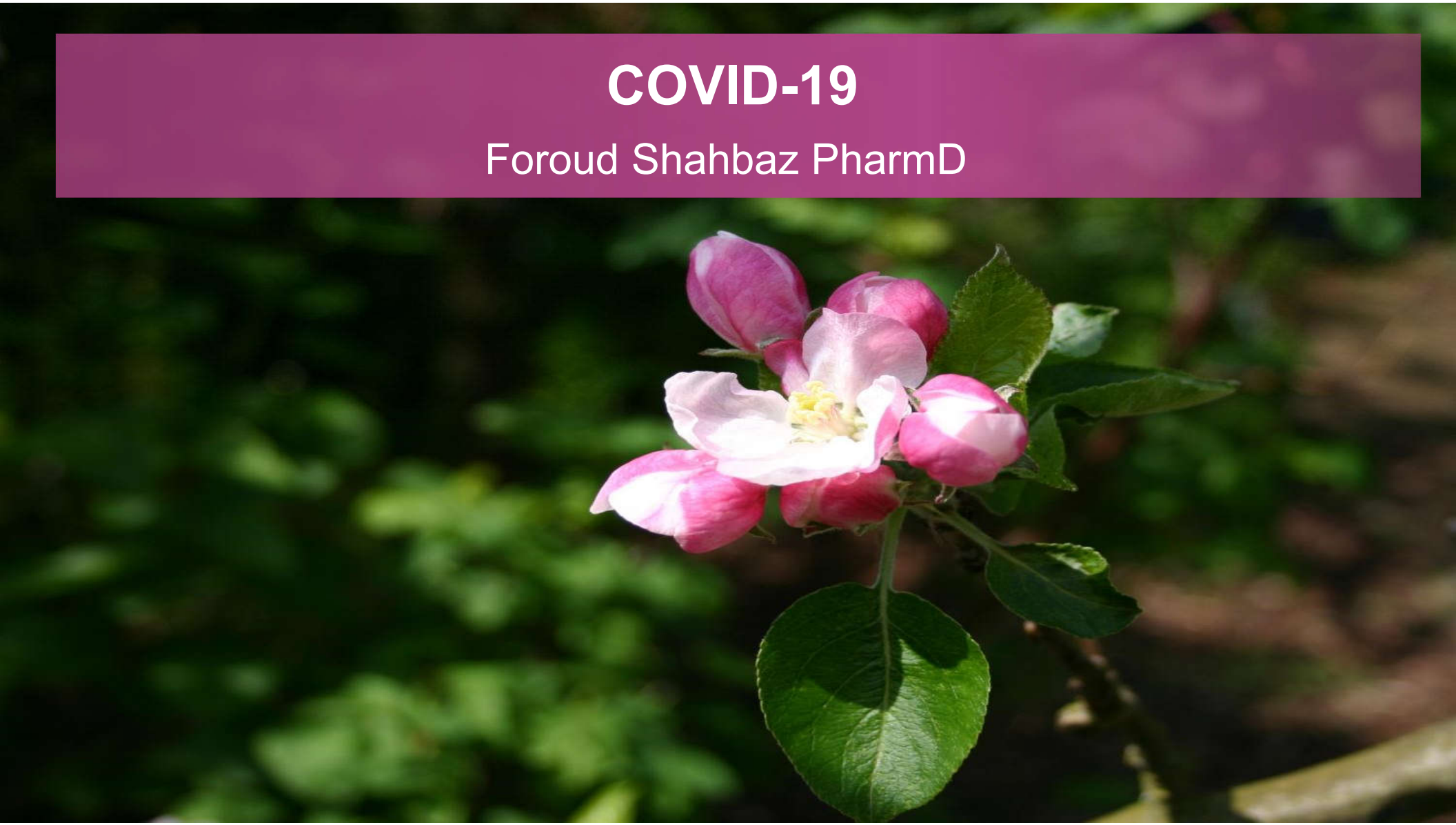
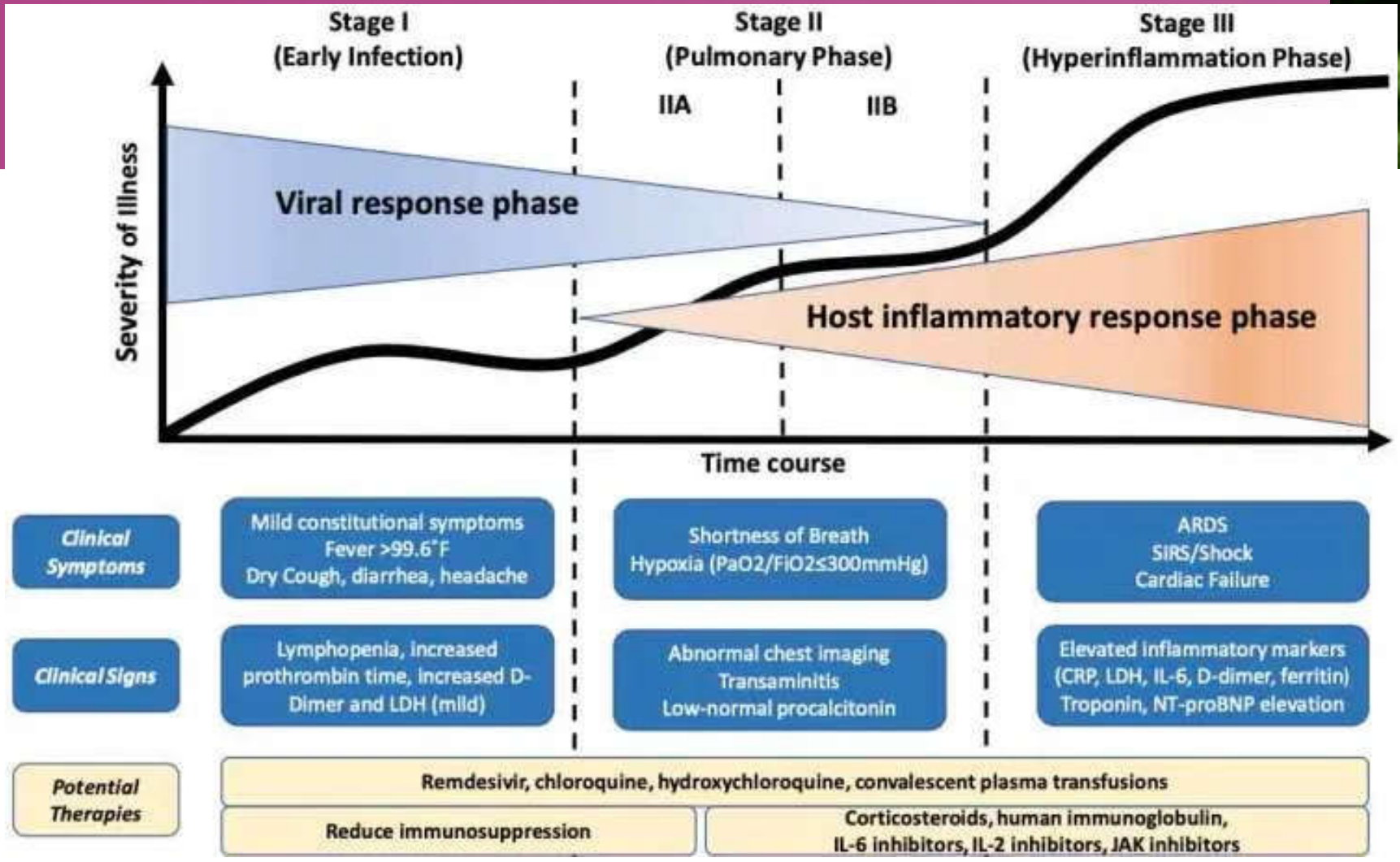
COVID-19

