

Neurological Manifestations of Coronavirus 19 in Children: Observation and Experience from an Epicenter Children's Hospital

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With Much Appreciation and Thanks

- BCH, BCHP, MFCH
- Leadership, Nurses, clerical, ER, Residents, Attendings
- ID team and Ped Hospitalist team surrounded the needed care with leadership in context of limitation of resources and fear
- Maintained the pediatric integrity of our hospital
 - Others were over whelmed by acute adult Covid – 19
- Disclosures: NONE
- Therapies are all Empirical and Provisionary
- Terminology
 - Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus which causes Covid-19 or just Covid (February 11, 2020)
 - Multisystem Inflammatory Syndrome in Children (MIS-C) or Pediatric Inflammatory Multisystem Syndrome (PIMS)

Introduction

- Maria Fareri Children's Hospital at Westchester Medical Center
- Geography Westchester County – New York City Initial Epicenter
- By late February and early March, 2020: Pandemic Awareness
- What does PEDS Neuro care look like with minimal resources?
 - Catherine Lucey, MD-The Transformational Effects of COVID-19 on Medical Education
 - Interesting intellectually, challenging operationally
 - Newer concept medical education –***Threshold Themes***
- Impact on Spectrum of pediatric neurology
 - In particular HA, Sz, IS (position paper)
- No insight Re: Neuro-Covid in pediatric patients (adults-vascular impact)
- In fact minimal illness and disease at first

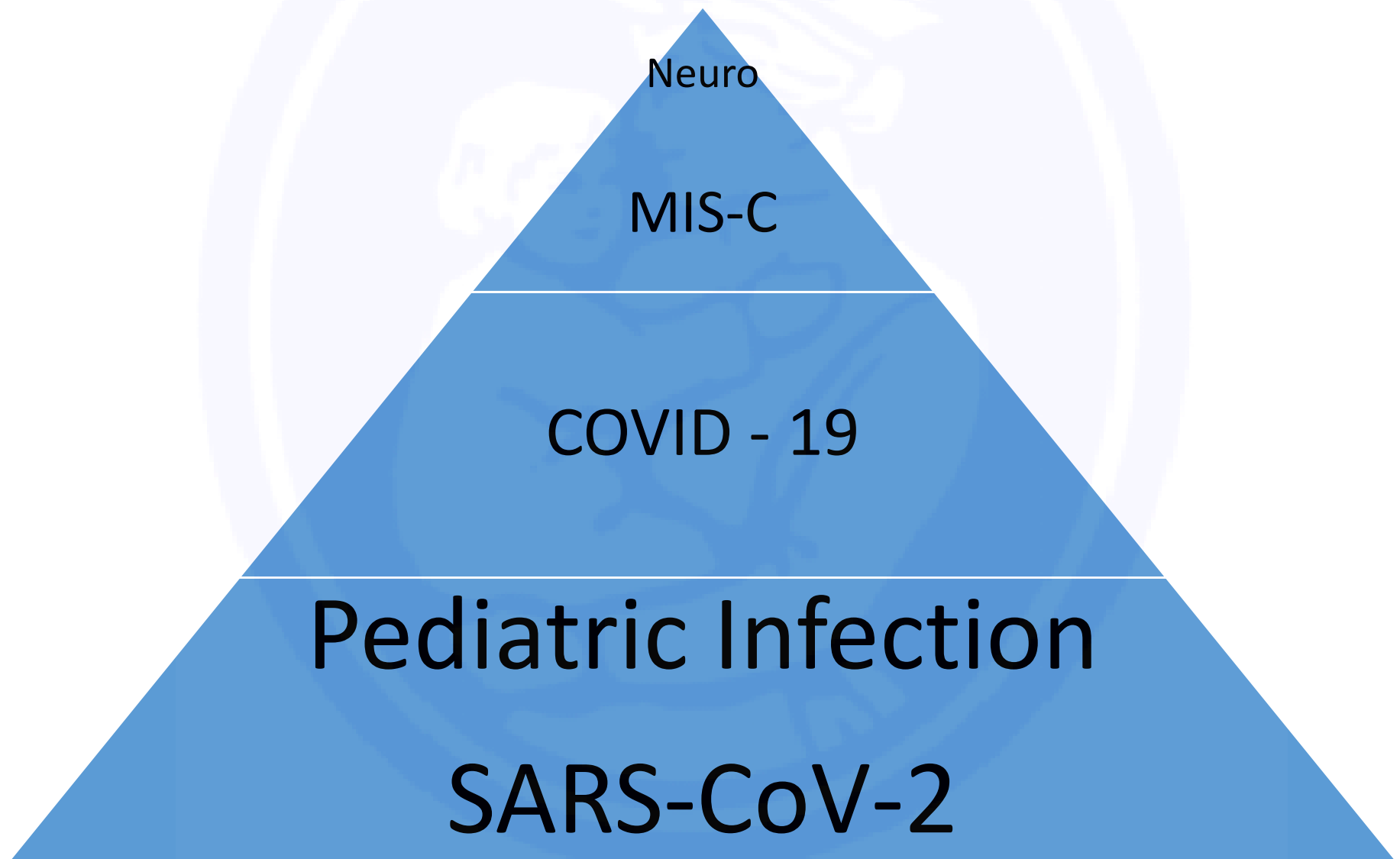
Reflections

- Model of novelty: PEDS Neurology Prior Experience and Novel Diseases
 - 1970's no CT scans, no MRI, no drug levels
 - Reyes syndrome, Lyme Disease, HIV, Autoimmune Encephalitis, AFP (enterovirus D 68)
- But never on a pandemic scale that threatened patients, staff, and institutions simultaneously
 - Challenging for clinicians, administrators, and educators
- Rapid Transformation in Pediatric Neurology
 - Tele-Neurology
 - Tele-Learning
 - Care of Neurology Patient in context Covid
 - Didn't yet imagine post-Covid syndromes or hyperimmune Neuro-Pathologies

The Story

- Summary SARS-CoV-2
- Geography New York State and WESTCHESTER COUTY
- Local data
- Pediatric Neuro-Covid
- Emerging new disorder(s)
- Kawasaki like
- Infectious, parainfectious, post infectious
- Pathophysiology
- Laboratory Biomarkers
- Association not causation: Neurology during epidemic - Covid or not
- Cases
- Treatment
- Treatment dilemmas
- Outcome
- Future

Pediatric SARS - CoV - 2



7:48 AM Sun Sep 6

74%



WORLD COUNTRIES ▾ | U.S.A. STATES ▾ | TESTING

New York Coronavirus Map and Case Counts

By The New York Times Updated September 6, 2020, 1:33 A.M. E.T.



Map

By county

New cases

Tips

Latest news »

At least 6 new coronavirus deaths and 799 new cases were reported in New York on Sept. 5. Over the past week, there have been an average of 768 cases per day, an increase of 26 percent from the average two weeks earlier.

As of Sunday morning, there have been at least 443,497 cases and 32,579 deaths in New York since the beginning of the pandemic, according to a New York Times database.

Hot spots Total cases Deaths Per capita

Average daily cases per 100,000 people in the past week



7:49 AM Sun Sep 6

73%



WORLD COUNTRIES ▾ | U.S.A. STATES ▾ | TESTING

Massachusetts Coronavirus Map and Case Counts

By The New York Times Updated September 6, 2020, 1:33 A.M. E.T.



Map

By county

New cases

Tips

Latest news »

At least 16 new coronavirus deaths and 438 new cases were reported in Massachusetts on Sept. 5. Over the past week, there have been an average of 321 cases per day, an increase of 4 percent from the average two weeks earlier.

As of Sunday morning, there have been at least 122,100 cases and 9,116 deaths in Massachusetts since the beginning of the pandemic, according to a New York Times database.

Note: As of Aug. 12, Massachusetts updates the number of cases and deaths by county once a week. The state previously updated these counts each day. This change affects daily county trends.

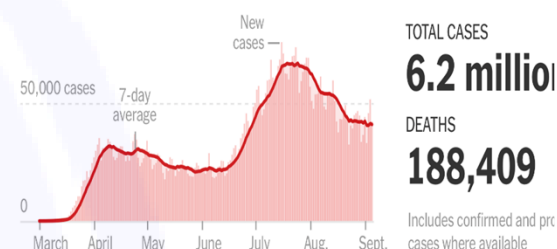
Hot spots Total cases Deaths Per capita

Average daily cases per 100,000 people in the past week



7:50 AM Sun Sep 6

73%



Cases by state

Hot spots

Clusters

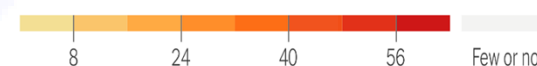
Latest news

711 new coronavirus deaths and 42,080 new cases were reported in the United States on Sept. 5. Over the past week, there have been an average of 40,867 cases per day, a decrease of 7 percent from the average two weeks earlier.

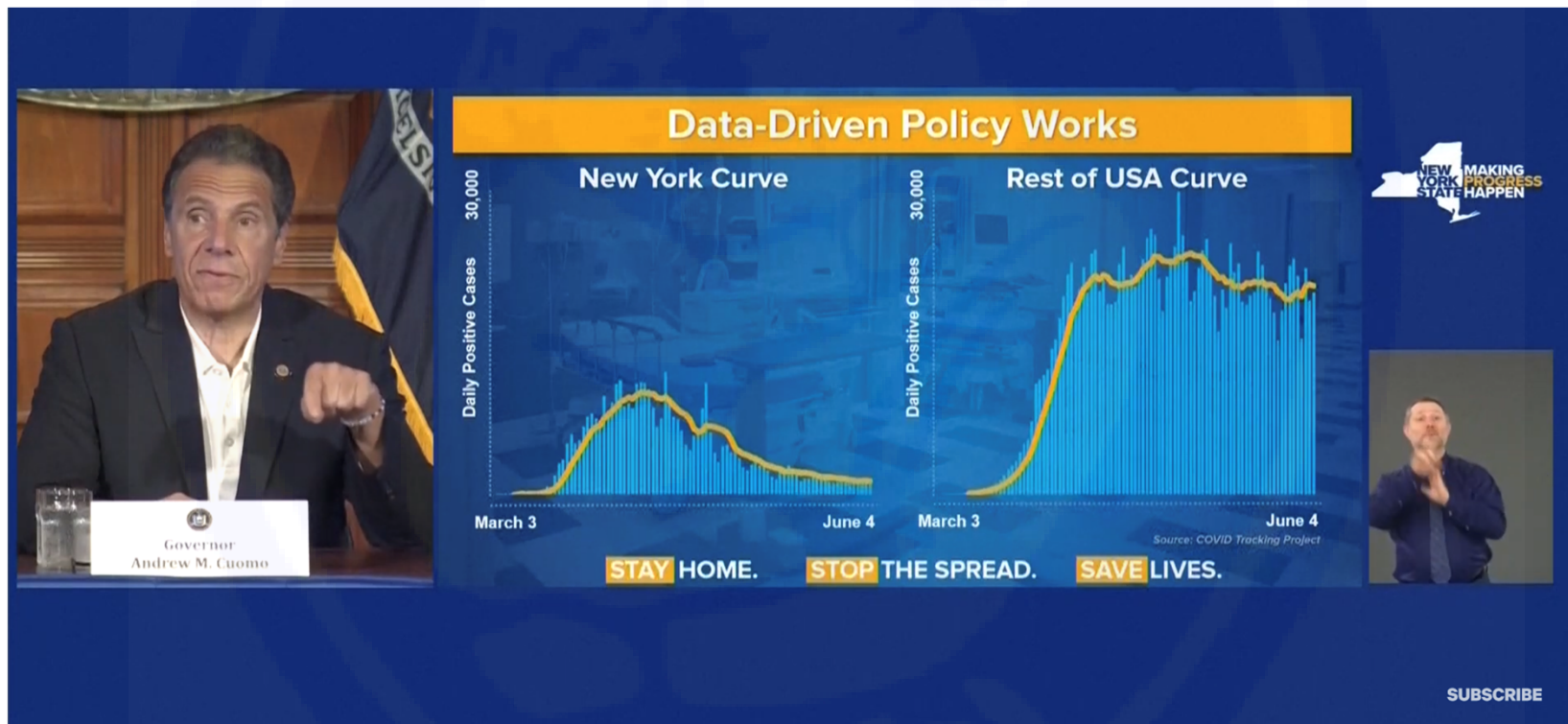
As of Sunday morning, more than 6,260,900 people in the United States have been infected with the coronavirus and at least 188,409 have died, according to a New York Times database.

