Suggested Pharmacotherapy of Confirmed Cases with COVID-19 Based on Investigational Drugs

This document was prepared by the COVID-19 Task Force of LSIDCM:

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- These recommendations are based on the available literature regarding the treatment of COVID-19 till 30/08/2020.
- These recommendations are subject to change and amendments according to emerging scientific data.

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Scope

- This is a live document used to guide the pharmacotherapy of COVID-19 infected patients; it can be changed with the appearance of new evidence.
- These recommendations are based on the available literature until 30/08/2020.
- The drugs mentioned are still under evaluation and the suggested options reflect different regimens that are being tested worldwide.
- Some drugs are not available in Lebanon at the time of document release.

Level of evidence

Table-1

Strength of Recommendation	**Quality of Evidence for Recommendation**
A: Strong recommendation for the statement	I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
B: Moderate recommendation for the statement	II: One or more well-designed, nonrandomized trials or observational cohort studies
C: Optional recommendation for the statement	III: Expert opinion

-**N.B.** This table is adapted from reference [1].

Definitions

Case definition (adapted from reference [2])

1-Suspect case

A. A person who meets the following clinical
    a. Clinical criteria:
        i. Acute onset of fever AND cough;
        OR
        ii. Acute onset of ANY THREE OR MORE of the following signs or symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, anosmia (loss of smell), ageusia (loss of taste), anorexia/nausea/vomiting, diarrhea, or altered mental status;
B. A patient with severe acute respiratory illness (SARI: acute respiratory infection with history of fever or measured fever of ≥ 38 °C; and cough; with onset within the last 10 days; and requires hospitalization).

2-Probable case

A. A patient who meets clinical criteria above AND is a contact of a probable or confirmed case, or epidemiologically linked to a cluster with at least one confirmed case
B. A suspect case with chest imaging showing findings suggestive of COVID-19 disease. Typical chest imaging findings suggestive of COVID-19 include the following:
    a. Chest radiography: hazy opacities, often rounded in morphology, with peripheral and lower lung distribution
    b. Chest CT: multiple bilateral ground glass opacities, often rounded in morphology, with peripheral and lower lung distribution
    c. Lung ultrasound: thickened pleural lines, B lines (multifocal, discrete, or confluent), consolidative patterns with or without air bronchograms.
C. A person with recent onset of anosmia or ageusia in the absence of any other identified cause.
D. Death, not otherwise explained, in an adult with respiratory distress preceding death AND was a contact of a probable or confirmed case or epidemiologically linked to a cluster with at least one confirmed case.

3-Confirmed case: A person with laboratory or pathologic confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.

Clinical staging of presenting illness (adapted from reference [1])

1. Mild: Individuals who have any of the various signs and symptoms of COVID 19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnea, or abnormal chest imaging.
2. Moderate: Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO_2) ≥94% on room air at sea level.
3. Severe: Individuals who have respiratory frequency >30 breaths per minute, SpO_2 <94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mmHg, or lung infiltrates >50%.
4. Sepsis/Cytokine Release Syndrome: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

Table 2- Recommended pharmacotherapeutic agents in COVID-19 based on severity of disease and those with insufficient evidence to be recommended for or against, yet accepted to be used in clinical trials

Stage	Agent(s)	Recommended to use	Insufficient data to recommend for or against*	Comments
Mild: Individuals who have any of the various signs and symptoms of COVID 19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnea, or abnormal chest imaging.	Azithromycin**		✔	Can be used within a clinical trial or national drug registry
	Vitamin C, Vitamin D and Zinc**		✔	Patients with adequate Vitamin D levels during the COVID pandemic have less risk of progressing to more severe infections
	Remdesivir	**BIII**		-Did not show superiority to SOC. -In case of prioritization of use, not recommended in mild/moderate infections. -Only if available for everybody, can be tried based on theoretical benefit. -Recommended in hospitalized patients at increased risk of severe infections *[References 3&4]*
Moderate: Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO2) ≥94% on room air at sea level.	Anticoagulation (Unfractionated heparin and low-molecular weight heparin)	**AII**		Check Table-4 for dosing.
	Interferon		✔	-If <7 days of illness onset -Can be used within a clinical trial. -Nebulized Interferon 1-alfa Recommendation against its use outside negative pressure rooms, for possibility of aerosol /airborne transmission.

