Dr Behnam Mahmoodiyeh

Intensivist , FCCM

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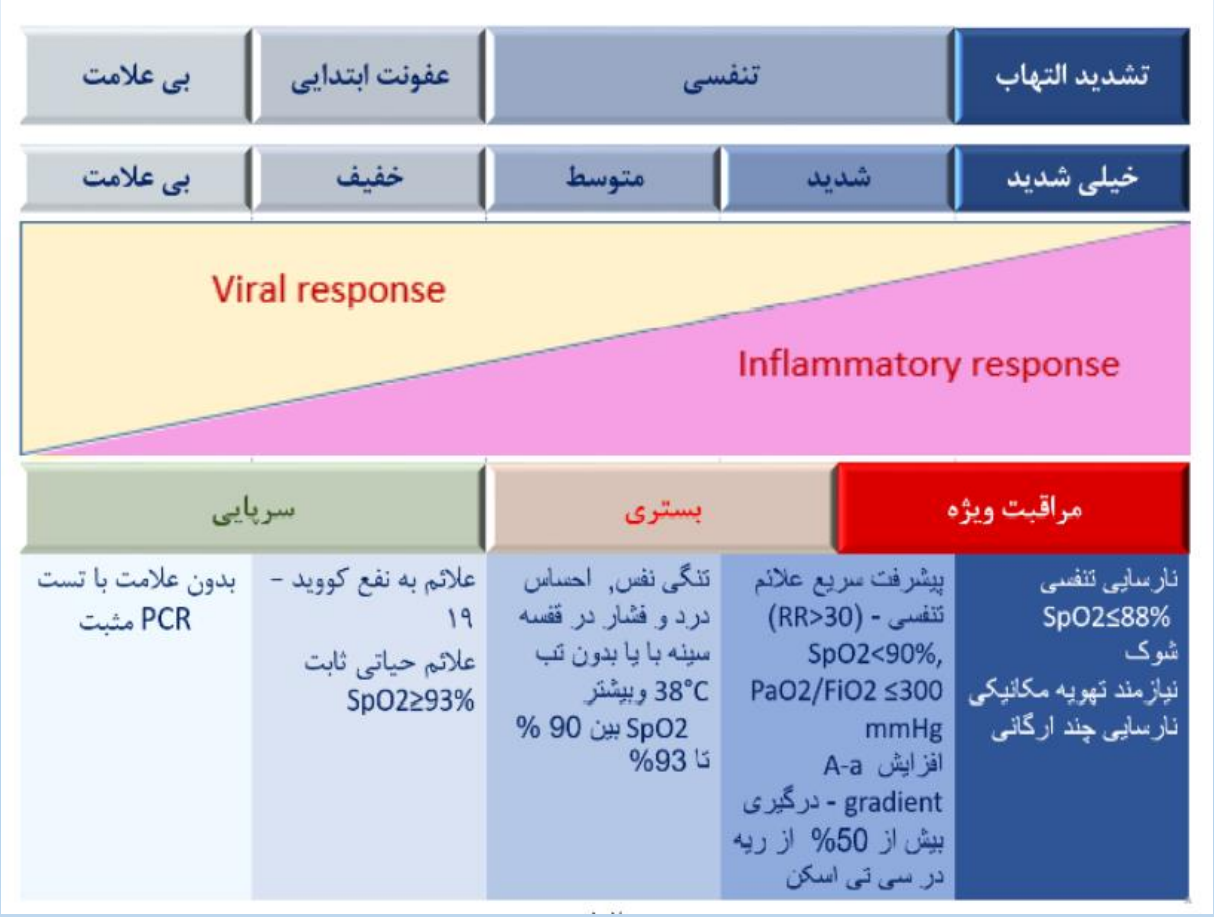
Titles:

1-Icu admission indications
2-Icu drug administrations

A-anti viral
B-anti inflammatory
C-anti oxidants
D-anti microbial therapy
E-salvage therapy

3-Oxygen therapy
4-CPR

1-icu admission indication



1-icu admission indication

Pao2/Fio2 < 300

Respiratory rate > 24

Spo2 <85

PaO2<60

Hemodynamic instability

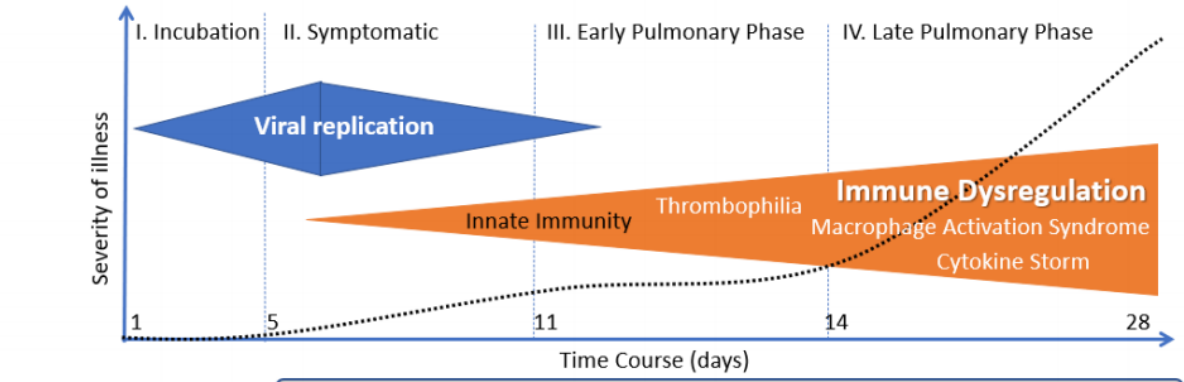
MAP<6(shock)

Impaired mental status

Multi organ dysfunction

2- Icu managment

Figure 1. The course of COVID-19 and General Approach to treatment



Ground-glass infiltrates	+	++	+++ ++++
Clinical Symptoms	Fever, malaise, cough, headache, diarrhea	SOB – Mild hypoxia ≤4 L/min N/C & aSat < 94%	Progressive hypoxia
Treatment approach	Antiviral Rx	Anti-inflammatory Rx	
Potential therapies	? Ivermectin	Methylprednisolone 40mg q 12 inc. to 80 mg q 12 if reqd.	
	? Interferon-α	Enoxaparin 60 mg/day	Enoxaparin 1mg/kg s/c q 12
	? Remdesivir (IV)		
	Vitamin C 500mg PO BID	Vit C 500-1000 mg PO q 6	Vitamin C 3g IV q 6

2- Icu managment

DRUGS:

- Anti viral
- Anti inflammatory
- Adjuvant agent
- Anti microbial therapy
- Salvage therapy agent

Anti viral

Anti viral

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EVMS
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EVMS CRITICAL CARE COVID-19 MANAGEMENT PROTOCOL

Developed and updated by Paul Marik, MD
Chief of Pulmonary and Critical Care Medicine
Eastern Virginia Medical School, Norfolk, VA
September 2nd, 2020

Anti viral

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Figure 1. Recommendations for Pharmacologic Management of Patients with COVID-19 Based on Disease Severity

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS *(Recommendations are listed in order of preference in each category below; however, all options are considered acceptable.)*
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]
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]

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

[a] The Panel recognizes that there may be situations in which a clinician judges that remdesivir is an appropriate treatment for a hospitalized patient with moderate COVID-19 (e.g., a patient who is at a particularly high risk for clinical deterioration). However, the Panel finds the data insufficient to recommend either for or against using remdesivir as routine treatment for all hospitalized patients with moderate COVID-19.
[b] Treatment duration may be extended to up to 10 days if there is no substantial clinical improvement by Day 5.
[c] The Panel recognizes there is a theoretical rationale for initiating remdesivir plus dexamethasone in patients with rapidly progressing COVID-19.
[d] For patients who are receiving remdesivir but progress to requiring oxygen through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or ECMO, remdesivir should be continued until the treatment course is completed.
[e] If dexamethasone is not available, equivalent doses of other corticosteroids, such as prednisone, methylprednisolone, or hydrocortisone, may be used.

Anti viral drugs

NIH | COVID-19 Treatment Guidelines

Antiviral Drugs That Are Under Evaluation for the Treatment of COVID-19

Last Updated: October 9, 2020

Summary Recommendations

There are no Food and Drug Administration-approved drugs for the treatment of COVID-19. In this section, the COVID-19 Treatment Guidelines Panel (the Panel) provides recommendations for using antiviral drugs to treat COVID-19 based on the available data. **As in the management of any disease, treatment decisions ultimately reside with the patient and their health care provider.**

For more information on the antiviral agents that are currently being evaluated for the treatment of COVID-19, see Table 2.

Remdesivir

The Remdesivir section of the Guidelines will be updated soon. See Therapeutic Management of Patients with COVID-19 for recommendations on using remdesivir with or without corticosteroids.

Recommendation for Prioritizing Limited Supplies of Remdesivir

- Because remdesivir supplies are limited, the Panel recommends prioritizing **remdesivir** for use in hospitalized patients with COVID-19 who require supplemental oxygen but who do not require oxygen delivery through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) **(BI)**.

Recommendation for Patients With Mild or Moderate COVID-19

- There are insufficient data for the Panel to recommend either for or against the use of **remdesivir** in patients with mild or moderate COVID-19.

Anti viral drugs

Recommendations for Patients with COVID-19 Who Require Supplemental Oxygen

For Patients Who Do Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO

- The Panel recommends using **remdesivir** for 5 days or until hospital discharge, whichever comes first **(AI)**.
- If a patient who is on supplemental oxygen while receiving remdesivir progresses to requiring delivery of oxygen through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or ECMO, the course of remdesivir should be completed.

For Patients Who Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO

- Because there is uncertainty regarding whether starting remdesivir confers clinical benefit in these groups of patients, the Panel cannot make a recommendation either for or against starting remdesivir.

Duration of Therapy for Patients Who Have Not Shown Clinical Improvement After 5 Days of Therapy

- There are insufficient data on the optimal duration of **remdesivir** therapy for patients with COVID-19 who have not shown clinical improvement after 5 days of therapy. In this group, some experts extend the total remdesivir treatment duration to up to 10 days **(CIII)**.

Chloroquine or Hydroxychloroquine With or Without Azithromycin

- The Panel **recommends against** the use of **chloroquine** or **hydroxychloroquine** with or without **azithromycin** for the treatment of COVID-19 in hospitalized patients **(AI)**.
- In nonhospitalized patients, the Panel **recommends against** the use of **chloroquine** or **hydroxychloroquine** with or without **azithromycin** for the treatment of COVID-19, except in a clinical trial **(AI)**.
- The Panel **recommends against** the use of **high-dose chloroquine** (600 mg twice daily for 10 days) for the treatment of COVID-19 **(AI)**.

Lopinavir/Ritonavir and Other HIV Protease Inhibitors

- The Panel **recommends against** using **lopinavir/ritonavir (AI)** or **other HIV protease inhibitors (AIII)** to treat COVID-19, except in a clinical trial.

Anti viral drugs

- Duration of Therapy Data from a multinational, open-label trial of hospitalized patients with severe COVID-19 showed that remdesivir treatment for 5 or 10 days had similar clinical benefit. The optimal duration of therapy for patients who do not improve after 5 days of receiving remdesivir is unclear. In the absence of data, some experts consider extending the total treatment duration of remdesivir to up to 10 days in patients who do not improve after 5 days of remdesivir therapy.

Participation in Solidarity

As of 2 October 2020, over 12 000 patients had been recruited in 500 participating hospitals worldwide. The Solidarity Trial is ongoing in 30 countries among the 43 countries that have approvals to begin recruiting. Overall, 116 countries in all 6 WHO regions have joined or expressed an interest in joining the trial

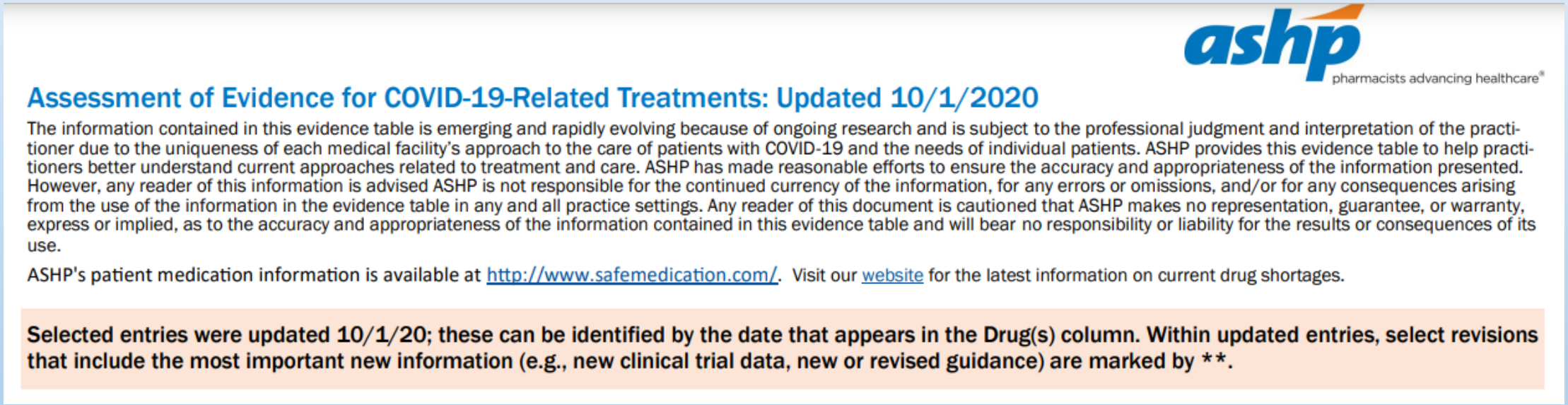
- No survival benefit from remdesivir, hydroxychloroquine, lopinavir/r or interferon-β1a in moderate and severe COVID-19: interim results from the WHO SOLIDARITY study

FDA NEWS RELEASE

FDA Approves First Treatment for COVID-19

For Immediate Release: October 22, 2020

Anti viral drugs



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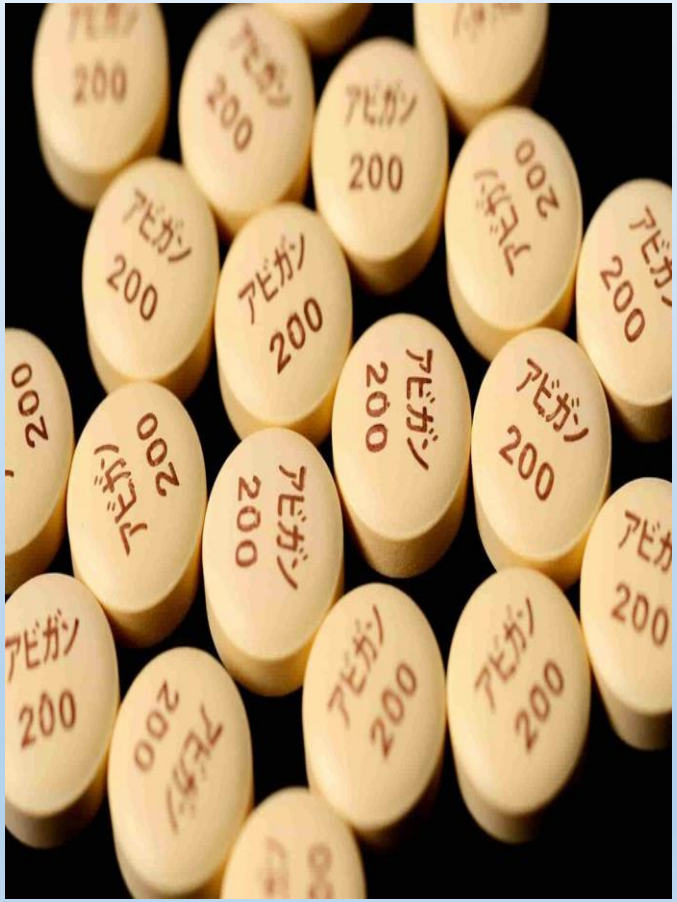
Favipiravir (Avigan®, Avifavir®, Favilavir) ***Updated 10/1/20***	8:18.32 Antiviral	Broad-spectrum antiviral with in vitro activity against various viruses, including coronaviruses [1–5] In vitro evidence of activity against SARS-CoV-2 in infected Vero E6 cells reported with high concentrations of the drug [1, 5, 16] Licensed in Japan and China for treatment of influenza [2, 4, 6]	**Only very limited clinical trial data available** to date to evaluate use of favipiravir in the treatment of COVID-19 **Open-label, prospective, randomized, multicenter study** in 236 adults with COVID-19 pneumonia in China (ChiCTR2000030254): Favipiravir (1600 mg orally twice daily on day 1, then 600 mg orally twice daily thereafter for 7–10 days) was associated with greater clinical recovery rate at 7 days (61 vs 52%) compared with the control group treated with umifenovir (Arbidol®; 200 mg 3 times daily for 7–10 days). Stratified by disease severity, clinical recovery rate at day 7 in pts with moderate COVID-19 pneumonia was 71% in the favipiravir group vs 56% in the umifenovir group; clinical recovery rate in those with severe to critical COVID-19 pneumonia was 6% vs 0%, respectively. Twice as many pts in the favipiravir group had severe to critical disease compared with the group receiving umifenovir. [6] **Open-label, prospective, randomized, multicenter study** in 60 hospitalized adults with moderate COVID-19 pneumonia in Russia (NCT04434248): Favipiravir (1600 mg orally twice daily on day 1, then 600 mg twice daily on days 2–14 or 1800 mg twice daily on day 1, then 800 mg twice daily on days 2–14) was associated with higher rate of viral clearance at 10 days (92.5 vs 80%) compared with the control group receiving the standard of care. Favipiravir also was associated with decreased median time to normalization of body temperature (2 vs 4 days) and higher improvement rate on	A favipiravir dosage of 1600 mg twice daily on day 1, then 600 mg twice daily thereafter for 7–10 or 14 days was used in several open-label COVID-19 studies in adults and adolescents ≥16 years of age in other countries [6, 15, 24] Protocols in many registered trials generally specify a favipiravir dosage of 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 for treatment of COVID-19 in adults [7] Protocol in one trial (NCT04448119) specifies a *prophylactic* favipiravir dosage of 1600 mg twice daily on day 1, then 800 mg twice daily on days 2–25 and a *treatment* favipiravir dosage of 2000 mg twice daily on day 1, then 1000 mg twice daily on days 2–14 in older adults in long-term care homes experiencing COVID-19 outbreaks. The prophylactic regimen is considered pre-exposure prophylaxis, post-exposure prophylaxis, or preemptive therapy in this setting; those diagnosed with COVID-19 will be offered the treatment regimen [7] Because high favipiravir concentrations are required for in vitro activity against SARS-CoV-2, [1, 5, 13] it has been suggested that high favipiravir dosages, like those used in the treatment of Ebola virus disease, should be	Not commercially available in the US Efficacy and safety of favipiravir for treatment of COVID-19 not established Additional data needed to substantiate initial reports of efficacy for treatment of COVID-19 and identify optimal dosage and treatment duration Given the lack of pharmacokinetic and safety data for the high favipiravir dosages proposed for treatment of COVID-19, the drug should be used with caution at such dosages. [19, 20] Favipiravir is associated with QT prolongation. [21] Some have suggested close cardiac and hepatic monitoring during treatment, as well as monitoring of plasma and tissue concentrations of the drug and, if possible, the active metabolite. [19, 20, 21] Some data suggest that favipiravir exposure may be greater in Asian populations. [17, 19] Early embryonic deaths and teratogenicity observed in animal studies. Favipiravir is contraindicated in women with known or suspected pregnancy and precautions should be taken to avoid pregnancy during treatment with the drug. [14] If favipiravir is used in pts receiving acetaminophen, the maximum recommended daily dosage of acetaminophen is 3 g. [17, 18]

Anti viral drugs



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Review Article

Favipiravir: A new and emerging antiviral option in COVID-19

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	≥ 1%	0.5 - < 1%	< 0.5%
Hypersensitivity		Rash	Eczema, pruritus
Hepatic	AST (GOT) increased, ALT (GPT) increased, γ-GTP increased		Blood ALP increased, blood bilirubin increased
Gastrointestinal	Diarrhoea	Nausea, vomiting, abdominal pain	Abdominal discomfort, duodenal ulcer, haematochezia, gastritis
Hematologic	Neutrophil count decreased, white blood cell count decreased	Glucose urine present	White blood cell count increased reticulocyte count decreased, monocyte increased
Metabolic disorders	Blood uric acid increased 4.79%), Blood triglycerides increased		Blood potassium decreased
Respiratory			Asthma, oropharyngeal pain, rhinitis, nasopharyngitis
Others			CPK increased, blood urine present, tonsil polyp, pigmentation, dysgeusia, bruise, vision blurred, eye pain, vertigo,