Hot spots Total cases Deaths Per capita

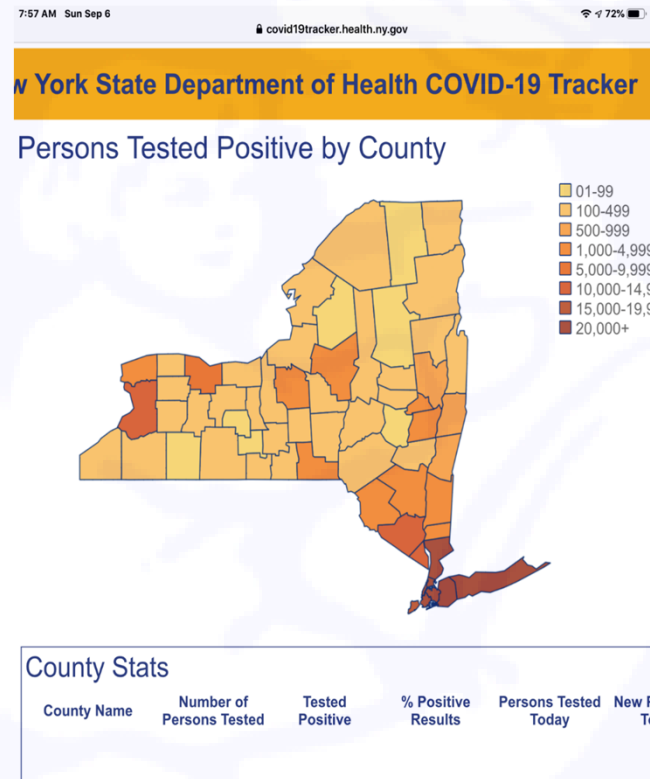
Average daily cases per 100,000 people in the past week



New York State



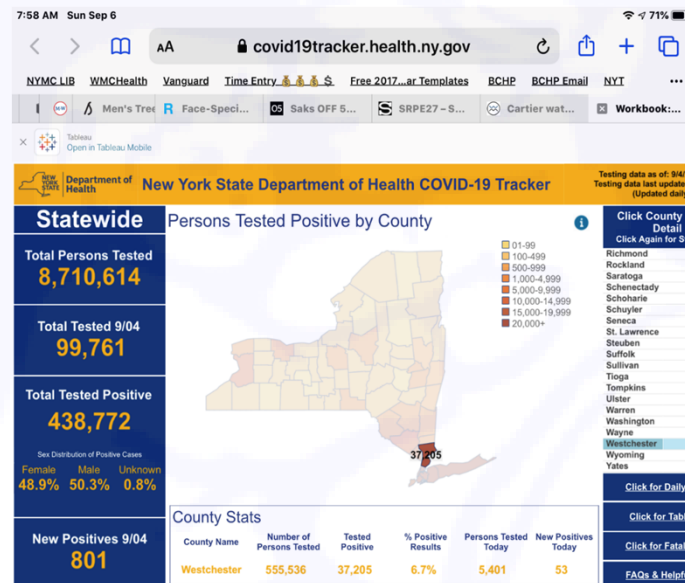
NYS Covid- 19



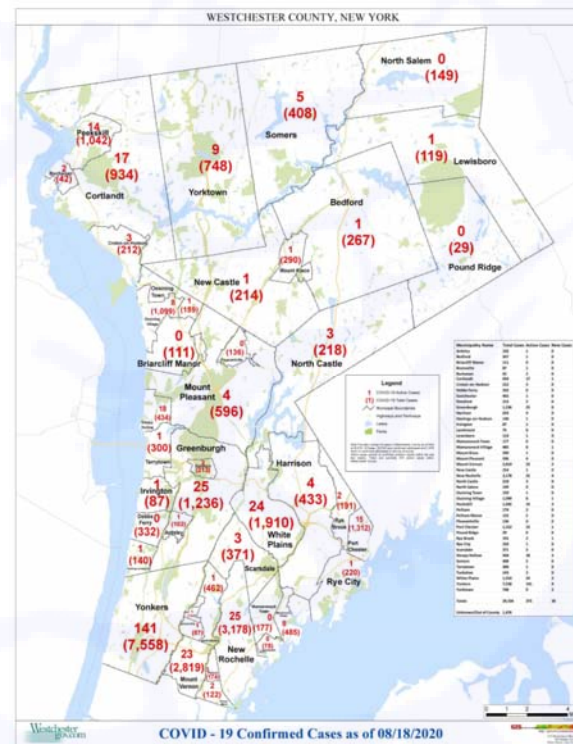
Westchester County NY

- Pandemic began in early March
 - 591,914 COVID-19 tests administered in Westchester
 - Resulting in 37,571 (6.3 percent of all tests taken) positive cases
 - 1,453 deaths related to the virus
- NYS 9,381,651 tests for COVID-19
- 444,948 testing positive
- There have been 32,579 virus-related fatalities in NYS

Westchester County Positive > Manhattan



Westchester County NY





ANDREW M. CUOMO
Governor

Department of Health

HOWARD A. ZUCKER, M.D., J.D.
Commissioner

SALLY DRESLIN, M.S., R.N.
Executive Deputy Commissioner

May 2020

Dear Colleagues:

The first day of spring this year coincided with the start of New York's rapt attention to "the curve"—the trajectory of a pandemic outbreak that has claimed the lives of at least 23,000 New Yorkers. Two months on, as we emerge from our COVID-19 battle positions and transition into a new normal, I want to discuss remaining challenges and important strategies for keeping residents safe and protected into the future.

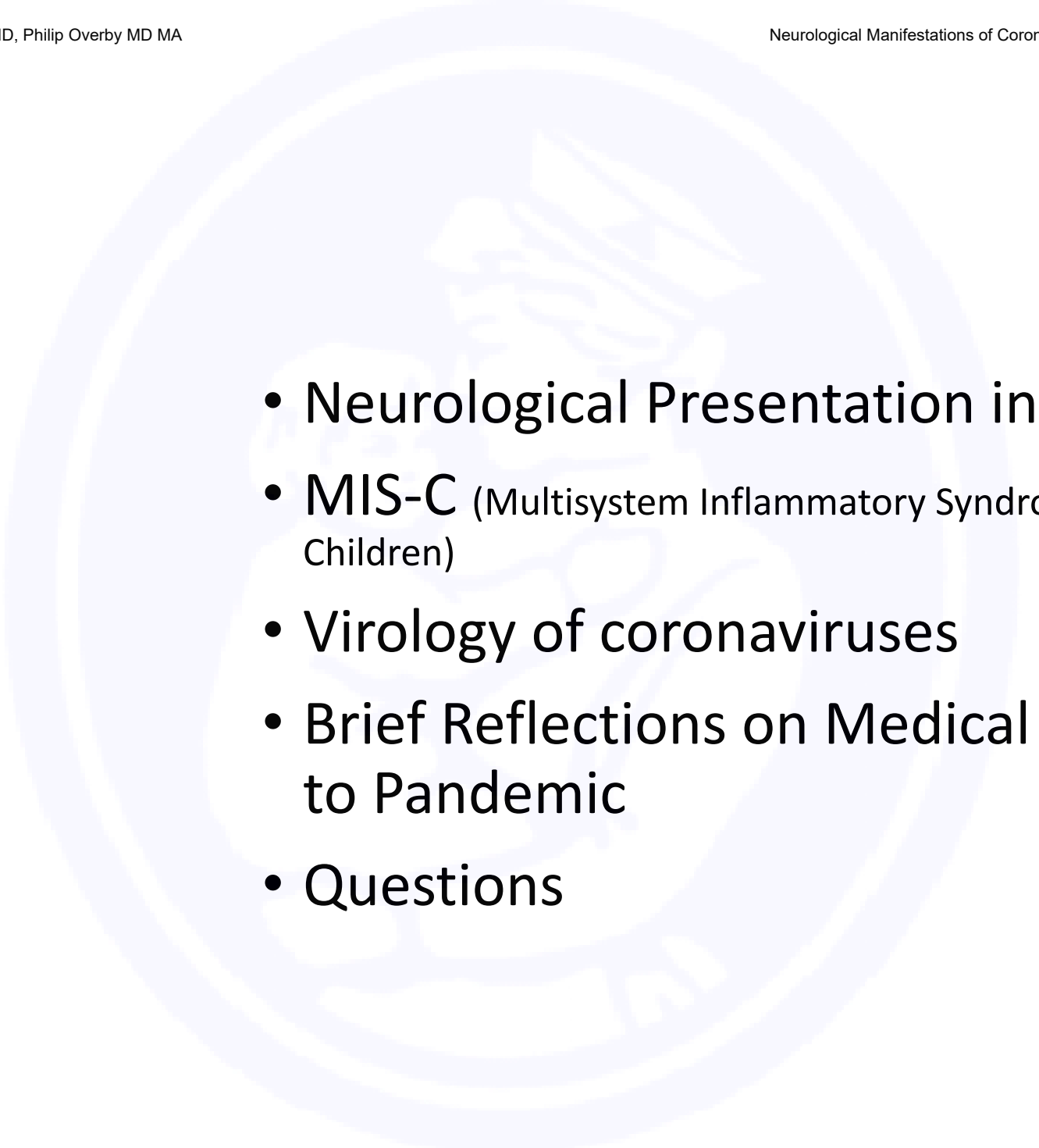
Multisystem Inflammatory Syndrome in Children (MIS-C). New York State was first alerted to a dangerous coronavirus-related condition in children by an April 27 [health advisory](#) from the United Kingdom. The condition has features similar to those of Kawasaki disease and toxic shock syndrome; described signs and symptoms include fever, rash, red eyes and lips, a swollen or "strawberry" tongue, and gastrointestinal manifestations. Inflammatory markers may be elevated, and myocarditis and other cardiovascular changes may be seen.

COVID-19 as “Multisystem Disease.” As the number of coronavirus cases continues to decline, I want to stress our need to remain vigilant about other syndromes that may be related to COVID-19 when a patient still has the virus or has recovered. We are fairly certain that COVID-19 can affect any organ beyond the respiratory system:

- It attacks the heart, causing myocarditis, cardiomyopathy, and arrhythmias.
- The immune system’s exaggerated response to the virus can create a storm of cytokines that attack the body’s own cells, causing lung damage and unusual hypercoagulability.

Empire State Plaza, Corning Tower, Albany, NY 12237 | health.ny.gov

-
- It causes microvascular dysfunction and varying sized thrombi throughout the body that break loose and result in significant morbidity and mortality via strokes and pulmonary emboli.
 - It can damage kidneys and lead to kidney failure.
 - It causes a range of neurological symptoms, from headache to confusion, delirium, and coma.