	Vitamin C, Vitamin D and Zinc**		✔	Patients with adequate Vitamin D levels during the COVID pandemic have less risk of progressing to more severe infections
	Interleukin-1 inhibitors (Anakinra)		✔	
	Remdesivir	**AIII**		Use in patients who require O_2 supplement for 5 days. (Not on high flow or MV or ECMO) and for 10 days in those who become critically ill
	Favipiravir		✔	Can be used within a clinical trial *[Reference 3]* Efficacy and safety of favipiravir for treatment of COVID-19 not established. Given the lack of pharmacokinetic and safety data for favipiravir for treatment of COVID-19, should be used with caution at high dosages. Associated with QT prolongation, suggested close cardiac and hepatic monitoring during treatment.
Severe: Individuals who have respiratory frequency >30 breaths per minute, SpO2 <94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 or lung infiltrates >50%.	Tocilizumab		✔	To be used only in clinical trial or part of a national registry. *Press Release: July 29, 2020:* The industry-sponsored Phase 3 COVACTA trial (*ClinicalTrials.gov* Identifier NCT04320615), failed to meet its primary endpoint or several key secondary endpoints.
	Convalescent COVID-19 Plasma		✔	
	Anticoagulation (Unfractionated	**AII**		Check Table-4 for dosing.

	heparin and low-molecular weight heparin)			
	Corticosteroids	**BI**		
	Interleukin-1 inhibitors (Anakinra)		✔	
	Famotidine		✔	Can be used within a clinical trial *[Reference 5]*
	Remdesivir	**BI**		
	Bruton's tyrosine kinase inhibitors (Acalabrutinib)		✔	Can be used within a clinical trial
Sepsis/Cytokine crisis: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.	Tocilizumab		✔	To be used only in clinical trial or part of a national registry. *Press Release: July 29, 2020:* The industry-sponsored Phase 3 COVACTA trial (*ClinicalTrials.gov* Identifier NCT04320615), failed to meet its primary endpoint or several key secondary endpoints.
	Convalescent COVID-19 Plasma		✔	
	Anticoagulation (Unfractionated heparin and low-molecular weight heparin)	**AII**		Check Table-4 for dosing.
	Corticosteroids	**AI**		

N.B.

-Recommendations are adapted from references [1, 3, 4, & 5].

*Some agents are still lacking clinical data on its use to treat COVID-19 and clinical trials are in development (e.g tofacitinib, zanubrutinib, ibrutinib, and SARS-CoV-2 immunoglobulins)

** Azithromycin and vitamin/mineral supplements can be used despite that there is no enough evidence to recommend for or against their use; the prescriber can chose not to give any treatment or to administer it in a context of clinical trial.

Table 3- Non-recommended drugs and those recommended against their use in COVID-19

Stage	Agent(s)	Not recommended to use	Recommended against use	Comments
Mild: Individuals who have any of the various signs and symptoms of COVID 19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnea, or abnormal chest imaging.	Hydroxychloroquine Chloroquine	**AII**		
	Hydroxychloroquine + Azithromycin		**AI**	
	Lopinavir/Ritonavir + Interferon alfa + Ribavirin	**BII**		
	Lopinavir/Ritonavir		**AII**	
	Corticosteroids		**AI**	
Moderate: Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO2) ≥94% on room air at sea level.	Hydroxychloroquine		**AI**	
	Lopinavir/Ritonavir + Interferon alfa + Ribavirin	**BI**		
	Lopinavir/Ritonavir		**AII**	
	Corticosteroids		**AI**	
	Janus kinase inhibitors (Baricitinib)		**BII**	
Severe: Individuals who have respiratory frequency >30 breaths per minute, SpO2 <94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 or lung infiltrates >50%.	Interferons		**AIII**	Nebulized Interferon 1-alfa: recommendation against its use outside negative pressure rooms, for possibility of aerosol /airborne transmission.
	Mesenchymal Stem Cells		**AII**	
	Interleukin-6 inhibitors (Sarilumab, Siltuximab)		**BI**	
	Ivermectin		**AIII**	
	Immunoglobulins: Non-SARS-CoV-2 Specific		**AIII**	This recommendation **should not preclude** the use of IVIG when

