



KAWASAKI DISEASE

*Tina Kwan, MD
Pediatric Cardiologist
Children's Heart Center - Nevada
Heart Conference - October 28, 2017*



DISCLOSURES

.....

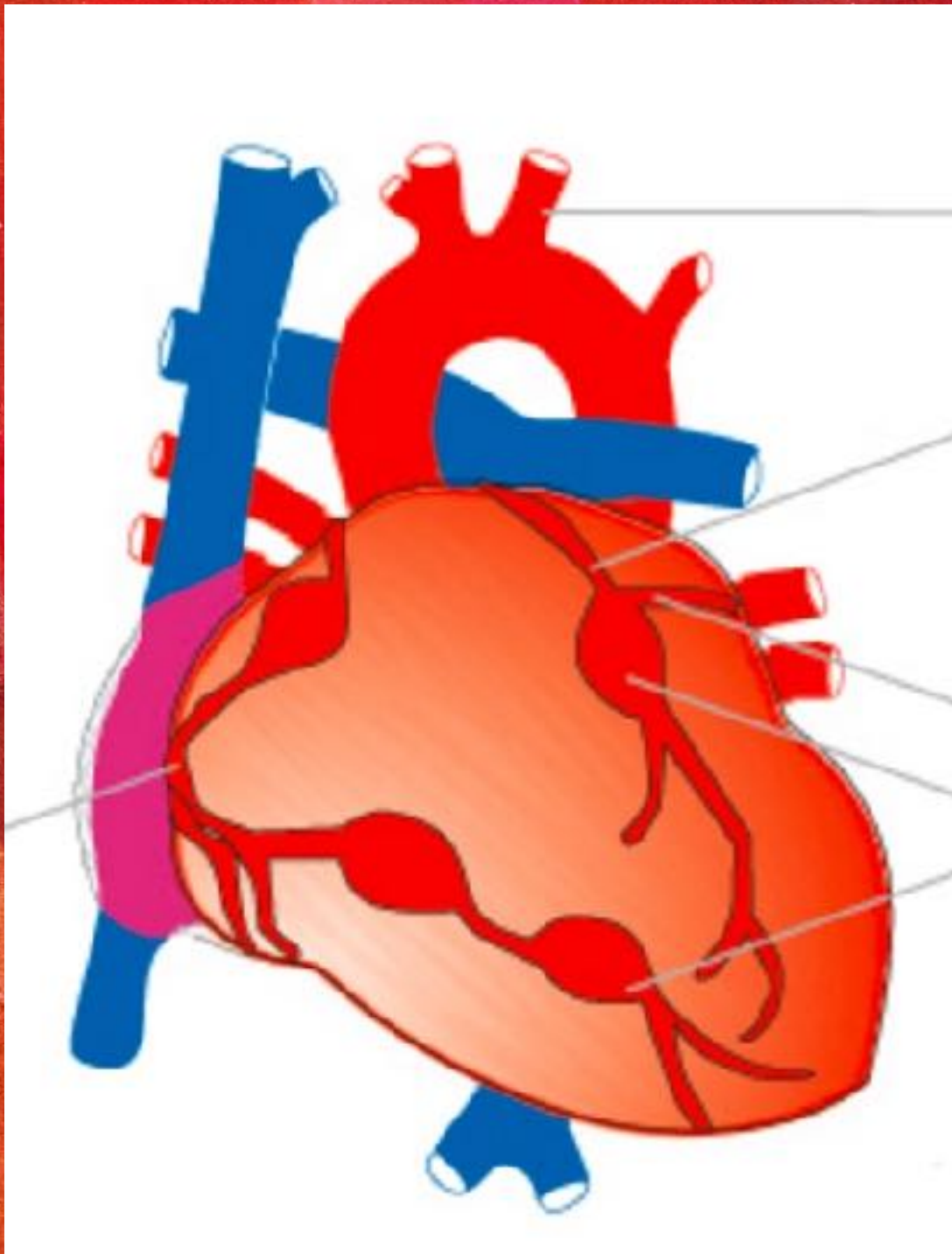
- I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services, but I am open to suggestions.
- I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.



INTRODUCTION

.....

- Acute self-limiting vasculitis occurring predominantly in infants and children
- Unknown etiology
- Targets coronary arteries and other cardiovascular structures
- Coronary artery aneurysms
- #1 cause of **acquired** heart disease in the U.S.



EPIDEMIOLOGY

.....

- 80% of patients are < 5 yo
- Can occur even in adolescence
- In U.S. 19 per 100,000 children < 5 yo
 - California 24.7 per 100,000
- On every continent and across all racial and ethnic groups
- Higher incidence in Asian/Pacific Islanders
- Boys $>$ Girls (1.5-1.7x)
- Recurrence rate 2-3%



PATHOPHYSIOLOGY

Infectious or antigenic trigger

- Infectious agent that replicates in the superficial epithelial cells of the upper airway **OR**
- An antigen widely dispersed in the environment



- Genetically susceptible host



- Immunologic reaction manifest (clinical Kawasaki Disease)



- Genetically determined outcome (modifiable by treatment)
- 25% of children will suffer irreversible damage to the coronary arterial wall



STAGES OF CV PATHOLOGY IN KD

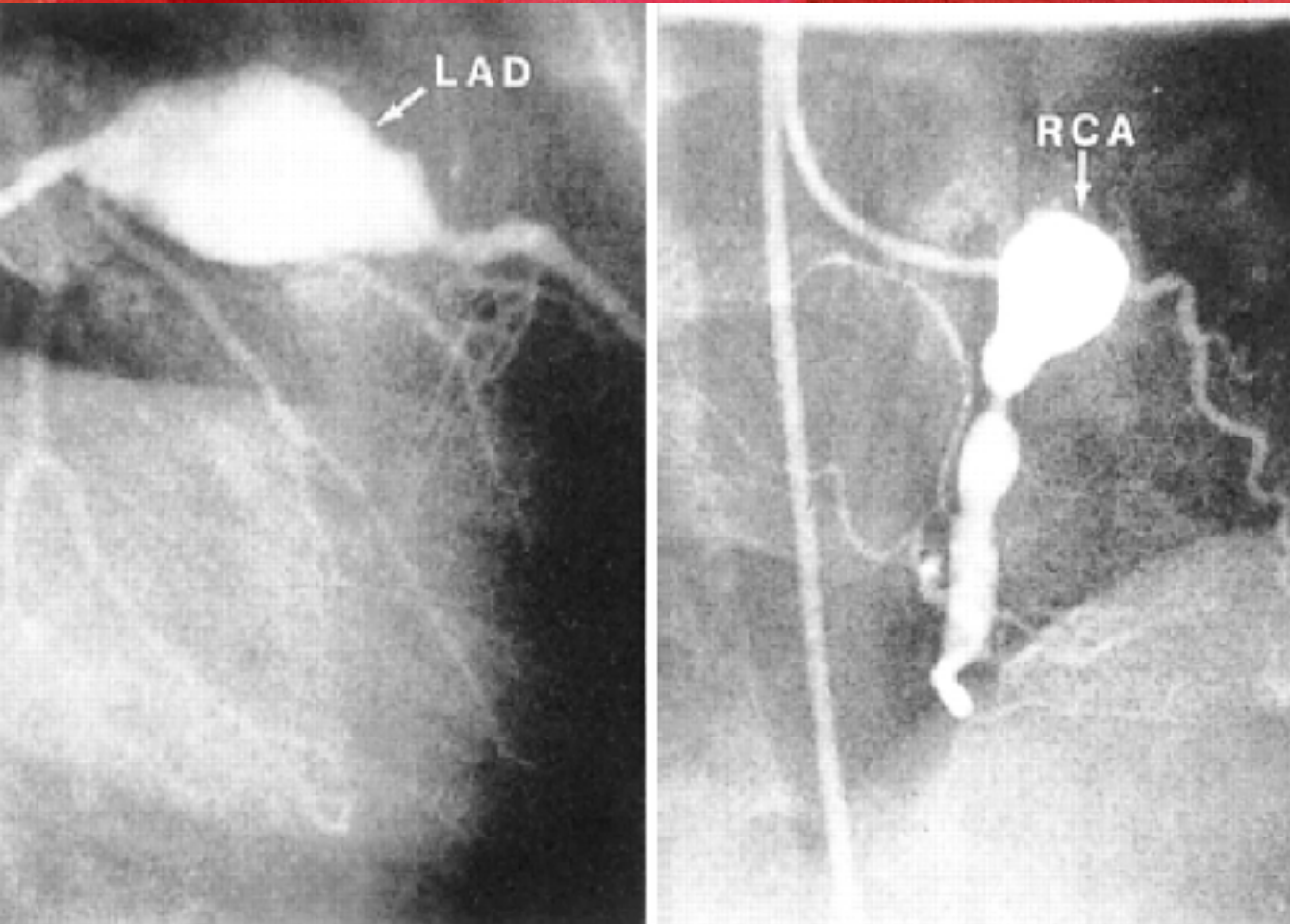
.....

