Interim Recommendation on Clinical Management of Adult Cases with Coronavirus Disease 2019 (COVID-19)

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1. Purpose

1.1. To provide guidance on clinical management of patients with Coronavirus Disease 2019 (COVID-19)

2. Scope

2.1. For all healthcare workers at hospitals

3. Introduction

3.1. A new strain of coronavirus (SARS-CoV-2) which has not been previously identified in human, was reported in Wuhan, China in December 2019. It belongs to a clade of betacoronavirus distinct from those associated with human severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). Coronavirus Disease 2019 (COVID-19) causes acute respiratory infection and pneumonia. Symptoms include fever, malaise, dry cough, shortness of breath, anosmia and ageusia. Some patients may have respiratory symptoms without fever and some patients may also have diarrhea. People of older age or having underlying chronic disease are at a higher risk of deterioration into serious condition.

4. Surveillance and reporting criteria

4.1. Please report suspected cases fulfilling the reporting criteria of Coronavirus Disease 2019 (COVID-19) to the Central Notification Office (CENO) of CHP via fax (2477 2770), phone (2477 2772) or CENO On-line (https://cdis.chp.gov.hk/CDIS_CENO_ONLINE/ceno.html). The case definition is available on the above website of CENO On-line. Both reporting criteria and case definition are subject to change upon availability of further epidemiological, clinical and virological data.

5. Clinical Management

5.1. Isolate the patient(s) in airborne infection isolation room (AIIR) with standard, contact, droplet and airborne precautions

5.2. Notify via NDORS/ eNID, and update the confirmed patient data when necessary

5.3. Diagnosis:

5.3.1. Specimens for RT-PCR of SARS-CoV-2

- Lower respiratory tract (always preferred): sputum or tracheal aspirate (TA) if intubated or bronchoalveolar lavage (BAL) (if bronchoscopy)

OR

- Upper respiratory tract: Nasopharyngeal Flocked swab (NPFS) or Nasopharyngeal Aspirate (NPA) [Pooled with throat swab in viral transport medium] or Deep throat saliva (DTS)
- Stool: For patient fulfilling reporting criteria with diarrhea, stool can be sent to PHLSB for RT-PCR for SARS-CoV-2 testing

5.3.2. For preliminarily positive cases, specimen should be re-tested and sent to PHLSB for confirmation

5.3.3. Repeated testing may be necessary to exclude the diagnosis. Please consult the clinical microbiologists or infectious disease physicians for advice

5.3.4. If patient has any stool sample being tested positive for SARS-CoV-2 previously, contact precaution should be maintained until negative result from stool has been obtained

5.3.5. Microbiological workup as appropriate, e.g.

- Sputum, urine and blood culture
- NPA +/- Tracheal aspirate for flu A/B and other respiratory viruses
- NPA +/- Tracheal aspirate for atypical pneumonia PCR
- Urine for legionella and pneumococcal antigen

5.3.6. Other investigations e.g. CBP with D/C, L/RFT, CaPO4, glucose, ESR, CRP, procalcitonin, CXR and ECG, etc.

5.4. Monitor vital signs and organ functions, and recognize complication(s) early

5.5. Liaise with ICU early for intensive care if anticipate clinical deterioration

5.6. Provide supportive treatments

5.6.1. Monitor for any concomitant bacterial infections and start empirical antibiotics if necessary

5.6.2. β lactam/β-lactamase inhibitor combination or 3rd generation cephalosporin +/- macrolide/doxycycline can be considered

5.6.3. Oxygen

5.6.4. IV fluid (conservative fluid management for severe respiratory failure)

5.6.5. Hemodynamic support

5.6.6. High-flow nasal oxygen (HFNO) may be considered in selected patients with hypoxemic respiratory failure. These patients should be closed monitored for clinical deterioration.