				otherwise indicated for the treatment of complications that arise during the course of COVID-19.
Sepsis/Cytokine crisis: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.	Interferons		**AIII**	Nebulized Interferon 1-alfa: recommendation against its use outside negative pressure rooms, for possibility of aerosol /airborne transmission.
	Mesenchymal Stem Cells		**AII**	
	Interleukin-6 inhibitors (Sarilumab, Siltuximab)		**BI**	
	Janus kinase inhibitors (Ruxolitinib)		**AIII**	
	Immunoglobulins: Non-SARS-CoV-2 Specific		**AIII**	This recommendation **should not preclude** the use of IVIG when otherwise indicated for the treatment of complications that arise during the course of COVID-19.

N.B. Recommendations are adapted from references [1 & 5].

Table 4-Approach to anticoagulation prophylaxis and management in COVID-19 (adapted from reference [6])

	Category 1 **D-dimer < 3,000 ng/ml** **FEU** **Standard prophylaxis**	**Category 2** **D-dimer > 3,000 ng/ml** **FEU** **High-intensity prophylaxis**	**Category 3** **Confirmed VTE**
Standard dose	Enoxaparin 40 mg SC q24h	Enoxaparin 40 mg SC q12h	IV Heparin DVT/PE nomogram OR Enoxaparin 1 mg/kg SC q12h
Renal Failure **AKI definition: doubling of serum creatinine in 48h or anuria*	CrCl > 10-30 ml/min: Enoxaparin 30 mg SC q24h	CrCl < 30 ml/min: Enoxaparin 40 mg SC q24h	IV Heparin DVT/PE nomogram
	CrCl < 10 ml/min or AKI*: UFH 5,000 U SC q12h	CrCl < 10 ml/min or AKI*: UFH 7,500 U SC q12h	
	CRRT: 500U/h through circuit Circuit clotting: IV Heparin ACS nomogram**	CRRT: 500U/h through circuit Circuit clotting: IV Heparin ACS nomogram**	
Obesity			
Standard dose	>100 kg: Enoxaparin 40 mg SC q12h >120 kg: Enoxaparin 60 mg SC q12h	>100 kg: Enoxaparin 60 mg SC q12h >120 kg: Enoxaparin 80 mg SC q12h	IV Heparin DVT/PE nomogram OR Enoxaparin 1 mg/kg SC q12h (up to 150 mg) Above 150 kg use UFH
Renal Failure **CrCl < 30 ml/min or AKI*** **AKI definition: doubling of serum creatinine in 48h or anuria*	≤120 kg: UFH 7,500 U SC q12h >120 kg: UFH 10,000 U SC q12h	≤120 kg: UFH 7,500 U SC q8h >120 kg: UFH 10,000 U SC q8h	IV Heparin DVT/PE nomogram
	CRRT: 500U/h through circuit Circuit clotting: IV Heparin ACS nomogram**	CRRT: 500U/h through circuit Circuit clotting: IV Heparin ACS nomogram**	

****IV Heparin ACS nomogram:** initial dose 60 U/kg bolus, 12 U/kg/h

- Target aPTT 49-67 seconds
- Target heparin anti-Xa 0.2-0.5 unit/ml

Abbreviations: ACS= Acute Coronary Syndrome, **AKI**= Acute Kidney Injury, **aPTT**= activated partial thromboplastin time, **CrCl**= Creatinine Clearance, **CRRT**= Continuous Renal Replacement Therapy, **DVT**= Deep Venous Thrombosis, **FEU**= Fibrinogen Equivalent Units, **IV**= Intravenous, **PE**= Pulmonary Embolism, **SC**= Subcutaneous, **UFH**= Unfractionated Heparin.