- 
- Neurological Presentation in Children
 - MIS-C (Multisystem Inflammatory Syndrome in Children)
 - Virology of coronaviruses
 - Brief Reflections on Medical Response to Pandemic
 - Questions

Neurological associations of COVID-19

Mark A Ellul, Laura Benjamin, Bhagteshwar Singh, Suzannah Lant, Benedict Daniel Michael, Ava Easton, Rachel Kneen, Sylviane Defres, Jim Sejvar, Tom Solomon

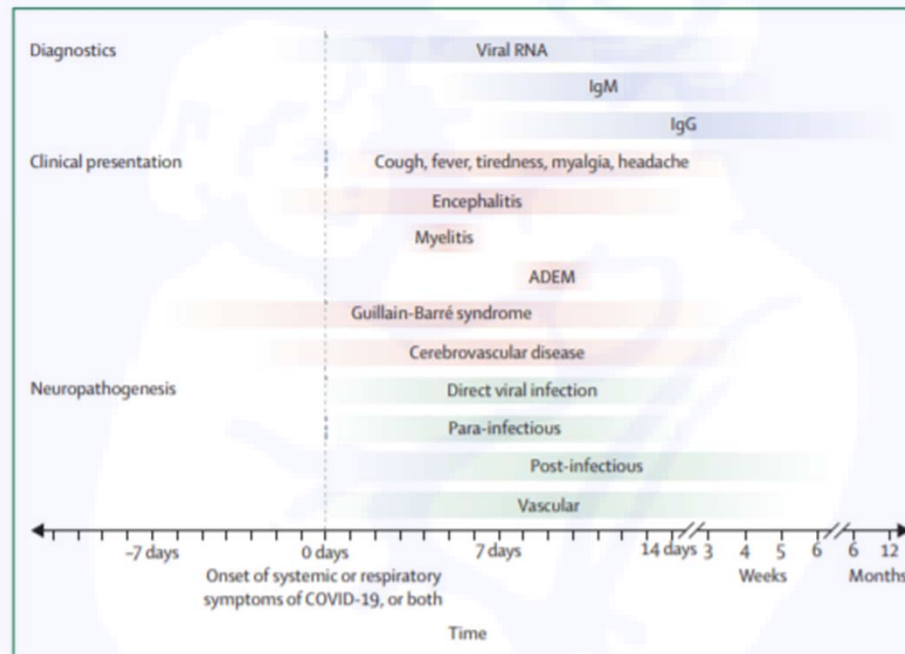


Figure 1: Approximate timeline for positive diagnostic tests, clinical presentation, and pathogenesis in COVID-19-associated neurological disease

Lancet Neurol 2020; 19: 767-83

CS Lewis Out of the Silent Planet

“It is impossible to see something,
until you can name it”

“CLASSIC MIS C”

HPI

- 11-year-old previously healthy boy
- Fever 3 days
- Conjunctival redness, hand swelling 2 days
- Nausea and vomiting and abdominal pain, intermittent diarrhea
- Headache and photophobia
- Confused past 24 hours but conversant about favorite subject (mathematics)

Initial Labs

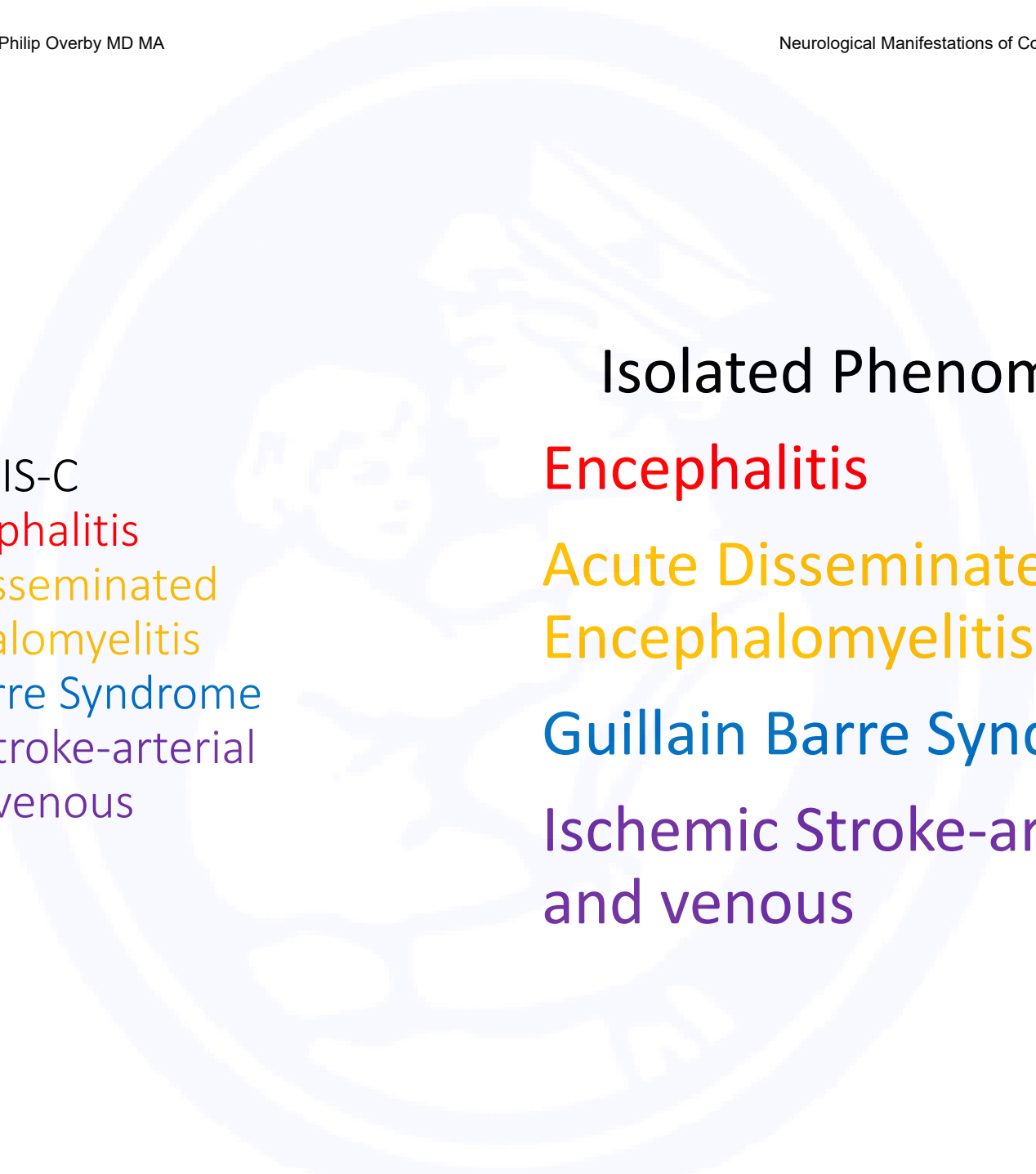
- Labs Highly Suggestive of MIS-C:
- Hyponatremia
- Normal WBC with 14 % (decreased) lymphocytes
- ALT twice normal, INR elevated, CRP elevated
- BNP > 600 (<100 pg/ml)
- Ferritin > 2000 (< 360 ug/L)
- D Dimer > 6000 (<500 ng/mL)
- Present but not always present in MIS C:
- Increased Creatinine, elevated troponin, + COVID 19 IgG, + COVID 19 NP swab

First 48 hours treatment and improvement

- First 48 hours:
- IVF and Dobutamine
- Ceftriaxone and Vancomycin meningitis doses.
- Solumedrol 20 mg/kg/d divided q 6 hours
- IVIG 2 grams/kg given once
- Enoxaparin 0.5 mg/dose q 12 hours. When MRI deferred due to persistent hypotension increased to 1 mg/kg/dose
- MRI brain: an ovoid region of T2 hyperintensity and DWI hyperintensity (not confirmed on ADC maps) is present in the splenium of the corpus callosum.
- No enhancement
- Transthoracic echo
 - Normal right ventricular size and systolic function.
 - Normal left ventricular dimensions with mildly depressed systolic function.

Pediatric Neurological Presentations Covid 19

Encephalitis
Acute Disseminated
Encephalomyelitis
Guillain Barre Syndrome
Ischemic Stroke-Arterial
and Venous



MIS-C
Encephalitis
Acute Disseminated
Encephalomyelitis
Guillain Barre Syndrome
Ischemic Stroke-arterial
and venous

Isolated Phenomenon
Encephalitis
Acute Disseminated
Encephalomyelitis
Guillain Barre Syndrome
Ischemic Stroke-arterial
and venous

Symptoms at Onset

- Ataxia, agitation, fever, headache, common (MIS-C)
- Back and limb (LEGS!) very common
- First 24-48 hours tempo and presence or absence of progression occur
- Early steroids and/or IVIG confound the progression but should still be considered
- Also true for anticoagulation

Ataxia (common) vs Guillain Barre (less common)

- Ataxia
 - Disinhibition
 - LEG PAIN
 - Diminished Reflexes
 - Self Limited 24-48 hours
- Ataxia
 - Constipation
 - Tachycardia, Hypertension
 - Cranial Neuropathy +/- increased somnolence
 - Diminished/Absent Reflexes
 - (And leg pain...)

Encephalopathy (Common) v Encephalitis (Rare)

Encephalopathy

- Headache
- Dizziness
- Agitation/*Disinhibition*
- *Ill Appearing*
- *Consider concurrent or alternative etiologies: hypoxia, drugs, toxins, and metabolic derangement*
- Non focal neurological exam
- *Self Limited * 24-72 hours*
 - (* or improved due to steroids/IVIG in MIS C cases)

Encephalitis

- Increased Somnolence
- Headache and vomiting
 - (nonspecific)
- Apraxia, ataxia, aphasia
- Progressive or not improving
- Deficits on neurological exam

Altered Mental Status

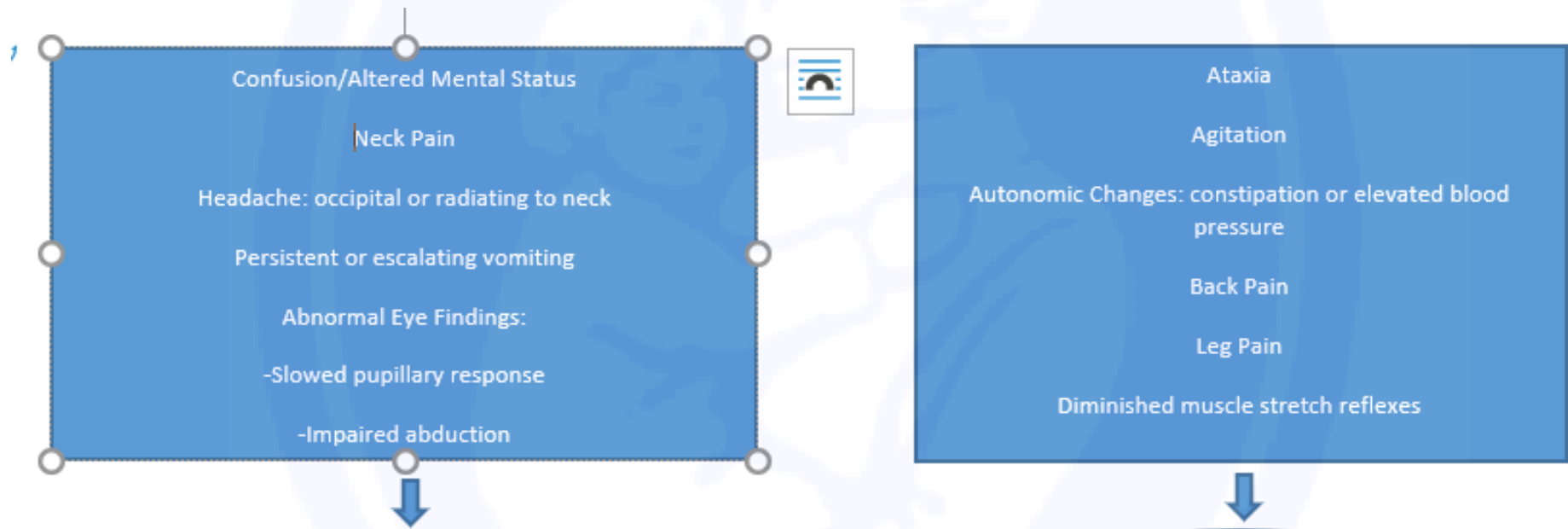
Who to scan or tap?