5.6.7. Mechanical ventilation with protective lung ventilation +/- consider ECMO for refractory respiratory failure

5.6.8. Renal replacement therapy (renal failure)

5.6.9. Consider proton pump inhibitors (PPI) for stress ulcer prophylaxis for prevention of GI bleeding per clinical judgment of ID physician/ Intensivist for moderate to severe cases

5.7. Anticoagulation

5.7.1. In patients hospitalized with COVID-19, use pharmacological prophylaxis, such as low molecular weight heparin (such as enoxaparin 40mg Q24H subcutaneous, according to local and international standards, to prevent venous thromboembolism, when not contraindicated. For those with contraindications, consider mechanical prophylaxis (intermittent pneumatic compression devices)

6. Use of Specific anti-COVID-19 treatments

6.1. Unlicensed treatment should be given under ethically-approved clinical trials as far as possible. In the absence of appropriate clinical trials, the following treatment regimens may be considered early, particularly in patients having following conditions with increased risk of severe disease

- Diabetes mellitus
- Obesity (body mass index [BMI of 30kg/m^2 or higher])
- Age >= 65
- Immunocompromised state
- Underlying chronic illnesses

6.2. The following table summarizes different available treatment regimens. These regimens are determined based on evidence extrapolated from research performed for other coronaviruses, expert opinion, non-randomized placebo controlled trials, case series and limited randomized placebo controlled trials on treatment of COVID19, as well as the availability of therapeutics in Hong Kong. This serves as an interim guidance and will be updated according to the availability of new evidence or drug availability.

		Setting and severity of illness		
		Mild-to-moderate disease without need of suppl. oxygen	**Severe** but non-critical disease (SaO2 <94% on room air)	**Critical** disease (e.g. in ICU needing HFNO, mechanical ventilation (MV), or septic shock, ECMO)
Anti-virals				
1	*Interferon beta-1b*	**Can be considered** for early onset disease (<14 days symptom)	**Can be considered** for early onset disease (<14 days symptom)	**Can be considered** for early onset disease (<14 days symptom)
2	*Remdesivir*	**Can be considered in high risk patients**	**Suggest use**	**Suggest against routine use**
3	*Ribavirin*	**Can be considered** as part of interferon-based regimens	**Can be considered** as part of interferon-based regimens	**Can be considered** as part of interferon-based regimens
4	*Lopinavir + ritonavir*	**Can be considered** as part of interferon-based regimens	**Can be considered** as part of interferon-based regimens	**Can be considered** as part of interferon-based regimens
Anti-inflammatory or immunotherapeutic				
1	*Corticosteroids*	**Suggest against use**	**Suggest use** Dexamethasone 6mg QD or equivalent glucocorticoids	**Recommend use**
2	*Convalescent plasma*	**Suggest against use**	**Suggest against use**	**Can be considered** at discretion of ID physicians/ ICU intensivist, or use in the context of a clinical trial
3	*Tocilizumab*	**Suggest against routine use**	**Suggest use in addition to standard of care (steroid) In patients with CRP >=75mg/L**	**Suggest use in addition to standard of care (steroid) In patients with CRP >=75mg/L**
4	*Baricitinib + remdesivir +/- corticosteroids*	**Suggest against use**	**Suggest use** at discretion of ID physicians/ ICU intensivist	**NA**
Anti-SARS-COV-2 Antibody products				
1	*Casirivimab + imdevimab*	**Can be considered** in high risk patients at discretion of ID physicians	**Suggest against use**	**Suggest against use**

6.3. Interferon-based regimen

6.3.1. May consider the following regimen in confirmed patients (Not a standard therapy)

Interferon beta-1b 0.25mg (8 MIU) subcutaneous alt day*
(maximum 7 doses),
up to 14 days of symptom onset

+

Ribavirin 400mg BD po for 7-14 days depending on clinical response

OR

lopinavir/ ritonavir 400mg/100mg (Kaletra) BD po for 7-14 days depending on clinical response

6.3.2. Interferon beta-1b is considered as the backbone therapy and combination therapy with ribavirin or kaletra is preferred. Interferon beta-1b monotherapy may be considered if use of ribavirin or kaletra is contraindicated or there is significant side effect due to either drugs

6.3.3. Reserve syrup formulation of kaletra in patients in ICU, paediatric patients or patients with swallowing difficulty