Foroud Shahbaz PharmD




Stage I
(Early Infection)
Stage II
(Pulmonary Phase)
IIA
IIB
Stage III
(Hyperinflammation Phase)
Severity of Illness
Viral response phase
Host inflammatory response phase
Time course
Clinical Symptoms
Mild constitutional symptoms
Fever >99.6˚F
Dry Cough, diarrhea, headache
Shortness of Breath
Hypoxia (PaO2/FiO2≤300mmHg)
ARDS
SIRS/Shock
Cardiac Failure
Clinical Signs
Lymphopenia, increased prothrombin time, increased D-Dimer and LDH (mild)
Abnormal chest imaging
Transaminitis
Low-normal procalcitonin
Elevated inflammatory markers (CRP, LDH, IL-6, D-dimer, ferritin)
Troponin, NT-proBNP elevation
Potential Therapies
Remdesivir, chloroquine, hydroxychloroquine, convalescent plasma transfusions
Reduce immunosuppression
Corticosteroids, human immunoglobulin,
IL-6 inhibitors, IL-2 inhibitors, JAK inhibitors

Stage I (early infection)

- Anti-viral therapies could be beneficial, especially in patients predicted to be at higher risk for poor outcome. Anti-viral therapies probably have *maximal* efficacy when given early, during this phase.
  - Interferon I-beta could theoretically be useful to augment the *innate* immune system response to the virus. This involves rendering cells resistant to viral infection, an intervention which would probably be most effective if deployed as early as possible (however this is a *theoretical* consideration, which currently is *not* recommended).
- Immunosuppression could theoretically be *dangerous* at this point, as it could delay the development of an adequate adaptive immune response. For example, *early* initiation of steroid has been shown to prolong virus shedding in SARS

Stage II (pulmonary phase)

- Antiviral-therapy could be beneficial (although the later on that antiviral treatment is initiated, the less effective it is likely to be).
- Some immunosuppression could be beneficial for patients with more severe manifestations (e.g., moderate dose steroid).

Stage III (hyperinflammation phase / cytokine storm)

- All the treatments from Stage II may be continued (e.g. moderate-dose steroid and antiviral therapy). Depending on the level of inflammation, a higher dose of steroid could be considered.

Stage	Characteristics
Asymptomatic or presymptomatic infection	▪ Positive test for SARS-CoV-2 but no symptoms
Mild illness	▪ Varied symptoms (eg, fever, cough, sore throat, malaise, headache, muscle pain) but no shortness of breath, dyspnea, abnormal imaging
Moderate illness	▪ $SpO_2 \geq 94\%$ and lower respiratory disease evidenced by clinical assessment or imaging
Severe illness	▪ $SpO_2 < 94\%$, $PaO_2/FiO_2 < 300$, respiratory rate > 30 breaths/min, or lung infiltrates > 50%
Critical illness	▪ Respiratory failure, septic shock, and/or multiorgan dysfunction

Mild disease

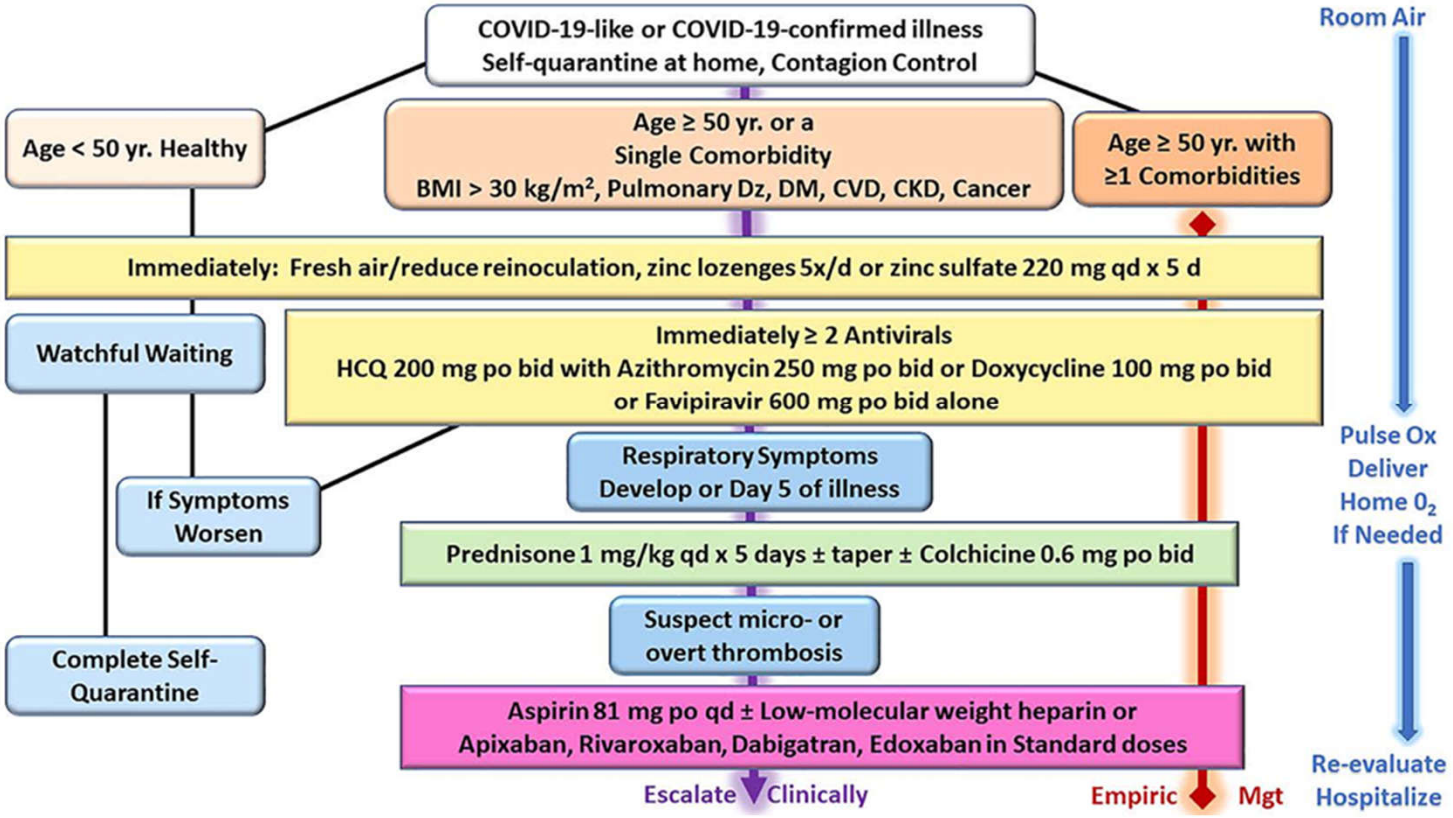
- WHO recommendations
- NIH recommendations

Not Hospitalized *or* **Hospitalized but Does Not Require Supplemental Oxygen**	No specific antiviral or immunomodulatory therapy recommended The Panel **recommends against** the use of **dexamethasone (AI)** See the Remdesivir section for a discussion of the data on using this drug in hospitalized patients with moderate COVID-19.[a]

Moderate disease

Not Hospitalized *or* **Hospitalized but Does Not Require Supplemental Oxygen**	No specific antiviral or immunomodulatory therapy recommended The Panel **recommends against** the use of **dexamethasone (AI)** See the Remdesivir section for a discussion of the data on using this drug in hospitalized patients with moderate COVID-19.[a]

Outpatients
level of evidence?



