Kawasaki Disease

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There are no relevant financial relationships with commercial interests to disclose

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Objectives

- Identify the criteria to diagnose Kawasaki Disease (KD)
- Describe the cardiac sequela of KD
- Describe medical management of cardiac problems associated with KD
- Categorize patients with KD into the proper risk stratification group

In 1967, Dr. Kawasaki thought…

The illness is self-limited and "resolves without intervention"

No sequelae

- There was no availability of echo imaging of coronary arteries at the time!

Kawasaki et al, *Arerugi* 1967
Slide courtesy of Dr. Newburger

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Background

- Acute, self-limited febrile illness of unknown cause
- Characterized by systemic inflammation in medium-sized arteries
- Predominantly affects children <5 years of age
- The most common cause of acquired heart disease in children in developed countries
- Timely initiation of treatment with intravenous immunoglobulin (IVIG) has reduced the incidence of coronary artery aneurysms from 25% to 4%
- The long-term prognosis is determined by the initial and current level of coronary artery involvement

Epidemiology

- First described in Japan, now worldwide
- US incidence (<5 years) 25/100,000
- Occurs in all ethnic groups
  - Japanese > Asians/Pac islands>African American>Hispanic>Caucasians
- Boys>Girls 1.5:1
- Recurrence rate %2-3
- Most common in winter and early spring in North America

Proposed KD pathogenesis Paradigm

Infectious or antigenic trigger

⇩

Genetically susceptible host

⇩

Manifest immunologic reaction (clinical KD)

⇩

Genetically determined outcome

AHA Scientific Statement

AHA Scientific Statement

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

A Statement for Health Professionals From the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association

Endorsed by the American Academy of Pediatrics

(*Circulation*. 2004;110:2747-2771.)

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Circulation. 2017;135:e927–e999. DOI: 10.1161/CIR.0000000000000484

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Diagnosis

Fever persisting at least 5 days and 4/5 following clinical criteria:

- **Oropharyngeal**: erythema and cracking of lips, strawberry tongue, and/or erythema of pharynx
- **Conjunctivitis**: Bilateral, non exudative that spares the limbus
- **Rash**: maculopapular, diffuse erythroderma, or erythema multiforme-like
- **Extremities changes**: erythema and edema of the hands and feet in acute phase and/or periungual desquamation in subacute phase
- **Cervical lymphadenopathy**: ≥1.5 cm diameter, unilateral

Diagnosis

- The clinical features are not all present at a single point in time
- In the presence of >4 principal clinical criteria, particularly when redness and swelling of the hands and feet are present, the diagnosis may be made with only 4 days of fever
- Patients who present after 1-2 weeks of fever, might loose some of the clinical features, so a careful review of prior signs and symptoms can help establish the diagnosis

Diagnosis - Fever

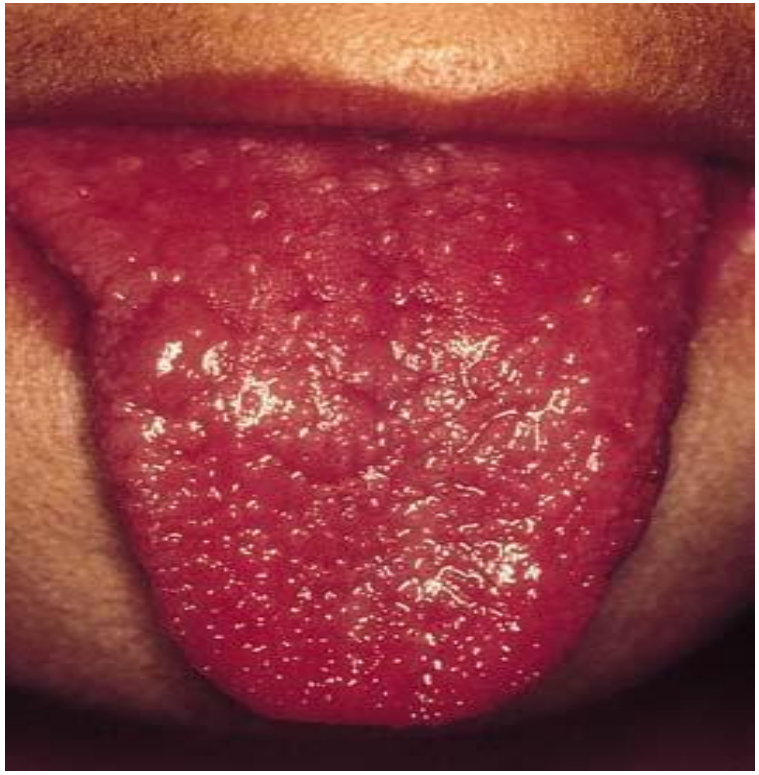
- High spiking (>39 C to 40 C) and remittent
- In the absence of appropriate therapy, fever continues for 1 to 3 weeks
- Spontaneous resolution of fever after 7 days does not exclude KD
- Fever usually resolves within 36 hours after IVIG infusion has been completed; if not, the patient is considered to have resistance to IVIG, and further therapy is required

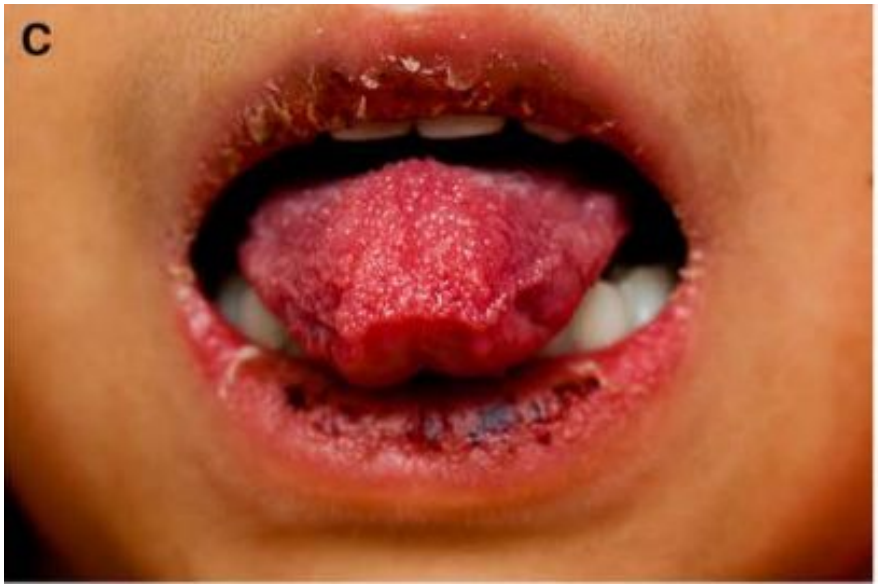
Diagnosis – Oropharyngeal Changes

- Erythema, dryness, fissuring, peeling, cracking, and bleeding of the lips
- “Strawberry tongue,” with erythema and prominent fungiform papillae
- Diffuse erythema of the oropharyngeal mucosa

 Oral ulcers and pharyngeal exudates are not consistent with KD.

Diagnosis – Oropharyngeal Changes





Diagnosis – Conjunctivitis

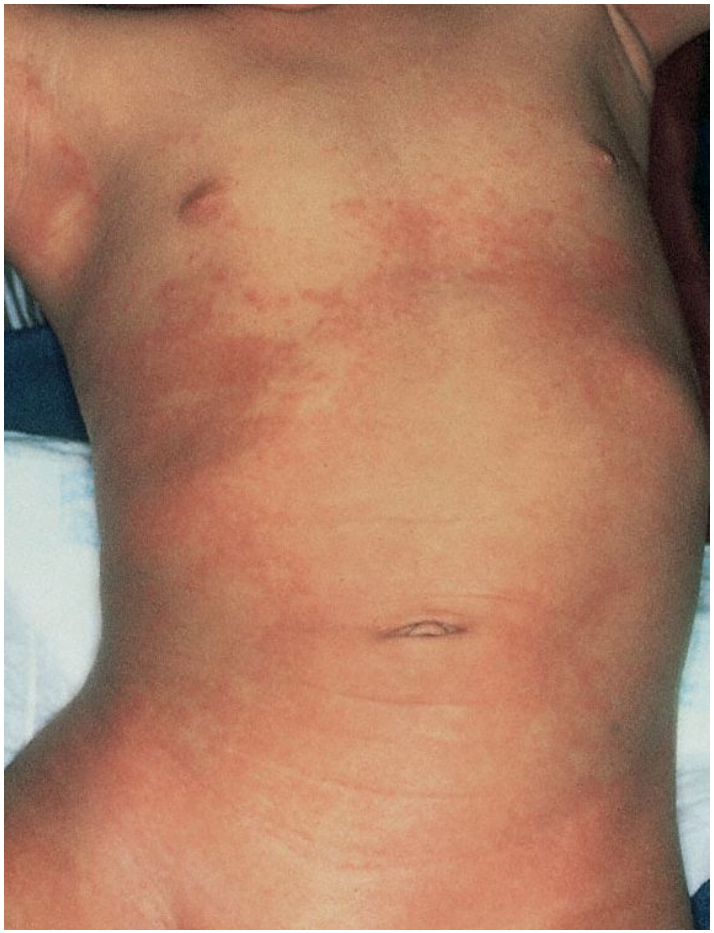
- Bilateral bulbar nonexudative conjunctival injection
- Usually begins shortly after fever onset
- Spares the limbus, an avascular zone around the iris
- Anterior uveitis is often observed by slit-lamp examination during the first week of fever
- Subconjunctival hemorrhage and punctate keratitis are occasionally observed

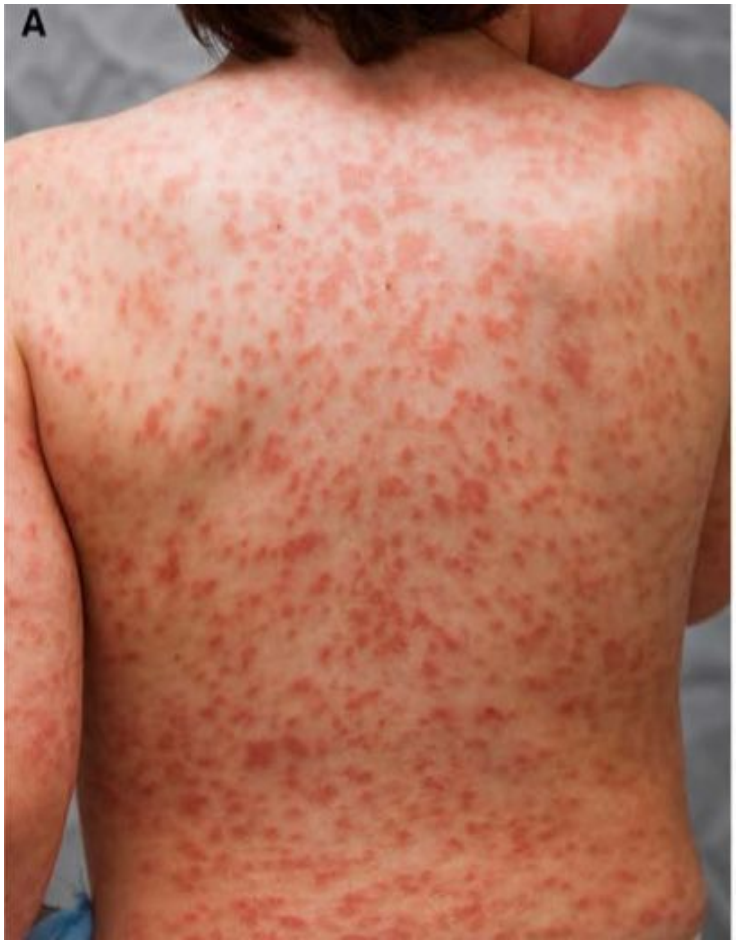
Diagnosis – Conjunctivitis

Diagnosis - Rash

- Most commonly, diffuse maculopapular eruption
- Erythroderma and erythema multiforme-like rashes are also common
- Less commonly, urticarial or fine micropustular eruptions
- The rash is usually extensive, primarily involving the trunk and extremities, and accentuation in the groin
- Early desquamation is a characteristic feature
- Bullous, vesicular, and petechial rashes are not consistent with KD and should prompt a search for an alternative diagnosis

