Memorial Regional Healthcare Services

Guidance on Diagnosis and Management of Adults with COVID-19

Last Updated: March 24, 2020

NOTE: The understanding of and emerging data related to COVID-19 is rapidly evolving. Below are guidelines to help consolidate information and is subject to change at any time. Please consult **Infectious Diseases (618-223-4115**) or the **Antimicrobial Stewardship Pharmacist (217-653-8170)** for up-to-date information.

Clinical Presentation[1-13]

- **Presentation:** ~80% ranging from asymptomatic to mild or moderate illness that are self-limiting. Advanced age and chronic conditions have much higher risk of severe illness, hospitalization, complications, and mortality.
- **Incubation period:** Range 2-14 days with median of ~4-5 days.
- **Clinical Course:** Typically, development of fever, cough, myalgia, and fatigue that can rapidly progress to shortness of breath and hypoxemia. CDC has noted a subset of patients are experiencing gastrointestinal symptoms (see below) prior to fever and respiratory symptoms. If a patient presents with GI symptoms and has had contact with a COVID-19 patient, it may be reasonable to test, if possible, for COVID-19. **Note**: Not all adults present with fever, especially elderly or those in long term care facilities. Thus, investigation of COVID-19 in atypical presentation without other explainable etiology may be warranted (i.e. negative influenza/RSV PCR). Unlike influenza, presentation is often insidious in the first week with rapid decompensation in week 2 in ~10-15% of cases. Average onset to decompensation is 7-8 days after initial symptoms. CDC has described this process as patients with mild-moderate symptoms throughout week 1 and then rapidly decompensate requiring medical support in week 2 of illness.
- **Transmission Rate**: ~1.5-3.5 additional cases for each identified patient. However, this rate is dependent on human behavior. Can be transmitted 5 days prior to symptom onset. Rates are expected to be much higher when proper infection control procedures are not followed and may be lower when they are followed appropriately. **Note:** Proper isolation and use of personal protective equipment (PPE) is paramount.
- **Complications:** pneumonia, ARDS, multi-organ failure, septic shock, viral myocarditis, cardiomyopathy, death.
- **Pregnancy**: The course of illness and presentation is similar to non-pregnant adults
- **Adolescents and Children**: Adolescents, especially children <10 years of age, are at much less risk for COVID-19. Symptoms are similar to adults. However, to date complications and especially death (0% <19 years of age) are much lower than that of adults.

Signs and Symptoms[1-13]

No single or combination of signs/symptoms or absence of signs/symptoms exclude the diagnosis of COVID-19.

- **Common**
  - Fever (77-98%)
    - Present in ~44% at hospital admission with ~90% of patients during hospitalization.
    - Absence does not exclude COVID-19
  - Cough (46-82%)
  - Myalgia or fever (11-52%)
  - Shortness of breath (3-31%)
  - Hypoxemia (~41% of hospitalized patients)
- **Uncommon <30%**
  - Gastrointestinal (GI) (may be more pronounced as ↑ in COVID-19 severity)[12]
    - However, present in ~49% of patients presenting to the hospital
      - Anorexia: ~84%, diarrhea: ~29%, vomiting and abdominal pain: ~<1%
      - Typically present prior to fever and respiratory symptoms
  - Sore throat
  - Headache
  - Cough with sputum production or hemoptysis
  - Asymptomatic or subclinical presentations

Laboratory Findings[1-13]

- **Common**
  - Cytopenias
    - Lymphopenia: ~63-83%
    - Leukopenia: ~34-34%
    - Thrombocytopenia: ~36%
  - ALT/AST elevations ~37%
  - Leukocytosis ~24-30%
  - Procalcitonin: ~85% within normal limits
  - CRP elevation ~66-81%
  - LDH elevation ~27-55%
  - Elevated Cardiac Biomarkers ~7-23%

Radiographic Findings[1-13]

- CDC has indicated many cases have normal imaging early on in the course of illness. CDC does not recommend CTs for diagnostic purposes.
- **Chest X-ray (CXR) and CT**
  - Bilateral involvement with patchy ground glass opacities
    - Mild or early in disease may be unilateral or absent
      - ~56% of patients who present within 2 days have normal CT imaging
    - CXR abnormal ~60% (~75% if severe)
    - Chest CT abnormal ~85% (~95% if severe)
  - Most involve lung bases with peripheral distributions
  - Nodules, lymphadenopathy, cavitations, effusions, etc. are infrequent and consideration into other etiologies may be warranted
- **Chest X-ray and no findings: May consider lung ultrasound**
  - May be useful to leverage to avoid unnecessary travel to and from Chest CT and to identify lung involvement in less severe cases to help better direct disposition, patient education, monitoring and consideration of treatment modalities

