Coagulopathy and multisystem inflammatory syndrome (MSI-C) among pediatric patients with COVID-19 Potential for developing a Canadian registry

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Objectives

- Clinical manifestations of COVID-19 in children
- Overview of MISC
- Environmental scan
- Importance of developing registry
- Primary and secondary aims
- Other variables

Clinical manifestations

Clinical manifestations in children

Clinical features	Proportion	Age considerations
Asymptomatic	**~4%**	**Most common between 6-15 years**
Mild to moderate viral syndrome	**~90%**	**Most common across all ages**
Severe (Pneumonia, hypoxia) **Critical (hypoxia, ARDS, multiorgan failure)**	**~6%**	**Most common 0-5 years**
Death	**1 patient**	**<1 year**

- Based on the largest pediatric case series in China (N =2143)
- Proportion of total COVID-19 cases <1%
- In Italy, pediatric cases were ~1.2% of all reported cases with 0 deaths. In USA, pediatric cases ~1.7% and <1% hospitalizations

COVID, CDC, and Response Team. "Severe outcomes among patients with coronavirus disease 2019 (COVID-19)—United States, February 12–March 16, 2020." MMWR Morb Mortal Wkly Rep 69.12 (2020): 343-346.
Dong, Yuanyuan, et al. "Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China." Pediatrics (2020).
Livingston, Edward, and Karen Bucher. "Coronavirus disease 2019 (COVID-19) in Italy." Jama 323.14 (2020): 1335-1335.
Coronavirus Disease 2019 in Children—United States, February 12–April 2, 2020.
MMWR Morb Mortal Wkly Rep. 2020; 69: 422-426

Other clinical features

Inflammatory/immunologic phenomena

- **DIC/SIC in adults(22%)**
- **High incidence of VTE (25%)**
- **Pediatrics: No reports of incidence. Thrombosis ppx. recommended for inpatients**

Newly recognized hyper inflammatory syndrome with cardiac issues-shares features with KD (multisystem vasculitis with predilection for coronary arteries)

Cui, Songping, et al. "Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia." Journal of Thrombosis and Haemostasis (2020).
Connors, Jean M., and Jerrold H. Levy. "COVID-19 and its implications for thrombosis and anticoagulation." Blood, The Journal of the American Society of Hematology 135.23 (2020): 2033-2040.

Multisystem Inflammatory syndrome in Children

Multisystem Inflammatory Syndrome

- Clusters of pediatric patients in US and UK with atypical Kawasaki disease
  - Significant cardiac involvement
  - Shock and inflammation (high ESR, CRP, Ferritin and D-Dimers)
- Presumed activation of innate immune response

Riphagen, Shelley, et al. "Hyperinflammatory shock in children during COVID-19 pandemic." The Lancet 395.10237 (2020): 1607-1608.

WHO case definition

General	Age 0-19 years Fever > 3 days
Symptoms (min. 2/5)	Rash/conjunctivitis/mucocutaneous inflammation Hypotension/shock Myocardial dysfunction Coagulopathy GI symptoms
Lab	Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin.
COVID-19	Evidence of COVID-19 (RT-PCR, antigen test or serology positive) OR Contact with patients with COVID-19.

Multisystem inflammatory syndrome in children and adolescents with COVID-19-Scientific Brief-15th May,2020

Reports of MIS-C

Study	No. of patients	COVID-19 diagnosis	KDSS	Cardiac involvement	Other features
Prospective case series (France)	21 12/21 African	19/21 (IgG pos)	12/21	16/21	21/21 had GI symptoms. 30-45 days from COVID-19
Retrospective case series (France and Swiss)	35	31/35 (IgG positive)	29/35 (6/35 needed ECMO)	35/35	No coagulopathy reported
Case series USA	6	5/6 (IgG pos)	6/6	6/6	

- All reported patients had GI symptoms
- Kawasaki disease shock syndrome (KDSS): Kawasaki disease with systolic hypotension/signs of poor clinical perfusion. Seen in 1-5% of patients with classic Kawasaki Disease (KD)
- Treatments used: Patients in all series were treated with high dose IVIG± steroids and cardiac/respiratory support
- Resolution of symptoms with no mortality

Toubiana, Julie, et al. "Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study." bmj 369 (2020).
Belhadjer, Zahra, et al. "Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic." Circulation (2020).
Chiotos, Kathleen, et al. "Multisystem Inflammatory Syndrome in Children during the COVID-19 pandemic: a case series." Journal of the Pediatric Infectious Diseases Society (2020).