Diagnosis - Rash



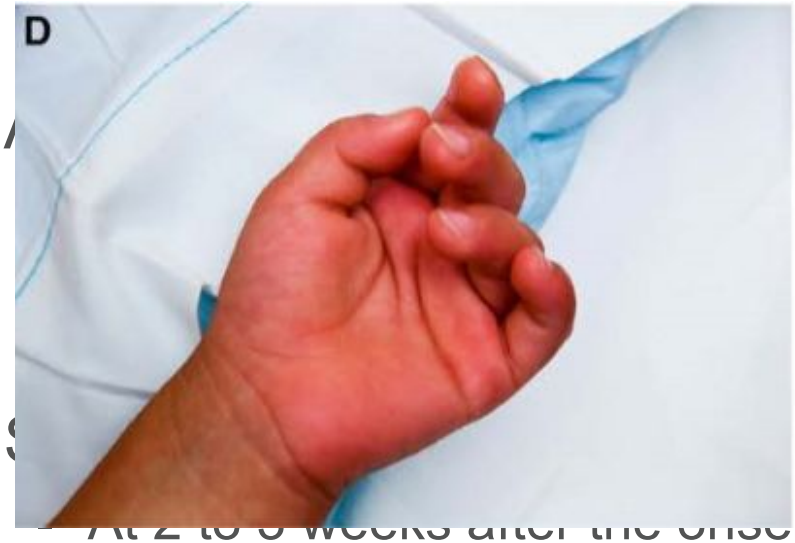


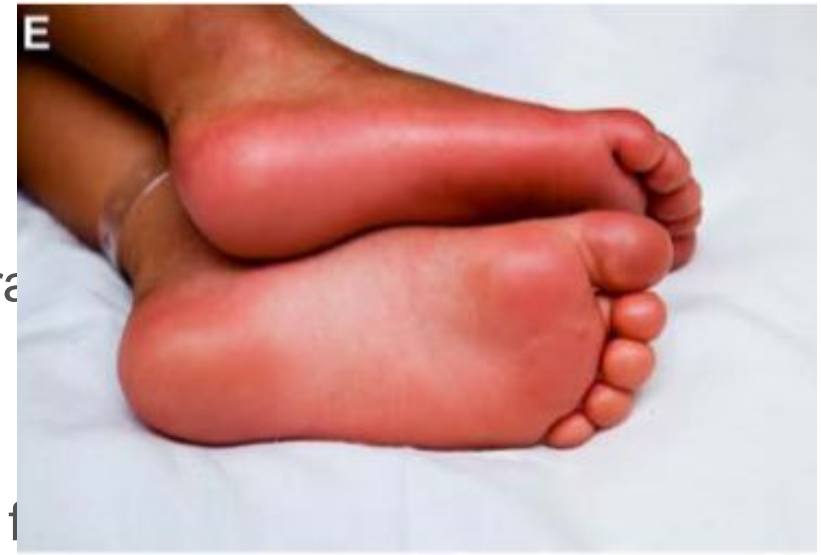
Diagnosis – Extremities changes

- Acute phase:
  - Erythema of the palms and soles
  - Firm and sometimes painful induration of the hands or feet

- Subacute Phase:
  - At 2 to 3 weeks after the onset of fever, desquamation of the fingers and toes begins in the periungual region and may extend to involve the palms and soles
  - At 1 to 2 months after fever onset, deep transverse grooves across the nails may be noted.

Diagnosis – Extremities changes





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Diagnosis - Cervical lymphadenopathy

- The least common of the principal clinical features
- Usually unilateral, ≥1.5 cm in diameter, and confined to the anterior cervical triangle
- Occasionally, it is the most notable and the only initial clinical finding, prompting a clinical diagnosis of bacterial lymphadenitis and significantly delaying KD diagnosis
- Imaging studies including ultrasound and computed tomography (CT) can be helpful in differentiating KD lymphadenopathy from bacterial lymphadenitis

Diagnosis - Cervical lymphadenopathy

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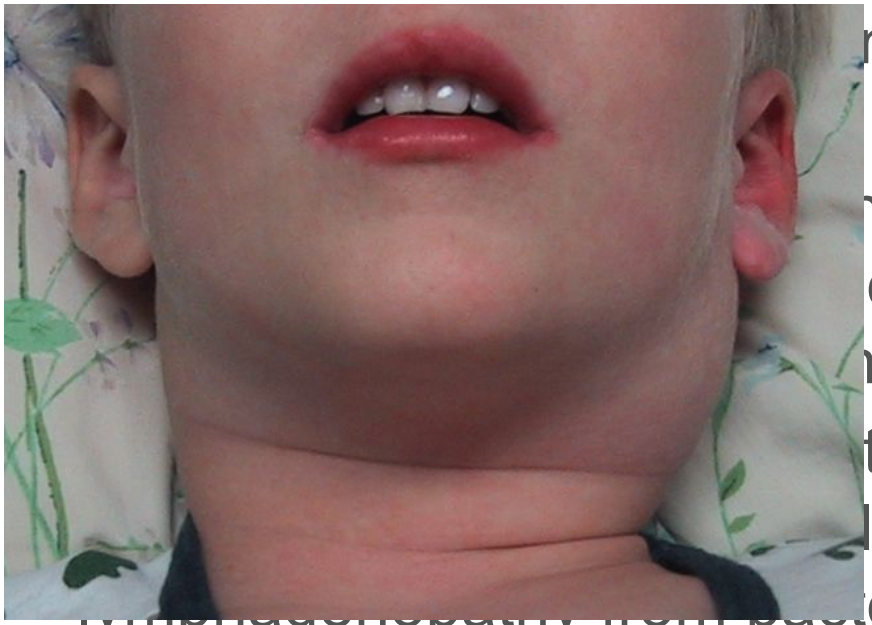

Systemic Vasculitis

Cardiovascular

- ✔ Myocarditis
- ✔ Pericarditis
- ✔ Valvular regurgitation
- ✔ Shock
- ✔ Coronary artery abnormalities
- ✔ Aneurysms of medium-sized noncoronary arteries
- ✔ Peripheral gangrene
- ✔ Aortic root enlargement

Respiratory

- ✔ Peribronchial and interstitial infiltrates on CXR
- ✔ Pulmonary nodules

Musculoskeletal

- ✔ Arthritis
- ✔ Arthralgia

Gastrointestinal

- ✔ Diarrhea, vomiting, abdominal pain
- ✔ Hepatitis, jaundice
- ✔ Gallbladder hydrops
- ✔ Pancreatitis

Nervous system

- ✔ Extreme irritability
- ✔ Aseptic meningitis
- ✔ Facial nerve palsy
- ✔ Sensorineural hearing loss

Genitourinary

- ✔ Urethritis, hydrocele

Other

- ✔ Retropharyngeal phlegmon
- ✔ Anterior uveitis by slit lamp examination
- ✔ Erythema and induration at BCG inoculation site

Differential Diagnosis

- Viral infections
- Scarlet fever
- Staph scalded skin syndrome
- Bacterial cervical lymphadenitis
- Drug hypersensitivity reaction
- Stevens-Johnson Syndrome
- Juvenile rheumatoid arthritis
- Rocky mountain spotted fever
- Leptospirosis
- Mercury hypersensitivity reaction (acrodynia)

Exam Findings

- Hyperdynamic precordium and tachycardia
- Innocent systolic flow murmurs - accentuated
- Gallop rhythm suggesting decreased compliance
- Pericardial rub - rare
- Holosystolic murmur - Mitral regurgitation (MR)

Cardiovascular Findings

- Coronary artery aneurysms
  - 15-25% of untreated patients
- Myocarditis
- Electrocardiogram changes
- Pericardial effusion
- Aortic root dilatation
- Mitral and aortic valve regurgitation
- Ischemic Heart Disease
- Myocardial infarction
- Death
  - 2%□0.5%

Cardiovascular Findings - Coronary Artery Abnormalities

- 20-25% of untreated patients, decreased to 4-5% after treatment
- Dilation only to aneurysms of various numbers, sizes, and characteristics
- Occurs in proximal segments and then extending distally
- Large/giant aneurysms might not cause symptoms unless myocardial ischemia develops
- Aneurysms of other medium-sized arteries might be seen in patients with severe coronary artery involvement. Common sites include the axillary, subclavian, brachial, femoral, iliac, splanchnic, and mesenteric arteries, usually near or at branching points.

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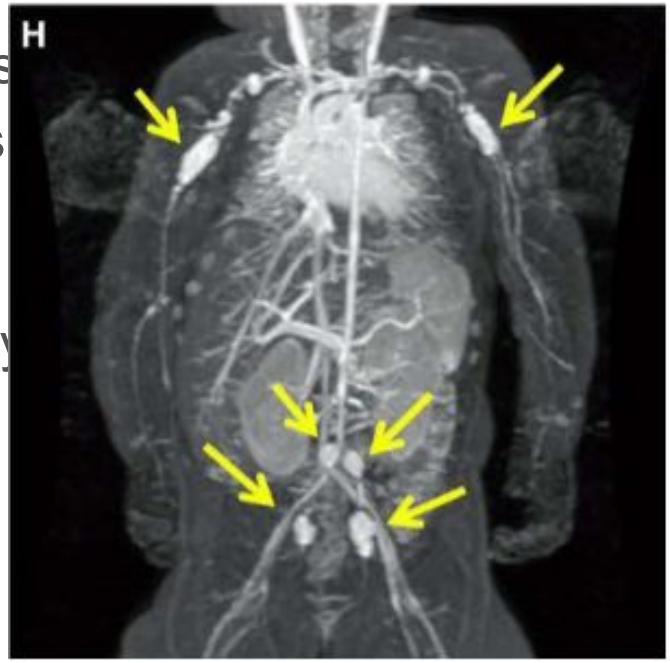

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Cardiovascular Findings - Electrocardiographic Changes

- Sinus node and atrioventricular node functional abnormalities, with prolonged PR interval
- Nonspecific ST and T-wave changes
- Low voltage if there is myocardial or pericardial involvement
- Left ventricular (LV) dilation
- Rarely, malignant ventricular arrhythmias

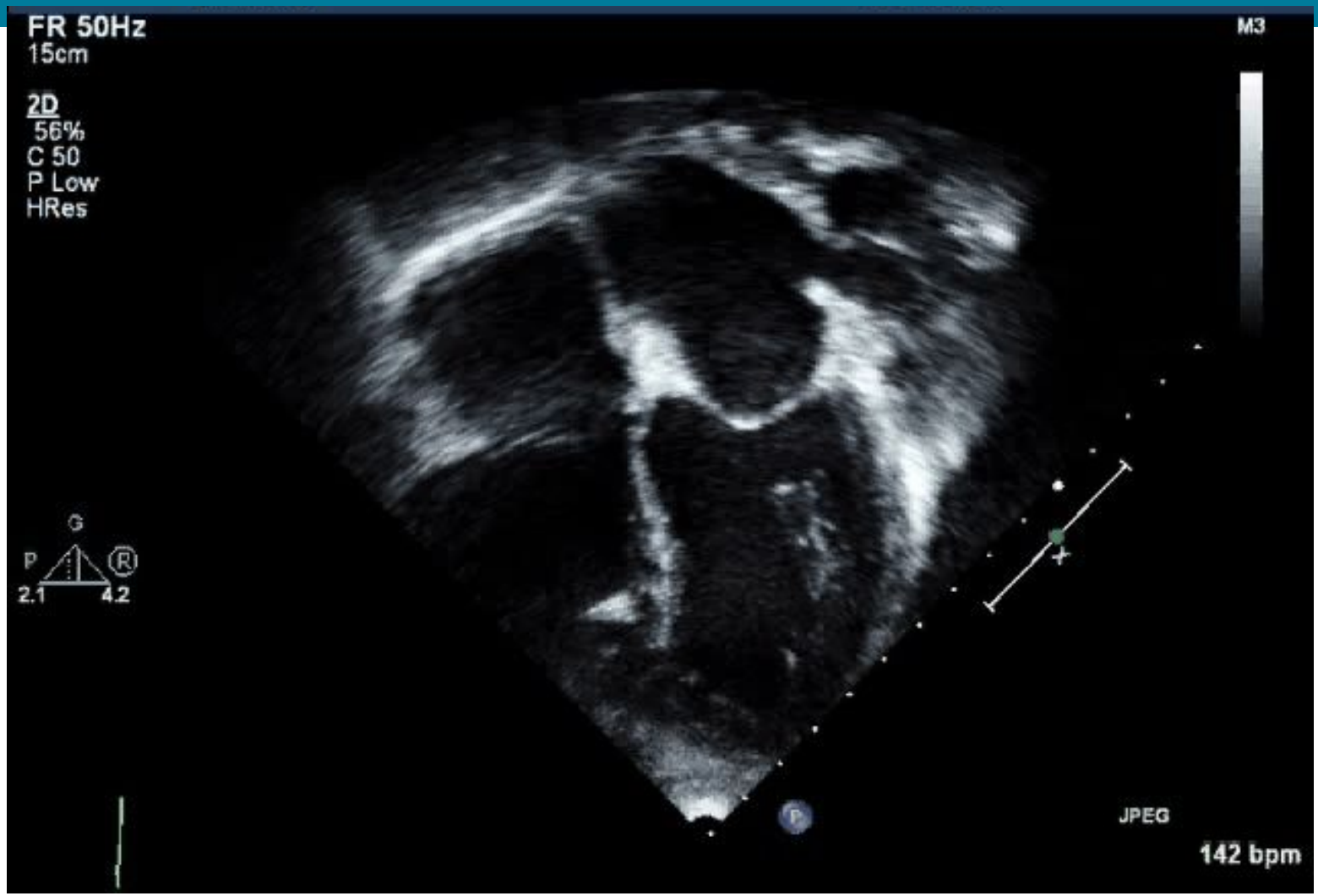
Cardiovascular Findings - Myocardial Dysfunction and Cardiovascular Collapse