Severe and critically (NIH)

Hospitalized and Requires Supplemental Oxygen (but Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO)	**Remdesivir** 200 mg IV for one day, followed by remdesivir 100 mg IV once daily for 4 days or until hospital discharge, whichever comes first **(AI)**[b,c,d] *or* **Remdesivir** (dose and duration as above) plus **dexamethasone**[e] 6 mg IV or PO for up to 10 days or until hospital discharge, whichever comes first **(BIII)**[f] If **remdesivir** cannot be used, **dexamethasone**[e] may be used instead **(BIII)**
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	**Dexamethasone**[d] plus **remdesivir** at the doses and durations discussed above **(AIII)**[f] *or* **Dexamethasone**[d,e] at the dose and duration discussed above **(AI)**
Hospitalized and Requires Invasive Mechanical Ventilation or ECMO	**Dexamethasone**[d,e] at the dose and duration discussed above **(AI)** *or* **Dexamethasone**[e] plus **remdesivir** for patients who have recently been intubated at the doses and durations discussed above **(CIII)**[f]

IDSA

- Recommendation 9: In hospitalized patients with severe* COVID-19 (SpO_2 ≤94% on room air; on supplemental oxygen, mechanical ventilation, or ECMO, the IDSA panel suggests remdesivir over no antiviral treatment. (Conditional recommendation, Moderate certainty of evidence)
- Recommendation 10: In patients on supplemental oxygen but not on mechanical ventilation or ECMO, the IDSA panel suggests treatment with five days of remdesivir rather than 10 days of remdesivir. (Conditional recommendation, Low certainty of evidence)

- **Recommendation 11: In patients with COVID-19 admitted to the hospital without the need for supplemental oxygen and oxygen saturation >94% on room air, IDSA suggests against the routine use of remdesivir. (Conditional recommendation, Very low certainty of evidence)**

Remdesivir

- Remdesivir is available in two bioequivalent formulations: a concentrated solution (5 mg/mL) and a lyophilized powder formulation. Vials contain 100 mg of remdesivir and are preservative free.

Metabolism

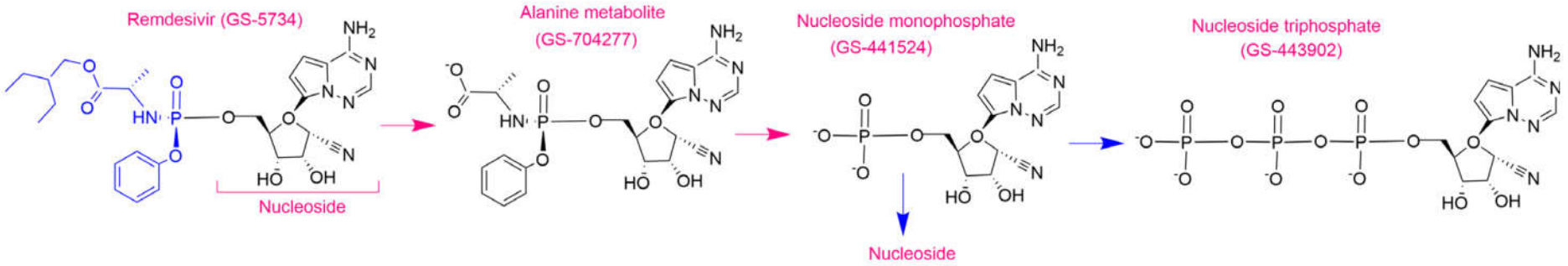


Figure 1. Chemical structures of remdesivir and its metabolites.

Remdesivir

- Hospitalized requiring low flow supplemental oxygen
- Hospitalized requiring high-flow oxygen or noninvasive ventilation
- Hospitalized requiring invasive mechanical ventilation or ECMO

Efficacy

- People treated w/ Remdesivir were less likely to be intubated: 17% vs 24%
- Remdesivir is more effective if given <10 days after symptoms
- Adverse events occurred at similar rates w/ Remdesivir & placebo

Supply and interaction?

- The NIH COVID-19 Treatment Guidelines Panel issued guidelines regarding prioritizing use of remdesivir when supplies are limited:
- The panel recommends the drug be prioritized for use in hospitalized pts with COVID-19 who require supplemental oxygen, but are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO, because efficacy in this patients population has been demonstrated (NCT04280705; ACTT-1).
- Concomitant use of remdesivir and chloroquine or hydroxychloroquine is not recommended.
- Remdesivir rifampin combination not recommended
- No interaction with dexamethasone

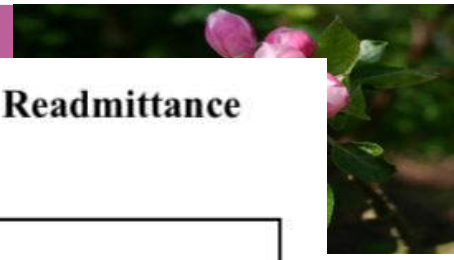
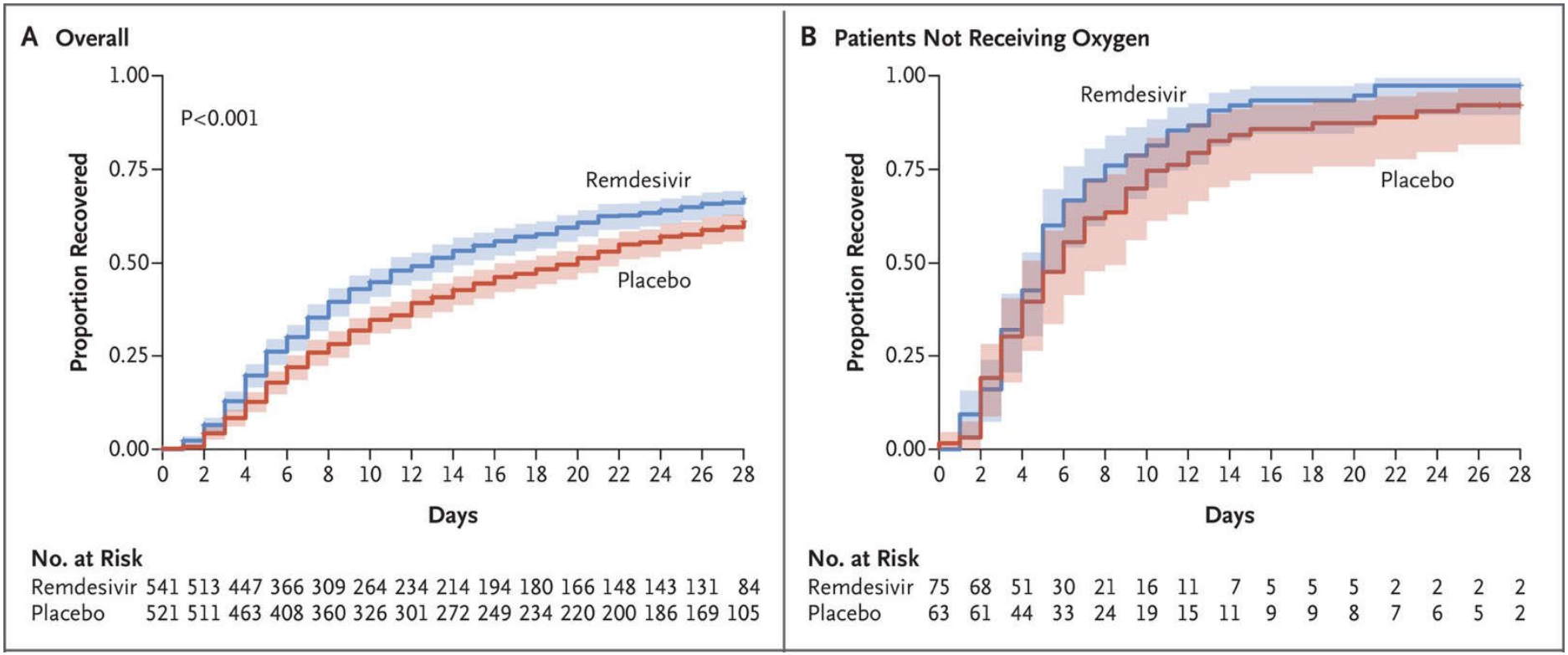


