The Heart of a Child with Inflammatory Dilemmas

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Objectives

- Identify similarities and differences between myocarditis and pericarditis diagnosis and management
- Identify the major diagnostic criteria for Kawasaki Disease plus short term and long term management
Myocarditis-definition

- Inflammation of the heart muscle
  - Response to an infection
  - Response to other non-infectious trigger (JRA, SLE, KD, RF)
- Caused by cell-mediated immunologic reaction
  - Lymphocytes and macrophages attack heart muscle
  - May cause damage to normal cells as well
- Inflamed myocardium is soft, flabby, pale
  - Scarring with patchy infiltrations
  - Weakened muscle = impaired contraction

Myocarditis-causes

- Viruses are most common cause in N. America
  - Coxsackie virus and echo virus most common
  - Poliomyelitis
  - Measles
  - Mumps
  - Cytomegalovirus
  - HIV
  - Adenovirus
  - Influenza
  - Rarely caused by bacteria, fungi, parasites

Myocarditis-diagnosis

- Difficulty d/t mimicking other diseases
- Fever d/t inflammatory response
- Exam findings
  - CHF with respiratory distress, edema, hepatomegaly
  - Soft heart murmur
  - May have irregular rhythm, tachycardia
- Slow investigation d/t lengthy testing
- Biopsy of heart muscle-more definitive for causative agent
Myocarditis-testing

- Serologies
  - Mycoplasma
  - Adenovirus
  - Enterovirus
  - CMV
  - EBV
  - HSV
  - VZV
- Extra tube save prior to blood products

Myocarditis-testing

- Respiratory viral panel
- Renal function
- Liver function
- Thyroid function
- Troponin T
- B-Natriuretic peptide (BNP)

Myocarditis

- Other findings
  - EKG-low voltages, ST-T wave changes, long QT interval
  - CXR-cardiomegaly-most important clinical sign
  - Echo-decreased LV function, increased chamber size
Cardiomegaly

LV thickness

Myocarditis-treatment

- Attempt viral ID by cultures of blood, stool, NP
- Limit activities during acute phase
- High dose IVIG
- Anti-congestive measures
  - Diuretics
  - Digoxin
  - Inotropic agents (milrinone)
- ACE inhibitors
  - Decrease workload
Myocarditis-outcomes

- Majority recover function over time
  - Treat underlying cause
  - Supportive care until heart muscle recovers
- Small number require inotropes to maintain cardiac function
  - Unable to wean $\rightarrow$ cardiac transplant

Pericarditis-definition

- Swelling and irritation of the pericardium, sac-like lining around the heart
- Inflammation of the parietal and visceral surfaces
- Effusion early: Serosanguineous, fibrinous, or purulent
- Large effusion leads to:
  - Systemic & pulm venous vasoconstriction
  - $\uparrow$ HR
- Can lead to tamponade
  - More common in purulent type
  - Distant/muffled heart sounds
  - Hypodynamic precordium
  - Tachycardia & tachypnea
  - Venous distention, hepatomegaly

Pericarditis-causes

- Infectious causes
  - Viral, bacterial, fungal
- Noninfectious cause
  - JRA, SLE, KD, RF, dermatomyositis
Pericarditis-symptoms

- URI common
- Pericardial pain-uncomfortable
  - Sternal, radiates to shoulder
  - Better: lean forward. Worse: supine & inspiration
- Fever common
- Tachycardia
- Tachypnea
- Distant/muffled heart sounds with hypodynamic precordium
- Friction rub possible

Pericarditis-findings

- EKG
  - Low voltage common
  - Early ST elevations
  - Later T-wave inversion (2-4 weeks)
- CXR
  - +/- cardiomegaly
  - Large effusion
  - ↑ PVM if tamponade
- Echo: diagnostic
  - Effusion, tamponade

Pericarditis-cardiomegaly
Pericarditis-treatment

- Pericardiocentesis:
  - Analyze fluid: cell count, glucose, protein, culture, gram stain
- If bacteria → 4-6 weeks antibiotics
- If viral → more problematic, symptoms
- Salicylates for pain, inflammation
- Steroids for refractory cases
- Recurrent effusions after drainage → surgical pericardial window

Pericarditis-outcomes

- Recovery is good once inflammation has resolved and infection treated
- Recurrence is common if underlying disease
Kawasaki Disease

**Introduction**

- First described in 1967 by Tomisaku Kawasaki, a Japanese pediatrician
  - 50 Japanese children with collection of clinical findings he termed mucocutaneous lymph node syndrome (MCLS)
- First cases described in US in 1976
- Inflammation in the walls of small and medium-sized vessels throughout the body
- Replaced rheumatic fever as leading cause of acquired heart disease in children in developed countries
  - 5000 cases/year in the US

**Epidemiology**

- Primarily affects young children
  - 76% of cases under 5 years of age
  - Median age is 1.5 years
- Males 1.5 x greater incidence than females
- Most prevalent in Asian population
  - Can affect all racial backgrounds
- 10 fold increase if sibling with diagnosis
- Cyclical outbreaks
  - Higher incidence in late winter and spring-similar to viral patterns
- Person to person spread not proven
- Not preventable
Etiology