- Myocardial Dysfunction
- Myocarditis occurs frequently in acute KD (50% to 70%)
- Transient and responds well to anti-inflammatory treatment

- Cardiovascular collapse
- Cardiovascular collapse and hypotension is seen in 5% of patients with KD, requiring the initiation of volume expanders, vasoactive agents, or transfer to the intensive care unit
- The presence of thrombocytopenia and coagulopathy is notable
- Diagnosis of bacterial sepsis is frequently suspected

Cardiovascular Findings – Valvar and aortic Abnormalities

- Mitral regurgitation (MR) seen in 25%
- MR does not persist on follow-up
- Aortic regurgitation (AR) is less common (1%)
- AR is usually associated with aortic root dilation
- Aortic root dilation seen in ≈10% of patients



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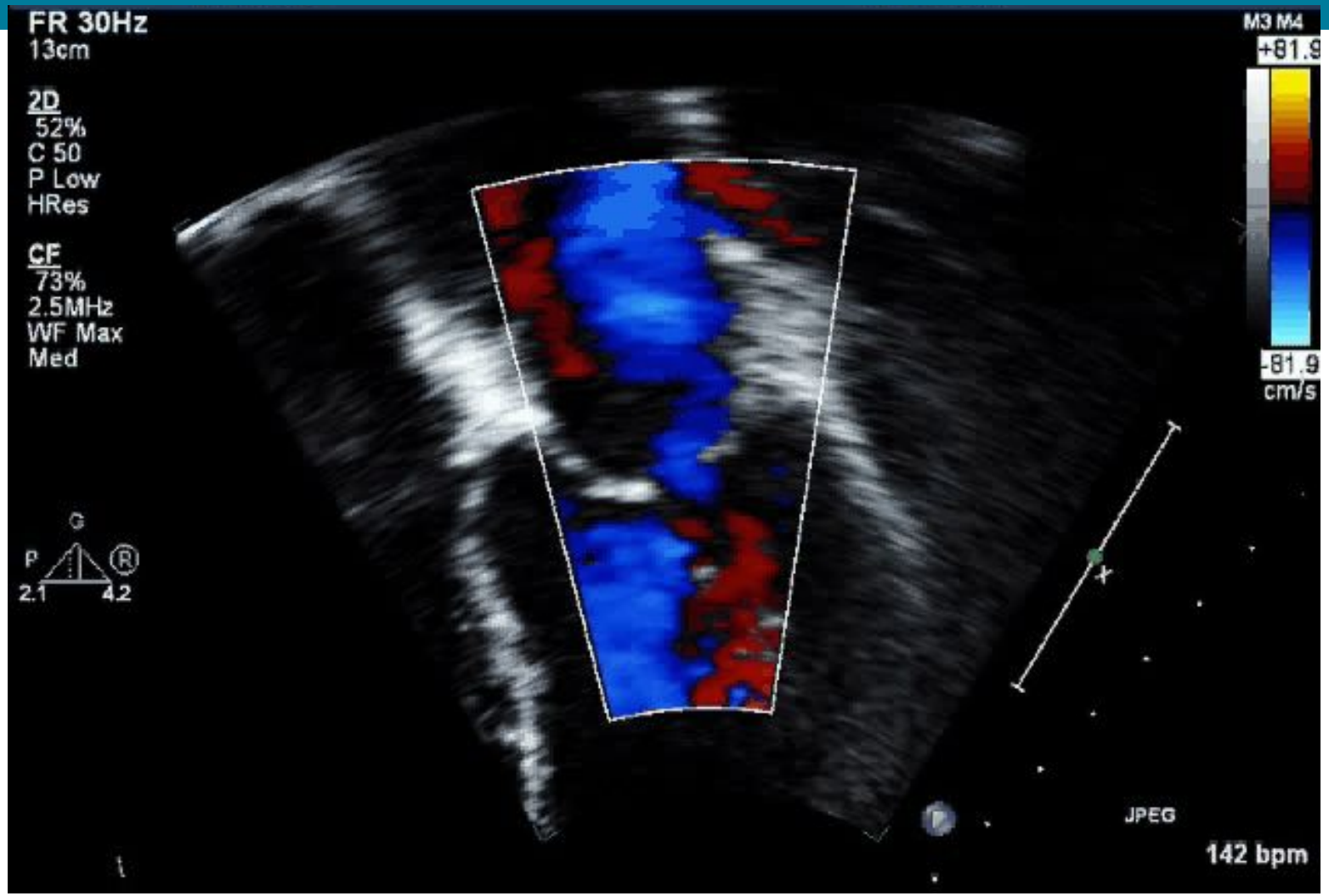

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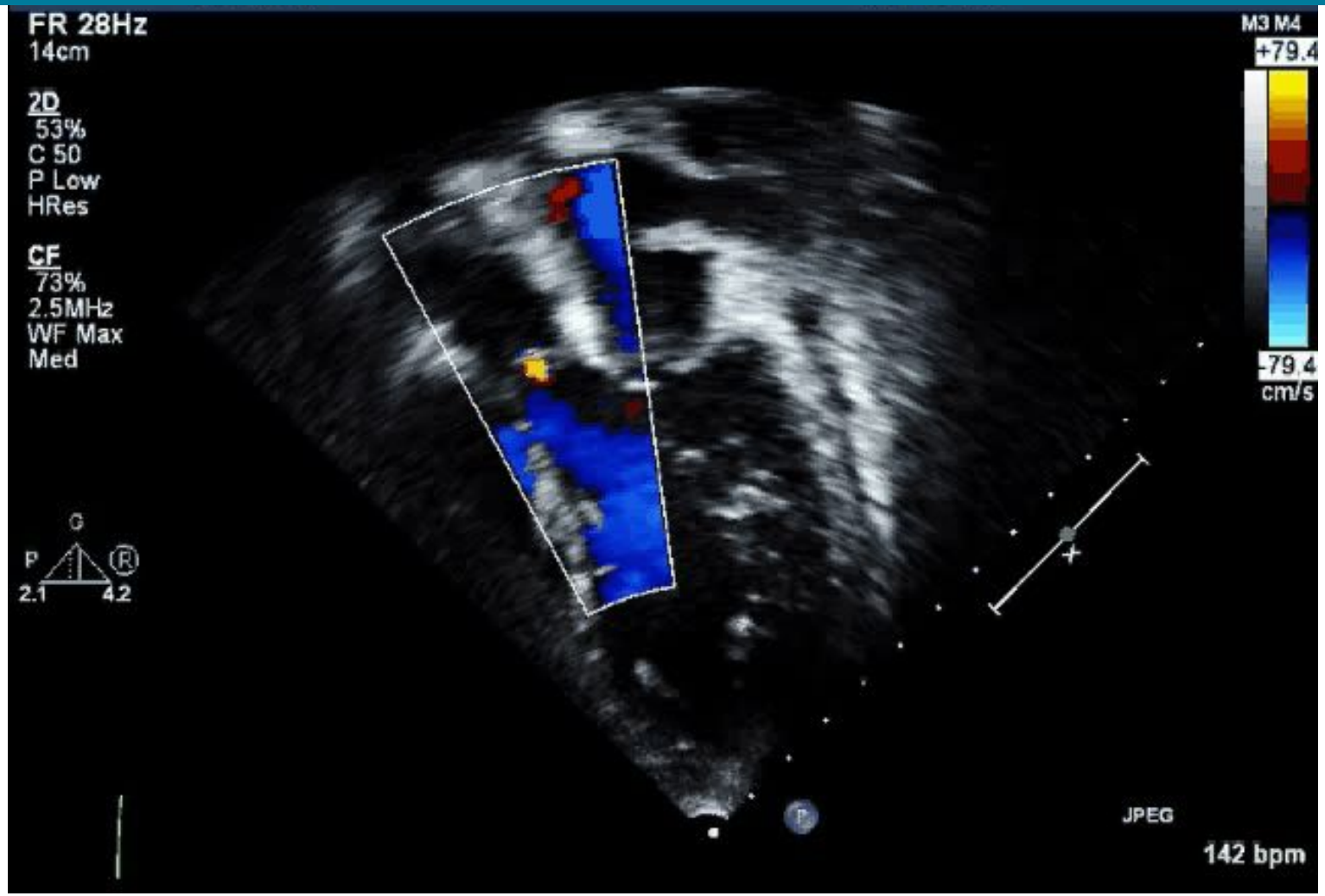

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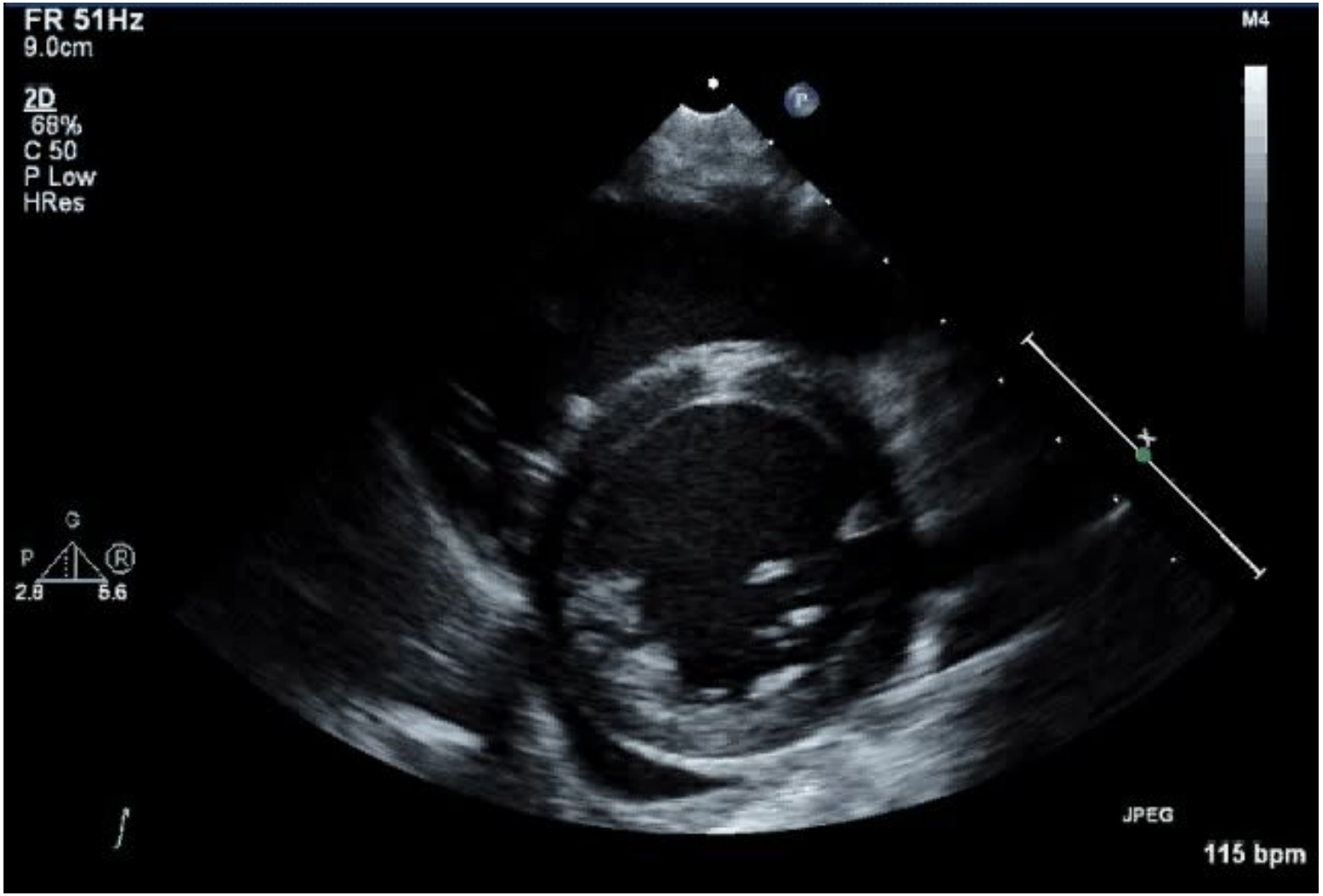