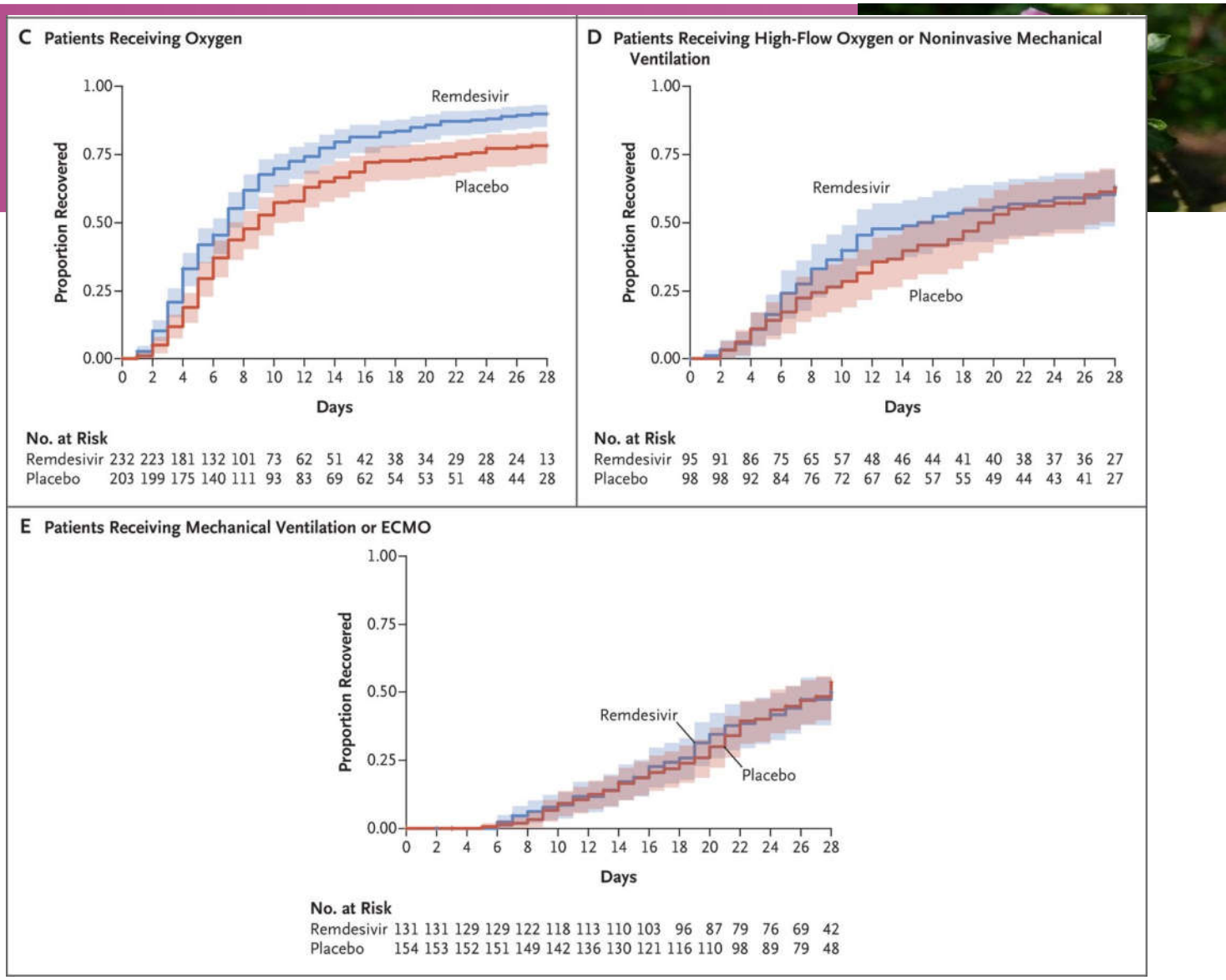
Table S7. Time to Recovery by Treatment Group and Randomized Disease Severity: Readmittance Sensitivity Analysis – ITT Population

					Median Time to Recovery		HR	
Analysis Population	**Treatment Group**	**Disease Severity**	**m**	**n**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
ITT Population	Remdesivir (N=82)	Mild/Moderate	5	70	6.0	5.0, 8.0	1.05	0.75, 1.47
	Placebo (N=77)		4	67	7.0	5.0, 10.0		
	Remdesivir (N=459)	Severe	21	303	13.0	11.0, 16.0	1.26	1.07, 1.49
	Placebo (N=444)		11	270	20.0	17.0, 22.0		
	Remdesivir (N=541)	Any Severity	26	373	11.0	10.0, 13.0	1.22	1.05, 1.41
	Placebo (N=521)		15	337	16.0	14.0, 20.0		

N= Number of participants in the specified treatment group, disease severity, and analysis population.
m = Number of participants who were readmitted.
n = Number of recovered participants.
HR for the 'Any Severity' group is the ratio of the hazard of recovery in each treatment group estimated from the stratified Cox Model. The ratio is Remdesivir to Placebo.
For this analysis, participants who recovered but were subsequently readmitted were censored at 28 days.


A Overall
1.00
0.75
0.50
0.25
0.00
P<0.001
Remdesivir
Placebo
Proportion Recovered
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
Days
No. at Risk
Remdesivir 541 513 447 366 309 264 234 214 194 180 166 148 143 131 84
Placebo 521 511 463 408 360 326 301 272 249 234 220 200 186 169 105
B Patients Not Receiving Oxygen
1.00
0.75
0.50
0.25
0.00
Remdesivir
Placebo
Proportion Recovered
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
Days
No. at Risk
Remdesivir 75 68 51 30 21 16 11 7 5 5 5 2 2 2 2
Placebo 63 61 44 33 24 19 15 11 9 9 8 7 6 5 2

Recovery


C Patients Receiving Oxygen
Proportion Recovered
1.00
0.75
0.50
0.25
0.00
Remdesivir
Placebo
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
Days
No. at Risk
Remdesivir 232 223 181 132 101 73 62 51 42 38 34 29 28 24 13
Placebo 203 199 175 140 111 93 83 69 62 54 53 51 48 44 28
D Patients Receiving High-Flow Oxygen or Noninvasive Mechanical Ventilation
Proportion Recovered
1.00
0.75
0.50
0.25
0.00
Remdesivir
Placebo
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
Days
No. at Risk
Remdesivir 95 91 86 75 65 57 48 46 44 41 40 38 37 36 27
Placebo 98 98 92 84 76 72 67 62 57 55 49 44 43 41 27
E Patients Receiving Mechanical Ventilation or ECMO
Proportion Recovered
1.00
0.75
0.50
0.25
0.00
Remdesivir
Placebo
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
Days
No. at Risk
Remdesivir 131 131 129 129 122 118 113 110 103 96 87 79 76 69 42
Placebo 154 153 152 151 149 142 136 130 121 116 110 98 89 79 48

Safety

- Cyclodextrin and nephrotoxicity (dosage forms)
- Cardiovascular side effects
- Liver dysfunction
- Pregnancy and lactation ?

Liver dose adjustment

FEATURE	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
ALT	<1.25	1.25-2.5	>2.5-5.0	>5.0-10	>10
AST	<1.25	1.25-2.5	>2.5-5.0	>5.0-10	>10
Alkaline Phosphatase	<1.25	1.25-2.5	>2.5-5.0	>5.0-10	>10
GGT	<1.25	1.25-2.5	>2.5-5.0	>5.0-10	>10
Bilirubin	Normal	>1.0-1.5	>1.5-2.5	>2.5-5	>5

Favipiravir

- Data
- Mechanism of action
- Effective dose
  - Influenza
  - SARS-Co-V2
- Duration
- Special population and safety
  - Renal failure
  - Liver disease and dose adjustment, role of child-Pugh score?
  - Interactions
  - QTc prolongation
  - Pregnancy
  - Maternal and paternal use

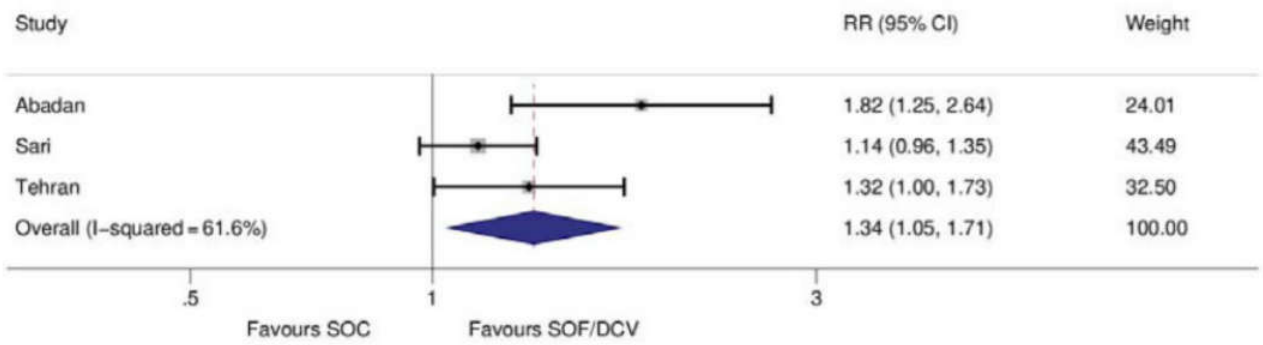
Protocols

- **Japan**
- Favipiravir was dosed at 1,800 mg orally at least four hours apart on the first day, followed by 800 mg orally twice a day, for 10-14 days.

