Version Number: v.1

June 15 , 2020

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale

Table of Contents

1.1 SCHEDULE OF ACTIVITIES (SOA)

Procedures	*Screening Day -2 to 1*	*Enrollment/Baseline Visit 1, Day A1+1*	*Day 3 +1* Study Visit (A or B or C)	Day 7 +/- 1 day Study Visit (A or B or C)	Day 10+/-1 Study Visit (A or B or C)	Day 28 +/-1 Study Visit (A or B or C)	ICU Hospital Study Visits (B)	Hospital Discharge Day Study Visit (B)	3 days Post Hospital Discharge Study Visits (C)	Day 45+/-3 Study Visit (A or B or C)	Day 60+/-3 Study Visit (A or B or C)	Day 75+/-3 Study Visit (A or B or C)	Day 90+/-3 Study Visit (A or B or C)	Final Study Visit if withdrawn from study or Day of Death Visits (A or B or C)
Informed consent	*X*													
Demographics	*X*													
Medical history	*X*													
Assignment to study arm based on randomization	*X*													
Administer study intervention		X	X	X										
Concomitant medication review	*X*----------													----------*X*
Physical exam	*X*	*X*	*X*	X	X	X	X	X	*	*	*	*	*	*
Vital signs	*X*	*X*	*X*	X	X	X	X	X	*	*	*	*	*	*
Height	*X*								*	*	*	*	*	*
Weight	*X*			X	X	X	X	X	*	*	*	*	*	*
SOFA or qSOFA (where all SOFA component data not available)	*X*	*X*	*X*	X	X	X	X	X	*	*	*	*	*	*
Hematology CBC, PT, PTT	*X*	*	*	*	*	*	*	*	*	*	*	*	*	*
ABO, blood group typing	X													
serum chemistry [d]	*X*	*	*	*	*	*	*	*	*	*	*	*	*	*
Pregnancy test [e]	*X*								*	*	*	*	*	*
EKG	*X*		*	*	*	*	*	*	*	*	*	*	*	*
Adverse event review and evaluation			X----------										----------X	
Radiologic/Imaging assessment	*X*		*	*	*	*	*	*	*	*	*	*	*	*
Other assessments: serum Ferritin, CRP, IL6 (if possible), SAA protein, S 100 A12, MRP 8/14; ADAMTS 13; Anti-phospholipid antibody if indicated	*X*	*	*	*	*	*	*	*	*	*	*	*	*	*
Obtain samples for virologic testing: Pharyngeal swab RTPCR	X			X	X			X						
Obtain ; Sputum or ET secretions or BAL; Blood; Stools; Urine if possible	X			X	X			X						
Complete Case Report Forms (CRFs)	*X*	*X*	*X*	X	X	X	X	X	X	X	X	X	X	X
Telephone interview for ADL; ROS; qSOFA and if necessary focused clinical exam									X	X	X	X	X	X

A: OP study visits; B: ICU/Hospital inpatient study visits; C: Post hospital discharge study visits.

d: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine (EGFR), glucose, LDH, phosphorus, potassium, total protein, AST, ALT, sodium. Troponin, CPK

e: Serum pregnancy test (women of childbearing potential).

**: Available data should be captured (where applicable information may be obtained by phone; telemedicine)*

2 INTRODUCTION

2.1 RATIONALE

Since January of 2020, COVID 19 has caused a global pandemic with around 4.41 million infections and 296883 deaths https://ourworldindata.org/grapher/covid-19-total-confirmed-cases-vs-total-confirmed-deaths accessed May 15, 2020. To date there is no accepted regimen of therapy established as a "Gold Standard" although clinical trials with antivirals are currently ongoing. For the individuals who develop severe illness and need support with mechanical ventilation the mortality with the current treatment strategy has a poor outcome. There is a need to evaluate repurposing medications approved for other

indications for possible efficacy against COVID 19. The combination of Ribavirin; Lopinavir/Ritonavir and Beta Interferon has demonstrated encouraging outcomes. Ribavirin is a broad-spectrum antiviral with activity against multiple viruses including some corona viruses in the laboratory. Ribavirin has been used clinically in a variety of viral infections and therefore there is a body of safety data available. Nitazoxanide is widely used as an antiparasitic agent and has an acceptable safety profile, interestingly Nitazoxanide and its metabolite Tizoxanide exhibit antiviral activity in the laboratory and also reduce IL6 production. Colchicine is used clinically for the treatment of gout as well as other hereditary inflammatory conditions and is known to attenuate NLRP3 which is implicated in the inflammatory condition caused by Coronaviruses. Interestingly Colchicine also appears to inhibit several kinds of viruses in replication in the laboratory although at the present time its activity against coronaviruses is not known. Lopinavir/Ritonavir has demonstrated activity in-vitro and in clinical trials. This protocol is testing the hypotheses that COVID 19 infections may be best addressed by multiple convergent strategies of using more than one agent with antiviral activity, and also to simultaneously mitigate inflammatory responses mediated by cytokines and inflammasomes. In individuals who have clinical signs and symptoms due to COVID 19 infection early administration of a combination of Favipiravir and Colchicine will lead to better clinical outcomes and perhaps reduction in viral shedding and mitigation of the epidemic due to reduction in horizontal spread. It is reported that individuals who have recovered from COVID 19 illness very often have a prolonged recovery with considerable long term disability which needs adequate evaluation. This protocol will also evaluate strategies of risk stratification of individuals with COVID 19 to understand how to optimize care and resource allocation.