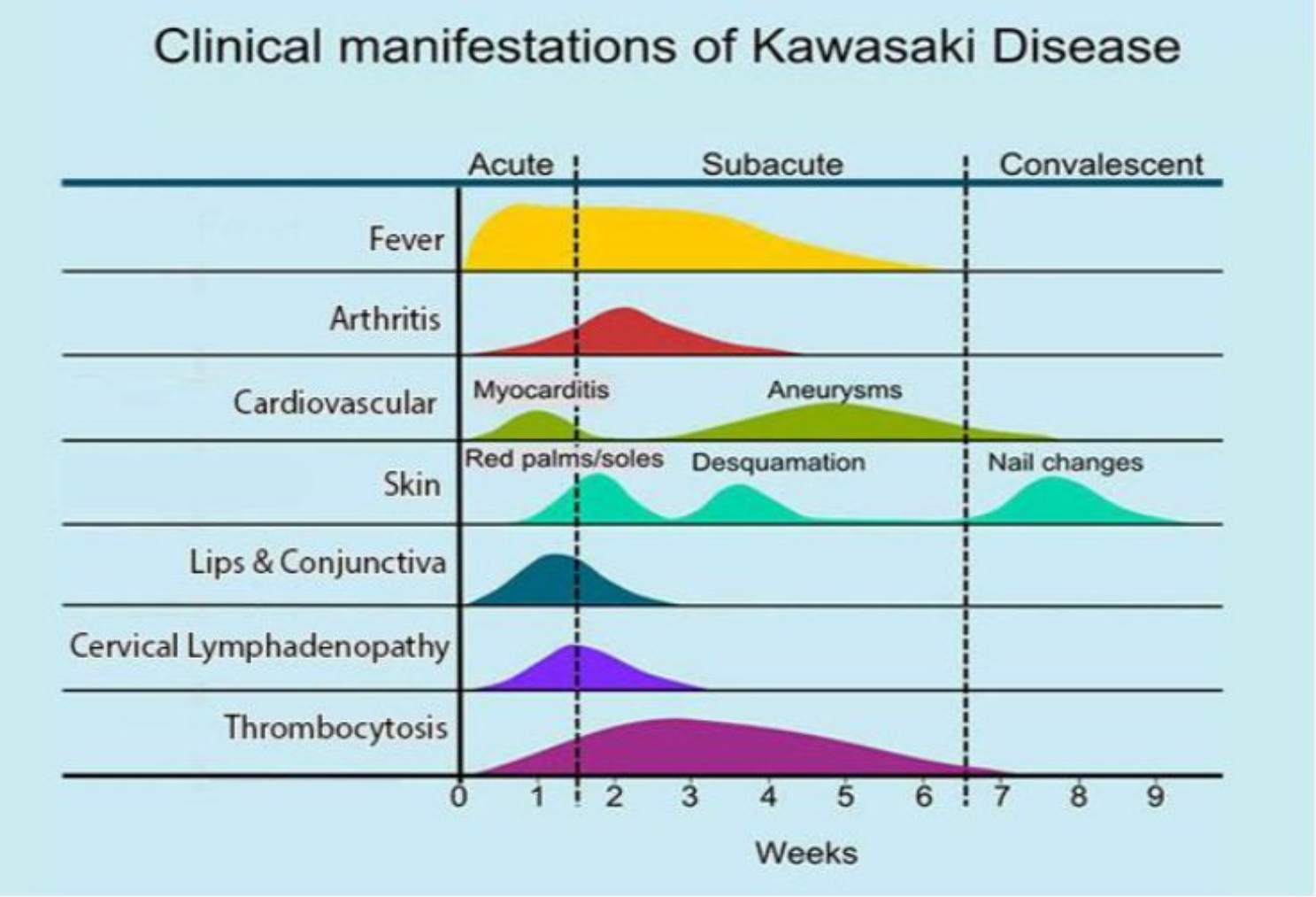
Laboratory Findings

- Leukocytosis
  - >15,000/mm^3
- Elevated ESR
  - ≥40mm/hr
- Elevated CRP
  - ≥3.0mg/dL
- Anemia
- Hypoalbuminemia
  - <3.0g/dL
- Thrombocytosis
  - >450,000/mm
- Sterile pyuria
  - >10 WBC/HPF
- Elevated serum liver enzymes
- Pleocytosis of CSF

Kawasaki Disease Clinical Phases

Acute	1-2 weeks	Fever, typical clinical features, myocarditis, pericarditis
Subacute	Between 1-2 weeks and 1 month	Resolution of fever & other acute features, desquamation, thrombocytosis, aneurysms
Convalescent	1-2 months	Resolution of clinical features; normalization of inflammatory indices

Kawasaki Disease Clinical Phases



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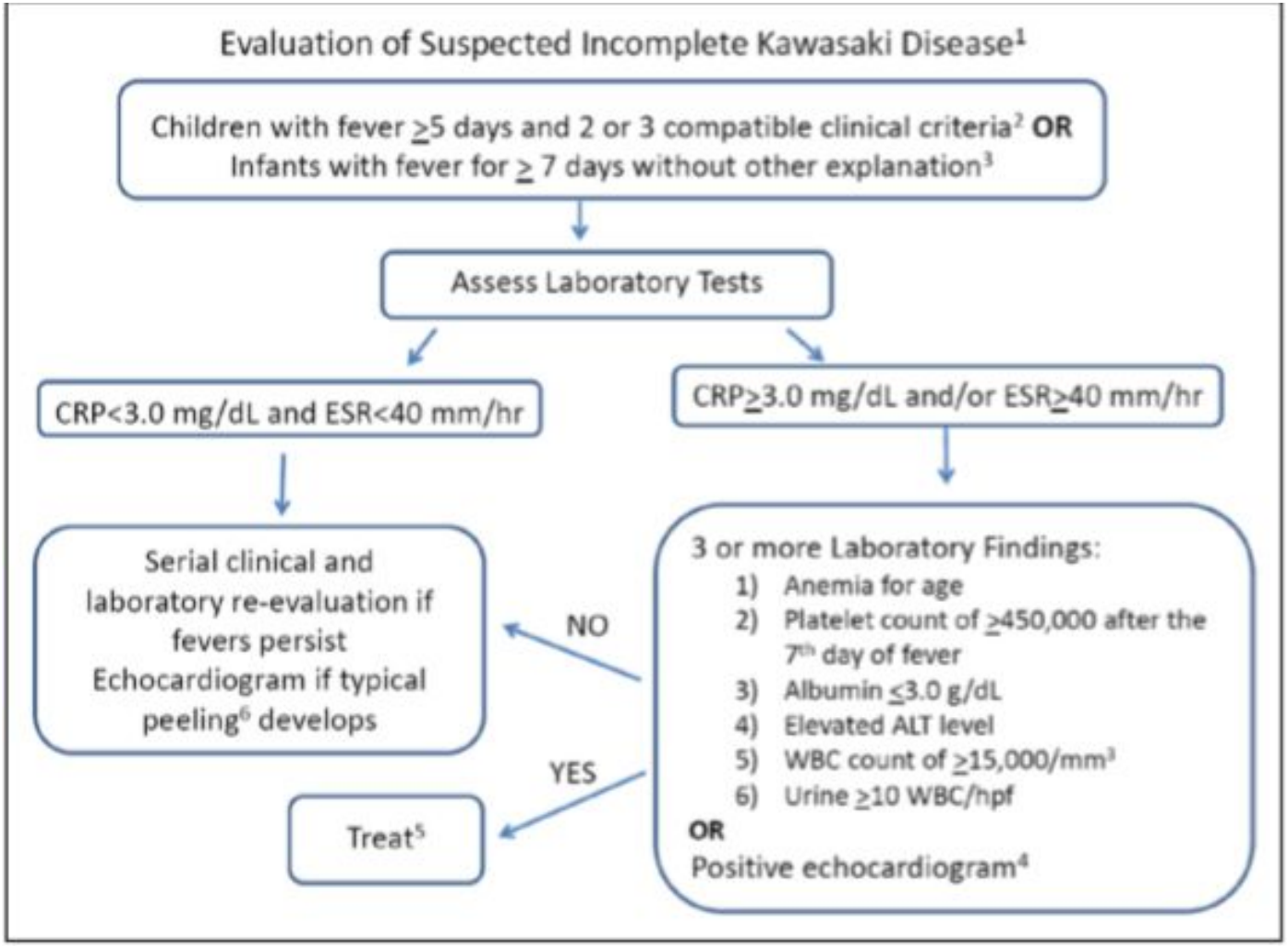
Incomplete/Atypical Kawasaki Disease

- Children with fever plus fewer than 4 of the 5 clinical criteria
- Most common at the extreme end of age spectrum
  - ✔ Infants and children over 8 years
- Does not refer to unusual clinical features
- Difficult diagnostic dilemma □ delayed diagnosis □ higher risk of coronary abnormalities
- Patients have some laboratory profile as classic cases

Incomplete/Atypical Kawasaki Disease



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Criteria for positive Echo

Any of the following 3 criteria:

1. LAD or RCA Z score ≥2.5
2. Coronary artery aneurysm
3. ≥3 other suggestive features:
    a. Decreased left ventricular function
    b. Mitral regurgitation
    c. Pericardial effusion
    d. LAD or RCA Z scores of 2 to 2.5

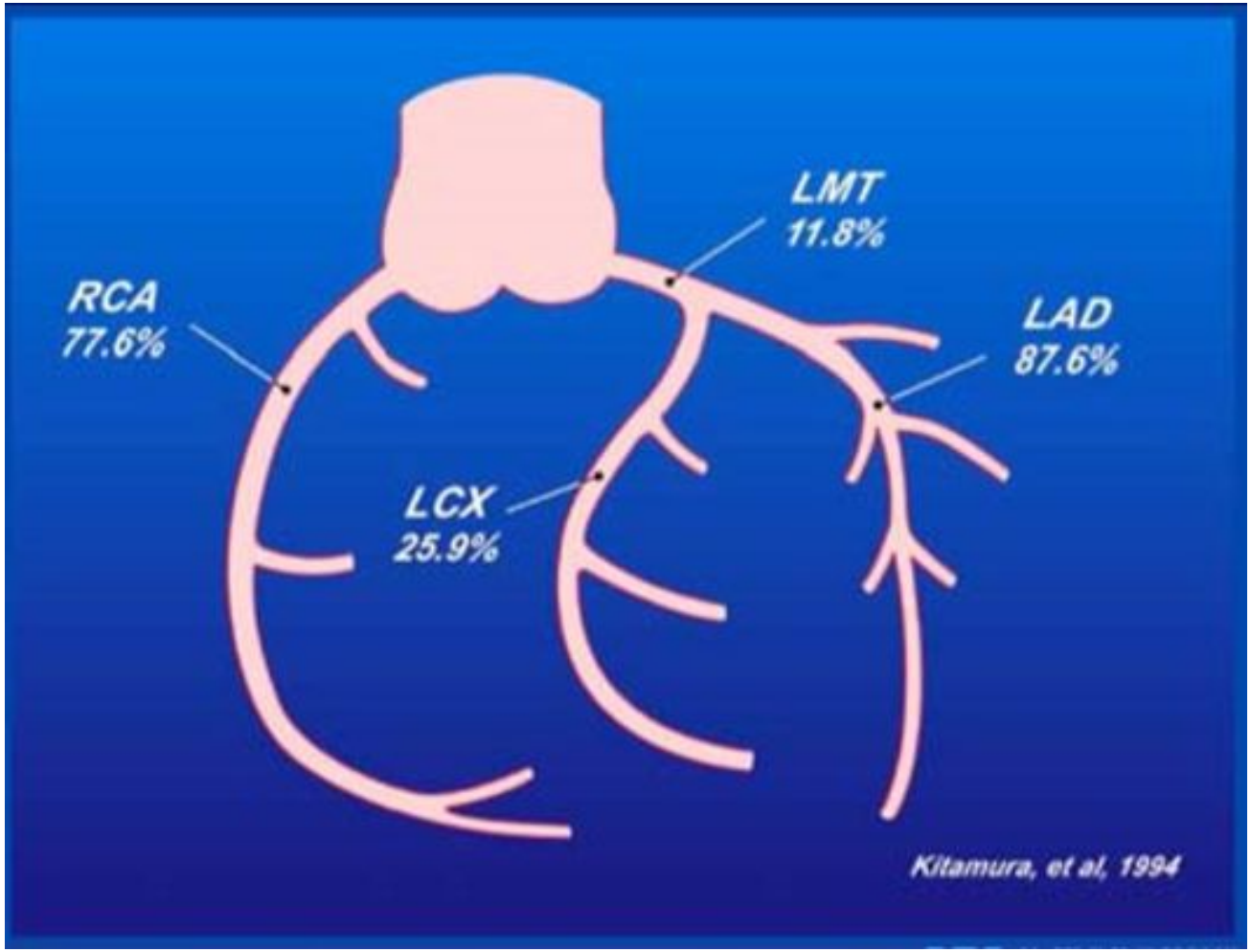
When to Obtain the Initial Echo

- As soon as the diagnosis is suspected
- Initiation of treatment should not be delayed by the timing of the study
- Purpose
  - Diagnosis
  - Establishes a baseline for longitudinal follow-up

Common Sites of Coronary Aneurysms

- Proximal left anterior descending
- Proximal right coronary
- Left circumflex
- Left main
- Distal right coronary
- Junction between right and posterior descending

