Multisystem inflammatory syndrome in children and adolescents with COVID – 19

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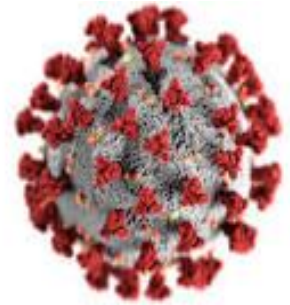


OUTLINE

- Epidemiology of cases
- Definitions
- Clinical features
- Laboratory investigations
- Management

Clinical Manifestations

- **Acute Covid** – Severe pulmonary disease without cardiac involvement

- **Multisystem Inflammatory Syndrome in Children (MIS-C)** – multiorgan involvement

CLASSIFICATION - Acute Covid-19

Of those who develop symptoms, patients are classified into:

- **Mild**
  - Features of acute URTI or digestive symptoms
- **Moderate**
  - Pneumonia without obvious hypoxemia
- **Severe** (progressing to **Critical**)
  - Pneumonia with hypoxemia (SPO2 <90%)
  - Features of ARDS, myocardial injury, heart failure, coagulopathy, shock or kidney injury

Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. Clin Immunol. 2020;215:108427. doi:10.1016/j.clim.2020.108427

MIS-C WHO definition

- Children and adolescents 0-19 years, fever > 3/7

and 2 of:

1. Rash or non-purulent conjunctivitis or mucocutaneous inflammation (oral, hands, feet)
2. Hypotension or shock
3. Features of myocardial dysfunction: pericarditis, valvulitis, coronary abn (echo, ↑ troponin)
4. Evidence of coagulopathy (↑PT, PTT, d-dimers)
5. Acute GE symptoms

MIS-C WHO definition

And:

Elevated CRP, ESR, procalcitonin

And:

No other obvious cause of inflammation: bacterial, staphylococcal, streptococcal shock syndrome

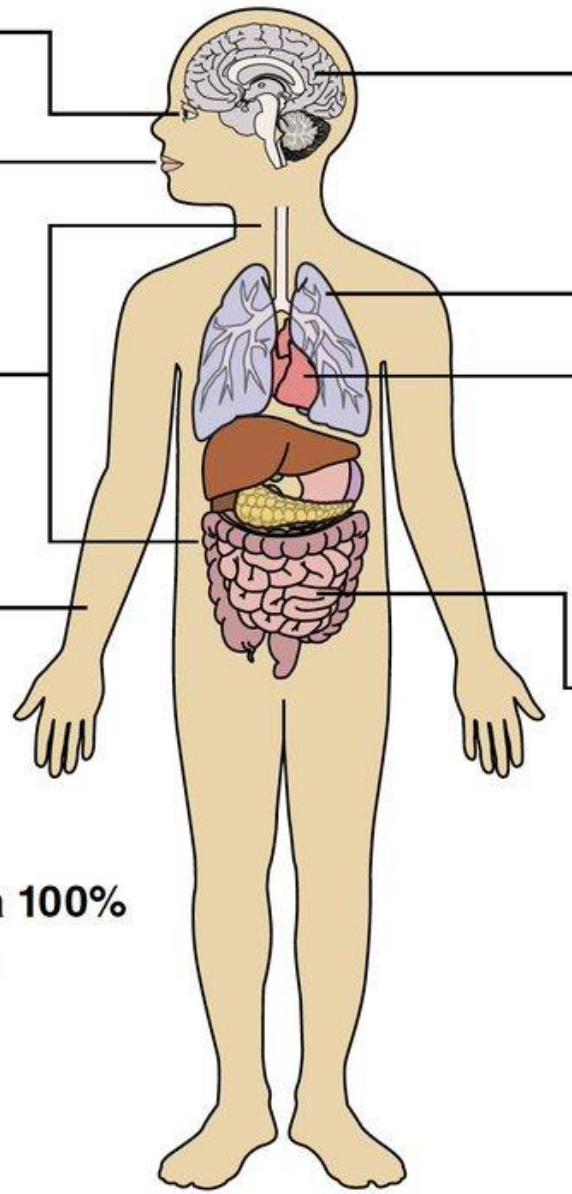
And:

Evidence of Covid – 19 – Ag, serology, or likely contact

Spectrum of illness

Acute COVID-19		COVID-19-associated MIS-C		
Mild	**Severe**	**Febrile inflammatory state**	**KD-like illness**	**Severe MIS-C**
In most children, COVID-19 causes no or only mild symptoms.	A small minority of children present with severe acute COVID-19 manifestations, including respiratory failure, ARDS, neurologic symptoms, coagulopathy, and shock. This occurs most commonly in children with underlying medical conditions. Some children with severe acute COVD-19 may develop signs of cytokine storm.	Some children may present with persistent fevers and mild symptoms (eg, headache, fatigue). Inflammatory markers may be elevated, but signs of severe multisystem involvement are lacking.	Some children meet criteria for complete or incomplete KD and do not develop shock and severe multisystem involvement.	Children with severe MIS-C have markedly elevated inflammatory markers and severe multisystem involvement. Cardiac involvement and shock are common.

