

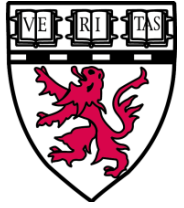
Multi-Inflammatory Syndrome in Children

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Disclosures:

*The speakers have no financial relationships
or conflicts of interest to disclose*

Objectives

- To define the Multisystem Inflammatory Syndrome in Children Associated with COVID-19
- To describe how it is similar and different from Kawasaki disease
- To describe mechanisms of cardiac injury
- To describe our local approach to therapy at Boston Children's Hospital

This is an official **CDC HEALTH ADVISORY**

Distributed via the CDC Health Alert Network
May 14, 2020, 4:45 PM ET
CDCHAN-00432

Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19)



Multisystem inflammatory syndrome in children and adolescents with COVID-19

Scientific Brief

15 May 2020



CDC Case Definition for Multisystem Inflammatory Syndrome in Children (MIS-C)

- An individual aged <21 years presenting with **fever**, laboratory evidence of **inflammation**, and evidence of clinically severe illness requiring **hospitalization**, with multisystem (≥ 2) **organ involvement** (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); **AND**
- No alternative plausible diagnoses; **AND**
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms

Fever $\geq 38.0^{\circ}\text{C}$ for ≥ 24 hours, or report of subjective fever lasting ≥ 24 hours

Additional comments

- Some individuals may fulfill full or partial criteria for **Kawasaki disease** but should be reported if they meet the case definition for MIS-C
- Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection



The Emergence of a New Syndrome in Children

4/25/2020: UK ALERT



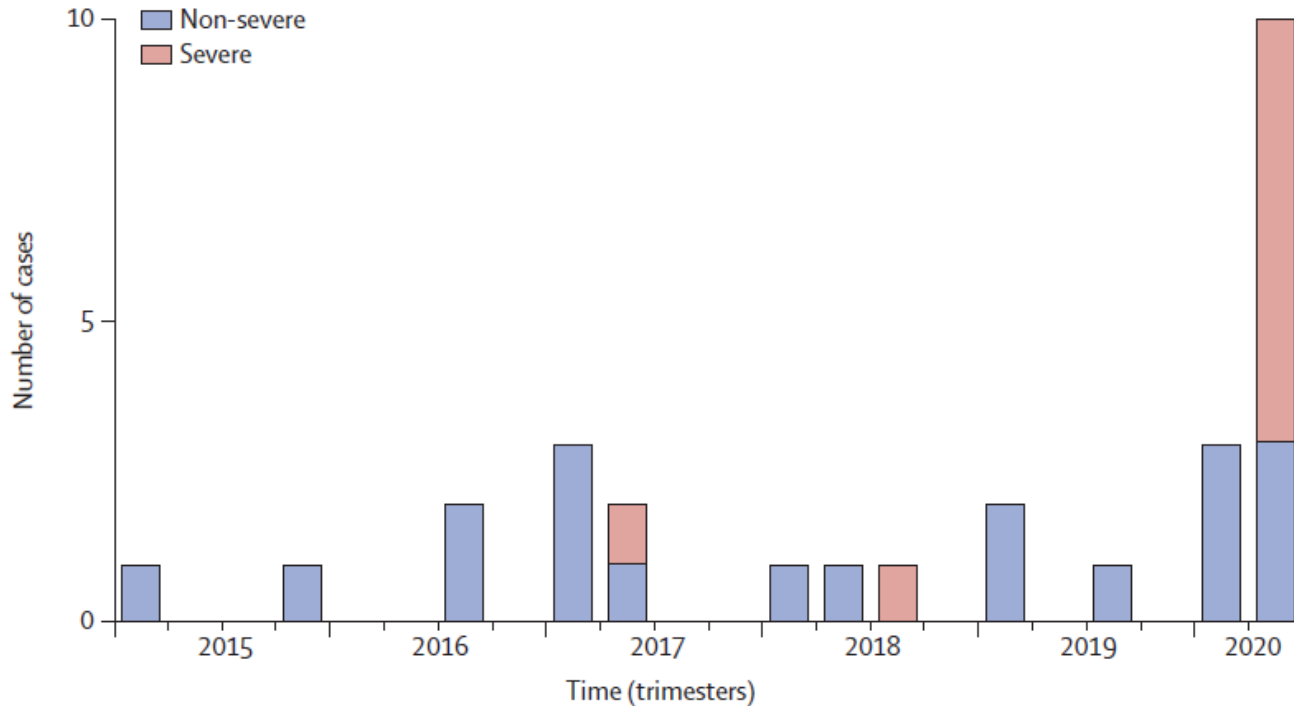
Reports to Date: Severe Disease?

IT Bergamo IT	GB London GB
<p>10 KD cases: 2 months</p> <ul style="list-style-type: none">• 5 had shock• 5 had cytokine storm• 8/10 prescribed steroids• 2 had aneurysms• SARS CoV-2 testing: 2/10 + PCR, 8/10 + Ab <p><i>Severe form of KD</i></p>	<p>8 PICU Admits: 10 days</p> <ul style="list-style-type: none">• 7/8 with BMI>75%ile• 5 intubated• All on inotropes• One needed ECMO; died• SARS CoV-2 testing: 6/8 negative <p><i>Severe illness</i></p>

Verdoni et al, Lancet 5/13/2020

Riphagen et al, Lancet 5/6/2020

Bergamo, Italy Experience



30-fold increase in KD incidence

- 50% with “Kawasaki shock syndrome”
- 50% LV dysfunction
- 20% with CAA

Verdoni et al. *Lancet* 2020

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Verdoni et al, Lancet 5/13/2020

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Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2