2.2 BACKGROUND

COVID 19 is a newly describes Beta corona virus that was first noted to cause severe illness in Wuhan the capital of the Hubei province in the Peoples Republic of China, that rapidly evolved into a significant pandemic with a large number of infected people.[1] In previously described (corona virus) outbreaks of serious illness due to SARS and MERS effective antiviral therapy has not been established.[17,25,] This has prompted multiple efforts to understand the mechanisms of infection with corona viruses, elucidating the role of the spike protein of corona viruses in cellular entry and the role of various antibodies in blocking the pathogenesis of corona virus infections.[8,9,10.] There has also been an effort to develop potential therapies (including small molecules) based on the understanding of the structure and pathogenesis of corona virus infections. [4,5,6,7,13] Laboratory studies have elucidated the promising role of antibody mediated therapeutic strategies for corona virus infections.[2,3,8,10,11,12] Anecdotal experience with treatment regimens for corona virus infection causing SARS and MERS have not yielded any regimen of great promise, that would establish any kind of precedent for the current COVID infection induced illness.[16,17,25,] Early experience with Influenza outbreaks and Ebola Virus Disease rekindled interest in the experience of the use of convalescent plasma for the treatment of illness during the "Spanish Flu" outbreak that suggested improved outcomes with consideration use for contemporary illness due to Influenza and Ebola Virus Disease.[20,21,32] There have been several instances of trials of convalescent plasma therapy either alone or in conjunction with other therapies for managing illness due to Ebola Virus Disease, SARS and MERS.[14,15,16,19,23,24,26,27,28,29,30,31,33,40] Since the first description of COVID 19 infection in the USA,[35] increasing anecdotal experience of severe illness due to COVID 19 infections exacting a high toll, interest has centered on anecdotal experience with convalescent plasma as a therapeutic adjunct in the treatment of serious illness due to COVID 19[34,36,38,39] It is important to obtain high quality data with strict adherence to established best practice guidelines,[37] in conjunction with standards of care for management of severe illness due to COVID 19 infection.[41]Although clinical trials with the combination of Lopinavir/Ritonavir; Ribavirin and Interferon beta have demonstrated encouraging results, it is not yet established as the "Gold Standard". *Hung IF-N, Lung K-C, Tso EY-K, et al.*

Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. The Lancet. 2020;0(0). doi:10.1016/S0140-6736(20)31042-4. It is important to obtain as far as possible comparative data with other regimens of treatment[42] either ongoing or contemplated to get the best possible determination of the value of the combination of Colchicine and Favipiravir in the treatment of COVID 19 infection, therefore obtaining high quality data with a controlled trial design is imperative.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Colchicine: Common adverse events with colchicine use are limited to diarrhea and gastrointestinal events. These resolve on dose reduction or drug discontinuation. More serious adverse events during colchicine use, including liver and hematological changes, muscle toxicity, neuropathy and death were in the past associated with high doses and with low doses used now are very infrequent. Drug interactions may be seen with agents metabolized through the cytochrome system.[58]

Favipiravir: The most frequently reported adverse events in both adults, adolescents and children include, diarrhea, and nausea, transient elevations of uric acid and transaminases that resolve on stopping Favipiravir.

2.3.2 KNOWN POTENTIAL BENEFITS

The potential benefits maybe faster resolution of clinical symptoms as it is hoped that the combined effect of multiple sites of blocking viral replication with the combination of other antiviral agents in combination with the possible theoretical antiviral effect of Colchicine [60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76] will be important in controlling rapidly the very high replication of COVID 19, in other similar situations with high replication rate of RNA viruses (HIV;HCV) therapy with multiple agents has demonstrated superior control of viral replication. Since COVID 19 is known to cause severe illness due to cytokine storm [93,94,95,96,97,98,99,100], it may be of benefit to use agents that mitigate the cytokine expression particularly with colchicine as it is known to reduce IL1 and attenuate NLRP3 [77,78,79,80,81,82,83,84,85,86,87,88]in a variety of clinical conditions.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

At the present time individuals with serious illness due to COVID 19 who are managed with currently accepted best practice [41,42,52] have an unacceptably high mortality particularly in the older age group,[1] The participation in this trial does not in any way impact on institution of best available practices for the optimal care of any subject with illness due to COVID 19 as recommended by experts in the field.[41,42,52] The ideal regimen must have reasonable efficacy and the logistical convenience of an oral dosing with an acceptable safety profile that also reduces viral shedding which is important in secondary transmission and therefore epidemic control. Since the study is an open label randomized trial all involved in the care of the subject are free to determine the potential risks of the investigational regimen in real time. All subjects are receiving medications along conventionally accepted standard of care[41,42]. All data will be obtained and stored with strict adherence to confidentiality so all subjects have minimal risk of loss of privacy.

Blood Groups in Infection and Host Susceptibility | Clinical Microbiology Reviews. Accessed April 6, 2020. https://cmr.asm.org/content/28/3/801

Liang W, Liang H, Ou L, et al. Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients With COVID-19. JAMA Intern Med. Published online May 12, 2020. doi:10.1001/jamainternmed.2020.2033.

Gong J, Ou J, Qiu X, et al. A Tool to Early Predict Severe Corona Virus Disease 2019 (COVID-19) : A Multicenter Study using the Risk Nomogram in Wuhan and Guangdong, China. Clin Infect Dis. doi:10.1093/cid/ciaa443.

It is increasingly recognized that some individuals who have recovered from COVID 19 illness and have been discharged home continue to have long term sequelae of illness. Whether these sequelae are unique to COVID 19 illness or similar to the sequelae of other critical illness needs evaluation.