Common Sites of Coronary Aneurysms



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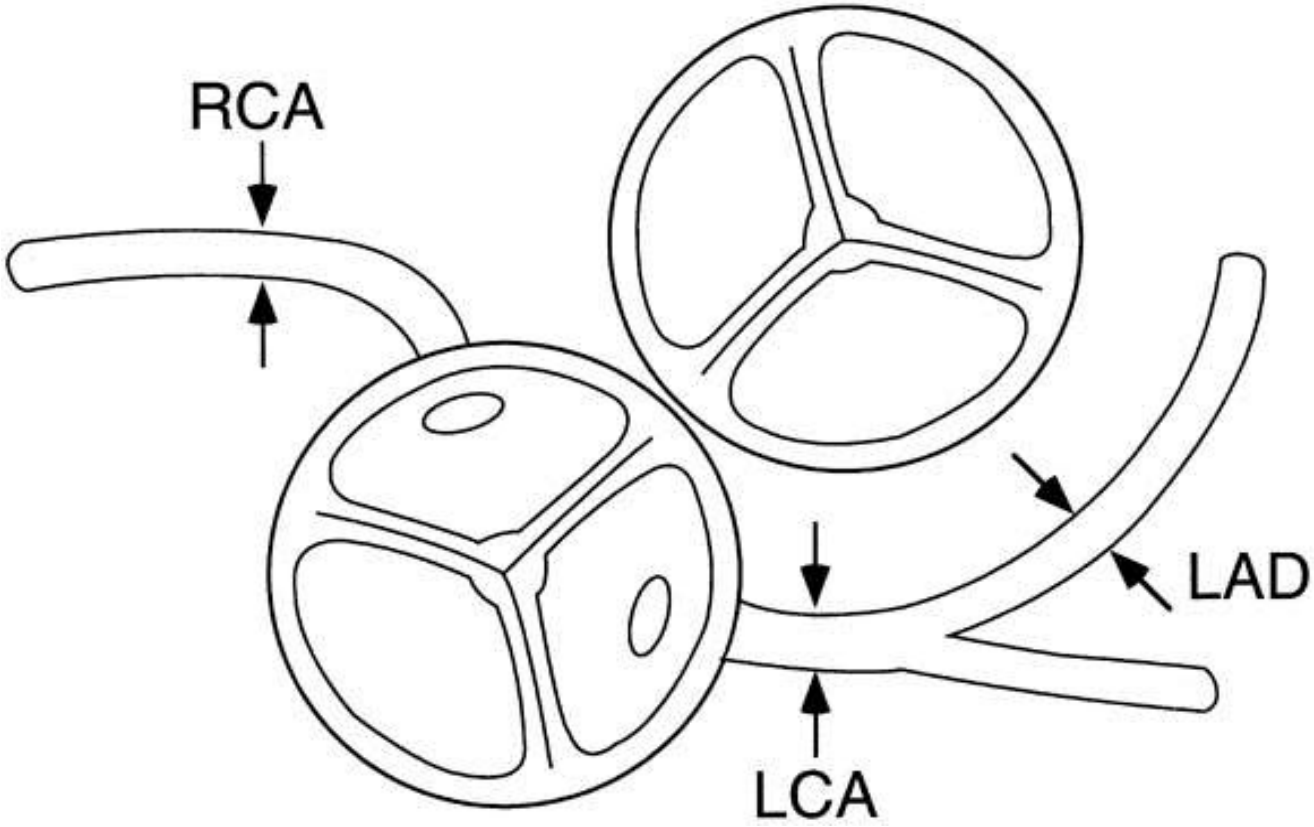
Natural History of Coronary Aneurysms

- Dilation appears ~7-10 days after illness onset (acute phase)
- Peak vessel diameter reached ~1 month after illness onset (subacute phase)
- Therefore, echo is recommended for all patients at diagnosis, 2 weeks, and 6-8 weeks after illness onset
- In patients with aneurysms, regression occurs by 1-2 years in 50-67%
  - More likely to occur with smaller aneurysms < 6 mm
- Larger aneurysms more likely to develop stenosis over time
  - 50% of aneurysms 6-8 mm
  - Nearly 85% of aneurysms > 8 mm

Technical Aspects of Coronary Imaging

- Use highest frequency transducer possible
- Center image in the middle of the screen
- Optimize depth to obtain highest possible frame rate
- Reduce 2D gain and dynamic range (compression) to improve demonstration of endovascular lumen
- Measurements should be made from inner edge to inner edge
  - Ideally in early diastole (at the end of the T wave)
- Use sedation when necessary

Where to Measure



Describing Coronary Involvement

- Number
- Location
- Distribution
- Qualitative appearance
  - Ectasia: Dilation without segmental aneurysm
  - Fusiform aneurysm: symmetric dilation (longitudinal>axial) with proximal and distal tapering (“sausage-like”)
  - Saccular aneurysm: axial and longitudinal dimensions are ~equal (“beads on a string” appearance)
- Quantitative measurement
  - 2004 AHA guidelines classified aneurysms on the basis of absolute dimension
  - 2017 AHA guidelines recommended a classification scheme based solely on Z scores
- Presence of thrombosis (or stenosis)

Describing Coronary Involvement

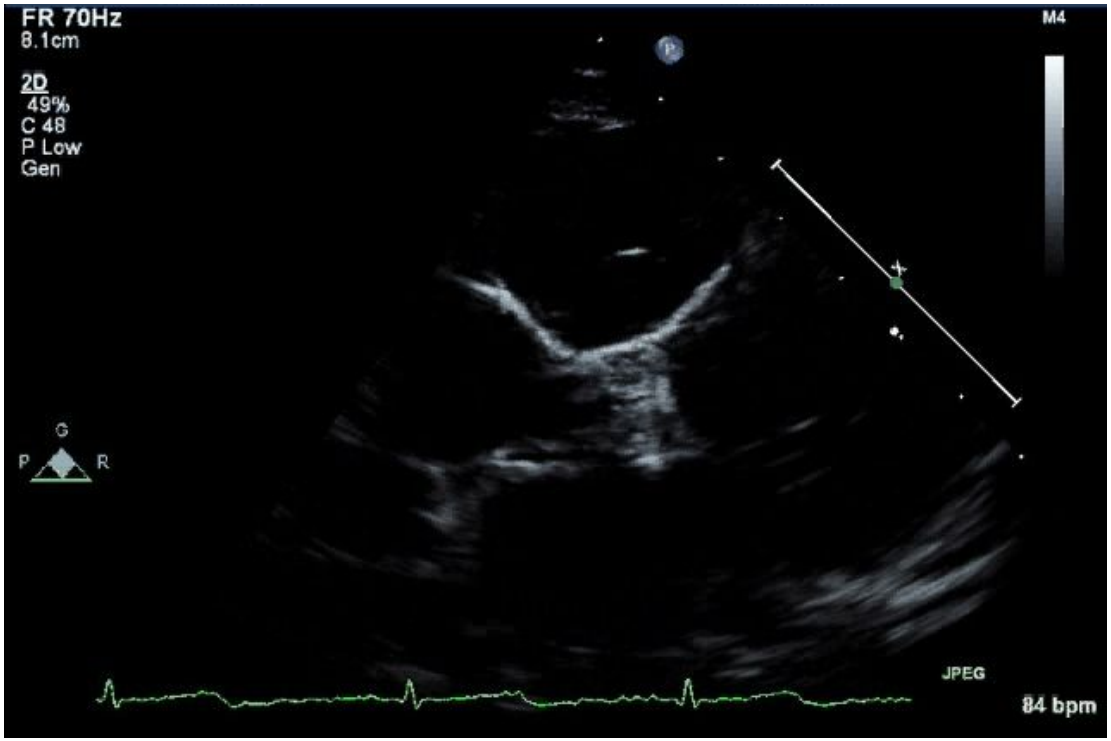
- The use of Z scores better allows for evaluation of the severity of coronary artery dilation by correcting for BSA

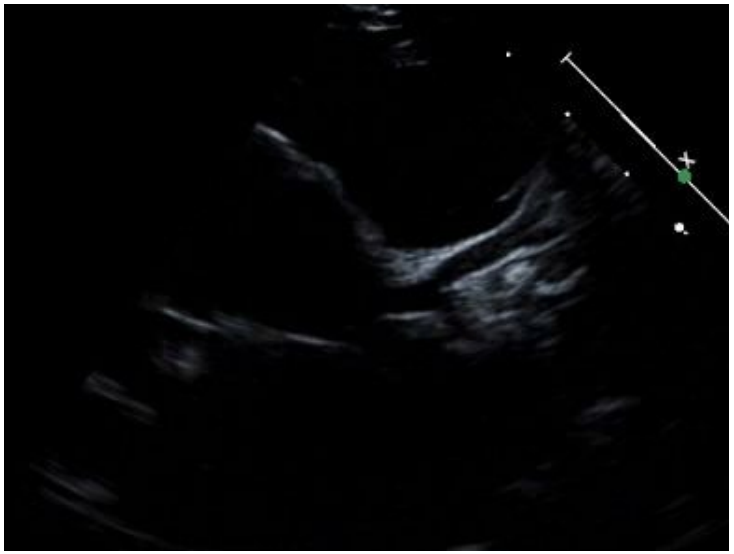
Z-Score Classification:

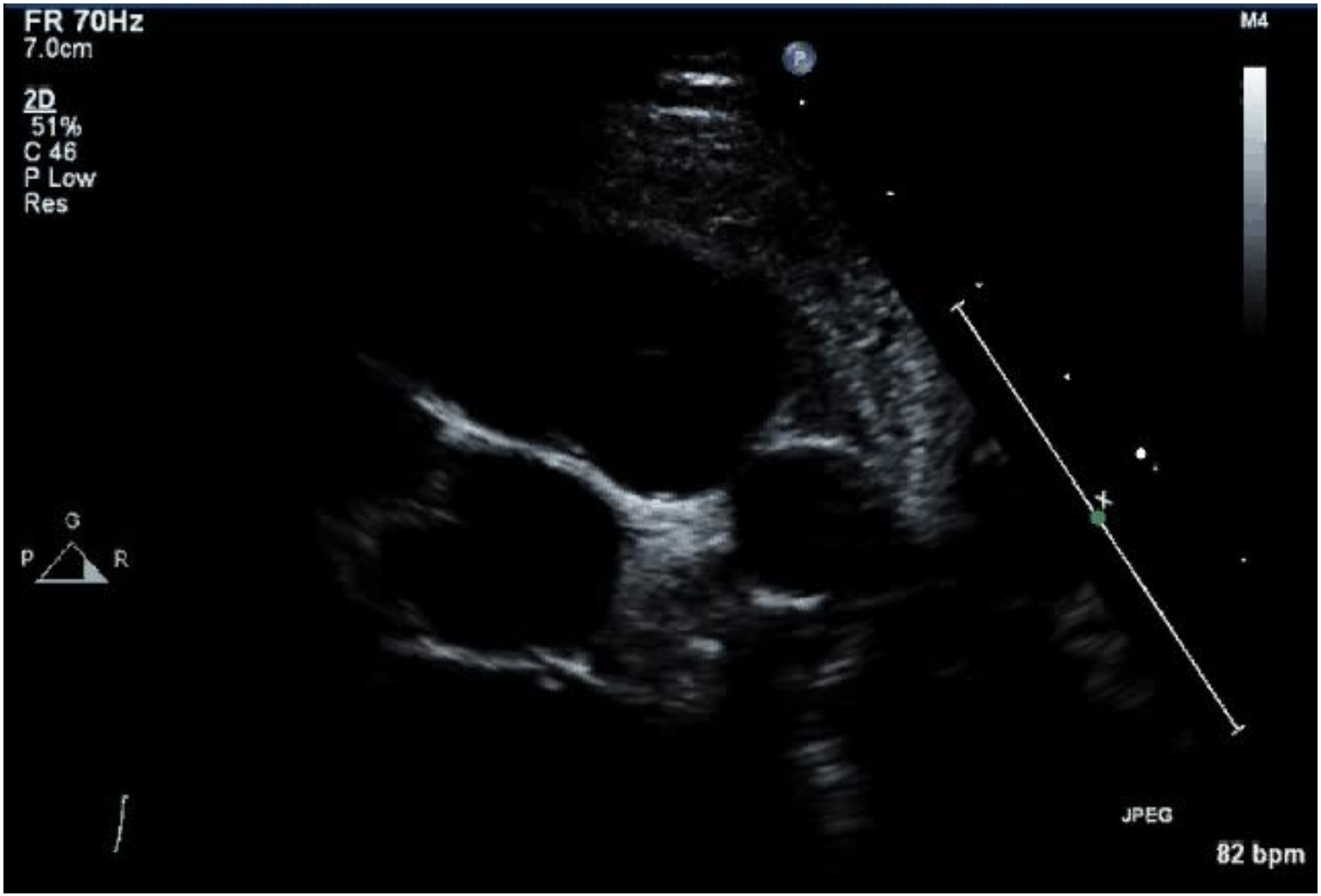
1. No involvement: Always <2
2. Dilation only: 2 to <2.5
3. Small aneurysm: ≥2.5 to <5
4. Medium aneurysm: ≥5 to <10, and absolute dimension <8 mm
5. Large or giant aneurysm: ≥10, or absolute dimension ≥8 m