Elizabeth Whittaker, MD; Alasdair Bamford, MD; Julia Kenny, MD; Myrsini Kaforou, PhD; Christine E. Jones, MD; Priyen Shah, MD; Padmanabhan Ramnarayan, MD; Alain Fraisse, MD; Owen Miller, MD; Patrick Davies, MD; Filip Kucera, MD; Joe Brierley, MD; Marilyn McDougall, MD; Michael Carter, MD; Adriana Tremoulet, MD; Chisato Shimizu, MD; Jethro Herberg, MD; Jane C. Burns, MD; Hermione Lyall, MD; Michael Levin, MD; for the PIMS-TS Study Group and EUCLIDS and PERFORM Consortia

- 58 children, 8 centers in UK from 3/23 – 5/16/2020
- Cardiac Findings :
 - elevated troponin 34/50 (68%) - elevated BNP 24/29 (83%)
 - CAA in 8/55 (15%), 2 giant
 - 4 arrhythmia: 2 AV block (1st/2nd degree), wide complex tachycardia → ECMO, atrial fibrillation
 - Shock with inotropes 47% - decreased LV fx 18/55 (33%)
 - Ventilation 43% - ECMO in 2 (3%)
 - Death 1 (2%)

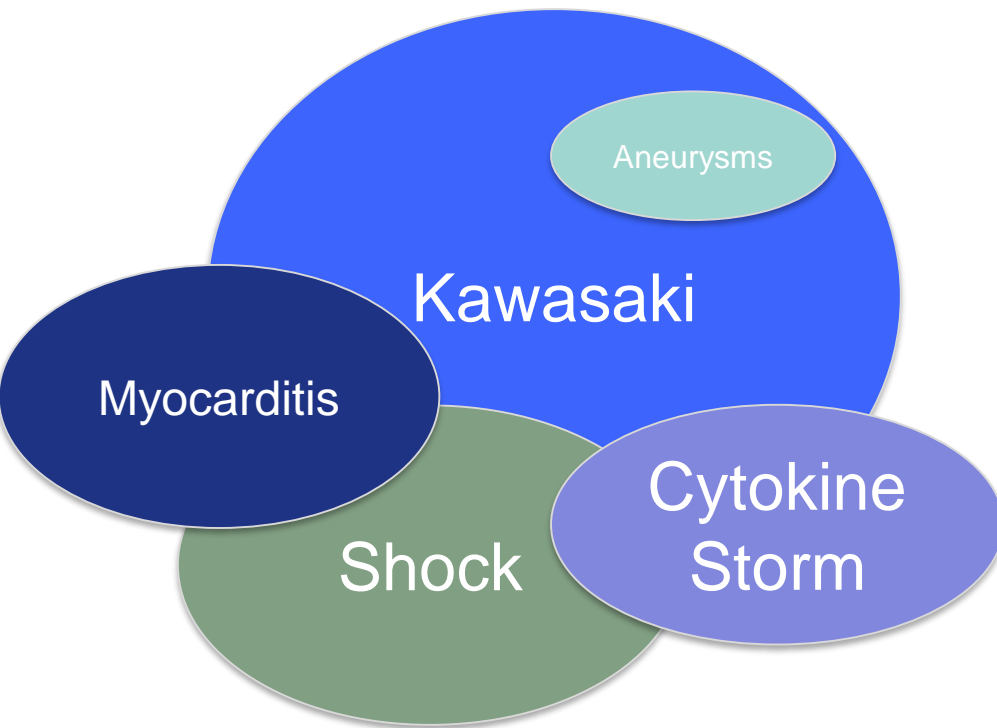
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- Median age 9 yo (IQR 5.7-14.0), 57% girls, 69% black or Asian
- PCR + 26%, Antibody + 87%
- Presentation findings:
 - fever 100%
 - conjunctivitis 52%
 - abdominal pain 53%
 - rash 52%
 - hand/foot swelling 16%
 - oral changes 29%

Whittaker et.al JAMA 2020

Spectrum of Clinical Phenotypes



History and PE Findings

- FEVER
- Prominent GI symptoms
- Respiratory symptoms *uncommon*
- Tachycardia, **hypotension**, gallop
- Kawasaki Disease features

Lab Findings:

- Neutrophilia/Low ALC
- **↑** CRP/ESR/procalcitonin
- **↑** D Dimer/fibrinogen
- **↑** Ferritin
- **↑** Troponin and BNP
- SARS-CoV-2 testing: positive or negative

How Is MIS-C Similar to KD

- Incomplete or complete KD criteria may be present.
- Coronary artery dilation and aneurysms may occur
- Children seem to respond to IVIG and steroids

Diagnostic Criteria for Kawasaki Disease

Fever > 101.3 F persisting at least 5 days AND 4/5 following criteria:



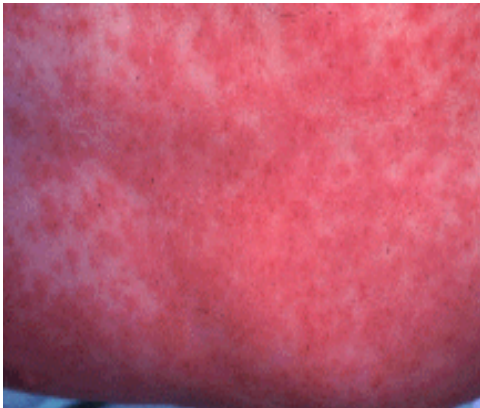
Conjunctival injection



Strawberry tongue,
pharyngeal erythema



Erythema & cracking
of lips



Polymorphous
exanthem



Hands and feet



Unilateral cervical
lymphadenopathy

How Is KD Different from MIS-C

- Age: KD occurs predominantly in early childhood (80% < 5 y.o), and MIS-C occurs predominantly in school age and adolescents.
- GI symptoms (diarrhea, vomiting, abdominal pain, even colitis) are strikingly prominent in MIS-C.
- MIS-C patients generally have a greater degree of “cytokine storm” and a lab profile with
 - Higher D-dimers, ferritin, troponin and BNP or NT-proBNP.
 - Lower platelets and absolute lymphocyte count.
- MIS-C patients are more likely to present with shock and with low left ventricular ejection fraction.