SARS-COV-2 related multisystem inflammation



Bulbar conjunctivitis 89%

Red and crackled lips 54%

Cervical and mesenteric **lymphadenopathies** 60%

Skin rash 57%

Neurological sign 31%

Respiratory signs 34%

Left ventricle dysfunction 100%
- Shock 68%
- VA ECMO 28.6%
- **Coronary dilatation** 17%
- **Pericarditis** 8%

Digestive involvement 83%
- Nausea, diarrhea 83%
- Exploratory laparoscopy 5.7% (2 patients)

Fever >4 days and asthenia 100%
Median age 10 years

Kawasaki disease - Clinical manifestations

1. **Acute phase**

Prolonged unexplained fever; follows prodrome of GIT/ respiratory symptoms poorly responsive to antipyretics with s/s of mucocutaneous inflammation:

- bilateral non-exudative **conjunctivitis**
- erythema of **lips** with cracking and **oral mucosa** with strawberry tongue
- polymorphous **rash** accentuated in the groin region; non bullous
- **extremity changes-** indurated oedema of dorsum hands and feet- last to develop
- **cervical lymphadenopathy –** painless, usually unilateral
- Extreme irritability especially in infants

Laboratory findings

Abnormal Blood counts	
Lymphocytopenia	80-95%
Neutrophilia	80-90%
Mild anaemia	70%
Thrombocytopenia	30-80%
Elevated inflammatory markers	
C reactive protein	90-95%
ESR	80%
D dimers	80-95%
Fibrinogen	90%
Ferritin	75%

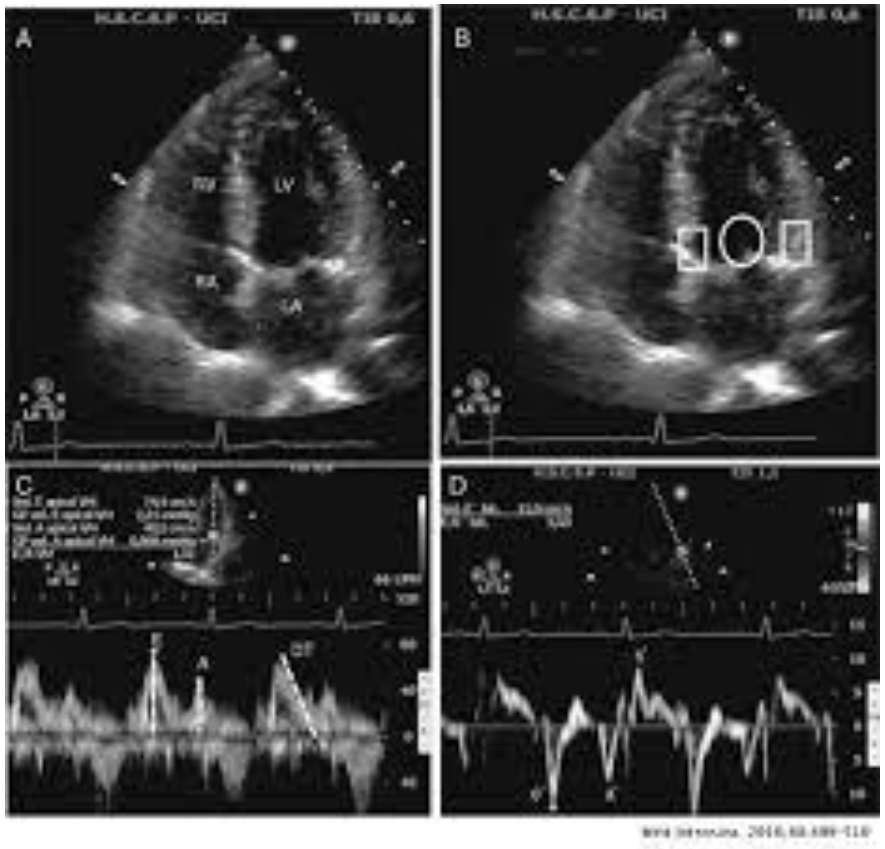
Laboratory findings

Elevated Cardiac markers	
Troponin	60-90%
Brain Naturetic peptide (BNP)	90-100%
Hypoalbuminaemia	73%
Mildly elevated liver enzymes	70%
Elevated LDH	50-60%

Imaging findings

- **Echocardiography**:

- Left ventricular dysfunction – 50-60%
- Mitral regurgitation
- Pericardial effusion



