UMassMemorial Health Care

COVID-19 Clinical Care Council

CLINICAL PRACTICE GUIDELINE: EMPIRIC EVALUATION AND MANAGEMENT OF COVID-19 IN ADULTS OCTOBER 23, 2020

PERSON UNDER INVESTIGATION (PUI)

Fever, cough (+/- sputum), shortness of breath, anosmia, anorexia, headache, fatigue, myalgias, nasal congestion, nausea, abdominal discomfort +/- diarrhea or per attending provider discretion.

Isolation: Initiate COVID PRECAUTIONS (STRICT AIRBORNE and CONTACT isolation + EYE PROTECTION)
Consider: Chest X Ray and/or EKG for respiratory complaints as indicated and COVID swab as indicated

MILD DISEASE

Upper respiratory tract symptoms
GI predominant symptoms
Mild-no dyspnea/chest tightness/DOE
Low grade fever/resolving fever
Normal oxygen saturation on RA
Minimal-no infiltrate

Consider discharge without further workup
OR
may consider:
Chemistry: CBC w/ diff, BMP, LFTs, troponin, BNP as indicated.
MISC: EKG, pregnancy test (as warranted)

DISCHARGE

If does not meet the admission criteria, then can be discharged to home with quarantine and test results follow-up instructions using the dot phrase .COVIDAVS in EPIC.

MODERATE TO SEVERE DISEASE

Moderate-severe dyspnea/DOE
Persistent fever or fever > 39C
Tachypnea
Hypoxia
Rales on exam
Infiltrates on initial imaging

Chemistry: CBC with diff, BMP, LFTs, troponin, BNP, CRP, d-dimer, PTT/PT/INR.
MISC: EKG, pregnancy test (as warranted)

If testing done and concerning abnormalities

ADMIT TO HOSPITAL

Goals of Care: Establish within 48 hours of admission.
Imaging: Consider CT chest in high risk PUIs with negative initial PCR results and a non-diagnostic chest X ray.
Chemistry: *Trend daily* CBC with diff, BMP, and LFTs.
Trend daily, if elevated at baseline: CRP, d-dimer, PT/PTT/INR
Trend daily troponin X 3 days (if normal) or trend to peak.
Microbiology: *If febrile*, send 2 sets of blood cultures. *If clinically indicated*: MRSA PCR, Respiratory cultures, and Legionella urinary antigen, HIV – 1 & 2 antibody (if not done previously)
Supportive care:

1. Oxygen supplementation to maintain O2 > 94% €
2. IV Fluids: as needed. Avoid overly aggressive hydration.
3. Fever management: NSAID (Avoid in AKI, elderly, HF), Acetaminophen (Monitor AST/ALT), Cooling blankets, Ice packs.
4. ACEI/ARB/STATIN: Do not disrupt or adjust treatment explicitly for COVID-19.
5. DVT prophylaxis should be initiated if not contraindicated (e.g platelets < 25, GI bleed)£

Antimicrobial Therapy*: Antibiotics should **NOT** be initiated on all patients with COVID as a matter of routine but should be initiated **ONLY** when there is clinical concern for a secondary bacterial infection (pleuritic chest pain, purulent sputum, leukocytosis, unilateral consolidation, worsening after few days of symptoms).

^Please refer to page 3 for antimicrobial management in the COVID19ClinCareCouncil CPG Evaluation and Management of COVID or https://downtime.umassmemorial.org/COVID19/Forms/AllItems.aspx
αPlease follow Infection Control precaution management guidelines on the hub regarding repeat testing and isolation. COVID19ClinCare Precautions Management
€COVID19ClinCare Respiratory Support and RT Utilization
£Refer to the adult VTE prophylaxis and treatment guidance during COVID

Modified: 10/23/20
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CLINICAL PRACTICE GUIDELINE
Empiric Evaluation and Management of COVID-19 in Adults
Updated 10/23/20

I. BACKGROUND AND AIM:

SARS-CoV-2 also referred to as COVID-19, is a novel respiratory virus with severe complications including multi-organ failure and death. Evaluation and management of COVID-19 is evolving daily. Management should involve a multidisciplinary approach to improve patient outcomes.