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	HIV Protease Inhibitors *Updated 9/3/20*	8:18.08.08 HIV Protease Inhibitors	**Lopinavir (LPV):** Some evidence of in vitro activity against SARS-CoV-2 in Vero E6 cells; [19] evidence of in vitro activity against SARS-CoV-1 and MERS-CoV; [1, 2, 9] some evidence of benefit in animal studies for treatment of MERS-CoV [2, 7, 9, 11] **Atazanavir (ATV):** Some evidence that ATV alone or with ritonavir (ATV/RTV) has in vitro activity against SARS-CoV-2 in Vero E6 cells, [17, 19] human epithelial pulmonary cells (A549), [17] and human monocytes [17] **Darunavir (DRV):** In one study, DRV with cobicistat had no in vitro activity against SARS-CoV-2 at clinically relevant concentrations in Caco-2 cells; [18] in another study, high DRV concentrations were required for in vitro inhibition of SARS-CoV-2 in Vero E6 cells [19] **Nelfinavir (NFV), Saquinavir (SQV), and Tipranavir (TPV):** Some evidence of in vitro activity against SARS-CoV-2 in Vero E6 cells [19]	**Lopinavir and Ritonavir (LPV/RTV; Kaletra®) randomized, open-label trial in China (Cao et al)** in hospitalized adults with severe COVID-19 compared LPV/RTV in conjunction with standard care (99 pts) vs standard care alone (100 pts). Primary end point was time to clinical improvement (time from randomization to improvement of two points on a seven-category ordinal scale or hospital discharge, whichever came first). In ITT population, **time to clinical improvement was not shorter with LPV/RTV compared with standard care** (median time to clinical improvement 16 days in both groups); in modified ITT population, median time to clinical improvement 15 days in LPV/RTV group and 16 days in standard care only group. The 28-day mortality rate was numerically lower in LPV/RTV group (19.2% vs 25% in ITT population; 16.7% vs 25% in modified ITT population). Some evidence that LPV/RTV initiation within 12 days after symptom onset is associated with shorter time to clinical improvement. **No significant differences in reduction of viral RNA load, duration of viral RNA detectability, duration of oxygen therapy, duration of hospitalization, or time from randomization to death.** LPV/RTV stopped early in 13 pts because of adverse effects. [3] **LPV/RTV vs chloroquine in small, randomized study in hospitalized adults with COVID-19 in China (Huang et al):** 10 pts (7 with moderate and 3 with severe disease) received chloroquine (500 mg twice daily for 10 days) and 12 pts (7 with moderate and 5 with severe disease) received LPV/RTV (lopinavir 400 mg/ritonavir 100 mg twice daily for 10 days). All 10 pts treated with chloroquine had negative RT-PCR results for SARS-CoV-2 by day 13 and were discharged from the hospital by day 14; 11/12 pts (92%) treated with LPV/RTV were negative for SARS-CoV-2 at day 14 and only	**LPV/RTV (COVID-19):** LPV 400 mg/RTV 100 mg orally twice daily for 10-14 days [3, 16, 24] **LPV/RTV (COVID-19):** LPV 400 mg/RTV 100 mg orally twice daily with or without umifenovir (Arbidol® 200 mg every 8 hours) [6] **LPV/RTV (COVID-19):** LPV 400 mg/RTV 100 mg orally twice daily for no longer than 10 days [13] with or without interferon (5 million units of interferon-α or equivalent twice daily given in 2 mL of sterile water by nebulization) and with or without ribavirin for up to 10 days [5, 13] **LPV/RTV (SARS):** LPV 400 mg/RTV 100 mg orally twice daily for 14 days with ribavirin (4-g oral loading dose, then 1.2 g orally every 8 hours or 8 mg/kg IV every 8 hours) [1] **LPV/RTV (MERS):** LPV 400 mg/RTV 100 mg orally twice daily with ribavirin (various regimens) and/or interferon-α ; LPV 400 mg/RTV 100 mg orally twice daily with interferon β-1b (0.25 mg/mL sub-Q on alternate days) for 14 days [1, 4, 8]	**LPV/RTV:** Efficacy for the treatment of COVID-19, with or without other antivirals, not established [22, 23] **Darunavir:** Manufacturer states they have no clinical or pharmacologic evidence to support use of DRV/c for treatment of COVID-19. Results of an open-label, controlled study in China indicated that a 5-day regimen of DRV/c was not effective for treatment of COVID-19 [21, 26] and there are no published clinical studies that have evaluated efficacy and safety of DRV/RTV or the fixed combination of DRV, cobicistat, emtricitabine, and tenofovir alafenamide for treatment of COVID-19. [21] **Atazanavir, Nelfinavir, Saquinavir, Tipranavir:** No data to date to support use in the treatment of COVID-19 [22] NIH COVID-19 Treatment Guidelines Panel **recommends against** the use of LPV/RTV or other HIV protease inhibitors for the treatment of COVID-19, except in the context of a clinical trial. The panel states that, based on the pharmacodynamics of HIV protease inhibitors, there are concerns whether drug concentrations achieved with oral doses of the drugs are adequate to inhibit SARS-CoV-2 protease. In addition, clinical trials to date using LPV/RTV have not demonstrated a clinical benefit in patients with COVID-19. [22] IDSA recommends that LPV/RTV be used for the treatment of COVID-19 *only* in the context of a clinical trial [23]	

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Chloroquine or Hydroxychloroquine With or Without Azithromycin

- The Panel **recommends against** the use of **chloroquine** or **hydroxychloroquine** with or without **azithromycin** for the treatment of COVID-19 in hospitalized patients **(AI)**.
- In nonhospitalized patients, the Panel **recommends against** the use of **chloroquine** or **hydroxychloroquine** with or without **azithromycin** for the treatment of COVID-19, except in a clinical trial **(AI)**.
- The Panel **recommends against** the use of **high-dose chloroquine** (600 mg twice daily for 10 days) for the treatment of COVID-19 **(AI)**.

Anti viral drugs

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Lopinavir/Ritonavir and Other HIV Protease Inhibitors • The Panel recommends against using lopinavir/ritonavir (AI) or other HIV protease inhibitors (AIII) to treat COVID-19, except in a clinical trial.

Ivermectin • The Panel recommends against the use of ivermectin for the treatment of COVID-19, except in a clinical trial (AIII).

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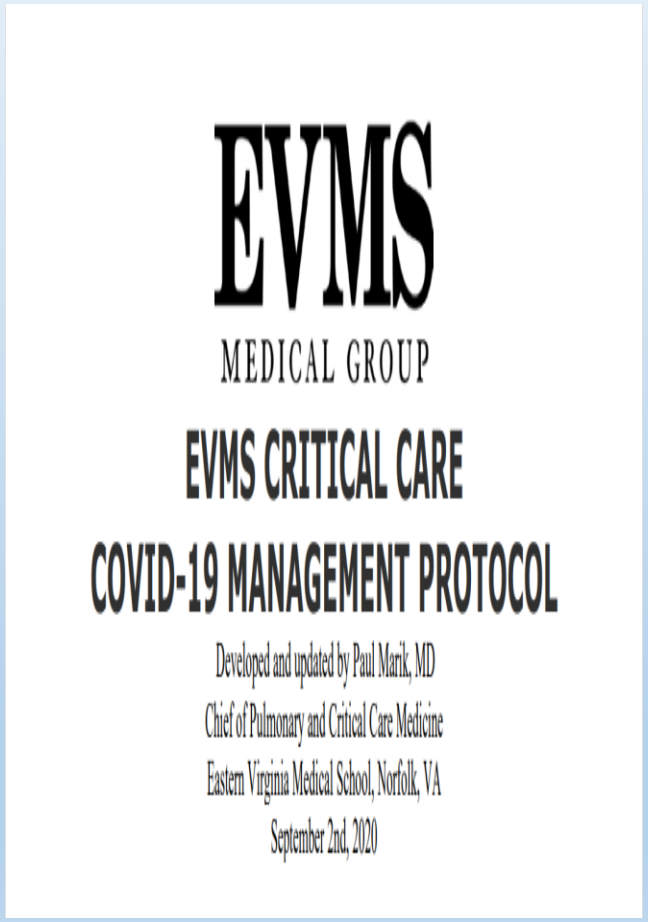

Critical Care COVID-19 Management Protocol

Please refer to the full protocol for optional treatments and explanations.

(updated 10-29-2020)

Prophylaxis

- Vitamin C 500 mg BID and Quercetin 250 mg daily
- B complex vitamins
- Zinc 30-50 mg/day
- Melatonin (slow release): Begin with 0.3mg and increase as tolerated to 2 mg at night
- Vitamin D3 1000-3000 u/day
- Ivermectin for postexposure prophylaxis and weekly prophylaxis in high risk groups (150-200 ug/kg)

Mildly Symptomatic patients (at home):

- Ivermectin 150-200 ug/kg daily for two doses
- Vitamin C 500mg BID and Quercetin 250-500 mg BID
- Vitamin D3 2000 - 4000 u/day
- B Complex vitamins
- Zinc 75-100 mg/day
- Melatonin 6-10 mg at night (the optimal dose is unknown)
- ASA aspirin 81-325 mg/day (unless contraindicated)

In symptomatic patients, monitoring with home pulse oximetry is recommended.
Ambulatory desaturation below 94% should prompt hospital admission

Mildly Symptomatic patients (on floor):

- Ivermectin 150-200 ug/kg daily for two doses
- Vitamin C 500 mg PO q 6 hourly and Quercetin 250-500 mg BID (if available)
- Vitamin D3 20 000 – 60 000 iu single oral dose. Calcifediol 200 -500 µg is an alternative. Then 20 000 iu D3 (or 200 µg calcifediol) weekly until discharged from hospital.
- B complex vitamins
- Zinc 75-100 mg/day
- Melatonin 10 mg at night (the optimal dose is unknown)
- Enoxaparin 60 mg daily

Anti viral drugs

EVMS

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COVID-19 MANAGEMENT PROTOCOL

Developed and updated by Paul Marik, MD
Chief of Pulmonary and Critical Care Medicine
Eastern Virginia Medical School, Norfolk, VA

September 2nd, 2020

Critical Care COVID-19 Management Protocol

(updated 10-29-2020)

Respiratory symptoms (SOB; hypoxia- requiring N/C ≥ 4 L min: admit to ICU):

Essential Treatment (dampening the STORM)

1. Methylprednisolone 80 mg loading dose then 40 mg q 12 hourly for at least 7 days and until transferred out of ICU. In patients with poor response, increase to 80-125 mg q 12 hourly.
2. Ascorbic acid (Vitamin C) 3g IV q 6 hourly for at least 7 days and/or until transferred out of ICU. Note caution with POC glucose testing.
3. Full anticoagulation: Unless contraindicated we suggest FULL anticoagulation (on admission to the ICU) with enoxaparin, i.e 1 mg kg s/c q 12 hourly (dose adjust with Cr Cl < 30mls/min). Heparin is suggested with CrCl < 15 ml/min.

Note: Early termination of ascorbic acid and corticosteroids will likely result in a rebound effect.

Additional Treatment Components (the Full Monty)

4. Ivermectin 150-200 ug/kg daily for two doses
5. Vitamin D3 20 000 – 60 000 iu single oral dose. Calcifediol 200 -500 µg is an alternative. Then 20 000 iu D3 (or 200 µg calcifediol) weekly until discharged from hospital.
6. Thiamine 200 mg IV q 12 hourly
7. B complex vitamins
8. Zinc 75-100 mg/day
9. Melatonin 10 mg at night (the optimal dose is unknown).
10. Atorvastatin 80mg/day
11. Escalation of respiratory support; See General Schema for Respiratory Support in Patients with COVID-19.

Salvage Treatments

- Plasma exchange. Should be considered in patients with progressive oxygenation failure despite corticosteroid therapy. Patients may require up to 5 exchanges.
- High dose corticosteroids; Bolus 250- 500mg/ day methylprednisolone
- Half-dose rTPA
- ECMO

Monitoring:

- On admission: PCT, CRP, BNP, Troponins, Ferritin, Neutrophil-Lymphocyte ratio, D-dimer and Mg.
- Daily: CRP, Ferritin, D-Dimer and PCT. CRP and Ferritin track disease severity closely (although ferritin tends to lag behind CRP).
- In patients receiving IV vitamin C, the Accu-Chek™ POC glucose monitor will result in spuriously high blood glucose values. Therefore, a laboratory glucose is recommended to confirm the blood glucose levels

Post ICU management

- Enoxaparin 40-60 mg s/c daily
- Methylprednisone 40 mg day, then wean slowly
- Vitamin C 500 mg PO BID
- Melatonin 3-6 mg at night

Post hospital discharge

1. Consider extended DVT prophylaxis in high risk patients.
2. Consider tapering course of corticosteroids (guided by CRP)
3. Omega-3 fatty acids
4. Atorvastatin 40mg daily
5. Melatonin
6. Multivitamins including B complex and Vitamin D

Anti inflammatory drugs

CORTICOSTROID

Anti inflammatory drugs

NIH | COVID-19 Treatment Guidelines

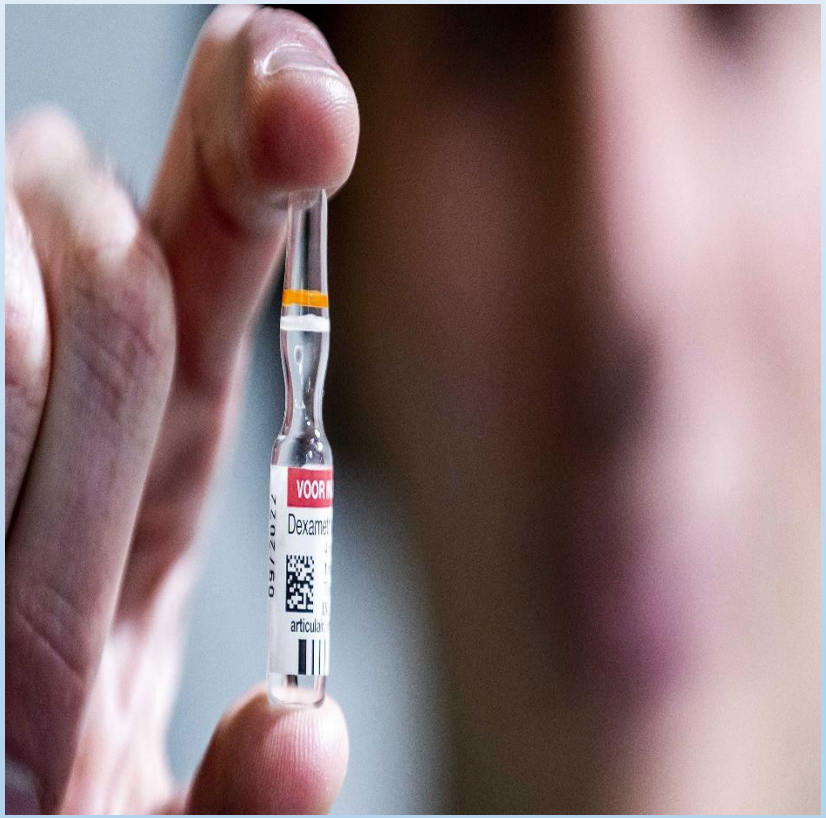
-On the basis of the preliminary report from the RECOVERY trial, the COVID-19 Treatment Guidelines Panel (the Panel) recommends using dexamethasone 6 mg per day for up to 10 days or until hospital discharge, whichever comes first, for the treatment of COVID-19 in hospitalized patients who are mechanically ventilated (AI) and in hospitalized patients who require supplemental oxygen but who are not mechanically ventilated (BI).

-The Panel recommends against using dexamethasone for the treatment of COVID-19 in patients who do not require supplemental oxygen (AI).

-A combination of remdesivir (dose and duration as above) plus dexamethasone 6 mg IV or orally for up to 10 days or until hospital discharge

Anti inflammatory drugs

NIH | COVID-19 Treatment Guidelines



- If dexamethasone is not available, an alternative corticosteroid such as prednisone, methylprednisolone, or hydrocortisone can be used

- In the RECOVERY trial, treatment with dexamethasone conferred a survival benefit among participants who required supplemental oxygen but not invasive mechanical ventilation at enrollment; 23.3% of participants in the dexamethasone group died within 28 days of enrollment compared with 26.2% in the standard of care arm (rate ratio 0.82; 95% CI, 0.72–0.94).2 The amount of supplemental oxygen that participants were receiving and the proportions of participants who required oxygen delivery through high-flow devices or noninvasive ventilation were not specified

Anti inflammatory drugs

COVID-19 Treatment Guidelines

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends against the use of chloroquine or hydroxychloroquine with or without azithromycin for the treatment of COVID-19 in hospitalized patients (AI).
- In nonhospitalized patients, the Panel recommends against the use of chloroquine or hydroxychloroquine with or without azithromycin for the treatment of COVID-19, except in a clinical trial (AI).
- The Panel recommends against the use of high-dose chloroquine (600 mg twice daily for 10 days) for the treatment of COVID-19 (AI).

Anti inflammatory drugs

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September 2nd, 2020

MATH+

HOSPITAL TREATMENT PROTOCOL FOR COVID-19

Intravenous **M**ethylprednisolone

High Dose Intravenous **A**scorbic Acid (Vitamin C)

Thiamine (Vitamin B1)

Low Molecular Weight **H**eparin

+

Statin – Zinc – Vitamin D – Famotidine – Melatonin – Magnesium

FLCCC ALLIANCE

Front Line Covid-19 Critical Care Alliance

www.covid19criticalcare.com

Anti inflammatory drugs

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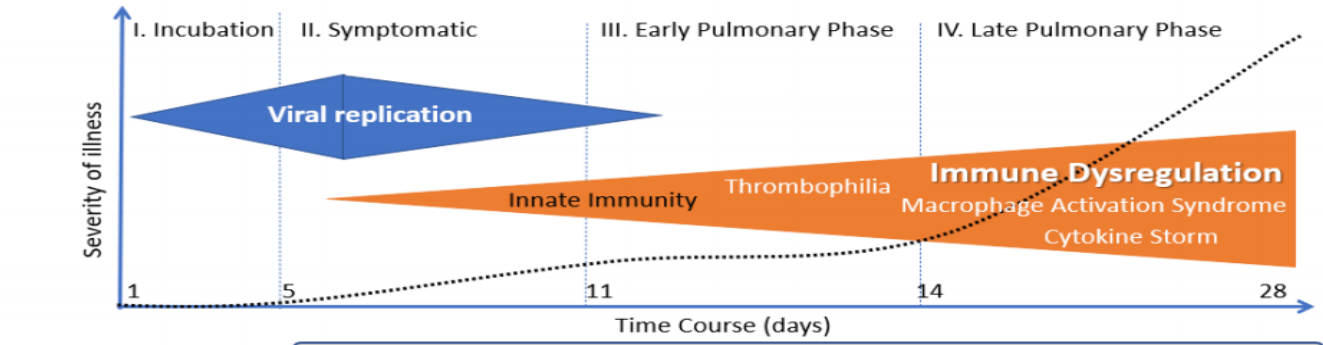

Ground-glass infiltrates	+	++	+++ ++++
Clinical Symptoms	Fever, malaise, cough, headache, diarrhea	SOB – Mild hypoxia ≤4 L/min N/C & aSat < 94%	Progressive hypoxia
Treatment approach	Antiviral Rx	Anti-inflammatory Rx	
Potential therapies	? Ivermectin	Methylprednisolone 40mg q 12 inc. to 80 mg q 12 if reqd.	
	? Interferon-α	Enoxaparin 60 mg/day	Enoxaparin 1mg/kg s/c q 12
	? Remdesivir (IV)		
	Vitamin C 500mg PO BID	Vit C 500-1000 mg PO q 6	Vitamin C 3g IV q 6

THIS IS A STEROID RESPONSIVE DISEASE:

HOWEVER, TIMING IS CRITICAL

Anti inflammatory drugs

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COVID-19 MANAGEMENT PROTOCOL

