Saudi MoH Protocol for Patients Suspected of/Confirmed with COVID-19

Supportive care and antiviral treatment of suspected or confirmed COVID-19 infection

(Version 3.7) September 29th, 2022

Disclaimer: This is a living guidance that is subject to change as more evidence accumulates. It will be updated regularly and whenever needed. The guidance should be used to assist healthcare practitioners select the best available pharmacotherapy for COVID-19 infection according the best available and current evidence and is not intended to replace clinical judgement but rather to complement it. The evidence is inconclusive regarding the efficacy of most medications for covid-19. It is important to explain this to patient and family and obtain informed consent for use of these medications for unapproved indications. Convalescent plasma transfusion should only be used according to an approved study protocol

COVID-19 Testing*	Category	Supportive Care	Pharmacotherapy	Precautions
Suspicious Cases (follow case definition published in Saudi CDC guideline)	**Mild to Moderate:** Symptoms with no shortness of breath	– Treat symptoms – If no hospital admission required, need to follow instructions and recommendations published by Saudi CDC https://covid19.cdc.gov.sa/professionals-health-workers/	– Not required – Do not stop ACEI/ARBs in patients with hypertension, post-MI, or heart failure	– Paracetamol (acetaminophen) is the prefered agent for pain/fever see below table *"Medication Related Information"* – Labs and work-up: CBC, Urea/Electrolytes, Creatinine, CRP, LFTs, Chest X-ray, COVID-19 PCR tests
	Mild to Moderate: Symptoms with no shortness of breath in high-risk patients[$]	– Treat symptoms – If hospital admission is not required, follow instructions and recommendations published by Saudi CDC https://covid19.cdc.gov.sa/professionals-health-workers/ – Consult Infectious Disease Specialist	– Case shall be discussed with infectious disease specialist, to initiate empirical antiviral therapy, while awaiting PCR result. – Do not stop ACEI/ARBs in patients with hypertension, post-MI, heart failure *If decision is to treat empirically, follow the treatment option under confirmed by PCR*	
	Mild to Moderate: Symptoms with shortness of breath in high-risk patients[$]			
PCR Confirmed Cases	**Asymptomatic**	– Follow instructions and recommendations published by Saudi CDC https://covid19.cdc.gov.sa/professionals-health-workers/	– Not required	

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PCR Confirmed Cases	**Mild to Moderate:** Symptoms (no O_2 requirements/no evidence of pneumonia but with other symptoms of covid-19 e.g., fever) – Inclusion criteria for using oral antiviral: 1. Aged ≥12 years, weighing at least 40 kg (for paxlovid) 2. At high risk for progression to severe COVID-19 (e.g., hospitalization or death) 3. Within 5 days of symptoms onset – Exclusion criteria for using oral antiviral 1. Age < 12 years (for paxlovid) 2. Weighing < 40 kg (for paxlovid) 3. History or current need for hospitalization/immediate medical attention in a clinic/emergency room service due to COVID 4. Not to be used for more that 5 days – Inclusion criteria for using Anti-SARS-CoV-2 Monoclonal Antibodies should only be used in patients with high risk for progression to severe COVID-19 and/or hospitalization. These include: 1. Confirmed documented positive PCR ≤ 3 days prior to Day 1 2. Within 7 days of symptom onset 3. ≥ 1 of signs and symptoms of COVID-19 within 24 hours prior Day 1 4. ≥ 1 of following risk factors: Aged ≥65 years, obesity (BMI >35), end-stage renal failure, sickle cell anemia, immunocompromising condition (or chronic immunosuppressive treatment), and/or age 55 – 65 years (with cardiovascular disease, hypertension, diabetes, or COPD). 5. Blood oxygen saturation ≥ 92% obtained at rest by attending physician within 24 hours – Exclusion criteria for using Anti-SARS-CoV-2 Monoclonal Antibodies: 1. Age < 18 years 2. History or current need for hospitalization/immediate medical attention in a clinic/emergency room service due to COVID 3. Receipt of COVID-19 vaccination any prior time 4. Received convalescent plasma treatment at any prior time 5. Receipt of systemic steroid or inhaled steroid within 30 days, unless a stable dose is used for chronic condition 6. Pregnant or breastfeeding females 7. Previous hypersensitivity, infusion related reaction, or adverse reaction to any monoclonal antibodies	– Treat symptoms – Follow instructions and recommendations published by Saudi CDC https://covid19.cdc.gov.sa/professionals-health-workers/	**In case of new onset cough and fever or anosmia, or both) within 7 days** – Consider inhaled budesonide (Pulmicort®) ○ Adult Dosing: 800 µg per actuation (two inhalations) twice a day until symptom resolution **For non-hospitalized patients at high risk of disease progression** – Consider ritonavir-boosted nirmatrelvir (Paxlovid) ○ ≥12 years and weighing ≥40 kg: nirmatrelvir 300 mg plus ritonavir 100 mg (oral) twice daily for 5 days.	**Inhaled budesonide (Pulmicort®)** see below table *"Medication Related Information"* – Bronchospasm, oral candidiasis, and vasculitis **Ritonavir and Nirmatrelvir (non-formulary)** see below table *"Medication Related Information"* – Patients treated with Ritonavir and Nirmatrelvir are at risk of hepatic effects and renal impairment – Patients on other ritonavir- or cobicistat-containing regimens, with HIV or hepatitis C virus taking ritonavir- or cobicistat-containing regimens should continue those regimens as indicated – Risk of HIV-1 protease inhibitor drug resistance – Check statins interaction management under medication related information **Anticoagulation** see below "*Thromboprophylaxis*"