Comparison with classic Kawasaki disease

	January 2015-February 2020	February-March 2020
No. and age of patients in years	**19 patients, Mean age: 3 years**	**10 patients, Mean age 7.5 yrs.**
Incidence	**0.3%/month**	**10/month**
COVID-19 testing		**6/10 with positive serology**
Cardiac disease	**2/19**	**6/10**
Shock (KDSS)	**0**	**5/10**
Response to treatment (IVIG and steroids)	**19/19**	**10/10**

Retrospective comparison of patients admitted with Kawasaki disease pre and post COVID-19 in Italy

Verdoni, Lucio, et al. "An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study." The Lancet (2020).

- MIS-C in children occurs at older age than classic KD
  - Maybe African predisposition
  - GI symptoms in vast majority of cases
- High incidence of cardiac involvement and shock
- All patients so far treated with IVIG and steroids
- Outcome favorable overall

Available information about pediatric COVID-19 patients

- COVID-19 infection in children
  - mild-moderate respiratory involvement in vast majority
  - Children with co-morbidities or infants have severe-critical respiratory disease
- Prothrombotic state is well documented in adults with SIC/DIC and DVT
  - No such reports exist in children
- MIS-C shares features of KD and MAS
  - Responds to IVIG
  - Higher incidence with shock and cardiac involvement

Environmental scan

- Pediatric Investigators Collaborative Network on Infections in Canada
  - Retrospective enrollment of pediatric patients with COVID-19
    - Focus: Clinical description
- Multiple local and national registries in US
- WHO registry on MIS-C
- NO registry to my knowledge on coagulopathy OR MIS-C/IVIG utilization in Canada

Rationale for developing registries addressing coagulopathy or MIS-C

- DIC and VTE is characterized in adults with COVID-19
  - No reports specific to children
  - Aid in appreciating differences in pediatric coagulopathy compared to adults
  - Optimize COVID-19 management in children

- No data yet to indicate if coagulopathy (evidenced by SIC/DIC or VTE) is at higher incidence in patients with MIS-C

AIMS and Objectives

- Primary AIM 1
  - In pediatric patients admitted with COVID-19, what is the incidence of coagulopathy (DIC like lab abnormalities) and overt venous thromboembolism?
- Primary AIM 2
  - In pediatric patients admitted in Canada with COVID-19 what is the incidence of MIS-C?

Secondary Aims

- What are the clinical features associated with coagulopathy
  - Difference from adults?
  - Treatment
    - Duration and outcomes
- What are the characteristics of MISC and treatment?
  - Focus on IVIG utilization and outcomes

One registry with focus on two secondary pediatric complications associated with COVID-19

Potential Variables (coagulopathy)

- Patient demographics
- Diagnosis/exposure to COVID-19
- Respiratory illness sevirity
- Underlying medical conditions
- Prophylactic anticoagulation
- Lab parameters
  - CBC
  - PT, PTT,DDIMERS, Fibrinogen
  - LFTS
  - Troponin and BNP
- ECHOand ECG
- Doppler US or CTPE (if performed)
- Duration of anticoagulation
- Outcomes

Variables (MIS-C)

- Patient demographics
- Diagnosis/exposure to COVID-19
- Underlying medical conditions
- Prophylactic anticoagulation
- Lab parameters
  - CBC
  - PT, PTT,DDIMERS, Fibrinogen
  - LFTS
  - Troponin and BNP
  - ESR,CRP,Ferritin
- ECHOcardiogram and ECG
- IVIG (dose, duration, other treatment)
- Outcomes

Questions

- How is coagulopathy in pediatric patients characterized (who should be enrolled)
  - Presents both as thromboembolism and prothrombotic type DIC in adults
  - Enrollment: All admitted patients with COVID-19 <18 years????
    - Should be getting coagulation studies as routine care
- Is MSI-C same as KDSS
  - I don't think anyone knows just yet

Thank you

More questions?