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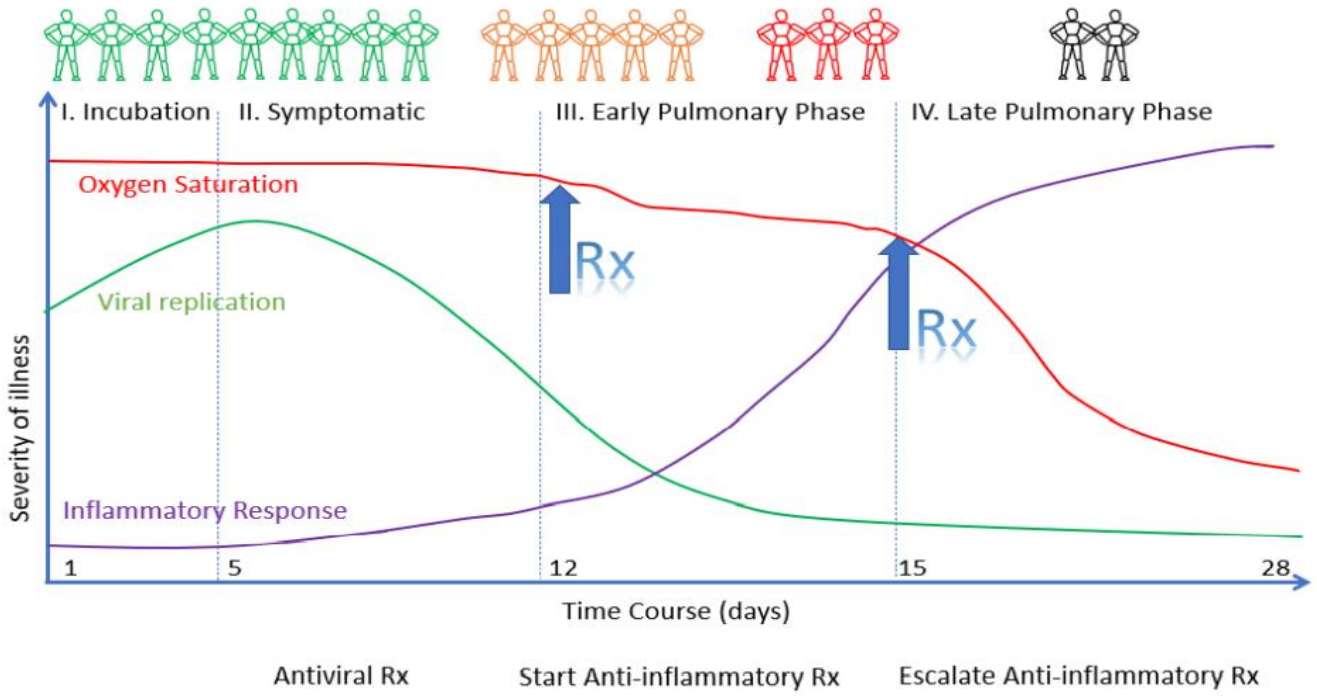
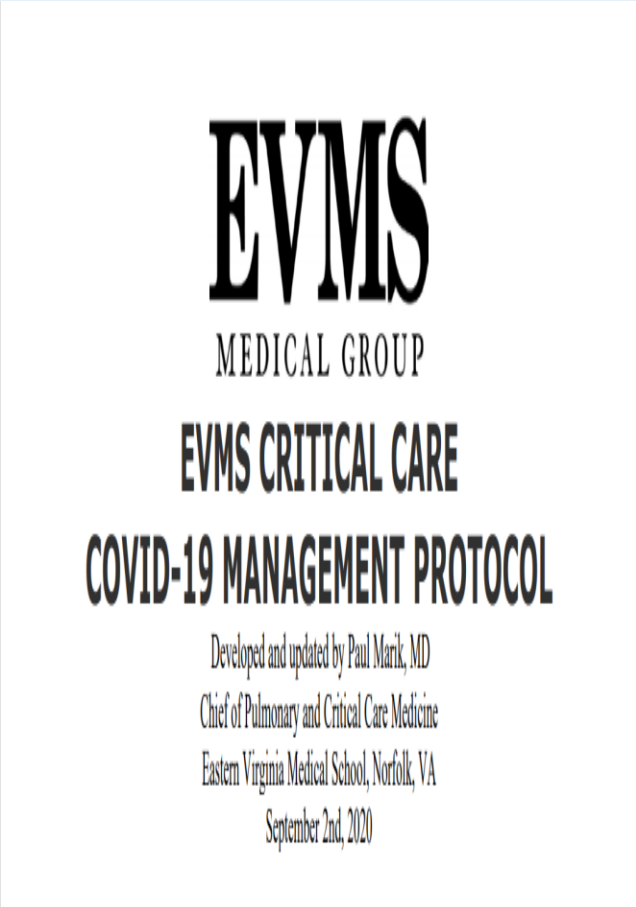
Figure 2. Timing of the initiation of anti-inflammatory therapy



Anti inflammatory drugs



- Methylprednisolone 80 mg loading dose then 40 mg q 12 hourly for at least 7 days and until transferred out of ICU. In patients with an increasing CRP or worsening clinical status increase the dose to 80 mg q 12 hourly (then 125mg q 12 hourly), then titrate down as appropriate.
- • High dose corticosteroids; 120 -250 mg methylprednisolone q 6-8 hourly

Anti inflammatory drugs

Roche's phase III EMPACTA study showed Actemra/RoActemra reduced the likelihood of needing mechanical ventilation in hospitalised patients with COVID-19 associated pneumonia

- EMPACTA is the first global phase III trial to show efficacy with Actemra/RoActemra in COVID-19 associated pneumonia and the first with a focus on enrolling largely underserved and minority patients
- There was no statistical difference in mortality between patients who received Actemra/RoActemra or placebo
- Roche plans to share these results with health authorities, including the US FDA

Anti inflammatory drugs

Assessment of Evidence for COVID-19-Related Treatments: Updated 10/1/2020

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Tocilizumab (Actemra®) *Updated 9/10/20*	92:36 Disease-modifying Anti-rheumatic Drug	Recombinant humanized monoclonal antibody specific for the interleukin-6 (IL-6) receptor; IL-6 is a proinflammatory cytokine. Tocilizumab may potentially combat cytokine release syndrome (CRS) and pulmonary symptoms in severely ill COVID-19 patients [1-3, 6, 9,10, 14]	Preliminary unpublished data from randomized clinical trials have not demonstrated efficacy in treatment of patients with COVID-19 [9] Case reports and observational and open studies describing use of tocilizumab in patients with COVID-19 reported from various areas of the world [1, 3, 5, 10, 12, 15, 17] In preliminary data from a non-peer-reviewed, single-arm, observational Chinese trial (Xu et al.) involving 21 patients with severe or critical COVID-19 infection, patients demonstrated rapid fever reduction and a reduced need for supplemental	Tocilizumab is typically given IV to treat cytokine release syndrome (CRS) and in patients with COVID-19; however, the drug has been given subcutaneously in some patients [9, 17] The subcutaneous formulation of tocilizumab is *not* intended for IV use [9] IV infusion: **China** recommends an initial dose of 4–8 mg/kg infused over more than 60 minutes. 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;	**In China**, tocilizumab can be used to treat severely or critically ill COVID-19 patients with extensive lung lesions and high IL-6 levels [2] NIH COVID-19 Treatment Guidelines Panel **recommends against** use of tocilizumab in the treatment of COVID-19, except in a clinical trial [9] The role of routine cytokine measurements (e.g., IL-6, CRP) in determining the severity of and treating COVID-19 requires further study [14]

Anti inflammatory drugs

Assessment of Evidence for COVID-19-Related Treatments: Updated 10/1/2020

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- A single-center, retrospective observational study of 20 kidney transplant recipients in Italy with COVID-19 hospitalized for pneumonia included 6 patients who received tocilizumab. Half of the patients experienced reduced oxygen requirements and 2 (33%) showed improved radiologic findings following administration; 2 (33%) of the 6 tocilizumab-treated patients died.

Anti inflammatory drugs

- Siltuximab and Tocilizumab (IL-6 inhibitors). Roche™ recently announced the results of the COVACTA study, which demonstrated that Tocilizumab did not improve patient outcome. Il-6 inhibitors may increase the risk of opportunistic infections.

Anti inflammatory drugs

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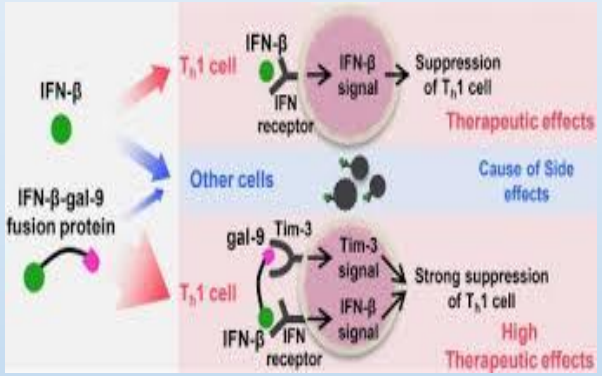

Interferons *Updated 9/17/20*	8:18.20 Interferons 10:00 Antineoplastic Agents 92:20 Immunomodulatory Agents	Interferons (IFNs) modulate immune responses to some viral infections; [2, 7, 19] in vitro studies indicate only weak induction of IFN following SARS-CoV-2 infection, and a possible role for IFNs in prophylaxis or early treatment of COVID-19 has been suggested to compensate for possibly insufficient endogenous IFN production [1, 3, 4, 7, 18] **Type 1 IFNs (IFN alfa and IFN beta)** are active in vitro against MERS-CoV in Vero and LLCMK2 cells and in rhesus macaque model of MERS-CoV infection; type I IFNs also active in vitro against SARS-CoV-1 in Vero, fRhK-4, and human cell lines; [8] IFN beta is more active than IFN alfa in vitro against SARS-CoV-1 and MERS-CoV [2, 8, 12] IFN alfa and IFN beta are active in vitro against SARS-COV-2 in Vero cells at clinically relevant concentrations; [1] in vitro study suggests SARS-CoV-2 is more sensitive than SARS-CoV-1 to IFN alfa [1, 3]	**Only limited clinical trial data available** to date specifically evaluating efficacy of IFNs for treatment of COVID-19; [10, 15, 20, 21] for information on additional studies including IFN alfa or IFN beta as a component of combination therapy (e.g., background regimen), see antiviral entries in this Evidence Table. Clinical trials are currently evaluating **IFN beta-1a or IFN beta-1b**, generally added to other antivirals, for treatment of COVID-19, including: [16] NCT04492475 (IFN beta-1a) NCT04465695 (IFN beta-1b) NCT04494399 (IFN beta-1b) NCT04324463 (IFN beta) NCT04343768 (IFN beta-1a, IFN beta-1b) NCT04385095 (SNG001 [inhaled IFN beta-1a]) (manufacturer announced very preliminary "positive" findings for a hospitalized subset of patients in a press release, but rigorous reporting of complete findings still pending [22]). Open-label, randomized study in Hong Kong in hospitalized adults with COVID-19, mainly mild disease (NCT04276688): Combination regimen of **LPV/RTV, ribavirin, and sub-Q IFN beta-1b** (IFN beta-1b was omitted to avoid proinflammatory effects when treatment was initiated 7-14 days after symptom onset) was associated with shorter median time from treatment initiation to negative RT-PCR result in nasopharyngeal swab (7 vs 12 days), earlier resolution of symptoms (4 vs 8 days), and shorter hospital stay (9 vs 14.5 days) compared with control (LPV/RTV). In the subset of	**IFN beta:** Various sub-Q dosages of IFN beta-1a and IFN beta-1b are being evaluated for treatment of COVID-19. [10, 16] Open-label, randomized study in hospitalized adults with COVID-19, mainly mild disease (NCT04276688**): IFN beta-1b** 8 million units was given sub-Q 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. [10, 16] In an open-label, randomized study in hospitalized adults with severe COVID-19, **IFN beta-1a** 12 million units was given sub-Q 3 times weekly for 2 weeks. [20] **IFN alfa:** Chinese guidelines suggest IFN alfa dosage of 5 million units (or equivalent) twice daily via atomization inhalation for treatment of COVID-19. [13] **Peginterferon lambda-1a:** For *treatment* of COVID-19 in adults (NCT04354259, NCT04388709): Peginterferon lambda-1a 180 mcg sub-Q; number of doses (1 dose or 2 doses given 1 week apart) depends on the protocol. [5] For *postexposure prophylaxis* of CoV-2 infection in adults (NCT04344600): Two 180-mcg sub-Q doses of peginterferon lambda-1a given 1 week	Efficacy and safety of IFNs for treatment or prevention of COVID-19 not established. Relative effectiveness of different IFNs against SARS-CoV-2 not established. [12] NIH COVID-19 Treatment Guidelines Panel **recommends against** use of IFNs for treatment of severe or critical COVID-19, except in the context of a clinical trial. The panel also states there are insufficient data to recommend either for or against use of IFN beta for the treatment of early (i.e., <7 days from symptom onset) mild or moderate COVID-19. No benefit was observed with use of IFNs for treatment of other severe or critical coronavirus infections (SARS, MERS), and toxicity of IFNs outweighs the potential for benefit. IFNs may have antiviral activity early in the course of SARS-CoV-2 infection; however, there are insufficient data to assess the potential benefit of IFN use during early disease versus the risk of toxicity. [11] Surviving Sepsis Campaign COVID-19 subcommittee states that there is insufficient evidence to issue a recommendation on use of interferons, alone or in combination with antivirals, in critically ill adults with COVID-19. [12] Interferon alfa via atomization inhalation is included in Chinese guidelines as a possible option for treatment of COVID-19. [13]

Anti inflammatory drugs

Assessment of Evidence for COVID-19-Related Treatments: Updated 10/1/2020

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Ruxolitinib (Jakafi®) *Updated 8/6/20*	10:00 Antineoplastic Agents	Janus kinase (JAK) 1 and 2 inhibitor; [7] may potentially combat cytokine release syndrome (CRS) in severely ill patients [4, 5] May reduce inflammation via JAK inhibition, but study based on artificial intelligence (AI)-derived methodology suggests that clinically tolerated concentrations of ruxolitinib may be unlikely to reduce viral infectivity by disrupting regulators of endocytosis	Limited published clinical trial evidence regarding efficacy and safety in patients with COVID-19 **Single-hospital retrospective chart review:** Based on the hospital's COVID-19 treatment algorithm, patients with severe COVID-19 were prospectively stratified using a newly developed clinical inflammation score (CIS; maximum score = 16); those identified as being at high risk for systemic inflammation (CIS ≥10, without sepsis) were evaluated for ruxolitinib treatment; 14 patients received ruxolitinib (median cumulative dose: 135 mg [52.5-285 mg], median treatment duration: 9 days [5-17	Various dosages are being evaluated [3, 6, 10] **Phase 3 study (NCT04362137):** Ruxolitinib 5 mg twice daily for 14 days with possible extension to 28 days [10] **Phase 3 study (NCT04377620):** Ruxolitinib 5 or 15 mg twice daily (approximately every 12 hours) [12]	NIH COVID-19 Treatment Guidelines Panel **recommends against** use of JAK inhibitors for the treatment of COVID-19 except in the context of a clinical trial. [8] **Severe reactions** requiring drug discontinuance observed in 2 COVID-19 patients following initiation of ruxolitinib: purpuric lesions with thrombocytopenia and deep-tissue infection in one patient, and progressive decrease in hemoglobin and erythrodermic rash over the whole body surface area in the second patient; these cases differed in the timing of ruxolitinib initiation and the severity of COVID-19 illness [11]

Anti inflammatory drugs

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Assessment of Evidence for COVID-19-Related Treatments: Updated 10/1/2020

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Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Sarilumab (Kevzara®) *Updated 9/10/20*	92:36 Disease-modifying Anti-rheumatic Drug	Recombinant humanized monoclonal antibody specific for the interleukin-6 (IL-6) receptor; IL-6 is a proinflammatory cytokine. Sarilumab may potentially combat cytokine release syndrome (CRS) and pulmonary symptoms in severely ill patients [1, 2, 5, 7]	Preliminary unpublished data from randomized clinical trials have not demonstrated efficacy in treatment of patients with COVID-19 [7, 11, 12] However, based on encouraging results in China with a similar drug, tocilizumab, **a large, U.S.-based, phase 2/3, randomized, double-blind, placebo-controlled, adaptively designed study** (NCT04315298) evaluating efficacy and safety of sarilumab in patients hospitalized with severe COVID-19 was performed. [3, 4, 7, 9, 10, 12] Patients in this study were randomized (2:2:1) to receive sarilumab 400 mg, sarilumab 200 mg, or placebo. Randomization was stratified by severity of illness (e.g., severe, critical, multisystem organ dysfunction) and use of systemic corticosteroids. [7, 12] In the phase 2 part of the study, sarilumab at both dosages reduced C-reactive protein (CRP) levels. [7] The primary efficacy outcome measure in phase 3 was the change on a 7-point scale; this phase was modified to focus on the 400-mg dose of sarilumab in the critically ill patient group. [7] During the course of the trial, there were many amendments that increased the sample size and modified the dosing strategies, and multiple interim analyses were performed. [7, 9] The results did not demonstrate a clinical benefit of sarilumab for any of the disease severity subgroups or dosing strategies studied. [7, 9, 12]	**Large US-based controlled study (NCT04315298):** Dosage of 400 mg IV as a single dose or multiple doses (based on protocol criteria); the lower-dose (200-mg) treatment arm was discontinued following a preliminary analysis of study results [9, 10] (see Trials or Clinical Experience) Note: IV formulation not commercially available in the U.S., but was studied in the above-mentioned clinical trial. The sub-Q formulation is not FDA-labeled to treat cytokine release syndrome (CRS) in the U.S. [7]	NIH COVID-19 Treatment Guidelines Panel **recommends against** use of sarilumab in the treatment of COVID-19, except in a clinical trial [7] No new safety findings observed with use in COVID-19 patients [9]

Anti inflammatory drugs

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Siltuximab (Sylvant®) *Updated 9/10/20*	10:00 Antineoplastic agents	Recombinant chimeric monoclonal antibody specific for the interleukin-6 (IL-6) receptor; may potentially combat cytokine release syndrome (CRS) symptoms (e.g., fever, organ failure, death) in severely ill patients [1-5]	Only limited, unpublished data available describing efficacy in patients with COVID-19 **Italy:** Non-peer-reviewed findings from an observational cohort study of 30 patients with COVID-19 and pneumonia/acute respiratory distress syndrome (ARDS) who participated in a compassionate use program in one hospital in Italy (SISCO study; NCT04322188) and were followed for at least 30 days showed reduced C-reactive protein (CRP) levels by day 14. The siltuximab-treated patients were compared with 30 propensity score-matched patients receiving best supportive care. The 30-day mortality rate was substantially lower in the siltuximab group compared with the matched-control cohort. Out of the 30 patients treated with siltuximab, 16 (53%) were discharged from the hospital, 4 (13%) remained hospitalized on mechanical ventilation, and 10 patients died. [4, 6]	In the SISCO study in Italy, patients received an initial dose of siltuximab 11 mg/kg by IV infusion over 1 hour; a second dose could be administered at the physician's discretion [4] Other clinical studies under way are evaluating a single siltuximab dose of 11 mg/kg by IV infusion [7, 8]	Efficacy and safety of siltuximab in the treatment of COVID-19 not established NIH COVID-19 Treatment Guidelines Panel **recommends against** use of siltuximab in the treatment of COVID-19, except in a clinical trial [9]

Anti inflammatory drugs

Letter to the Editor

ACCP
American College of Clinical Pharmacology
Advancing Clinical Care through Pharmacology

Can Colchicine as an Old Anti-Inflammatory Agent Be Effective in COVID-19?