Hospitalized Patients Risk Factors for Severe Disease, ARDS and Mortality[1-13]

- Overall, case fatality rate is ~1.8-3.4%. Careful interpretation of the available data is key as the mortality rates are likely over reported. The same principles occur for the below statements.
- Per CDC report below, advanced age and underlying conditions increase risk of severe disease, hospitalization, ICU admission and death

CDC Morbidity and Mortality Weekly Report

TABLE. Hospitalization, intensive care unit (ICU) admission, and case–fatality percentages for reported COVID–19 cases, by age group — United States, February 12–March 16, 2020

Age group (yrs) (no. of cases)	%*		
	Hospitalization	ICU admission	Case-fatality
0–19 (123)	1.6–2.5	0	0
20–44 (705)	14.3–20.8	2.0–4.2	0.1–0.2
45–54 (429)	21.2–28.3	5.4–10.4	0.5–0.8
55–64 (429)	20.5–30.1	4.7–11.2	1.4–2.6
65–74 (409)	28.6–43.5	8.1–18.8	2.7–4.9
75–84 (210)	30.5–58.7	10.5–31.0	4.3–10.5
≥85 (144)	31.3–70.3	6.3–29.0	10.4–27.3
Total (2,449)	**20.7–31.4**	**4.9–11.5**	**1.8–3.4**

* Lower bound of range = number of persons hospitalized, admitted to ICU, or who died among total in age group; upper bound of range = number of persons hospitalized, admitted to ICU, or who died among total in age group with known hospitalization status, ICU admission status, or death.

Prognostics in COVID-19 pneumonia associated with progression to ARDS, ARDS and death, organ and coagulation dysfunction[11]

ARDS	**ARDS and Death**
• ≥ 65 years of age (HR, 3.26; 95%CI 2.08-5.11) • Neutrophilia (HR, 1.14; 95%CI, 1.09-1.19) **Organ Dysfunction** • LDH ≥ 100 U/L (HR, 1.61; 95%CI, 1.44-1.79) • Elevated D-dimer (HR, 1.03; 95%CI, 1.01-1.04)	• ≥ 65 years of age (HR, 6.17; 95%CI, 3.26-11.67) • Neutrophilia (HR, 1.08; 95%CI, 1.01-1.17) **Coagulation Dysfunction** • LDH ≥ 100 U/L (HR, 1.30; 95%CI, 1.11-1.52) • Elevated D-dimer (HR, 1.02; 95%CI, 1.01-1.04)
• High Fever ≥ 39 °C or 102.2°F resulted in higher risk of ARDS (HR, 1.77; 95%CI, 1.11-2.84) but not death (HR, 0.41; 95%CI, 0.21-0.82)	

COVID-19 Testing

- Real-Time Polymerase Chain Reaction (RT-PCR) with a nasopharyngeal swab.
- Please consult with **Cheryl Wright, Infection Prevention RN:** 314-356-0466
- **Please note:** A negative test does **NOT** necessarily exclude the diagnosis of COVID-19. Please consult with Infectious Diseases for questions concerning interpretation of results.

SPECIMEN COLLECTION / DIRECTION: (contact microbiology at ext. 75094 for questions)

1) Ask the patient if they have any nose problems that would prevent the collection of a nasal swab
2) Consult with microbiology or eve. charge tech, dependent upon time of day, if collection concerns exist
3) Insert mini-tipped, (green E-swab), into the nose to the nasopharyngeal cavity to the point of resistance
   NOTE: Green swabs – Use on children less than five years of age since this is a smaller swab
   White swabs – Use on patients greater than 5 years of age since this is a larger swab
4) Gently rotate the swab, (as to not cause too much discomfort to the patient), to absorb the secretions and then gently redraw the swab
5) Return E-swab into the original transport tube following instructions on the kit
6) Promptly transport specimen to microbiology

Laboratory Recommendations	**Microbiology Recommendations**
• CBC with diff • CMP • Procalcitonin • CRP • Consider D-dimer, LDH, fibrinogen	• Influenza/RSV If signs or symptoms of bacterial pneumonia or superinfection, consider • Blood cultures • Respiratory cultures (NOT induced sputum) • Urine Legionella, Urine Strep antigens

Prophylaxis

There is currently no human evidence or FDA approval of for any agent for the prophylaxis of COVID-19.