Covid-19 and Post Intensive Care Syndrome: A Call for Action. doi:10.2340/16501977-2677

Hough CL, Curtis Jr. Long-term sequelae of critical illness: memories and health-related quality of life. Critical Care. 2005;9(2):145. doi:10.1186/cc3483

In this study we will use SF-36 to evaluate the impact of COVID 19 on Quality of Life (QOL) and possible disability in individuals after discharge from the hospital.

https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form.html

2.4 JUSTIFICATION FOR DOSE

Favipiravir: A dose of 1800 mg twice followed by 800 mg twice daily is chosen based on the PK and acceptable safety profile as reported, and manufacturers recommended dose as approved for marketing in India.

Colchicine: A dose of 0.5 mg orally twice daily is chosen based on experience with other viral infections as well as treatment of other inflammatory disorders and to minimize the risk of adverse effects.[70,79,80,81,82,83,84,85.] .

Terkeltaub RA, Furst DE, Digiacinto JL, Kook KA, Davis MW. Novel evidence-based colchicine dose-reduction algorithm to predict and prevent colchicine toxicity in the presence of cytochrome P450 3A4/P-glycoprotein inhibitors. Arthritis Rheum. 2011;63(8):2226-2237. doi:10.1002/art.30389

3 POPULATION

3.1 INCLUSION CRITERIA

Inclusion Criteria at screening:

- Must have laboratory confirmed COVID-19 infection (NAAT based testing) within 72 hours of enrollment
- Additionally, must have at least one of the following signs or symptoms:
    - Fever (Oral temperature of at least 100.5° F or 38. 5° C)
    - Agusia/Dysgusia
    - Anosmia
    - Nausea/vomiting or Diarrhea
    - Malaise
    - Myalgia
    - Headache
    - Nasal congestion/coryza
    - Cough
    - Dyspnea (RR> 22) or blood oxygen saturation ≤ 95%,
    - Tachycardia (HR >80)

- New pulmonary abnormalities on chest imaging (Ultra Sound; Plain radiograph or CT)

In order to be eligible to participate in this study, an individual must meet all the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, aged at least 18 years.
4. Willing to adhere to the study intervention regimen
5. For females of reproductive potential: use of highly effective contraception during study participation and for an additional 6 weeks after the end of study intervention
6. For males of reproductive potential: use of condoms or other methods to ensure effective contraception with partner

3.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Unable or unwilling to give informed consent
2. Pregnancy or lactation
3. May have severe or immediately life-threatening COVID-19, for example:

- Severe disease is defined as:
  - respiratory frequency ≥ 30/min,
  - blood oxygen saturation ≤ 93%,
  - partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and/or
  - lung infiltrates > 50% of the imaged chest within 24 to 48 hours

- Life-threatening disease is defined as:
  - respiratory failure,
  - septic shock, and/or
  - multiple organ dysfunction or failure

4. Has been committed to comfort care only or restriction of resuscitation modes such as CPR or intubation or use of vasopressors
5. Has been determined to be unlikely to survive > 24 hours by critical care physicians involved in care
6. End stage renal disease; Advanced liver disease Childs Pugh C or greater.
7. Judged to be in a vegetative state due to irreversible brain injury
8. Known hypersensitivity to any of the study medications

4 INTERVENTION

4.1 INTERVENTION(S) ADMINISTRATION

4.1.1 INTERVENTION DESCRIPTION

After informed consent subjects will be prescribed 14 days of Favipiravir and Standard of Care or to 7 days of a Combination of Favipiravir; Colchicine along with standard of care.

4.1.2 DOSING AND ADMINISTRATION

After informed consent eligible subjects shall be prescribed medications according to group allocation that consists of 14 days of Favipiravir (1800 mg twice daily on day one followed by 800 mg twice daily) and Standard of Care.

or

Standard of care with 7 days of Favipiravir (1800 mg twice daily on day one followed by 800 mg twice daily) along with Colchicine orally half milligram twice daily. After completion of the seven day course of study medications, any subject is allowed to receive colchicine for other recognized anti-inflammatory indications such as myocarditis; pericarditis or pleuritis. The duration of colchicine treatment shall be at the discretion of the treating clinician.

4.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

4.2.1 ACQUISITION AND ACCOUNTABILITY

Study related medications will be prescribed using approved brands currently marketed in the country.

4.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The formulation, appearance, packaging, and labelling are in accordance with approved and marketed packages with the manufacturer's recommendations for storage and dispensation.

4.2.3 PRODUCT STORAGE AND STABILITY

As per manufacturer's specifications and recommendations

4.2.4 PREPARATION

All medications are prepared and marketed as per approved processes and procedures prescribed by the concerned regulatory agencies. (CDSCO)

All subjects shall have the following baseline procedures:

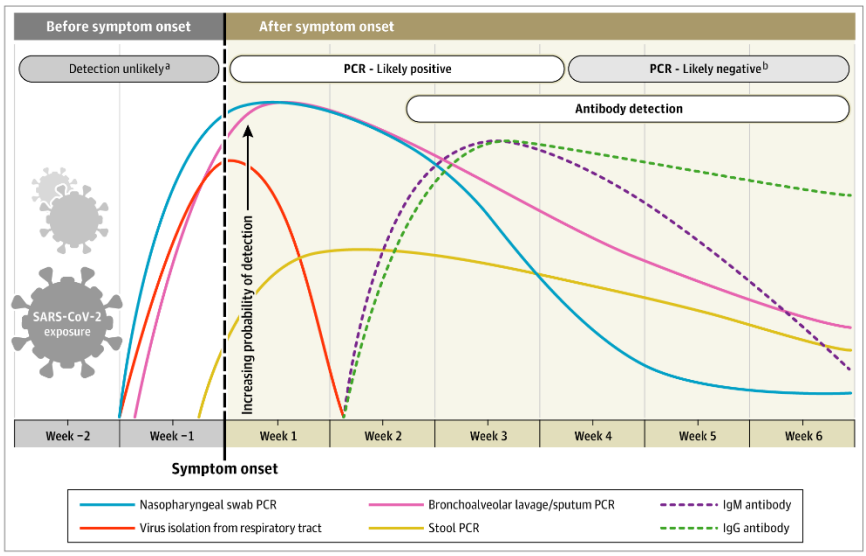
1. A complete medical history, including social history, occupational and family history.
2. Review of prior and concomitant medications.
3. Physical examination.
4. Vital signs, height, weight , SOFA score and qSOFA scores.[47,48]
5. EKG
6. Radiologic imaging (Ultra Sound, Chest radiographs and where available CT; MRI)
7. Pregnancy test (For women of childbearing potential)
8. Hematology; ABO blood group typing, PT, PTT.
9. Chemistry: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine (EGFR), glucose, LDH, phosphorus, potassium, total protein, AST, ALT, sodium, Troponin, CPK, Serum Ferritin, CRP, Serum Amyloid A protein, where appropriate anti-phospholipid antibodies. S 100 A12 protein, MRP 8/14 Protein.
10. Evaluation of risks for VTE (thromboprophylaxis as indicated)
11. Review for possible drug-drug interactions and appropriate adjustment
12. Evaluation for supplemental oxygen and early proning where appropriate
13. Unless contraindicated addition of Statins (HMG Co A reductase inhibitors) and Famotidine should be considered.
14. Review for adverse events.

It is strongly recommended that all subjects receive careful evaluation with appropriate diagnostic tests for COVID 19, for the inclusion only NAAT or antigen based testing is acceptable. Please see :

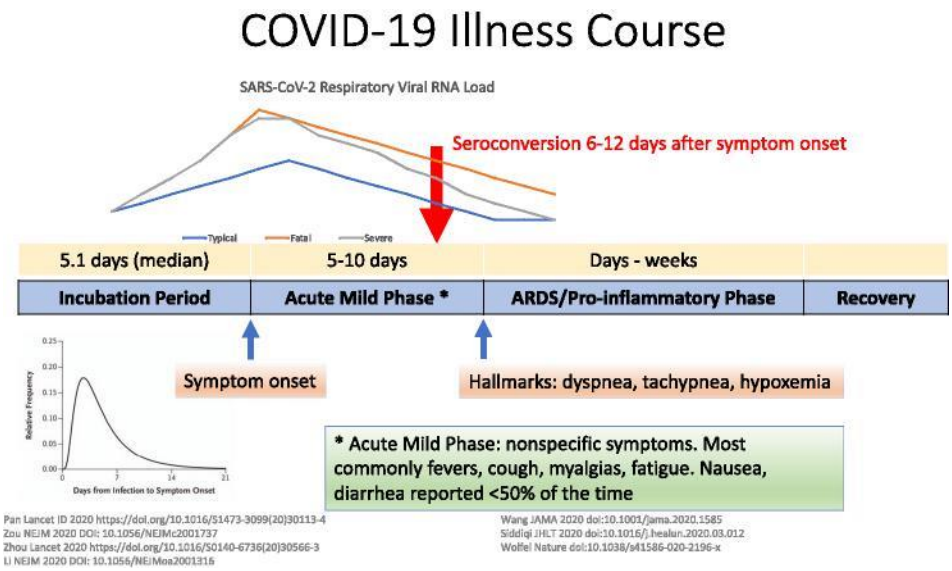
Sethuraman N, Jeremiah SS, Ryo A. Interpreting Diagnostic Tests for SARS-CoV-2. JAMA. Published online May 6, 2020. doi:10.1001/jama.2020.8259.

Estimated Variation Over Time in Diagnostic Tests for Detection of SARS-CoV-2 Infection Relative to Symptom Onset. Estimated time intervals and rates of viral detection are based on data from several published reports. Because of variability in values among studies, estimated time intervals should be considered approximations and the probability of detection of SARS-CoV-2 infection is presented qualitatively. SARS-CoV-2 indicates severe acute respiratory syndrome coronavirus 2; PCR, polymerase chain reaction.

a) Detection only occurs if patients are followed up proactively from the time of exposure.
b) More likely to register a negative than a positive result by PCR of a nasopharyngeal swab.



All subjects need to be characterized as to the stage of illness:



COVID-19 clinical course of illness. The first phase of COVID-19 infection involves an incubation period of variable duration, with a median of 5.1 days. The second is an acute mild phase that most commonly includes flu-like symptoms like cough, fevers, and myalgias, but can also include gastrointestinal symptoms. Some patients progress to an ARDS hyperinflammatory phase that is often marked by dyspnea, tachypnea, and hypoxemia. The respiratory viral load rises before the onset of symptoms and peaks around the onset of symptoms. It declines over the first week. Severe cases have higher viral loads compared with mild cases. Prolonged viral shedding in severe and mild cases is reported.

Meyerowitz EA, Vannier AGL, Friesen MGN, et al. Rethinking the role of hydroxychloroquine in the treatment of COVID-19. The FASEB Journal. 2020;34(5):6027-6037. doi:10.1096/fj.202000919.