➤ Stage 1 (0-9 days)

- Microvascular angiitis
- Acute endoarteritis and perivasculitis
- Pericarditis, valvulitis, endocarditis
- Myocarditis (including conduction anomalies)
- Causes of death: heart failure and arrhythmia

➤ Stage 2 (12-25 days)

- Panvasculitis with aneurysm and thrombus formation
- Intimal proliferation
- Myocarditis, endocarditis, pericarditis
- Causes of death: heart failure, arrhythmia, M.I., aneurysm rupture



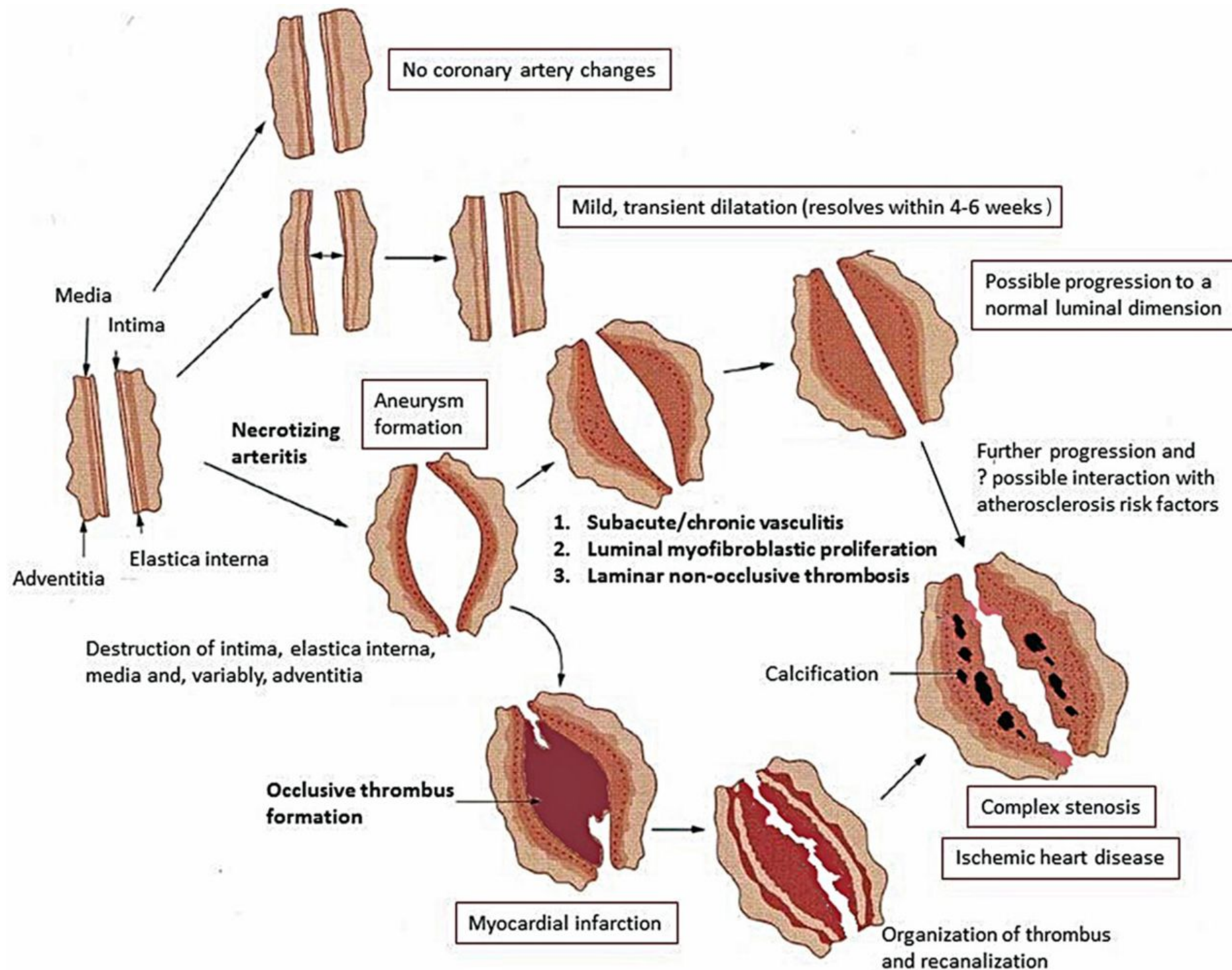
STAGES OF CV PATHOLOGY IN KD

.....

- Stage 3 (28-31 days)
 - Granulation
 - Marked intimal thickening
 - Disappearance of angiitis
 - Causes of death: M.I.
- Stage 4 (40 days - years/decades)
 - Scarring, stenosis, calcification, recannulization
 - Myocardial/endocardial fibrosis
 - Causes of death: M.I.



Natural history of coronary artery abnormalities.