- No cause has been identified
  - Infectious cause is strongly suspected based on clinical exam
  - Genetically predisposed individuals susceptible to immune response
  - By older childhood, adulthood do not respond to causative agent since already had infection?
- Microorganisms and toxins have been suspected (indoor and outdoor environmental factors)
  - Bacterial theory (Staph aureus)
  - Viral theory (specific T and B cell immune responses)
- Increased incidence in siblings and offspring of those with KD

Diagnosis

- Diagnostic criteria developed in 1970-continue to serve as basis for dx, epidemiology studies, and treatment trials
- No specific test designed for diagnosis
  - Often diagnosed after ruling out other possible diseases
- Based on characteristic clinical signs and symptoms
- Classic vs atypical or incomplete KD

Classic Clinical Criteria for KD

- Fever-5 days or longer
  - PLUS 4 of the following major clinical features:
    - Conjunctival injection without exudate
    - Changes in oral mucosa
    - Rash
    - Swelling or redness of extremities
    - Cervical lymphadenopathy, unilateral
Fever

- First sign to appear
- Must be 5 days or longer
- Usually >102, and often > 104°F
- Abruptly spikes and remits over 1-2 weeks
  - Avg 11 days if untreated

Conjunctival injection

- Bilateral
- Painless
- Extremely red sclera
- Non-purulent
- May have photophobia but less common

Changes in oral mucosa

- Erythema and cracking of lips
- "Strawberry" tongue
  - Prominent papillae on an erythematous base
- Diffuse oropharyngeal erythema
- Can develop secondary oral/skin infections
  - Impetigo
Lips and conjunctiva

Strawberry tongue

Rash

- Appears within first 5 days of illness
- Often involves trunk, extremities and genital area
- No definitive pattern
- Most commonly erythematous and maculopapular
- May be urticarial, pruritic
- Bullous and vesicular lesions usually not present
- May involve face
  - Mask-like in appearance
- May resemble candidal diaper dermatitis
- Can resemble measles, scarlet fever, erythema multiforme
Rash

Diaper rash

Swelling or redness of extremities

- Acute phase:
  - Erythema and edema of hands and feet-bilateral finding
  - Sharp demarcation at wrist and ankle-almost a banding pattern
  - May be very painful-refusal to walk or hold objects
- Subacute phase:
  - 10-21 days into illness
  - Fever has typically resolved
  - Membranous desquamation of fingertips, palms and soles
Peeling of extremities

Cervical lymphadenopathy

- Usually unilateral
- > 1.5 cm diameter
- Least common clinical feature, especially infants
- May be presenting and most prominent sign, especially in older children
  - Treated with abx for bacterial cervical adenitis
  - Usually affects anterior cervical nodes, overlying sternocleidomastoid muscles
Incomplete or Atypical KD

- Meet fever criteria but only 2 or 3 of the clinical criteria
  - Elevated inflammatory markers
  - Other compatible lab and echo features
- More common <1 year of age
- High rate of CA aneurysms in younger age if not treated
- Follow closely if untreated

Associated findings with KD

- CNS-most common
  - Striking irritability
  - Increased cell count in CSF
  - Seizures
  - Rarely facial palsy
- Urethritis, sterile pyuria
- Arthritis and arthralgia
  - Due to inflammatory process

Associated findings with KD

- GI issues
  - Poor appetite
  - Vomiting and diarrhea
  - Abdominal pain
  - Hydrops of gallbladder
  - Mild jaundice
Laboratory findings

- Increased ESR and CRP
  - Markers for inflammation
  - Elevated more than with common viral infections
  - ESR (erythrocyte sedimentation rate) often >40, sometimes >100
  - CRP (C-reactive protein) typically 3 or more
- CRP preferred to ESR following IVIG therapy

Laboratory findings

- Elevated WBC
  - Leukocytosis with left shift
- Mild anemia in acute phase
  - Increases with prolonged illness
- Thrombocytosis in subacute phase
- Elevated liver enzymes, bilirubin

Cardiac findings

- Gallop rhythm, distant heart sounds
- EKG changes
  - Arrhythmias
  - Abnormal Q waves, prolonged PR or QTc, ST or T wave changes
- Cardiomegaly per CXR
- Echocardiographic changes-establish baseline for CA morphology for long term treatment, flu, prognosis
  - Pericardial effusions
  - Decreased contractility
  - Possible aneurysms of peripheral vessels
Coronary involvement

- 15-25% at risk for development of coronary artery abnormalities if untreated
- Decreases to 5% with prompt treatment
- IVIG given within 10 days
  - Decreases morbidity and mortality
- Aneurysms appear 7-28 days after onset of symptoms
- Aneurysms regress by one year in ~50% patients

>70% myocardial infarctions occur in first yr after onset of disease
- Sudden events
- ~20% mortality
- Giant aneurysms → morbidity and mortality d/t thrombotic occlusion or stenotic obstruction and subsequent myocardial infarction
  - Stenosis most common with giant aneurysms
  - Entrance to or exit from aneurysmal area
- Risk factors for coronary aneurysms
  - Significant fever (high beyond 10 days)
  - Fever >14 days