Planes for Left Coronary Artery System

- Left main:
  - Parasternal short axis at level of aortic root
- Left anterior descending:
  - Parasternal short axis rotated clockwise and cranially to visualize anterior interventricular groove
  - Parasternal long axis with leftward angulation
- Left circumflex:
  - Parasternal short axis rotated clockwise to visualize anterior left AV groove
  - Parasternal long axis with leftward angulation
  - Distal vessel may be visualized from apical 4 chamber view (anterior) or subcostal sagittal view at level of left AV groove







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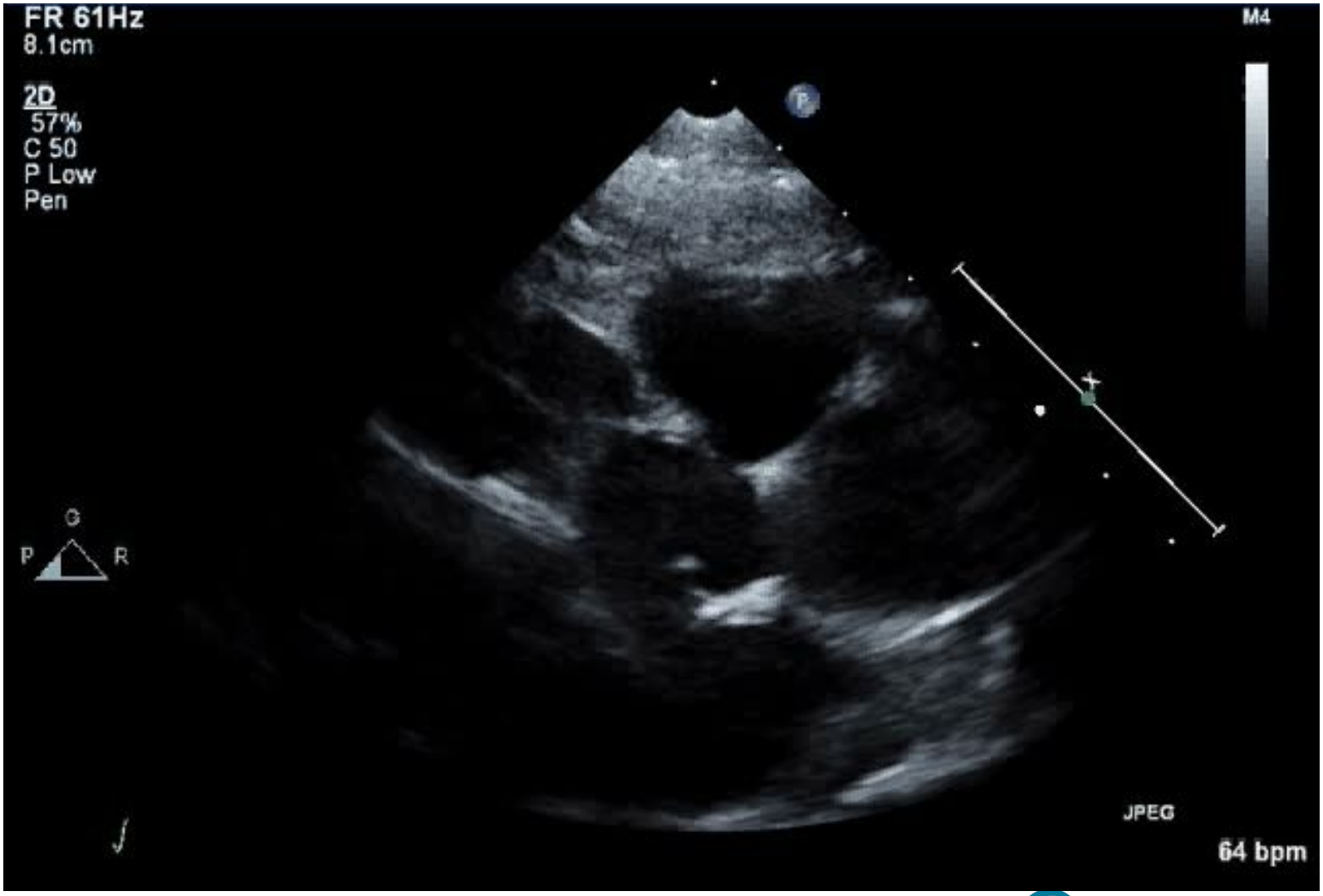

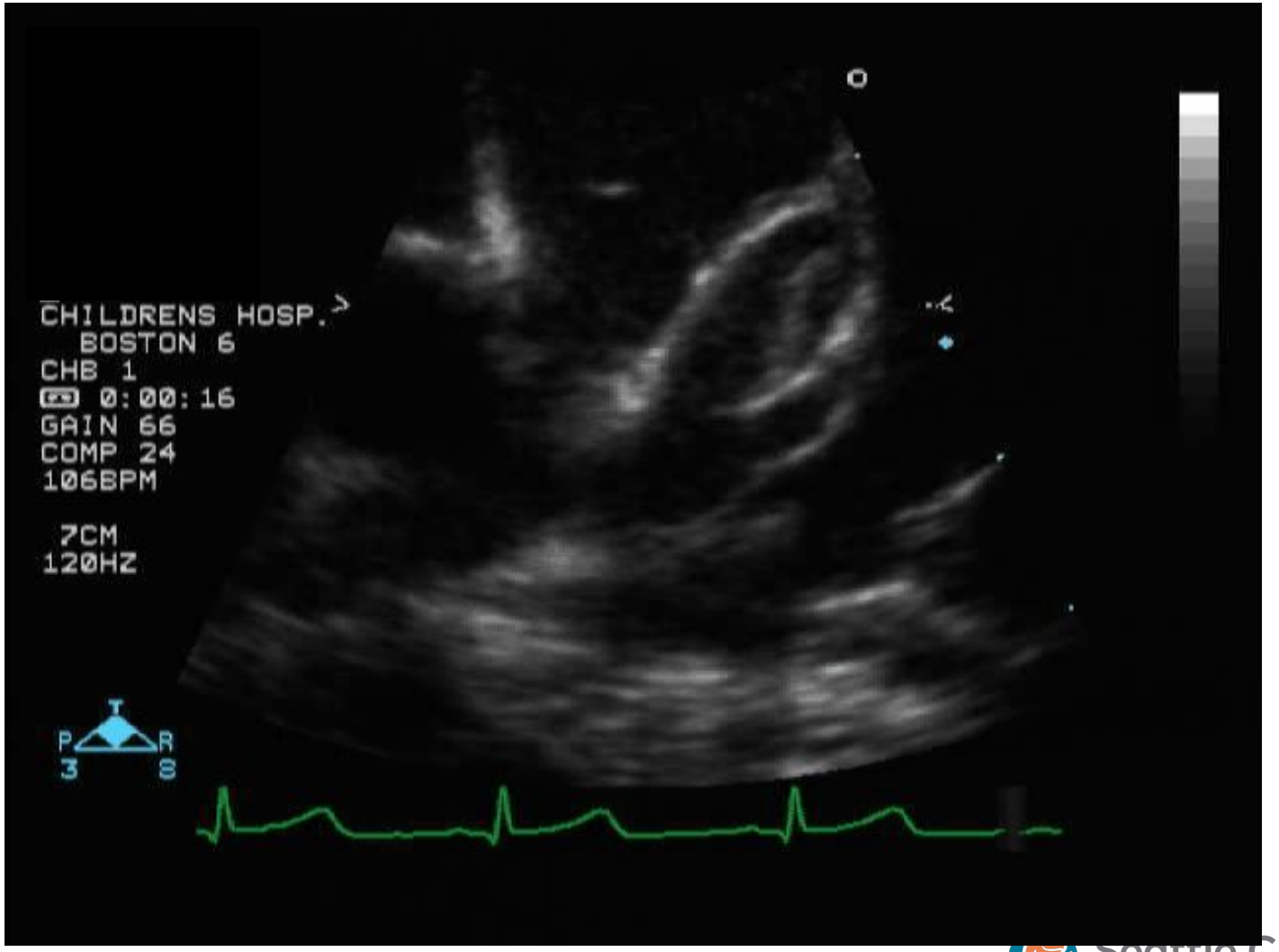

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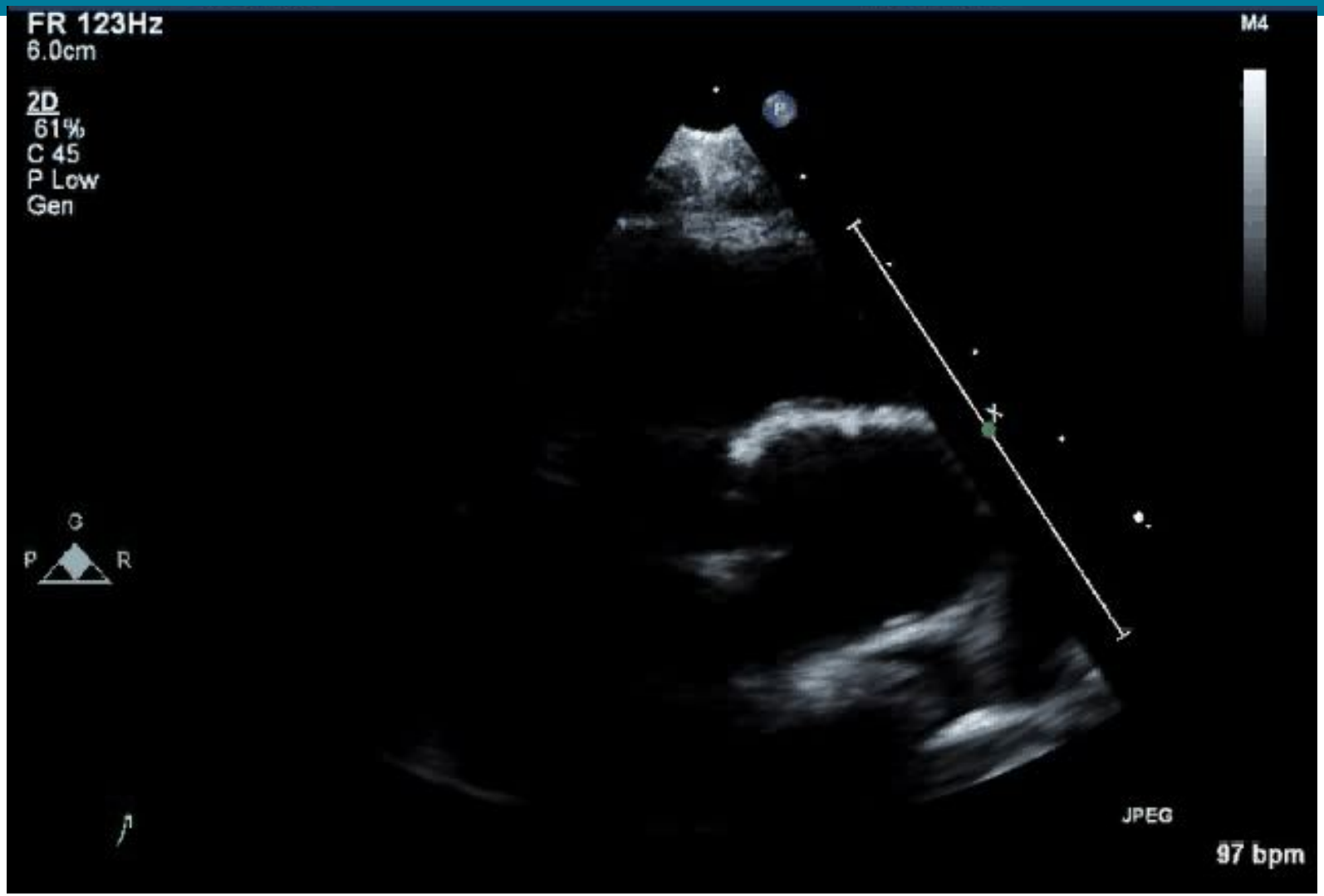
Planes for Right Coronary Artery and Posterior Descending Artery

- Proximal RCA
  - Parasternal short axis at level of aortic root
  - Parasternal long axis
  - Subcostal coronal
- Mid RCA
  - Right parasternal short axis with patient in right lateral decubitus position may offer best visualization
  - Parasternal long axis angulated toward tricuspid valve and lateral AV groove
- Distal RCA
  - Apical 4 chamber view (posterior)
- Posterior Descending Artery
  - Apical 4 chamber view (posterior)
  - Parasternal long axis directed posteriorly