Is this different from Acute COVID-19?

Reported cases from First Wave

- Ill children: co-morbidities
- Fever, cough, sore throat
- Critical illness rare
 - Intubated for hypoxic failure

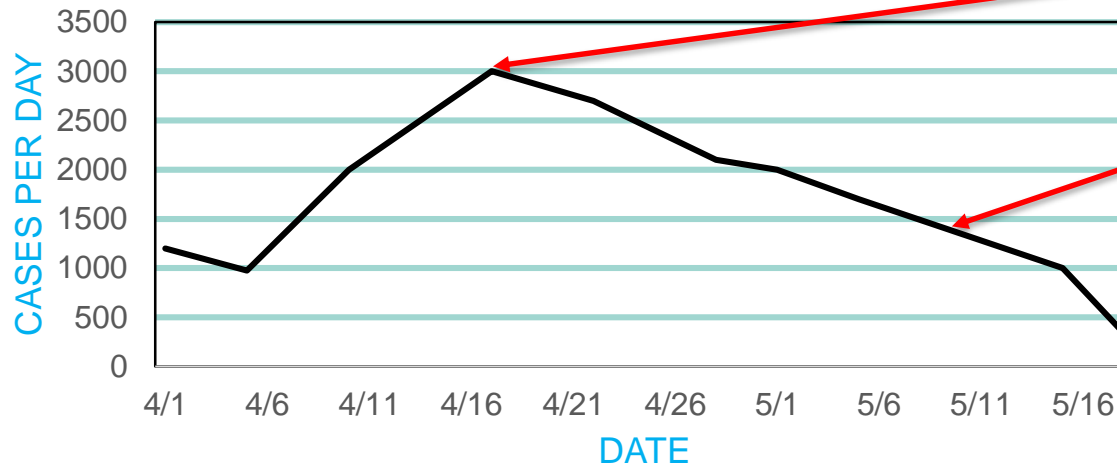
Lu et al, NEJM.4/23/2020
Shekerdemian, JAMA Peds.5/11/2020

Reported cases of MIS-C

- Previously healthy children
- Fever, GI sx, Shock, KD signs
- ICU care common for shock
 - Intubated for cardiovascular instability