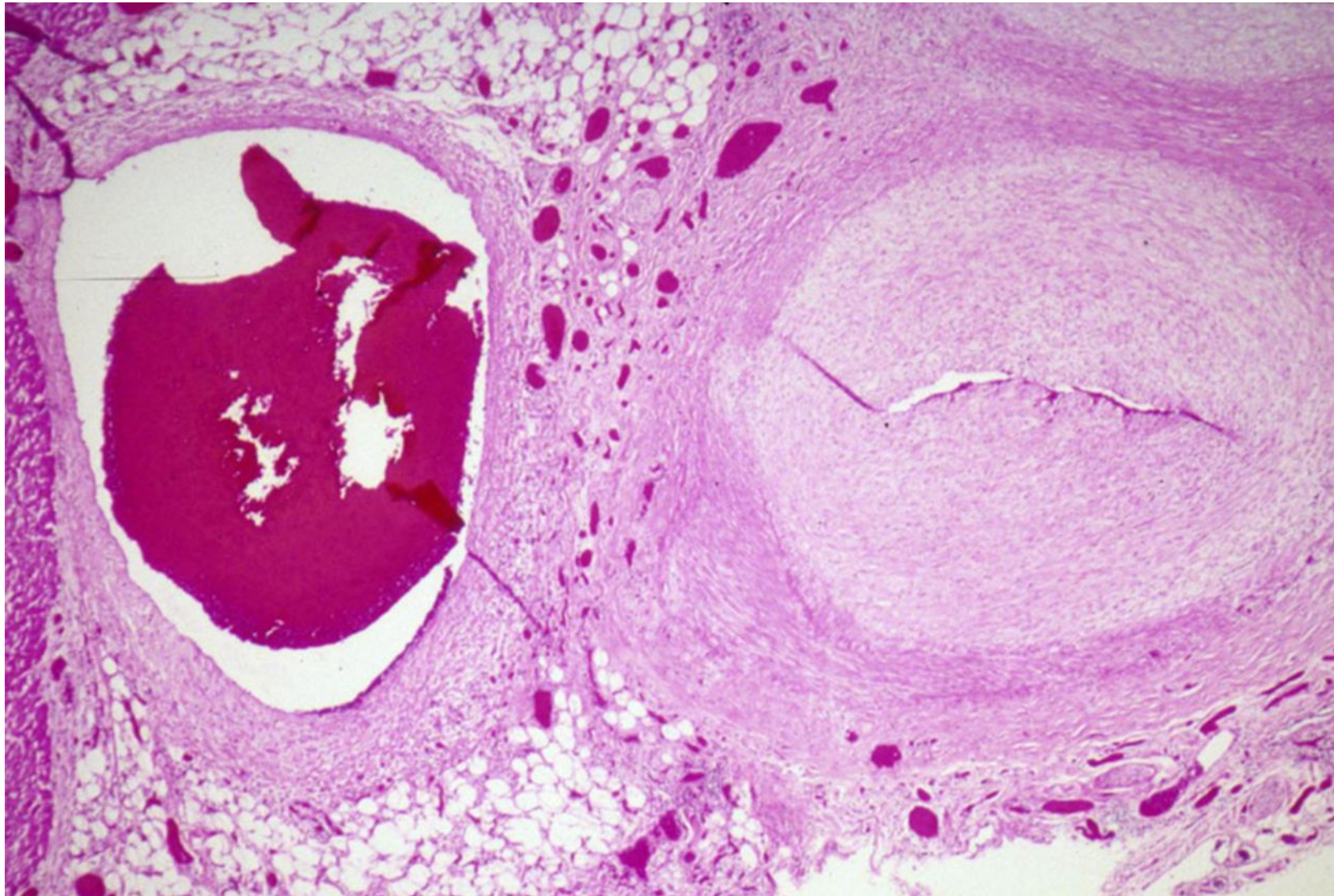


Brian W. McCrindle et al. Circulation. 2017;135:e927-e999



HISTOLOGY

.....

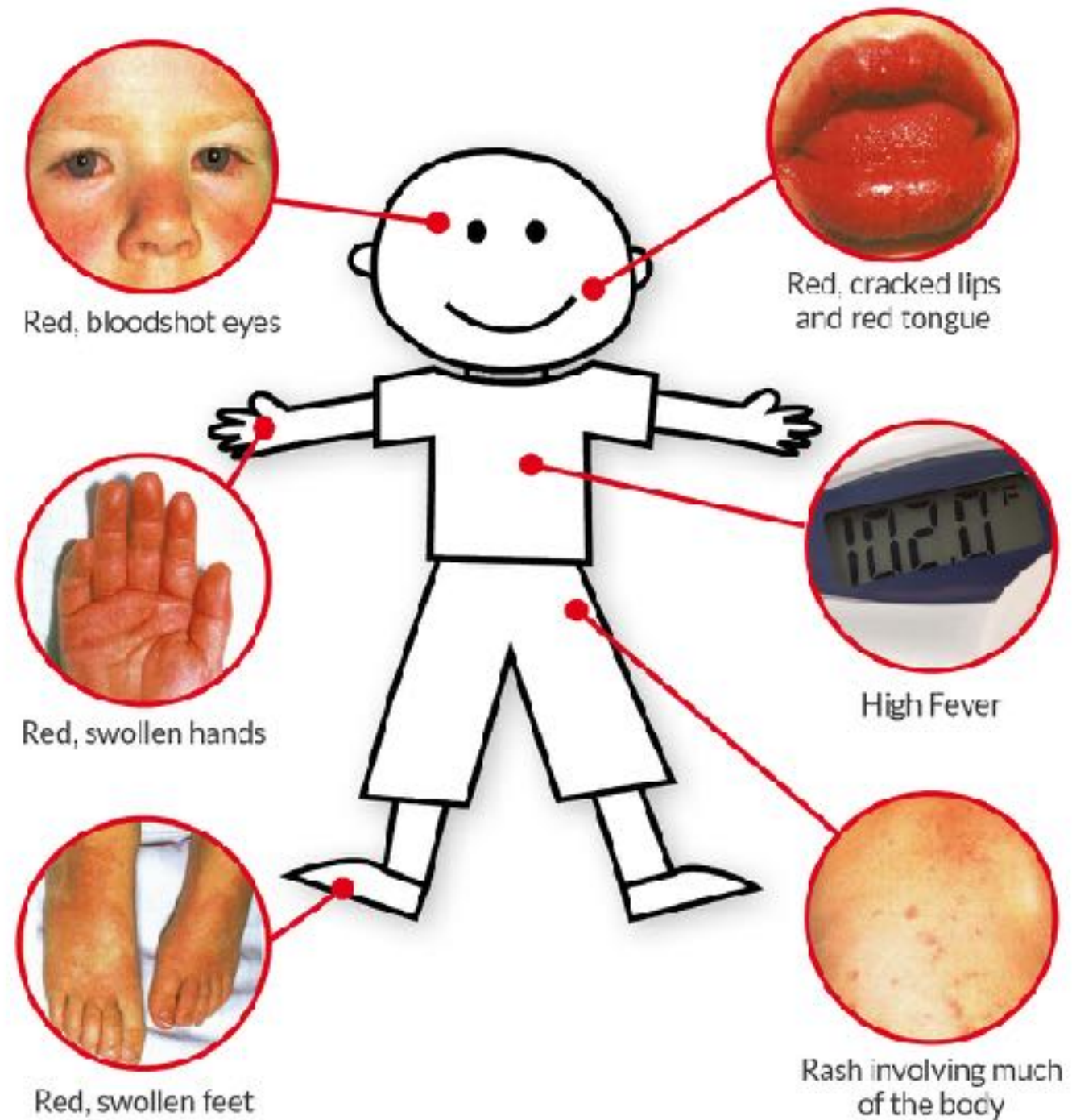


Epicardial coronary vein and artery. The epicardial vein shows blood and mild thickening of the wall. The coronary artery shows almost complete occlusion by luminal myofibroelastic proliferation with a fine slit-like lumen.



DIAGNOSIS

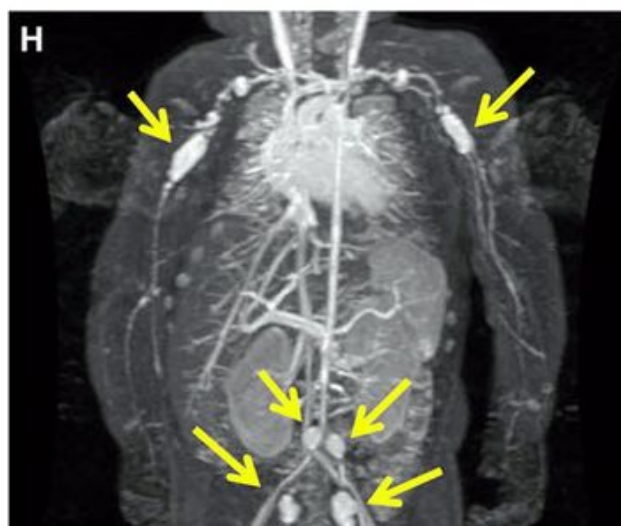
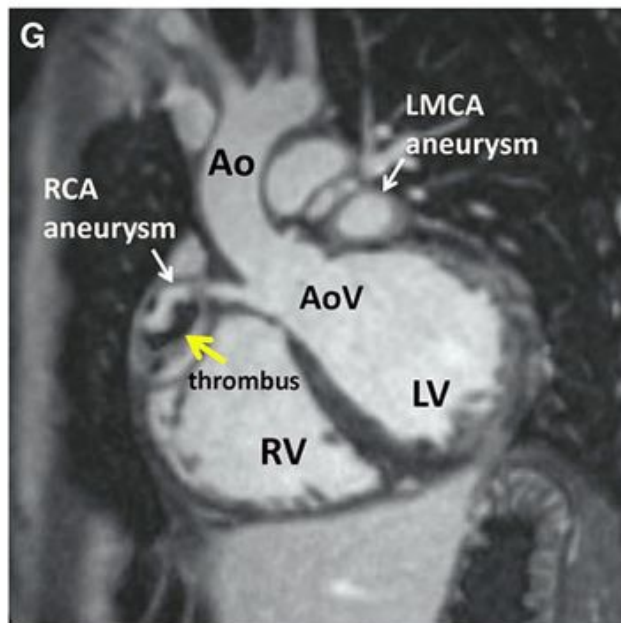
- Fever - persisting at least 5 days and 4/5 of the following principal clinical criteria:
 - Conjunctivitis - bilateral, nonexudative conjunctival injection that spares the limbus
 - Oropharyngeal - erythema and cracking of the lips; strawberry tongue and erythema of the pharynx
 - Extremity changes - erythema and edema of the hands/feet; periungual peeling at 14-21 days
 - Rash - polymorphous erythema, truncal, perineal accentuation
 - Cervical Lymphadenopathy - at least 1.5 cm, unilateral, nonfluctuant, nontender