Clinical care of the individual with COVID 19 infection requires evaluation for risk stratification and levels of CRP; LDH; Ferritin; Lymphopenia and alteration of the lymphocyte to neutrophil ratio may assist in identifying individuals at high risk for developing serious illness. See:

Liang W, Liang H, Ou L, et al. Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients With COVID-19. JAMA Intern Med. Published online May 12, 2020. doi:10.1001/jamainternmed.2020.2033

Gong J, Ou J, Qiu X, et al. A Tool to Early Predict Severe Corona Virus Disease 2019 (COVID-19) : A Multicenter Study using the Risk Nomogram in Wuhan and Guangdong, China. Clin Infect Dis. doi:10.1093/cid/ciaa443

Care of the seriously ill individual requires expeditious evaluation of hypoxemia; risk of thrombotic events; coagulopathy; derangements of neurologic, cardiac, hepatic and renal function.

Evaluation and Management of Severe Covid-19. Please see:

Guideline title Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults With COVID-19
Developer Surviving Sepsis Campaign (SSC)
Release date March 23, 2020
Target population Critically ill adults with COVID-19
Selected major recommendations:

Infection Control and Testing:

1. For health care workers performing aerosol-generating procedures (e.g., endotracheal intubation, nebulized treatments, open suctioning) use of fitted respirator masks is recommended (N95 respirators, FFP2), instead of surgical masks, in addition to other personal protective equipment (PPE) (best practice statement).

2. For usual care of nonventilated patients, or for performing non–aerosol-generating procedures on patients receiving mechanical ventilation, use of medical masks is recommended, instead of respirator masks, in addition to other PPE (weak recommendation, low-quality evidence [LQE]).

3. Diagnostic lower respiratory tract samples (endotracheal aspirates) are preferred over bronchial washings, bronchoalveolar lavage, and upper respiratory tract (nasopharyngeal or oropharyngeal) samples (weak recommendation, LQE).

Hemodynamic Support:

1. For acute resuscitation of adults with shock, the following are suggested: measuring dynamic parameters to assess fluid responsiveness (weak recommendation, LQE), using a conservative fluid administration strategy (weak recommendation, very LQE), and using crystalloids over colloids (strong recommendation; moderate QE). Balanced crystalloids are preferred over unbalanced crystalloids (weak recommendation, moderate QE).

2. For adults with shock, the following are suggested: using norepinephrine as the first-line vasoactive (weak recommendation, LQE), use of either vasopressin or epinephrine as the first line if norepinephrine is not available (weak recommendation, LQE). Dopamine is not recommended if norepinephrine is not available (strong recommendation, high QE). Adding vasopressin as a second-line agent is suggested if the target (60-65 mm Hg) mean arterial pressure cannot be achieved by norepinephrine alone (weak recommendation, moderate QE).

Ventilatory Support:

1. Starting supplemental oxygen is recommended if the SpO_2 is less than 90% (strong recommendation, moderate QE). SpO_2 should be maintained no higher than 96% (strong recommendation, moderate QE).

2. For acute hypoxemic respiratory failure despite conventional oxygen therapy, use of high-flow nasal cannula (HFNC) is suggested relative to conventional oxygen therapy and noninvasive positive pressure ventilation (NIPPV) (weak recommendation, LQE). If HFNC is not available, a trial of NIPPV is suggested (weak recommendation, very LQE). Close monitoring for worsening of respiratory status and early intubation if worsening occurs is recommended (best practice statement).

3. For adults receiving mechanical ventilation who have acute respiratory distress syndrome (ARDS), use of low tidal volume ventilation (4-8 mL/kg of predicted body weight) is recommended and preferred over higher tidal volumes (>8 mL/kg) (strong recommendation, moderate QE). Targeting plateau pressures of <30 cm H_2O (strong recommendation, moderate QE) is recommended. Using a higher positive end-expiratory pressure (PEEP) strategy over lower PEEP strategy is suggested (weak recommendation, LQE).