- Encephalitis
- ADEM
- CVST
- Ischemic Stroke
- In ALL instances, patients had either confusion, impaired speech or abnormal exam
- Agitation is common
- Prepare to be punched
- Better in 24-48 hours
- Other than diminished reflexes exams typically normal

EVALUATION PATHWAYS

Red Flags for CNS Pathology

Signs/Symptoms of Guillain Barre



EVALUATION PATHWAYS



Maria Fareri Children's Hospital

March 27, 2020- June 15, 2020

- 90 Covid patients
- 65 NP swab +
- 25 NP swab –
 - 9 Covid Ab +
 - 16 MP swab -, Ab -
- 32 patients with MIS- C
- 1 possible MIS- C

MFCH Hospital Neurological Diagnoses (15/90 cases or 17% of all COVID+ pts)

Central Nervous System

- Encephalitis-1
- Cerebellitis-1
- Altered Mental Status (2)
 - + Fever, HA, irritability, vomiting. MR brain normal.
- Demyelination (1)
- Ischemic Stroke-3
 - (2 arterial, 1 venous)
- Meningitis (infant 40 days)
- Seizures (1)

Peripheral Nervous System

- Ataxia/Leg pain- 3 identified, (many more in retrospect)
- Guillain Barre-Fischer type (1)
- Bickerstaffs Encephalitis (1)

MFCH Hospital Neurological Diagnoses

MIS-C+: 15/32: 47% had neurological symptoms

Central Nervous System

- Encephalitis-1
- Cerebellitis-1
- Altered Mental Status (2)
 - + Fever, HA, irritability, vomiting. MR brain normal.
- Demyelination (1)
- Ischemic Stroke-3
 - (1/2 arterial, 1 venous)
- Meningitis (infant 40 days)
- Seizures (1)

Peripheral Nervous System

- Ataxia/Leg pain- 3 identified, (many more in retrospect)
- Guillain Barre-Fischer type (1)
- Bickerstaffs Encephalitis (1)

CS Lewis
Out of the
Silent Planet

- “It is impossible to see something, until you can name it”

Pediatric
Neurological
Presentations
Covid 19

Encephalitis
Acute Disseminated
Encephalomyelitis
Guillain Barre Syndrome
Ischemic Stroke-arterial and venous

Case definition for
MIS-C includes:

Clinical presentation
Elevated inflammatory
markers of inflammation
Evidence of infection or
COVID 19 contact
Exclusion of other obvious
causes

June 2020

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Multisystem Inflammatory Syndrome in U.S. Children and Adolescents

R. Feldstein, E.B. Rose, S.M. Horwitz, J.P. Collins, M.M. Newhams, M.B.F. So W. Newburger, L.C. Kleinman, S.M. Heidemann, A.A. Martin, A.R. Singh, S. L M. Tarquinio, P. Jaggi, M.E. Oster, S.P. Zackai, J. Gillen, A.J. Ratner, R.F. Wals J.C. Fitzgerald, M.A. Keenaghan, H. Alharash, S. Doymaz, K.N. Clouser, S. Giuliano, Jr., A. Gupta, R.M. Parker, A.B. Maddux, V. Havalad, S. Ramsingh I. Bukulmez, T.T. Bradford, L.S. Smith, M.W. Tenforde, C.L. Carroll, B.J. Riggs J. Gertz, A. Daube, A. Lansell, A. Coronado Munoz, C.V. Hobbs, K.L. Marohn N.B. Halasa, M.M. Patel, and A.G. Randolph, for the Overcoming COVID-19 Investigators and the CDC COVID-19 Response Team*

2020 Jul 23;383(4):334-346. doi: 10.1056/NEJMoa2021680

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Multisystem Inflammatory Syndrome in Children in New York State

Elizabeth M. Dufort, M.D., Emilia H. Koumans, M.D., M.P.H., Eric J. Chow, M.D., M.P.H., Elizabeth M. Rosenthal, M.P.H., Alison Muse, M.P.H., Jemma Rowlands, M.P.H., Meredith A. Barranco, M.P.H. Angela M. Maxted, D.V.M., Ph.D., Eli S. Rosenberg, Ph.D., Delia Easton, Ph.D. Tomoko Udo, Ph.D., Jessica Kumar, D.O., Wendy Pulver, M.S., Lou Smith, M.D. Brad Hutton, M.P.H., Debra Blog, M.D., M.P.H., and Howard Zucker, M.D., for the New York State and Centers for Disease Control and Prevention Multisystem Inflammatory Syndrome in Children Investigation Team*

2020 Jul 23;383(4):347-358. doi: 10.1056/NEJMoa2021756

Common Presenting Symptoms

Fever > 5 days

GI symptoms: vomiting and or diarrhea

Decreased LV Function
Hypotension +/- pressor support

Conjunctival Injection

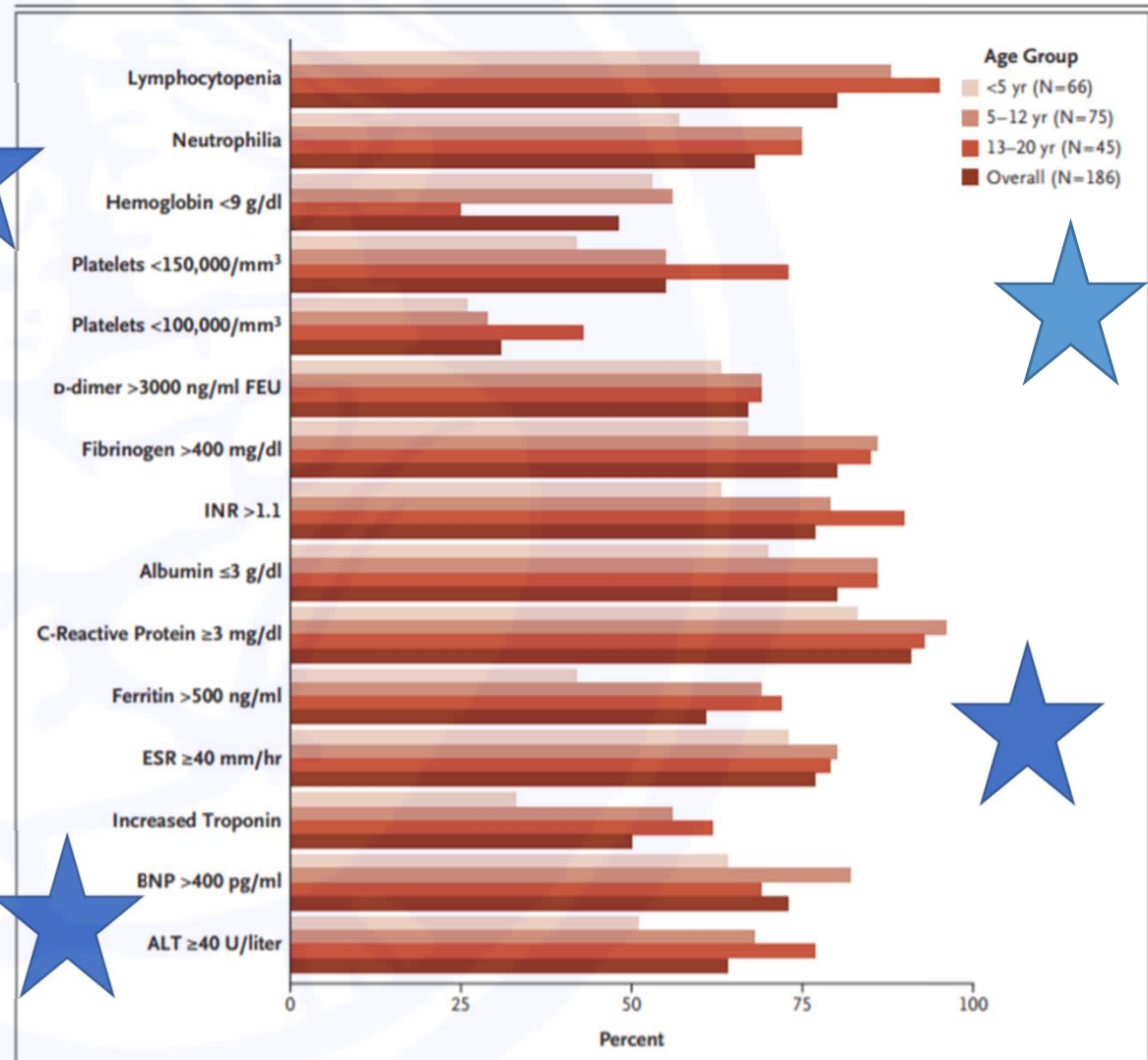
HA, agitation, neck pain/stiffness,
leg pain

Therapy

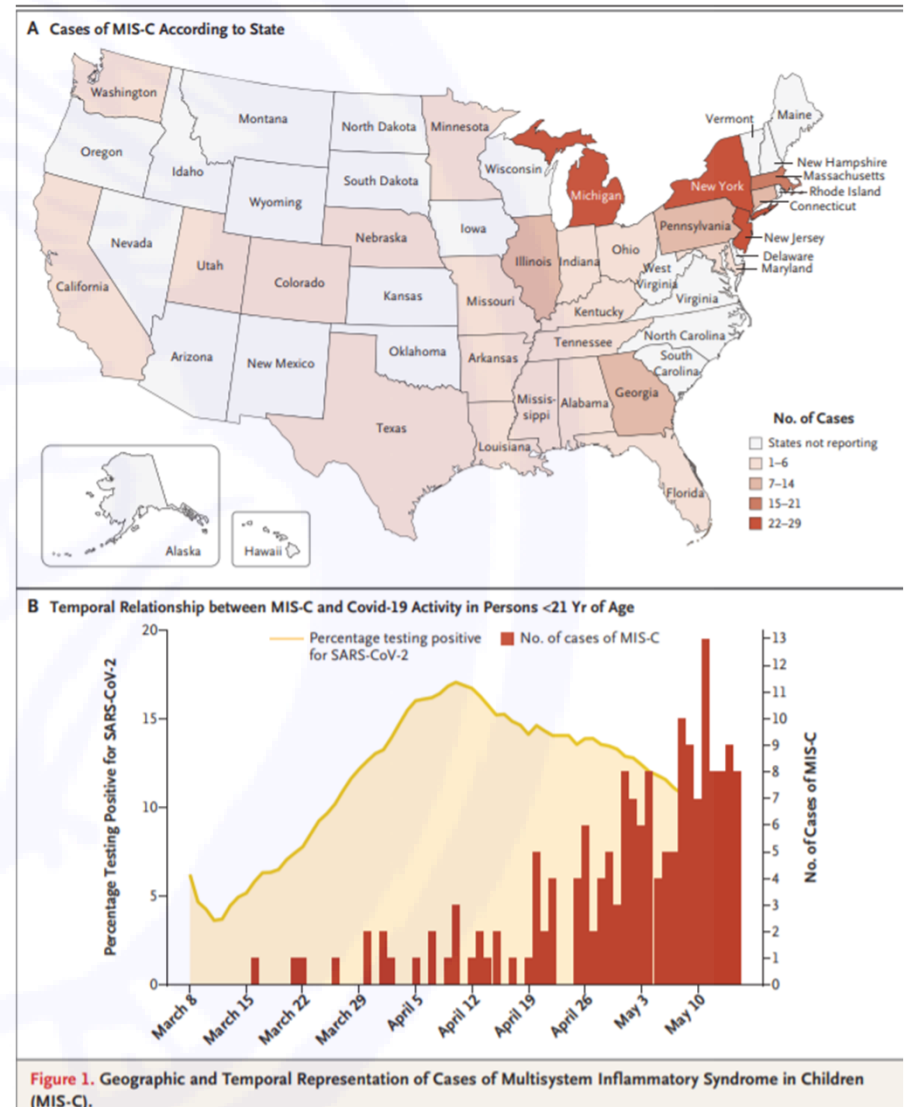
- IVIG 2 grams/kg
- Solumedrol
- Enoxaparin
- Aspirin *