CLINICAL FEATURES OF KD

.....

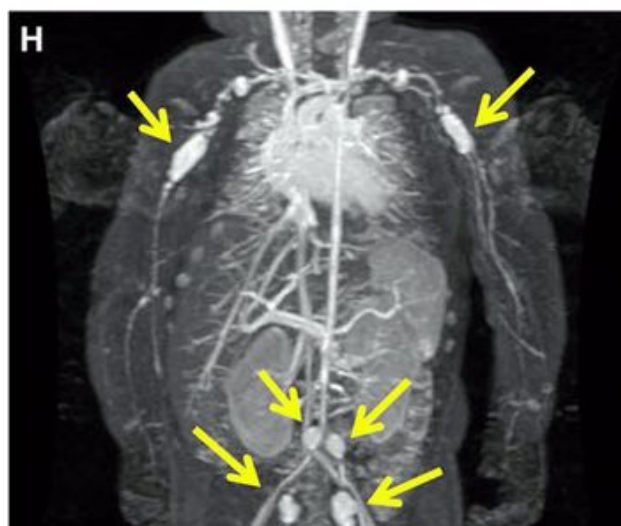
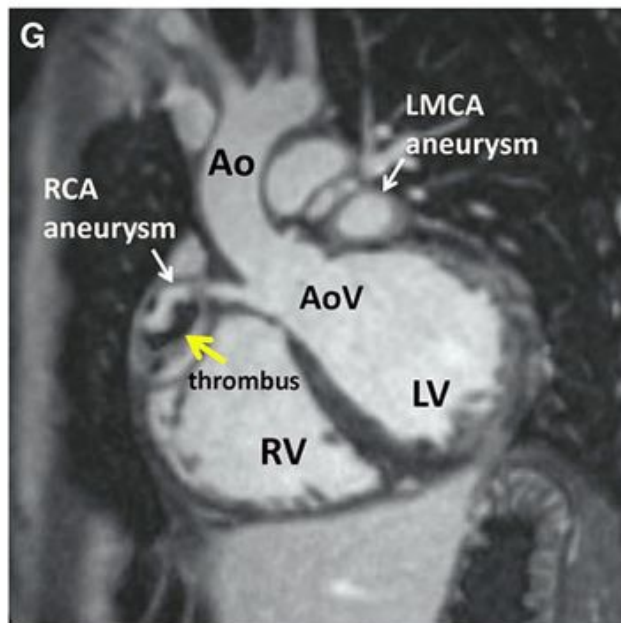
- A. Rash - maculopapular, diffuse erythroderma or erythema multiform-like
- B. Conjunctivitis - bulbar conjunctival injection without exudate, bilateral
- C. Oral changes - erythema and cracking of the lips (chelitis); strawberry tongue; erythema of oral and pharyngeal mucosa
- D. Palmar erythema
- E. Plantar erythema
 - Usually accompanied by swelling; resolves with subsequent periungual desquamation in subacute phase



CLINICAL FEATURES OF KD

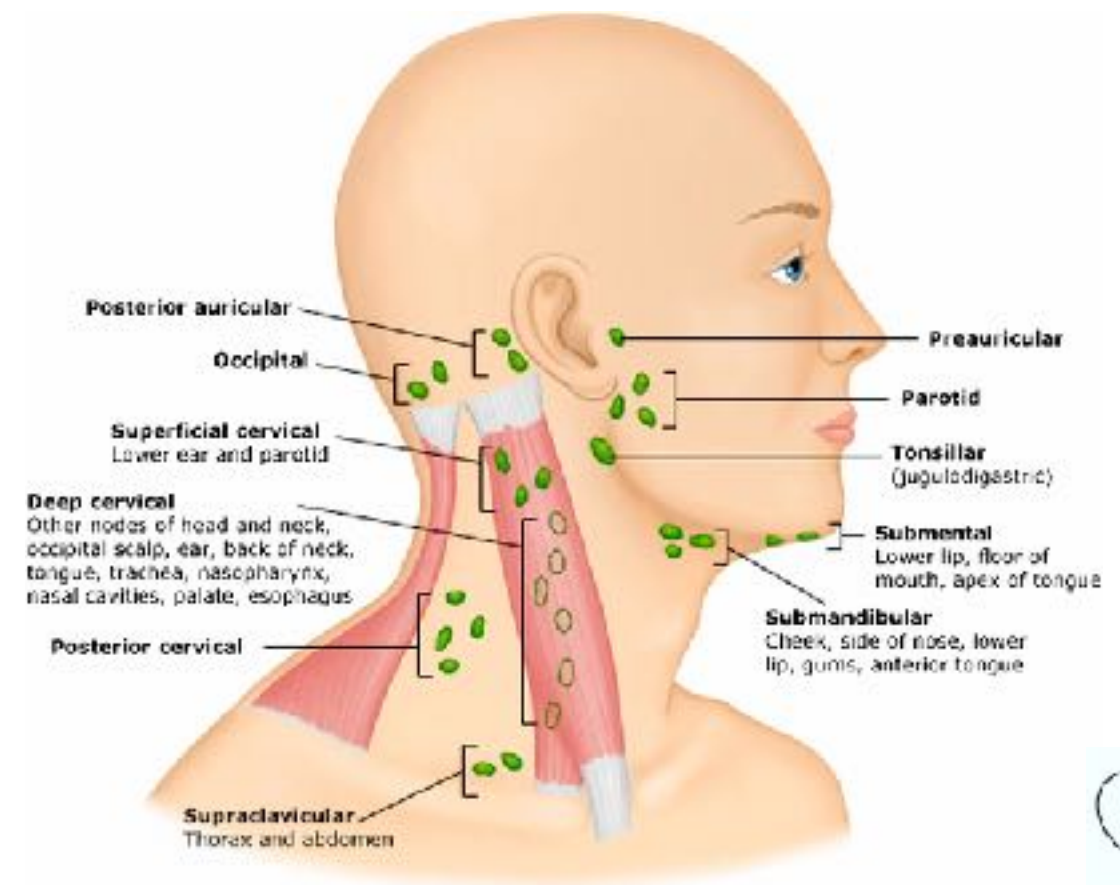
.....