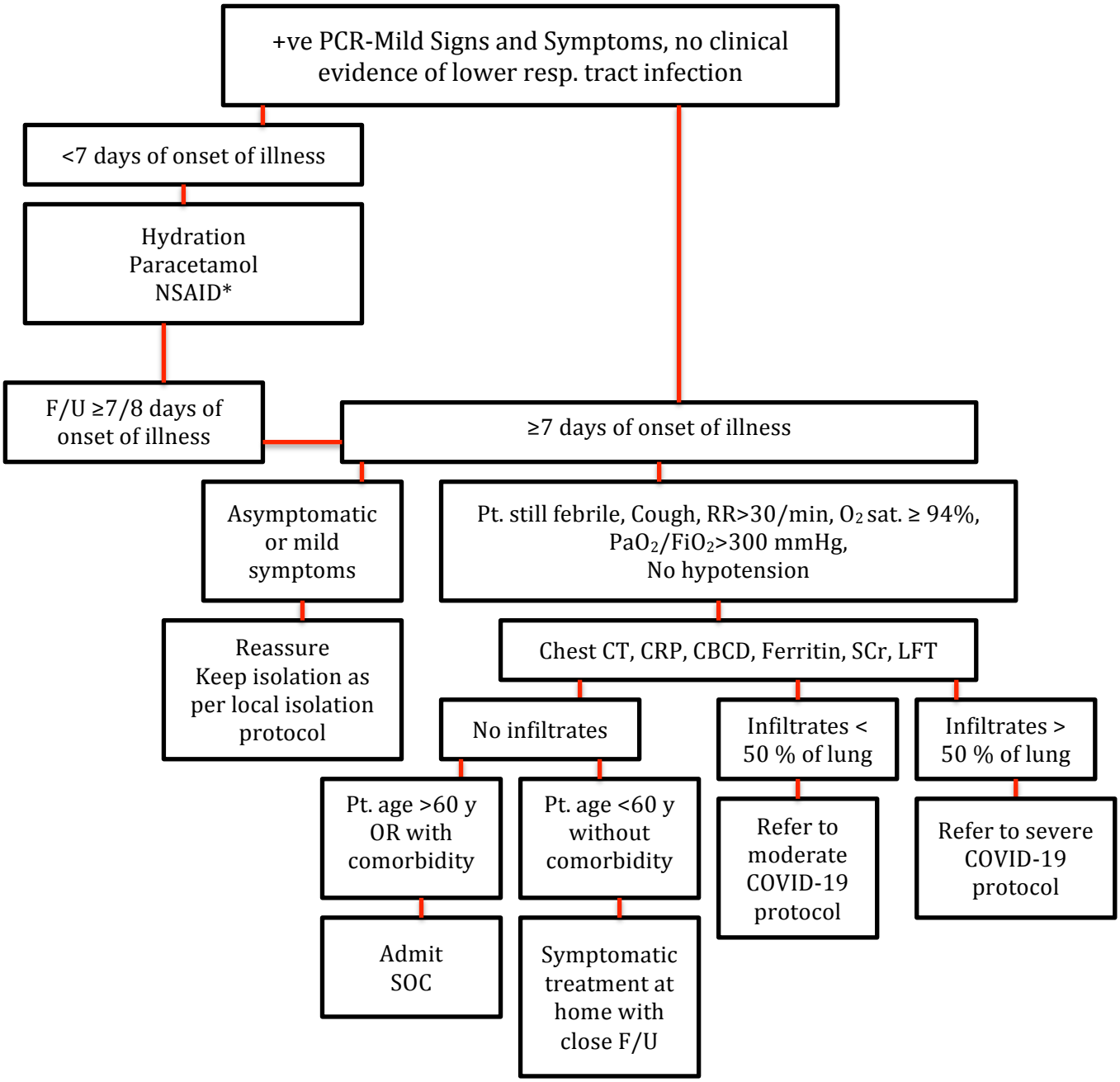
Table 5- COVID-19 adult drug dosing (with normal renal and hepatic function) for agents recommended to be used and others with insufficient evidence yet accepted to be used in clinical trials (adapted from references [1,3, & 5])