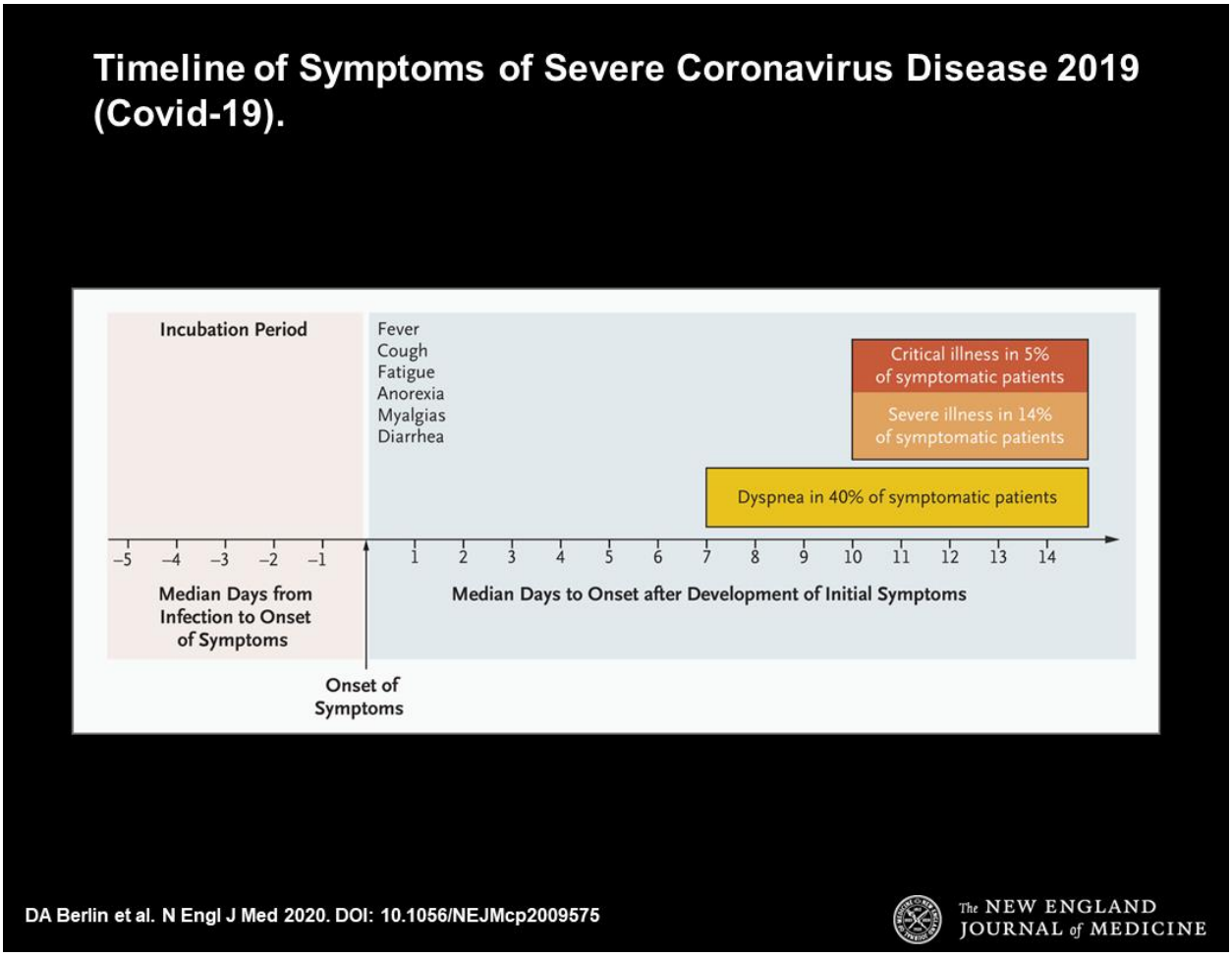
4. For adults receiving mechanical ventilation who have moderate to severe ARDS, prone ventilation for 12 to 16 hours is suggested over no prone ventilation (weak recommendation, LQE). Using as-needed neuromuscular blocking agents (NMBAs) instead of continuous NMBA infusion to facilitate protective lung ventilation is suggested (weak recommendation, LQE).

5. For adults receiving mechanical ventilation who have severe ARDS and hypoxemia despite optimizing ventilation, a trial of inhaled pulmonary vasodilator is suggested. If no rapid improvement in oxygenation is observed, the treatment should be tapered (weak recommendation, very LQE). The use of lung recruitment maneuvers (intended to open otherwise closed lung segments, such as 40 cm H_2O inspiratory hold for 40 seconds) is suggested, over not using recruitment maneuvers (weak recommendation, LQE), but using staircase (incremental PEEP) recruitment maneuvers is not recommended (strong recommendation, moderate QE). Use of veno-venous circulation for extracorporeal membrane oxygenation (ECMO) or referral to an ECMO center is suggested, if available, for selected patients (weak recommendation, LQE).

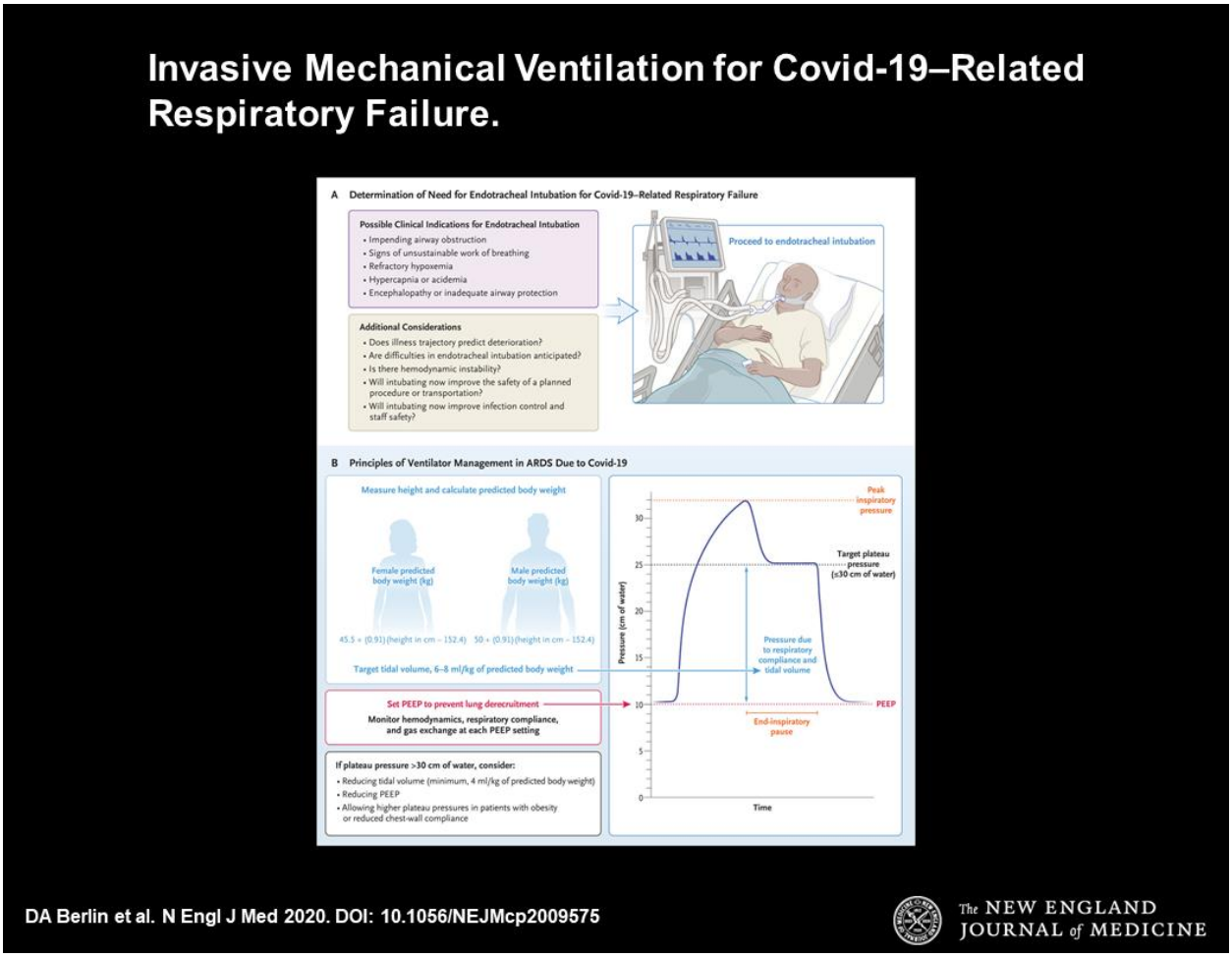
Therapy:

