

Treatment of Corona Virus COVID-19 with a More Concise on Pediatric Population

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Abstract

Corona Virus (COVID-19) are a large family of RNA viruses that cause illnesses ranging from the common cold to a more severe disease.

Corona Virus are named for the crown-like spikes on their surface.

There are four main sub-groupings of Corona viruses known as alpha, beta, gamma and delta.

Human corona virus were first identified in the mid-1960s.

Clinical research to learn about the virus, and its management are going.

Keywords: *Coronavirus; RNA Viruses*

Introduction

What is the definition of COVID-19 infection?

A potentially severe acute respiratory infection.

Coronaviruses are a large family of RNA viruses that cause illnesses ranging from common cold to a more severe disease including Croup, Asthma Exacerbations, Bronchiolitis and Pneumonia, also can cause Enteritis or Colitis in neonate and infants and may be under-appreciated as agents of Meningitis or Encephalitis and are named from the crown-like spikes on their surface.

[Coronam is later from Crown]

Four Corona Viruses are endemic in humans: HCoV229E, OC43, NL63 and HKU1 plus two epidemics of previously unknown coronavirus caused significant respiratory distress and high mortality rate, SARS-COV, MERS-COV.

Discussion

Etiology

Corona Virus are enveloped viruses of medium to large size (80-220 nm) that possess the largest known-stranded positive-sense RNA genomes divided into α , β which has a Four Human Pathogens Lineages.

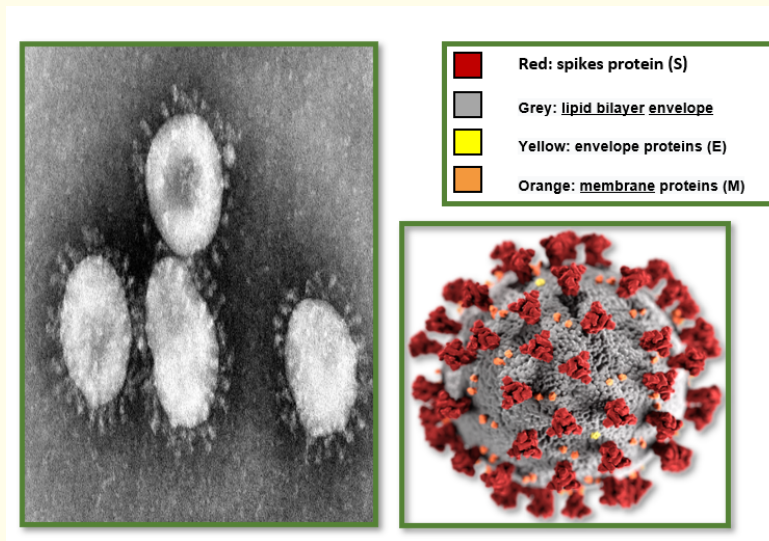
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Linage A, Linage B, Lineage C and D: are exclusively comprised of bat coronavirus.

Also γ coronavirus and Δ coronavirus presently include exclusively a non-human pathogen.

And on the cell we can find a receptor for SRAS-COV like: dipeptidyl peptidase 4, carcinoembryonic antigen-like cell-adhesion molecules and ACE₂.

For coronaviruses there is a possibility of movement between multiple species.



Figure

Epidemiology

Sero prevalence study have demonstrated that by adulthood 90-100% of persons are sero positive to many virus antigens (229E, OC43, NKU1, NL63).

Also, reinfections are common and occur despite the presence of strain-specific antibodies commonly coinfectd with other respiratory viruses including: RSV, Adenovirus, Rhinovirus and Human metapneumovirus.

Transmitted mainly by droplet spread, but aerosol transmission was less common and occurring mainly in the setting of endotracheal intubation, bronchoscopy or treatment with aerosolized medications.

And for SARS transmission occurred almost exclusively during symptomatic disease.

Pathophysiology

SARS COV-2 binds to the angiotensin converting enzyme-2 (ACE-2) receptor in humans and the spike glycoprotein responsible for the entry of the virus into the host cells with high affinity for ACE₂ on host cells, and can cause a down regulations of ACE₂ leading to a toxic over accumulation of plasma angiotensin-II which may induce Acute Respiratory Distress Syndrome and Fulminant Myocarditis.