6.3.4. Dosage adjustment of ribavirin is required for renal impairment

6.3.5. Pre-treatment workup

- Check blood x CBP, LRFT, RG, LDH, CK, HBsAg, anti-HCV, anti-HIV
- + blood x TFT, ANA (for starting interferon)
- CXR (+/- HRCT thorax if indicated)
- ECG (if preexisting cardiac abnormalities or disease or clinically indicated). For patients with underlying pre-existing cardiac problems, follow-up monitoring of the cardiac condition is suggested.
- Pregnancy test for females with reproductive potential (Before starting interferon or ribavirin)
- Avoid pregnancy in female patients and female partners of male patients during ribavirin therapy; use effective contraceptive measures during treatment and for at least 6

months after completion of therapy

- Check any drug interactions with concomitant medications (in particular with ritonavir)
- Obtain consent for treatment
  - (i) Unlicensed indication and treatment is experimental
  - (ii) Side effects of treatment
  - (iii) Contraindications:
    - Interferon beta-1b: history of hypersensitivity to interferon beta, albumin; decompensated liver disease, current severe depression and/or suicidal ideation
    - Ribavirin: history of hypersensitivity to ribavirin; pregnant: patients with hemoglobinopathies (e.g. thalassemia major, sickle cell anemia)
    - Kaletra: history of hypersensitivity to lopinavir, ritonavir, avoid in patients with congenital long QT syndrome and cautious use in patients using other drugs that prolong QT interval
  - (iv) For pregnant women, detailed explanation on the benefits and potential risks should be provided before the commencement of interferon beta-1b
  - (v) For mentally incapacitated patients, may communicate with next of kin and attain consent from them with proper documentation.

*Dosing and frequency of interferon beta 1b can be adjusted at the discretion of the Infectious Diseases Physician in charge

6.4. Remdesivir

6.4.1. Remdesivir is an antiviral and inhibits SARS-CoV-2 RNA polymerase which perturbs viral replication. Remdesivir is given intravenously, once daily after an initial loading dose.

(i) Eligibility criteria:

- Hospitalized with coronavirus disease 2019 (COVID-19) AND
- Adults, and adolescents >=12 years of age and >= 40kg AND
- eGFR based on Cockcroft-Gault equation >= 30ml/min AND
- ALT below 5 times the upper limit normal at baseline

With

- pneumonia and SaO2 <94% on room air requiring supplemental oxygen
  AND
- Clinical deterioration with impending respiratory failure AND
- NPS/TS SARS-CoV-2 or sputum CT value <30
  OR
- Failed or contraindicated for interferon based treatment regimen

(ii) Dosage: 200mg IV loading dose following by 100mg IV daily as maintenance. The total duration of treatment should be 5 days

(iii) Remdesivir should be sensibly used in cases with better recovery potential and quality of life after recovery, in view of limited drug supply

(iv) Remdesivir may be considered in mild to moderate COVID-19 patients who are at high risk of deterioration, at discretion of ID physicians

(v) Pregnancy: Remdesivir should be avoided in pregnancy unless clinicians believe the benefits of treatment outweigh the risks to the individual

(vi) Obtain consent for treatment. Major side effects: Phlebitis, Nausea, vomiting, ALT elevations, hyperglycemia, hyperbilirubinemia, hypersensitivity reactions, bradycardia

(vii) Coadministration of remdesivir and interferon beta-1b may be considered in the discretion of ID physicians, particularly in severe patients with early onset of disease

(viii) Stopping criteria:

Remdesivir should be discontinued in patients who develop any of the following:

- ALT >= 5 times ULN during treatment with remdesivir
- ALT elevation accompanied by signs and symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphates, or INR
- EGFR <30 ml/min

6.5. Corticosteroids

6.5.1. Consider dexamethasone 6mg daily PO/IV up to 10 days in patients with pneumonia, and requiring oxygen supplement or invasive mechanical ventilation, Prolonged duration or higher dose of dexamethasone may be considered according to individual clinical condition

6.5.2. Equivalent total daily doses of alternative glucocorticoids are methylprednisolone 32mg and prednisolone 40mg

6.5.3. Dexamethasone may cause hyperglycemia, viral rebound of SARS-CoV-2 and increased risk of bacterial, fungal and parasitic infections

6.5.4. Use of short-period, stress dose steroids (hydrocortisone 200mg max daily) for refractory septic shock or other clinical indications on physician discretion

6.6. Convalescent Plasma (CP)

6.6.1. Transfusion with convalescent plasma in COVID19 patients is unlicensed. The use may be considered in patients with severe COVID-19 infection, at the discretion of intensivist and ID Physician