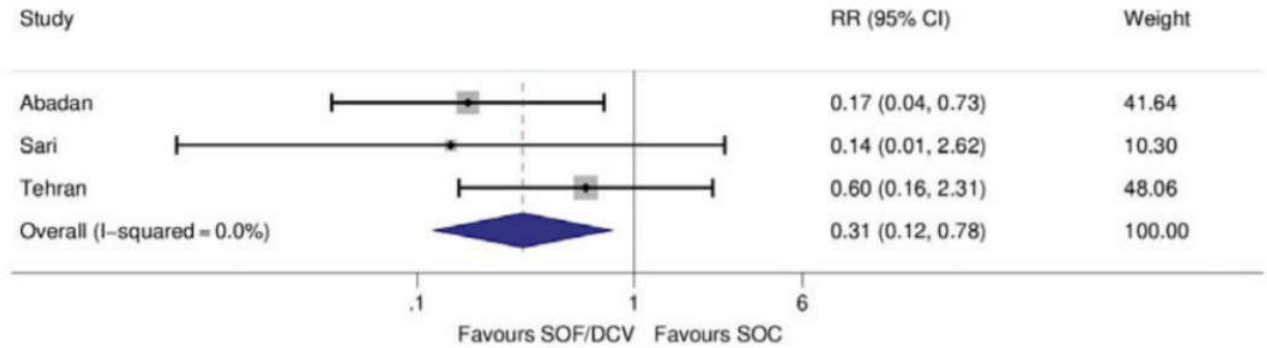
- **Russia**
- Patients weighing less than 75 kg as 1600 mg BID on day 1 and 600 mg BID from days 2-10.
- Patients weighing from 75 kg to 90 kg (inclusive): 2000 mg BID on day 1 and 800 mg BID on days 2-10.
- Patients weighing over 90 kg: 2400 mg BID on day 1 and further 1000 mg BID on days 2-10.

Sofosbuvir/daclatasvir

(a) **Clinical recovery within 14 days**

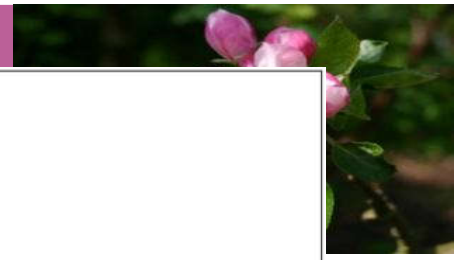


(b) **All-cause mortality**



HCQ

- Efficacy in experimental models?
- Effective doses?
  - EMA
  - FDA
- Hospitalized vs. outpatients ?
- Recovery trial results ?
  - Not effective in hospitalized patients
- Solidarity



JAMA Network™

QUESTION Does treatment with hydroxychloroquine improve clinical outcomes of adults hospitalized with coronavirus disease 2019 (COVID-19)?

CONCLUSION This randomized trial found that the distribution of the day 14 clinical status score was not significantly different for patients who received hydroxychloroquine vs placebo; findings did not support use of hydroxychloroquine for COVID-19 among hospitalized adults.

POPULATION

267 Men
212 Women

Adults hospitalized with respiratory symptoms from COVID-19

Median age: **57** years

LOCATIONS

34
Hospitals in the US

INTERVENTION

479 Patients randomized

242
Hydroxychloroquine
400 mg twice daily for 2 doses, then 200 mg twice daily for 8 doses

237
Placebo
Placebo in the same dosing frequency

PRIMARY OUTCOME

Clinical status 14 days after randomization as assessed with a 7-category ordinal scale, the COVID Outcomes Scale

FINDINGS

COVID Outcomes Scale score at 14 days

Hydroxychloroquine
Median score, 6
(interquartile range, 4-7)

Placebo
Median score, 6
(interquartile range, 4-7)

Adjusted odds ratio,
1.02
(95% CI, 0.73 to 1.42)

Self WH, Semler MW, Leither LM, et al; The National Heart, Lung, and Blood Institute PETAL Clinical Trials Network. Effect of hydroxychloroquine on clinical status at 14 days in hospitalized patients with COVID-19: a randomized clinical trial. *JAMA*. Published November 9, 2020. doi:10.1001/jama.2020.22240

Safety

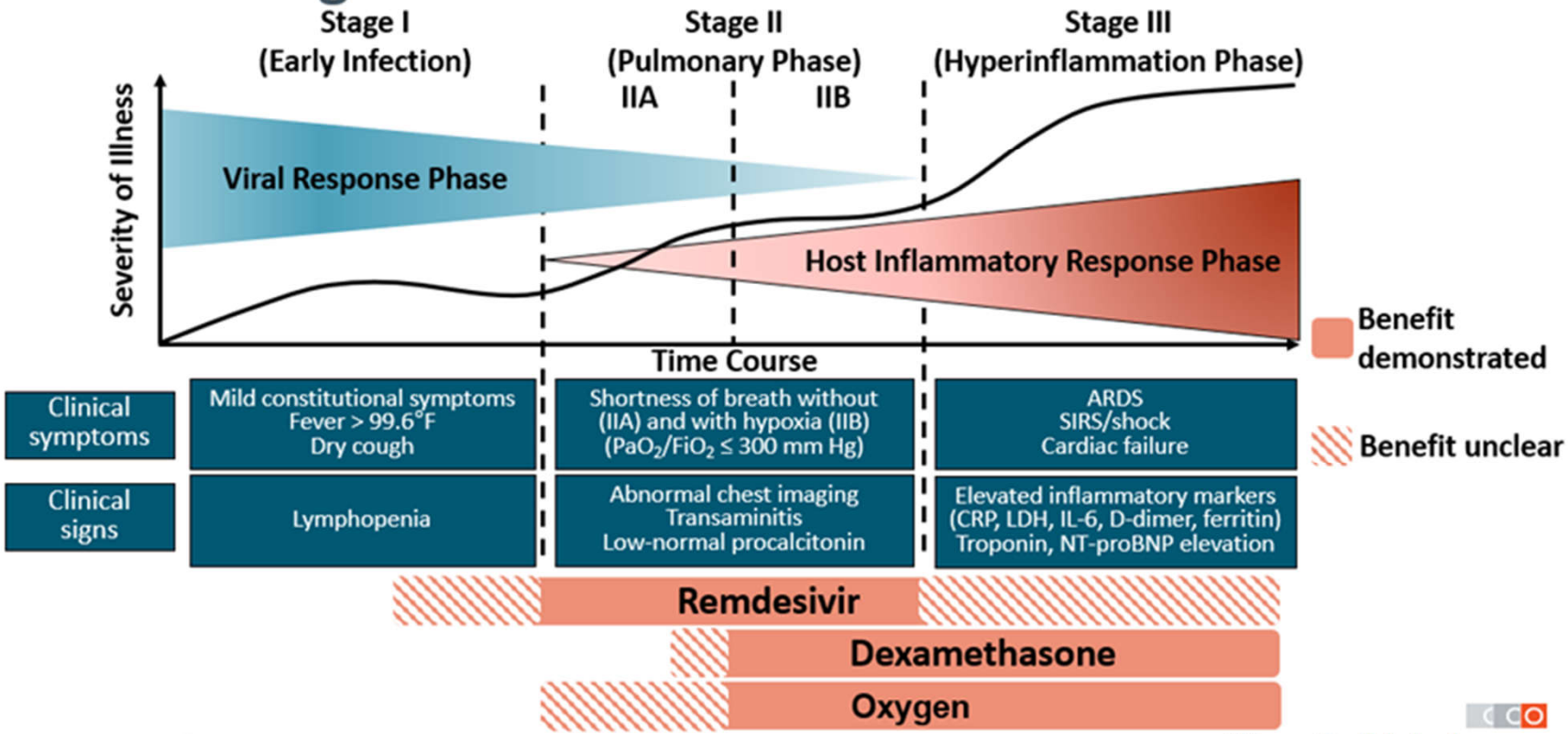
- Safety
  - Higher mortality (alone or in combination with azithromycin) in hospitalized patients who received HCQ
  - Interactions and QTc prolongation

- Place in therapy?