1. In adults receiving mechanical ventilation who do not have ARDS, routine use of systematic corticosteroids is suggested against (weak recommendation, LQE). In those with ARDS, use of corticosteroids is suggested (weak recommendation, LQE).
2. In COVID-19 patients receiving mechanical ventilation who have respiratory failure, use of empiric antimicrobial/antibacterial agents is suggested (no evidence rating); assess for de-escalation.
3. In critically ill adults with fever, use of pharmacologic agents for temperature control is suggested over nonpharmacologic agents or no treatment. Routine use of standard IV immunoglobulins is not suggested. Convalescent plasma is not suggested. There is insufficient evidence to issue a recommendation on use of any of the following: antiviral agents, recombinant interferons, chloroquine/hydroxychloroquine, or tocilizumab.

Poston JT, Patel BK, Davis AM. Management of Critically Ill Adults With COVID-19. JAMA. 2020;323(18):1839-1841. doi:10.1001/jama.2020.4914



A key management issue is the timing of invasive mechanical ventilation for critically ill COVID 19 individuals and the supportive/ancillary care needed.



Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. New England Journal of Medicine. 2020;0(0):null. doi:10.1056/NEJMcp2009575

Other considerations for supportive care such as use of Dexamethasone (Short course of 3 days); Tocilizumab; Eculizumab; Convalescent plasma; HMG CoA reductase inhibitors and/or use of N Acetylcysteine should be considered in each individual as appropriate.

1. *Berndt MC, Andrews RK. Thrombotic thrombocytopenic purpura: reducing the risk? Journal of Clinical Investigation. 2011;121(2):522-524. doi:10.1172/JCI46091*

2. *Knobl P. Inherited and acquired thrombotic thrombocytopenic purpura (TTP) in adults. [Review]. Seminars in Thrombosis & Hemostasis. 2014;40(4):493-502. doi:10.1055/s-0034-1376883*

3. *Martinez de Lizarrondo S, Gakuba C, Herbig BA, et al. Potent Thrombolytic Effect of N-Acetylcysteine on Arterial Thrombi. Circulation. 2017;136(7):646-660. doi:10.1161/CIRCULATIONAHA.117.027290*

4. *Levi M, Scully M, Singer M. The role of ADAMTS-13 in the coagulopathy of sepsis. Journal of Thrombosis and Haemostasis. 2018;16(4):646-651. doi:10.1111/jth.13953*

5. *Fenton JW, Jeske WP, Catalfamo JL, Brezniak DV, Moon DG, Shen GX. Statin Drugs and Dietary*

Isoprenoids Downregulate Protein Prenylation in Signal Transduction and Are Antithrombotic and Prothrombolytic Agents. Biochemistry (Moscow). 2002;67(1):85-91. doi:10.1023/A:1013956215394

6. *Weitz-Schmidt G. Statins as anti-inflammatory agents. Trends in Pharmacological Sciences. 2002;23(10):482-487. doi:10.1016/S0165-6147(02)02077-1*

7. *Greenwood J, Steinman L, Zamvil SS. Statin therapy and autoimmune disease: from protein prenylation to immunomodulation. Nature Reviews Immunology. 2006;6(5):358-370. doi:10.1038/nri1839*

At discharge and post discharge the long term impact including ongoing symptoms and disability must be evaluated and a plan for appropriate rehabilitation is strongly recommended.

See:

Covid-19 and Post Intensive Care Syndrome: A Call for Action. doi:10.2340/16501977-2677

Hough CL, Curtis Jr. Long-term sequelae of critical illness: memories and health-related quality of life. Critical Care. 2005;9(2):145. doi:10.1186/cc3483

In this study we will use SF-36 to evaluate the impact of COVID 19 on Quality of Life (QOL) and possible disability in individuals after discharge from the hospital.

https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form.html

Other Resources:

https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

Informed Consent Form

Title : Treatment of Illness due to COVID 19 infection.