Drug	Dose
Recommended Drugs	
Remdesivir	***Adolescents,* Adults, Elderly *(weighing 40 kg or more)*** ***Requires mechanical ventilation and/or ECMO*** • Day 1 LD: 200 mg IV infused over 30-120 min, THEN • Days 2-10 MD: 100 mg IV q Day ***Does not require mechanical ventilation and/or ECMO*** • Day 1 LD: 200 mg IV infused over 30-120 min, THEN • Days 2-5 MD: 100 mg IV q Day • If clinical improvement not demonstrated, treatment may be extended for up to 5 additional days (i.e., up to 10 days total) ***Adolescents weighing 39 kg or less:*** Safety and efficacy have not been established; however, investigational doses of 5 mg/kg/dose IV on day 1, followed by 2.5 mg/kg/dose IV once daily have been used.
Azithromycin	• 500 mg once daily • 500 mg on day 1, then 250 mg once daily on days 2-5.
Vitamin C (IV ascorbic acid)	50 mg/kg IV every 6 hours for 4 days used in NCT03680274 and NCT04401150.
Vitamin D	Estimated Average Requirement (EAR) in adults of 70 years of age and less is 400 units (10 mcg) daily; Recommended Dietary Allowance (RDA) in these age groups is 600 units (15 mcg) daily. In adults >70 years of age, EAR is 400 units (10 mcg) daily and RDA is 800 units (20 mcg).
Zinc	Zinc Recommended Dietary Allowance: Adult males: 11 mg/day; adult females: 8 mg/day. Various supplementation regimens being evaluated in clinical trials, with a maximum dosage of zinc sulfate of 220 mg (50 mg of elemental zinc) twice daily. Oral zinc supplementation likely safe in dosages up to 40 mg of elemental zinc daily in adults.
Corticosteroids	Dexamethasone 6 mg IV or PO for 10 days (or until discharge if earlier) (preferred agent) or equivalent glucocorticoid dose may be substituted if dexamethasone unavailable. Equivalent total daily doses of alternative glucocorticoids to dexamethasone 6 mg daily are methylprednisolone 32 mg and prednisone 40 mg.
Drugs with insufficient evidence and can be used in the context of clinical trials	
Tocilizumab	**IV infusion (China):** • Initial dose of 4–8 mg/kg/dose infused over more than 60 minutes (Usual dose: 400 mg; Max dose: 800 mg).

	• If initial dose not effective, may administer second dose (in same dosage as initial dose) after 12 hours. • No more than 2 doses should be given; maximum single dose is 800 mg. **<u>IV infusion (US/Global randomized, placebo-controlled trial; manufacturer sponsored; COVACTA):</u>** • Initial IV infusion of 8 mg/kg (up to a maximum dose of 800 mg); • One additional dose may be given if symptoms worsen or show no improvement -*One protocol suggests a possible third dose administered 16 to 24 hours after the first dose.* **<u>Subcutaneous dosage</u>** • 324 mg via subcutaneous injection once. • A second dose administered 24 to 72 hours after the first injection has been given to some patients. • The subcutaneous formulation of tocilizumab is *not* intended for IV use.
Interferons (IFN beta-1a, IFN beta-1b, IFN alfa, Peginterferon lambda-1a)	**IFN beta:** 1. **<u>Open-label, randomized study in hospitalized adults with COVID-19, mainly mild disease (NCT04276688):</u> IFN beta-1b** 8 million units SC on alternate days for 1, 2, or 3 doses (when initiated on day 5-6, 3-4, or 1-2, respectively, following symptom onset) in conjunction with 14-day regimen of LPV/RTV and ribavirin. 2. **<u>Open-label, randomized study in hospitalized adults with COVID-19 (NCT04324463)</u>**: **IFN beta-1b** 0.25 mg SC on days 1, 3, 5, and 7, either alone or in conjunction with 7-day regimen of hydroxychloroquine (or chloroquine) and 5-day regimen of azithromycin. 3. **<u>Adaptive, open-label, randomized study in hospitalized adults with moderate or severe COVID-19 (NCT04315948):</u> IFN beta-1a** 44 mcg SC on days 1, 3, and 6 in conjunction with 14-day regimen of LPV/RTV. **IFN alfa:** Chinese guidelines suggest IFN alfa dosage of 5 million units (or equivalent) twice daily via atomization inhalation for treatment of COVID-19. **Peginterferon lambda-1a:** 1. <u>For *treatment* of COVID-19 in adults (NCT04354259, NCT04388709):</u> **Peginterferon lambda-1a** 180 mcg SC; number of doses (1 dose or 2 doses given 1 week apart) depends on the protocol. **2.** <u>For *postexposure prophylaxis* of CoV-2 infection in adults (NCT04344600):</u> Two 180-mcg SC doses of **Peginterferon lambda-1a** given 1 week.
COVID-19 Convalescent Plasma	• Consider initiating therapy with one unit (approximately 200 mL) of COVID-19 convalescent plasma

