have some similar clinical features.
  - Adenoviruses can persist in tonsil or adenoid tissue following resolution of symptoms from adenovirus infection
  - KD is extremely unlikely if the patient has exudative pharyngitis and exudative conjunctivitis
    - if nonexudative then still consider KD in a patient who tests positive for adenovirus
- In a child with some clinical features of KD who tests positive (antigen or culture) for group A streptococcus and do not improve after 24-48 hours of antibiotics (streptococcal carrier), the diagnosis of KD should still be considered.

# Other Clinical Findings

- Cardiovascular
  - myocarditis, pericarditis, valvular regurgitation, shock
  - coronary abnormalities
  - aneurysms of medium-sized noncoronary arteries
  - aortic root enlargement
  - peripheral gangrene
- Respiratory
  - peribronchial and interstitial infiltrates on CXR
  - pulmonary nodules
- Musculoskeletal
  - arthritis, arthralgia, pleocytosis of synovial fluid

# Other Clinical Findings

- Gastrointestinal
  - diarrhea, vomiting, abdominal pain
  - hepatitis, jaundice
  - gallbladder hydros
  - pancreatitis
- Nervous system
  - extreme irritability
  - aseptic meningitis
  - facial palsy,
  - sensorineural hearing loss

# Other Clinical Findings

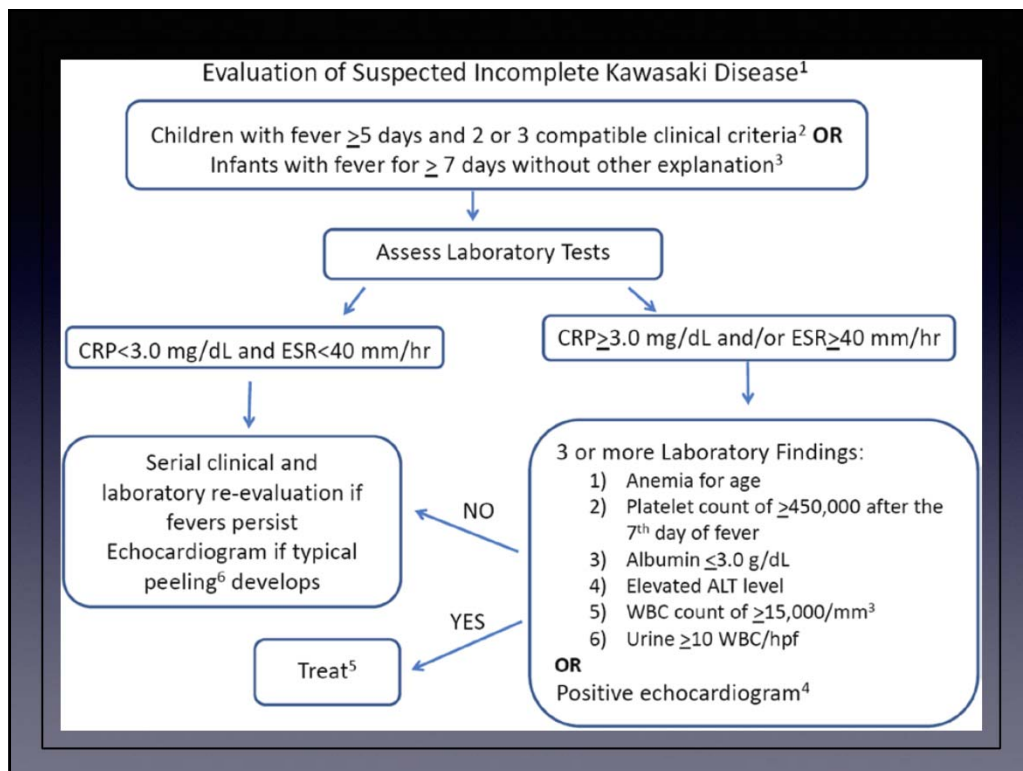
- Genitourinary
  - urethritis/meatitis, hydrocele
- Other
  - desquamating rash in the groin
  - retropharyngeal non-suppurative phlegmon
  - anterior uveitis by slit lamp exam
  - erythema and induration at BCG inoculation site

# Differential Diagnosis

- Measles
- Other viral infections (eg, adenovirus, enterovirus)
- Staphylococcal and streptococcal toxin-mediated diseases (eg, scarlet fever and toxic shock syndrome)
- Drug hypersensitivity reactions, including Stevens Johnson syndrome
- Systemic onset JIA
- RMSF or other rickettsial infections
- Leptospirosis

# Incomplete KD

- KD should be considered in the DDX of prolonged unexplained fever in childhood associated with any of the principal features of KD
- KD diagnosis considered confirmed if echo notes coronary aneurysms
- However, coronary artery abnormalities not generally detected until after the first week
- Coronary artery abnormalities early in the course lack sensitivity but have a very high specificity





## Key Points to Consider KD in the DDx

- Infants <6 months old with prolonged fever and irritability
- Infants with prolonged fever and unexplained aseptic meningitis
- Infants or children with prolonged fever and cervical lymphadenitis unresponsive to antibiotic therapy
- Infants or children with prolonged fever and retropharyngeal or parapharyngeal phlegmon unresponsive to antibiotic therapy

## Findings That Suggest An Alternative Diagnosis

- Bullous, vesicular, and petechial rashes
- Oral ulcers and pharyngeal exudates
- Splenomegaly
- Leukopenia and lymphocyte predominance

# Cardiovascular Assessment

- Echocardiography should be performed when the diagnosis of KD is considered
  - unavailability or technical limitations should not delay treatment
- For uncomplicated patients, echo should be repeated both within 1-2 weeks and 4-6 weeks after treatment