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PCR Confirmed Cases	**Severe:** Clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) **and** one of the following: – Respiratory rate >30/min (adults); ≥40/min (children < 5 years) – Blood oxygen saturation <93% on room air – Severe respiratory distress	– Treat symptoms – Follow instructions and recommendations published by Saudi CDC https://covid19.cdc.gov.sa/professionals-health-workers/ – ICU admission, decision by ICU treating team – Antibiotics and antifungals according to local antibiogram and institutional pneumonia management guidelines/ pathways.	**Systemic Corticosteroids use:** – For all patients who require supplemental oxygen inlcuding (but not limited to) those requiring non-invasive and invasive ventilation. – To be used up to 10 days, until discharged, or if patient becomes asymptomatic. – Dexamethasone (Preferable Systemic Corticosteroids): ○ Adult Dosing: 6 – 12 mg once daily oral (liquid or tablet) or intravenous preparation. Patients on chronic steroids, follow the usual recommendation of doubling steroids dose or start stress dose steroids based on clinical case basis on patients' condition **OR** – Prednisolone/ Prednisone ○ Adult Dosing: In pregnant or breastfeeding women, prednisolone/ Prednisone 40 mg PO twice daily should be used instead of dexamethasone. ○ Pediatric Dosing: Prednisolone/ Prednisone (Oral/NG): 1 mg/kg once daily (max: 40 mg) **OR** – Hydrocortisone ○ Adult Dosing: In pregnant or breastfeeding women that cannot take oral, IV hydrocortisone 80 mg twice daily should be used instead of dexamethasone. ○ Preterm infants with a corrected gestation age of <40 weeks: 0.5 mg/kg every 12 hours **OR** Methylprednisolone sodium succinate (IV): 0.8 mg/kg once daily (max: 32 mg) **Consider starting any of the following according to clinical evaluation and treating consultant's discretion:** – Consider Remdesivir (Start as early as possible) ○ Adult Dosing: 200 mg loading dose (IV, within 30 min), 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 q24h for 5 to 10 days • ≥40 kg: 200 mg IV load, then 100 mg IV q24h for 5 to 10 days	**Systemic Dexamethasone** see below table *"Medication Related Information"* – Cardiovascular disease: Use with caution in patients with heart failure and/or hypertension; use has been associated with fluid retention, electrolyte disturbances, and hypertension. Use with caution following acute myocardial infarction; corticosteroids have been associated with myocardial rupture. – Diabetes: Use corticosteroids with caution in patients with diabetes mellitus; may alter glucose production/regulation leading to hyperglycemia. – Gastrointestinal disease: Use with caution in patients with GI diseases (diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, ulcerative colitis, abscess or other pyogenic infection) due to perforation risk. – Myasthenia gravis: Use with caution in patients with myasthenia gravis; exacerbation of symptoms has occurred especially during initial treatment with corticosteroids. – Seizure disorders: Use corticosteroids with caution in patients with a history of seizure disorder; seizures have been reported with adrenal crisis. Labs and workup: Hemoglobin, occult blood loss, blood pressure, serum potassium, glucose, weight, and height in children; HPA axis suppression **Remdesivir (non-formulary)** see below table *"Medication Related Information"* – Exclusion criteria evidence of multiorgan failure, need of inotropes,