Echocardiogram

- Acute: r/o myocarditis/pericarditis
- Aneurysms: present 10-30 days after acute onset
- Frequency of vessels involved:
  - LAD>right>left main>circumflex
- Sensitivity (proximal) 100%; specificity 96%
Echocardiogram

- Baseline test at time of suspected diagnosis
  - Do not delay treatment for study
- If CA normal, consider decreasing anti-platelet therapy
- If CA abnormal, follow more closely with serial ECHOs at 6 weeks, then reevaluate based on size
- Aneurysm sizes: small (3 mm), medium (3-8 mm), giant (8 mm)

Normal coronary patterns

- Parasternal short axis plane of aorta
- LEFT: 4 o’clock
- RIGHT: 11 o’clock
- Caliber at 1 cm beyond ostia
- Range: Infants 2mm; teens 5mm
- Dilated: > 1.5x adjacent vessel (or > 3mm under age 5)
- UNIFORMITY of caliber distinguishes normal from abnormal

ECHO-Short Axis
Right coronary artery aneurysm

Treatment goals

- Control inflammation
- Lower fever
- Prevent coronary thrombosis

Treatment

- Aspirin therapy
  - High dose at 80-100 mg/kg divided QID until fever subsides for 48-72 hrs (~14 d into illness) then lower dose to 3-5 mg/kg daily for at least 6-8 weeks
  - Some providers use normalizing of ESR to stop
  - If no CA abnormalities by ECHO, stop by 6-8 weeks
  - Must be stopped with other viral illnesses to decrease chance of Reye’s syndrome
    - Do not initiate if have concurrent documented influenza or varicella
**Treatment**

- High dose IVIG (immune protein fraction of human blood)
  - Before day 10 of illness, reduces morbidity
  - Reduces coronary abnormalities from 15-25% to <5%
  - Single, high dose as effective as smaller, frequent doses intravenously (2 gm/kg)
  - 15-20% do not respond to first dose
    - Repeat IVIG dose within 48 hours
    - IV steroids 1-3 days
    - IV infliximab
    - Refer to KD experts

**Other Management Options**

- Steroids
- Pentoxifylline (Trental)
- Infliximab (Remicade)
  - Monoclonal antibody against tumor necrosis factor G
- Plasma exchange
- Ulinastatin
  - Human trypsin inhibitor used in Japan
- Abciximab
  - Monoclonal platelet glycoprotein IIb/IIIa receptor inhibitor
- Cyclophosphamide
- Other biologics

**Long term management**

- Treatment guidelines based on risk level I-V
- Those without CA abnl tend to return to previous state of health
- Long term surveillance should be completed
AHA Guidelines

- 2004
- Endorsed by AAP
- Almost 40 years of since described
- More updates to follow

Risk Level I

- No CA changes at any stage of illness
  - ASA for 6-8 wk only
  - Restrict activity for 6-8 wk
  - No invasive tests needed
  - Initial f/u ECHO at 6-8 wks then none needed
  - Counseling re: CV risk factors Q 5 years to assess for long term epithelial dysfunction

Risk Level II

- Transient CA dilation that disappears during acute phase
  - ASA for 6-8 wk only
  - Restrict activity for 6-8 wk
  - Initial f/u ECHO at 6-8 wks
  - One yr f/u, then as needed based on cardiac disease
  - CV risk factor counseling Q 3-5 years
Risk Level III

- Small to medium solitary CA aneurysms
  - ASA 3-5 mg/kg/d until aneurysm regresses
  - No restriction activity <10 yrs, >10 yrs guided by stress testing every other yr
  - Competitive endurance athletics discouraged
  - Annual f/u with ECHO until 10 yrs
  - Consider angiography or other imaging if stenosis suspected

Risk Level IV

- One or more giant CA aneurysms without obstruction
  - Long term ASA 3-5 mg/kg/d +/- Coumadin or Lovenox
  - < 10, no activity restriction after 6-8 wk
  - > 10 restrictions guided by annual stress testing
  - Strenuous athletics strongly discouraged
  - Annual f/u with ECHO, EKG; some 6 mo EKG
  - Angiography or other non-invasive imaging if stenosis per ECHO at 6-12 mos, as needed

Risk Level V

- CA obstruction
  - Long term ASA 3-5 mg/kg/d +/- Coumadin or Lovenox
  - Consider Ca channel blockers to reduce myocardial oxygen consumption
  - Contact sports, isometrics, wt training avoided
  - Other physical activity guided by stress testing
  - f/u with ECHO, EKG at 6 mo intervals
  - Annual stress testing/Holter
  - Angiography or other imaging-assist with selecting options or with onset or worsening ischemia
Conclusion

• Consider carditis in differential if fever, infectious symptoms or history
• Prompt evaluation and treatment affect outcome
• Long term f/u recommended for those with CA aneurysms as the risk for stenosis and sudden thrombosis is life long