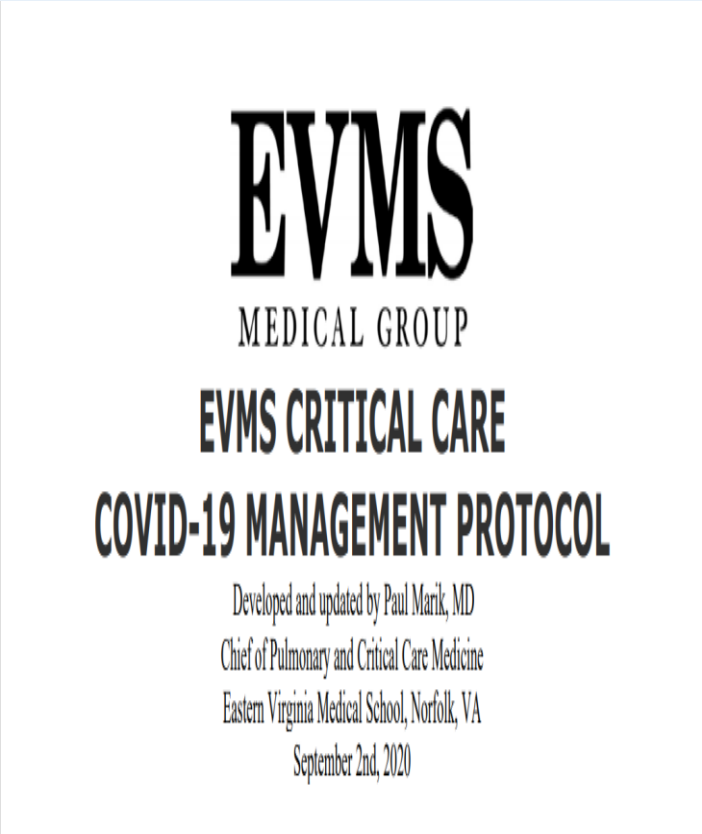
Somayyeh Nasiripour, PharmD[1], Farhad Zamani, MD[2], and Maryam Farasatinasab, PharmD[3]

The Journal of Clinical Pharmacology
2020, 00(0) 1–2

DOI: 10.1002/jcph.1645

Adjuvant therapy

Adjuvant therapy

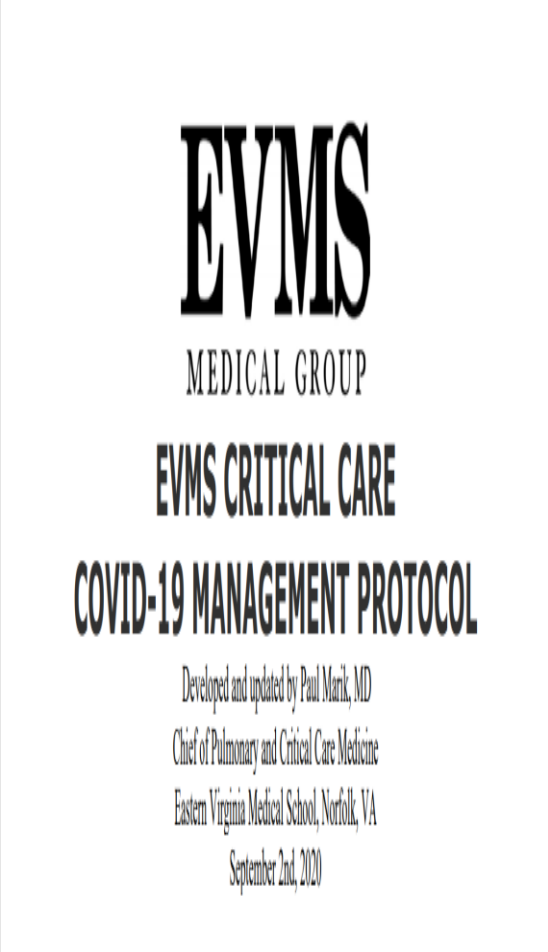


Ascorbic acid (Vitamin C) 3g IV q 6 hourly for at least 7 days and/or until transferred out of ICU

Note caution with POC glucose testing (see below). Oral absorption is limited by saturable transport and it is difficult to achieve adequate levels with PO administration. However, unfortunately, IV Vitamin C is not available in many hospitals; in this situation attempts should be made to administer PO vitamin C at a dose of 1g every 4-6 hours.

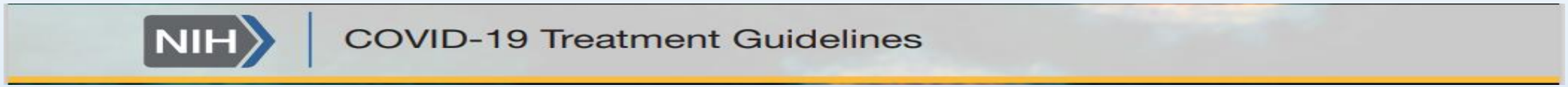
ASA 81 -325 mg/day (unless contraindicated). ASA has antiinflammatory, antithrombotic, and antiviral effects.[37,38] Platelet activation may play a major role in propagating the prothrombotic state associated with COVID-19.

Adjuvant therapy



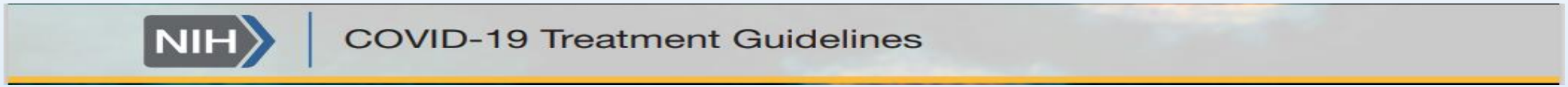
- *Melatonin 6-12 mg at night* (the optimal dose is unknown).
- *Famotidine 40-80mg BID daily* (20-40 mg/day in renal impairment)
- *Vitamin D 4000 u PO daily*
- *Thiamine 200 mg IV q 12 hourly*
- *Magnesium: 2 g stat IV.* Keep Mg between 2.0 and 2.4 mmol/l. Prevent hypomagnesemia (which increases the cytokine storm and prolongs Qtc).
- *Atorvastatin 80 mg/day.* Statins have pleotropic anti-inflammatory, immunomodulatory, antibacterial, and antiviral effects. In addition, statins decrease expression of PAI-1.
- *Simvastatin* has been demonstrated to reduce mortality in the hyper-inflammatory ARDS phenotype. Preliminary data suggests atorvastatin may improve outcome in patients with COVID-19. Due to numerous drug-drug interactions simvastatin should be avoided.

Adjuvant therapy



- Recommendation for Critically Ill Patients With COVID-19
- There are insufficient data for the Panel to recommend either for or against the use of vitamin C for the treatment of COVID-19 in critically ill patients.
- There are insufficient data to recommend either for or against the use of vitamin D for the prevention or treatment of COVID-19.
- There are insufficient data to recommend either for or against the use of zinc for the treatment of COVID-19. • The COVID-19 Treatment Guidelines Panel (the Panel) recommends against using zinc supplementation above the recommended dietary allowance for the prevention of COVID-19, except in a clinical trial
- (AIII).

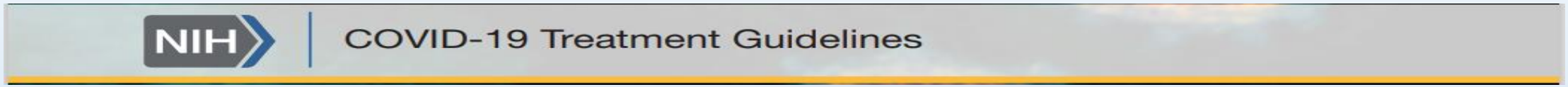
Adjuvant therapy



- Angiotensin-Converting Enzyme (ACE) Inhibitors and Angiotensin Receptor Blockers (ARBs) • Persons with COVID-19 who are prescribed ACE inhibitors or ARBs for cardiovascular disease (or other indications) should continue these medications (AIII)
- The COVID-19 Treatment Guidelines Panel (the Panel) recommends against the use of ACE inhibitors or ARBs for the treatment of COVID-19, except in a clinical trial (AIII).

• Persons with COVID-19 who are prescribed statin therapy for the treatment or prevention of cardiovascular disease should continue these medications (AIII). • The Panel recommends against the use of statins for the treatment of COVID-19, except in a clinical trial (AIII).

Adjuvant therapy



- Persons with COVID-19 who are taking NSAIDs for a comorbid condition should continue therapy as previously directed by their physician (AIII).
- The Panel recommends that there be no difference in the use of antipyretic strategies (e.g., with acetaminophen or NSAIDs) between patients with or without COVID-19 (AIII).

Adjuvant therapy

Assessment of Evidence for COVID-19-Related Treatments: Updated 10/1/2020

The information contained in this evidence table is emerging and rapidly evolving because of ongoing research and is subject to the professional judgment and interpretation of the practitioner due to the uniqueness of each medical facility's approach to the care of patients with COVID-19 and the needs of individual patients. ASHP provides this evidence table to help practitioners better understand current approaches related to treatment and care. ASHP has made reasonable efforts to ensure the accuracy and appropriateness of the information presented. However, any reader of this information is advised ASHP is not responsible for the continued currency of the information, for any errors or omissions, and/or for any consequences arising from the use of the information in the evidence table in any and all practice settings. Any reader of this document is cautioned that ASHP makes no representation, guarantee, or warranty, express or implied, as to the accuracy and appropriateness of the information contained in this evidence table and will bear no responsibility or liability for the results or consequences of its use.

ASHP's patient medication information is available at http://www.safemedication.com/. Visit our website for the latest information on current drug shortages.

Selected entries were updated 10/1/20; these can be identified by the date that appears in the Drug(s) column. Within updated entries, select revisions that include the most important new information (e.g., new clinical trial data, new or revised guidance) are marked by **.

Drug(s)	AHFS Class	Rationale	Trials or Clinical Experience	Dosage[a]	Comments
Vitamin D *Updated 9/17/20*	88:16 Vitamin D	Vitamin D receptor is expressed on immune cells (e.g., B cells, T cells, antigen-presenting cells); these cells can synthesize and respond to active vitamin D. [10, 13] Vitamin D modulates innate and adaptive immune responses; may downregulate proinflammatory cytokines and upregulate anti-inflammatory cytokines, increase T regulatory cell activity, and reduce cytokine storm induced by innate immune system. [10, 12, 13] Vitamin D deficiency is associated with increased autoimmunity and increased susceptibility to infection. [10, 13] In observational studies, low vitamin D concentrations have been associated with increased risk of community-acquired pneumonia in older adults and upper respiratory viral infections in children. [1, 8, 9] Vitamin D deficiency is common in the U.S., particularly in Hispanic and Black populations (groups overrepresented among U.S. COVID-19 cases). [1, 14, 20]	No known published controlled clinical trial evidence supporting efficacy of vitamin D supplementation for treatment or prevention of COVID-19. **Prevention of respiratory infections:** Efficacy of vitamin D supplementation for prevention of influenza or other respiratory infections is unclear. [10] Meta-analysis of 25 randomized, double-blind, placebo-controlled trials including a total of 11,321 participants, either healthy or with comorbidities, indicated a protective effect for oral vitamin D supplementation against acute respiratory infection. [5] A second systematic review and meta-analysis of 15 randomized controlled trials involving approximately 7000 healthy individuals found that vitamin D supplementation did not reduce the risk of respiratory infections compared with placebo or no treatment. [11] **Outcomes in critically ill patients:** Results of 2 randomized, double-blind, placebo-controlled clinical trials (VIOLET, VITdAL-ICU) in critically ill patients with vitamin D deficiency (but not with COVID-19) indicated that high-dose vitamin D did not reduce hospital stay or mortality rate compared with placebo. Patients in both studies received a single enteral dose of 540,000 international units (IU; units) of vitamin D_3; patients in VITdAL-ICU also received oral maintenance doses (90,000 units monthly for 5 months). [6, 7] **Ongoing COVID-19 trials:** Clinical trials are evaluating effects of vitamin D supplementation on COVID-19-	Various dosages of vitamin D are being evaluated for prevention or treatment of COVID-19. [4] High concentrations of vitamin D may cause hypercalcemia and nephrocalcinosis; [1] currently no convincing scientific evidence that very high intake of vitamin D will be beneficial in preventing or treating COVID-19. [14] National Academy of Sciences (NAS) guidelines for **adequate dietary intake of vitamin D for bone health in US population**: Estimated Average Requirement (EAR) in children and adults 1-70 years of age 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). These reference values assume minimal sun exposure. [26] NAS states that data indicate that a serum 25-hydroxyvitamin D concentration of 50 nmol/L is sufficient to meet the needs of 97.5% of the population and concentrations <30 nmol/L are associated with clinical deficiency. [26]	Efficacy of vitamin D supplementation in the prevention or treatment of COVID-19 has not been established. [1, 2, 3] Some experts recommend maintaining recommended levels of vitamin D intake during the COVID-19 pandemic to maintain bone and muscle health and avoid deficiency. [2, 3, 14] NIH COVID-19 Treatment Guidelines Panel states that there are insufficient data to recommend either for or against use of vitamin D for prevention or treatment of COVID-19. [1] Joint guidance from the American Society for Bone and Mineral Research (ASBMR), American Association of Clinical Endocrinologists (AACE), Endocrine Society, European Calcified Tissue Society (ECTS), National Osteoporosis Foundation (NOF), and International Osteoporosis Foundation (IOF) emphasizes importance of obtaining the recommended daily dosage of vitamin D; for those unable to obtain recommended durations of direct sun exposure during the pandemic, recommended intake of vitamin D can be obtained through supplemental vitamin D. The joint guidance states that current data do not provide any evidence that vitamin D supplementation will help prevent or treat COVID-19. [2] Advisory statement from the UK National Institute for Health and Care Excellence (NICE) states that there is no evidence to support taking vitamin D supplements to specifically prevent or treat COVID-19. However, all individuals

Adjuvant therapy

Assessment of Evidence for COVID-19-Related Treatments: Updated 10/1/2020

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Zinc *Updated 8/6/20*		Trace mineral involved in immune function, including antibody and white blood cell production; an important cofactor for many enzymes; [1,3] may improve wound healing [8] Zinc deficiency increases proinflammatory cytokine concentrations (interleukin -1 [IL-1], IL-6, TNF alpha) and decreases antibody production; zinc supplementation increases the ability of polymorphonuclear cells to fight infection [1] Possible antiviral activity; zinc appears to inhibit virus RNA polymerase activity and viral replication in an in vitro and cell culture model of severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1). [1, 7] High-dose zinc supplementation reduced the duration but not severity of	No evidence from controlled trials that zinc is effective in the prevention or treatment of COVID-19 [5, 6] Because of its role in immune function and potential to decrease coronavirus replication, zinc is being evaluated in a number of clinical trials in both the prophylaxis and treatment of COVID-19, sometimes in combination with other supplements (including vitamin C, vitamin D, and selenium) and drugs (including hydroxychloroquine) [1, 2, 5, 6] **Retrospective observational study in New York City (Carlucci et al; non-peer-reviewed):** Data were collected from electronic medical records to compare outcomes between hospitalized patients with COVID-19 who received hydroxychloroquine, azithromycin, and zinc (411 patients) and those who received hydroxychloroquine and azithromycin alone (521 patients). Zinc was given as a zinc sulfate 220-mg capsule (50 mg of elemental zinc) twice daily for 5 days. The addition of zinc did not affect the length of hospitalization, duration of ventilation, or duration of ICU stay, but patients in the treatment group that included zinc were discharged home more frequently and the need for ventilation, ICU	Zinc Recommended Dietary Allowance (RDA): Adult males: 11 mg/day; adult females: 8 mg/day [3, 8] Some clinicians have recommended an elemental zinc intake of 30-50 mg/day in the short-term treatment of influenza and coronavirus infections [3, 4] Appropriate dosage regimens not established in either the prophylaxis or treatment of COVID-19; 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 [2, 5, 6, 9, 10] Oral zinc supplementation likely safe in dosages up to 40 mg of elemental zinc daily in adults; safety of dosages exceeding those used in the management of the common cold not known [3, 6, 8]	Despite some anecdotal claims in the media that zinc is effective in treating COVID-19,[6] unclear whether zinc supplementation is beneficial in the prophylaxis and/or treatment of COVID-19; further study is needed [1, 3, 6] NIH COVID-19 Treatment Guidelines Panel states that there are insufficient clinical data to recommend either for or against use of zinc in the *treatment* of COVID-19 [9] NIH COVID-19 Treatment Guidelines Panel *recommends against* using zinc supplementation above the RDA for the *prevention* of COVID-19, except in a clinical trial [9] Zinc concentrations are difficult to measure accurately since it is distributed as a component of various proteins and amino acids [9] Adverse effects may include nausea (possibly dose dependent), vomiting, and changes in taste [1, 6, 7, 8]

Adjuvant therapy

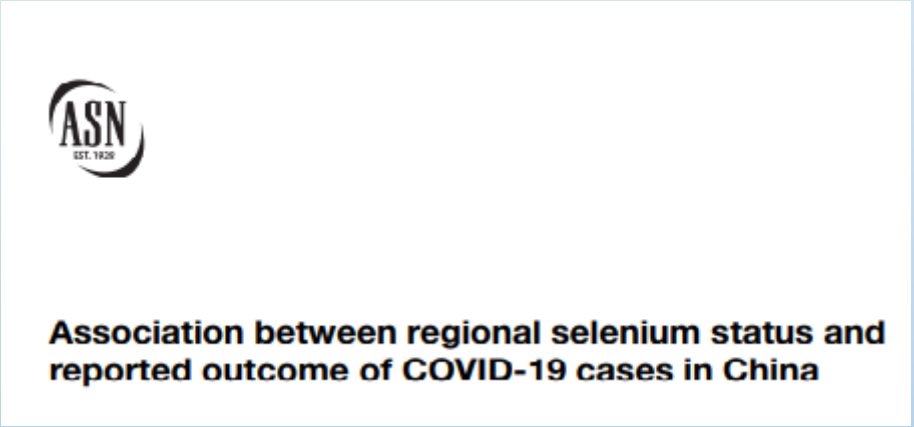
JAMA Internal Medicine | Original Investigation

Effect of Sodium Selenite Administration and Procalcitonin-Guided Therapy on Mortality in Patients With Severe Sepsis or Septic Shock

A Randomized Clinical Trial

Frank Bloos, MD, PhD; Evelyn Trips, MSc; Axel Nierhaus, MD, EIDEC; Josef Briegel, MD; Daren K. Heyland, MD; Ulrich Jaschinski, MD; Onnen Moerer, MD; Andreas Weyland, MD; Gernot Marx, MD; Matthias Gründling, MD; Stefan Kluge, MD; Ines Kaufmann, MD; Klaus Ott, MD; Michael Quintel, MD; Florian Jelschen, MD; Patrick Meybohm, MD; Sibylle Rademacher, MD; Andreas Meier-Hellmann, MD; Stefan Utzolino, MD; Udo X. Kaisers, MD; Christian Putensen, MD; Gunnar Elke, MD; Maximilian Ragaller, MD; Herwig Gerlach, MD, PhD, MBA; Katrin Ludewig, MD; Michael Kiehntopf, MD; Holger Bogatsch, MD; Christoph Engel, MD; Frank M. Brunkhorst, MD; Markus Loeffler, MD; Konrad Reinhart, MD; for SepNet Critical Care Trials Group

Adjuvant therapy



Adjuvant therapy

Intensive Care Med (2011) 37:1120–1127
DOI 10.1007/s00134-011-2212-6

ORIGINAL

William Manzanares
Alberto Biestro
María H. Torre
Federico Galusso
Gianella Facchin
Gil Hardy

High-dose selenium reduces ventilator-associated pneumonia and illness severity in critically ill patients with systemic inflammation

Immune-Based Therapy

Immune-Based Therapy

- Given the hyperactive inflammatory effects of severe acute respiratory syndrome coronavirus 2 (SARSCoV-2), agents that modulate the immune response are being explored as adjunctive treatments for the management of moderate to critical COVID-19.1 These agents include human blood-derived products and immunomodulatory therapies:
- convalescent plasma
- mesenchymal stem cells
- neutralizing monoclonal antibodies directed against SARS-CoV-2

Immune-Based Therapy

NIH | COVID-19 Treatment Guidelines

Blood-Derived Products Under Evaluation for the Treatment of COVID-19

Last Updated: July 17, 2020

Summary Recommendations

• There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of the following blood-derived products for the treatment of COVID-19:
  • **COVID-19 convalescent plasma**
  • **Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulins**
• The Panel **recommends against** the use of the following blood-derived products for the treatment of COVID-19, except in a clinical trial:
  • **Mesenchymal stem cells (AII)**
  • **Non-SARS-CoV-2-specific intravenous immunoglobulins (IVIG) (AIII)**. This recommendation should not preclude the use of IVIG when it is otherwise indicated for the treatment of complications that arise during the course of COVID-19.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

Immune-Based Therapy

NIH | COVID-19 Treatment Guidelines

- Convalescent Plasma

Plasma from donors who have recovered from COVID-19 may contain antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that may help suppress the virus and modify the inflammatory response.

Recommendation • There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of COVID-19 convalescent plasma for the treatment of COVID-19.

However, >70,000 patients in the United States have received COVID-19 convalescent plasma through the Mayo Clinic's Expanded Access Program (EAP), which was designed primarily to provide broad access to investigational convalescent plasma and thus did not include an untreated control arm. Both the Food and Drug Administration (FDA) and the Mayo Clinic performed retrospective, indirect evaluations of efficacy by using the Mayo Clinic EAP data, hypothesizing that patients who received plasma units with higher titers of SARS-CoV-2 neutralizing antibodies would have better clinical outcomes than those who received plasma units with lower antibody titers. The results of their analyses suggest that convalescent plasma with high antibody titers may be more beneficial than low-titer plasma in nonintubated patients, particularly when administered within 72 hours of COVID-19 diagnosis.

Immune-Based Therapy

NIH | COVID-19 Treatment Guidelines

- Adverse Effects

The available data suggest that serious adverse reactions following the administration of COVID-19 convalescent plasma are infrequent and consistent with the risks associated with plasma infusions for other indications.

transfusion-transmitted infections allergic reactions,

anaphylactic reactions,

febrile nonhemolytic reactions,

transfusion-related acute lung injury (TRALI),

transfusion-associated circulatory overload (TACO),

and hemolytic reactions.

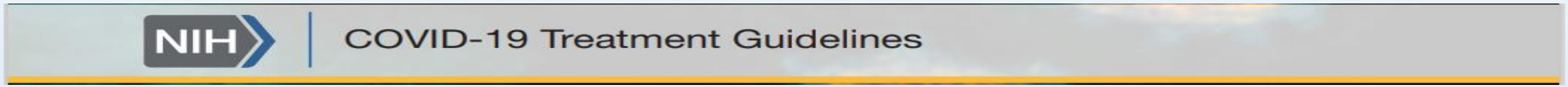
Hypothermia,

metabolic complications,

and post-transfusion purpura have also been described.