- F. Cervical adenopathy - usually unilateral, node $\geq$ 1.5 cm in diameter
- G. Coronary artery aneurysms - MRI of the LVOT showing a giant RCA aneurysm with nonexclusive thrombus and a giant LMCA aneurysm
- H. Peripheral artery aneurysms - MRI showing aneurysms in the axillary and subclavian arteries and the iliac and femoral arteries



CHARACTERISTICS THAT SUGGEST OTHER DISEASES

- Exudative Conjunctivitis
- Exudative Pharyngitis
- Discrete intraoral lesions
- Bullous or vesicular rash
- Generalized lymphadenopathy



CV MANIFESTATIONS

- Leading cause of long-term morbidity and mortality
- Involves: pericardium, myocardium, endocardium, valves, and coronary arteries
- Physical Exam: hyperdynamic precordium, tachycardia +/- gallop, +/- murmur (innocent or MR)
- ECG: Nonspecific changes
- Echo:
 - Coronary ectasia, perivascular brightness, or aneurysm
 - Pericardial effusion
 - LV dysfunction - responds to IVIG (56%)
 - Mitral regurgitation (27% on baseline echo, 9% persists 6-8 weeks)
 - Aortic root dilatation persists at least 1 year



CORONARY ABNORMALITIES

.....

- Untreated patients - 25% aneurysms
- Treated patients - 5% aneurysms
- 27-50% have ectasia
- Potential for thrombus, stenosis, rupture
- Endothelial dysfunction, increased risk for CV disease
- Primary cause of associated morbidity and mortality
 - MI, SCD, ischemic HD, early onset acquired HD



LAB FINDINGS

- WBC - leukocytosis typical
 - Leukopenia rare
- H/H - anemia in some with normal indices
- Acute phase reactants
 - ESR - can be related to IVIG
 - CRP
- Platelets - thrombocytosis characteristic at 2-3 weeks
 - Thrombocytopenia is rare (indicates DIC)
- Liver enzymes
 - Mild-moderate transaminitis in $< 40\%$
 - Hyperbilirubinemia in $\sim 10\%$
 - Elevated GGT in $\sim 67\%$
- Albumin - hypoalbuminemia common and associated with more severe disease
- UA - sterile pyuria in 33%
- CSF - 50% aseptic meningitis
- Troponin i - may be elevated in some



CLINICAL PHASES (AND WHEN TO GET ECHOS)

- Acute (1-2 weeks)
 - Fever, typical clinical manifestations, myocarditis, pericarditis
- Subacute (1-2 weeks to 1 month)
 - Resolution of fever and other acute clinical features, desquamation, thrombocytosis, aneurysm formation
- Convalescent (1-2 months)
 - Resolution of clinical features, normalization of inflammatory indices



INCOMPLETE KAWASAKI'S DISEASE



INCOMPLETE (ATYPICAL) KAWASAKI DISEASE

- Children with fever plus < 4 diagnostic criteria
- More common at extreme ends of age spectrum
 - Infants
 - 6mo and younger have the highest incidence of coronary artery aneurysms and incomplete/atypical disease
 - If fever ≥ 7 days with labs consistent with inflammation in the *absence* of any other explanation... **ECHO**
 - Children > 8 yo
- Does **NOT** refer to unusual clinical features
- Diagnostic dilemma leads to delayed diagnosis and therefore higher risk for coronary anomalies
- Same lab findings as complete Kawasaki Disease



Evaluation of Suspected Incomplete Kawasaki Disease¹

Children with fever ≥ 5 days and 2 or 3 compatible clinical criteria² **OR**
Infants with fever for ≥ 7 days without other explanation³

Assess Laboratory Tests

CRP < 3.0 mg/dL and ESR < 40 mm/hr

CRP ≥ 3.0 mg/dL and/or ESR ≥ 40 mm/hr

Serial clinical and
laboratory re-evaluation if
fevers persist
Echocardiogram if typical
peeling⁶ develops

Treat⁵

3 or more Laboratory Findings:

- 1) Anemia for age
- 2) Platelet count of $\geq 450,000$ after the 7th day of fever
- 3) Albumin ≤ 3.0 g/dL
- 4) Elevated ALT level
- 5) WBC count of $\geq 15,000/\text{mm}^3$
- 6) Urine ≥ 10 WBC/hpf