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PCR Confirmed Cases			**In case of corticosteroids contraindication:** – Consider Remdesivir and Baricitinib (once available) ○ Adult Dosing: Remdesivir 200 mg loading dose (IV, within 30 min), followed by 100 mg once Plus Baricitinib 4 mg (oral) once daily for 5 days. ○ Pediatric dosing for Remdesivir • <40 kg: 5 mg/kg IV load, then 2.5 mg/kg q24h • ≥40 kg: 200 mg IV load, then 100 mg IV q24h Plus ○ Pediatric dosing for Baricitinib • ≥ 9 years: 4 mg (oral) once daily for 5 days. • 2 - 9 years: 2 mg (oral) once daily for 5 days.	Creatinine clearance < 30 ml/min, dialysis/hemofiltration, transaminases > 5X ULN, or concomitant use of lopinavir/ritonavir **Baricitinib** see below table *"Medication Related Information"* – Patients treated with baricitinib are at risk for developing serious infections, malignancies, and thrombosis **Anticoagulation** see below "*Thromboprophylaxis*"
	Critical: – Symptoms of the following: ○ ARDS ○ Respiratory failure requiring ventilation ○ Sepsis ○ Septic Shock – Criteria for using tocilizumab: 1. Within 24 hours of ICU admission for MV, NIV, or HFNC oxygen 2. Patients who are exhibiting rapidly increasing oxygen needs while on dexamethasone and have a C-reactive protein level ≥75 mg/L (715 nmol/L).	– Treat symptoms – Follow instructions and recommendations published by Saudi CDC https://covid19.cdc.gov.sa/professionals-health-workers/ – ICU admission and management by ICU treating team – Antibiotics and antifungals according to local antibiogram and institutional pneumonia management guidelines/ pathways.	**Systemic Corticosteroids use:** • For all patients who require supplemental oxygen inlcuding (but not limited to) those requiring non-invasive and invasive ventilation. • To be used up to 10 days, until discharged, or if patient becomes asymptomatic. • Dexamethasone (Preferable Systemic Corticosteroids): ○ Adult Dosing: 6 – 12 mg once daily oral (liquid or tablet) or intravenous preparation. Patients on chronic steroids, follow the usual recommendation of doubling steroids dose or start stress dose steroids based on clinical case basis on patients' condition **OR** • Prednisolone/ Prednisone ○ Adult Dosing: In pregnant or breastfeeding women, prednisolone/ Prednisone 40 mg PO twice daily should be used instead of dexamethasone. ○ Pediatric Dosing: Prednisolone/ Prednisone (Oral/NG): 1 mg/kg once daily (max: 40 mg) **OR** • Hydrocortisone ○ Adult Dosing: In pregnant or breastfeeding women that cannot take oral, IV hydrocortisone 80 mg twice daily should be used instead of dexamethasone. ○ Preterm infants with a corrected gestation age of <40 weeks: 0.5 mg/kg every 12 hours	**Systemic Dexamethasone**: *(see precautions above)* **Remdesivir (non-formulary)** *(see precautions above)* **Baricitinib (non-formulary)** *(see precautions above)* **Tocilizumab** see below table *"Medication Related Information"* – Should perform IL6 and other inflammatory markers testing prior to start (CRP, Ferritin, D-dimer) – Watch for infusion reaction – Do not initiate if ANC is <2,000/mm^3, platelets are <100,000/mm^3, or if ALT or AST are >1.5 times ULN. – Interrupt therapy if a patient develops a serious infection until the infection is controlled. **Anticoagulation** see below "*Thromboprophylaxis*"