2020 Jul 23;383(4):334-346. doi: 10.1056/NEJMoa2021680

MULTISYSTEM INFLAMMATORY SYNDROME IN U.S. CHILDREN



The NEW ENGLAND JOURNAL of MEDICINE JULY 23, 2020



34

Understanding SARS-CoV-2-related multisystem inflammatory syndrome in children

Anne H. Rowley^{1,2,3}

The NEW ENGLAND JOURNAL of MEDICINE

Characteristic	Overall (N = 99)
Positivity for SARS-CoV-2 — no./total no. (%)	
On RT-PCR assay	50/98 (51)
On serologic assay for IgG antibodies	76/77 (99)

Overall (N = 99)	0–5 Years (N = 31)	6–12 Years (N = 42)	13–20 Years (N = 26)
50/98 (51)	15/31 (48)	19/41 (46)	16/26 (62)
76/77 (99)	24/25 (96)	33/33 (100)	19/19 (100)

NATURE REVIEWS | IMMUNOLOGY COMMENT

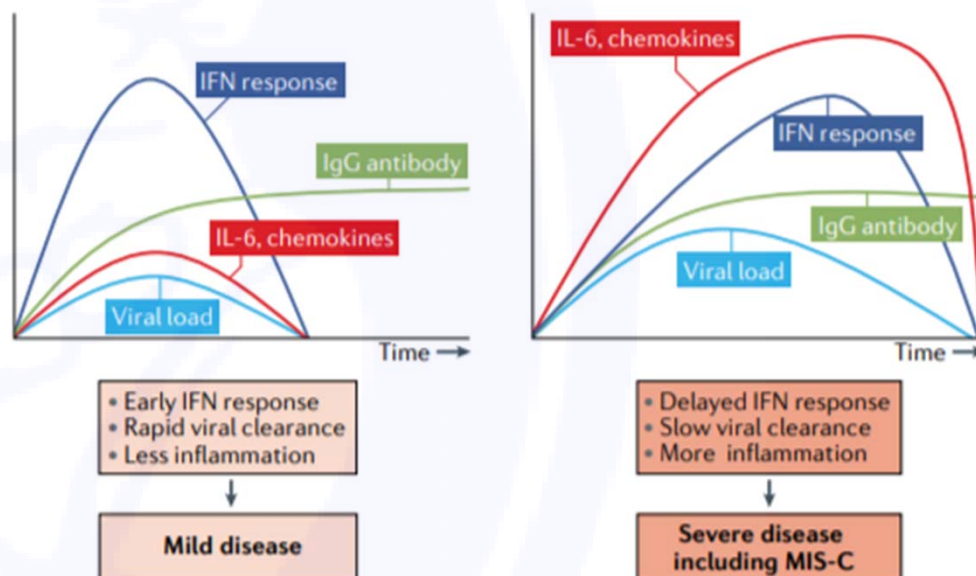


Fig. 1 | Pathogenesis of multisystem inflammatory syndrome in children: a hypothesis. The timing of the interferon (IFN) response to SARS-CoV-2 infection can vary with viral load and genetic differences in host response. When viral load is low, IFN responses are engaged and contribute to viral clearance, resulting in mild infection. When viral load is high and/or genetic factors slow antiviral responses, virus replication can delay the IFN response and cytokine storm can result before adaptive responses clear the virus, resulting in severe disease including multisystem inflammatory syndrome in children (MIS-C). Adapted with permission from REF.⁹, Elsevier.

2020 Jul 27;ciaa1080. doi: 10.1093/cid/ciaa1080.

COVID-19 and multisystem inflammatory syndrome in children and adolescents

Li Jiang*, Kun Tang*, Mike Levin, Omar Irfan, Shaun K Morris, Karen Wilson, Jonathan D Klein, Zulfiqar A Bhutta

August 17, 2020

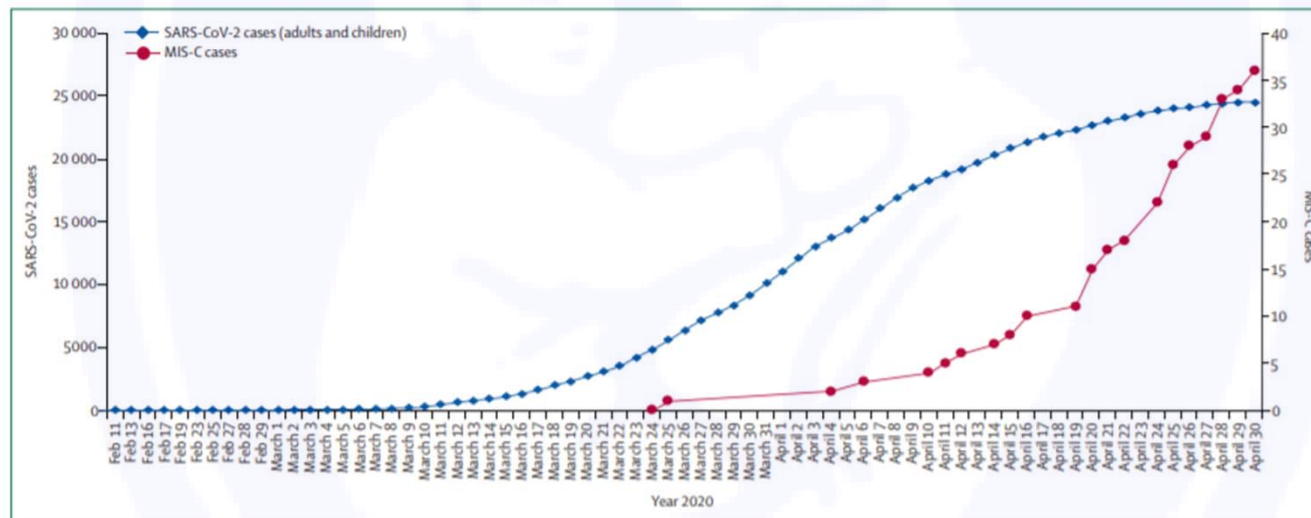


Figure 1: Time course of MIS-C in PCR-positive COVID-19 cases

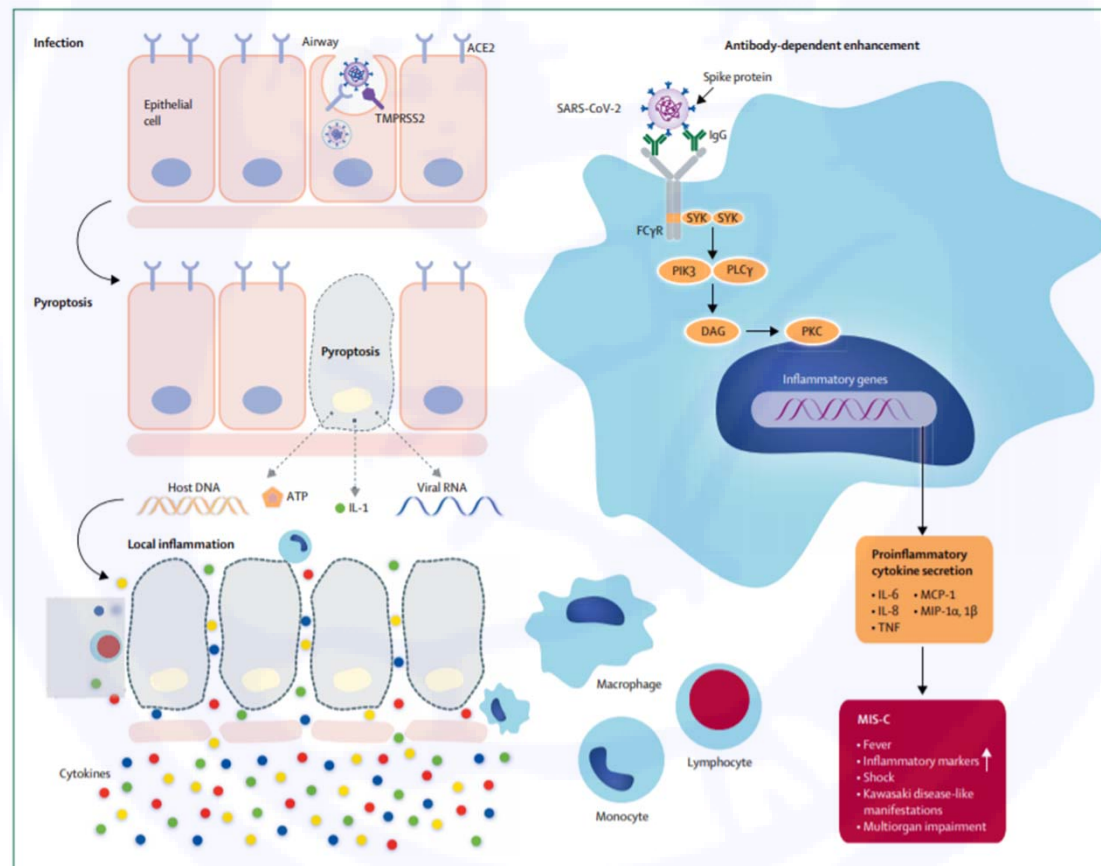
Only includes PCR-positive cases in London, UK. Data taken from Public Health England.²⁰ Figure courtesy of Alasdair Bamford and Myrsini Kaforou. MIS-C=multisystem inflammatory syndrome in children. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

Lancet Infect Dis. 2020 Aug 17:S1473-3099(20)30651-4. doi: 10.1016/S1473-3099(20)30651-4.

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Li Jiang*, Kun Tang*, Mike Levin, Omar Irfan, Shaun K Morris, Karen Wilson, Jonathan D Klein, Zulfiqar A Bhutta

1 August 17, 2020

	Royal College of Paediatrics and Child Health ³⁹	US Centers for Disease Control and Prevention ³⁷
Supportive care	Only recommended for mild to moderate disease; discuss early with paediatric intensive care unit and paediatric infectious disease, immunology, and rheumatology team; if clinically deteriorating or in cases of severe disease, discuss transfer with paediatric intensive care unit retrieval teams	Fluid resuscitation, inotropic support, respiratory support, and in rare cases, extracorporeal membranous oxygenation
Directed care against underlying inflammatory process	Immunotherapy should be discussed with a paediatric infectious diseases unit and experienced clinicians on a case-by-case basis and used in the context of a trial if eligible and available	Intravenous immunoglobulin, steroids, aspirin, and anticoagulation treatment
Antiviral therapy	Should be given only in the context of a clinical trial and should be discussed at multidisciplinary team meetings with a clinician from an external trust	--
Antibiotics for sepsis	--	Given while waiting for bacterial cultures
Other	All children treated as if they have COVID-19 and all should be considered for recruitment in research studies	--

Table 2: Published guidance on the management of multisystem inflammatory syndrome in children associated with COVID-19

Lancet Infect Dis. 2020 Aug 17:S1473-3099(20)30651-4. doi: 10.1016/S1473-3099(20)30651-4.