Treatment Considerations

Key Principles[1,8]

Supportive care measures are the mainstay of therapy. WHO Clinical Care Guidance for more information on staging of disease and management of details. https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected

Society of Critical Care Medicine Surviving Sepsis Campaign: COVID-19 Guidelines https://www.sccm.org/getattachment/Disaster/SSC-COVID19-Critical-Care-Guidelines.pdf?lang=en-US

Supplemental O_2 for respiratory distress, hypoxemia, and shock. Target SPO_2 92- 96%

If failing conventional supplemental O2, High Flow Nasal Cannula (HFNC) is preferred to Non-Invasive Positive Pressure Ventilation (NIPPV)

Closely Monitor for signs of clinical deterioration, such as rapid progressive respiratory failure and sepsis

- **For COVID-19 patients receiving NIPPV or HFNC, consider early intubation in a controlled setting if worsening occurs**

Conservative fluid management when no evidence of shock, especially in ARDS

For mechanically ventilated adults with COVID-19 and moderate to severe ARDS, consider prone ventilation for 12 to 16 hours

Avoid open suctioning of airways and nebulized medications[1,8,9]

- Considered aerosol generating procedures. Please utilize alternative medication delivery such as metered dose inhalers**.**

Corticosteroids[1,8,9,11]

Should be avoided, including inhaled corticosteroids, due to lack of efficacy, possible harm, and concerns of prolonged viral replication, unless indicated for other reasons such as COPD exacerbation, asthma, refractory shock, ARDS, etc. The available evidence in general does not support corticosteroids in MERS, SARS, or influenza. Therefore, it is recommended to avoid in routine management of COVID-19.

NOTE: Emerging data shows an association with improvement in mortality when ARDS is present. Please evaluate on a case-to-case basis and weigh risk vs. benefit. Methylprednisolone was the drug associated with this decreased mortality (HR, 0.38; 95%CI,0.20-0.72).[8]

- If felt necessary, a short-term (3-5 days) regimen of methylprednisolone at 1-2 mg/kg/day is suggested as a potential option as the high-dose glucocorticoid may delay viral clearance. Italian COVID-19 guidelines suggest dexamethasone 20 mg/day x 5 days then, 10 mg x 5 days for patients with ARDS.

Antipyretics[8]: preference for inpatient management is acetaminophen as less risk of nephrotoxicity and ADEs compared to NSAIDS. The World Health Organization released a statement stating inconclusive evidence to avoid NSAIDS. If medically stable and no contraindications/precautions, may consider NSAIDS.

Stop all non-essential medications to help limit traffic in and out of rooms and exposure.

Antibiotic Guided Therapy[13,14]

NOT ROUTINELY RECOMMENDED: Bacterial co-infections are uncommon. Only recommended in the presence of signs/symptoms consistent with bacterial infections (elevated WBC or procalcitonin, hemodynamic instability, etc.). If bacterial infection is suspected initiate antibiotic therapy accordingly while establishing a definitive diagnosis. **Recommend AGAINST azithromycin + hydroxychloroquine** (safety not established, QTc prolongation may occur).

Note: Procalcitonin is within normal limits on the majority (>80%) of COVID-19 patients and bacterial co-infections are uncommon. Consider stopping or de-escalating antibiotic therapy if no other signs/symptoms are consistent with bacterial infection. Prevention of bacterial infections is **NOT recommended**.

Community-Acquired Pneumonia

Outpatient

- **No comorbidities**
  - Amoxicillin 1 g PO TID x 5 days
  - Doxycycline 100 mg PO BID x 5 days

PCN and tetracycline class allergy or intolerance

  - Azithromycin 500 mg PO x1, 250 mg PO days 2-5

- **Comorbidities**
  - Amox/clav 875/125 mg BID **OR** cefuroxime 500 mg BID x 5 days + azithromycin 500 mg x 1, then 250 mg days 2-5

Macrolide allergy or contraindication (QTc prolongation)

  - Amox/clav 875/125 mg BID **OR** cefuroxime 500 mg BID + doxycycline 100 mg BID x 5 days