OR

Positive echocardiogram⁴

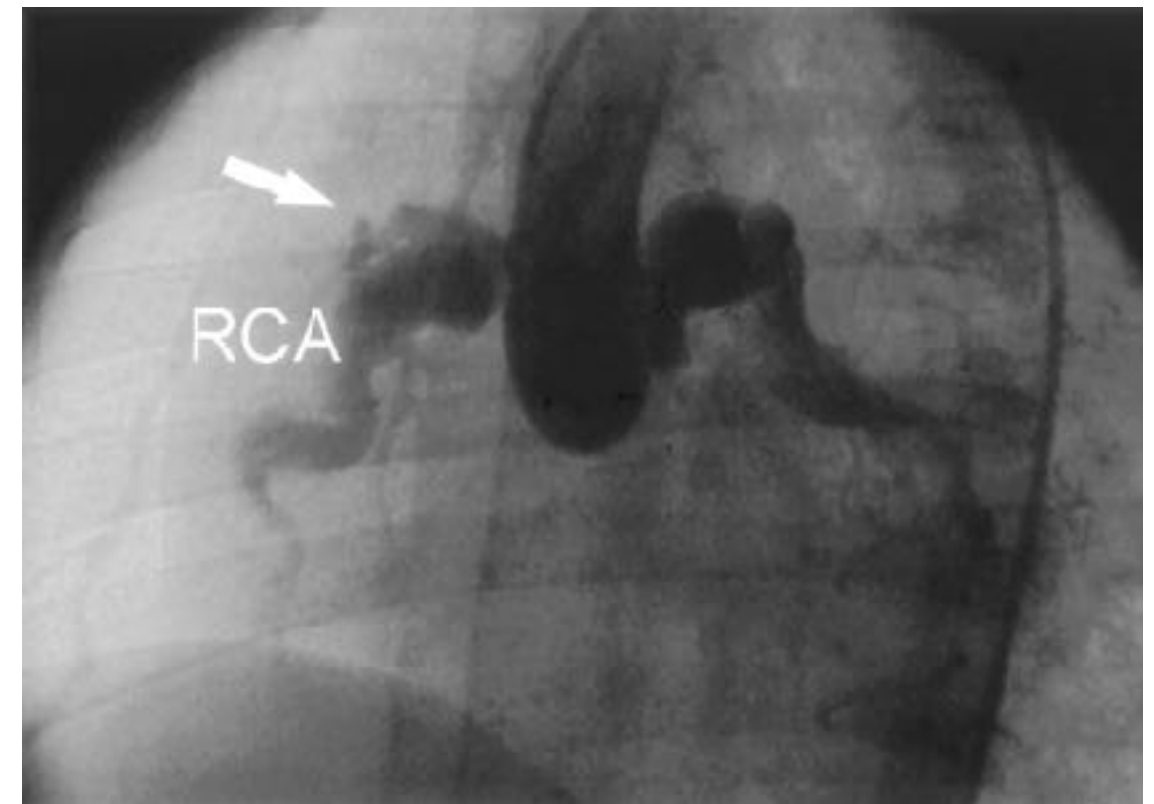
NO

YES



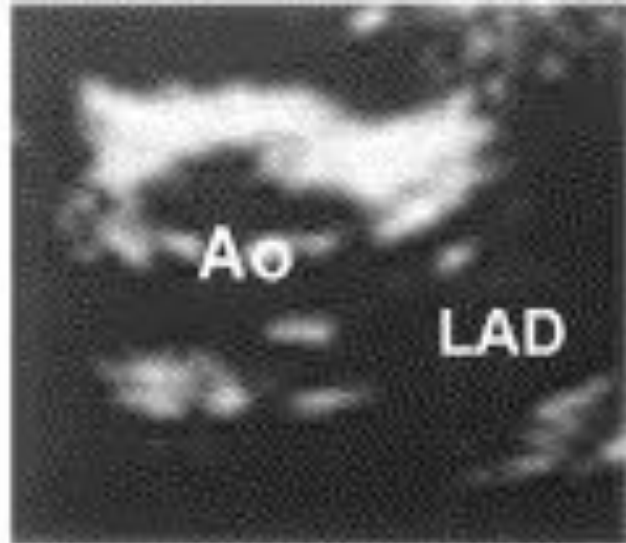
CRITERIA FOR POSITIVE ECHO

- Any of the following:
 - LAD or RCA z-score $\geq +2.5$
 - Japanese Ministry of Health Criteria
 - Coronary diameter $> 3\text{mm}$ in children $< 5\text{yo}$ or $> 4\text{mm}$ in children $\geq 5\text{yo}$
 - Lumen diameter $\geq 1.5\text{x}$ an adjacent segment
 - Irregular lumen
 - ≥ 3 of the following suggestive features:
 - Perivascular coronary brightness
 - Lack of coronary tapering
 - Diminished LV function
 - MR
 - Pericardial effusion
 - LAD or RCA Z-score = $+2-2.5$
- Z-scores: $\geq +2.5$ to $< +5.0$ (small), $\geq +5.0$ to $< +10.0$ (large), $\geq +10.0$ (giant)



CORONARY EVOLUTION BY ECHO

.....



