UAMS Targeted Treatment Considerations for Patients Admitted with COVID-19 Infections

SEPTEMBER 25, 2020

UAMS Health

Clinical data on potential therapies for COVID-19 infections are severely limited. Therapies referenced in this document should be used with caution and consideration of potential benefits and harms should be measured prior to individual use. The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of remdesivir to treat hospitalized patients with COVID-19 for whom a clinical trial is not available, or participation is not feasible. The FDA has also approved convalescent plasma infusion for EUA.

Potential treatment options for COVID-19 infections (see table for dosing). All below treatments require Infectious Diseases approval:

1. **Mild/Moderate disease:** Admitted with minimal or no oxygen requirement
    a. Supportive care

2. **Severe disease:** Admitted with any of the following [SpO2 <94% on room air, RR>30 bpm, PaO2/FiO2 300mmHg]
    a. Consider remdesivir (See detailed inclusion below and contact Infectious Diseases)
    b. Consider convalescent plasma infusion (See detailed inclusion below and consider contacting Infectious Diseases)
    c. Consider dexamethasone
    d. Consider tocilizumab (See detailed inclusion below and contact Infectious Diseases)

3. **Critical disease:** ICU care with respiratory failure, shock, or multiple organ dysfunction or failure
    a. Consider remdesivir (See detailed inclusion below and contact Infectious Diseases)
    b. Consider convalescent plasma infusion (See detailed inclusion below and consider contacting Infectious Diseases)
    c. Consider dexamethasone
    d. Consider tocilizumab (See detailed inclusion below and contact Infectious Diseases)

***HIGH RISK criteria for developing severe or critical disease (any of the following apply):**

1. Age > 60yo
2. Chronic Medical Conditions such as pulmonary disease, chronic kidney disease, transplant, DM, HTN, CVD, cardiomyopathy, obesity, biologic immune modulators (many), other immunosuppressive medications including chronic corticosteroid treatment >20 mg oral prednisone daily, HIV, pregnancy
3. Any of the following lab abnormalities: ALC < 1,000 cells/uL, LDH >250IU/L, Ferritin>600ng/mL, CRP>50mg/L, AST or ALT >2x ULN

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Studies recommended for COVID-19 infections:

1. CBC with differential (admission and daily)
2. **BMP (admission and daily)**
3. Liver function tests (AST, ALT, TBili) (admission and daily)
4. Coags (PT, PTT, DDimer, fibrinogen) (admission and daily if in ICU)
5. **LDH (admission and daily)**
6. Inflammatory markers (CRP, ESR, Ferritin) (admission and daily)
7. Triglycerides (admission and daily if in ICU)
8. Troponin (admission and prn)
9. **EKG (admission and prn)**
10. Sputum culture (admission and prn)
11. MRSA nares PCR (if starting vancomycin for VAP/HAP coverage)
12. **IL-6 level (at ICU admission and prn if giving tocilizumab)**
13. Type and Screen **(admission and if needed again for CP transfusion)**