Riphagen et al, Lancet 5/6/2020
Verdoni et al, Lancet 5/13/2020

Confirmed COVID-19 Cases in MA



Peak

MIS-C cases

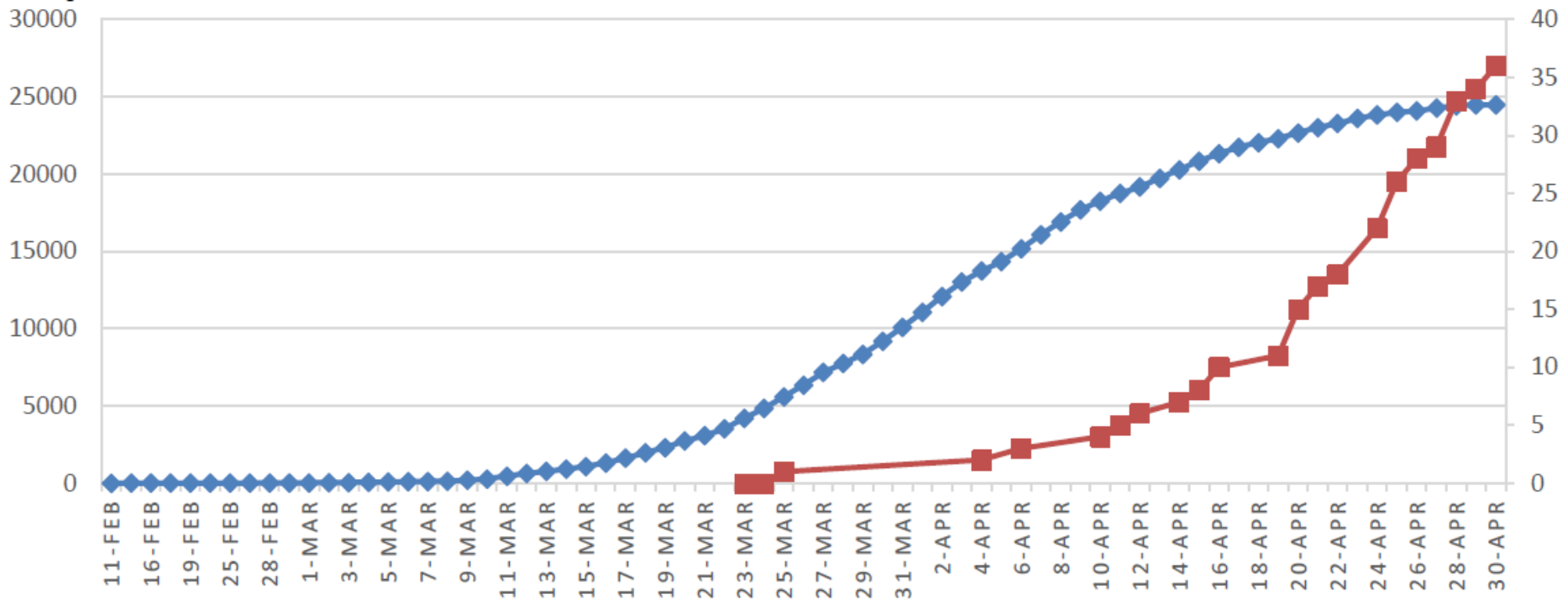
Data from mass.gov/doc/covid-19

PIMS-TS appear to be a month behind the COVID19 peak in the population



Public Health
England

Laboratory Confirmed COVID-19 cases, London



Dr. Mike Levin, Imperial College London



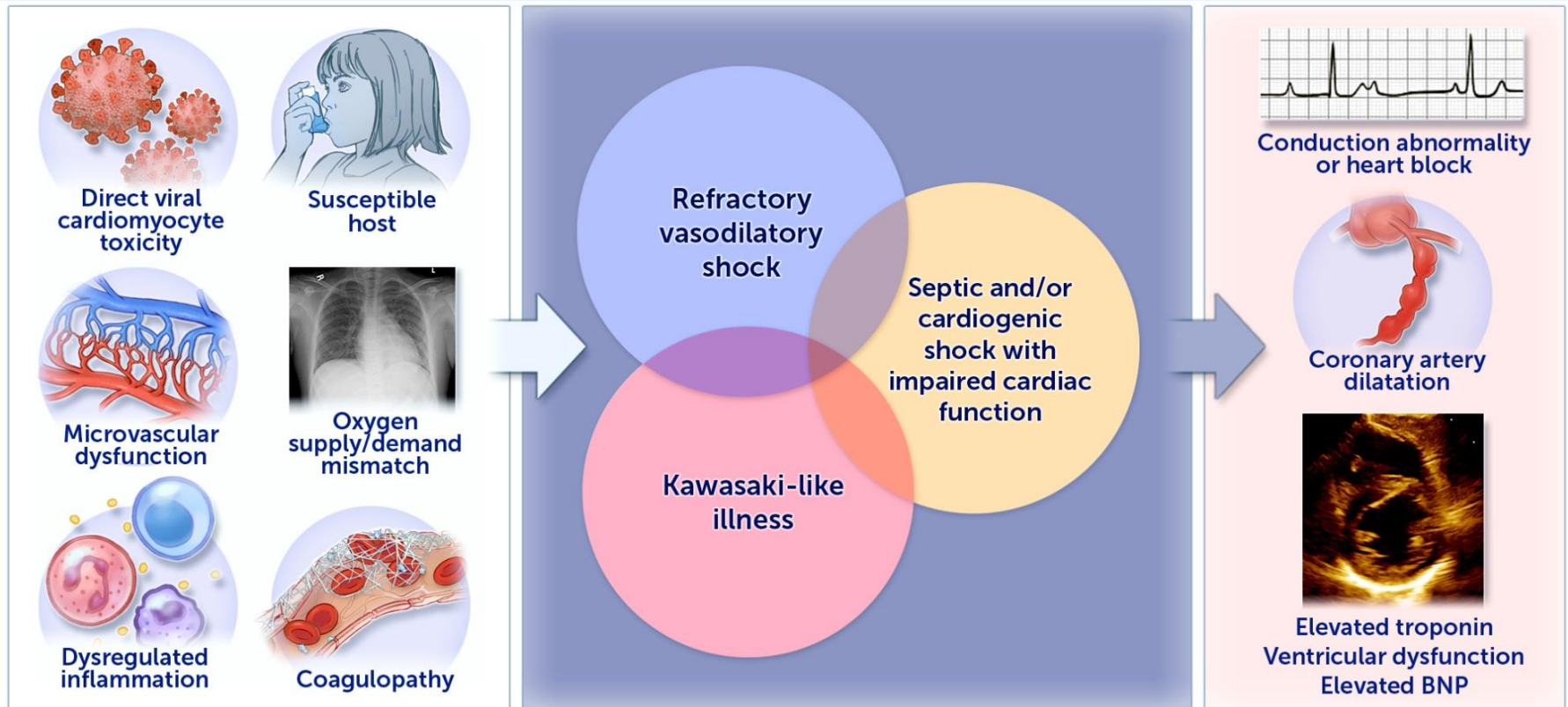
Boston Children's Hospital
Until every child is well™



HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Mechanisms of Cardiac Injury in MIS-C

Cardiovascular injury in children with COVID-19



MIS-C with Coronary Involvement

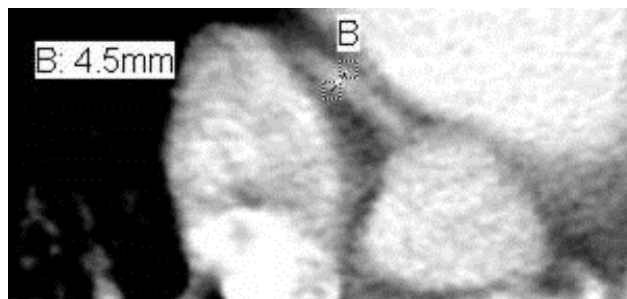
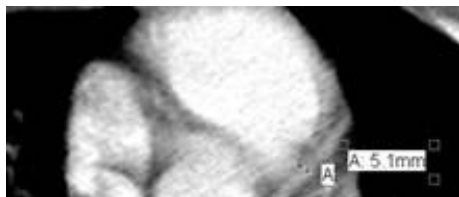
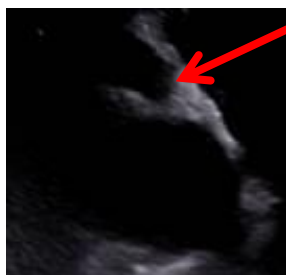
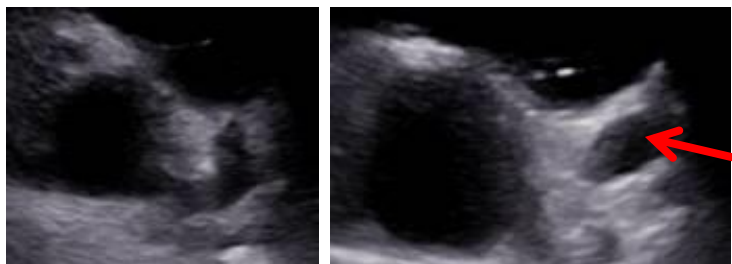
18 year old with 4 days of fever, GI, symptoms
Presented in hemodynamic shock

Echo

LAD = 7.2mm, z-score = +7.6 (long fusiform dilation)

Prox RCA = 10mm, z-score = +12.5

Normal function, EF = 57%, normal valve function, no



case courtesy of pediatric cardiology at Children's Pittsburgh

There is likely a spectrum of SARS-CoV-2 immune-mediated syndromes

SARS-CoV-2 triggered shock

SARS-CoV-2 triggered KD-like illness

?