- **Recommendation 1. Among hospitalized patients with COVID-19, the IDSA guideline panel recommends against hydroxychloroquine*. (Strong recommendation, Moderate certainty of evidence)**
  - **Remark:** Chloroquine is considered to be class equivalent to hydroxychloroquine.
- **Recommendation 2. Among hospitalized patients with COVID-19, the IDSA guideline panel recommends against hydroxychloroquine* plus azithromycin. (Strong recommendation, Low certainty of evidence)**
  - **Remark:** Chloroquine is considered to be class equivalent to hydroxychloroquine.

Corticosteroids

COVID-19 Therapies Predicted to Provide Benefit at Different Stages



Siddiqi. J Heart Lung Transplant. 2020;39:405.

Slide credit: clinicaloptions.com

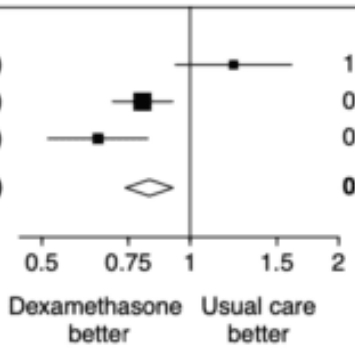
- Stage I: Administration of steroid during the early infection could increase viral replication and perhaps delay development of adaptive immunity. This might be expected to be detrimental.
- Stage II: Low-dose steroid: might be expected to be beneficial (by blunting the severity of inflammation and thereby preventing a severe hyper-inflammation phase).
- Stage III: For those patients who develop a marked hyper-inflammation phase, low-dose steroid might be *inadequate* to treat this.
  - Higher doses of steroid or targeted immunosuppressives (e.g. tocilizumab) could be necessary to treat established hyper-inflammation.

Effects on Mortality

Figure 2: Effect of allocation to dexamethasone on 28–day mortality by level of respiratory support received at randomization

Respiratory support at randomization	Dexamethasone	Usual care	RR (95% CI)
No oxygen received	85/501 (17.0%)	137/1034 (13.2%)	1.22 (0.93–1.61)
Oxygen only	275/1279 (21.5%)	650/2604 (25.0%)	0.80 (0.70–0.92)
Invasive mechanical ventilation	94/324 (29.0%)	278/683 (40.7%)	0.65 (0.51–0.82)
All participants	**454/2104 (21.6%)**	**1065/4321 (24.6%)**	**0.83 (0.74–0.92) p<0.001**

Trend across three categories: χ^2_1=11.49; p<0.001

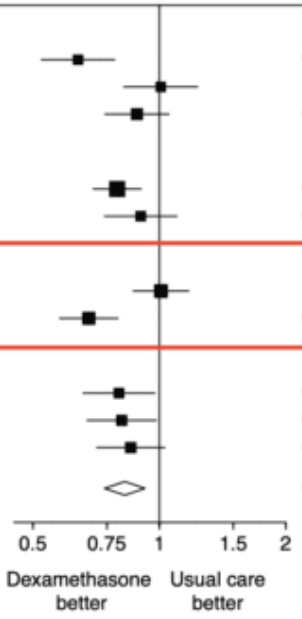


RR=age–adjusted rate ratio. CI=confidence interval. Subgroup–specific RR estimates are represented by squares (with areas of the squares proportional to the amount of statistical information) and the lines through them correspond to the 95% confidence intervals. The 'oxygen only' group includes non–invasive ventilation. Note: in the RECOVERY trial press release of 16 June 2020, effects in subgroups of level of respiratory support received were shown with 99% CIs, not 95% CIs as inadvertently stated. The age–adjusted rate ratio and 99% confidence intervals remain unchanged in this analysis: no oxygen required, RR 1.22 (99% CI 0.86–1.75); oxygen only, RR 0.80 (99% CI 0.67–0.96); invasive mechanical ventilation, RR 0.65 (99% CI 0.48–0.88).

Corticosteroids (recovery trial)

Figure S2: Effect of allocation to dexamethasone on 28–day mortality by other pre–specified baseline characteristics

Characteristic	Dexamethasone	Usual care	RR (95% CI)
Age, years (χ^2_1= 4.87; p=0.03)			
<70	124/1142 (10.9%)	413/2506 (16.5%)	0.64 (0.52–0.78)
≥70 <80	146/467 (31.3%)	262/860 (30.5%)	1.01 (0.82–1.23)
≥80	184/495 (37.2%)	390/955 (40.8%)	0.88 (0.74–1.05)
Sex (χ^2_1= 1.13; p=0.29)			
Men	312/1338 (23.3%)	754/2750 (27.4%)	0.79 (0.70–0.91)
Women	142/766 (18.5%)	311/1571 (19.8%)	0.90 (0.74–1.10)
Days since symptom onset (χ^2_1= 12.26; p<0.001)			
≤7	252/916 (27.5%)	478/1801 (26.5%)	1.01 (0.87–1.17)
>7	201/1184 (17.0%)	581/2507 (23.2%)	0.68 (0.58–0.80)
Baseline risk (χ^2_1= 0.22; p=0.64)			
<30%	137/1255 (10.9%)	361/2680 (13.5%)	0.80 (0.66–0.98)
≥30% <45%	157/500 (31.4%)	340/926 (36.7%)	0.81 (0.67–0.98)
≥45%	160/349 (45.8%)	364/715 (50.9%)	0.85 (0.71–1.03)
All participants	**454/2104 (21.6%)**	**1065/4321 (24.6%)**	**0.83 (0.74–0.92) p<0.001**



RR=age–adjusted (or age–specific) rate ratio. CI=confidence interval. Subgroup–specific RR estimates are represented by squares (with areas of the squares proportional to the amount of statistical information) and the lines through them correspond to the 95% confidence intervals.

RESEARCH ARTICLE

Second week methyl-prednisolone pulses improve prognosis in patients with severe coronavirus disease 2019 pneumonia: An observational comparative study using routine care data

Guillermo Ruiz-Irastorza[1,2,3]*, Jose-Ignacio Pijoan[2,4,5], Elena Bereciartua[2,3,6], Susanna Dunder[2,7], Jokin Dominguez[2,7], Paula Garcia-Escudero[2,8], Alejandro Rodrigo[2,7], Carlota Gomez-Carballo[2,7], Jimena Varona[2,7], Laura Guio[2,3,6], Marta Ibarrola[2,3], Amaia Ugarte[1,2], Agustin Martinez-Berriotxoa[2,3,7], On behalf of the Cruces COVID Study Group[¶]

1 Autoimmune Diseases Research Unit, Service of Internal Medicine, Hospital Universitario Cruces, Barakaldo, Bizkaia, Spain, **2** Biocruces Bizkaia Health Research Institute, Barakaldo, Bizkaia, Spain, **3** University of the Basque Country (UPV/EHU), Leioa, BI, Spain, **4** Clinical Epidemiology Unit, Hospital Universitario Cruces, Barakaldo, Bizkaia, Spain, **5** CIBER of Epidemiology and Public Health (CIBERESP), Madrid, Spain, **6** Infectious Diseases Unit, Hospital Universitario Cruces, Barakaldo, Bizkaia, Spain, **7** Service of Internal Medicine, Hospital Universitario Cruces, Barakaldo, Bizkaia, Spain, **8** Service of Rheumatology, Hospital Universitario Cruces, Barakaldo, Bizkaia, Spain

Predictors of death or intubation. Final models using the type of glucocorticoid therapy.