COVID-19 and multisystem inflammatory syndrome in children and adolescents

Li Jiang*, Kun Tang*, Mike Levin, Omar Irfan, Shaun K Morris, Karen Wilson, Jonathan D Klein, Zulfiqar A Bhutta

August 17, 2020

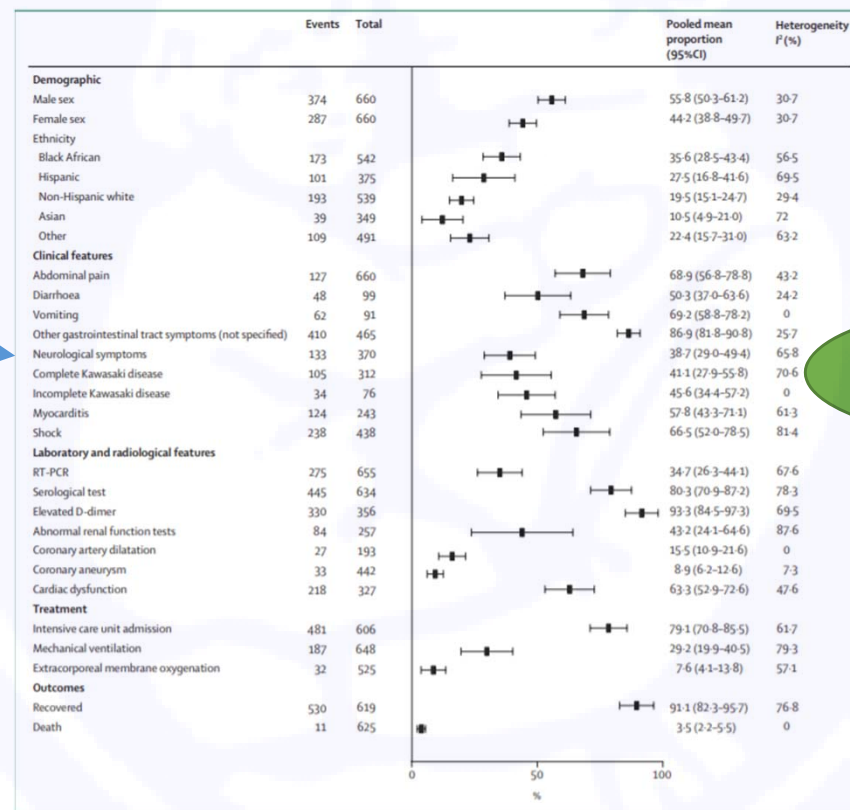


Figure 3: Pooled meta-analysis of patient characteristics in multisystem inflammatory syndrome in children associated with COVID-19^{a,b}

30-40%
Neurological
Symptoms

Lancet Infect Dis. 2020 Aug
17:S1473-3099(20)30651-4. doi:
10.1016/S1473-3099(20)30651-4.

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

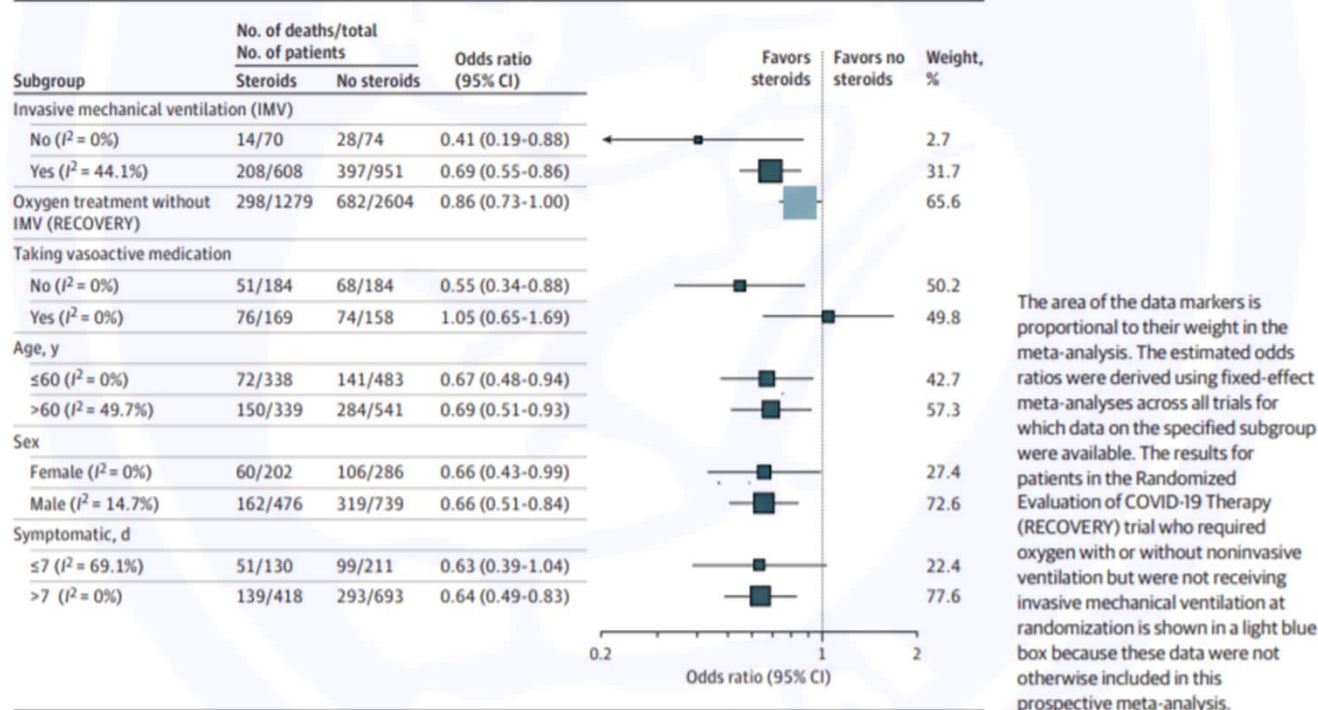
Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19

A Meta-analysis

JAMA Published online September 2, 2020

doi: 10.1001/jama.2020.17023.

Figure 3. Association Between Corticosteroids and 28-Day All-Cause Mortality Within Subgroups Defined by Patient Characteristics at the Time of Randomization



JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

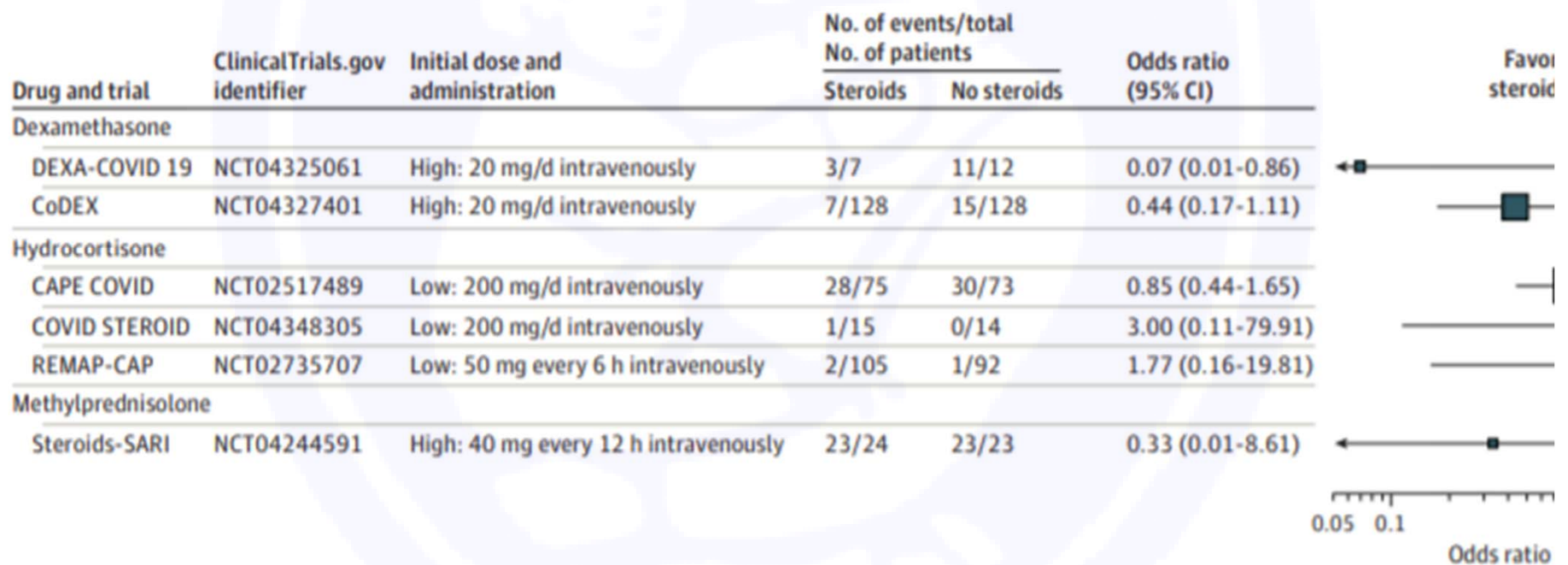
Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19

A Meta-analysis

JAMA Published online September 2, 2020

doi: 10.1001/jama.2020.17023.

Figure 4. Association Between Corticosteroids and Serious Adverse Events in Each Trial



Contents

- Neurological Presentation in Children
- MIS-C
- Virology of coronaviruses (and quick history)
- Brief Reflections on Medical Response to Pandemic
- Questions

History

- In December 2019, adults in Wuhan, capital city of Hubei province and a major transportation hub of China started presenting to local hospitals with severe pneumonia of unknown cause.
- Identified a common exposure to the Huanan wholesale seafood market that also traded live animals
- December 31, 2019, China notified the outbreak to the World Health Organization and on 1st January the Huanan sea food market was closed.
- On January 7, 2020, the virus was identified as a coronavirus that had >95% homology with the bat coronavirus and > 70% similarity with the SARS-CoV-1 (China SARS outbreak 2002-2004)
- Transmission to healthcare workers caring for patients was described on Jan. 20, 2020
- January 23, 2020, the 11 million population of Wuhan was placed under lock down

REVIEW ARTICLE

A Review of Coronavirus Disease-2019 (COVID-19)

Tanu Singhal¹

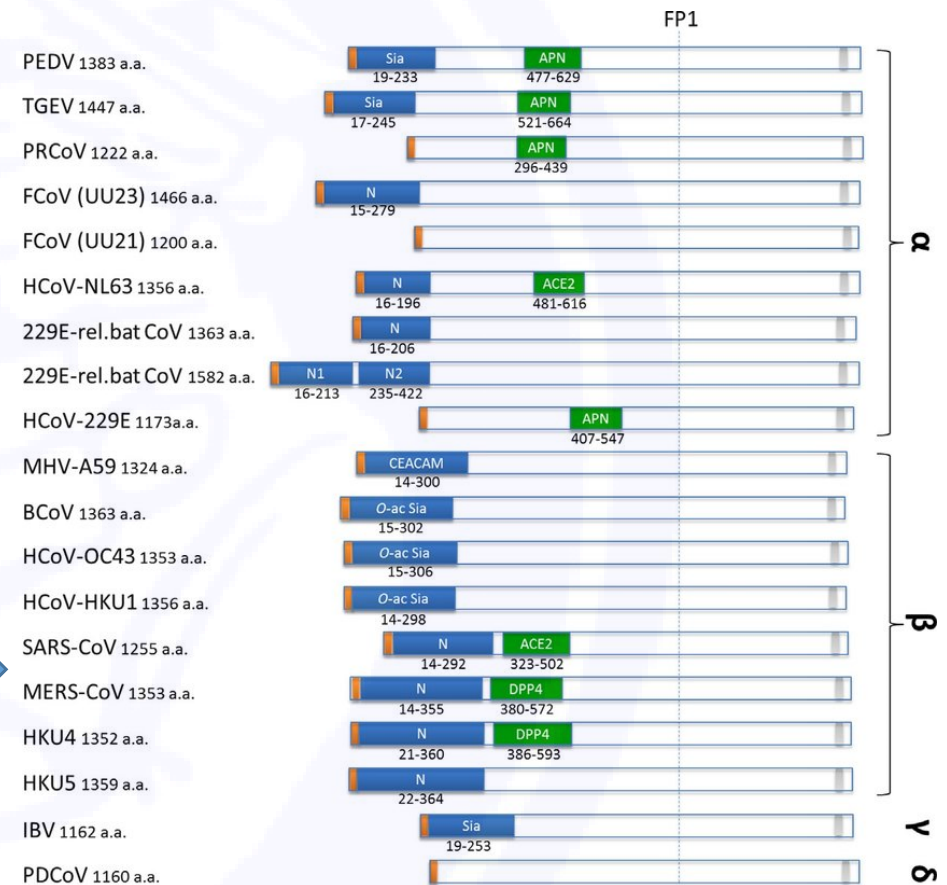
Received: 23 February 2020 / Accepted: 25 February 2020 / Published online: 13 March 2020