SARS-CoV-2 immune-mediated fever and other symptoms in less sick children presenting to pediatric practices

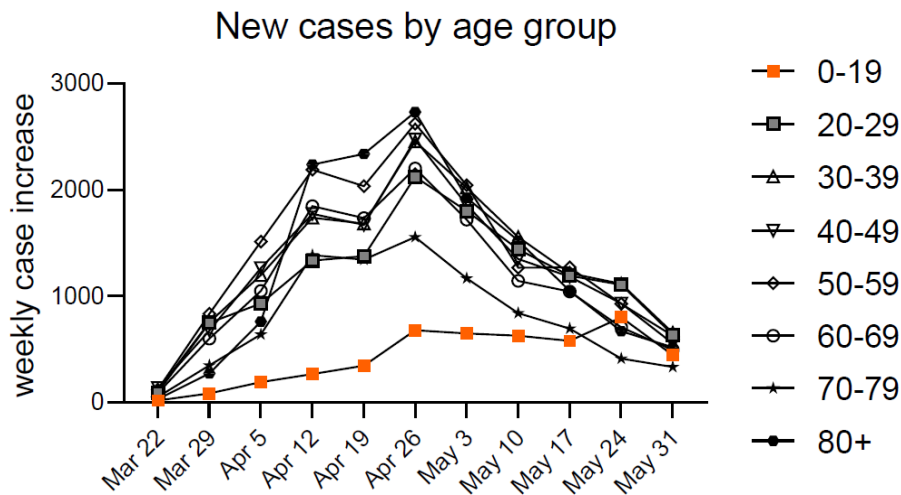
MIS-C Associated with COVID-19: The Boston Children's Experience



SARS-CoV-2 in Massachusetts

- > 104,000 cases and > 7000 deaths
- Community spread started in early March and peaked in late April
- 5% of cases are children under 19; Case trajectory lags behind adult groups

Weekly COVID-19 reporting in MA



MIS-C cohort at Boston Children's Hospital

Number of patients	28
CDC case definition	100%
WHO case definition	93%
Demographics	
Age, median (range)	9.0 y (0.1-17)
Female (%)	43%
White (%)	36%
Black or African American (%)	18%
Hispanic or Latino (%)	43%
Pre-existing condition	50%
Duration of symptoms at admission	5 d (1-10)
Reported contact with COVID-19	29%
SARS-CoV-2 testing	100%
SARS-CoV-2 serology +	95% (18/19)
Nasopharyngeal swab PCR +	61% (17/28)



Laboratory features of MIS-C

Inflammatory markers

Procalcitonin ≥ 0.1 ng/mL	96% (24/25)
CRP ≥ 0.5 mg/dL	93% (26/28)
Ferritin ≥ 200 ng/mL	86% (24/28)
LDH ≥ 250 U/L	74% (14/19)
ESR ≥ 30 mm/h	63% (15/24)

Hematologic parameters

ALC $< 2 \times 10^3/\mu\text{L}$	75% (21/28)
Platelets $< 200 \times 10^3/\mu\text{L}$	64% (18/28)
WBC $> 10 \times 10^3/\mu\text{L}$	39% (11/28)
Hemoglobin < 11 g/dL	32% (9/28)
WBC $< 5 \times 10^3/\mu\text{L}$	25% (7/28)
ANC $< 2 \times 10^3/\mu\text{L}$	18% (5/28)

Coagulation parameters

D-dimer > 0.5 mg/mL	96% (26/27)
Fibrinogen > 400 mg/dL	71% (15/21)
PT > 14.6 seconds	62% (16/26)
PTT > 37 seconds	38% (10/26)

Organ function parameters

BNP > 100 pg/mL	52% (12/23)
Troponin > 0.09 ng/mL	27% (6/22)
AST > 50 U/L	46% (13/28)
BUN > 18 mg/dL	25% (7/28)
Creatinine > 0.8 mg/dL	21% (6/28)

Coronary artery abnormalities in MIS-C

Cardiopulmonary diagnostics

X-ray evidence of pneumonia 25%

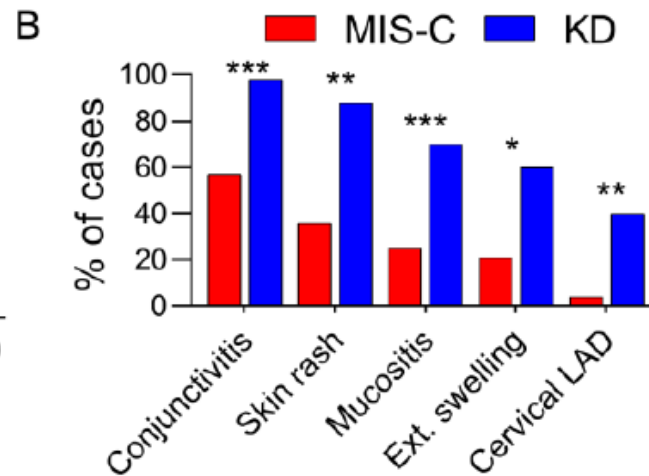
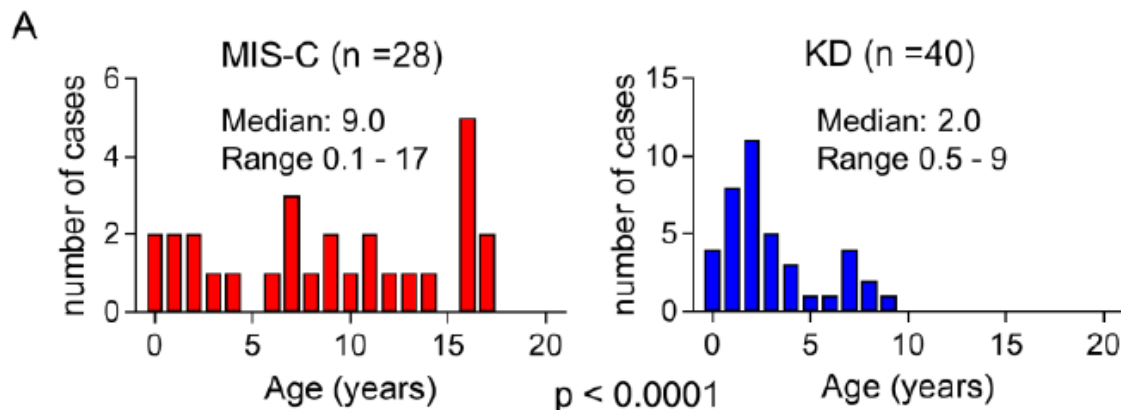
Ejection fraction < 55% 39%