The aim of this guideline is to ensure that certain practices are a part of routine care of COVID-19 patients at UMMMC. It provides guidance for evaluation and management of patients to improve patient outcomes and avoid adverse events. This guideline is subject to change as new information becomes available and should not replace clinical judgement.

II. DEFINITIONS

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

COVID-19: The disease caused by SARS-CoV-2 virus

Mild Disease: URI, no dyspnea/chest tightness/DOE; normal O2 saturations on RA; low grade/resolving fevers/chills; minimal-no infiltrate

Moderate to Severe Disease/Lower Respiratory Tract infection:
Signs and Symptoms: Persistent fever or fever >39C, Moderate to severe dyspnea/DOE, tachypnea, Hypoxia
Laboratory Findings: Lymphopenia (elevated neutrophil to lymphocyte ratio is associated with severe illness, normal NLR = 1-3), Elevated inflammatory markers (CRP, ferritin), Elevated troponin, infiltrates on imaging

Risk factors associated with poor prognosis: Clinical assessment is the best predictor for progression of disease. Age > 65, patients living in a long-term care facility, immunosuppressed state (prolonged use of steroids or other immunosuppressants, transplant, poorly controlled HIV or AIDS), morbid obesity with BMI > 40, ESRD, poorly controlled diabetes mellitus, chronic lung disease, end-stage liver disease, cardiovascular disease, HTN, and pregnant patients

III. CLINICAL PRACTICE GUIDELINES FOR THE EVALUATION OF COVID-19

1. **SIGNS AND SYMPTOMS**: The following symptoms are associated with COVID-19 and should be evaluated on initial screening. If COVID-19 is suspected based upon symptoms or per attending provider discretion, patient should be placed into COVID precautions (see section V):
    a. Fever, cough, shortness of breath are the most common symptoms. Other symptoms that have been associated with COVID-19 include anosmia, anorexia, nasal congestion, headache, fatigue, myalgias, nausea, abdominal discomfort, diarrhea.

2. DISPOSITION

a. Mild Disease: discharged to home with strict instructions for home quarantine.
   i. Please refer to section VI for additional guidance regarding discharge
b. Moderate to Severe Disease: admitted to the hospital for monitoring

3. DIAGNOSTIC WORK UP

a. Microbiology
   i. Oropharyngeal/nasopharyngeal/ saliva PCR for COVID-19 – COVID Testing
   ii. If febrile, send 2 sets of blood cultures
   iii. If clinically indicated:
      1. MRSA PCR
      2. Sputum for bacterial culture
      3. Legionella urinary antigen
      4. HIV – 1 & 2 antibody (if not done previously)
   iv. In immunocompromised, HIV and transplant patients further work-up maybe required. Consider ID consult.
b. Chemistry

Based upon current literature and standards of care, the labs below are recommended for monitoring in hospitalized patients with COVID-19.