Severe PCN allergy

  - Levofloxacin 750 mg **OR** moxifloxacin 400 mg daily x 5 days

Community-Acquired Pneumonia

Inpatient

Non-severe CAP with no MRSA or *P. aeruginosa* risk factors

- Risk factors: respiratory isolation within the last year or hospitalization with receipt of IV antibiotics in the previous 90 days
  - Ceftriaxone 1-2 g IV daily x 5 days + azithromycin 500 mg IV/PO daily x 3 days

Macrolide contraindication (QTc prolongation) or allergy

  - Ceftriaxone 1-2 g IV daily x 5 days + doxycycline 100 mg PO/IV x 5 days

Severe PCN Allergy (anaphylaxis, erythema multiforme or acute allergic interstitial nephritis)

  - Levofloxacin 750 mg PO/IV daily x 5 days

Severe CAP with no MRSA or *P. aeruginosa* risk factors

- Risk factors: respiratory isolation within the last year or hospitalization with receipt of IV antibiotics in the previous 90 days
  - Ceftriaxone 1-2 g IV daily x 5 days + azithromycin 500 mg IV/PO daily x 3 days

Macrolide or allergy

  - Ceftriaxone 1-2 g IV daily + levofloxacin 750 mg daily x 5 days

Severe PCN Allergy (anaphylaxis, erythema multiforme or acute allergic interstitial nephritis)

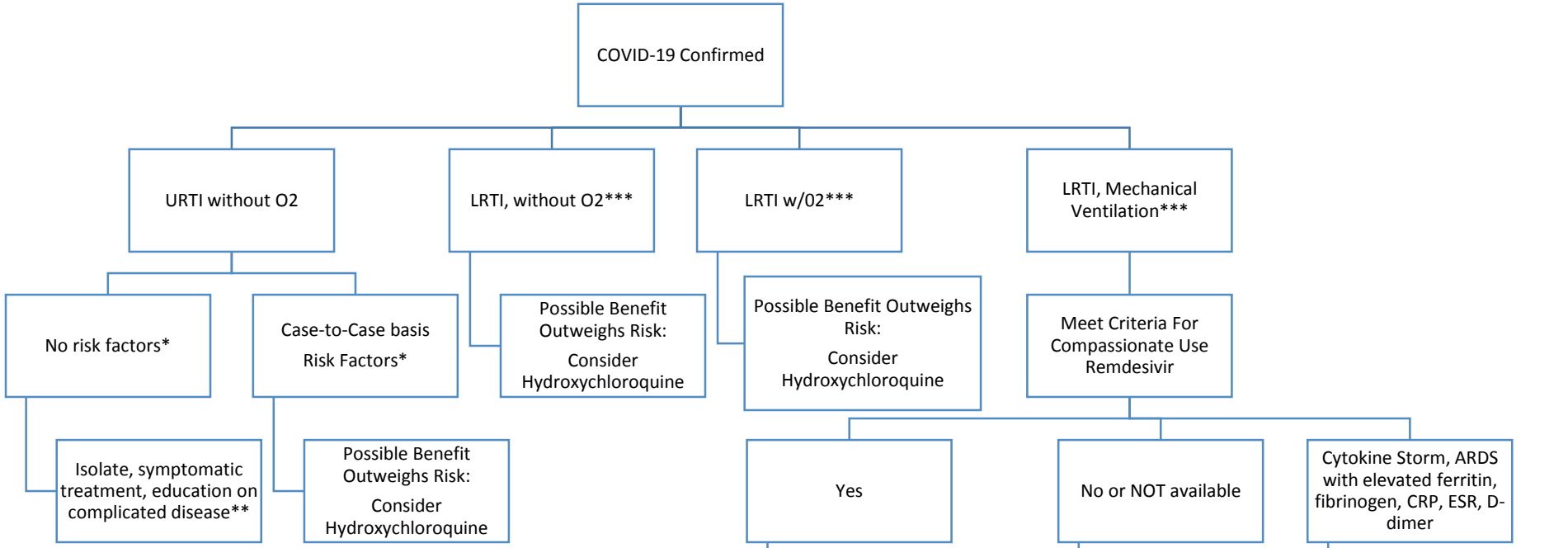
  - Levofloxacin 750 mg PO/IV daily + aztreonam 2g q8hr x 5 days