# Initial Treatment

- IVIG 2 grams/kg as a single continuous infusion within 10 days of illness onset but as soon as possible
- It is reasonable to administer IVIG to children presenting after the 10th day of illness if they have ongoing systemic inflammation manifested by elevation of CRP (CRP > 3.0 mg/dl) or ESR together with either persistent fever without other explanation or coronary artery aneurysms (luminal dimension Z score > 2.5)
- ESR is increased by IVIG and should not be used to assess response to IVIG therapy. A persistently high ESR alone should not be interpreted as a sign of IVIG resistance

# Initial Treatment

- Administration of moderate (30-50 mg/kg/day) to high-dose (80-100 mg/kg/day) ASA is reasonable until the patient is afebrile
  - no evidence that it reduces coronary artery abnormalities
  - decrease ASA to 3-5 mg/kg (antiplatelet effect) once a day when afebrile 48-72 hours
  - concomitant ibuprofen antagonizes the irreversible platelet inhibition induced by ASA
  - ibuprofen generally should be avoided in children with coronary artery aneurysms taking ASA for its antiplatelet effects

# Adjunctive Therapies for Primary Treatment

- Single-dose pulse methylprednisolone should not be administered with IVIG as routine primary treatment
- Administration of a longer course of corticosteroids (eg, tapering over 2-3 weeks), together with IVIG and ASA, may be considered for treatment of high-risk patients
  - when high risk patients can be identified prior to initiation of treatment

# IVIIG Resistance

- Recrudescence or persistent fever at least 36 hours after the end of the IVIG infusion
  - ~10% to 20% of patients
- Thought that host genetic factors play a role in the response to IVIG treatment
- Many studies have noted that IVIG resistant patients are at greater risk of developing coronary artery abnormalities
- Currently available risk prediction models for Asian populations are insufficiently accurate to be clinically useful for North American patients in predicting response to treatment

## Treatment of IVIG Resistance

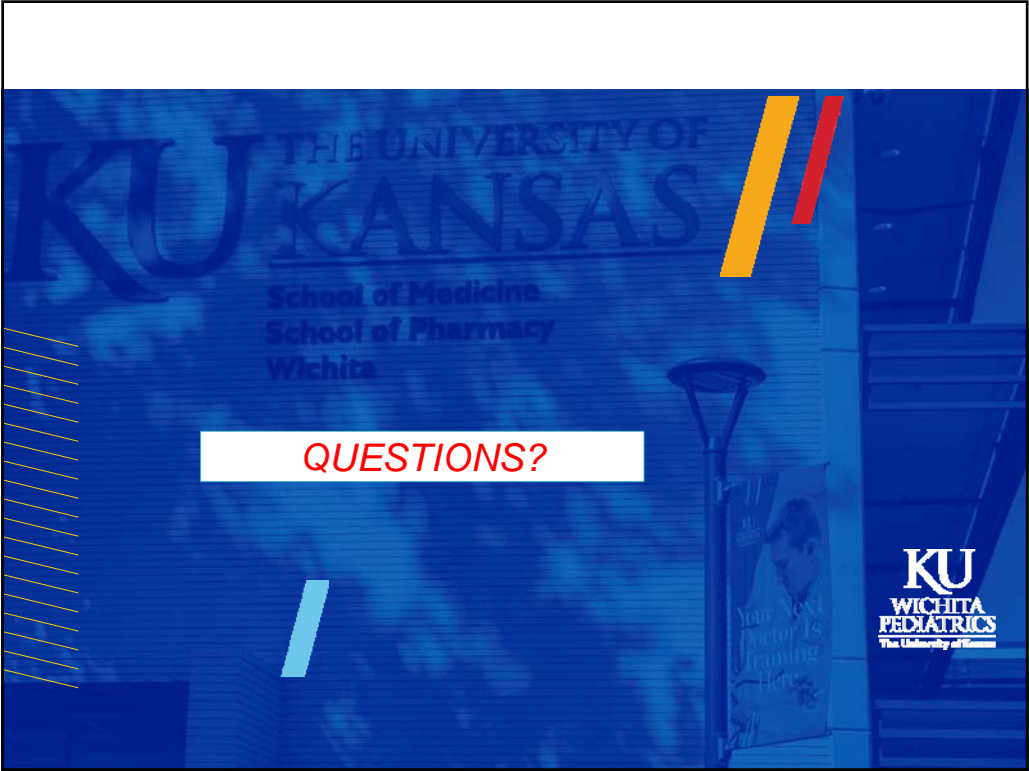
- It is reasonable to administer a second dose of IVIG (2 g/kg)
- Administration of high-dose pulse steroids (usually methylprednisolone 20-30 mg/kg IV for 3 days, with or without a subsequent taper of oral prednisone) may be considered as an alternative to a second infusion of IVIG or for retreatment of patients who have had recurrent or recrudescence fever after a second dose of IVIG

## Treatment of IVIG Resistance

- Administration of a longer (eg, 2-3 weeks) tapering course of prednisolone or prednisone, together with IVIG 2 g/kg and ASA, may be considered
- Administration of infliximab (5 mg/kg) may be considered as an alternative to a second infusion of IVIG or corticosteroids

## Treatment of IVIG Resistance

- Administration of cyclosporine may be considered in whom a second IVIG infusion, infliximab, or a course of steroids has failed
- Administration of immunomodulatory monoclonal antibody (anakinra, an IL-1 receptor antagonist) therapy (except TNF blockers), cytotoxic agents, or rarely plasma exchange may be considered in highly refractory patients who have failed to respond to a second infusion of IVIG, an extended course of steroids, or infliximab.



*QUESTIONS?*

**KU**  
**WICHITA**  
**PEDIATRICS**  
The University of Kansas