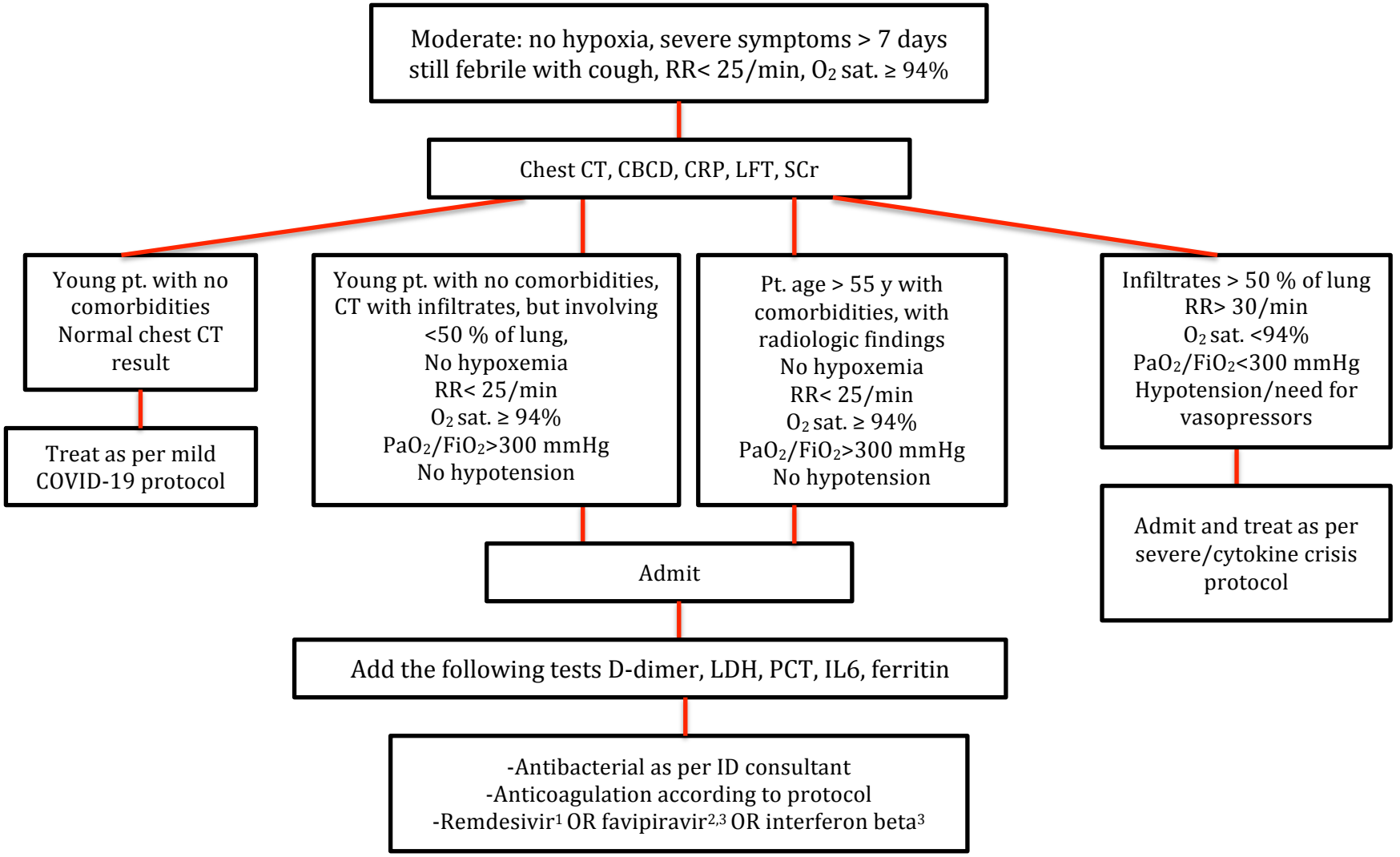
	given IV through a peripheral or central venous catheter based on the prescribing physician's medical judgment. • Additional units may be administered based on the prescribing physician's medical judgment and the patient's clinical response. • Smaller volumes or prolonged transfusion times may be necessary in patients with impaired cardiac function and heart failure.
Anakinra	**<u>Intravenous dosage</u>** Doses evaluated in different studies • 100 mg via intravenous infusion given every 6 hours for 15 days is being evaluated. • 200 mg intravenously every 8 hours for 7 days (SARS-CoV-2 infected patients with macrophage activation syndrome or immune dysregulation) • 5 mg/kg infused over 1 hour twice daily (COVID-19 patients with moderate-to-severe acute respiratory distress and hyperinflammation) **<u>Subcutaneous dosage</u>** Doses evaluated in different studies • 100 mg once daily via subcutaneous injection for 28 days or until hospital discharge. • 100 mg subcutaneously twice daily for 72 hours, followed by 100 mg daily for 7 days.
Favipiravir	• In one study, 1600 mg twice daily on day 1, then 600 mg twice daily thereafter for 7–10 or 14 days • Protocols in other registered trials for treatment of COVID-19 in adults: 1600 or 1800 mg twice daily on day 1, then a total daily dosage of 1200–2000 mg in 2, 3, or 4 divided doses for 4–13 days
Famotidine	• Randomized, double-blind, placebo-controlled, comparative trial (NCT04370262) is evaluating high-dose IV famotidine plus standard care vs. placebo plus standard care in hospitalized adults with moderate to severe COVID-19; • **Dosage in NCT04370262:** Given IV in 120-mg doses (proposed total daily dosage of 360 mg) for maximum of 14 days or until hospital discharge, whichever comes first. • Proposed daily dosage in NCT04370262 is 9 times the usual manufacturer-recommended IV adult dosage; the study excludes patients with creatinine clearance ≤50 mL/minute, including dialysis patients.