Dilated coronary vessel ^C 7%

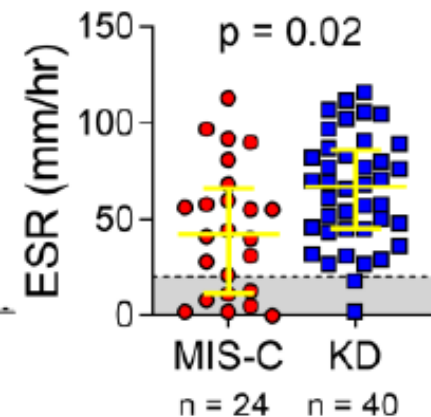
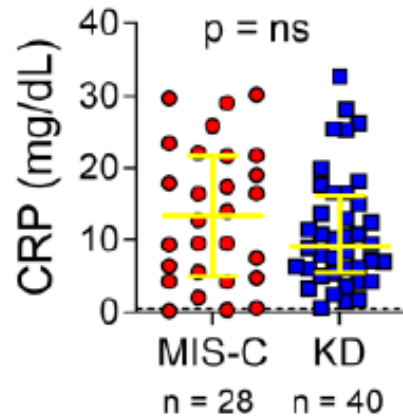
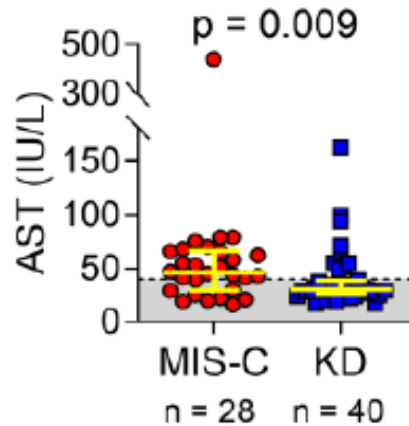
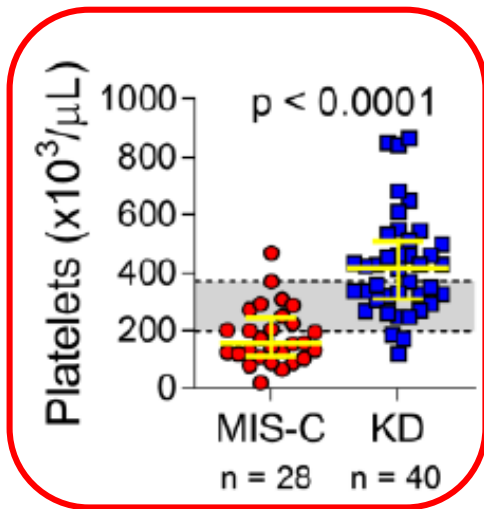
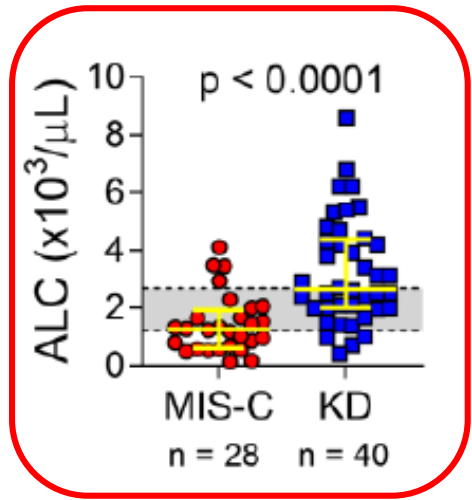
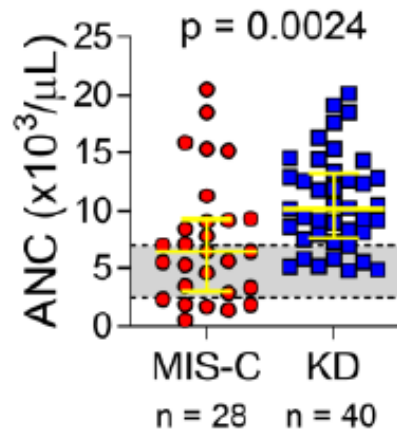
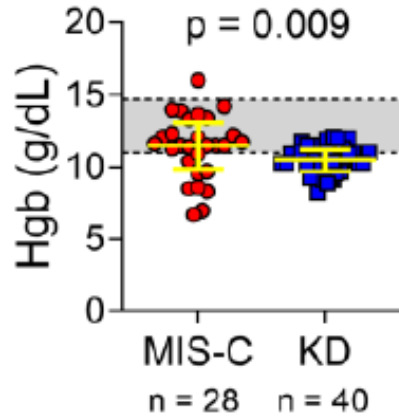
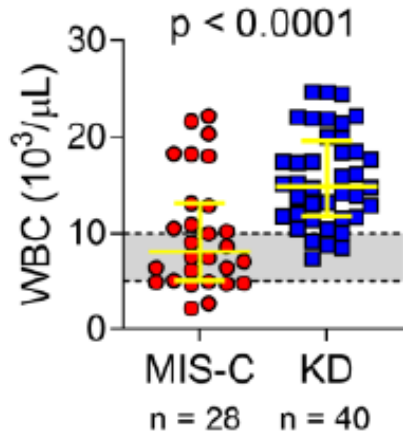
Coronary aneurysm ^D 14%