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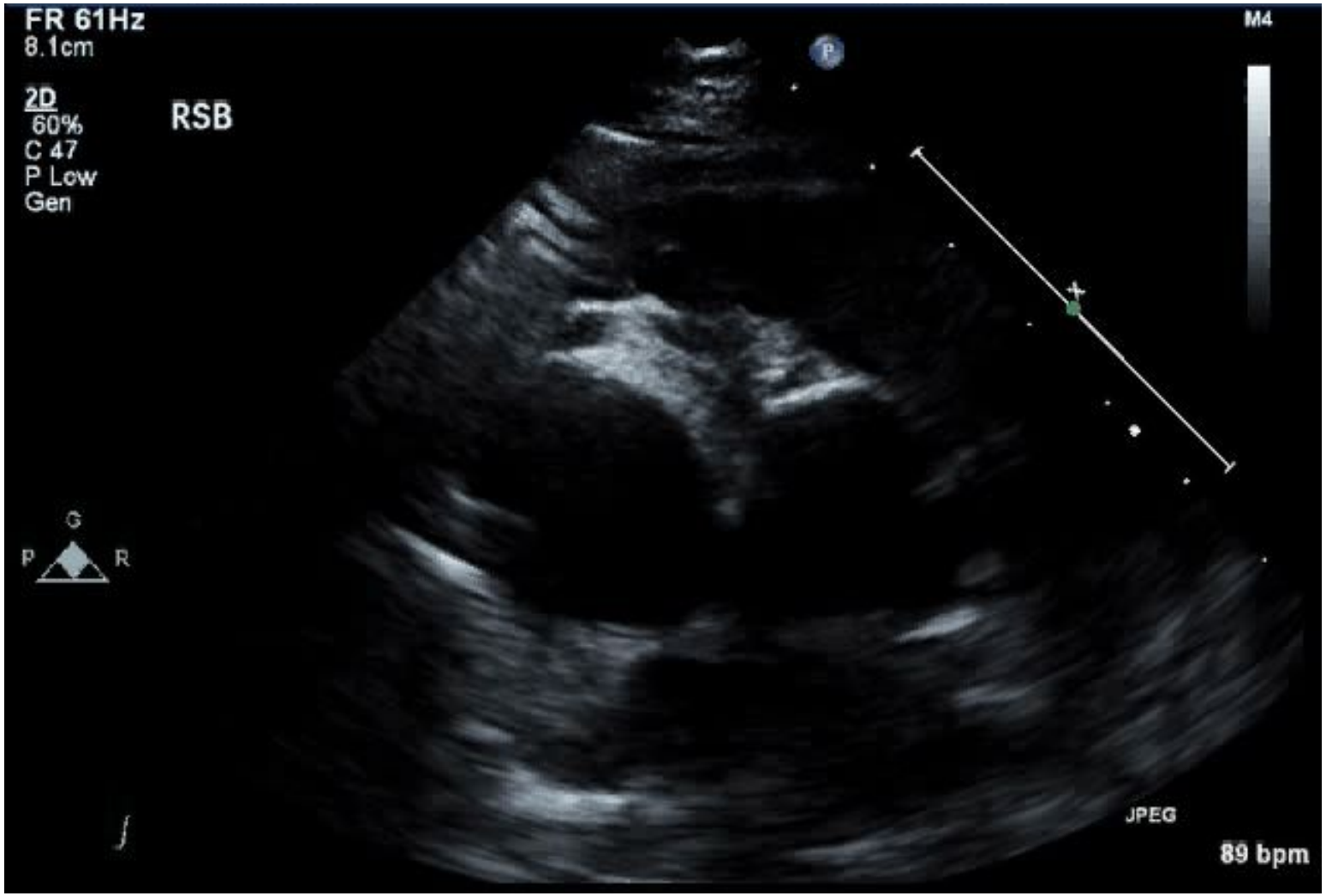

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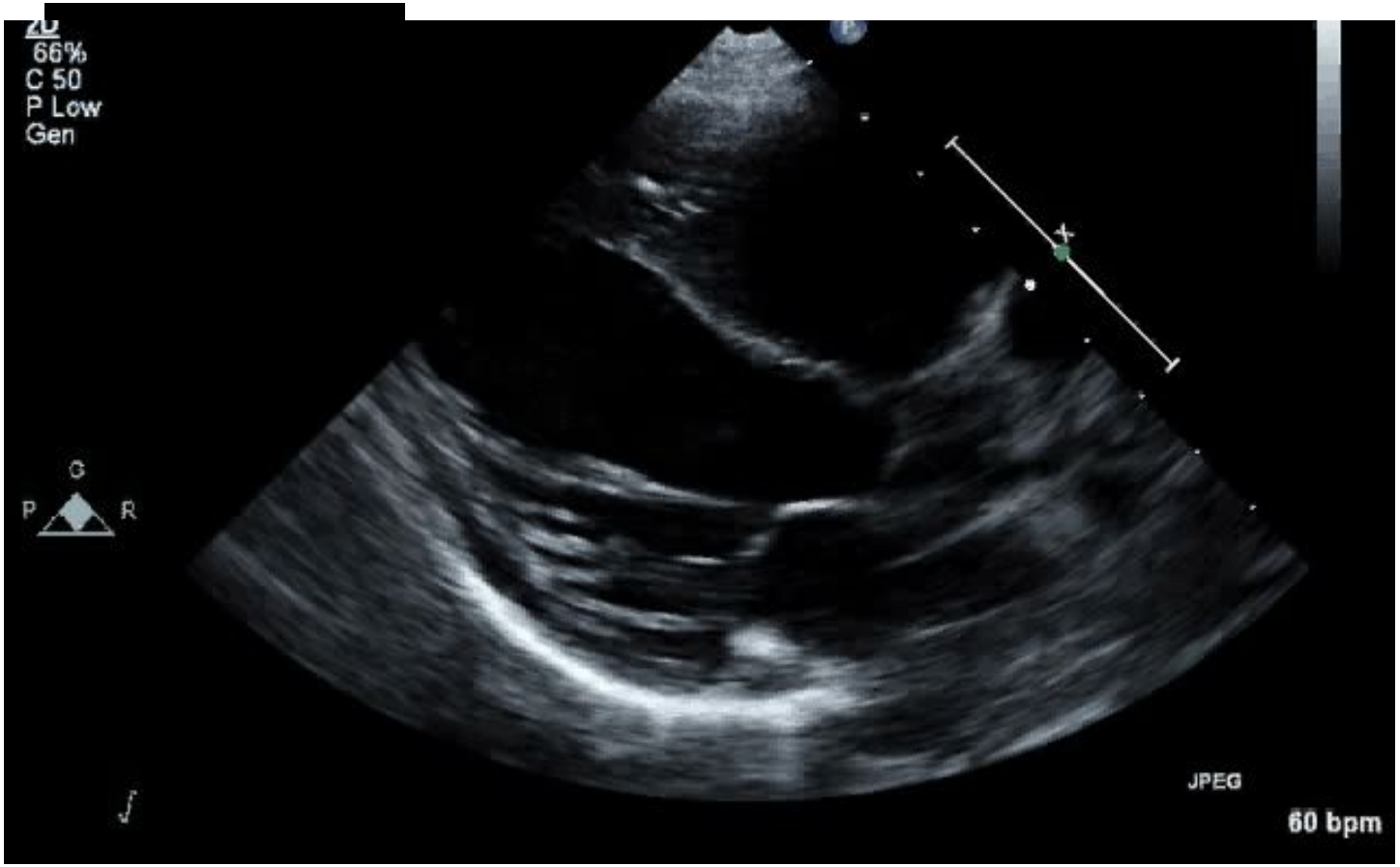

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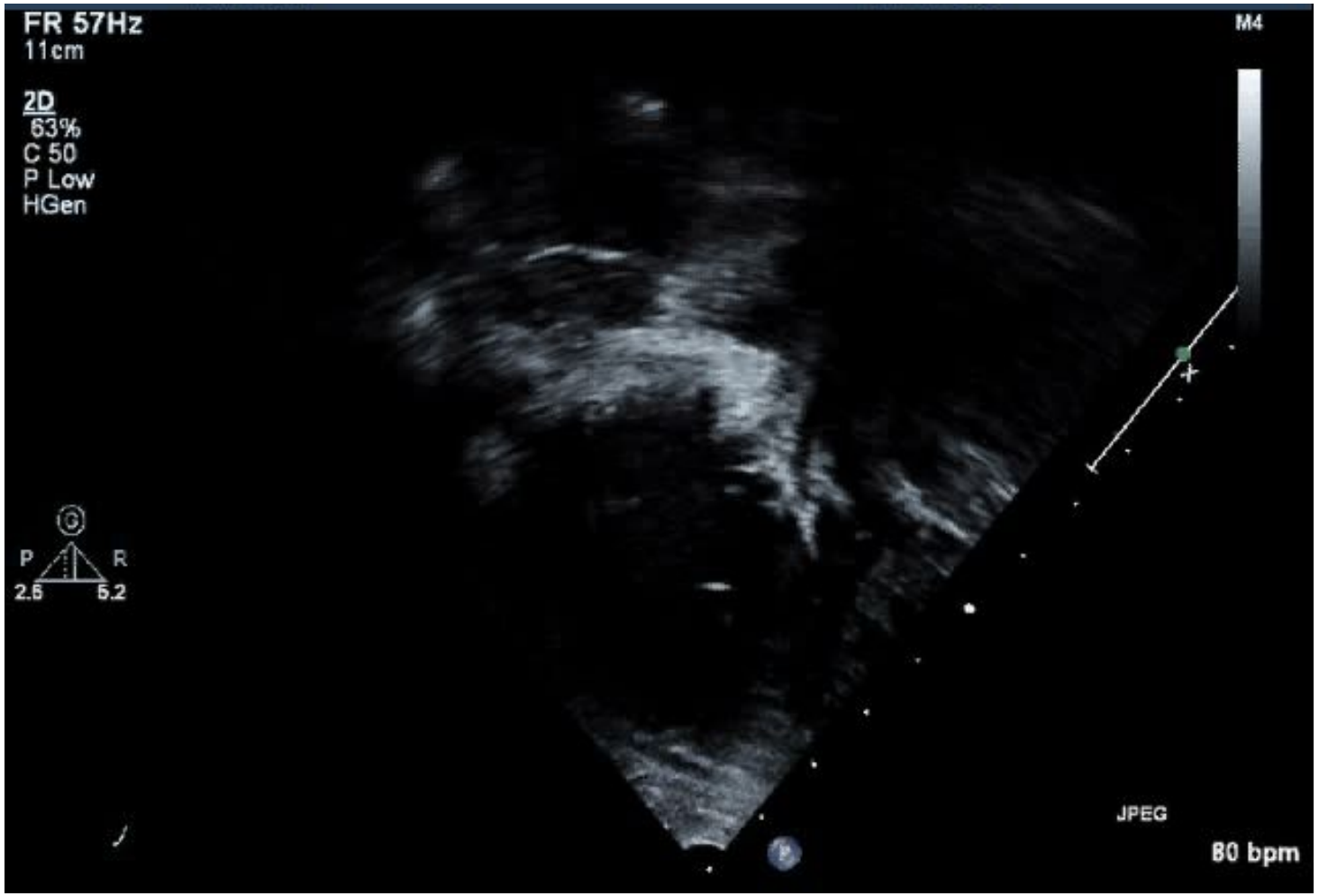