And based on an analysis of single-cell RNA sequencing datasets, divided from major human physiological systems, the organs considered more vulnerable to SARS-COV2 infection due to their ACE₂ expression levels including the lungs, heart, esophagus, kidneys, bladder and ileum.

The lower expression of ACE₂ in the nasal epithelium of children ages < 10 years compared with adults, may explain why COVID-19 is less prevalent in children however a further research on this is required.

There is also a severe endothelial injury associated with the presence of intracellular virus and disrupted cell membrane, this will identify why there is signs of Pulmonary Artery and Generalized Thrombotic Micro angiography.

A significant new blood vessel growth through intussuscepted angiogenesis distinguishes the pulmonary pathology of COVID-19 from severe Influenza infection.

Endotheliopathy and PLT activation appear to be an important feature of COVID-19 in hospitalized patients and are likely to be associated with coagulopathy, critical illness and death.

Hyperviscosity has a potential comorbid thrombotic events but this need a more research.

Classification

According to WHO and NHI:

- **Mild illness:** People who have any of various signs and symptoms (fever, cough, sore throat, malaise, headache, muscle pain and loss of smell/taste) without shortness of breath, dyspnea and abnormal imaging.
- **Moderate illness:** People who have evidence of lower respiratory disease by clinical assessment or imaging and an O₂ Saturation SpO₂ > 93% on room air at sea level.
- **Severe illness:** People who have RR> 30 breaths per minute, SpO₂ ≤ 93% on room air at sea level, PaO₂ < 300 or lung infiltrates > 50%.
- **Critical illness:** People who have respiratory failure, septic shock and/or multi organ dysfunction.

High risk patients for critical illness:

1. Elderly age > 65 years
2. Underlying end organ dysfunction
3. Diabetes Mellitus "DM"
4. History of cardiovascular disease
5. History of pulmonary disease
6. Immunocompromised
7. Pregnancy.

Treatment

Management of Mild COVID-19

Either suspected or confirmed cases.

A suspected COVID-19 case is defined as:

Patient with acute respiratory illness: (Sudden onset of at least one of the following fever, cough and/or shortness of breath).

plus

An epidemiological link: within 14 days prior to symptom onset.

- a. Had a history of travel abroad, or
- b. Travel to an identified high risk area in the country, or
- c. A close physical contact prior to the symptom onset with a confirmed COVID-19 case, or
- d. Working in health care facility.

Adult patient with severe acute respiratory illness: (ICU admission, ARDS or CURB-65 score ≥ 3 points).

and

All the following conditions fulfilled:

- e. Testing for Influenza and MERS-COV are negative.
- f. Clinical assessment indicating that the patient isn't improving and has no clear underlying causes.

What is CURB-65

Age > 65, C: Confusion, U: BUN > 20 mg/dL, R: RR ≥ 30 breaths/min, B: BP Systolic < 90 mmHg, Diastolic < 60 mmHg.

Place of care

Could be managed at home (home isolation) and discontinue isolation either 10 days after positive test in asymptomatic patient, or 10 days after symptoms onset and at least 3 days without fever or respiratory symptoms (Note that these can differ between countries).

Symptom management

- **Fever and pain:** Paracetamol or Ibuprofen. Ibuprofen should only be taken at the lowest effective dose or the shortest period.
- **Cough:** Advise patient not to lay on his back and we can use one teaspoon of honey in children > 1-year-old, we can consider some anti-cough syrups in severe cases.

Olfactory dysfunction: Often improve spontaneously and doesn't require specific treatment.

For all these symptoms cough and fever or anosmia within 7 days we can use inhaled budesonide (pulmicort).

Adult dose: 800 mcg per actuation (two inhalations) twice a day until symptom resolution.

Supportive care

Good nutrition and appropriate rehydration (too much fluid can worsen oxygenation).

Vitamin C: Has a benefit "Some centers use a high dose IV Vitamin C".

Vitamin D: Some studies showed a link between Vitamin D insufficiency and Covid-19 severity, yet still no recommendations for the use of Vitamin D either for treatment or prophylaxis from Covid-19.

Improve air circulation by opening windows or doors, but don't use fan which can spread infection.

Provide a psychosocial support for all patients.