COVID-19 Testing*	Category	Supportive Care	Pharmacotherapy	Precautions
PCR Confirmed Cases			**OR** • Methylprednisolone sodium succinate (IV): 0.8 mg/kg once daily (max: 32 mg) **Consider starting any of the following according to clinical evaluation and treating consultant's discretion:** – Consider Remdesivir (start as early as possible) ○ Adult Dosing: 200 mg loading dose (IV, within 30 min), 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 q24h for 5 to 10 days • ≥40 kg: 200 mg IV load, then 100 mg IV q24h for 5 to 10 days **For patients with severe ARDS on MV with high settings or ECMO or corticosteroids contraindication.** – Consider Remdesivir and Baricitinib (once available) ○ Adult Dosing: Remdesivir 200 mg loading dose (IV, within 30 min), followed by 100 mg once Plus Baricitinib 4 mg (oral) once daily for 5 days. ○ Pediatric dosing for Remdesivir • <40 kg: 5 mg/kg IV load, then 2.5 mg/kg q24h • ≥40 kg: 200 mg IV load, then 100 mg IV q24h Plus ○ Pediatric dosing for Baricitinib • ≥ 9 years: 4 mg (oral) once daily for 5 days. • 2 - 9 years: 2 mg (oral) once daily for 5 days. **If rapid respiratory decompensation due to COVID-19, consider tocilizumab with dexamethasone** ○ Adult Dosing: - Single dose of tocilizumab 8 mg/kg of actual body weight (maximum 800 mg) by IV infusion in combination with dexamethasone 6 – 12 mg daily for up to 10 days - **If Tocilizumab IV is not available**, use subcutaneous 162mg (a dose of 324 mg as two simultaneous 162 mg injections (< 100 kg bodyweight) or 486 mg (as three simultaneous 162 mg injections) (≥100 kg bodyweight. ○ Pediatric Dosing (<18 years): • <30 kg: 12 mg/kg repeated within 12 hours for maximum of 2 doses • ≥30 kg: 8 mg/kg (max: 800 mg/dose) repeated within 12 hours for maximum of 2 dose	

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NOTES:

Criteria for patients at high-risk for developing cytokine storm (1 or more of the following):
- Serum IL-6 ≥3x upper normal limit
- Ferritin >300 ug/L (or surrogate) with doubling within 24 hours
- Elevated D-dimer (>1 mcg/mL)
- Ferritin >600 ug/L at presentation and LDH >250
- CRP > 75 mg/L

Tocilizumab is registered medications in Saudi Arabia and available in MoH formulary for other indications but have not shown proven efficacy in many randomized clinical trials as of yet and their use in this setting is considered off-label. Remdesivir, and paxlovid, are conditionally registered by SFDA.

Pregnancy and Lactation: Management of infection with SARS-COV2 in pregnancy is mainly based on supportive care. Consideration of antiviral therapy should be based on patient condition, safety profile and preference of the patient and treating team. Refer to the MoH COVID-19 guidance in pregnancy

Thromboprophylaxis:

Recommendations

- All admitted patients should be evaluated upon admission, and daily thereafter for both thrombotic and bleeding risk.
- Laboratory evaluation and monitoring: Baseline CBC, fibrinogen, PT, aPTT, D-dimer on admission, and serially.
- Baseline or surveillance imaging are not recommended in the absence of clinical symptoms of VTE
- Patients on chronic VTE prophylaxis should continue as planned before.
- Warfarin, DOAC and antiplatelet medications are not recommended to be used as prophylaxis
- For patients whom anticoagulant therapy is contraindicated, mechanical thromboprophylaxis, preferably with intermittent pneumatic compression devices, should be utilized, although there is limited evidence of efficacy in hospitalized medically ill patients
- Thromboprophylaxis should continue until the time of discharge at least. Continuation of anticoagulation is subject to assessment of VTE risk by the treating medical team.
- Heparin induced thrombocytopenia (HIT)
- Platelets below 50 x 10^9/L
- Unexplained bleeding
- Inherited bleeding disorder (Hemophilia, thrombasthenia)
- Inherited red blood disorder (sickle cell disease)
- Previously on anticoagulation therapy
- Radiological evidence of thrombosis

Adults:

- Therapeutic doses should not be offered because of the risk of bleeding
- Thromboprophylaxis with low molecular weight heparin (LMWH) should be considered in ALL patients (including non-critically ill) within 24 hours of hospital admission for COVID-19 infection, in the absence of any contraindications (active bleeding and platelet count less than 25 x 109/L; monitoring is advised in severe renal impairment; abnormal PT or APTT is not a contraindication)
- Enoxaparin prophylaxis doses:
  - 40 mg subcutaneously once daily
  - Obesity BMI > 40 kg/m^2: 40 mg subcutaneously every 12 hours
  - Pregnancy: 40 mg subcutaneously once daily
  - Renal impairment:
    - CrCl ≥ 30 mL/minute: no adjustments required
    - CrCl < 30 mL/minute: 30 mg subcutaneously once daily
  - Hemodialysis and CRRT: Avoid use if possible but If used, anti-Xa levels should be frequently monitored, as accumulation may occur with repeated doses.
- Patients with Heparin-induced thrombocytopenia (HIT), please follow MoH HIT protocol for alternative anticoagulation.
- In high-risk patients (VTE score of ≥4 or 2–3 with a D-dimer >500 ng/mL) after hospital discharge, apixaban 2.5 mg twice a day **OR** rivaroxaban 10 mg/day (NOT available in MOH formulary) for 35 days should be considered.