MIS-C vs. Kawasaki Disease



MIS-C vs. Kawasaki Disease



MIS-C learning points

- MIS-C affects children of all ages
- Most cases have detectable antibodies to SARS-CoV-2
- Disproportionate impact on underrepresented minority groups
- Cardiac complications >> pulmonary complications
- Hypotension and shock are common on initial presentation
- KD features are present in some, but not all cases
- Coronary aneurysms can develop in the absence of KD features
- Lymphopenia, thrombocytopenia, ↑ inflammatory markers and D-dimer are the most common laboratory findings

1) How do we treat patients with MIS-C?

2) How do we triage febrile children for MIS-C ?



Management of MIS-C patients

- Multi-disciplinary team: ED, ICU, general pediatrics, cardiology, hematology, infectious disease, rheumatology and more.



Post-hospitalization follow up of MIS-C patients

- Almost all patients have been discharged home!
- Follow up by Rheumatology and Cardiology
 - Designated MIS-C attending / nursing coverage
 - Medication taper (corticosteroids, anakinra, ASA / other anticoagulants)
 - Communication with family regarding clinical status
 - Coordinate repeat labs
 - Coordinate repeat EKG / Echocardiography studies

BCH ED Guidance for evaluation of MIS-C

Patient presents to ED with:

1. Fever $\geq 38\text{ C}^\circ$ for ≥ 4 days

OR

2. Fever $\geq 38\text{ C}^\circ$ for ≥ 3 days **PLUS** any one of the following:

- GI symptoms without a clear source
- Conjunctivitis
- Adenitis
- Diffuse rash
- Mucositis (red or cracked lips, strawberry tongue)
- Hand or foot swelling

OR

3. Presentation consistent with Toxic Shock Syndrome

Signs of shock ?