Monitor

Close monitor for patient with risk factors for severe illness.

Counsel patients about signs and symptoms of deterioration or complications that require prompt urgent care (difficult breathing or chest pain).

Management of moderate COVID-19

Again either suspected or confirmed:

1. **Location of care:** Either home care or in a health care facility stop isolation after 10 days of symptom onset, plus at least 3 days without fever and respiratory symptoms, or the CDC recommend a two negative RT-PCR test on respiratory specimen collected 24 hours apart if a test based strategy is used.

Also apply infection prevention and control measures.

2. **Symptoms management and Supportive care**

- Manage symptoms as above.
- Antibiotics: Consider empirical antibiotics if there is a clinical suspicion of bacterial infection.
- Also considered in older people "particularly those in long-term care facilities".
- And in children less than 5 years old of age.
- Don't stop ACE/ARBs in patient with hypertension, post MI or heart failure.

- Consider favipiravir.
- Adult: 1800 mg/dose twice daily for one day followed by 800 mg/dose twice daily for 7 - 10 days.
- Pediatric: Weight 10 - 15 kg loading one tablet (200 mg) PO, BID for one-day.
- Maximum 400 mg/day.
- From day 2, ½ tablet (100) mg PO, BID.
- Weight 16 - 21 kg loading (400 mg) BID one-day PO.
- Maintenance (200 mg) BID, PO.
- Weight 22 - 35 kg loading (600 mg) BID, one day.
- Maintenance (200 mg) TID.
- Weight 36 - 45 kg loading (800 mg) BID, one-day.
- Maintenance (400 mg) BID.
- Weight 46 - 55 kg loading (1000 mg) BID, one-day.
- Maintenance (400 mg) morning, (600 mg) evening.
- For > 55 kg adult dose if age ≥ 16 years.
- If age < 16 years old use dosing of 46 - 55 kg.
- Favipiravir is contraindicated in:
 - Pregnancy “teratogenic”:
 - Hematopoietic disease such as ↓RBC production.
 - Elevated liver function parameters.
 - Testis toxicity.
- No dose adjustment studied and has many drug interactions.

3. Monitoring: Monitor signs and symptoms of disease progression “especially in home isolation” like difficult breathing or chest pain.

Management of severe COVID-19

Severe disease in children is defined as having clinical symptoms of Pneumonia plus at least one of the following:

1. Central cyanosis or $SpO_2 < 90\%$.
2. Severe respiratory distress: $RR \geq 40$ in children < 5 years.
3. General danger sign.
4. Inability to breastfeed or drink, lethargy or unconsciousness or convulsions.

Location of care: In general, you need to manage the patient in an appropriate healthcare facility under the guidance of a specialist team.

Oxygen: No benefit of O_2 therapy in patient with Covid-19 in absence of Hypoxemia. The target $SpO_2 > 90\%$ in children and non-pregnant adult. And $SpO_2 \geq 92 - 95\%$ in pregnant women.

Nasal prongs or nasal cannula are preferred in young children. Consider positioning technique: high supported sitting, or prone position. Early self-proning of awake, non-intubated patients, has been shown to improve O_2 saturation, and may delay or reduce the need for intensive care.

Symptom management and supportive care:

1. Fluid and electrolyte: Aggressive fluid resuscitation may worsen oxygenation.
2. Fever and pain: Paracetamol and Ibuprofen.
3. Cough: Advise patient to avoid lying on their back as this makes coughing ineffective.

We can use inhaled Budesonide for cough and/or anosmia (as previous).

4. Breathlessness: Keep the room cool, encourage relaxation, changing body position, identify and treat any reversible causes of breathlessness (like Pulmonary Edema).

Also consider a trial of O_2 , or an opioid and benzodiazepine combination in patient with moderate to severe breathlessness or a patient who are distressed.

5. Anxiety, Delirium and Agitation:
 - a. Consider Benzodiazepines for anxiety or agitation that doesn't respond to other measures.

Also, consider Haloperidol or Phenothiazine for the management of delirium.

- b. Provide basic mental health and psychosocial support for all patients, and manage any symptoms of insomnia, depression or anxiety as appropriate.

Venous thromboembolism prophylaxis:

- For adult follow the same protocol as non-covid.
- For children: Covid-19 has no special consideration.