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Pediatrics:

- Enoxaparin prophylaxis doses:
  - Infants 1 - < 2 months: 0.75 mg/kg/dose subcutaneously every 12 hours
  - Infants ≥ 2 months, children, and adolescents: 0.5 mg/kg/dose subcutaneously every 12 hours
  - Renal impairment: No pediatric specific recommendations (use with caution and monitor patient closely.
  - Dialysis: not approved but If used, dosages should be reduced and anti-Xa levels frequently monitored, as accumulation may occur with repeated doses.
  - Hemodialysis: Not dialyzable and supplemental dose is not necessary.

Enoxaparin monitoring

- Routine anti-Xa levels are not recommended.
- If an anti-Xa level is deemed necessary, it should be drawn 4-6 hours after enoxaparin administration with an anti-Xa goal of 0.2- 0.4 units/mL for prophylaxis and 0.5-1 Units/ml for therapeutic dose.
- Consider re-checking anti-Xa if the patient experiences active bleeding or has evidence of renal dysfunction while on enoxaparin therapy

Contraindications to Anticoagulation (Bleeding Risk Factors)

- Intracranial hemorrhage, Brain ischemia/acute stroke, ongoing and uncontrolled bleeding /hematoma, congenital bleeding disorder
- Uncorrected coagulopathy: INR >1.5, APTT >44 seconds, fibrinogen <100 g/dL, or platelet <50,000/microliter

Consider Avoiding Anticoagulation

- Intracranial mass, Recent lumbar puncture / Epidural (<24 hours ago), 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 antiplatelet use (<5-7 days ago), Uncontrolled hypertension

Multisystem Inflammatory Syndrome in Children (MIS-C)

Clinical features

May include one or more of the following:

- Fever: Usually 3 -5 days, but fewer days have been reported
- Neurocognitive symptoms: such as lethargy, Headache, irritability and confusion
- GI symptoms: such as abdominal Pain, Diarrhea and Vomiting
- Rash/Conjunctivitis/mucous membranes involvement
- Cardiorespiratory symptoms: such as hypotension, cardiac involvement, tachypnea and labored breathing. Cough is uncommon.

Laboratory/Imaging findings

- Abnormal CBC: lymphocytopenia, Neutrophilia, Mild anemia and 7hrombocytopenia
- Elevated inflammatory markers: CRP, ESR, D-Dimer, Fibronogen, Ferritin, Procalcitonin, Interlukin-6 (IL-6)
- Elevated cardiac markers: Troponin and N-terminal pro-BNP (NT-pro-BNP)
- Hypoalbuminemia, Mildly elevated liver enzymes, elevated LDH and triglycerides
- Chest x-ray or CT: Usually normal. Abnormal findings include pleural effusions, consolidation or atelectasis.
- Abdominal US or CT: ascites, and bowel and mesenteric inflammation including terminal ileitis, mesenteric adenopathy/adenitis, and pericholecystic edema

Criteria for Management:

All 4 criteria must be met:

- Patient aged < 21 years presenting with fever (>38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours)
- laboratory evidence of inflammation (Including, but not limited to, one or more of the following: an elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, or IL-6; elevated neutrophils; reduced lymphocytes; and low albumin), and evidence of clinically severe illness requiring hospitalization, with multisystem (at least 2) (a) Rash, conjunctivas, mucositis, swollen hands, or feet; (b) Hypotension or shock; (c) Coagulopathy; (d) Acute GI symptoms (diarrhea, vomiting, abdominal pain)
- No alternative plausible diagnoses
- 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

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Management:

There are no established therapies for COVID-19-associated CSS or MIS-C. These medications are to be used only with guidance from Rheumatology, Cardiology and Infectious Diseases. Patients who are being evaluated for immunomodulatory therapy should also be considered for antiviral therapy if they are not already receiving it.