Lab Test	Upon Admission	Daily	Trend if abnormal
CBC with differential	X	X	
BMP	X	X	
AST/ALT	X	X (q48 hours)	
~~~~~~Consider sending if clinically indicated~~~~~			
Troponin	X	X for 3 days if normal	X trend to peak
BNP or NT-proBNP	X		
INR/PT/aPTT	X		X
D-dimer	X		X
CRP	X		X

   i. Additional tests to consider if concerned for secondary HLH associated with severe COVID-19: ferritin, fibrinogen and triglycerides

c. Imaging/Procedures
   i. Chest X-ray
   ii. Chest CT
      1. CT chest should be considered in high risk PUIs with negative initial PCR results and a non-diagnostic chest X ray.
      2. In most cases, diffuse patchy infiltrates are seen on the CT chest. Bilateral, rounded or geographic areas of ground glass opacities are associated with less severe and recovering pneumonia while consolidations in the periphery are seen in more severe cases.
   iii. Electrocardiogram (ECG)

d. Pulse Oximetry
   i. Oxygen saturation should be monitored continuously through pulse oximetry.

4. GOALS OF CARE

a. Evaluate within 48 hours of admission.

IV. CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF COVID-19

Severe COVID-19 is associated with a variety of medical complications including acute respiratory distress syndrome (ARDS), septic shock, acute kidney injury, elevated LFTs, myocardial infarction, secondary bacterial infection and multi-organ failure. Please review the guidance below for recommendations on management of COVID-19 patients.

1. ANTIMICROBIAL THERAPY

1. **Clinical trials** are the best way to evaluate therapies for COVID-19. Consider enrolling patients in trials available at UMMMC, see **Appendix A**.
2. See **Appendix A** for approving providers, inclusion/exclusion criteria**,** monitoring and dosing recommendations
   a. **Remdesivir**: Remdesivir is available through the health system based upon eligibility criteria. Please see the Remdesivir Process posted on the C4 page.

Table 1 COVID-19 Treatment Recommendations for Confirmed Infections

SEVERITY OF ILLNESS ***(see definitions)***	***TREATMENT***
Mild illness and patient does not require hospitalization	Supportive management at home and advise patient to seek medical attention if he/she gets worse.
Mild illness but needs hospitalization for another reason	Supportive management
Moderate – Severe illness in a hospitalized patient requiring supplemental O2 (invasive or non-invasive)	Supportive management Consider the following therapy options either alone or in combination: • Dexamethasone • Convalescent Plasma • Remdesivir Consider enrollment in anti-viral/immunomodulator clinical trials **(See Appendix A)**
Special populations: **Pregnancy, age< 18 years old**	Supportive management Consider enrollment in Remdesivir Clinical Trial

3. Suspected Secondary Bacterial Pneumonia in COVID-19 Positive Patient
    1. Antibiotics should **NOT** be initiated on all patients with COVID as a matter of routine but should be initiated **when there is clinical concern for a secondary bacterial infection**
    2. It is unclear how many patients have a superimposed bacterial pneumonia in addition to COVID-19 at this time. Patients with COVID-19 pneumonia may have persistent fever for an extended period and secondary bacterial pneumonia is uncommon early in the course. New fever in a patient who has been afebrile, a new infiltrate, leukocytosis in a patient who initially presented with leukopenia could be used as predictors of a secondary bacterial infection as well as an indication for starting empiric antibiotics.
    3. For empiric treatment of other infections, please see the UMMMC Empiric Antibiotic Card.

Table 2 Pneumonia Treatment Recommendations

Adults without risk factors for MRSA and P. aeruginosa.	Ceftriaxone 1-2 gm IV q24h *PLUS* *EITHER* Azithromycin 500 mg IV/PO q24h X 3 days *OR* Doxycycline 100 mg PO twice daily x 5 days
Adults with Risk Factors for MRSA and/or *P. aeruginosa* or mechanically ventilated patients – obtain respiratory culture	Vancomycin IV 15 mg/kg every 8-12 hours Δ *PLUS* Piperacillin/tazobactam 4.5 gm every 8 hours prolonged infusionΔ OR Cefepime 1 gm every 6 hours prolonged infusionΔ

Risk factors for MRSA:

- Known colonization with MRSA
- Gram-positive cocci in clusters on sputum Gram stain
- ESRD
- Recent influenza-like illness