Non-severe or severe CAP with MRSA or *P. aeruginosa* risk factors

- Risk factors: respiratory isolation within the last year or hospitalization with receipt of IV antibiotics in the previous 90 days
- **Obtain respiratory and blood culture**
- **MRSA risk factor with no *P. aeruginosa* risk factors**
  - Vancomycin 15 mg/kg IV q12hr + ceftriaxone 1-2 g IV daily + azithromycin 500 mg IV/PO daily x 3 days
- ***P. aeruginosa* risk factor with no MRSA risk factor**
  - Cefepime 2g q8 hr IV + azithromycin 500 mg IV/PO daily x 3
- **MRSA risk factor with *P. aeruginosa* risk factors**
  - Vancomycin 15 mg/kg IV q12hr + cefepime 2 g q8hr IV + azithromycin 500 mg IV/PO daily x 3 days

COVID-19 Directed Therapies: These agents are currently under investigational use and clinical trials are underway. Currently, NO therapy is FDA-approved for the management of COVID-19. Limited evidence and anecdotal reports are emerging and should be viewed with extreme caution. Any possible COVID-19 therapies should be guided in collaboration with Infectious Diseases and/or the Antimicrobial Stewardship Pharmacist.

- **Duration:** Optimal duration of COVID-19 directed therapies has not been established and ranges in available literature. Please consider stopping COVID-19 therapies as signs and symptoms improve to help conserve treatments.



*Risk factors: ≥ 65 or presence of significant underlying conditions associated with higher risk of an adverse outcome such as advanced lung or heart disease, immunosuppression, etc. or combination thereof.

**Shortness of breath, difficulty breathing, increased respiratory rate, etc.

***MHE to MHB Transfer to Critical Care Team

- Acute or impending respiratory failure (Any of the below)
  - Respiratory Rate > 30 breaths/min
  - SpO_2 < 93% on room air
  - PaO_2:FiO_2 < 300

COVID-19 Directed Therapies

Remdesivir (Must consult with Antimicrobial Stewardship Pharmacist (Ext. 76627 or 217-653-8170) to coordinate IRB reporting)
Dose, Route, and Duration ○ 200 mg IV Loading dose, then 100 mg IV daily x 5-10 days.
Dose Adjustments – Renal: IHD, once daily dosing is warranted – Hepatic: None, use with caution
Contraindications/Precautions – Drug interactions most significantly LPV/r but cannot be utilized as exclusion criteria per compassionate use below
Adverse Effects: Investigational
Drug Monitoring: Investigational
Clinical Considerations: Preferred if approved for compassionate use per below inclusion exclusion criteria. Bridge with another agent until arrival.
Evidence: Investigational and exclusion criteria for compassionate use
Pregnancy: Unknown
Use through compassionate use (academic or community HSOs) **Compassionate use through Gilead Portal https://rdvcu.gilead.com/** ○ Anecdotal reports this takes up to 72 hrs to get approval and receive drug ○ **Key Inclusion Criteria:** Hospitalization, Confirmed SARS-CoV-2 by PCR, Invasive Mechanical Ventilation ○ **Key Exclusion Criteria:** Evidence of Multi-organ failure, vasopressor requirement to maintain BP, ALT >5x ULN, CrCl <30 ml/min or dialysis or CVVH, conjunctive use with other experimental COVID-19

Hydroxychloroquine[14-26] (Low quality evidence, safety and efficacy not established)

Dose, Route and Duration

- 200 mg PO TID x 5-10 days
- Can be crushed and dispersed with water

Dose Adjustments

- Renal: None
- Hepatic: None

Contraindications/Precautions

- Cardiac disease
- QTc prolongation or QTc prolonging medications

Adverse Effects

- GI: Nausea, vomiting, diarrhea (take with food)
- Cytopenias
- Hepatotoxicity
- Cardiotoxic (cardiomyopathy and QTc prolongation)
- Acute Kidney Injury
- Retinol toxicity
- CNS
- Dermatological

Drug Monitoring

- G6DP prior to administration. Do not have to wait to initiate. Risk is very low.
- EKG at baseline and daily thereafter (discontinue if bundle branch block/AV block, QTc prolongation, etc.)
- CBC
- CMP to evaluate LFTs, electrolytes, and SCr
- Assess visual and mental status

Clinical Considerations

- Avoid antacids
- Emerging data suggesting reduced viral load and more rapid viral clearance. Exclusion to this trial was QTc prolongation at baseline.