- Supportive Care: Children with moderate to severe signs and symptoms should be admitted to the hospital. Admission to a pediatric intensive care unit is appropriate for children with hemodynamic instability (shock, arrhythmia), significant respiratory compromise, or other potentially life-threatening complications
  - If signs of shock, fluid resuscitation 10 ml/kg normal saline
  - If no improvement with fluid, start inotropes according to local ICU protocol.
  - If sepsis cannot be ruled out, start broad spectrum antibiotics according to local ICU protocol.
- Thromboprophylaxis
  - All patients with MIS-C should receive low-dose aspirin (3 to 5 mg/kg daily)
  - Patients with current or prior VTE should receive LWMH (therapeutic dose of 1 mg/kg/dose subcutaneously every 12 hours)
  - Patients with severe LV dysfunction should receive therapeutic anticoagulation (EF ≤ 30 %) if no contraindication (e.g., no thrombocytopenia, bleeding diathesis, or active bleeding)
  - Patients with other severe MIS-C manifestations requiring PICU care should be on therapeutic anticoagulation if no contraindication (e.g., severe cases include D-Dimer >10 times upper limit of normal)
- Antiviral therapy (see above based of patient category)
- Immunomodulator Dosing and Monitoring

Immunomodulator	Dosing	Safety monitoring
IVIG with methylprednisolone see below table *"Medication Related Information"* MIS-C with or without features of Kawasaki disease or signs of myocardial dysfunction OR Severe or critical COVID-19 with evidence of CSS	- IVIG 2 g/kg + methylprednisolone at 0.8 to 1 mg/kg every 12 hours (maximum of 30 mg for 12 hours) for 5 days - IVIG 2 g/kg + methylprednisolone bolus of 15 to 30 mg/kg/d for 3 days	- Assess cardiac function and fluid status prior to giving to avoid fluid overload - Baseline renal function tests, urine output, IgG level, CBC - Monitor clinically for signs of hemolysis after first dose - Potential adverse reactions: anaphylaxis, - Infusion reaction, hemolysis, transaminitis, aseptic meningitis - Pulmonary adverse reactions; blood pressure (prior to, during, and following infusion); clinical response. - For patients at high risk of hemolysis (dose ≥2 g/kg, given as a single dose or divided over several days, and non-O blood type): Hemoglobin or hematocrit prior to and 36 to 96 hours post-infusion and again at 7 to 10 days post-infusion
Glucocorticoids MIS-C with features of shock or coronary artery dilation/aneurysm OR Severe or critical COVID-19 with evidence of CSS	- 1-2 mg/kg/day divided BID (prednisone, prednisolone, methylprednisolone) - 5 mg/m2 daily (dexamethasone)	- (See precautions above)
Intensification Immunomodulatory Therapy (for children with refractory MIS-C who do not improve within 24 hours of initial immunomodulatory therapy) Infliximab with higher-dose glucocorticoids	- 10 to 30 mg/kg/day methylprednisolone (or an equivalent corticosteroid) for 1 to 3 days + infliximab 5–10 mg/kg/day as single injection	- Latent tuberculosis screenings prior to initiating and during therapy - Signs/symptoms of infection - Hepatitis B virus screening prior to initiating - Signs and symptoms of hypersensitivity reaction - Symptoms of malignancy

Abbreviations:

ANC: Absolute neutrophil count, ARDS: Acute respiratory distress syndrome, COVID-19: Coronavirus Disease 2019, CBC: Complete Blood Count, CRP: C-Reactive Protein, ECMO: Extracorporeal Membrane Oxygenation, IL6: Interleukin 6, LFT: Liver Function Test, PCR: Polymerase Chain Reaction, ECG: Electrocardiogram, G6PD: Glucose-6-Phosphate Dehydrogenase, ACEI: Angiotensin-converting enzyme inhibitors, ARBs: Angiotensin II receptor

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blockers, MI: Myocardial infarction, MIS-C: Multisystem Inflammatory Syndrome in Children, CSS: Cytokine Storm Syndrome, mechanical ventilation (MV), noninvasive mechanical ventilation (NIV), high-flow nasal canula (HFNC), VTE : venous thromboembolism				
Footnotes: *Testing for SARS-COV2 virus shall be performed in accordance with published case definition by Saudi CDC guidelines. $High risk patients have one or more: 1. Elderly (age > 65 years), 2. With underlying end organ dysfunction, 3. Diabetes, 4. History of cardiovascular disease, 5. History of pulmonary disease, 6. Immunocompromised, and/or 7. Pregnancy				