Treating Physician: Vijay Yeldandi, M.D., FACP, FCCP, FIDSA

Participant's Printed Name:

Introduction:

At the present time there are no proven medications for the treatment of COVID 19 illness. The medication FabiFlu (Favipiravir) may be of benefit for the treatment of COVID 19 infection based on laboratory based research and limited data in human studies of COVID 19 infection. FabiFlu has received conditional approval in India for treatment of mild to moderate illness caused by COVID 19, in view of the emergency situation of the COVID 19 pandemic.

Taking this medication is entirely voluntary. We urge you discuss any questions about this medication with our staff members. Talk to your family and friends about it and take your time to make your decision. If you decide to take the medication you must sign this form to show that you want to do so.

Procedures:

Your doctor will obtain your medical history; results of your physical examination; review all of your test results to determine if it is appropriate for you to take this medication. We may need to have you take additional tests to monitor your progress and or any side effects of FabiFlu.

1. Tests to look for the COVID 19 virus and other tests to look for the responses of the body to the infection. These tests may be repeated if applicable.
2. At the time of the start approximately 10 ml (one tablespoon) of blood will be obtained to look for markers of inflammation in the body such as CRP, Ferritin, LDH.
3. Your doctor may do a scan (Ultra Sound) of your lungs or obtain a Chest radiograph or CT to look for evidence of lung infection (pneumonia)
4. You will receive prescriptions for medications to take.
5. If you are hospitalized, during your hospital stay and after your discharge from the hospital you will be followed to monitor your progress.

Time Duration of the Treatment

If you agree the total duration of the treatment is 14 days, unless your clinical condition dictates otherwise.

Discomforts and Risks

We may require obtaining samples for testing from your throat which may cause some discomfort. Although uncommon all medications can cause nausea, an upset stomach, diarrhea, or dizziness. Very rarely medications may cause abnormalities in your blood counts. These side effects may require the use of other medications to reduce the impact of such conditions.

OTHER POSSIBLE RISKS ASSOCIATED WITH TREATMENT

Venipuncture: The risks of drawing blood include temporary discomfort from the needle stick, bruising, bleeding, and rarely, infection. There also may be other side effects or discomforts that we cannot predict, especially to a fetus or embryo. Medications in this study may affect an unborn baby, you should not become pregnant or father a baby while on this study. Your doctor will discuss this with you.

Possible benefits to you:

The possible benefit you may experience is speedier recovery from the illness caused by COVID 19. However, there is no guarantee that you will benefit.

Privacy and confidentiality measures

We will keep your participation in this treatment confidential to the extent permitted by law. However, it is possible that other people may become aware of your treatment. For example, the following people/groups may inspect and copy records pertaining to your treatment.

The Government Health and Research agencies in the Republic of India.

Some of these records could contain information that personally identifies you. Reasonable efforts will be made to keep the personal information in your record private and confidential but absolute confidentiality cannot be guaranteed.

Costs for Participation

You will have to pay for the medications used and some of the laboratory or other tests as part of your care for COVID 19 illness.

Treatment and compensation for injury:

Every effort to prevent injury as a result of your participation will be taken. It is possible, however, that you could develop complications or injuries as a result of treatment with FabiFlu. In the event of injury resulting from this treatment , medical treatment is available but will be provided at the usual charge. It is the policy of this institution to provide neither financial compensation nor free medical treatment for treatment - related injury.

You will not lose any legal rights by signing this form.

Compensation for Participation

You will not receive any compensation.

Voluntary Participation

Taking treatment is voluntary. You do not have to take the medication. If you choose to take treatment, you have the right to stop at any time. If you decide not to take medication at a later date, there will be no penalty or loss of benefits to which you are otherwise entitled.

During the course of the research you will be provided with any significant new findings that may affect your willingness to continue participating in this treatment.

Contact Information for Questions or Concerns

You have the right to ask any questions you may have about this treatment. If you have questions, complaints or concerns or believe you may have developed an injury related to this treatment , contact Dr. Vijay Yeldandi *(91-7893003300)*.

Signature and Consent/Permission to be in the Treatment

Before making the decision regarding enrollment in this research you should have:

- Discussed this study with Dr. Yeldandi,
- Reviewed the information in this form, and

- Had the opportunity to ask any questions you may have.

Your signature below means that you have received this information, have asked the questions you currently have about the research and those questions have been answered. You will receive a copy of the signed and dated form to keep for future reference.

PARTICIPANT: By signing this consent form, you indicate that you are voluntarily choosing to take part in this treatment.

[Signature of participant]	[date]	[time]	[print name]
Signature of Participant	Date	Time	Printed Name

PARTICIPANT'S LEGALLY AUTHORIZED REPRESENTATIVE: By signing below, you indicate that you give permission for the participant to take part in this treatment.

[Signature of participant]	[date]	[time]	[print name]
Signature of Participant's Legally Authorized Representative	Date	Time	Printed Name

(Signature of Participant's Legally Authorized Representative is required for people unable to give consent for themselves.)

Description of the Legally Authorized Representative's Authority to Act for Participant:

[Description of the authority]

PERSON EXPLAINING THE TREATMENT: Your signature below means that you have explained the research to the participant/participant representative and have answered any questions he/she has about the treatment.

[Signature of participant]	[date]	[time]	[print name]
Signature of person who explained this treatment	Date	Time	Printed Name

5 REFERENCES

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