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Drug	Contra-indications	Monitoring	Data
Remdesivir Dose for adult >40kg: 200mg IV q24h x1d (load) 100mg IV q24h x4-9d (See further details below) Adverse effects: - Liver failure, AKI, infusion rxn	Relative contra-indications: 1. ALT level > 5 X ULN 2. eGFR<30 mL/min 3. Breastfeeding 4. Pregnancy: Comp use thru Gilead if ill	Routine: - CBC with diff - SCr - LFTs	COVID-19 Clinical Data: - Holshue (NEJM case report): C1 pt clinically improved. No adverse event - Grein (NEJM case series): 53 pts no control. 68% O2 improved. 57% MV pts->extubated - Wang (Lancet): 237 pts RCT (2:1) 14d imp 27% vs 24%-NS; 28d 65% vs 58%-NS - Beigel (NEJM ATCC trial): 1063 pts. 11 vs 15d imp (p<0.01); death 8% vs 11.6% (p=0.059) - Goldman (NEJM Simple trial): 397 pts. Severe w/o MV. 5 and 10d course same 14d imp - Spinner (JAMA RCT): 584 pts (1:1:1) 10d vs 5d vs SOC. 5d improved clinically (OR 1.7) COVID-19 In vitro Data: - Wang: very good in vitro efficacy similar to chloroquine
Tocilizumab (See further details below) Dose: 4-8mg/kg IV x1 (max 800mg) Round to nearest 100mg. If no benefit, consider redose at 24h Adverse effects: - Liver failure, cytopenias	1. Active bacterial infection Relative contra-indications: 1. Active hepatic disease or impairment (LFTs >3x ULN) 2. ANC< 1,000 cells/uL 3. Platelets <50,000 cells/uL 4. Pregnancy/Breastfeeding	Screen: 1. HBV profile 2. T-Spot Routine: - LFTs (d/c if >5x ULN) - IL6 level pre and post dosing	COVID-19 Clinical Data: - Xu, 21 case series severe/critical pts. All survived 91% d/c, 9% improving. By day 5, Imaging improved (91%), normalization of ALC (53%) and CRP (84%), and O2 req improved (75%). 18-1x dose; 3-2x doses. - Luo (JMV): 15 pts (2mod/6sev/7crit). 240-620mg. steroids 8/15. 5/15 redose. CRP normalized 14/15. 3/15 died (IL6 >3000 post toci- 4 pts: 3 died, 1 "disease aggravated") - Morrison (JA): Toci 81 pts; 46 surv vs 35 died: Early admin (sx<13d 83% vs 63%; p=.05) - Guaraldi (Lancet Rheum): Retro 179 toci vs 365 SOC. Death 7% vs 20%; HR 0.36, p<.001.
Dexamethasone 6mg PO or IV q24h x10d Adverse effects: - Adrenal suppression, immunosuppression, psych disturbance	Relative contra-indications: Invasive fungal infections		COVID-19 Clinical Data: - Horby (NEJM RECOVERY Trial): 2104 Dex vs 4321 SOC pts. 28d mortality vent pts (RR 0.65; p=0.0003), O2 pts (RR 0.8; p=0.002). No benefit if not on O2 (RR 1.2; p=0.14) - Fadel (CID): Mod/Sev MethylPred 0.25-0.5mg/kg/bid x3d. Tx ICU/Tube/death less with 35% vs 54% SOC; p=0.005.
Convalescent Plasma Infusion 1 unit (~200mL) Can consider additional units	Relative contra-indications: 1. Known IgA deficiency 2. History of transfusion reaction 3. Overt volume overload	Routine: Monitor for transfusion Reaction	COVID-19 Clinical Data: - Li (JAMA RCT): 101 pts CP vs SOC. 28d Mortality (16% vs 24%; OR 0.7; NS); Clinical Improvement: Critical (21% vs24%; NS) Severe (91% vs 68%; p=0.03) All (52% vs 43%; NS) - Joyner (MedRx Mayo EAP): 35K pt 2K sites. High IgG improved 7d (OR 0.65) & 30d (OR 0.77) mortality. <3d admit improve 7 (9% vs 12%) & 30d (22% vs 27%) mortality (p<.001)

Medications without clinical data to recommend for or against use in patients with known COVID-19 infection: IVIG, Ribavirin +/-interferon-(alpha or beta), NSAIDS, Ace inhibitors, ARBs

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Remdesivir treatment recommendations for UAMS patients with COVID-19 infection (ID approval required)

1. Highly Consider use when both of the following criteria are met:
    a. Recent positive SARS-CoV2 RT-PCR (within 72h) or recent symptom onset (<14d)
    b. Critical patients requiring mechanical ventilation <5d or are on advanced respiratory support (HFNC, CPAP, BiPAP)