5 Days



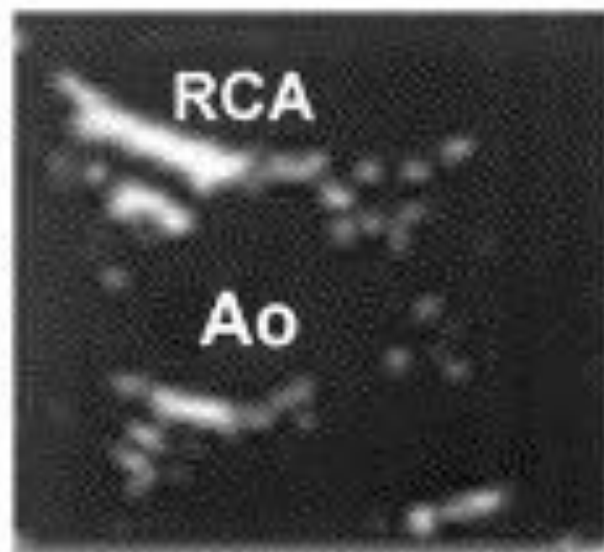
10 Days



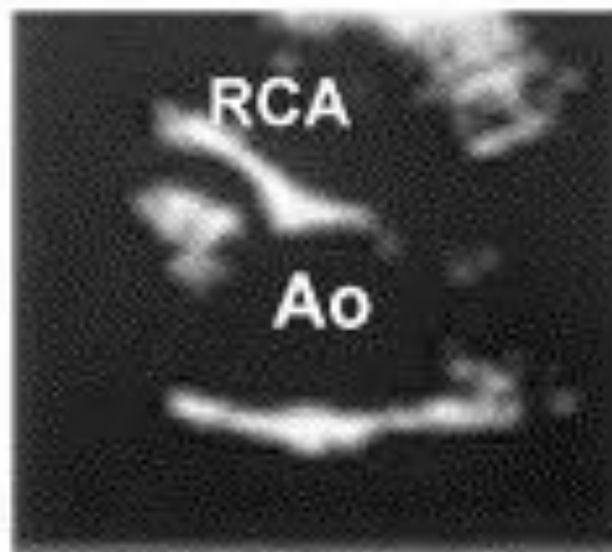
16 Days



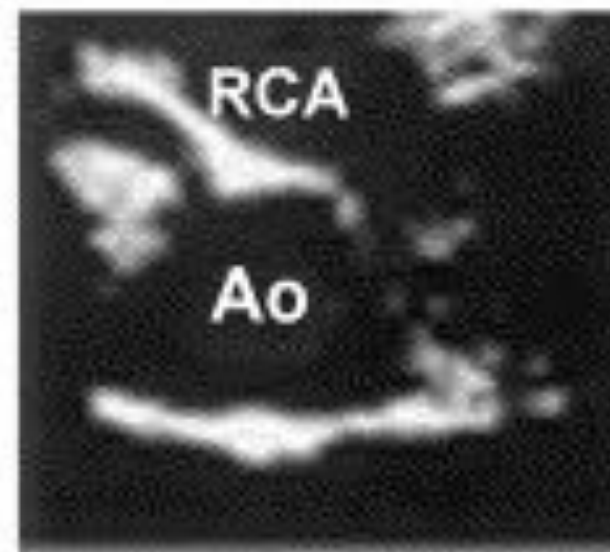
22 Days



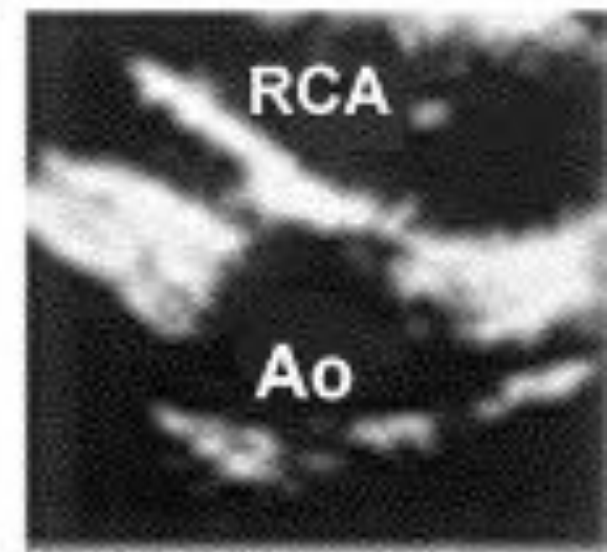
5 Days



10 Days

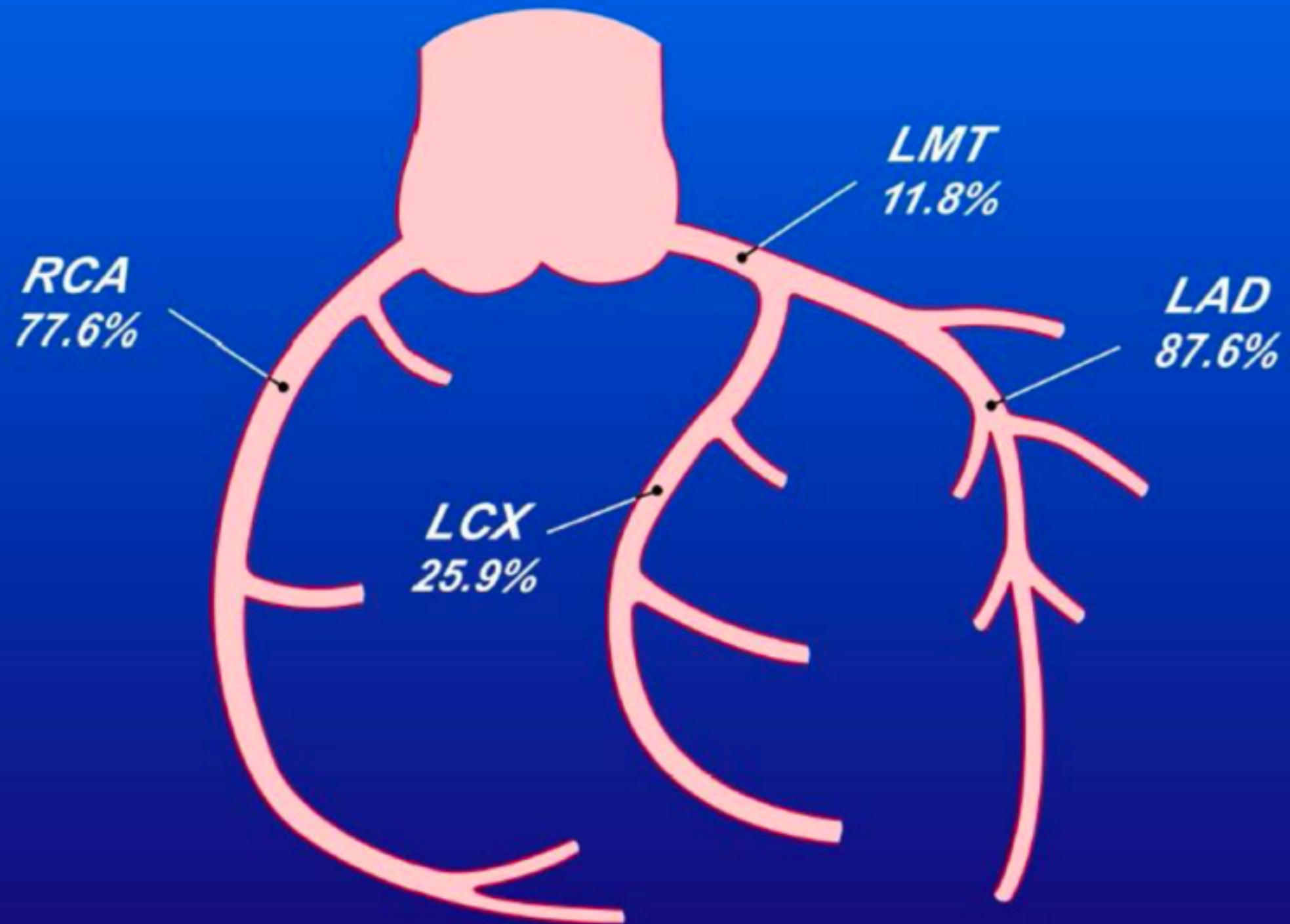


16 Days



22 Days





Kitamura, et al, 1994

RISK FACTORS FOR CORONARY ANEURYSMS

- Male
- Young or old (< 6mo or > 8 yo)
- Resistance to IVIG (persistent fever)
- Systolic dysfunction on initial echo
- Labs at presentation
 - Anemia
 - Thrombocytopenia
 - Hypoalbuminemia
 - High CRP
 - High absolute band count
 - Hyponatremia

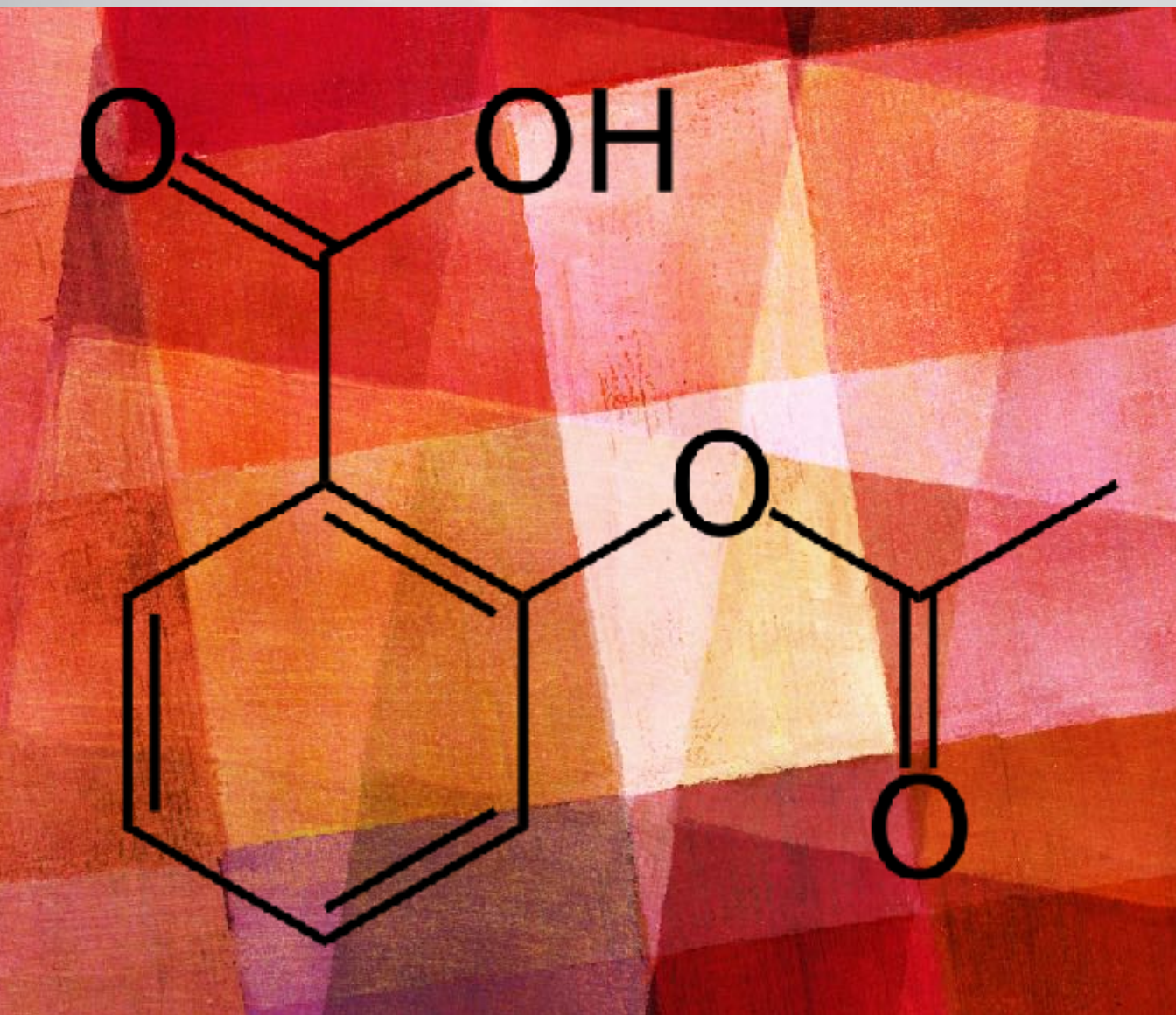




ACUTE TX

.....

- Goal to prevent complications and treat inflammatory symptoms
 - IVIG - 2gm/kg x 1
 - Before Day 10, preferably by day 7
- High dose ASA (80-100 mg/kg/day) until afebrile
 - 48-72 hours vs 14 days
- Low dose ASA (3-5 mg/kg/day) at discharge
 - If coronaries normal at 6-8 week follow up then may discontinue ASA