- Recent antimicrobial therapy (particularly with a fluoroquinolone) in prior 90 days;
- Necrotizing or cavitary pneumonia
- Empyema

Risk factors for Pseudomonas:

- Known colonization with Pseudomonas
- Immunocompromised state (HIV, transplant recipients, neutropenic hosts, and those on immunosuppressive or immunomodulatory agents such as TNF-alfa inhibitors)
- Recent antimicrobial therapy (particularly with a fluoroquinolone) in prior 90 days
- Structural lung abnormalities such as cystic fibrosis or bronchiectasis
- Repeated exacerbations of COPD requiring frequent glucocorticoid and/or antibiotic use

Δ Consult pharmacy for questions on renal adjustment; Pharmacy will adjust administration times to cluster care

4. Viral Co-infection
    1. Co-infection of other respiratory viruses, such as influenza, can occur with COVID-19.
        a. The pharmacologic treatment of influenza, including oseltamivir, is the same in all patients regardless of SARS-CoV-2 coinfection.
        b. Remdesivir is not active against influenza A/B.
            i. There is no known drug – drug interaction between oseltamivir and remdesivir.

2. OTHER THERAPY CONSIDERATIONS

1. Volume repletion
    1. Intravenous Fluids should be given as needed for AKI, hypovolemia, etc.
2. Fever management
    1. Patients with COVID-19 often present with high fevers. There is no convincing evidence that fever is itself detrimental and does not automatically require suppression.

a. **NSAIDS:** There is no clinical data to support the recommendation to avoid NSAIDS in patients with COVID-19. NSAID therapy should be treated the same as in any other condition.
    i. Ibuprofen: 400 mg to 600 mg every 6 hours PRN; DO NOT EXCEED 3200 mg/ 24 hours
    ii. Aspirin: 325 mg to 1 g every 4-6 hours PRN; DO NOT EXCEED 4000 mg/24 hours
b. **Acetaminophen:** COVID-19 patients have been shown to have mild to moderate transaminitis. Consider limiting acetaminophen use in these patients. Patients enrolled in the NIH Remdesivir clinical trial (Appendix A) for investigational treatment of COVID-19 should not receive acetaminophen. DO NOT EXCEED 4000 mg/24 hours, in cirrhotic patients do not exceed 2000 mg/ 24 hours
c. **Non-pharmacologic cooling:**
    i. Cooled normal saline, Arctic Sun, Blanketrol, ice packs per ICU discretion.
    ii. Please refer to Therapeutic Normothermia/Shiver Control Guideline For Critically Ill Patients.

3. Steroids
    1. The use of corticosteroids, early in the disease course, has been associated with prolonged viral shedding and heightened risk of secondary bacterial infections.

    2. Dexamethasone 6 mg PO or IV once daily for up to 10 days (or until discharge if sooner) for confirmed SARS-COV2 patients with pneumonia and a requirement for supplemental oxygen or mechanical ventilation. Treatment may begin as early as the onset of the oxygen requirement but should not begin any later than 13 days from the onset of Acute Respiratory Distress Syndrome.

    3. At this time, for standard asthma/COPD exacerbations, would recommend usual care with prednisone or equivalent steroids. Dexamethasone is discouraged in this scenario, especially considering the limited benefit earlier in the course of therapy.

4. Inflammatory immunomodulators
    1. The role of immunomodulatory agents for the treatment of cytokine release syndrome associated with severe COVID-19 disease is currently being evaluated.
    2. Clinical trials using ruloxitinib or selinexor are available at the Medical Center (see Appendix A).
    3. Treatment outside of these pathways is discouraged.

5. ACE/ARBs/Statins

1. Do not disrupt or adjust treatment with ACE-inhibitor or ARB therapy in the treatment of COVID-19, unless needed for the management of other problems (e.g. hypotension).
2. Patients who are already on a statin should remain on this medication
    a. If a patient is not yet on a statin, but has an accepted indication to start a statin, can consider initiating statin therapy

6. H2-blockers (e.g. famotidine)
    1. Do not disrupt or adjust treatment with H2-blockers in the treatment of COVID-19, unless needed for the management of other problems (e.g. heartburn).
    2. Patients who are already on a H2-blocker should remain on this medication
        a. If a patient is not yet on a H2-blocker, but has an accepted indication to start a H2-blocker, can consider initiating therapy