- Pregnant women: should be managed by specialist.
- A routine post-discharge VTE prophylaxis isn't generally recommended except in certain high-risk patients.

Recommendations:

1. Evaluate the patient upon admission and then daily for both thrombotic and bleeding risk.
2. Do baseline CBC, Fibrinogen, PT, aPTT, D-Dimer on admission and then serially.
3. Baseline or surveillance imaging aren't recommended in the absence of clinical symptoms of VTE.
4. Patients on chronic VTE prophylaxis should continue as planned before.
5. Warfarin, DOAC (Dabigatran "Pradaxa^R 110mg", Rivaroxaban, Apixaban and Endoxaban) considered as direct thrombin inhibitor.
6. In case that the use of anticoagulant considered contraindicated we can use a mechanical methods even though it is considered much less effective.
7. Thromboprophylaxis should continue until the time of discharge or the patient becomes asymptomatic.

When to consult hematology?

- In HIT Heparin Induced Thrombocytopenia
- $PLT < 50,000$
- Unexplained bleeding
- Inherited bleeding disorder (Hemophilia-Thrombasthenia)
- Inherited RBC disorder (Sickle Cell Disease)
 - Previously anticoagulant therapy
 - Radiological evidence of thrombosis.

The dose of Enoxaparin in pediatrics as prophylaxis:

- Infant from 1 → <2 months 0.75 mg/kg/dose every 12 hours.
- Infant ≥ 2 months, children and adolescents: 0.5 mg/kg/dose every 12 hours.
- Renal Impairment: No pediatric specific recommendations but with caution and monitor patient closely.

The dose of Enoxaparin in adult as prophylaxis 40 mg SC once daily, but in obesity with BMI >40kg/m² the dose will be 40 mg SC every 12 hours.

In Renal Impairment if CrCl > 30ml/mint: No adjustment required, CrCl < 30 ml/mint: 30mg SC once daily.

In dialysis: not approved but if used, dosage should be reduced and anti-Xa levels frequent monitoring, as accumulation may occur with repeated doses.

In hemodialysis: not dialyzable and supplemental doses isn't necessary.

Enoxaparin monitoring:

- Routine anti-Xa levels isn't recommended.
- If anti-Xa level is deemed necessary it should be drawn 4 - 6 hours after Enoxaparin dose, with an anti-Xa goal of 0.2 - 0.4 unit/ml for prophylaxis and 0.5 - 1 unit/ml for therapeutic dose.

Consider to recheck anti-Xa if the patient experiences active bleeding or has evidence of renal dysfunction while on Enoxaparin therapy.

Contraindications to anticoagulation (Bleeding risk factor):

1. Intracranial hemorrhage, brain ischemia/acute stroke, ongoing uncontrolled bleeding/congenital bleeding disorder.
2. Uncorrected coagulopathy INR > 1.5, aPTT > 40, fibrinogen < 100 g/dl, PLT < 50,000/microliter.

Consider avoiding anticoagulant:

1. Intracranial mass, recent LP/epidural < 24hr ago.
2. The patient is likely to require an invasive procedure within 24 hours of starting Enoxaparin, Neurosurgical procedure, Pelvic Fracture within past 48 hours. Recent Aspirin or anti platelet use < 5 - 7 days ago uncontrolled hypertension.

Antimicrobial

Consider empirical antibiotic, base the regimen on the clinical diagnosis (Community or Hospital Acquired Pneumonia or Sepsis), don't wait for microbiology results, and reassess antibiotic use daily. Continue anti-microbial therapy for up to 5 to 7 days.

Also treat a lab-confirmed co-infection (Malaria-TB-Influenza) as appropriate according to local protocols.

Corticosteroids:

- Consider a low dose Dexamethasone, as Dexamethasone associated with reduced mortality risk in patient with severe Covid-19.
- NICE recommend against using Dexamethasone in patient who don't require supplemental O₂.
- The safety of co administering Dexamethasone and Remdesivir isn't known.
- The duration of Corticosteroid use is up to 10 days, or until discharge or if the patient become asymptomatic.
- The adult dose is 6mg once daily (orally or IV).