Life Cycle of Coronavirus

- **Attachment**
- Penetration
- Biosynthesis
- Maturation
- Release

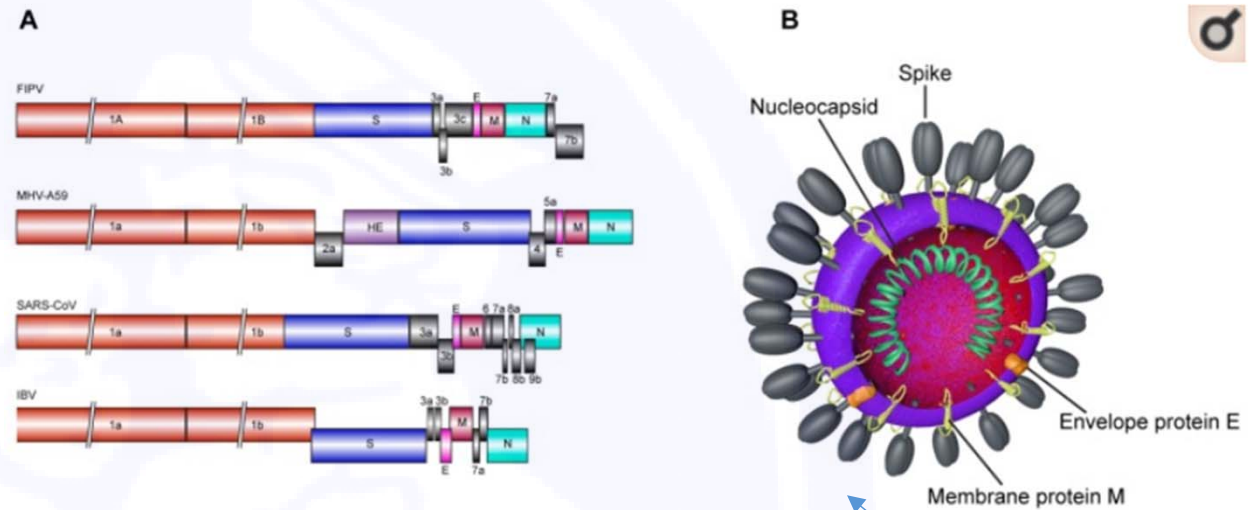


Spike Protein Mutations



Hulswit, Ruben & Haan, C.A.M. & Bosch, B.J.. (2016).
Coronavirus Spike Protein and Tropism Changes.

Diseases caused by coronaviruses



Tropism of coronaviruses derives from changes in the **Spike (S) Protein**:

- Mouse Hepatitis Virus (MHV)-encephalitis and hepatitis
- Feline Cov-Enteric Infection

The difference in tropism mediated by S proteins results from different mechanisms linked to the two main functions of the protein: receptor binding and fusion

Mechanisms of Coronavirus Cell Entry Mediated by the Viral Spike Protein

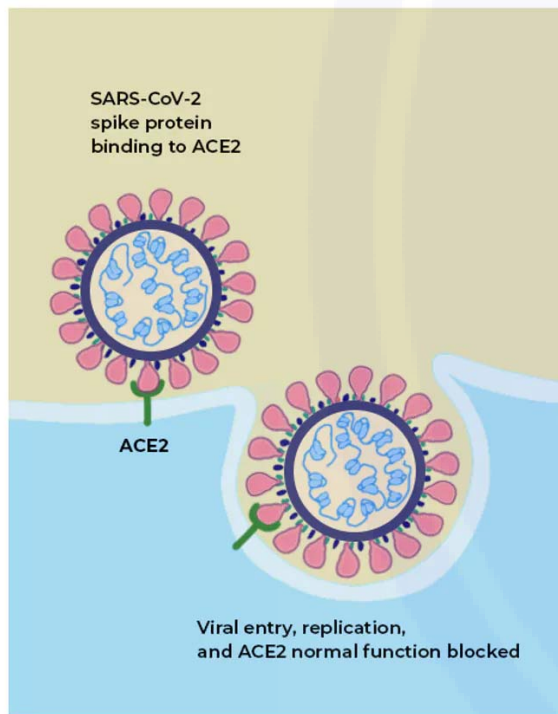
Sandrine Belouzard ¹, Jean K. Millet ², Beth N. Licitra ² and Gary R. Whittaker ^{2,*}

Viruses **2012**, *4*, 1011-1033;

ACE2 receptors

- Target of entry for SARS-COV2
- Located in multiple different organ systems
 - Enterocytes of the small intestine (remember this for kids)
 - Arterial and venous endothelial cells
 - Lung alveolar epithelial cells
 - Subset of CD 14 and CD 16 monocytes

ACE receptors



Journal of Microbiology, Immunology and Infection (2020) 53, 425–435

ACE2 polymorphism and COVID-19 disease

431

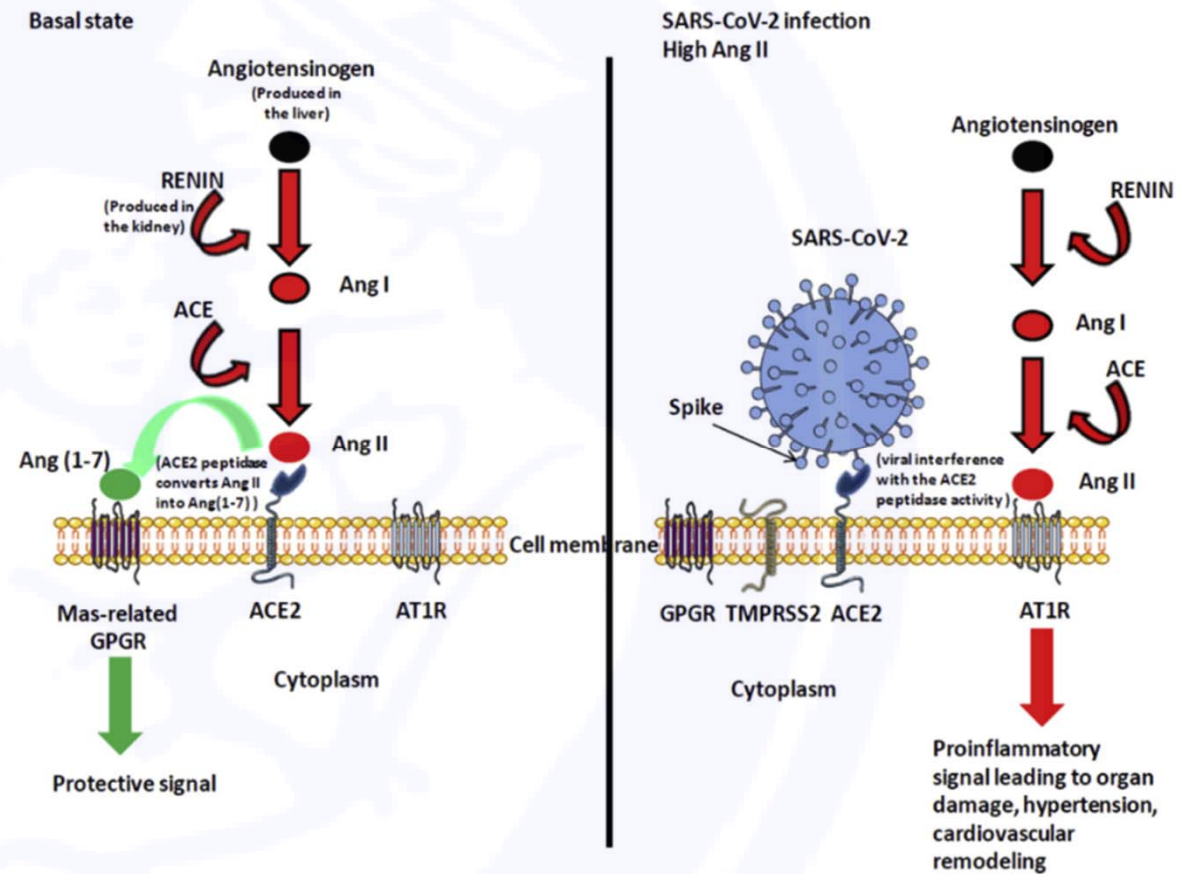


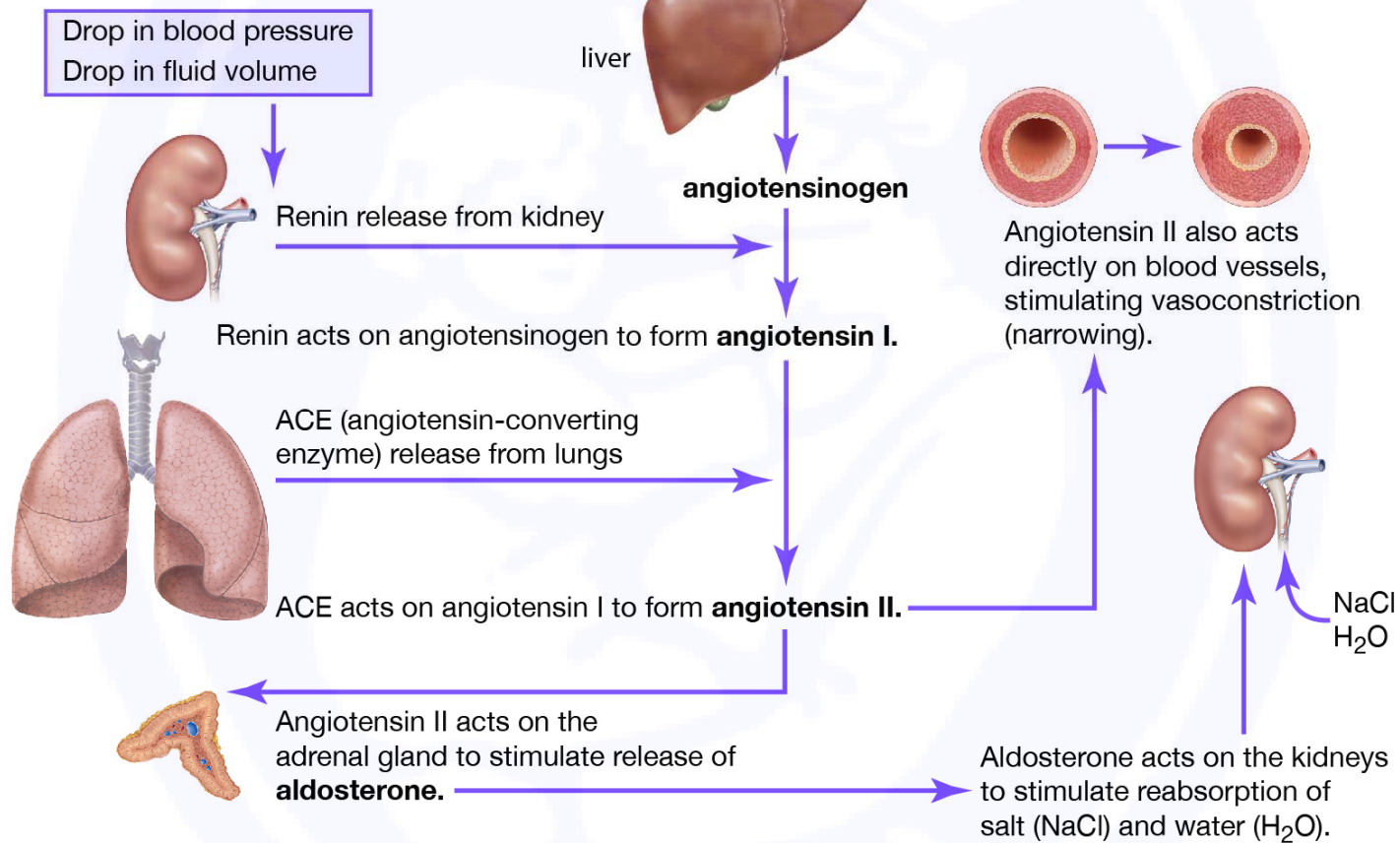
Figure 2. Simplified diagram of the renin-angiotensin system in normal and pathologic conditions. The left panel indicates that ACE2 converts Ang II to Ang (1–7) leading to protective signal. The right panel illustrates the possible dysfunction of signals when