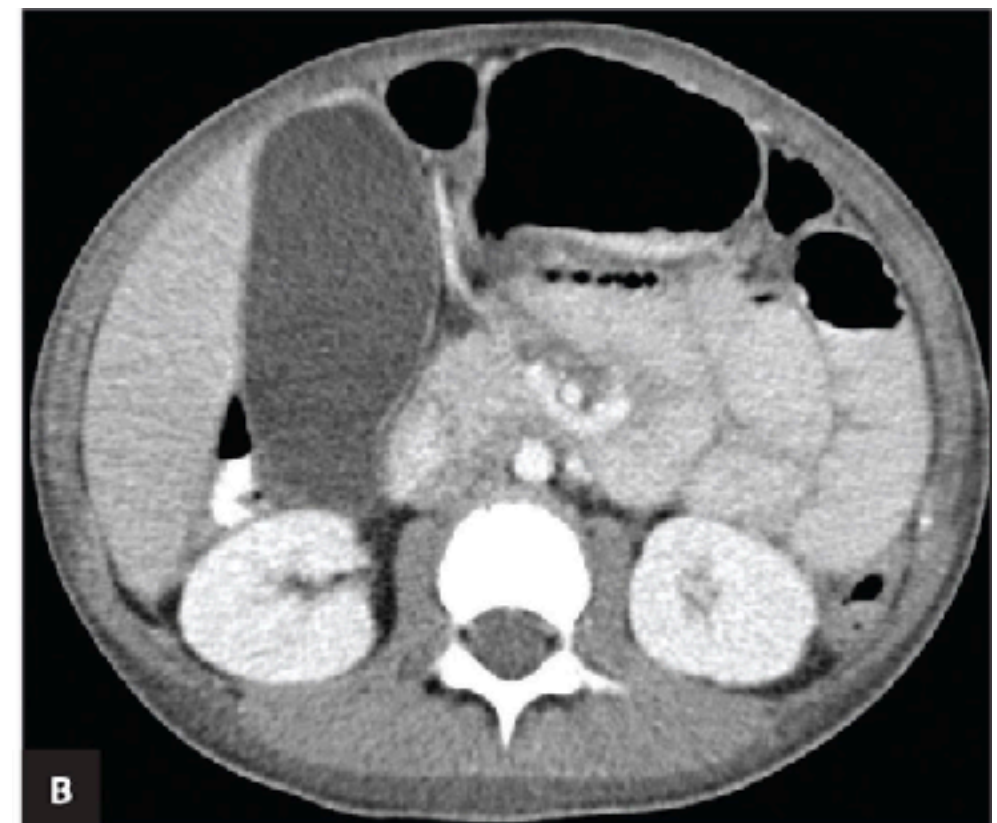
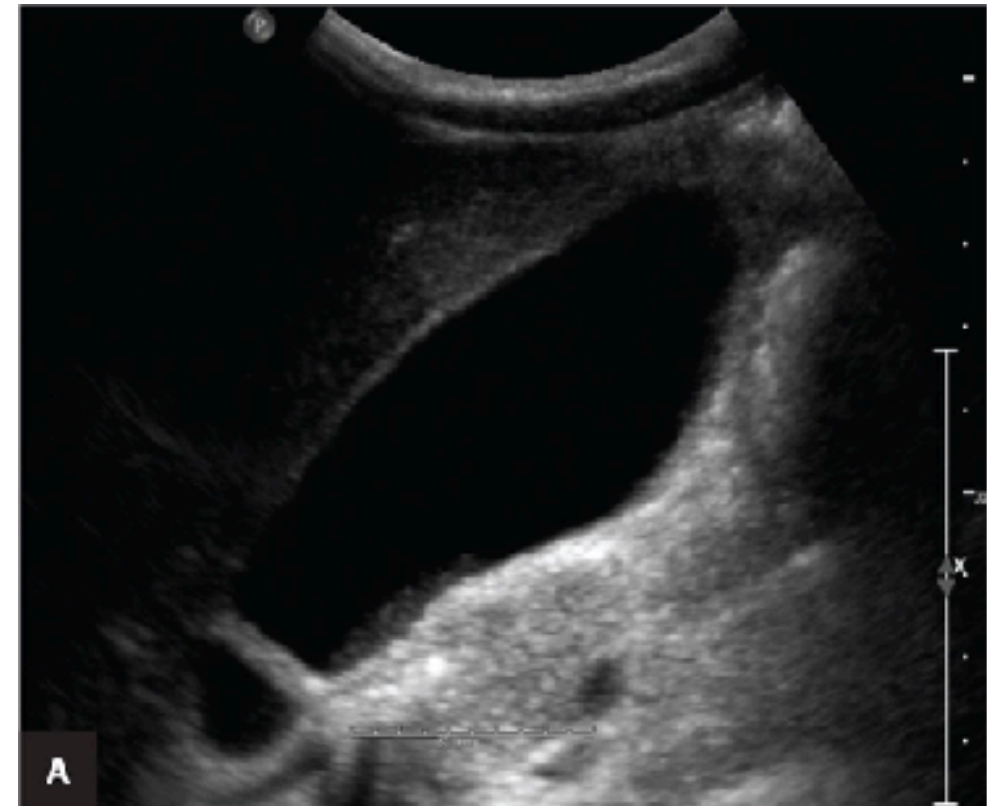
TREATMENT OF REFRACTORY KD

- 15% of patients will FAIL primary treatment
 - Persistent or recurrent fever > 36 hours after initial IVIG
- Options
 - Retreatment with IVIG - 2gm/kg (most common recommendation)
 - IVIG + steroids
 - Infliximab
 - Others
 - Anakinra
 - Cyclosporine A
 - Cyclophosphamide
 - Methotrexate
 - Pentoxifylline



COMPLICATIONS

- Early
 - Myocarditis, rarely CHF
 - Peripheral ischemia, especially in young infants
 - Pericardial effusion
 - Hydropic gallbladder
- Convalescent (weeks - months)
 - Coronary artery aneurysms +/- thrombosis
- Late (months - years)
 - Coronary stenosis or thrombosis +/- ischemia, infarct
 - Valvular insufficiency



RISK STRATIFICATION AND LONG TERM FOLLOW-UP

- Level 1: no coronary changes
 - No ASA or activity restriction after 6-8 weeks
 - Preventative counseling every 5 years
- Level 2: Transient ectasia that resolves by 8 weeks
 - No ASA or activity restriction after 6-8 weeks
 - Preventative counseling every 3-5 years
- Level 3: Small-medium coronary artery aneurysm of ≥ 1 major coronary artery
 - ASA therapy until aneurysms regress
 - No activity restrictions < 10 yo, then guided by stress testing every 2 years
 - High-impact sports discouraged while on ASA
 - Annual cardiology follow up with EKG and Echo
 - Coronary angiography if reversible ischemia on stress test or angina
 - Preventative monitoring/counseling



RISK STRATIFICATION AND LONG TERM FOLLOW-UP

- Level 4: ≥ 1 large (6mm) or giant coronary artery aneurysm
 - Anti-thrombotic therapy
 - ASA for everyone (or clopidogrel)
 - If giant aneurysms, add warfarin or LMWH (Lovenox)
 - Echo/EKG every 6 months
 - Stress testing with myocardial perfusion scan annually or with symptoms
 - Exercise recommendations guided by stress test, but avoid high-impact sports and isotonic exercise
 - Cardiac catheterization and coronary angiography at 6-12 months or sooner if clinical indications such as angina or infarct **OR** if follow up non-invasive studies suggest ischemia
 - Reproductive counseling for women
 - Preventative monitoring/counseling



RISK STRATIFICATION AND LONG TERM FOLLOW-UP

- Level 5: Coronary artery obstruction
 - Anti-platelet therapy +/- anti-coagulation
 - Beta blockers
 - Echo and EKG every 6 months with stress test and myocardial perfusion scan yearly or with symptoms
 - Exercise recommendations per stress test and symptoms with at least the same restrictions as Level 4
 - Angiography to assist in deciding therapeutic options
 - Catheter intervention
 - Surgery
 - Transplant
 - Reproductive counseling for women
 - Preventative monitoring/counseling





PREVENTATIVE CARE

.....

- Focus on early prevention of acquired heart disease
 - Tobacco and substances
 - Hyperlipidemia
 - Hypertension
 - Fasting glucose (DM)
 - BMI and obesity
 - Physical activity
 - Reproductive health
- ALL RISK LEVELS



SUMMARY

.....



- Important cause of acquired heart disease in children
- Accurate and timely diagnosis is important because treatment decreases risk of cardiac sequelae
- Coronary aneurysms develop in ~20-25% of untreated children
 - IVIG reduces risk to ~5%
- Giant aneurysms carry highest risk of ischemic heart disease
- Long term management is focused on degree of coronary artery involvement and disease





Questions?