YES

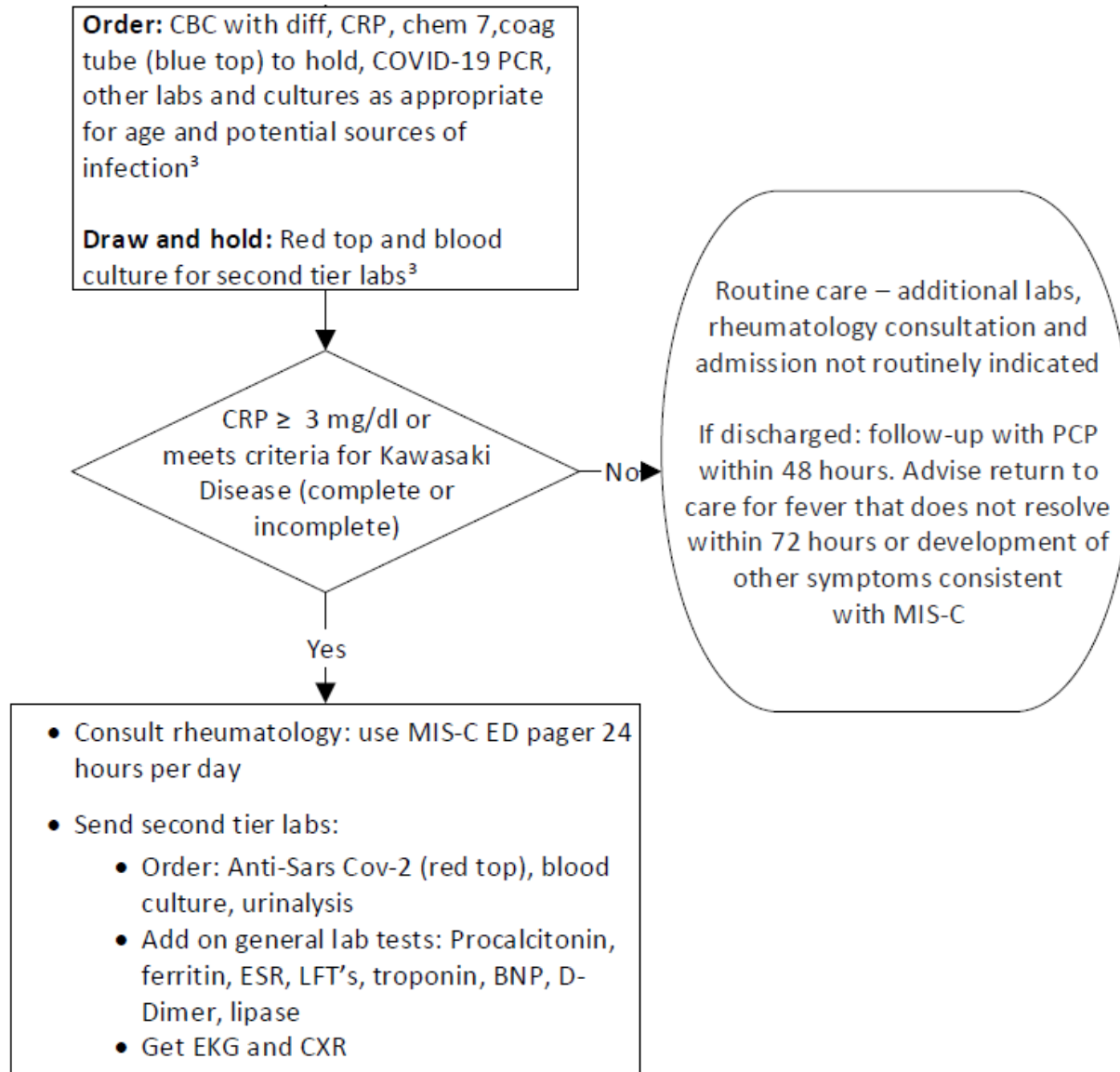
No

Resuscitation, labs, EKG, CXR, pressors →
admit to ICU

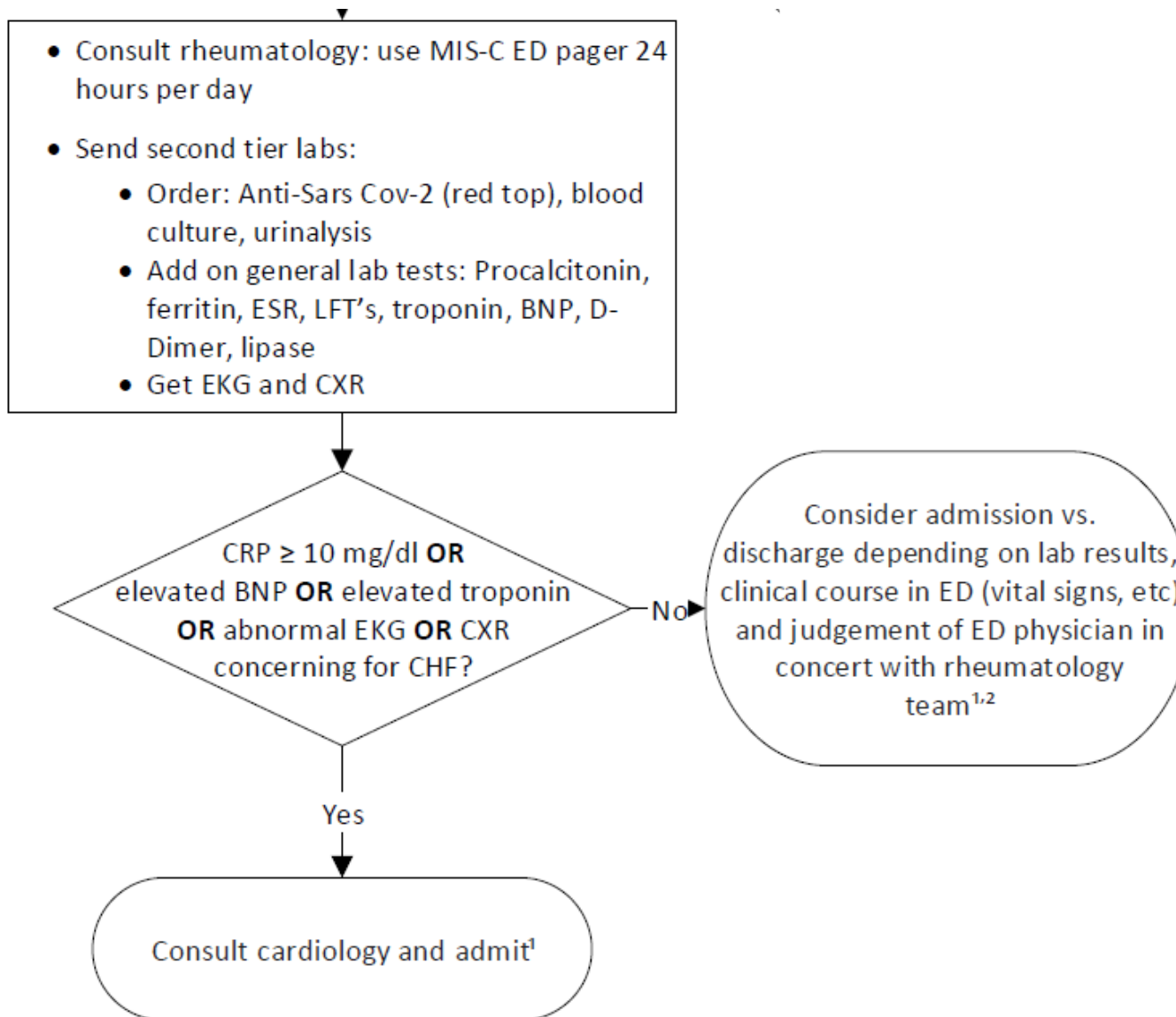
Labs: CBC with diff, CRP, chem 7, COVID-19 PCR, and other labs and cultures as appropriate for age and potential sources of infection.
Draw and hold: Coag tube (Blue top), Red top and blood culture for second tier labs³



BCH ED Guidance for evaluation of MIS-C



BCH ED Guidance for evaluation of MIS-C



Acknowledgement

BCH Rheumatology

- Mary Beth Son MD
- Megan Day-Lewis RN MSN CPNP
- Pui Y. Lee MD PhD
- Jeffrey Lo MD
- Jordan Roberts MD
- Mindy S. Lo MD PhD
- Margaret H. Chang MD
- Ezra Cohen MD
- Olha Halyabar MD
- Jonathan Hausmann MD
- Melissa M. Hazen MD
- Kacie J. Hoyt MSc
- Erin Janssen MD PhD
- Esra Meidan MD
- Robert P. Sundel MD
- Fatma Dedeoglu, MD
- Peter Nigrovic, MD

BCH Cardiology

- Kevin G. Friedman MD
- Jane W. Newburger MD
- Sarah D. de Ferranti MD MPH
- Audrey Dionne MD
- Annette Baker RN MSN CPNP
- Christina VanderPluym MD

BCH Immunology

- Craig D. Platt MD PhD
- Janet Chou MD
- Saddiq Habiballah, MBBS
- Ryan W. Nelson MD PhD
- Alan A. Nguyen
- Tina Banzon MD

BCH ICU

- Adrienne Randolph MD