7. Anticoagulation
    1. Use DVT prophylaxis with LMWH in all patients, if not contraindicated (active bleeding or severe thrombocytopenia – platelet < 25,000).
    2. Please see Adult VTE Prophylaxis and VTE Treatment Interim Guidance for COVID-19

8. Cardiovascular Management
    1. Please refer to the COVID-19 CPG: Cardiovascular Complications, Evaluation and Management.

9. Glycemic Control
    1. Use ICU Glycemic Control SQ Insulin for COVID 19 order set in ICU patients to conserve PPE, cluster care and optimize blood glucose management
    2. Please see Adult ICU Glycemic Control Interim Guidance for COVID-19

3. **DISCOURAGED THERAPIES**
    1. Some therapies have either not been shown to be effective in the treatment of COVID-19 or do not have enough evidence to support therapy at this time.
    2. Treatment with these agents is not recommended at this time: See **Appendix B** for further information.

V. PRECAUTIONS:

1. PERSONAL PROTECTIVE EQUIPMENT

1. The importance of hand hygiene and appropriate donning/doffing of PPE cannot be understated with this highly infectious disease. For further information on the appropriate measures please review the materials listed under the HUB PPE . All healthcare employees should avoid touching their face and eyes and should wash their hands after touching the outer surface of their mask.

2. REMOVAL OF PRECAUTIONS

As per Infection Control Management of Hospitalized Patients guidelines. Call Infection Control once the initial COVID test has resulted negative.

VI. DISCHARGE

Please refer to the COVID-19 Discharge guide for further instructions.

VII. ASSOCIATED TOOLS:

See COVID-19 Website on the Hub – Information for Health Care Professionals- Click Here

VIII. REFERENCES:

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APPENDIX A: Clinical Trials and Available Treatments

Consult pharmacy for drug-drug interactions

ACTT-3 Remdesivir +/- Interferon B double blind placebo controlled trial		
Dose	**Inclusion**	**Exclusion**

Remdesivir 200 mg x 1, then 100 mg IV daily for 5-10 days + /- Interferon 44 mcg subq every other day for 4 doses	1. Admitted to a hospital with symptoms suggestive of COVID-19. 2. Male or non-pregnant female adults ≥ 18 years of age at time of enrollment. 3. Has laboratory-confirmed SARS-CoV-2 infection as determined by PCR or other commercial or public health assay (e.g., NAAT and antigen tests) in any respiratory specimen, as documented by either of the following: • PCR or other assay positive in sample collected < 72 hours prior to randomization; OR • PCR or other assay positive in sample collected ≥ 72 hours but < 7 days prior to randomization AND progressive disease suggestive of ongoing SARS-CoV-2 infection. *Note: if written documentation of the positive test result is not available at the time of enrollment (e.g., report came from other institution), the subject may be enrolled but the PCR should be repeated at the time of enrollment.* 4. Illness of any duration, and at least one of the following: • Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), OR • SpO2 ≤ 94% on room air, OR • Requiring supplemental oxygen, OR • Requiring mechanical ventilation.	1. Anticipated discharge from the hospital or transfer to another hospital which is not a study site within 72 hours. 2. Subject is on or being prepared to go on ECMO at the time of screening. 3. Subjects with an estimated glomerular filtration rate (eGFR) < 30 mL/min are excluded unless in the opinion of the PI, the potential benefit of receiving remdesivir outweighs the potential risk of study participation. 4. ALT or AST > 5 times the upper limits of normal. 5. Total white cell blood cell count (WBC) <1500 cells/µL. 6. Platelet count <50,000/µL. 7. History of chronic liver disease (e.g., jaundice, ascites, hepatic encephalopathy, history of bleeding esophageal or gastric varices). No laboratory testing is needed. 8. Received three or more doses of remdesivir, including the loading dose, outside of the study for COVID-19. 9. Received convalescent plasma or intravenous immunoglobulin [IVIg] for the treatment of COVID-19. 10. Received any interferon product within two weeks of screening, either for the treatment of COVID-19 or for a chronic medical condition (e.g., multiple sclerosis, HCV infection). 11. Received any of the following in the two weeks