2. Moderately Consider use when **all three** of the following criteria are met:
    a. Recent positive SARS-CoV2 RT-PCR (within 72h) or recent symptom onset (<14d)
    b. Pulmonary opacities by imaging (CXR or CT)
    c. Evidence of hypoxia (at least 2 of the following):
        i. SpO2 <94% on room air
        ii. RR>30
        iii. PaO2/FiO2 <300

3. Dosing for adult >40kg:
    a. Patients requiring mechanical ventilation with Critical COVID-19 infection:
        i. 200mg IV once x1d followed by 100mg IV q24h x9d
    b. Patients NOT requiring mechanical ventilation with Severe or Critical COVID-19 infection:
        i. 200mg IV once x1d followed by 100mg IV q24h x4d
        ii. If patient requires mechanical ventilation during course, treatment may be extended for up to 5 additional days (total of 10).

4. Relative contraindications:
    a. Active hepatic disease with AST or ALT >5x ULN
    b. Renal insufficiency with eGFR<30ml/min
    c. Pregnancy (not enough evidence to guide safety recommendation). Can consider compassionate use through Gilead
    d. Actively breastfeeding (No evidence to guide recommendation)

5. Baseline and daily monitoring labs:
    a. CBC with Diff
    b. BUN/SCr
    c. LFTs

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Tocilizumab Treatment recommendations for UAMS patients with COVID-19 infection (ID approval required)

1. Consider use when all of the following four criteria are met:
    a. Recent positive SARS-CoV2 RT-PCR
    b. Pulmonary opacities by imaging (CXR or CT)
    c. Illness of sufficient severity to require admission or transfer to the ICU
    d. Laboratory evidence supportive of cytokine storm (any of the following):
        i. IL-6 >3x ULN pg/mL
        ii. Ferritin >600 ng/mL
        iii. D-dimer >1000 ng/mL
        iv. CRP >50 mg/L
        v. LDH >250 IU/L

2. Recommend use when above 4 criteria are met plus any of the following:
    a. Worsening gas exchange over the preceding 24 hours defined as (any of the following):
        i. Worsening of SpO2 >3% or decrease in PaO2 >10%, with stable FiO2
        ii. Need of increase FiO2 in order to maintain a stable SpO2 or new onset need of mechanical ventilation
        iii. Increase in number and/or extension of pulmonary areas of consolidation
    b. Hypotension requiring vasopressor support
    c. Persistent fever during the preceding 24 hours, not due to other obvious infection

3. Dosing: 4-8 mg/kg iv once (max 800 mg), rounded off to the nearest 100 mg; repeat same dose in 24 hours if fever or shock persists or if gas exchange does not improve.

4. Relative contraindications:
    a. Bacterial infection
    b. Active hepatic disease
    c. Hematologic malignancy
    d. Absolute neutrophil count <1000/uL
    e. Platelet count <50,000/uL
    f. Alanine aminotransferase (ALT) >5x ULN
    g. Pregnancy or actively breastfeeding

5. Baseline testing:
    a. IL-6 if not already done; test should not be repeated after tocilizumab is administered
    b. HBV profile
    c. T-spot

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Convalescent plasma infusion therapy recommendations for UAMS patients with COVID-19 infection (ID consult recommended)

1. Consider use when **all three** of the following criteria are met:
    a. Recent positive SARS-CoV2 RT-PCR (within 72h) or recent symptom onset (<14d)
    b. Pulmonary opacities by imaging (CXR or CT)
    c. Evidence of hypoxia (at least 2 of the following):
        i. SpO2 <94% on room air
        ii. RR>30
        iii. PaO2/FiO2 <300

2. Dosing: 1 unit (~200mL) and can consider additional unit pending clinical response

3. Relative Contraindications:
    a. Known IgA deficiency
    b. History of transfusion reaction
    c. Overt volume overload

4. Baseline labs:
    a. Type and Screen