Algorithm 1-Mild cases with positive COVID-19 PCR



*N.B.*Azithromycin and vitamin/mineral supplements can be used despite that there is no enough evidence to recommend for or against their use in this category; the prescriber can chose not to give any treatment or to administer it in a context of clinical trial.*

Algorithm 2-Moderate COVID-19 Cases

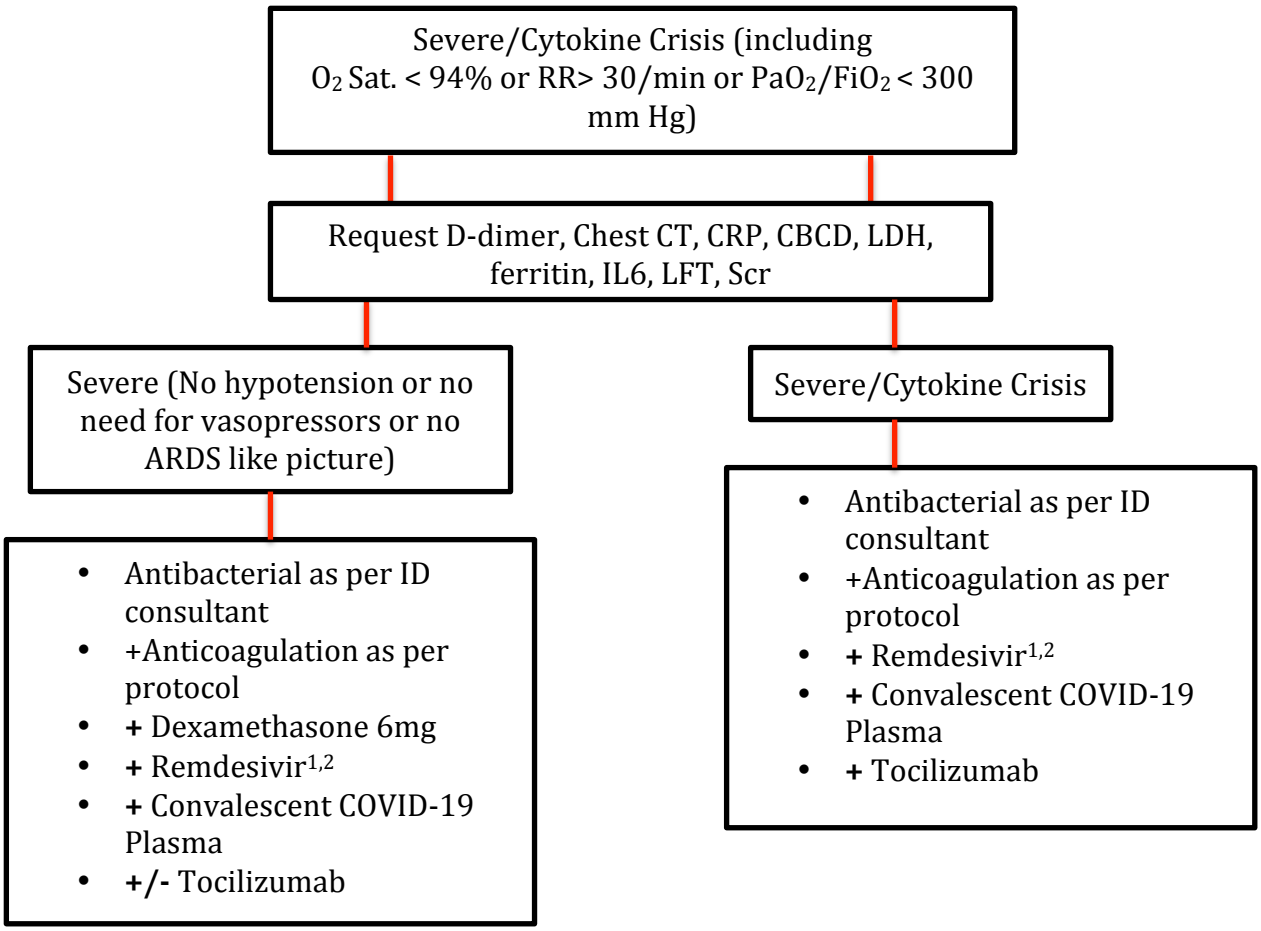


*N.B. [1]Remdesivir should be prioritized to treat severe cases with O_2 Sat. < 94% or RR> 30/min or PaO_2/FiO_2 < 300 mm Hg, **YET NOT ON** high O_2 flow or mechanical ventilation or ECMO. However, if remdesivir is available, it can be used in the moderate category.*

[2] Close observation of cardiac and hepatic side effects (ECG monitoring/LFT).

[3]Favipiravir or interferon-beta: there is no enough evidence to recommend for or against their use; can be used in context of a clinical trial.

Algorithm 3-Severe COVID-19/Cytokine Crisis



N.B [1]Remdesivir should be prioritized for severe cases with O_2 Sat. < 94% or RR> 30/min or PaO_2/FiO_2 < 300 mm Hg, ***YET NOT ON*** *high O_2 flow or mechanical ventilation or ECMO.*
[2]Duration of therapy when patient is NOT on high O_2 flow or mechanical ventilation or ECMO: 5 days (6 vials); Duration of therapy when patient is on high O_2 flow or mechanical ventilation or ECMO: 10 days (11 vials)

References:

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