Evidence

Chloroquine has been reported to have *in vitro* activity against SARS-CoV-2. Also, a clinical trial out of China showed significant effect, both in terms of clinical outcome and viral clearance compared to control group. Chinese guidelines currently include chloroquine for treatment of COVID-19 in mild, moderate, or severe cases. Hydroxychloroquine is an analog of chloroquine and has demonstrated *in vitro* activity against SARS-CoV-2 with potential to have greater potency than chloroquine. Hydroxychloroquine tolerability and safety profile is better than that of chloroquine. A recent small, open-label, non-randomized clinical trial showed encouraging anti-viral activity with reduction in viral load and clearance of COVID-19 compared to the control group. This study suggests combination with azithromycin is beneficial in reducing time to negative COVID-19 results. It is prudent to take caution interpreting these results as it is not known if the routine combination is safe as both can cause QTc prolongation. More data is needed to assess the safety and efficacy of combination therapy. Recommend AGAINST azithromycin + hydroxychloroquine **(safety not established, QTc prolongation may occur).**

Pregnancy

- Risk has not been observed but further studies needed. Is a treatment utilized for lupus and malaria in pregnant women.

Lopinavir/Ritonavir[27-36] (Low quality evidence, safety and efficacy not established)
Dose, Route and Duration – LPV/r 400-100 mg BID x7-14 days – Could be crushed but AUC reduced by ~50% in a pediatric study and thus increase in dose by 50% may be needed to compensate
Dose Adjustments – Renal: None – Hepatic: Best to avoid if possible
Contraindications/Precautions – Previous hypersensitivity to lopinavir or ritonavir – Drug interactions, highly dependent on CYP3A, are significant. Run a drug interaction screen prior to initiation. – Best to avoid in liver disease, cardiac disease (ischemic heart disease or cardiomyopathy), QTc prolongation, any cytopenias.
Adverse Effects – Cytopenias (i.e. leukopenia, thrombocytopenia) – GI: Nausea, vomiting, diarrhea, anorexia, gastritis – Hepatotoxicity – QTc prolongation
Drug Monitoring – EKG at baseline and daily thereafter – CBC – LFTs – GI adverse effects: Nausea, vomiting, diarrhea and potentially pancreatitis – Consider HIV testing prior to initiating
Clinical Considerations – High rates of nausea/vomiting. While on supplemental oxygen, this needs to be carefully monitored and taken into consideration. – Solution may not be available, currently is not, tablets could be considered for crushing. Would need to outline details and stability data is lacking and immediate use would need to be suggested – Possible combination with ribavirin

Evidence

- Listed as a potential treatment option as monotherapy and combination therapy.
- A recent randomized, single center, open-label trial was conducted that compared LPV/r 400-100 mg PO BID x 14 days vs. standard of care and failed to show difference in clinical improvement and mortality compared to standard of care. Also, it did not appear to have an effect on viral load or duration of detection in these patients. However, sampling methods were suboptimal and performed intermittently vs. consecutively. Lastly, gastrointestinal adverse effects were more common in the LPV/r group. However, only ~14% discontinued the treatment early due to adverse events. Mortality rates were higher in this trial compared to initial descriptive reports indicating more severely ill patients were enrolled and could have impacted results. Duration and severity of illness was heterogeneous and a post hoc subgroup suggested mortality benefit in those treated <12 days. Complications were also higher in the standard of care group compared to LPV/r plus standard of care. These findings may suggest earlier treatment may offer advantage but more studies would be required. Lastly, in the modified intention-to-treat population where three early deaths were excluded, median time to improvement was statistically significantly reduced by 1 day. This could possibly play a role in getting patients ready for discharge more quickly in the event of crisis.[1]
- Descriptive case series from Singapore on COVID-19. 3 of the 5 patients after initiation was followed by reduction in supplemental oxygen. The other 2 went on to have respiratory failure. 4 of 5 developed nausea, vomiting, and/or diarrhea and 3 developed abnormal LFTs. Only 1 patient completed the 14 day treatment course as a result of these ADEs. Conclusion: variable clinical outcomes, several limitations and high discontinuation rate from ADEs.[2]
- May rapidly reduce SARS-CoV-2 viral loads as described in an anecdotal report.[3]
- Evidence in SARS-CoV-1[4,5]:
    - LPV/r + ribavirin + steroid protocol compared against historical controls + ribavirin + steroid protocol.
    - Dose: LPV/r 400-100 mg BID x 14 days or historical controls also received Ribavirin 4 g oral loading dose followed by 1.2 g every 8 hours, or 8 mg/kg IV if the patient could not tolerate PO. A reducing regimen of corticosteroids for 21 days of hydrocortisone 100–200 mg every 6–8 hours or methylprednisolone 3 mg/kg/day) was also utilized. Pulses of intravenous methylprednisolone (0.5–1 g/day up to 4 g) were used if patients developed increasing shortness of breath, oxygen desaturation, or radiological worsening.
    - Outcome: Earlier initiation of LPV/r was associated with lower mortality, intubation rate, steroids, viral loads and nosocomial infections. These findings also support that the COVID-19 NEJM article listed above may have limitations with late initiation of LPV/r.
- Studies in MERS and SARS were always in combination of ribavirin. SARS likely best representation of COVID-19. However, ribavirin has yet to be studied in COVID-19 and *in vitro* studies have shown that high concentrations were required and thus it may not play a role in COVID-19. In addition, ribavirin toxicities may be additive to other therapies.