Imaging Findings

- Chest radiograph: Normal, small effusions, patchy consolidation
- Chest CT Scan: similar to CXR, few ground glass
- Abdominal ultrasound: ascites, bowel inflammation

Outline

- Management based on severity
  - Management of mild and moderate disease
  - Management of severe and critical disease including MIS- C
- Agents used in management
  - Supportive vs definitive
  - Approved therapies vs investigational
- Protocol summary

Management: Mild Disease

- Do not require hospitalization
- Provide supportive medication as indicated:
  - Antipyretics such as paracetamol[1]
  - Vitamin C[2] and Vitamin D[4]
  - Zinc[3]
- Encourage adequate hydration
- Explain to parents danger signs
- Use of recombinant monoclonal antibodies (Bamlanivimab or casirivimab plus imdevimab) in patient groups at high risk of disease progression [EUA][4]

1. Interim Guidelines on Management of COVID-19 in Kenya (MOH)
2. Carr C, Rowe S- The Emerging Role of Vitamin C in the Prevention and Treatment of COVID-19, *Nutrients* **2020**, *12*, 3286; doi:10.3390/nu12113286
3. Kumar A, Kubota Y et al- Potential role of zinc supplementation in prophylaxis and treatment of COVID-19 A. *Medical Hypotheses 144 (2020) 109848* https://doi.org/10.1016/j.mehy.2020.109848
4. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 24/01/2020

Moderate Disease

- Require oxygen support- select method of delivery based on patient requirement- target SPO2 92-96%
- Supportive care as above
- Assess for secondary bacterial infection and treat
- Use of remdesivir in those requiring minimal oxygen supplementation
- May consider utilization of dexamthasone in those with rising oxygen requirements (+/- remdesivir)

- COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 24/01/2021
- Recovery Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with COVID-19 - preliminary report. *N Engl J Med*. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32678530.

Severe Disease

- Supportive care as above with addition of PPI
- High flow oxygen and monitor for requirement of invasive ventilation
- Fluid management- conservative
- Manage empirically for bacterial infection, de escalate or stop antibiotics if no evidence of infection.
- Administer dexamethasone or dexamethasone in combination with remdesivir
- Assess coagulation parameters- case by case consideration

- COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 24/01/2021
- Goldenberg NA, Sochet A, Albisetti M, et al; the Pediatric/Neonatal Hemostasis and Thrombosis Subcommittee of the ISTH SSC. Consensus-based clinical recommendations and research priorities for anticoagulant thromboprophylaxis in children hospitalized for COVID-19– related illness. *J Thromb Haemost*. 2020;18:3099–3105. https://doi.org/10.1111/jth.15073

MIS-C Management

- Restrictive fluid management (2/3 of total)
- Use sepsis guidelines to manage suspected sepsis- assess daily and descalate as necessary (collect cultures prior to empiric antibiotics)
- Preferred ionotropes and vasopressors- adrenaline and noradrenaline
- IVIG - 2g/kg
- Glucocorticoids – Methylpred1mg/kg bd- given with IVIG, oral prednisone
- Lifethreatening infection: methylprednisone 30mg/kg max 1 gm
- Assess clotting risk- consider aspirin or enoxoparin prophylaxis
- Low dose aspirin 3-5 mg/kg daily
- PICU: LMWH, therapeutic doses if D Dimers > 10 ULN

- COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 24/01/2021
- COVID-19 and multisystem inflammatory syndrome in children and adolescents- Jiang L et al, https://doi.org/10.1016/S1473-3099(20)30651-4

Special considerations:

- Standard KD therapies – IVIG, aspirin, glucocorticoids if there is persistent inflammation
- Cardiac involvement: IVIG, glucocorticoids, diuretics, inotropes: milrinone, dopamine,dobutamine
- Serial evaluations and ECHO