Additional risks include a theoretical risk of antibody-dependent enhancement and a theoretical risk of suppressed long-term immunity

Immune-Based Therapy



- Considerations in Pregnancy The safety and effectiveness of COVID-19 convalescent plasma during pregnancy have not been evaluated. Several ongoing clinical trials that are evaluating COVID-19 convalescent plasma include pregnant individuals.

- Considerations in Children The safety and effectiveness of COVID-19 convalescent plasma have not been evaluated in pediatric patients. Clinical trials of COVID-19 convalescent plasma in children are ongoing.

Immune-Based Therapy

NIH | COVID-19 Treatment Guidelines

Immunoglobulins: SARS-CoV-2 Specific

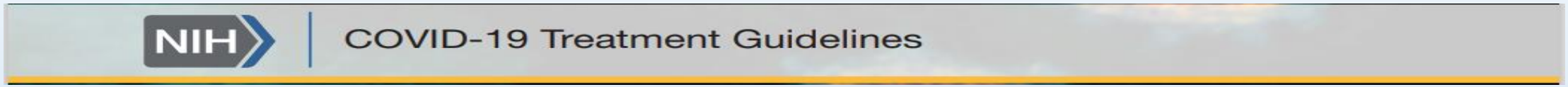
Recommendation :

There are insufficient data for the COVID-19 Treatment Guidelines Panel to recommend either for or against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulins for the treatment of COVID-19

Currently, there are no clinical data on the use of SARS-CoV-2 immunoglobulins. Trials evaluating SARS-CoV-2 immunoglobulins are in development but not yet active and enrolling participants.

There are no clinical data on the use of SARS-CoV-2 immunoglobulins for the treatment of COVID-19. Similarly, there are no clinical data on use of specific immunoglobulin or hyperimmunoglobulin products in patients with severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS).

Immune-Based Therapy

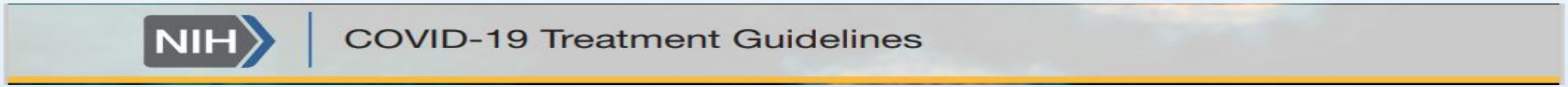


- Immunoglobulins: Non-SARS-CoV-2 Specific

Recommendation :

- The COVID-19 Treatment Guidelines Panel recommends against the use of non-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-specific intravenous immunoglobulin (IVIG) for the treatment of COVID-19, except in a clinical trial (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.

Immune-Based Therapy



- Mesenchymal Stem Cells
- Mesenchymal stem cells are investigational products that have been studied extensively for broad clinical applications in regenerative medicine and for their immunomodulatory properties. It is hypothesized that mesenchymal stem cells could reduce the acute lung injury and inhibit the cell-mediated inflammatory response induced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
- Recommendation
- The COVID-19 Treatment Guidelines Panel recommends against the use of mesenchymal stem cells for the treatment of COVID-19, except in a clinical trial (AII)

Immune-Based Therapy

NIH | COVID-19 Treatment Guidelines

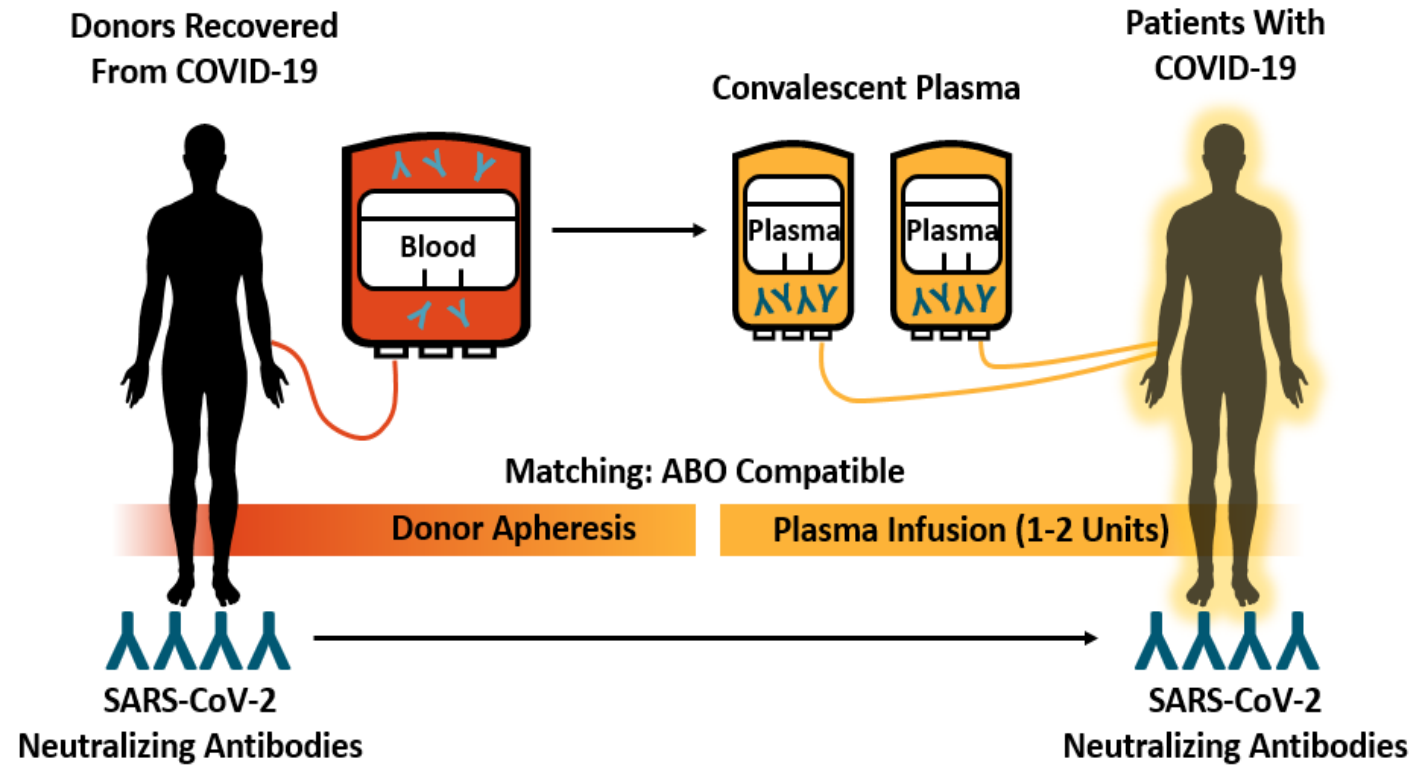
Drug Name	Dosing Regimen *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Blood-Derived Products					
COVID-19 Convalescent Plasma	1 or more transfusions based on patient response	• TRALI • TACO • Allergic reactions • Antibody-mediated enhancement of infection • Red cell alloimmunization • Transmission of infectious pathogens[1] • Thrombotic events	• Monitor for transfusion-related reactions. • Vital signs at baseline and during and after transfusion	Drug products **should not be added** to the IV infusion line for the blood product.	• There are insufficient data for the Panel to recommend either for or against the use of COVID-19 convalescent plasma or SARS-CoV-2 immunoglobulins for the treatment of COVID-19. • A list of clinical trials is available: Convalescent Plasma
Immunoglobulins: SARS-CoV-2 Specific	Doses vary by clinical trial.	• TRALI • TACO • Allergic reactions • Antibody-mediated enhancement of infection • Red cell alloimmunization • Transmission of infectious pathogens	• Monitor for transfusion-related reactions. • Vital signs at baseline and during and after transfusion	Drug products **should not be added** to the IV infusion line for the blood product.	• There are insufficient data for the Panel to recommend either for or against the use of SARS-CoV-2 immunoglobulins for the treatment of COVID-19. • A list of clinical trials is available: Immunoglobulin

Immune-Based Therapy

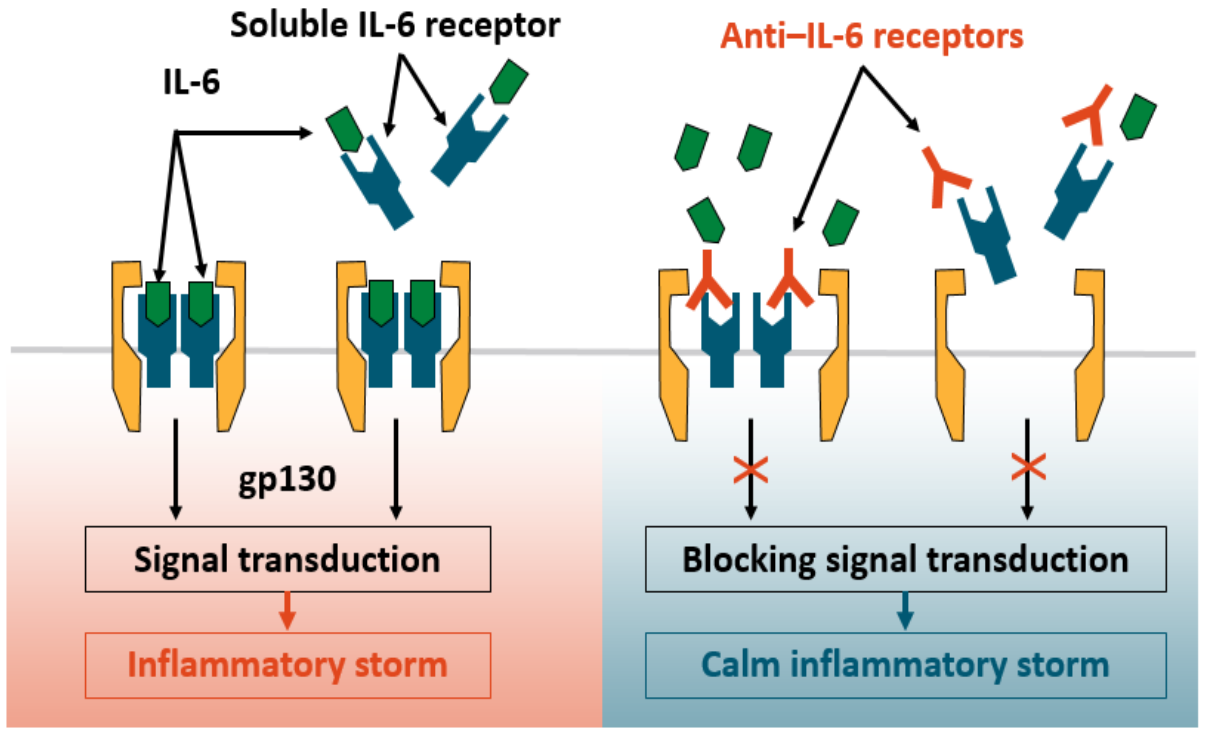
NIH | COVID-19 Treatment Guidelines

Drug Name	Dosing Regimen *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Blood-Derived Products, continued					
Immunoglobulins: Non-SARS-CoV-2 Specific	Doses vary based on indication and formulation.	• Allergic reactions including anaphylaxis • Renal failure • Thrombotic events • Aseptic meningitis syndrome • Hemolysis • TRALI • Transmission of infectious pathogens	• Monitor for transfusion-related reactions. • Vital signs at baseline and during and after infusion • Discontinue if renal function deteriorates during treatment.	IVIG may interfere with immune response to certain vaccines.	• The Panel **recommends against** the use of non-SARS-CoV-2 specific IVIG for the treatment of COVID-19, except in a clinical trial **(AIII)**. This recommendation **should not preclude** the use of IVIG when otherwise indicated for treatment of complications that arise during COVID-19. • AEs may vary by formulation. • AEs may be precipitated by high-dose, rapid infusion, or underlying conditions. • A list of clinical trials is available: Intravenous Immunoglobulin
Mesenchymal Stem Cells	Doses vary by clinical trial. In the United States, mesenchymal stem cells **should not be used** in the United States for the treatment of COVID-19 outside of an FDA-approved clinical trial, expanded access protocol, or EIND process.	• Failure of the cells to work as expected[2] • Potential for mesenchymal stem cells to multiply or change into inappropriate cell types • Product contamination • Growth of tumors • Infections • Thrombus formation[3] • Administration site reactions[4,5]	• Monitor for administration site reactions.	Drug products **should not be added** to the IV infusion line for the mesenchymal stem cell product.	• The Panel **recommends against** the use of mesenchymal stem cells for the treatment of COVID-19, except in a clinical trial **(AII)**. • The FDA has issued several warnings about patients being potentially vulnerable to stem cell treatments that are illegal and potentially harmful.[4] A number of cord blood-derived products are currently licensed by the FDA for various indications such as the treatment of cancer (stem cell transplant) and rare genetic diseases. These products are not FDA approved for the treatment of COVID-19. • A list of clinical trials is available: Mesenchymal Stem Cells

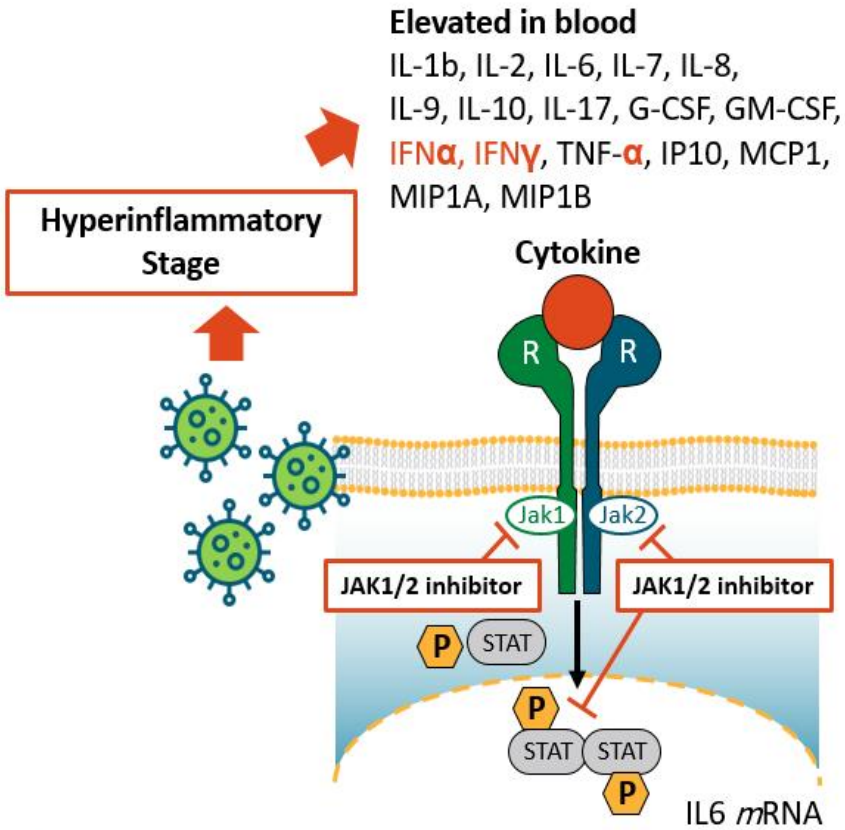
Theory of Using Convalescent Plasma to Treat COVID-19



Anti–IL-6 Receptors



JAK1/2 Inhibitors



Stebbing. EMBO Mol Med.2020;12:e12697.

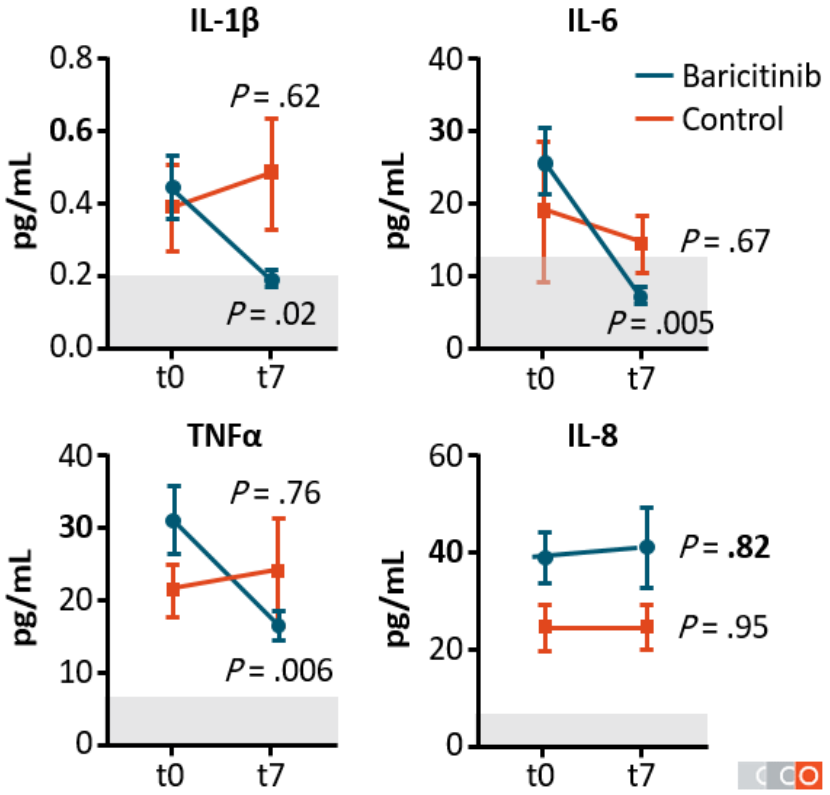
Slide credit: clinicaloptions.com

Baricitinib and Immune Dysregulation in COVID-19

- Observational study assessing baricitinib 4 mg BID for 2 days followed by QD for 7 days vs no baricitinib in patients hospitalized with COVID-19 pneumonia

Outcomes	Baricitinib (n = 20)	No Baricitinib (n = 56)	*P* Value
Deaths, n (%)	1 (5)	25 (45)	< .001
ARDS, n (%)	3 (15)	15 (27)	.37
Median duration of hospitalization, days (range)*	12 (5-24)	11 (3-46)	.28

***Assessable in 19 patients in baricitinib arm and 31 patients in no baricitinib arm.**



Bronte. J Clin Invest. 2020;[Epub].

Slide credit: clinicaloptions.com

REGN-COV2 to Treat Nonhospitalized Patients With COVID-19

New

- Randomized, double-blind, placebo-controlled phase II/II trial

- Primary endpoints: change in viral load through Day 7 in patients and proportion of patients with at least 1 COVID-19–related medical visit

- Average daily change in viral load through Day 7 for combined REGN-COV2 dose groups vs placebo
  - Patients with high viral load ($> 10^7$ copies/mL): -0.68 ($P < .0001$)
  - All patients: -0.36 ($P = .0003$)
- REGN-COV2 reduced COVID-19–related medical visits by 57% through Day 29
  - 2.8% with REGN-COV2 vs 6.5% with placebo ($P = .0065$)

Immune-Based Therapy

FDA NEWS RELEASE

Coronavirus (COVID-19) Update: FDA Authorizes Monoclonal Antibody for Treatment of COVID-19

"The FDA's emergency authorization of bamlanivimab provides health care professionals on the frontline of this pandemic with another potential tool in treating COVID-19 patients," said Patrizia Cavazzoni, M.D., acting director of the FDA's Center for Drug Evaluation and Research. "We will continue to evaluate new data on the safety and efficacy of bamlanivimab as they become available."

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COVID-19 MANAGEMENT PROTOCOL

Developed and updated by Paul Marik, MD
Chief of Pulmonary and Critical Care Medicine
Eastern Virginia Medical School, Norfolk, VA

September 2nd, 2020

Table 1. Pharmacological therapy for COVID by stage of illness: What has worked and what has failed*

	Pre-exposure/ Post-Exposure/ Incubation	Symptomatic Phase	Pulmonary/ inflammatory phase
Hydroxychloroquine	Unclear benefit	No benefit	?Trend to harm
Remdesivir	n/a	?? Reduced time to recovery No mortality benefit	No benefit
Lopivinar-Ritonavir	n/a	No benefit	No benefit
Interferon α/β	Inhaled ? Benefit	No benefit	?Trend harm
Tocilizumab	n/a	n/a	No Benefit
Convalescent Serum	n/a	Unlikely	No Benefit
Corticosteroids	n/a	Trend to harm	BENEFIT
Ivermectin	BENEFIT	BENEFIT	BENEFIT

*based on randomized controlled trials (see supporting information below)

Figure 1. Recommendations for Pharmacologic Management of Patients with COVID-19 Based on Disease Severity

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS *(Recommendations are listed in order of preference in each category below; however, all options are considered acceptable.)*
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]
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]

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

[a] The Panel recognizes that there may be situations in which a clinician judges that remdesivir is an appropriate treatment for a hospitalized patient with moderate COVID-19 (e.g., a patient who is at a particularly high risk for clinical deterioration). However, the Panel finds the data insufficient to recommend either for or against using remdesivir as routine treatment for all hospitalized patients with moderate COVID-19.
[b] Treatment duration may be extended to up to 10 days if there is no substantial clinical improvement by Day 5.
[c] The Panel recognizes there is a theoretical rationale for initiating remdesivir plus dexamethasone in patients with rapidly progressing COVID-19.
[d] For patients who are receiving remdesivir but progress to requiring oxygen through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or ECMO, remdesivir should be continued until the treatment course is completed.
[e] If dexamethasone is not available, equivalent doses of other corticosteroids, such as prednisone, methylprednisolone, or hydrocortisone, may be used.