- If the patient is on chronic steroid dose, follow the usual recommendation of doubling steroid dose or start stress dose steroid based on clinical patient's condition.

OR

You can use Prednisolone:

- Adult: In pregnant and breastfeeding women Prednisolone or Prednisone 40mg orally BID (twice daily) instead of Dexamethasone.
- Pedia: 1mg/kg/OD orally (maximum 40 mg).

OR

Hydrocortisone:

- Adult: pregnant and breastfeeding women that can't take an orally, can take 80mg, IV, BID.
- Preterm infants with a corrected gestational age of <40 weeks 0.5 mg/kg every 12 hours.
- Methylprednisolone sodium succinate: 0.8 mg/kg/once daily (OD) maximum 32 mg.

Some special recommendations for dexamethasone use:

1. Use with caution in patients with cardiovascular disease or heart failure or ↑BP (can cause fluid retention, electrolyte abnormality and ↑BP).

Follow in acute MI (Can cause myocardial rupture).

2. In DM patient can cause hyperglycemia.
3. GI disease like (Diverticulitis, peptic ulcer, ulcerative colitis). Risk of perforation.
4. Myasthenia gravis: Exacerbation of symptoms.
5. Seizure disorders.
6. Lab work up before use (Hgb, occult blood loss, BP, Serum K⁺, Serum glucose, weight and height in children).
7. Systemic fungal infection (contraindication).
8. Concomitant use of more than single dose of Dexamethasone with Rilpivirine (contraindication).

Experimental therapies:

1. Favipiravir as previous, or
2. Remdesivir.

Adult dosing: 200 mg loading dose (IV, within 30 minutes) followed by 100 mg once daily for 5 to 10 days.

Pediatric dosing: < 40 kg: 5 mg/kg IV load, then 2.5 mg/kg q24hrs for 5 to 10 days, ≥ 40 kg: 200 mg IV load, then 100 mg IV q24hrs for 5 to 10 days.

Exclusion criteria:

- Evidence of multi organ failure.
- Need for inotropes.
- Crea clearance < 30 ml/min.
- Dialysis/hemofiltration.
- Transaminases 5x upper limit of normal.
- Concomitant use of lopinavir/ritonavir.

Monitor

Close monitoring for signs of clinical deterioration.

Discharge and rehabilitation

Routinely assess the patient for mobility, functional swallow, cognitive impairment and mental health and accordingly determine whether the patient is ready for discharge and whether the patient has any rehabilitation and follow up requirements.

Management of critical COVID-19

Location of care: in ICU or PICU under the guidance of specialized team:

1. High flow nasal oxygen or non-invasive ventilation CPAP used in mild “ARDS” either HFNC or CPAP or BiPAP, airborne precautions care recommended for these interventions, but in case of Hypercapnia Hemodynamic instability, multi organ failure or abnormal mental status you should use an invasive ventilation.
2. Mechanical ventilation:

Do endotracheal intubation by an experienced provider using an airborne precautions, use a lung protective strategy [Low TV, Low IP, High Peep in moderate to severe ARDS].

Peep should always be carefully titrated, also consider the use of appropriate sedation and neuromuscular blockade.
3. Inhaled pulmonary vasodilator: In adult with severe ARDS and Hypoxemia despite optimizing ventilation taper off if there is no rapid improvement in oxygenation.
4. ECMO: Not for all patients, only for whom meet certain inclusion criteria.

5. Management of septic shock/sepsis.
6. Symptom management and supportive care:
 - a. Fluid and electrolyte management.
 - b. Antimicrobial treatment (\pm antifungal).
 - c. Fever, pain, cough, breathlessness, anxiety, agitation, delirium, depression, or insomnia as appropriate (see above).
 - d. VTE prophylaxis “LMWH” is the preferred option.
7. Corticosteroids:
 - a. Low dose dexamethasone.
 - b. Surviving sepsis campaign guidelines suggest that adult with ARDS who are receiving MV and adult with refractory shock should receive corticosteroids “although this recommendation is based on weak evidence”.
8. Discharge and rehabilitation: According to estimation of mobility, functional swallow, cognitive impairment and mental health concerns.
9. Palliative care: Follow a local palliative care guideline.
10. Experimental therapies:
 - Consider Remdesivir: as above or in patient with severe ARDS on mechanical ventilation with high settings or ECMO consider Remdesivir and Baricitinib “once available”.
 - For Adult dose: Remdesivir 200 mg loading dose (IV within 30 minutes) followed by 100 mg once, plus Baricitinib 4 mg orally once daily for 5 days.
 - Pediatric dosing for remdesivir:
 - i. < 40 kg: 5 mg/kg/IV load, then 2.5mg/kg q 24hrs.
 - ii. ≥ 40 kg: 200 mg IV load, then 100 mg IV q 24hrs.
 - Pediatric dosing for baricitinib:
 - i. ≥ 9 years: 4 mg orally OD for 5 days.
 - ii. 2 - 9 years: 2 mg orally OD for 5 days.