ACE2 function-breakdown

Angiotensin II

- ACE 2-target of entry for SARS-COV2
- Located in multiple different organ systems
 - Enterocytes of the small intestine (remember this for kids)
 - Arterial and venous endothelial cells
 - ACE2 modulates
 - Lung alveolar epithelial cells
 - Subset of CD 14 and CD 16 monocytes

Renin-angiotensin system



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Take Home : SARS-COV2 targets CV system

- Renin Angiotensin (RAAS) system goal is to modulate BP
- SARS-COV 2 decreases Angiotensin II production by interfering with the ACE2 receptor.
- SARS-COV2 most vulnerable populations
 - Diabetes (microvascular disease)
 - HTN
 - Coronary Artery Disease
- This should not be surprising!
- But CV system is not only target of the virus

Coronavirus and Mechanisms of Disease: Entry to the CNS

Lancet Neurol 2020; 19: 767-83

- Angiotensin converting enzyme 2 receptor, to which SARS-CoV-2 binds for entry into cells is found in brain vascular endothelium and smooth muscle
- Breakdown of BBB following viremia, infected leukocytes
- **Direct invasion**: Viral entry to the brain through the olfactory bulb—the only part of the CNS not protected by dura—is one plausible route for SARS-CoV-2, especially given the anosmia in COVID-19. This entry route is thought to be used by the herpes simplex virus, the most common cause of sporadic viral encephalitis
- **Immune mediated mechanisms** remain poorly understood

Coronavirus and Mechanisms of Disease: Cerebrovascular Disease

Lancet Neurol 2020; 19: 767-83

- Early indicators suggest that cerebrovascular disease in COVID-19 might be due to a coagulopathy. SARS-CoV-2 can cause damage to endothelial cells, activating inflammatory and thrombotic pathways
- Endothelial cell infection or monocyte activation, upregulation of tissue factors, and the release of microparticles, which activate the thrombotic pathway and cause microangiopathy
- Thrombocytopenia with elevated D-dimer and C-reactive protein in severe COVID-19 and stroke are consistent with a virus-associated microangiopathic process
- Endothelial dysfunction can potentially lead to microvascular and macrovascular complications in the brain

Summary

- History-December 2019-present
- Mutations in **Spike Proteins** change receptor binding and fusion
- Spike Protein mutation in **ACE2** results in human infection
- **ACE2** receptors in multiple organs: kidney, heart, gastrointestinal tract, blood vessels, and lung alveolar epithelial cells
- **ACE2** inhibition increases Angiotensin II
- *Increased Angiotensin II leads to increased vascular permeability, inflammation, hypertension*
- *Endothelial injury with focal inflammation and activated coagulation cascade*

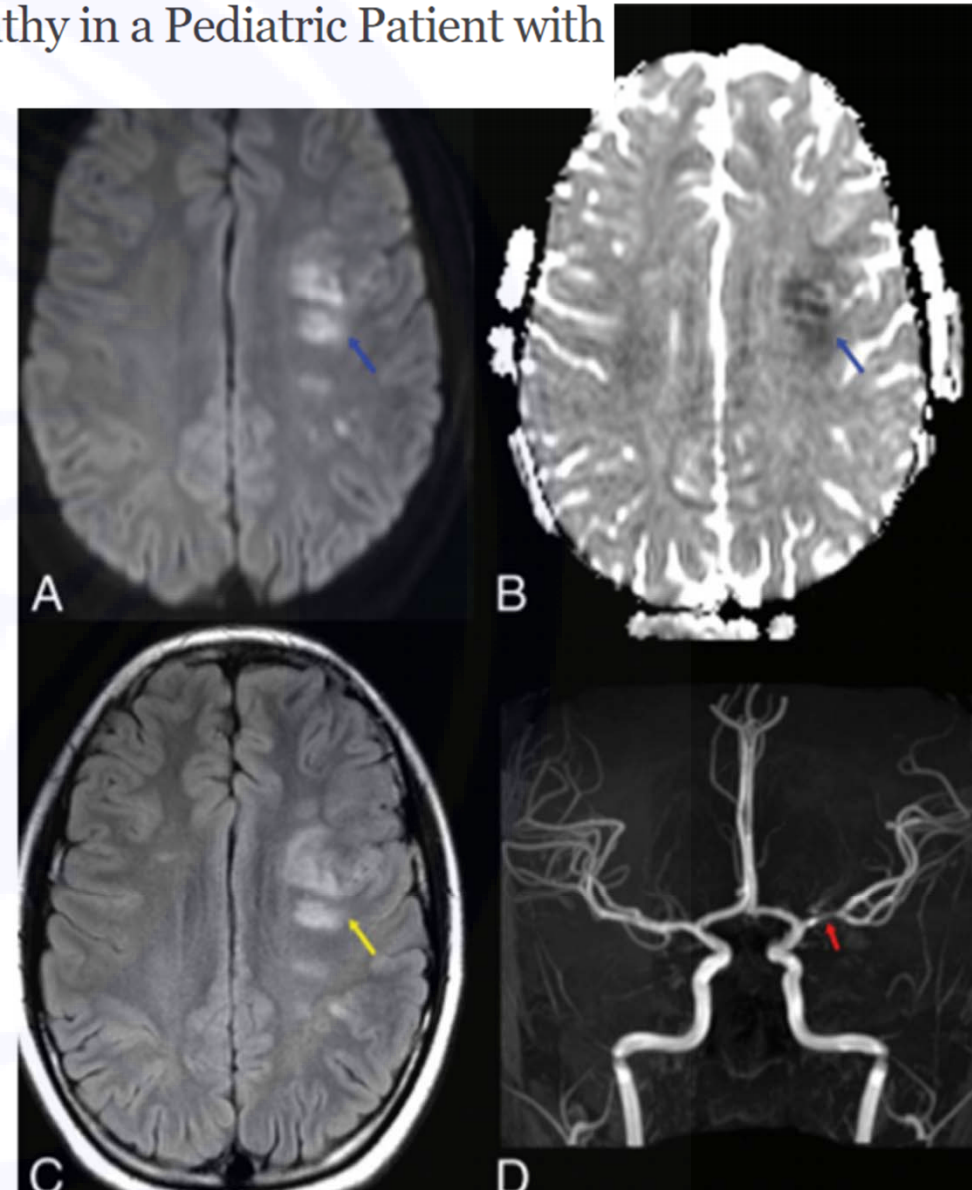
Vessel Wall Enhancement and Focal Cerebral Arteriopathy in a Pediatric Patient with Acute Infarct and COVID-19 Infection

fluctuating but-persistent headache, speech difficulty, and right upper and lower extremity weakness for 4 days. Two months before presentation, she and other family members experienced fever, myalgias, and anosmia, which subsequently resolved. One month before admission, she and other family members tested positive for SARS-CoV-2 qualitative antibodies

- There was no family history of thrombophilia. Thrombophilia evaluation and TTE unremarkable.
- On presentation: viral nasopharyngeal PCR positive.

E. Gulko, P. Overby, S. Ali, H. Mehta, F. Al-Mufti and W. Gomes

American Journal of Neuroradiology August 2020



Vessel wall enhancement within the M1 left MCA. Vessel wall imaging targeted to the left middle cerebral artery with axial contrast (D) 3D T1 volume isotropic turbo spin-echo acquisition sequences, with reformatted coronal images; B and E, respectively. Contrast (F) reformatted sagittal images en face to the M1 left middle cerebral artery at the level of the blue and yellow arrows. There is wall thickening (blue arrow) and marked concentric contrast enhancement of the M1 left middle cerebral artery at this level (yellow arrows). The imaging findings, in conjunction with the clinical history, were consistent with FCA-inflammatory t

COVID-19 and multisystem inflammatory syndrome in children and adolescents

Li Jiang*, Kun Tang*, Mike Levin, Omar Irfan, Shaun K Morris, Karen Wilson, Jonathan D Klein, Zulfiqar A Bhutta

1 August 17, 2020

	Royal College of Paediatrics and Child Health ³⁹	US Centers for Disease Control and Prevention ³⁷
Supportive care	Only recommended for mild to moderate disease; discuss early with paediatric intensive care unit and paediatric infectious disease, immunology, and rheumatology team; if clinically deteriorating or in cases of severe disease, discuss transfer with paediatric intensive care unit retrieval teams	Fluid resuscitation, inotropic support, respiratory support, and in rare cases, extracorporeal membranous oxygenation
Directed care against underlying inflammatory process	Immunotherapy should be discussed with a paediatric infectious diseases unit and experienced clinicians on a case-by-case basis and used in the context of a trial if eligible and available	Intravenous immunoglobulin, steroids, aspirin, and anticoagulation treatment
Antiviral therapy	Should be given only in the context of a clinical trial and should be discussed at multidisciplinary team meetings with a clinician from an external trust	--
Antibiotics for sepsis	--	Given while waiting for bacterial cultures
Other	All children treated as if they have COVID-19 and all should be considered for recruitment in research studies	--

Table 2: Published guidance on the management of multisystem inflammatory syndrome in children associated with COVID-19

Lancet Infect Dis. 2020 Aug 17:S1473-3099(20)30651-4. doi: 10.1016/S1473-3099(20)30651-4.

Questions and Confounders

- Elevated D Dimers-how to stratify risk for CVST, other thromboses.
- Early evaluation-many patients, especially MIS C, look ill
- Post exposure/illness risk of vascular disease and duration
- Therapy for MIS-C: immune therapy and anticoagulation
- Should treatment of AIS be different in any way, especially arterial stroke? That is, should IVIG/PLEX or steroids be considered?
 - Pragmatic: MIS C +, yes
 - Not so pragmatic: Isolated vascular syndrome-unclear

‘What do we not owe to Mr Fildes for showing the world the typical doctor, as we would like to be shown — an honest man and a gentleman, doing his best to relieve suffering? A library of books in our honour would not do what this picture has done and will do for the medical profession in making the hearts of our fellow man warm to us with confidence and affection.’ *British Medical Journal* 1892 On Sir Luke Fildes’ (1843–1927) ‘The Doctor’

Tragedy and Hegel. 2 irreconcilable truths

Thumos. Athens. Honor

- Patton

**Mercy. Jerusalem. Virtue
(modern)**

- Luke Fildas, The Doctor

Tragedy and Hegel. 2 irreconcilable truths:

Henry V

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Tragedy and Hegel. 2 irreconcilable truths:


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Thumos. Athens. Honor

- Henry V

**Mercy. Jerusalem. Virtue
(modern)**

- Henry V

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- Thank You!
 - Questions?
 - Comments?

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