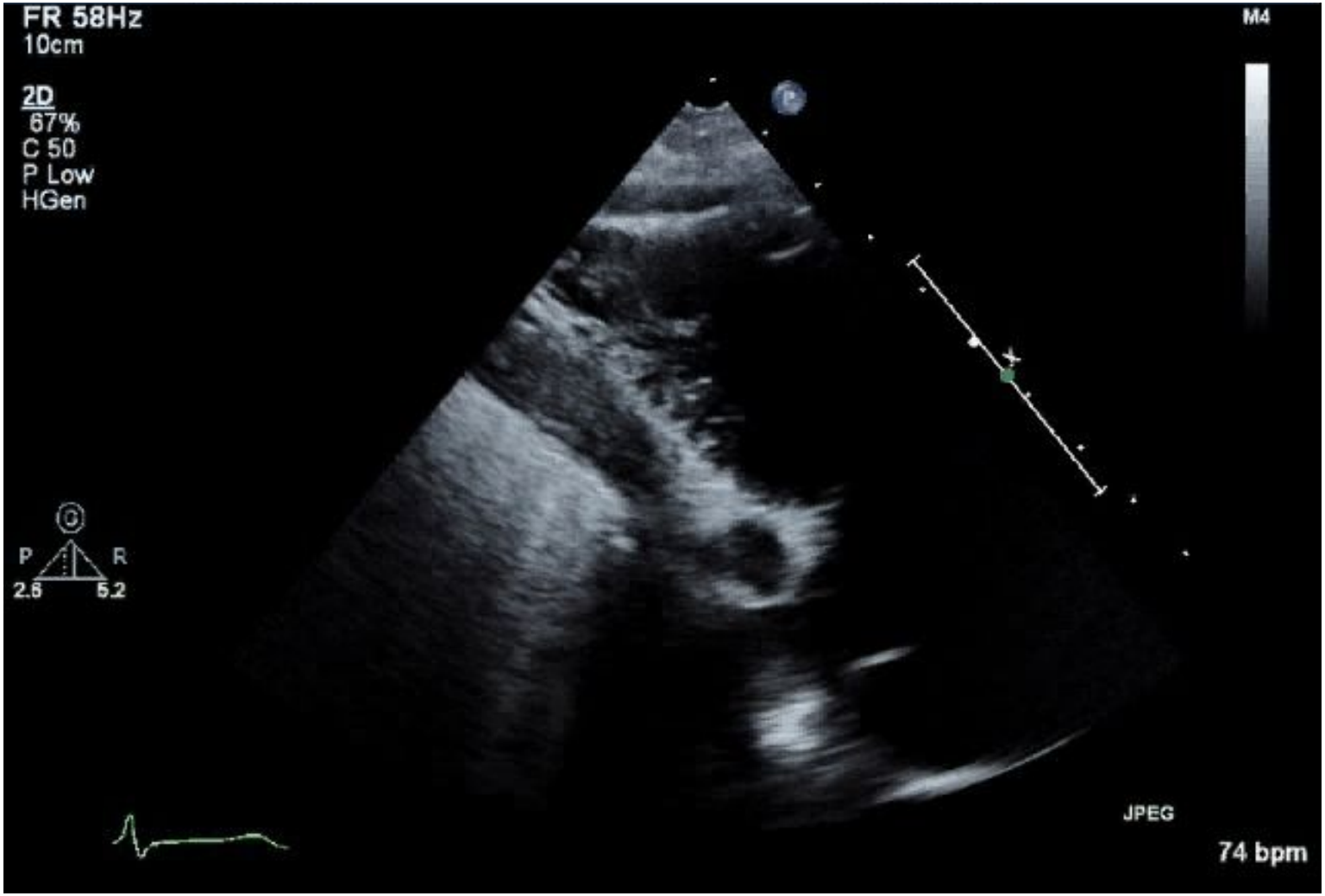

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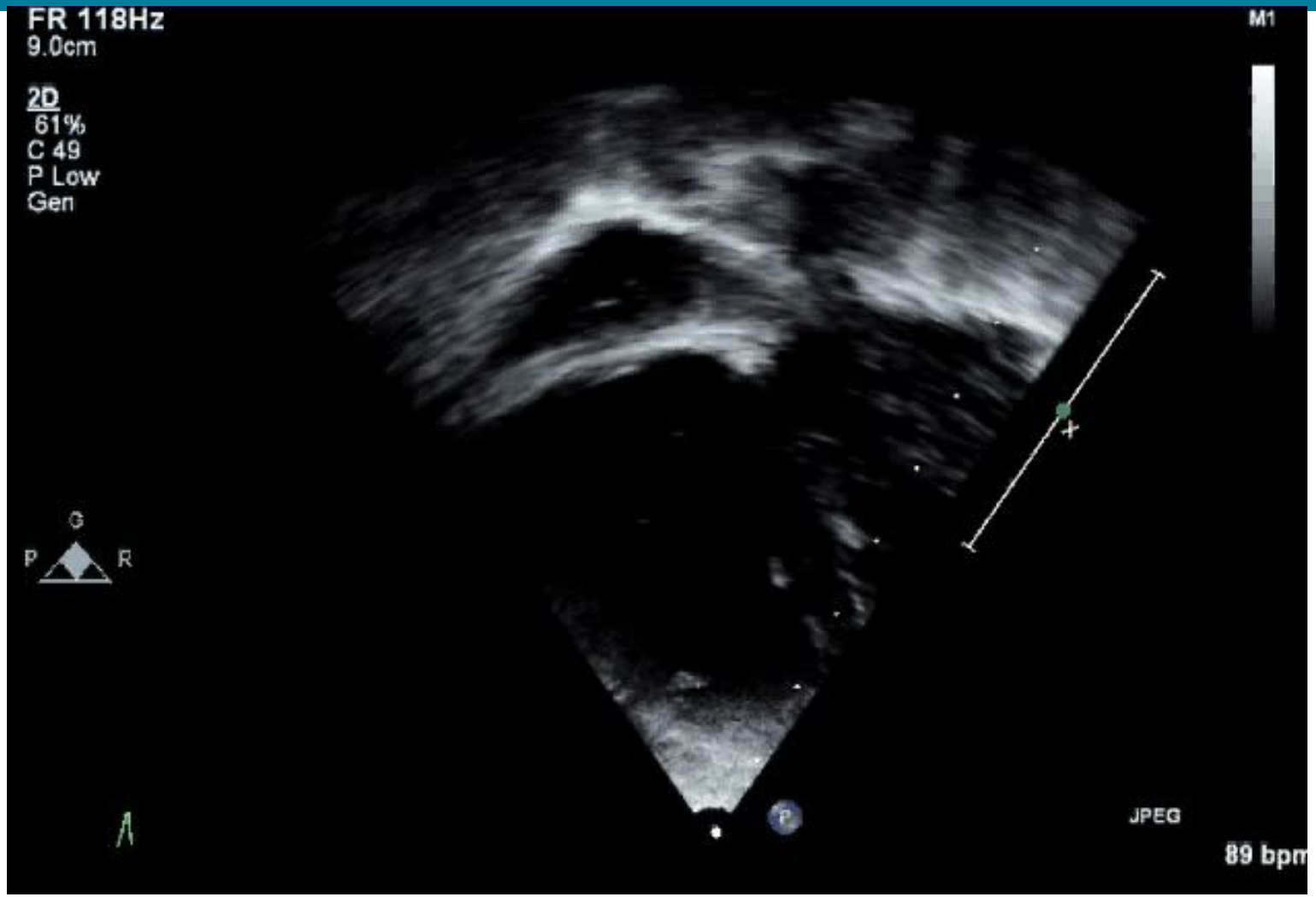

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Treatment of the acute illness

- The goal of therapy is to reduce inflammation and arterial damage and to prevent thrombosis in those with coronary artery abnormalities
- IVIG
  - 2g/kg in a single infusion
  - Within the first 10 days of onset of illness
- Aspirin
  - 80-100mg/kg/day
    - Until afebrile (48-72 hours v.s 14 days)
  - 3-5 mg/kg/day thereafter
    - Until 6 to 8 weeks
    - Indefinitely if coronary abnormalities present

Primary Treatment - Intravenous Immunoglobulin

- Patients should be treated with IVIG 2 g/kg as a single infusion, usually given over 10 to 12 hours, together with ASA
- Treat before day 10, and preferably by day 7
- Children presenting after the 10th day of illness:
  - Elevation of ESR or CRP, with either persistent fever without other explanation or coronary artery aneurysms (luminal dimension Z score >2.5): IVIG should be administered
  - Normal ESR/CRP, afebrile, normal echocardiogram: don't require IVIG

- IVIG administration in the acute phase of KD reduce the prevalence of coronary artery abnormalities

Primary Treatment - Intravenous Immunoglobulin

- The mechanism of action of IVIG in treatment of KD is unknown. IVIG appears to have a generalized anti-inflammatory effect
- IVIG is a biological product made from pooled donor plasma
- Adverse effects:
  - Coombs-positive hemolytic anemia
  - Aseptic meningitis: resolves quickly without neurological sequelae
- Measles, mumps, and varicella immunizations should be deferred for 11 months after receiving high dose IVIG

Primary Treatment - Acetylsalicylic Acid

- Anti-inflammatory activity (at high doses) and antiplatelet activity (at low doses)
- Does not appear to lower the frequency of development of coronary abnormalities
- ASA is administered every 6 hours, with a total daily dose:
  - 80 to 100 mg/kg in the United States
  - 30 to 50 mg/kg in Japan and Western Europe
  - No data to suggest that either dose is superior
- Duration of high dose ASA administration vary across institutions:
  - After the child has been afebrile for 48 to 72 hours
  - Until the 14th day of illness and at least 48 to 72 hours after cessation of fever
- When high-dose ASA is discontinued, low-dose ASA (3 to 5 mg/kg/d) is begun and continued until the patient has no evidence of coronary changes by 6 to 8 weeks after onset of illness. For children who develop coronary abnormalities, ASA may be continued indefinitely
- Ibuprofen should be avoided in children with coronary artery aneurysms taking ASA

Reye Syndrome

- Reye syndrome is a risk in children who receive salicylates while they are experiencing active infection with varicella or influenza
- Reported in patients taking high-dose ASA for a prolonged period of time after KD
- Low-dose therapy has not been associated with the development of Reye syndrome
- Patients who presents with influenza and KD:
  - Administration of high-dose IVIG without aspirin
  - Alternative antiplatelet agent
  - Antipyretic drugs (ie, acetaminophen) as needed for fever
- Only inactivated vaccine should be administered to children on aspirin therapy
- Children with acute KD during influenza season who have not yet been immunized should receive the inactivated influenza vaccine before leaving the hospital, as should any family members who have not yet been vaccinated for the season
- Those who are taking chronic ASA therapy should receive an annual inactivated influenza vaccine

Adjunctive Therapies for Primary Treatment

- Corticosteroids
- Infliximab
- Etanercept

Treatment of refractory KD

- 10% to 20% of patients with KD develop recurrent or persistent fever at least 36 hours after the end of their IVIG infusion and are termed IVIG resistant
- Patients who are resistant to initial IVIG are at increased risk of developing coronary artery abnormalities
- Options:
- Most recommended retreatment with IVIG 2 gm/kg
- Corticosteroids
- Infliximab
- Other Treatments
  - Cyclosporine
  - Monoclonal Antibodies
  - Plasma Exchange
  - Cytotoxic Agents

Prevention of Thrombosis in Patients with Coronary Disease

- Anti-platelet therapy
  - Aspirin
  - Clopidogrel, dipyridamole
- Anti-coagulation therapy
  - Warfarin
    - INR 2.0 – 2.5
  - Low molecular weight heparin
    - anti-Xa 0.5-1.0U/mL
- Both anti-platelet and anti-coagulation

Thrombosis Prevention

- Normal coronaries:
  - Low-dose ASA (3–5 mg/kg/day) until 6-8 weeks after onset of illness
- Large aneurysms or rapidly expanding coronary aneurysms:
  - LMWH or warfarin (INR target 2.0–3.0) + low dose ASA
- Large aneurysms and recent history of coronary artery thrombosis:
  - Triple therapy with ASA, a second antiplatelet agent, and anticoagulation with warfarin or LMWH

Treatment of Acute Thrombus

- Thrombolytic therapy
  - Tissue plasminogen activator (tPA)
  - Heparin
- Platelet Glycoprotein IIb/IIIa receptor antagonist (abciximab)
- Percutaneous coronary intervention
- Coronary artery bypass grafting
  - Internal mammary artery

Long-term follow up Risk stratification

- Level 1: no coronary artery changes
- Level 2: transient coronary artery ectasia
- Level 3: small coronary artery aneurysms
- Level 4: medium size coronary artery aneurysms
- Level 5: Large or giant coronary aneurysms

Focus Early on Preventive Care

- Tobacco and substances
- Other cardiac risk factors
  - Hyperlipidemia
  - Hypertension
  - Fasting glucose
  - BMI
  - Physical activity
- Reproductive health

Long-Term Thromboprophylaxis and Medical Therapy Algorithm

Risk Level	Low-Dose ASA	Anticoagulation (Warfarin or LMWH)	Dual Antiplatelet Therapy (ASA+Clopidogrel)	β-Blocker	Statin
1: No involvement	6–8 wk then discontinue	Not indicated	Not indicated	Not indicated	Not indicated
2: Dilation only	Continuation after 6–8 wk is reasonable	Not indicated	Not indicated	Not indicated	Not indicated
3.1: Small aneurysm, current or persistent	Continue	May be considered	May be considered as an alternative to anticoagulation	Not indicated	Empirical therapy may be considered
4.1: Medium aneurysm, current or persistent	Continue	May be considered	May be considered as an alternative to anticoagulation	Not indicated	Empirical therapy may be considered
5.1: Large and giant aneurysm, current or persistent	Continue	Reasonably indicated	May be considered in addition to anticoagulation	May be considered	Empirical therapy may be considered

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Long-Term Assessment and Counseling Algorithm

Risk Level	Frequency of Cardiology Assessment*	Assessment for Inducible Myocardial Ischemia†	Type and Frequency of Additional Cardiology Assessment	Cardiovascular Risk Factor Assessment and Management‡	Physical Activity Counseling§	Reproductive Counseling
1: No involvement	May discharge between 4 wk and 12 mo	None	None	Assess at 1 y	Promotion counseling at every visit	Age-appropriate counseling without modification
2: Dilation only	May discharge after 1 y if normal; assess every 2–5 y if persists	None	None	Assess at 1 y	Promotion counseling at every visit	Age-appropriate counseling without modification
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	Precautions for contraception and pregnancy
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	Precautions for contraception and 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	Precautions for contraception and pregnancy

Non-Invasive Testing

- MRI and MRA
- CT scan
- Stress test
  - Exercise
  - Nuclear perfusion scan with exercise
  - Exercise echocardiography
  - Stress echo with pharmacological agents
    - Dobutamine
    - Dipyridamole
  - Stress MRI

Cardiac Catheterization in KD

- Not recommended for mild cases
- 6 to 12 months after onset of illness
  - Guided by echocardiogram findings
  - Evidence of ischemia
- Intervention for coronary thrombosis
  - Ischemia symptoms
  - Reversible ischemia by stress testing
  - ≥75% stenosis in the the LAD

QUESTIONS

THANK YOU ☺

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