6.6.2. Obtain consent for treatment. Potential side effects: transfusion allergic reactions, transfusion-associated circulatory overload (TACO),

transfusion-related acute lung injury (TRALI)

6.6.3. Limited by availability

6.6.4. It is recommended the use of CP to be arranged through clinical trial. Meanwhile, liaise with QMH (HKU) and Hong Kong Red Cross for arrangement if indicated

6.6.5. The safety and effectiveness during pregnancy have not been evaluated

6.6.6. Potential side effects: transfusion-transmitted infections (e.g. Human immunodeficiency virus (HIV), hepatitis B, hepatitis C), allergic reactions, anaphylactic reactions, febrile nonhemolytic reactions, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), and hemolytic reactions. Hypothermia, metabolic complications, and post-transfusion purpura

6.7. Tocilizumab

6.7.1. Monoclonal antibody to IL6 receptor

6.7.2. There are data from clinical trials suggesting use of tocilizumab in combination with dexamethasone in certain hospitalized patients who are exhibiting rapid respiratory decompensation due to COVID-19, including:

- Recently hospitalized patients (i.e. within first 3 days of admission) who have been admitted to intensive care unit (ICU) within the prior 24 hours and who require invasive mechanical ventilation, noninvasive ventilation, or high-flow nasal cannula (HFNC) oxygen (>0.4 FiO2/ 30L/min of oxygen flow) or
- Recently hospitalized patients (i.e. within first 3 days of admission) not admitted to the ICU who have rapidly increasing oxygen needs and require noninvasive ventilation or HFNC oxygen and who have significantly increased markers of inflammation (CRP >=75mg/L)

6.7.3. Dose: 8mg/kg (Max: 800mg/dose), one dose

6.7.4. Use at the discretion of Infectious Disease (ID) Physician and intensivist for severe patients with evidence of cytokines release syndrome (Supported by elevated inflammatory markers like CRP, d-dimer, ferritin, etc)

6.7.5. Contact QMH and arrange serum IL-6 level test prior to giving tocilizumab if possible

6.7.6. Major side effects: hypertension, increased ALT, injection site infections, risk of opportunistic infections particularly bacterial, anaemia; serious side effects: gastrointestinal perforation, neutropenia

6.7.7. Live vaccines should be avoided for at least 3 months, after commencement of tocilizumab.

6.8. Baricitinib

6.8.1. An orally administered, selective inhibitor of Janus Kinase (JAK) 1 and 2. Baricitinib inhibits the intracellular signaling pathway of cytokines known to be elevated in severe COVID-19.

6.8.2. Among hospitalized adults with severe COVID-19 having elevated inflammatory markers but not on invasive mechanical ventilation, concomitant use of baricitinib with remdesivir can be considered. Baricitinib appears to demonstrate the most benefit in those with severe COVID-19 on high flow oxygen or non invasive ventilation at baseline. The benefits for persons on mechanical ventilation are uncertain.

6.8.3. Dosing: oral 4mg once daily for up to 14 days of treatment or until hospital discharge, whichever is first. Longer duration can be considered at the discretion of ID physician/ ICU intensivist.

6.8.4. Renal adjustment: oral 2mg daily (30 to <60 ml/min), 1mg daily (15 to <30 ml/min)

6.8.5. Use in combination with remdesivir. Limited information on the use of baricitinib in combination with systemic corticosteroids. Consider use at ID physician's discretion

6.8.6. Potential side effects: Infection (particularly upper respiratory tract infection, herpes zoster), nausea, raised ALT, neutropenia, arterial thrombosis, malignant lymphoma (<1%), malignant neoplasm (<1%)

6.8.7. Not recommended for patients on dialysis, having eGFR <15ml/min, having acute kidney injury, or having known active tuberculosis

6.8.8. Pregnancy: Should be used during pregnancy only if potential benefit justifies the potential risk for the mother and the fetus

6.8.9. Avoid use of live vaccines with baricitinib

6.8.10. Monitoring: CBP, LRFT (Consider interruption if ALC <0.2 or ANC <0.5)

6.9. Casirivimab plus imdevimab

6.9.1. Anti-SARS-CoV-2 monoclonal antibody products currently have Emergency Use Authorizations (EUAs) from the Food and Drug Administration (FDA) for the treatment of mild to moderate COVID-19 patients who are at risk of progressing to severe disease and/or hospitalization.