Variable	HR (95%CI)	p
WHOLE COHORT (n = 242)		
Glucocorticoid therapy		
No glucocorticoids	reference	
Non-pulse glucocorticoids	3.83 (1.51–9.68)	0.004
Out-of-week-2-MP	2.06 (0.71–6.00)	0.183
Week-2-MP	0.28 (0.07–1.12)	0.072
SpO2/FiO2*	0.92 (0.89–0.95)	<0.001
CURB65		
Low risk	reference	
Intermediate risk	2.38 (1.00–5.65)	0.049
High risk	3.98 (1.58–9.89)	0.003
PATIENTS WITH SpO2/FiO2 ≤353 (n = 122)		
Glucocorticoid therapy		
No glucocorticoids	reference	
Non-pulse glucocorticoids	3.06 (1.06–8.85)	0.039
Out-of-week-2-MP	1.92 (0.61–6.00)	0.263
Week-2-MP	0.20 (0.04–1.00)	0.050
SpO2/FiO2*	0.88 (0.83–0.93)	<0.001
CURB65		
Low risk	reference	
Intermediate risk	2.49 (0.91–6.80)	0.075
High risk	5.00 (1.73–14.47)	0.003

MP: methyl-prednisolone pulses; Week-2-MP: methyl-prednisolone pulses in week 2. HR: hazard ratio; CI: confidence interval.

*HR here estimates change in hazard by 10 units increase in SaO2/FiO2.

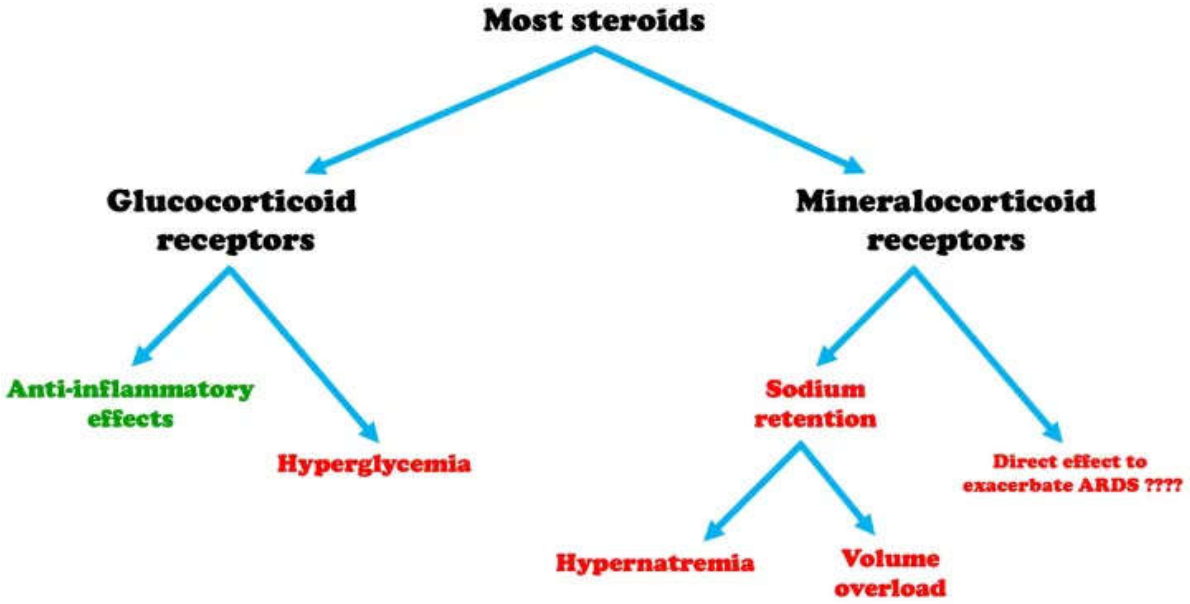
Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial

Maryam Edalatifard, Maryam Akhtari, Mohammadreza Salehi, Zohre Naderi, Ahmadreza Jamshidi, Shayan Mostafaei, Seyed Reza Najafizadeh, Elham Farhadi, Nooshin Jalili, Masoud Esfahani, Besharat Rahimi, Hossein Kazemzadeh, Maedeh Mahmoodi Aliabadi, Tooba Ghazanfari, Mohammad Reza Satarian, Hourvash Ebrahimi Louyeh, Seyed Reza Raeeskarami, Saeidreza Jamali Moghadam Siahkali, Nasim Khajavirad, Mahdi Mahmoudi, Abdorahman Rostamian

Table 3. Primary outcomes in methylprednisolone and standard care group.

Characteristic	Methylprednisolone (N=34)	Standard care (N=28)	*P* value
Time to event (discharge or death), day	11.62 ± 4.81	17.61 ± 9.84	**0.006**
Time to improvement, day	11.84 ± 4.88	16.44 ± 6.93	**0.011**
The outcome, no (%)			**<0.001**
Recover	32 (94.1%)	16 (57.1%)	
Death	2 (5.9%)	12 (42.9%)	

P value in the bold form is statistically significant (*P* value< 0·05)



It's possible that dexamethasone (a pure glucocorticoid agonist) could be a cleaner steroid than most.

-@PulmCrit

- Half-life, duration of action, and frequency of administration vary among corticosteroids.
- Long-acting corticosteroid: dexamethasone; half-life: 36 to 72 hours, administer once daily.
- Intermediate-acting corticosteroids: prednisone and methylprednisolone; half-life: 12 to 36 hours, administer once daily or in two divided doses daily.
- Short-acting corticosteroid: hydrocortisone; half-life: 8 to 12 hours, administer in two to four divided doses daily.

Dexamethasone vs. other corticosteroids

- Long biological half-life (~36-48 hours).
  - It allows dexamethasone to auto-taper itself gradually (thereby potentially avoiding rebound inflammation).
- Dexamethasone has little mineralocorticoid activity, which is potentially beneficial for a few reasons.
  - Mineralocorticoid stimulation may promote fluid retention and hypernatremia (which are especially undesirable in patients with ARDS).
  - There are some weak hints in the literature that mineralocorticoid stimulation might conceivably be harmful in ARDS.
  - As a pure glucocorticoid agonist, dexamethasone is one of the “cleaner” steroids mechanistically.

- Dexamethasone has superior penetration of the central nervous system compared to some other steroids. This is a desirable property among patients with hemophagocytic lymphohistiocytosis (HLH), but it's unclear whether it is coming into play here.

what happens when dexamethasone runs out?

- The paradox of pandemic medicine is that if a medicine is actually found to be beneficial, its supply may be immediately exhausted.
- Reasonable substitutions would include equivalent doses of methylprednisolone (32 mg), prednisone (40 mg), or prednisolone (40 mg).
- If using one of these agents, a very short taper at the end of the steroid course might be considered to mimic the prolonged half-life of dexamethasone.

Betamethasone

- Betamethasone sodium phosphate could be another option.
- Betamethasone is an attractive option because it has nearly identical properties as dexamethasone (long biological half-life and lack of mineralocorticoid activity).
- Betamethasone and dexamethasone have the same exact chemical formula, differing only by the chirality of a single methyl group (figure above).
- Most parenteral formulations of betamethasone contain a 50-50 mixture of betamethasone sodium phosphate (immediate-acting) and betamethasone acetate (which takes longer to absorb) – making this less desirable than the oral form.
  - Betamethasone acetate
  - Betamethasone long acting

Side effects

- Prolonged use of systemic corticosteroids may increase the risk of reactivation of latent infections (e.g., hepatitis B virus [HBV], herpesvirus infections, strongyloidiasis, tuberculosis)

Interferon

- NIH recommend against
- Sepsis campaign recommend against
- Effective in nebulized form?
- Safety and efficacy

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ANTIVIRAL AGENTS

A Randomized Clinical Trial of the Efficacy and Safety of Interferon β-1a in Treatment of Severe COVID-19

Effat Davoudi-Monfared,[a] Hamid Rahmani,[a] Hossein Khalili,[a] Mahboubeh Hajiabdolbaghi,[b] Mohamadreza Salehi,[b] Ladan Abbasian,[b] Hossein Kazemzadeh,[c] Mir Saeed Yekaninejad[d]