Some important notes regarding baricitinib:

- Contraindicated in case of hypersensitivity.
- Avoid combination with live vaccines.

- Not recommended in breastfeeding.
- Information related pregnancy is limited.
- Require dose adjustment in patient with renal and liver failure.
- Patient at risk for developing serious infection, malignancies and thrombosis.
- Tablet can be mixed with room temperature water.

Oral dispersion 10 ml, gastrostomy tube 15 ml, NGT 30 ml.

Consider tocilizumab with dexamethasone in rapid respiratory decompensation due to Covid-19.

Criteria for using tocilizumab

1. Within 24 hrs of ICU admission for MV, NIV, or HFNC oxygen.
2. Patient who are exhibiting rapidly increasing O₂ need while on Dexamethasone and have CRP \geq 75 mg/dl (715 nmol/L).

Adult dosing: Single dose of 8 mg/kg of actual body weight “max 800 mg” by IV infusion.

Pediatric dosing: < 18 year:

- < 30 kg 12 mg/kg repeated within 12 hours, for a maximum of 2 doses.
- \geq 30 kg 8 mg/kg “max 800 mg/dose” repeated within 12 hours for maximum of 2 doses.

Before use perform: IL6 and other inflammatory markers, CRP, ferritin and D-dimer.

And also watch for any infusion reaction. Also require dose adjustment in patient with hepatotoxicity.

Tocilizumab considered as an off-label drug for the treatment of Covid-19.

Criteria for patients at high risk for developing cytokine storm [Needs one or more of the following]:

1. Serum IL-6 \geq 3x upper normal limit.
2. Ferritin > 300 mcg/L or “surrogate” with doubling within 24hrs or Ferritin > 600 mcg/L at presentation and LDH > 250.
3. Elevated D-dimer > 1 mcg/ml.
4. Contraindications in:
 - Hypersensitivity and
 - Active infection also fetal risk cannot be ruled out.

Management of pregnant women

- In general, pregnant women should be managed with same supportive therapies taking into account the physiological changes that occur with pregnancy.

One in five pregnant women hospitalized with Covid-19 infection, were admitted to the ICU unit or required urgent delivery due to respiratory deterioration.

Also postpone routine antenatal or postnatal health visits for women who are in home isolation and reschedule them after the isolation period is completed.

- Corticosteroids used for fetal lung maturation haven't been shown to cause more harm in patients with Covid-19.
- Labor and delivery: you have to implement the local infection prevention and control measures "a negative pressure isolation room is recommended if available" with preference of vaginal delivery, also delayed cord clamping is recommended for improved maternal and infant health and nutrition outcome.

It is recommended to isolate these babies from other newborns and test them for infection 24 hrs after birth, and if negative again 48 hrs after birth.

- Newborn care: Consider to separate the mother and baby (recommended by CDC and AAP), but WHO recommends that mother and infant remain together unless the mother is too sick to care for the baby.

Breastfeeding is encouraged while applying appropriate (IPC) measures "hand hygiene" wearing a mask while breastfeeding" WHO advises that the benefits of breastfeeding outweigh the potential risks for transmission.

According to AAP the IPC measures stopped either after 10 days have passed since symptoms first appeared, and they are afebrile for 72 hrs without use of antipyretics, or they have at least "2" consecutive negative SARS-COV₂ test from specimen collected ≥ 24 hrs apart.