Medication Related Information

Medication	Contraindication	Major Drug Interactions	Required dose adjustment	Pregnancy and Lactation
Baricitinib	– Hypersensitivity to Baricitinib or any component of formulation	– Need therapy modification and monitoring:5-Aminosalicylic Acid Derivatives, Chloramphenicol (Ophthalmic), CloZAPine Deferiprone, Denosumab, Echinacea, Fingolimod, Leflunomide, Nitisinone, Nivolumab, Pidotimod, Pretomanid, Probenecid, Promazine, Roflumilast, Sipuleucel-T, and Tertomotide – Avoid combination: Vaccines (Live), Talimogene Laherparepvec, Tacrolimus (Topical), Belimumab, Biologic Disease-Modifying Antirheumatic Drugs, Cladribine, Cladribine, Dipyrone, Natalizumab, Pimecrolimus,	– Requires dose adjustment with patient with renal and liver impairment	– Not recommended in breastfeeding – Information related to pregnancy is limited
Enoxaparin	– Active major bleeding – History of immune-mediated heparin-induced thrombocytopenia within the past 100 days or in presence of circulating antibodies – Hypersensitivity to benzyl alcohol (present in multi-dose formulation) – – Hypersensitivity to enoxaparin.	Avoid combination: – Vorapaxar: May enhance the adverse/toxic effect of Anticoagulants. More specifically, this combination is expected to increase the risk of bleeding. – Urokinase: May enhance the anticoagulant effect of Anticoagulants. – Rivaroxaban: Anticoagulants may enhance the anticoagulant effect of Rivaroxaban – Omacetaxine: Anticoagulants may enhance the adverse/toxic effect of Omacetaxine – MiFEPRIStone: May enhance the adverse/toxic effect of Anticoagulants. Specifically, the risk of bleeding may be increased – Hemin: May enhance the anticoagulant effect of Anticoagulants. – Edoxaban: May enhance the anticoagulant effect of Anticoagulants. – Dabigatran Etexilate: May enhance the anticoagulant effect of Anticoagulants. – Apixaban: May enhance the anticoagulant effect of Anticoagulants.	– Renal impairment (CrCl 30 to 80 mL/min): No adjustment necessary – Renal impairment (CrCl less than 30 mL/min): reduce usual recommended dose by 50%. *See MoH online formulary*	– Low molecular weight heparin (LMWH) does not cross the placenta; increased risks of fetal bleeding or teratogenic effects have not been reported (Bates 2012).
Infliximab	– Hypersensitivity to infliximab, murine proteins, or any component of the formulation	– Need therapy modification and monitoring: AzaTHIOprine, Brincidofovir, Denosumab, COVID-19 Vaccine – Avoid combination: Abatacept, Abrocitinib, Anakinra, Anifrolumab, Baricitinib, Belimumab, Brincidofovir, Canakinumab, Cladribine, Vaccines (Live), and Upadacitinib	– No dose adjustment necessary	
Inhaled budesonide (Pulmicort®)	– Hypersensitivity to budesonide – Allergenic cross-reactivity for corticosteroids is limited – Patients with cirrhosis	– Diminish the effect of: Aldesleukin and Cosyntropin – Enhance the effect/toxicity of: Desmopressin and Loxapine – Increase the serum concentration of Budesonide: CYP3A4 Inhibitors – Diminish the effect of Budesonide: Tobacco	– Use cautiously in hepatic impairment See MoH online formulary	– Present in breast milk.
IVIG	– Hypersensitivity to IVIG or any component of the formula – Documentation of allergic cross-reactivity	– MMR, varicella vaccines	– Use cautiously with Renal impairment due to risk of immune globulin-induced renal dysfunction; Discontinue if renal function deteriorates. *See MoH online formulary*	
Nirmatrelvir and ritonavir	– Significant hypersensitivity – Coadministration with drugs that are highly dependent on CYP3A	– Significant drug interactions exist – Discontinue use of lovastatin and simvastatin at least 12 hours prior to initiation of paxlovid, during the 5 days of paxlovid treatment and for 5 days after completing PAXLOVID. – Consider temorary discontinuation of atorvastatin and rosuvastatin during treatment with paxlovid. Atorvastatin and rosuvastatin do not need to be held prior to or after completing paxlovid.	Requiring dose/frequency adjustment or avoidance.	– Not studied
Paracetamol (acetaminophen)	– Hypersensitivity to acetaminophen or any component of the formulation – Severe hepatic impairment or active liver disease	– Acetaminophen may increase the levels/effects of: Busulfan; Dasatinib; Imatinib; Local Anesthetics; Mipomersen; Phenylephrine (Systemic); Prilocaine; Sodium Nitrite; SORAfenib; Vitamin K Antagonists – The levels/effects of Acetaminophen may be increased by: Alcohol (Ethyl); Dapsone (Topical); Dasatinib; Flucloxacillin; Isoniazid; MetyraPONE; Nitric Oxide; Probenecid; SORAfenib	– Requires dose adjustment with patient with hepatic impairment *See MoH online formulary*	– Oral paracetamol is considered safe in normal therapeutic doses for short-term use as a minor analgesic/antipyretic in pregnancy. – Consider Administering IV paracetamol to a pregnant woman only if clearly needed