Figure 6. Premature discontinuation of corticosteroids and IV vitamin C (after 4 day) and the effect of reinitiation of this combination on the CRP profile.

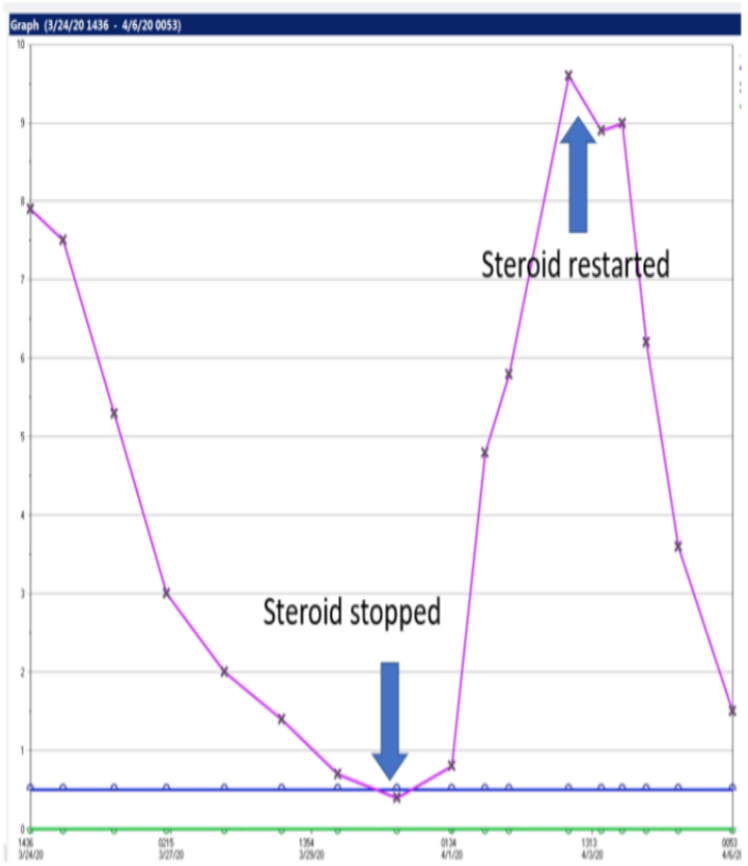
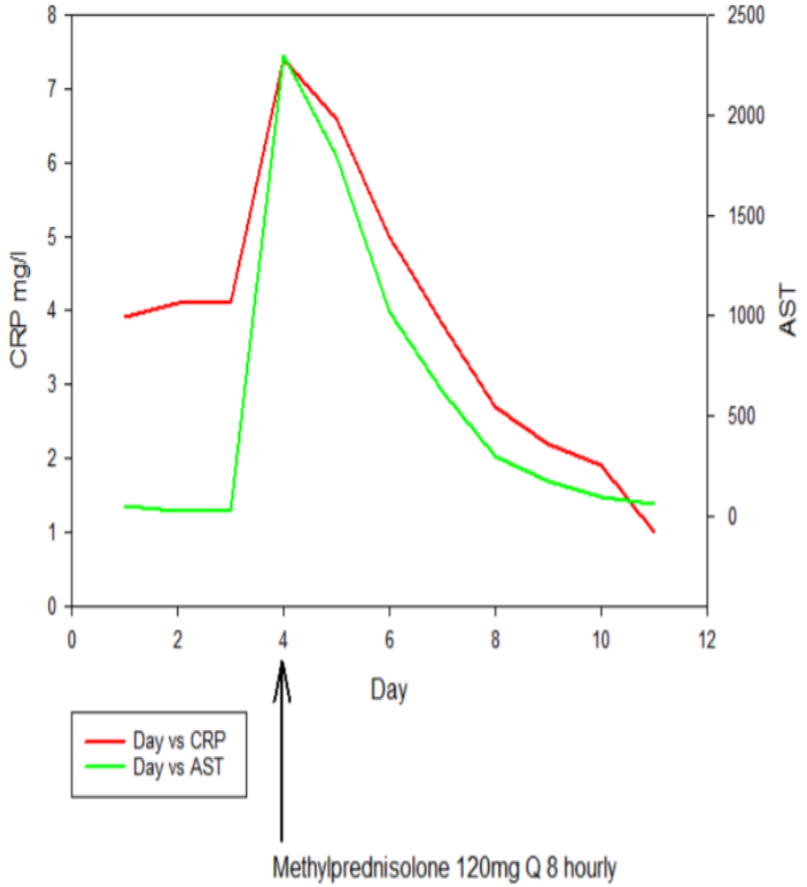
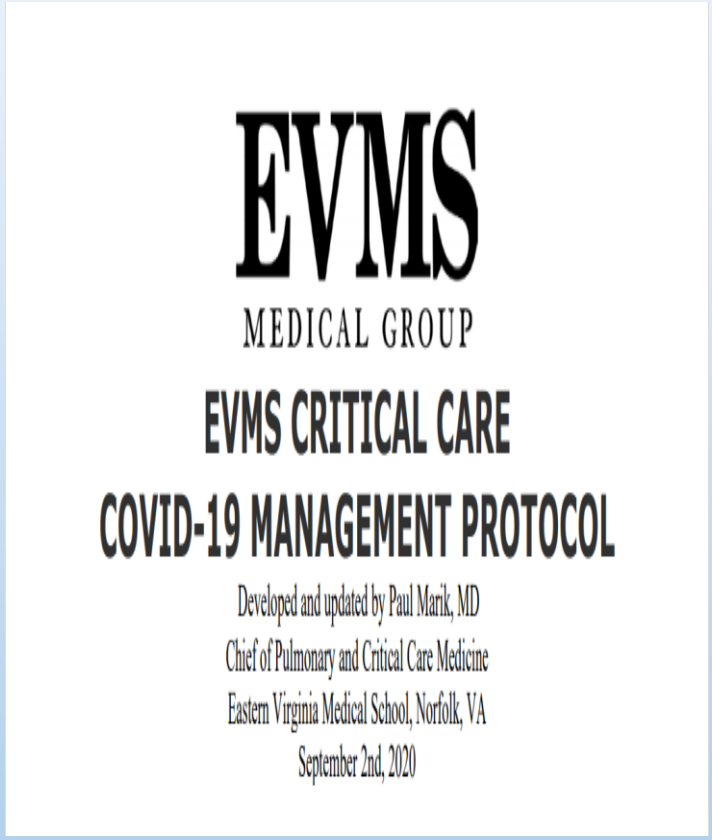


Figure 8. SARS-CoV-2 induced Macrophage Activation Syndrome (MAS) treated with Vitamin C 3g IV q 6 and increased methylprednisolone (125 mg q 8 hourly)



Salvage therapy

Salvage therapy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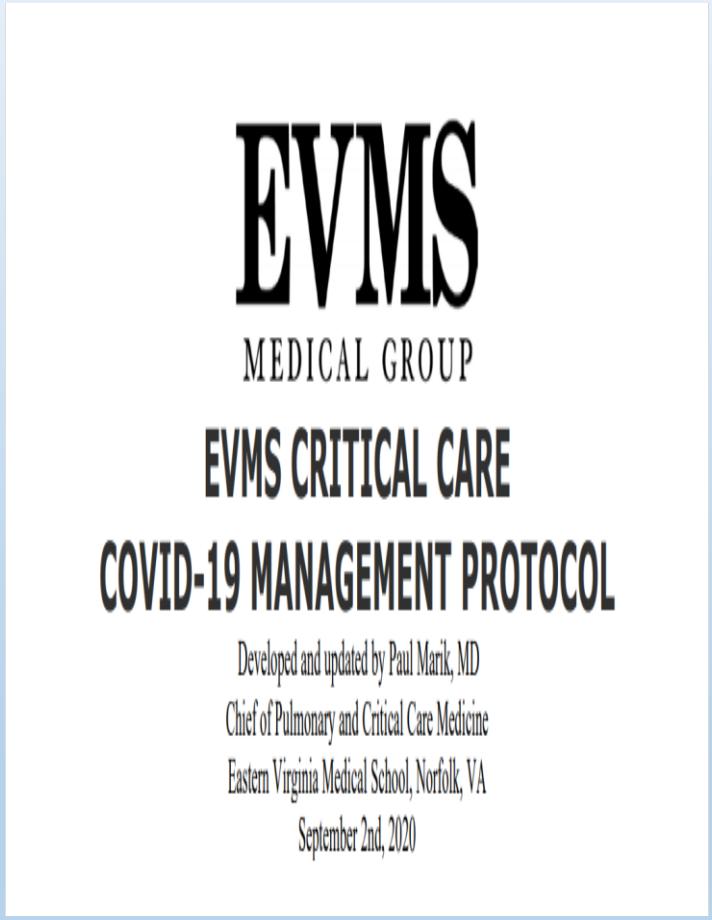
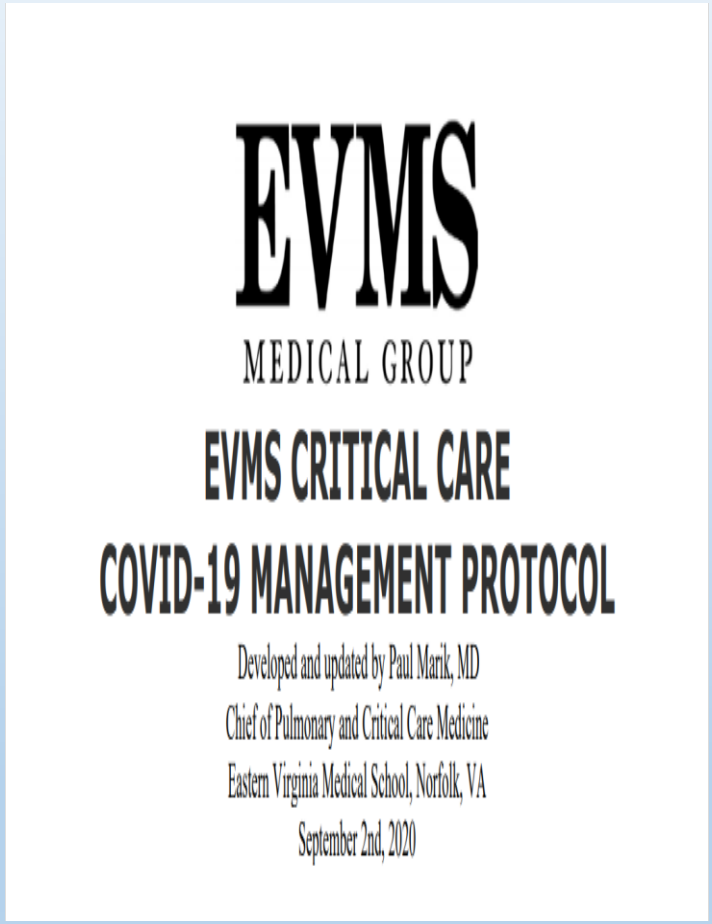
- High dose corticosteroids; 120 - 250 mg methylprednisolone q 6-8 hourly

Salvage therapy



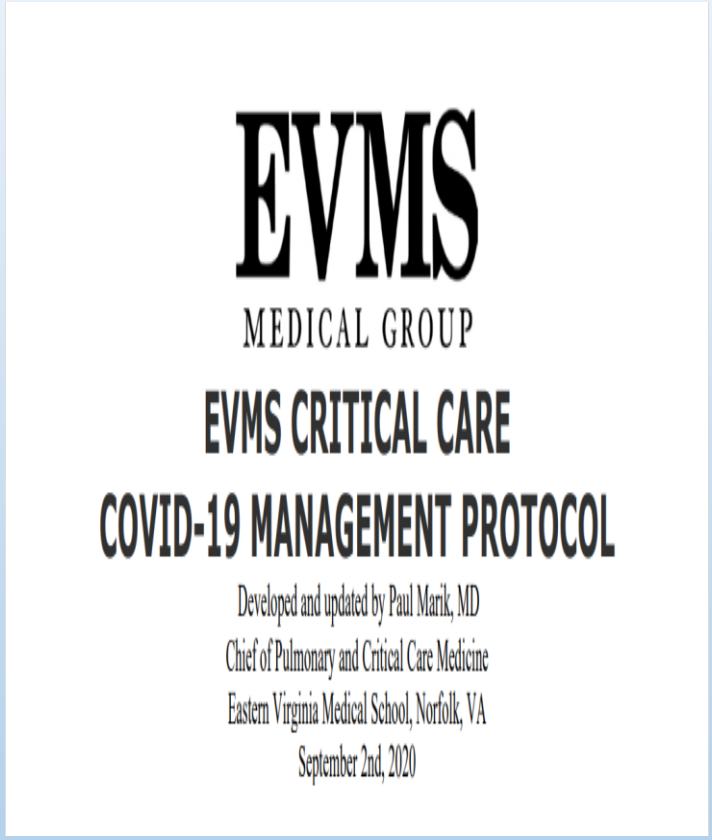
- • Plasma exchange [135-141]. Should be considered in patients with progressive oxygenation failure despite corticosteroid therapy as well as in patients with severe MAS. Patients may require up to 5 exchanges. FFP is required for the exchange; giving back “good humors” appears to be more important than taking out “bad humors”.

Salvage therapy



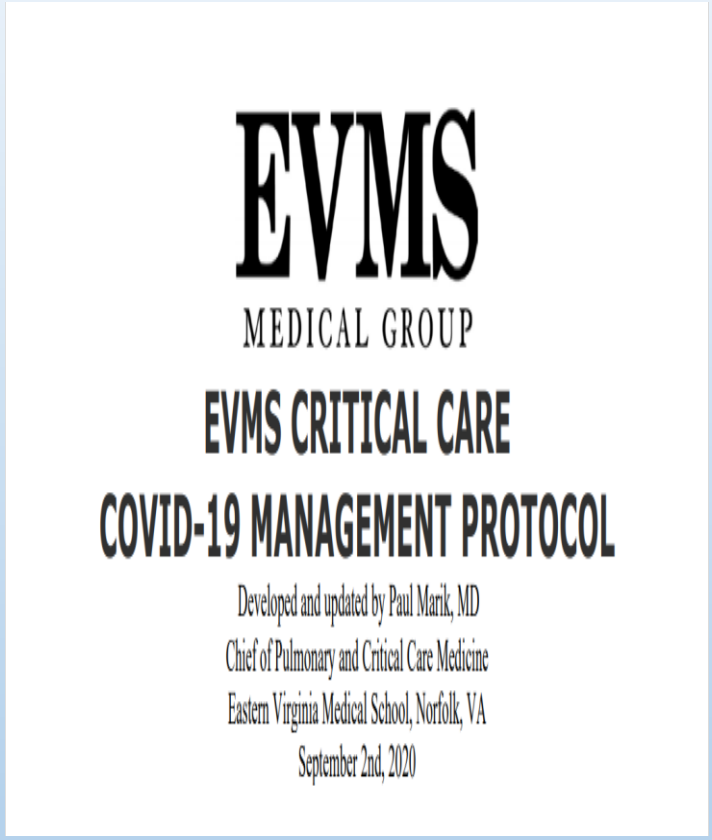
- • In patients with a large dead-space ventilation high PaCO2 despite adequate minute ventilation consider “Half-dose rTPA” to improve pulmonary microvascular blood flow; 25mg of tPA over 2 hours followed by a 25mg tPA infusion administered over the subsequent 22 hours, with a dose not to exceed 0.9 mg/kg followed by full anticoagulation.

Salvage therapy



- Siltuximab and Tocilizumab (IL-6 inhibitors).[144,145] Roche™ recently announced the results of the COVACTA study, which demonstrated that Tocilizumab did not improve patient outcome. Il-6 inhibitors may increase the risk of opportunistic infections.

Salvage therapy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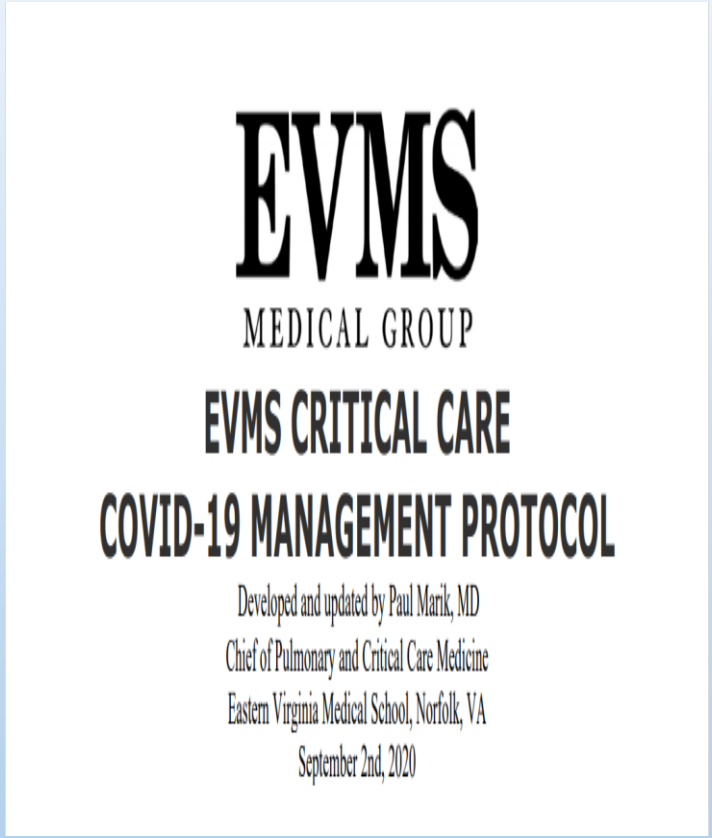
- Convalescent serum: the role and timing of convalescent serum are uncertain. [147-150] COVID-19 pulmonary disease is immune mediated, and it would therefore appear paradoxical to enhance the antibody response with convalescent serum.

Salvage therapy



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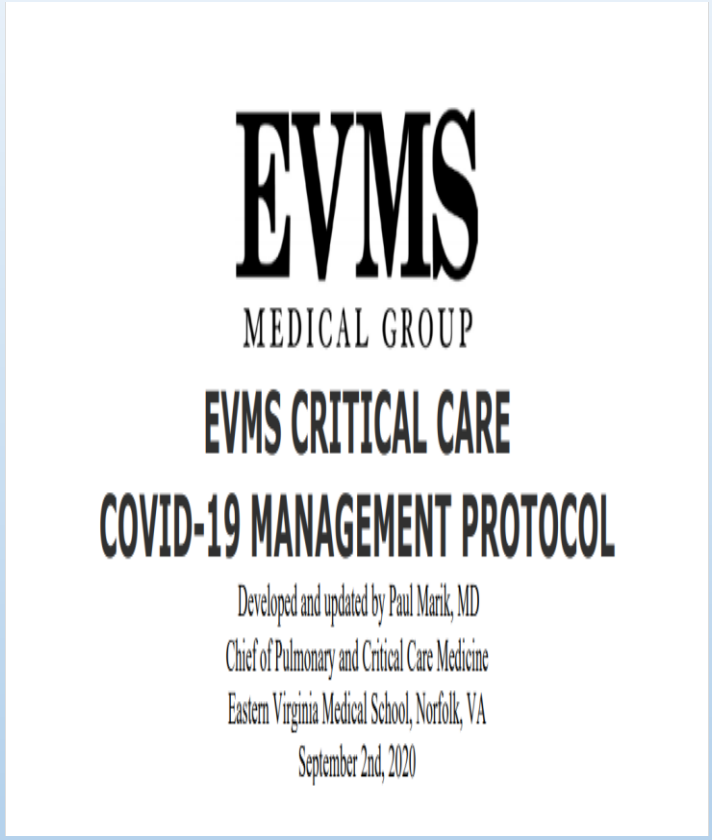
- CVVH with cytokine absorbing/filtering filters [159] This treatment strategy appears to have a very limited role.

Salvage therapy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- ECMO. Unlike “typical ARDS” patients do not progress into a resolution phase. Rather, patients with COVID-19 progress to a severe fibro-proliferative phase and ventilator dependency. ECMO in these patients would likely serve little purpose.