Pregnancy

- Safety established in HIV

Tocilizumab[37-39] (Low quality evidence, experimental)

Dose, Route, and Duration

- Based on the 7th edition of Chinese National COVID-19 Guideline, the first dose should be 4-8 mg/kg (each dose capped at 800 mg)
- 400 mg is reasonable for 50-100 kg
- A second dose may be given in 8-12 hours if patient dose not respond well. Max of 2-3 doses. Interval must be at least 8 hours.
- Dilute with 0.9% NaCl to 100 ml and infuse over 1 hour.

Dosages Tocilizumab in COVID-19 for body weight

PATIENT Weight	ACTEMRA Dosage	Dose Range mg / Kg
35-45 kg	320 mg (4 fl 80 mg)	9.1 to 7.1
46-55 kg	400 mg (1 vial of 400 mg)	8.7- 7.3
56-65 kg	480 mg (1 fl 400 mg + 1 fl 80 mg)	8.6 to 7.4
66-75 kg	560 mg (1 fl 400 mg + 2 fl 80 mg)	8.5 to 7.5
76-85 kg	600 mg (1 fl 400 mg + 1 fl 200 mg)	7.9 to 7.0
> 86 kg	800 mg (2 fl 400 mg)	9.3

Contraindications/Precautions

- Prohibited in patients with active infections like tuberculosis
- <18
- AST or ALT>5x UNL
- ANC<500 cells/mm^3
- Platelets < 50,000 cells/mm^3
- Sepsis secondary to other etiologies
- Complicated diverticulitis or intestinal perforation
- Cutaneous infection not controlled on antimicrobials
- Anti-rejection immunosuppressive therapy
- CNS demyelinating disease like multiple sclerosis

Adverse Effects

- Potential for developing serious infections or reactivation of latent infections
- Hepatotoxicity
- Hypersensitivity reactions
- Neutropenia, thrombocytopenia
- GI perforation

Drug Monitoring

- CBC
- LFTs
- GI perforation

Clinical Considerations

- Treatment of the cytokine storm. Must be accompanied by antiviral treatment and steroids. Expensive.
- Consider for patients with extensive, bilateral lung disease and severely ill patients with elevated D-dimers, ferritin or fibrinogen levels

Evidence

- Currently under investigations use in the treatment of COVID-19 associated pulmonary complications with elevated IL-6.
- A very small open-label study in China with COVID-19 patients who had severe oxygenation impairment, including RR≥30 breaths/min, Sp02≤93% on room air, PaO2/FiO2<=300mmHg, or need for mechanical ventilation, shock, or combined organ failure, tocilizumab reduced oxygen requirement, normalized the CRP, and increased the lymphocyte count to normal; 19 of the 21 patients were discharged.

Pregnancy

- As a monoclonal antibody tocilizumab is a teratogenic drug. Concentration in fetal circulation appears to be higher than in the maternal circulation towards the end of pregnancy. Consider the risks and benefits of treatment as the infant exposed in utero during the third trimester of pregnancy has the ability to be temporarily immunosuppressed.

Resources

General CDC and WHO Information including patient information: https://www.coronavirus.gov/ or https://www.who.int/emergencies/diseases/novel-coronavirus-2019

CDC and WHO Information for Healthcare Professionals: https://www.cdc.gov/coronavirus/2019-nCoV/hcp/index.html or https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected

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