Medication Related Information

Medication	Contraindication	Major Drug Interactions	Required dose adjustment	Pregnancy and Lactation
Remdesivir	– Safety and efficacy not established	– Avoid Concomitant Use: There are no known interactions where it is recommended to avoid concomitant use. – Increased Effect/Toxicity: There are no known significant interactions involving an increase in effect. – Decreased Effect: There are no known significant interactions involving a decrease in effect.	– No dose adjustment studied	– Not studied
Systemic Dexamethasone	– Concomitant use of more than a single dose of dexamethasone with rilpivirine – Hypersensitivity to dexamethasone or any component of the product – Systemic fungal infection	– Avoid concomitant use of DexAMETHasone (Systemic) with any of the following: Aldesleukin; BCG (Intravesical); Cladribine; Conivaptan; Desmopressin; Fusidic Acid (Systemic); Idelalisib; Indium 111 Capromab Pendetide; Lapatinib; Lasmiditan; Macimorelin; Mifamurtide; MiFEPRIStone; Natalizumab; Pimecrolimus; Rilpivirine; Simeprevir; Tacrolimus (Topical); Upadacitinib	– Use cautiously in the elderly at the lowest possible dose *See MoH online formulary*	– Pregnant or breastfeeding women, use prednisolone (Oral) or intravenous hydrocortisone instead of dexamethasone
Tocilizumab	– Known hypersensitivity to tocilizumab or any component of the formulation – Active infections	– Avoid Concomitant Use: Anti-TNF Agents; BCG (Intravesical); Belimumab; Biologic Disease-Modifying Antirheumatic Drugs (DMARDs); Cladribine; Natalizumab; Pimecrolimus; Tacrolimus (Topical); Vaccines (Live) – Increased Effect/Toxicity: Anti-TNF Agents; Biologic Disease-Modifying Antirheumatic Drugs (DMARDs); Fingolimod; Leflunomide; Natalizumab; Siponimod; Vaccines (Live) – The levels/effects of Tocilizumab may be increased by: Belimumab; Cladribine; Denosumab; Ocrelizumab; Pimecrolimus; Roflumilast; Tacrolimus (Topical); Trastuzumab – Tocilizumab may decrease the levels/effects of: BCG (Intravesical); Coccidioides immitis Skin Test; CYP3A4 Substrates (High risk with Inducers); Nivolumab; Pidotimod; Sipuleucel-T; Smallpox and Monkeypox Vaccine (Live); Tertomotide; Vaccines (Inactivated); Vaccines (Live) – The levels/effects of Tocilizumab may be decreased by: Echinacea	– Requires dose adjustment with patient with hepatotoxicity *See MoH online formulary*	– Fetal risk cannot be ruled out

Drug Administration in patients with Swallowing Difficulties

Drug	Formulation	Remarks
Baricitinib	Tablet	– Tablets can be mixed with room temperature water.
Nirmatrelvir and ritonavir	Tablet	– Administer with or without food. Swallow tablets whole; do not chew, break, or crush. Nirmatrelvir must be coadministered with ritonavir

Administration via	Dispersion Volume	Container Rinse Volume
– Oral dispersion	10 mL	10 mL
– Gastrostomy tube	15 mL	15 mL
– Nasogastric tube	30 mL	15 mL

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Summary of Protocol changes
- Deletion of Molnupiravir under mild to moderate non-hospitalized patients at high risk with confirmed PRC and under medication related information - Addition of drug-drug interaction management of statins with Nirmatrelvir and ritonavir under medication related information