		prior to screening as treatment of COVID-19: • small molecule tyrosine kinase inhibitors (e.g., baricitinib, imatinib, gefitinib, acalabrutinib, etc.); • monoclonal antibodies targeting cytokines (e.g., TNF inhibitors, anti-interleukin-1 [IL-1], anti-IL-6 [tocilizumab or sarilumab], etc.); • monoclonal antibodies targeting T-cells or B-cells as treatment for COVID-19.

Convalescent Plasma Compassionate Use – Please e-mail UMASSCOVIDplasma@umassmed.edu

Rationale: Plasma that contains antibodies against COVID-19

Dose	**Inclusion**	**Exclusion**
Infusion of one unit of anti-SARS-CoV-2 convalescent plasma~300 mL over 4 hours, may repeat dose	• Greater than equal to 18 • Willing and able to provide informed consent • Laboratory confirmed COVID-19 infection • Severe or life-threatening COVID-19 • Less than 21 days from start of illness	• Pregnancy • Breastfeeding • Receipt of pooled immunoglobulin in past 30 days • Enrolled in other drug trials for treatment of COVID-19

Ruxolitinib Clinical Trial – randomized, double-blind, placebo-controlled- 5/28/20

Rationale: Inhibit cytokine storm associated with ARDS in COVID-19

Dose	Inclusion	Exclusion
Ruxolitinib 5 mg BID OR Ruxolitinib 15 mg BID OR Placebo	• >18 years old • SARs-CoV-2 positive test within 2 weeks of randomization • Invasive mechanical ventilation due to COVID-19 associated ARDS • $PaO_2/FiO_2 \leq 300$ mmHg within 6 hours of randomization	• CrCl< 15 mL/min or CRRT or HD • AST/ALT > 5X ULN • ANC < 1000 • Thrombocytopenia < 50,000 • Suspected active uncontrolled bacterial,

	• Imaging with bilateral or diffuse pulmonary infiltrates on CXR or CT Scan	fungal, viral or other infection (besides COVID-19) • Known Active TB Infection • Long-term use of JAK inhibitors • Treatment with IL=6 within 30 days of randomization • Cirrhosis
Regeneron Antibody Compassionate Use		
Compassionate Use for REGN-COV2 is principally for adult patients with recently diagnosed mild to moderate coronavirus disease who are at high risk of poor outcomes.	e-mail compassionateUse_Requests@regeneron.com	See Compassionate use Criteria

Appendix B Discouraged Treatments

Agent	Discouraged/Disproven
Azithromycin (for COVID-19)	Additional data needed before any conclusions can be made regarding possible benefits of using a combined regimen of hydroxychloroquine and azithromycin in pts with COVID-19 Because both azithromycin and hydroxychloroquine are associated with QT prolongation, caution is advised if considering use of both drugs in pts who have chronic medical conditions (e.g., renal failure, hepatic disease) or are receiving other drugs that cause arrhythmias *Azithromycin can be utilized for the treatment of atypicals in pneumonia*
Baloxavir	No currently known published clinical trial data regarding efficacy or safety in the treatment of COVID-19 at this time 2 trials ongoing in China
Oseltamivir	Neither oseltamivir nor zanamivir has demonstrated inhibition of cytopathic effect against SARS-CoV in in vitro cell culture.
Lopinavir/ritonavir	No significant differences in reduction of viral RNA load, duration of viral RNA detectability, duration of oxygen therapy, duration of hospitalization, or time from randomization to death. Cao et al. N Engl J Med Mar 2020

Nitric Oxide	Randomized controlled studies of inhaled nitric oxide in ARDS patients generally demonstrated modest improvements in oxygenation, but no effect on mortality and possible harm (e.g., renal impairment) 2 clinical trials ongoing
Ribavirin/Interferon Beta-1b	Ribavirin and IFN was associated with higher 90-day mortality compared with no treatment
IVIG	Prevalence of patients who have recovered from COVID-19 is likely very low in the blood donor population currently, so unlikely to be useful for patients at this time
Ivermectin	Only in vitro data available currently – area for further research
Vitamin C, D and Zinc	No current data evaluating use in COVID-19. Clinical trials are on-going. Initiation of these agents should not be solely be based upon treatment of COVID-19. Supplementation should be based upon micronutrient deficiencies.
Hydroxychloroquine	IDSA and NIH do not recommend use outside of a clinical trial. Use has been shown to increase adverse events, especially when administered with azithromycin.