6.9.2. Casirivimab plus imdevimab: These are recombinant human monoclonal antibodies that bind to nonoverlapping epitopes of the spike protein RBD of SARS-CoV-2.

6.9.3. Dosing: Casirivimab 600mg plus imdevimab 600mg intravenous infusions for one dose. If intravenous route is not feasible, administration by four subcutaneous injections (2.5ml per injection) can be used as an alternative.

6.9.4. The use of casirivimab plus imdevimab can be considered in patients with mild to moderate severity and at risk of progression to severe COVID-19 infection.

6.9.5. Medical conditions or other factors that were represented in clinical trials that evaluated anti-SARS-CoV-2 monoclonal antibodies

- Age >=65
- Obesity (BMI >30)
- Diabetes
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung disease (e.g. COPD, moderate to severe asthma, interstitial lung disease, cystic fibrosis, pulmonary hypertension)

6.9.6. Monoclonal antibodies should be used at discretion of ID physicians, particularly for other conditions or factors at risk of progressing into severe disease.

6.9.7. Side effects: Uncommon (up to 1 %): allergic reactions or reactions following infusions: fever, chills, headache, difficulty breathing, hypotension, facial swelling, itching, myalgia

6.9.8. Pregnancy: The safety for use in pregnancy is inadequate. Use if potential benefits of treatment outweigh the potential risks to the mother and fetus.

6.10. Monitoring during treatment

6.10.1. Blood x CBP, LRFT, LDH, CRP

6.10.2. Repeat NPS +/- Throat swab or deep throat saliva x SARS-CoV-2 twice, 24 hours apart before isolation release

6.10.3. Blood x SARS-CoV-2 antibody for patients who are asymptomatic or 7 days after symptom onset or with SARS-CoV-2 RT-PCR CT value >=30

6.10.4. Repeat Stool x SARS-CoV-2 if there are previous positive results before isolation release

6.10.5. Monitor for any concomitant bacterial or fungal infections

6.10.6. Observe for any side effects

7. Release from Isolation

7.1. Confirmed cases can be released from isolation if they fulfil the following criteria:

For symptomatic patients:

(i) Clinical conditions improve and afebrile; AND

(ii) Either one of the following criteria:

- With two clinical specimens of the same type* (i.e. respiratory or stool) tested negative for nucleic acid of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by reverse transcription polymerase chain reaction (RT-PCR) taken at least 24 hours apart; OR three clinical specimens of the same type* taken at least 24 hours apart in which RT- PCR test results showed consistent Ct value 33 or above; AND 10 days have passed since the onset of illness; OR
- With a transition of the test results for SARS-CoV-2 IgG from negative to positive results with at least one PCR Ct value 33 or above

For patients who did not develop any COVID-19 compatible symptoms all along:

Either one of the following laboratory criteria:

(i) With two clinical specimens of the same type* (i.e. respiratory or stool) tested negative for nucleic acid of SARS-CoV-2 by RT-PCR taken at least 24 hours apart; OR three clinical specimens of the same type* taken at least 24 hours apart in which RT-PCR test results showed consistent Ct value 33 or above; AND 10 days after the first positive RT-PCR for SARS-

CoV-2; OR

(ii) Serology test result for SARS-CoV-2 IgG change from negative to positive with at least one PCR Ct value 33 or above

7.2. Discussion with MCO of CHP for lifting of isolation order is necessary

* For patient ever with stool specimen(s) tested positive, they should have two negative stool specimens collected 24 hours apart before release from isolation **OR** three stool specimens taken at least 24 hours apart in which RT-PCR test results showed consistent Ct value 33 or above.

8. Follow-up arrangement

8.1. Follow-up arrangement should be subject to parent team's decision. In general, patients who developed pneumonia or complications during hospitalization should be monitored for any long term sequelae from COVID-19 infection

8.2. Subject to patient's need, referral may be sent to clinical psychologist, medical social worker, physiotherapist, occupational therapist, traditional Chinese medicine practitioner or District Health Centre

8.3. Monitoring during follow-up

- Blood tests (e.g. CBP, LRFT, CRP) +/- 2 clotted blood for SARS-CoV2 antibody if not taken previously
- CXR
- Consider lung function tests for moderate to severe cases
- Consider HRCT for cases with residual lung changes

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