KAWASAKI DISEASE

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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 < 5yo
➤ Can occur even in adolescence
➤ In U.S. 19 per 100,000 children < 5yo
  ➤ 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%
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.

**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 multiforme-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 ≥ 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 ~10%
  - Elevated GGT in ~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 > 8yo
  - 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 Disease

Children with fever $\geq 5$ days and 2 or 3 compatible clinical criteria $^2$ OR
Infants with fever for $\geq 7$ days without other explanation $^3$

Assess Laboratory Tests

- CRP $< 3.0$ mg/dL and ESR $< 40$ mm/hr
  - Serial clinical and laboratory re-evaluation if fevers persist
  - Echocardiogram if typical peeling $^6$ develops

- CRP $\geq 3.0$ mg/dL and/or ESR $\geq 40$ mm/hr
  - 3 or more Laboratory Findings:
    1) Anemia for age
    2) Platelet count of $\geq 450,000$ after the 7th day of fever
    3) Albumin $\leq 3.0$ g/dL
    4) Elevated ALT level
    5) WBC count of $\geq 15,000$/mm$^3$
    6) Urine $\geq 10$ WBC/hpf
  - OR
    - Positive echocardiogram $^4$

Treat $^5$
CRITERIA FOR POSITIVE ECHO

➤ Any of the following:
  ➤ LAD or RCA z-score ≥ +2.5
  ➤ Japanese Ministry of Health Criteria
    ➤ Coronary diameter > 3mm in children < 5yo or ≥ 4mm in children ≥ 5yo
    ➤ Lumen diameter ≥ 1.5x 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: ≥ +2.5 to < +5.0 (small), ≥ +5.0 to < +10.0 (large), ≥ +10.0 (giant)
CORONARY EVOLUTION BY ECHO

5 Days      10 Days      16 Days      22 Days
Ao LAD     Ao LAD     Ao LAD     Ao

5 Days      10 Days      16 Days      22 Days
RCA Ao     RCA Ao     RCA Ao     RCA Ao
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
  - Hypoalbumiemia
  - 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?