Salvage therapy

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23. Treatment of Macrophage Activation Syndrome (MAS)

- A sub-group of patients will develop MAS, particularly those patients with severe COVID-19 disease.[222] While the pathophysiology of MAS in the setting of COVID-19 is unclear this appears to be driven by SARS-CoV-2 induced inflammasome activation and increased IL-18 production as well as increased GM-CSF and INFγ production. [223-226] The role of IL-1 and IL-6 in the pathogenesis of MAS is unclear.
- A ferritin > 4400 ng/ml is considered diagnostic of MAS. Other diagnostic features include increasing AST/ALT and CRP and progressive multi-system organ failure.[227]
- *"High dose corticosteroids."* Methylprednisolone 120 mg q 6-8 hourly for at least 3 days, then wean according to Ferritin, CRP, AST/ALT (see Figure 8). Ferritin should decrease by at least 15% before weaning corticosteroids.
- Consider plasma exchange.
- The role of inhibition of IL-1 (Anakinra) and IFNγ (emapalumab) is unclear (NCT04324021).

Salvage therapy

Haemoperfusion should only be used for COVID-19 in the context of randomized trials

Edward G. Clark[1]✉, *Swapnil Hiremath*[1], *Lauralyn McIntyre*[2], *Ron Wald*[3], *Gregory L. Hundemer*[1] *and Michael Joannidis*[4]

Interest in the use of haemoperfusion for severe COVID-19 has been spurred by anecdotal reports of its efficacy and expert reviews suggesting theoretical benefits. However, on the basis of the limited current evidence, haemoperfusion remains an experimental therapy that should only be applied within the context of well-designed randomized trials.

Salvage therapy

Despite widespread interest, potential theoretical benefits and approval from regulatory bodies, the use of haemoperfusion in patients with severe COVID-19 is an expensive experimental therapy that seems unlikely to provide much added benefit for patients who are treated with dexamethasone. We are hopeful that haemoperfusion ultimately proves to be an effective rescue therapy for critically ill patients with COVID-19 who do not respond to dexamethasone, but at present we conclude that it should be available for use only in the context of properly designed RCTs that are powered for clinically important outcomes.

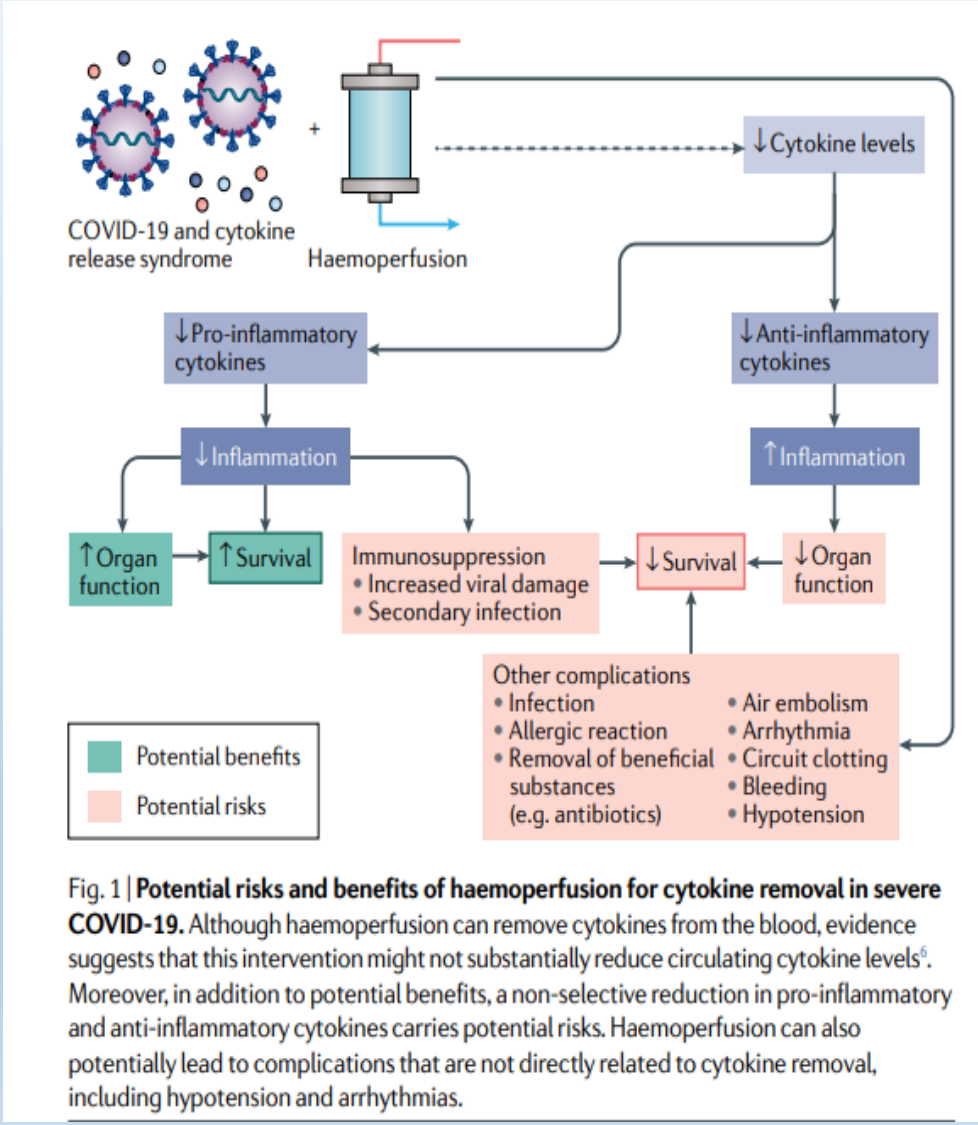


Fig. 1 | **Potential risks and benefits of haemoperfusion for cytokine removal in severe COVID-19.** Although haemoperfusion can remove cytokines from the blood, evidence suggests that this intervention might not substantially reduce circulating cytokine levels[6]. Moreover, in addition to potential benefits, a non-selective reduction in pro-inflammatory and anti-inflammatory cytokines carries potential risks. Haemoperfusion can also potentially lead to complications that are not directly related to cytokine removal, including hypotension and arrhythmias.

Oxygen therapy in covid 19

Oxygen therapy in covid 19

Oxygen therapy in covid 19

Simple oxygenation method:

• Nasal canula 6L/min	44%fio2
• Simple face mask 6-10L/min	60% fio2
• Reserveal mask 10-15L/min	80-90%fio2
• Ventury mask 10L/min	as preset for device

Oxygen therapy in covid 19

- Advanced respiratory therapy
- 1-diagnose of respiratory failure
- 2-high flow nasal canula
- 3-non invasive mechanical ventilation
- 4-invasive mechanical ventilation

Oxygen therapy in covid 19

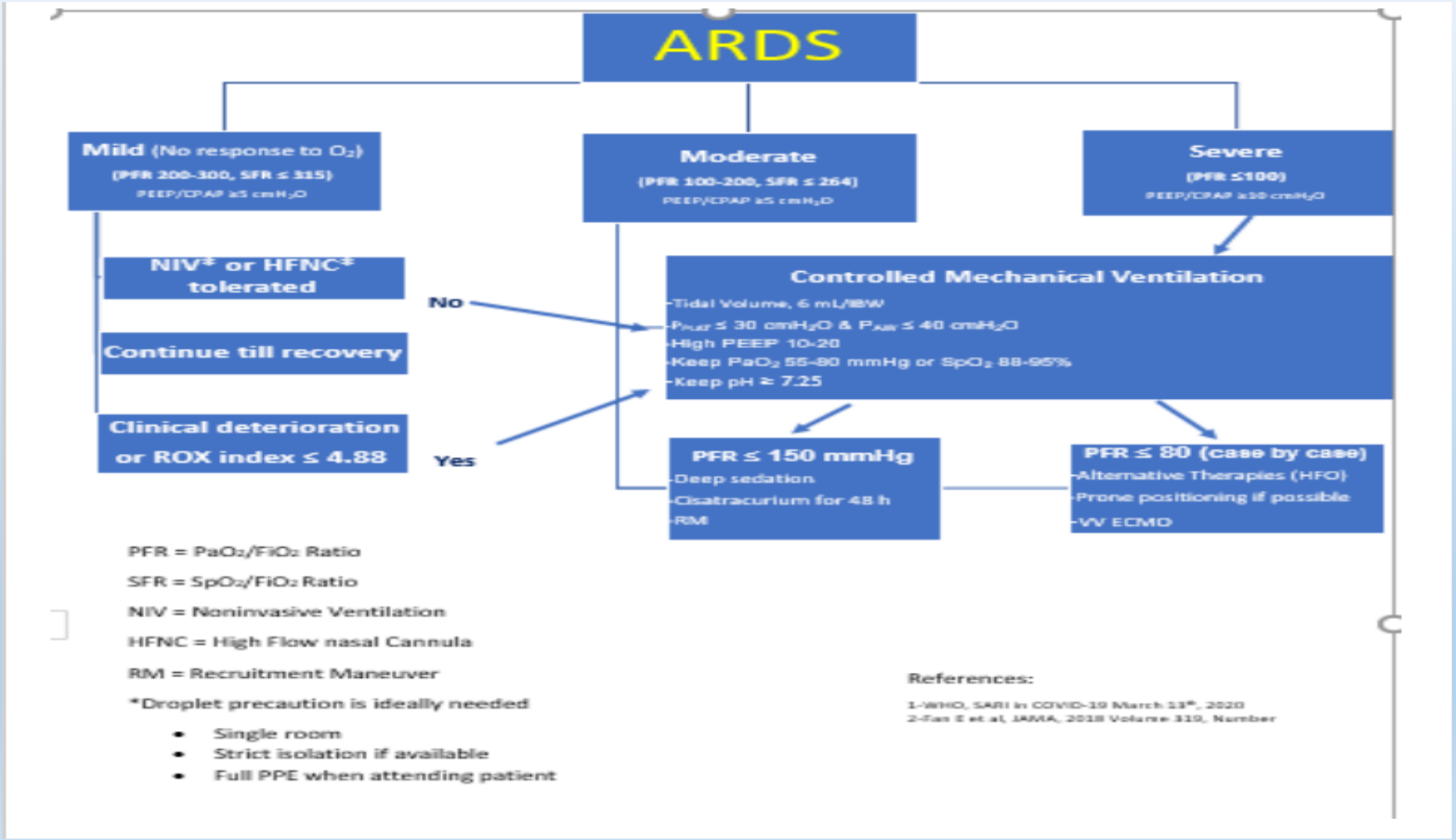
Respiratory failure :

- 1-PaO2/FIO2< 300
- 2-Respiratory rate > 24/min in adults
- 3-Respiratory disteresis
- 4-Central cyanosis
- 5-Respiratory acidosis(PaCO2>45 , PH<7.35)

Oxygenation impairment in adults (PaO_2/FiO_2 Ratio)

- **Mild ARDS:** 200 mmHg < PaO2/FiO2 a ≤ 300 mmHg (with PEEP or CPAP ≥ 5 cmH2O، or non-ventilated)
- **Moderate ARDS:** 100 mmHg < PaO2/FiO2 ≤ 200 mmHg (with PEEP ≥ 5 cmH2O، or non-ventilated)
- **Severe ARDS:** PaO2/FiO2 ≤ 100 mmHg (with PEEP ≥ 5 cmH2O، or non-ventilated)
- When PaO2 is not available، SpO2/FiO2 ≤ 315 suggests ARDS (including in non-ventilated patients).

Oxygen therapy in covid 19



Oxygen therapy in covid 19

- 1) Make sure about the oxygen outlet delivery of at least 90%
- 2) Nasal Cannula up to 6 L/min
- 3) Face Mask 7-10 L/min
- 4) NRBFM or Reservoir mask (good fit) 10-15 L/min
- 5) High Flow Nasal Cannula (HFNC) titer to target SpO2

Oxygen therapy in covid 19

- 6) Non-invasive Ventilation (NIV) with high flow oxygen (10-20 L/min)
- a) Tight fit mask ،helmet if available
- b) CPAP : 10 to 16 cmH2O
- c) BIPAP : I/E = 10-24 cmH2O/4-10 cmH2O (results in PS of 6 to 14)
- d) It depends on patient’s tolerance
- e) Staff availability to control delivery of NIV

Oxygen therapy in covid 19

If above fail : Intubation and Mechanical Ventilation (MV)

Oxygen therapy in covid 19

- a) Continuous hypoxia ،SpO2 <85-90% ،for 1-2 hours
- b) Continuous respiratory distress with

i) Respiratory acidosis, pH <7.25

ii) Rising PaCO2 ≥ 70 mmHg

iii) ROX index ≤ 4.88**

iv) Decreasing GCS/altered mental status

v) Convulsions

vi) Persistent hypotension, BP <90 mmHg or MAP <65 mmHg for over 1 hour despite resuscitation

Oxygen therapy in covid 19

**ROX index

ROX Index = SpO2 /FiO2/RR

ROX Index = Normal Range 18-33 (Awaits full validation)

ROX Index = ≤ 18-4.88 Management with Oxygen Escalation Nasal Cannula Face Mask (Ordinary/Venturi), Non-Rebreather Face Mask (Reservoir Mask) High Flow Nasal Cannula Non-Invasive Ventilation.

ROX Index = ≤ 4.88 Usually Needs Intubation and Mechanical Ventilation.

Oxygen therapy in covid 19

Intubation :

- Ventilator preparation
- Check HME filter and ventilator exhalation filter quality
- Pre-oxygenate with 100% FiO2 for 5 minutes with reservoir ‹NIV or HFNC
- Rapid-sequence intubation

Oxygen therapy in covid 19

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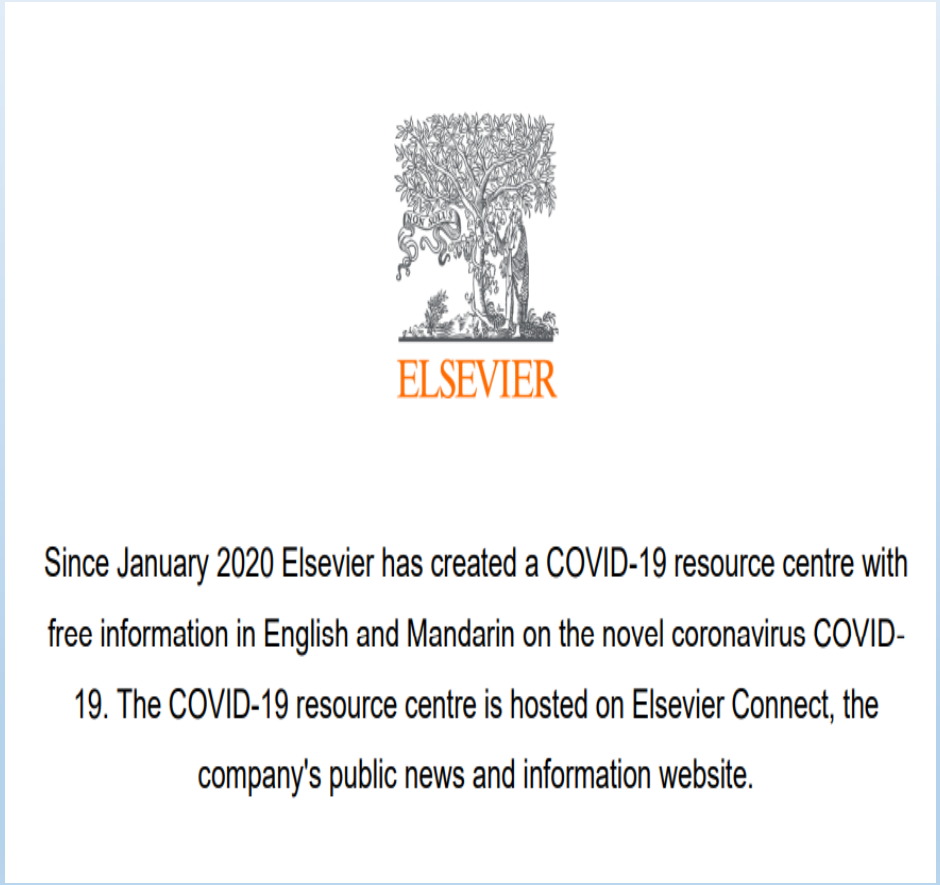
Escalation of respiratory support (steps); ***Try to avoid intubation if at all possible,*** (see Figure7)

- Accept "permissive hypoxemia" (keep O2 Saturation > 84%); follow venous lactate and Central Venous O_2 saturations ($ScvO_2$) in patents with low arterial O_2 saturations
- N/C 1-6 L/min
- High Flow Nasal canula (HFNC) up to 60-80 L/min
- Trial of inhaled Flolan (epoprostenol)
- Attempt proning (cooperative repositioning-proning) [193,194]
- Intubation … by Expert intubator; Rapid sequence. No Bagging; Full PPE. Crash/emergency intubations should be avoided.
- Volume protective ventilation; Lowest driving pressure and lowest PEEP as possible. Keep driving pressures < 15 cmH_2O.
- Moderate sedation to prevent self-extubation
- Trial of inhaled Flolan (epoprostenol)
- Prone positioning.

Oxygen therapy in covid 19



Invasive Ventilation and high frequency nasal oxygenation Chris Carter Helen Aedy Joy Notter

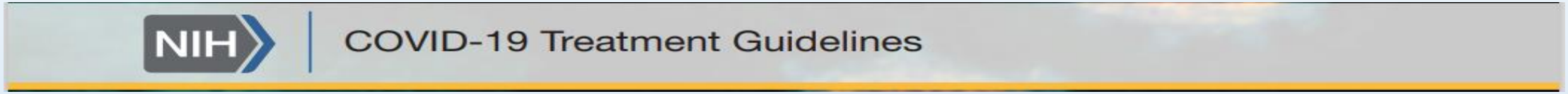
Current thinking suggests that NIV and HFNO may be an appropriate bridging adjunct in the early part of the disease progress and may prevent the need for intubation or invasive ventilation. Patients requiring NIV or HFNO may be nursed in locations outside of the critical care unit. Therefore, this article reviews the different types of NIV and HFNO, indications and the nursing care.

Oxygen therapy in covid 19

NIH | COVID-19 Treatment Guidelines

- Recommendations
- • For adults with COVID-19 who are receiving supplemental oxygen, the COVID-19 Treatment
- Guidelines Panel (the Panel) recommends close monitoring for worsening respiratory status
- and that intubation, if it becomes necessary, be performed by an experienced practitioner in a
- controlled setting (AII).
- • For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen
- therapy, the Panel recommends high-flow nasal cannula (HFNC) oxygen over noninvasive
- positive pressure ventilation (NIPPV) (BI).
- • In the absence of an indication for endotracheal intubation, the Panel recommends a closely
- monitored trial of NIPPV for adults with COVID-19 and acute hypoxemic respiratory failure for
- whom HFNC is not available (BIII).
- • For patients with persistent hypoxemia despite increasing supplemental oxygen requirements in
- whom endotracheal intubation is not otherwise indicated, the Panel recommends considering a
- trial of awake prone positioning to improve oxygenation (CIII).
- • The Panel recommends against using awake prone positioning as a rescue therapy for refractory
- hypoxemia to avoid intubation in patients who otherwise require intubation and mechanical
- ventilation (AIII).