Multisystem inflammatory syndrome in children MIS-C associated with COVID-19

Case definition: According to WHO

- Age: 0-19 years.
- Fever: > 38°C for > 3 days.
- Clinical findings and laboratory changes: We need two of the following:
 1. Rash or BIL non purulent conjunctivitis, or mucocutaneous inflammation signs "oral, hand or feet".
 2. Hypotension or shock.
 3. Acute GI problem "diarrhea, vomiting or abdominal pain".
 4. Features of Myocardial dysfunction, pericarditis, valvulitis or coronary abnormalities "including Echo findings, or elevated troponin/NT-proBNP".

5. Evidence of Coagulopathy “by PT, aPTT, elevated D-dimer”

And

Elevated markers of inflammation such as ESR, CRP or procalcitonin

And

No other obvious microbial cause of inflammation including Bacterial Sepsis, Staph or Strep Shock Syndrome

And

Evidence of Covid-19 “RT-PCR, antigen test, or serology positive” or likely contact with patient with Covid-19 within 4 weeks prior to the onset of symptom.

NB₁: Consider this syndrome in children with features of typical or atypical Kawasaki Disease or Toxic Shock Syndrome.

NB₂: Pulmonary involvement in MIS-C is generally mild or non-existent.

Case definition of according to CDC

1. Presence of fever for ≥ 24hrs, > 38°C.
2. Elevated inflammatory markers.
3. Multi organ dysfunction “≥ 2 systems.
Cardiac, Dermatological, GI, Renal, Respiratory, Hematological and/or Neurological”.
4. No plausible alternative diagnosis.
5. Positive viral or Serological testing for SARS-COV₂ or close contact with a person Covid-19 within 4 weeks of symptom onset.

Differential diagnosis of acute Covid-19 and MIS-C

Acute COVID-19	MIS-C
Infectious Causes	
1. Other viral infection “Influenza, Adenovirus, RSV, Rhinovirus	1. Acute Covid-19 or other viral infection “adeno, enterovirus/ coxsackie”
2. Atypical Pneumonia	2. TSS
3. Acute Bacterial Pneumonia	3. Bacterial Sepsis
4. Bacterial Sinusitis	4. Appendicitis
5. Tuberculosis	5. Abdominal Abscess
Non Infectious Causes	
1. Asthma	1. Intussusception
2. Cardiac Dysfunction	2. Myocarditis
3. Hyperglycemia	3. Kawasaki Disease

4. Dehydration	4. Hematological Malignancy
5. DKA	5. Macrophage Activation Syndrome
6. Foreign body	6. Hemophagocytic Lymphohistocytosis
	7. Systemic Juvenile Idiopathic Arthritis
	8. SLE
Chief Concern	
Respiratory Tract Symptoms	Fever with abdominal pain and/or rash

Echocardiography and ECG

ECG:

- Prolonged QT interval.
- Aspect of acute coronary syndrome.
- Nonspecific changes in the ST segment “Diffuse ST elevation”.
- Prolonged PR and elevation or depression of ST, “indicative of severity and worse prognosis”.
- Ventricular arrhythmias.

Echo:

- Dysfunction.
- Hypo contractility, general or segmental absence of contractility in the myocardial chambers, both indicative of severity and worse prognosis.
- Myocarditis 76%, Pericardial Effusion 48%, drop in LVEF drop, coronary abnormalities 38%:
 - More pronounce brilliance.
 - Dilation without identification of aneurysm.

Treatment:

1. Supportive treatment like O₂ supplement, ventilator, cardiovascular and renal support, which doesn’t differ from other situation.
2. Antibiotic administration can’t be delayed due to the possibility of TSS.
3. IV IG intravenous human immunoglobulin:
 - a. Dose 2 g/kg, associated with a better prognosis.
 - b. Act as an anti-inflammatory agent, with cytokine production modulation, neutralization of toxins and other pathogens, and increased regulatory activity of T cell.

4. Corticosteroids:

- a. The use of IV IG and corticosteroids in Kawasaki Disease with reduced risk of Coronary Aneurysm compared to isolated IV IG therapy.
- b. European Consensus of Kawasaki Disease recommend the use of corticosteroids and IV IG in:
 - i. Resistance to IV IG.
 - ii. Presentation as HLH hemophagocytic lympho histocytosis.
 - iii. Presence of shock.
 - iv. Evidence of coronary and/or peripheral aneurysm.
 - v. Age < 1 year.
 - vi. Kobayashi score ≥ 4 .