- Primary outcome, time to the clinical response was not significantly different between the IFN and the control groups (9.7 5.8 versus 8.3 4.9 days, respectively, P 0.95).
- On day 14, 66.7% versus 43.6% of patients in the IFN group and the control group, respectively, were discharged (odds ratio [OR], 2.5; 95% confidence interval [CI], 1.05 to 6.37).
- The 28-day overall mortality was significantly lower in the IFN than the control group (19% versus 43.6%, respectively, P 0.01)

Anticoagulation

REVIEW Open Access

Comparison of published guidelines for management of coagulopathy and thrombosis in critically ill patients with COVID 19: implications for clinical practice and future investigations

Adam Flaczyk[1], Rachel P. Rosovsky[2*], Clay T. Reed[3], Brittany K. Bankhead-Kendall[4], Edward A. Bittner[1] and Marvin G. Chang[5*]

Anticoagulation

- Out patients?
- Hospitalized

- Critically ill patients
- The Anticoagulation Forum suggests increased doses of VTE prophylaxis (e.g., enoxaparin 40 mg BID, enoxaparin 0.5 mg/kg BID, heparin 7500 units sub-Q 3 times daily, or low-intensity heparin infusion) for critically ill patients (e.g., in the ICU) with confirmed or suspected COVID-19.
- Intensive care society [intermediate dose (2*usual doses)]

NIH

- Venous Thromboembolism Prophylaxis and Screening:
- For non-hospitalized patients with COVID-19, anticoagulants and antiplatelet therapy should not be initiated for prevention of venous thromboembolism (VTE) or arterial thrombosis unless there are other indications **(AIII)**.

- Hospitalized adults with COVID-19 should receive VTE prophylaxis per the standard of care for other hospitalized adults **(AIII)**.
- There are currently insufficient data to recommend for or against the use of thrombolytics or increasing anticoagulant doses for VTE prophylaxis in hospitalized COVID-19 patients outside the setting of a clinical trial **(BIII)**

- Hospitalized patients with COVID-19 should not routinely be discharged on VTE prophylaxis **(AIII)**. Using Food and Drug Administration-approved regimens, extended VTE prophylaxis can be considered in patients who are at low risk for bleeding and high risk for VTE as per protocols for patients without COVID-19 (see text for details on defining at-risk patients) **(BI)**.
- There are currently insufficient data to recommend for or against routine deep vein thrombosis screening in COVID-19 patients without signs or symptoms of VTE, regardless of the status of their coagulation markers **(BIII)**.
- For hospitalized COVID-19 patients, the possibility of thromboembolic disease should be evaluated in the event of rapid deterioration of pulmonary, cardiac, or neurological function, or of sudden, localized loss of peripheral perfusion **(AIII)**.

Table 2 Major societal recommendations regarding using biomarkers to guide anticoagulation

Biomarkers to guide anticoagulation	
CDC	Insufficient data to recommend for or against using hematologic and coagulation parameters to guide management decisions.
ISTH-IG	Not mentioned
ACF	Biomarker thresholds such as D-dimer for guiding anticoagulation management should not be done outside the setting of a clinical trial.
ASH	No particular change to regimen recommended for patients with lupus like inhibitors. TEG and ROTEM should not be used routinely to guide management.
ACCP	Not mentioned
SSC-ISTH	D-dimer levels should not be used solely to guide anticoagulation regimens.
ACC	Further investigation is required to determine the role of antiphospholipid antibodies in pathophysiology of COVID-19-associated thrombosis. D-dimer > 2 times the upper limit may suggest that patient is at high risk for VTE and consideration of extended prophylaxis (up to 45 days) in patients at low risk of bleeding.

Table 7. Clinical Considerations for the Prevention and Treatment of VTE in Patient with COVID-19

Clinical consideration	Comment
Coagulopathy monitoring should include a PT, aPTT, platelets, D-dimer, and fibrinogen	D-dimer should be used as a measure of disease severity, but should not be used as a marker to increase VTE prophylaxis intensity or use of therapeutic anticoagulation. Fibrinogen will typically be elevated, and a decrease in severely ill patients, along with elevations in PT, can be an indicator of the patient transitioning to DIC.
Symptomatic patients treated at home with an elevated IMPROVE or Padua score should be considered for VTE prophylaxis	Significant fatigue and myalgia are common symptoms of COVID-19 leading patients to have immobility. With the addition of additional risk factors, especially previous VTE, and hypercoagulability of infection, VTE prophylaxis can be considered.
All general ward and ICU patients should receive VTE pharmacologic prophylaxis without risk assessment	Observational studies have demonstrated a higher rate of VTE than expected in both general ward and ICU patients. Due to the coagulopathy in patients with COVID-19, VTE prophylaxis without risk assessment is recommended in all guideline and consensus documents that address the issue.
Patients with contraindications to pharmacologic prophylaxis (current bleeding, platelet count $< 50 \times 10^9$) should receive mechanical prophylaxis with pneumatic compression.	This is consistent with recommendations in patients without COVID-19
VTE prophylaxis in general ward patients should be provided with standard dose LMWH (enoxaparin[a] 40 mg QD) or UFH (5000 units TID), with preference to the use of LMWH.	Use of standard dose LMWH or UFH in general ward patients is consistent with most guideline and consensus documents. Both agents may provide an anti-inflammatory effect that may be beneficial in patients with COVID-19, but this is not proven. LMWH is preferred to UFH due to the need for less injections per day, which decreases health care professional exposure to infected patients and preserves personal protective equipment.

Increased doses of enoxaparin[a] should be provided in patients with obesity (60 mg QD if BMI> 30 kg/m^2, 40 mg BID if BMI> 40 kg/m^2, or 0.5 mg/kg). If UFH is used, consider 7500 units TID.	Data suggests that higher doses of enoxaparin provide better anti-Xa response and/or a reduction of VTE events.
Decreased doses of enoxaparin[a] of 30 mg QD should be used in patients with a CrCl 15-30 ml/min. If UFH is used, consider BID dosing. Patients with a CrCl < 15 ml/min should receive UFH.	This dose of enoxaparin is consistent with the labeling for the drug. Use of enoxaparin in this setting still allows for less doses per day compared to UFH. Data with anticoagulants with end stage renal disease is limited and UFH is preferred.
Intermediate-dose enoxaparin[a] (60 mg QD, 40 mg BID, or 0.5 mg/kg) should be used in ICU patients, especially in patients on mechanical ventilation or with ARDS.	Observational studies have demonstrated a higher risk of VTE than would be expected in ICU patients. Most of these studies demonstrated these high rates of VTE while patients were receiving standard dose VTE prophylaxis.
The use of therapeutic doses of enoxaparin[a] or UFH should not be used for VTE prophylaxis.	Although a few reports suggest benefit of this approach, these data have significant limitations. Although bleeding is rare in patients with COVID-19, this approach requires evaluation in randomized controlled trials, which are currently underway.
At the time of discharge, patients should be evaluated as potential candidates for extended VTE prophylaxis using trial criteria, rivaroxaban is preferred over enoxaparin. Apixaban, dabigatran, and edoxaban should be avoided.	Although not specifically evaluated in the clinical trials, many hospitalized patients with COVID-19 would have met the trial entry criteria and should recognize similar benefits. Rivaroxaban is preferred due to benefit without an increase in major bleeding. Enoxaparin demonstrated benefit, but with more major bleeding. Apixaban demonstrated no benefit and more major bleeding. Dabigatran and edoxaban have not been evaluated for extended VTE prophylaxis.
Patients with VTE should receive therapeutic doses of enoxaparin[a] (1 mg/kg BID or 1.5 mg/kg QD) or UFH (80 unit/kg bolus followed by 18 units/kg/hr), with preference given to use of LMWH.	UFH requires frequent monitoring and dose adjustments, especially early in therapy. LMWH allows for QD or BID dosing and decreases health care professional exposure to infected patients and preserves personal protective equipment. This is also consistent with the preference of LMWH over UFH for treatment of VTE in patients without COVID-19.

Miscellaneous

- Famotidine
- Fluvoxamine
- Vitamins and minerals
- Melatonin
- Ivermectin
- Colchicine
- Immunoglobulins: Non-SARS-CoV-2 Specific

Special populations

- Pregnancy
- Poisoning

با تشکر