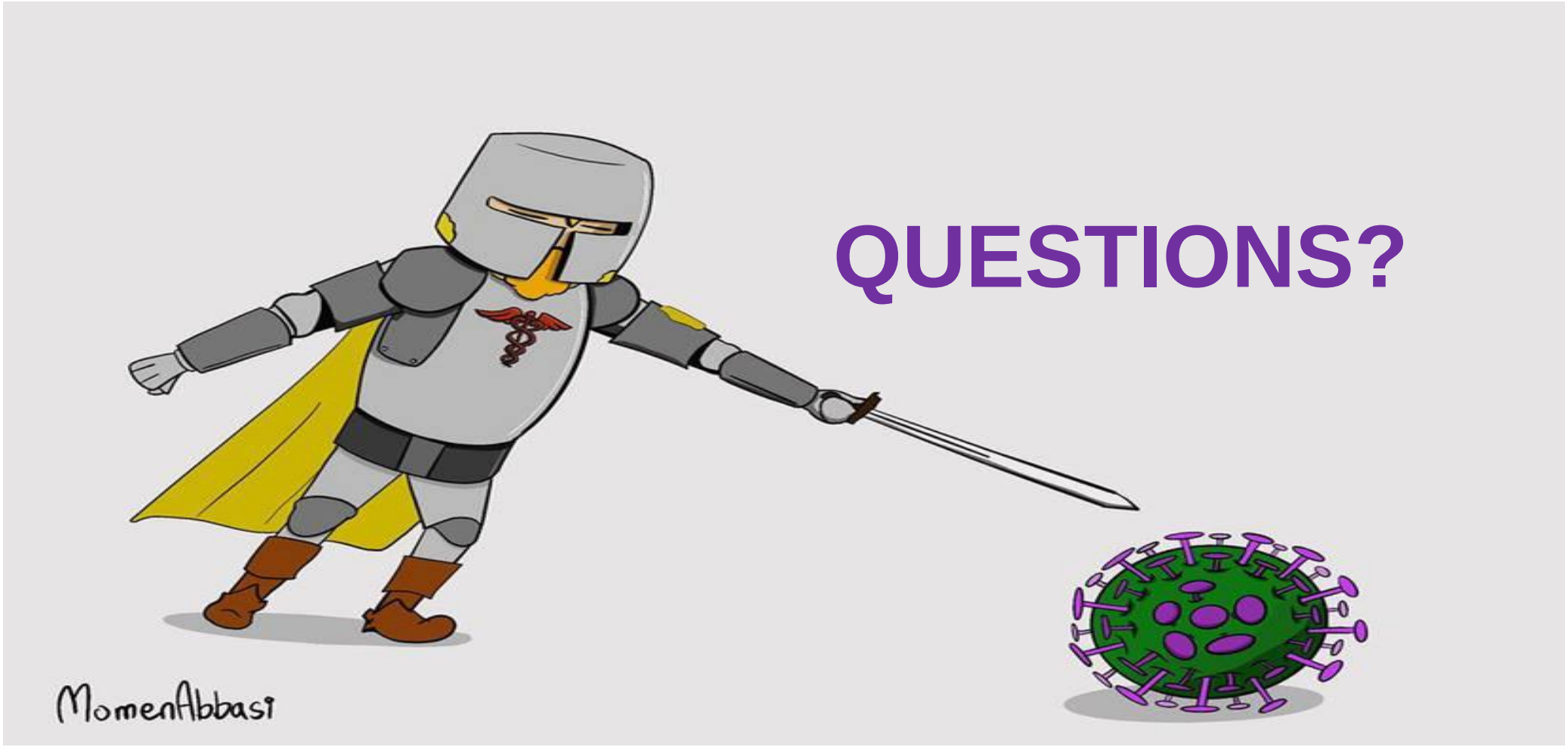
Approved Therapeutic Agents

AGENT	DOSE	DURATION	PROPOSED MoA
REMDESIVIR	**≥3.5 to <40 kg**: 5 mg/kg intravenous (IV) loading dose on day 1, followed by 2.5 mg/kg IV every 24 hours **≥40 kg**: 200 mg IV loading dose on day 1, followed by 100 mg IV every 24 hours	5 days but may extend to 10 if no substantial improvement by D5	prodrug of a nucleotide analog inhibits RNA-dependent RNA polymerase
DEXAMETHASONE	0.15mg/kg/OD max 6mg/day	To D10 or discharge- whichever comes first	Immune modulatory
BAMLANIVIMAB	700 mg IV	Single dose over ≥60 minutes	Monoclonal ab- block viral entry
CASIRIVIMAB PLUS IMDEVIMAB	Casirivimab 1200 mg & imdevimab 1200 mg	single IV infusion over ≥60 minutes	Monoclonal ab- block viral entry

Therapeutic Agents under investigation

AGENT	CATEGORY	COMMENT
Anakinra[1]	IL-1 inhibitor (receptor antagonist)	Insufficient data- only case series available
Sarilumab, tocilizumab[1]	anti-IL-6 receptor monoclonal antibodies	Phase 2 and 3 clincal trials respectively
Siltuximab[1]	anti-IL-6 monoclonal antibodies	Limted unpublished data
Favipiravir[2]	viral RNA-dependent RNA polymerase inhibitor	Multiple ongoing trials
Azithromycin[3]	Binds to 50S ribosomal subunit of susceptible microorganisms.	Ongoing randomised trial for effect in COVID 19 (>18yrs)

1. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 24/01/2021
2. Potential repurposing of Favipiravir in COVID-19 outbreak based on current evidence- Khambholja k, Asudani D, *Travel Medicine and Infectious Disease 35 (2020) 101710*
3. Safety and Effectiveness of azithromycin in Patients with COVID-19 Referred to Zeiaeian Hospital : A clinical trial study- IRCT20200415047092N1


QUESTIONS?
MomenAbbasi