Methylprednisolone 1.6 - 2 mg/kg/day ÷ 12 hourly for 5 - 7 days, max 30 mg for 12 hours.

Or Methylprednisolone bolus 30 mg/day for 3 days.

Or Prednisone, Prednisolone 1 - 2 mg/kg/day.

Or Dexamethasone 5 mg/m² daily.

IL-6 inhibitors

- Tocilizumab: A monoclonal antibody binds directly to the IL6 receptor so there is a reduction in cytokine production can cross the BBB and release a PGE₂ and this will trigger an increase in temperature.
- Otocilizumab: Approved in adult and children with autoimmune diseases associated with cytokine release syndrome.

IL-1 inhibitors

Anakinra: Are combination IL-1 receptor antagonist, considered in the treatment of MIS-C that is refractory to IV IG and corticosteroids.

TNF inhibitors "Infliximab"

TNF is one among the factors that trigger the cytokine storm.

Medication with antiviral activity like Remdesivir.

Acetyl salicylic acid "MIS-C with Kawasaki-like criteria":

- 30 - 50 mg/kg/day as an anti-inflammatory effect till fever subsided.

- 3 - 5 mg/kg/day as an anti-platelet effect indicated 48 hours after fever defervescence and should be maintained for 6 - 8 weeks in case there are no coronary change, and some authors have suggested the continuous use of ASA in patient with coronary abnormalities to prevent thrombosis.

Anticoagulation:

- Clinical studies demonstrate that 20 to 55 % of hospitalized patients show laboratory evidence of coagulopathy: elevated D-dimer, prolonged PT time, mild thrombocytopenia, and/or decreased fibrinogen.

Also there is an evidence that a high D-dimer level is associated with a worse prognosis and increased mortality rate.

- The use of anticoagulant in Pediatrics should be individualized with early hematological consultation.
- The most common drug is Enoxaparin.

Dose	Prophylaxis dose	Treatment
Under 2 months	0.75 mg/kg/dose SC 12 hourly Or 1.5 mg/kg/dose SC 24 hourly	1.7 mg/kg/SC every 12 hourly
Over 2 months	0.5 mg/kg/dose SC 12 hourly Or 1 mg/kg/dose SC 24 hourly	1 mg/kg/SC every 12 hourly

NB₁ if CrCl 30 - 80 ml/min No dose adjustment necessary.

If CrCl < 30 ml/min reduce the usual dose by 50%.

NB₂ LMWH doesn't cross the placenta so there is no increase in fetal bleeding or teratogenic effects.

ECMO

In patient with Hypoxemia and refractory Hypercapnia, Septic and/or Cardiogenic shock refractory to vasoactive drug, and failure of single organ with minor comorbidity ECMO used only in 5 - 12.5% with MIS-C only, so the true impact of therapy isn't yet possible [1-5].

Conclusion

There are currently no drugs licensed for the treatment or prevention of Covid-19 and also you have to know that vitamin and mineral supplements cannot cure Covid-19 and fortunately most people who get Covid-19 recover from it.

And lately, the health care workers are the greatest hero in this story, your intelligence, bravery and compassion are the saving grace of this nation during this dark episode.

Thank you for your service to humanity.

Important Notice

All information mentioned here are up to date 5/5/2021, and due to rapid change in our understanding of the disease and its pathophysiology. So, I advise the reader to be updated with these changes.

The new Saudi Protocol (19/08/2021) said:

- If Tocilizumab IV isn't available, use Subcutaneous 162mg injection.
If BW <100kg use 342 mg (162x2 injections)
If BW ≥ 100kg use 486 mg (162x3 injections)
- For mild to moderate non hospitalized ≥ 12 years of age patient at high risk of clinical progression.

Treatment should start after PCR and within 10 days of symptom onset

(when available)

Gasirivimab 600mg +Imdevimab 600mg: Iv Infusion once for patient weight ≥ 40kg

In case there is no IV line or would cause a delay in treatment

Gasirivimab 600mg + Imdevimab 600mg: SC in four doses 2.5 ml per injection

or

Consider Sotrovimab 500mg IV infusion once for patient weight ≥ 40kg

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