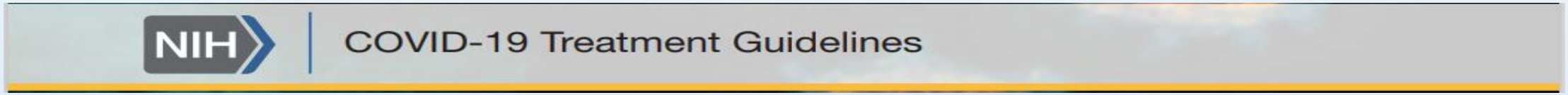
Oxygen therapy in covid 19



Recommendations for non-invasive ventilation and high flow nasal cannula

- They need to be closely monitored
- Patient support and education increases cooperation
- They may reduce the need for intubation
- Use only in highly selected patients
- Use should be with air-borne precaution till further studies
- HFNC 40-60L/min with 60-100% FiO2
- Trial of these modalities should not exceed 1 hour if ineffective

Oxygen therapy in covid 19



Contraindications :

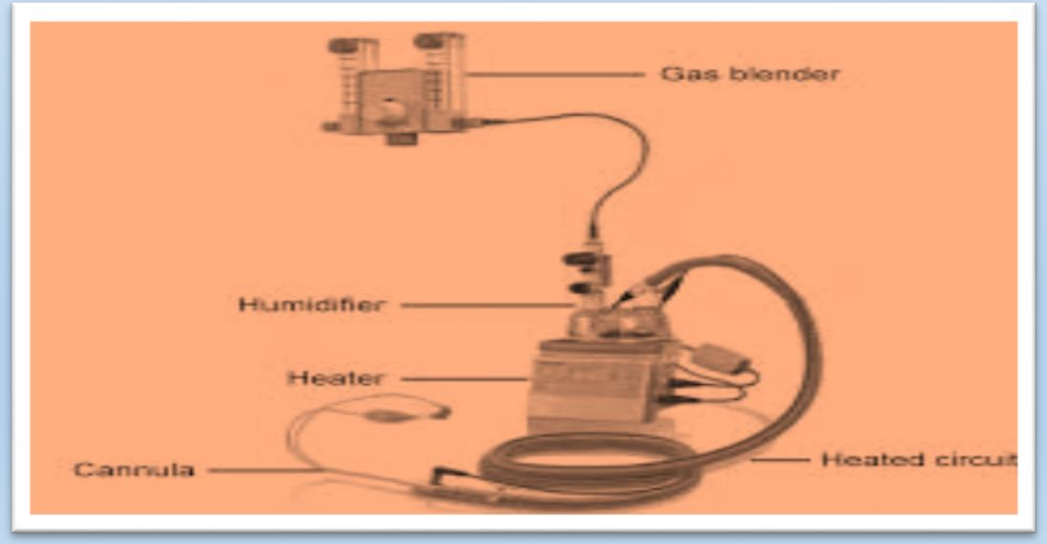
HFNC*

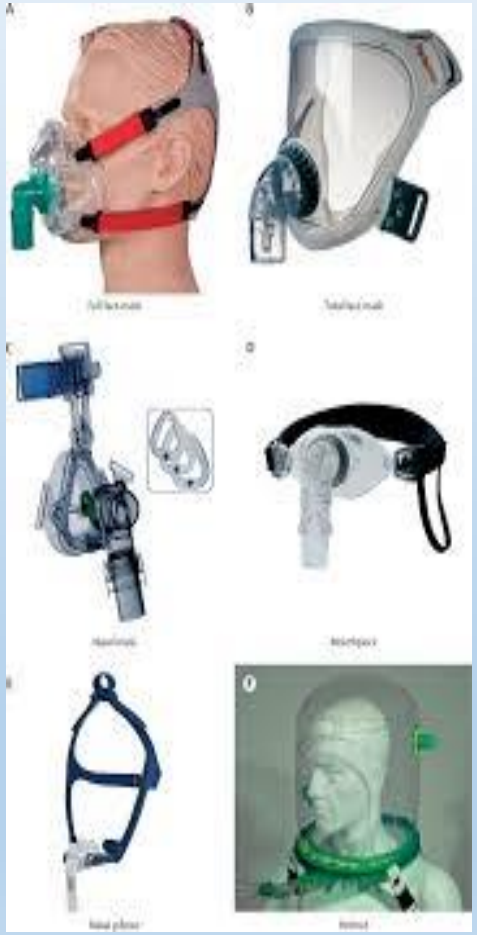
- Hypercapnia (exacerbation of obstructive lung disease, cardiogenic pulmonary edema)
- Hemodynamic instability
- Multi-organ failure
- Abnormal mental status

NIV*

- Hemodynamic instability
- Multi-organ failure
- Abnormal mental status

Oxygen therapy in covid 19





Oxygen therapy in covid 19

**ROX index

ROX Index = SpO2 /FiO2/RR

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ROX Index = ≤ 18-4.88 → Management with Oxygen Escalation → Nasal Cannula → Face Mask (Ordinary/Venturi), → Non-Rebreather Face Mask (Reservoir Mask) → High Flow Nasal Cannula → Non-Invasive Ventilation.

ROX Index = ≤ 4.88 → Usually Needs Intubation and Mechanical Ventilation.

Oxygen therapy in covid 19

Traditional modes

- Volume-CMV
- Pressure-CMV
- Adaptive-CMV
- Volume-SIMV
- Pressure-SIMV
- Adaptive-SIMV
- Pressure support
- Volume support

Advanced modes

- ASV
- INTELLIVENT-ASV

Biphasic modes

- DuoPAP
- APRV

Oxygen therapy in covid 19

Initial modes of MV

- Mode should be the one that physician is familiar with the most
- Consider neuromuscular blockade → Cisatracurium for 48 hours (PFR <150)

SIMV

1.Tidal Volume	→ 6 mL/ideal body weight (Height m^2 x 22)
2. Respiratory Rate	→ 18-26/min
3.FiO_2	→ Start 100%. decrease by 5 if target is achieved to minimum FiO_2
4.PEEP	→ Start 8-20 cmH_2O depending on oxygenation and blood pressure
5. RM (PFR<150)	→ Depending on the experience of the intensivists
6.PS	→ 12-18 cmH_2O
7. Peak Airway Pressure	→ <40 mmHg
8. Plateau Pressure	→ <30 mmHg

Oxygen therapy in covid 19

Pressure SIMV /BiLevel :

- if peak or plateau pressures remain high (>40 and >30)
- try to keep tidal volumes between 4-6 ml/kg”

1. Peak Inspiratory Pressure	→20-30 cmH_2O
2.FiO_2	→ Start 100%. decrease by 5 if target is achieved to minimum FiO_2
3. Respiratory Rate	→ 20-30/min (effected by the I/E ratio)
4. I/E ratios	→ 1 to 2 or 1 to 1. IRV if well sedated (watch for hypercapnia)
5.PEEP	→ Start 10-24 cmH_2O decrease per tolerance
6. RM (PFR<150)	→ Start PEEP 30-40. decrease by 5 every 30 to 40 seconds
7.PS	→ 12-18 cmH_2O
8. Peak Airway Pressure	→ <40 mmHg
9. Plateau Pressure	→ <30 mmHg

Oxygen therapy in covid 19

Goals of mechanical ventilation :

- 1-Spo2> 90%
- 2-Pao2> 60
- 3-PH:7.30-7.45
- 4-No respiratory distresis

Oxygen therapy in covid 19

Intensive Care Med (2020) 46:1927–1929
https://doi.org/10.1007/s00134-020-06182-4

LETTER

Efficacy of early prone position for COVID-19 patients with severe hypoxia: a single-center prospective cohort study

Xuefeng Zang[1], Qian Wang[3], Hua Zhou[6*], Sanhong Liu[2,5*] and Xinying Xue[4,7*] on behalf of COVID-19 Early Prone Position Study Group

Oxygen therapy in covid 19

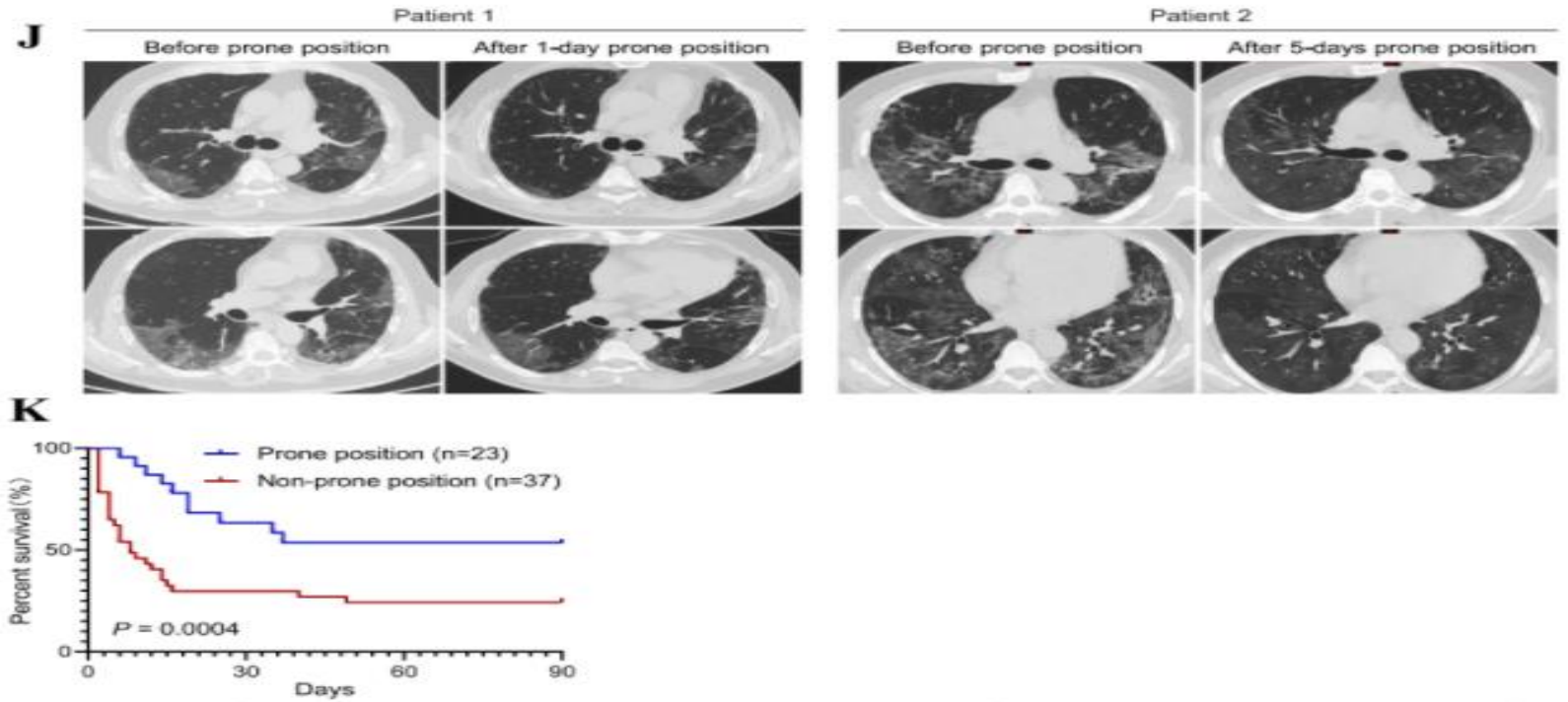


Fig. 1 Early prone position significantly improves SpO_2, RR, ROX index, CT imaging performance and reduce the mortality of COVID-19 patients with severe hypoxia. **a**–**c** The single SpO_2 (**a**), RR (**b**), and ROX index (**c**) change in the prone position group. **d**–**f** The single SpO_2 (**d**), RR (**e**), and ROX index (**f**) change in the non-prone position group. **g**–**i** The average SpO_2 (**g**), average RR (**h**), and average ROX index (**i**) change between prone position and non-prone position groups. **j** In patient 1, CT imaging showed that the density and scope of diffuse patch shadow in both lungs was significantly improved after 1-day prone position. In patient 2, CT imaging showed that the patch shadow was completely absorbed after 5-day prone position. **k** Survival curve of COVID-19 patients with severe hypoxia between prone position group and non-prone position group

Oxygen therapy in covid 19

Xu *et al. Critical Care* (2020) 24:250
https://doi.org/10.1186/s13054-020-02991-7

Critical Care

RESEARCH LETTER Open Access

Early awake prone position combined with high-flow nasal oxygen therapy in severe COVID-19: a case series

Qiancheng Xu[1†], Tao Wang[1†], Xuemei Qin[1†], Yanli Jie[2], Lei Zha[3] and Weihua Lu[1*]

Oxygen therapy in covid 19

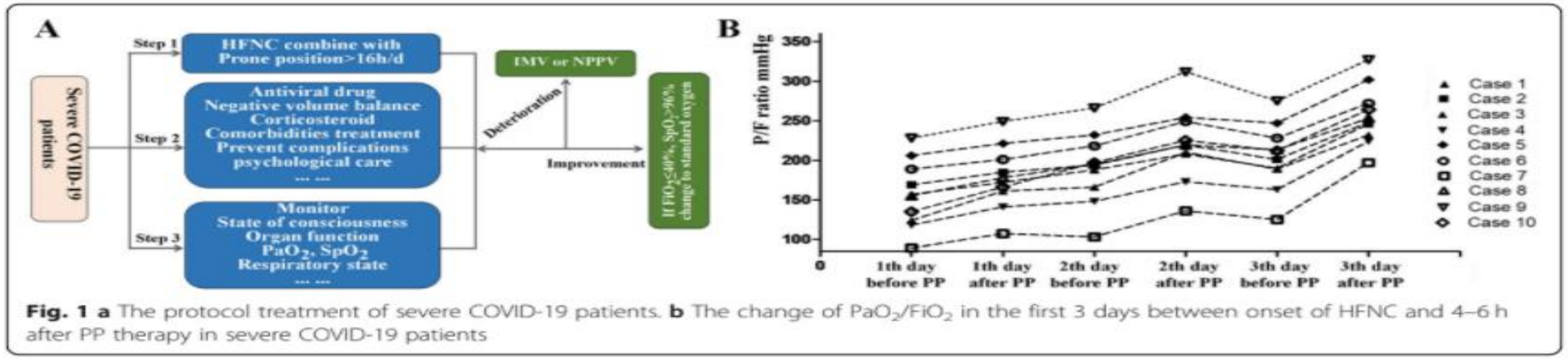


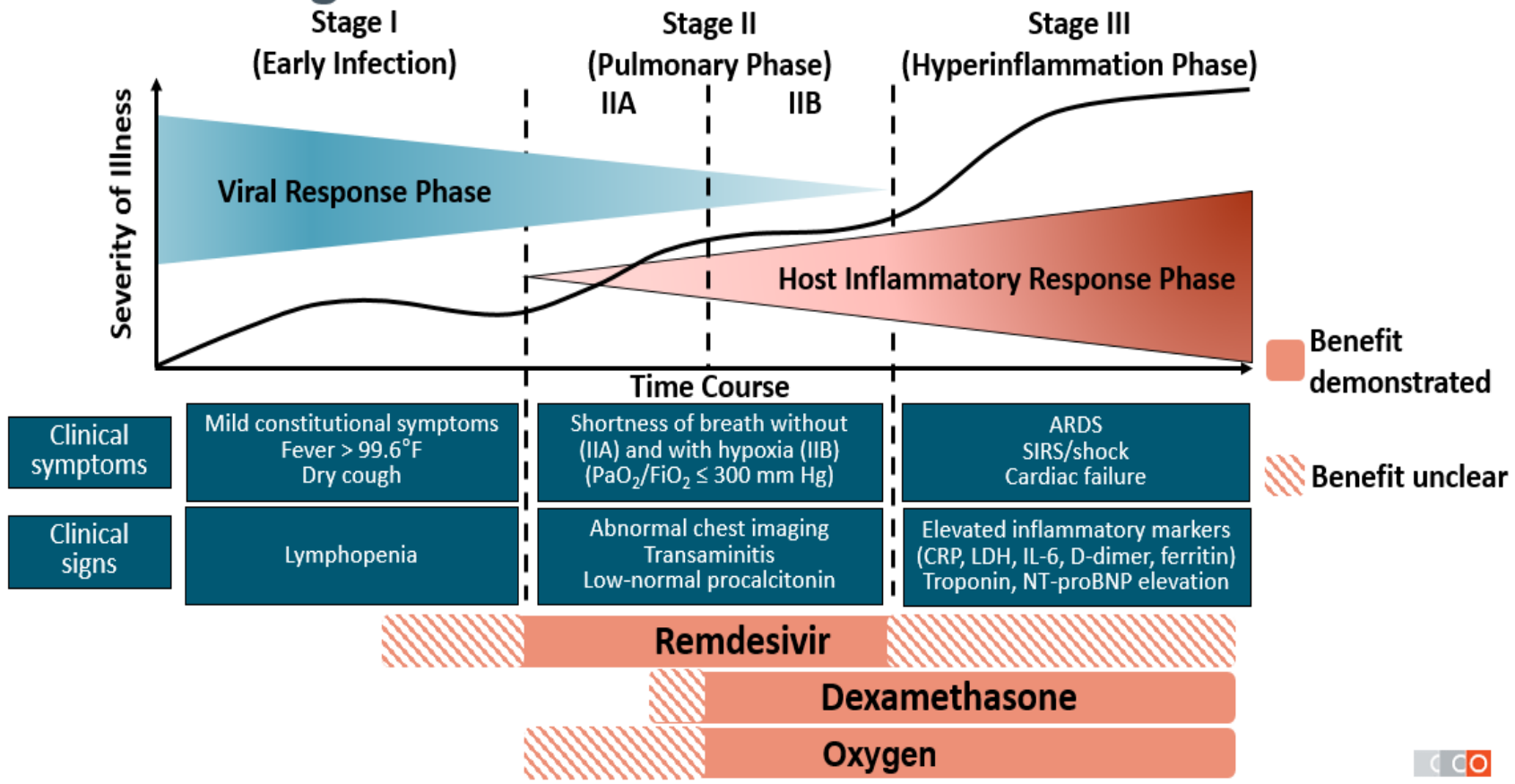
Fig. 1 a The protocol treatment of severe COVID-19 patients. **b** The change of PaO_2/FiO_2 in the first 3 days between onset of HFNC and 4–6 h after PP therapy in severe COVID-19 patients

Compared to non-invasive ventilation (NIV), patients felt more comfortable when using HFNC therapy, and the demand for medical staff was reduced. Awake PP combined with HFNC therapy could be used safely and

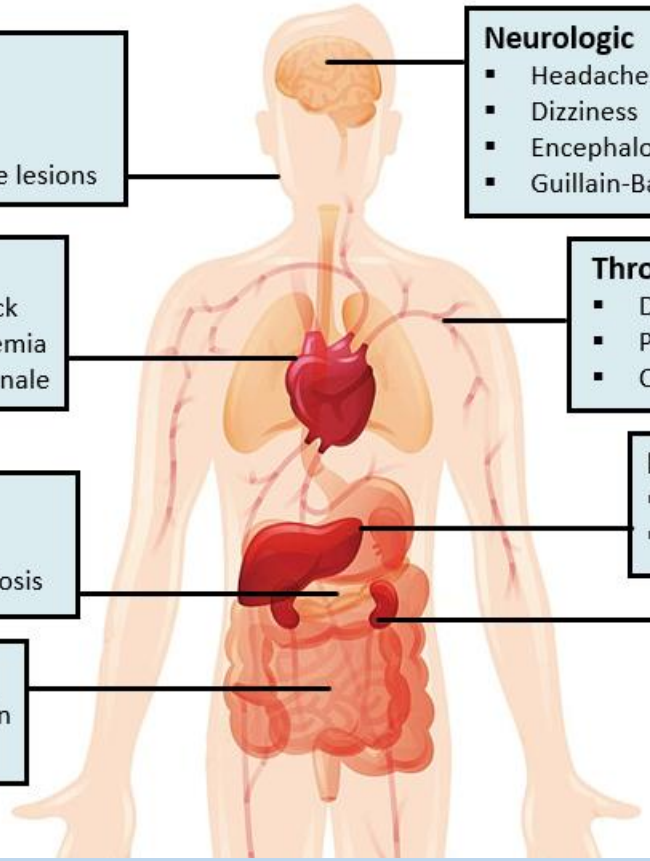
effectively in severe COVID-19 patients, and it may reduce the conversion to critical illness and the need for

tracheal intubation.

COVID-19 Therapies Predicted to Provide Benefit at Different Stages



Extrapulmonary Manifestations



Dermatologic
- Petechaie
- Livedo reticularis
- Erythematous rash
- Urticaria
- Vesicles
- Pernio-like lesions

Neurologic
- Headaches
- Dizziness
- Encephalopathy
- Guillain-Barré
- Ageusia
- Myalgia
- Anosmia
- Stroke

Cardiac
- Takotsubo cardiomyopathy
- Myocardial injury/myocarditis
- Cardiac arrhythmias
- Cardiogenic shock
- Myocardial ischemia
- Acute cor pulmonale

Thromboembolism
- Deep vein thrombosis
- Pulmonary embolism
- Catheter-related thrombosis

Hepatic
- Elevated ALT/AST
- Elevated bilirubin

Endocrine
- Hyperglycemia
- Diabetic ketoacidosis

Renal
- Acute kidney injury
- Proteinuria
- Hematuria

Gastrointestinal
- Diarrhea
- Nausea/vomiting
- Abdominal pain
- Anorexia

Covid 19 sequellae

Cardiovasular Sequelae

- Prospective, observational cohort study sourcing recovered patients from the University Hospital Frankfurt COVID-19 Registry (N = 100)[1]
  - CV magnetic resonance performed at median 71 days from diagnosis
  - Abnormal findings in 78% of patients, myocardial inflammation in 60%; independent of preexisting comorbidities, severity of acute SARS-CoV-2 infection, and time from diagnosis
  - Reduced left ventricular ejection fraction, increased left ventricle volumes and native T1/T2 vs risk-matched controls

"There are no data on how acute treatment of COVID-19 may affect . . . long-term cardiac recovery and function. Patients with ostensibly recovered cardiac function may still be at risk of cardiomyopathy and cardiac arrhythmias."[2]

Neurologic Sequelae

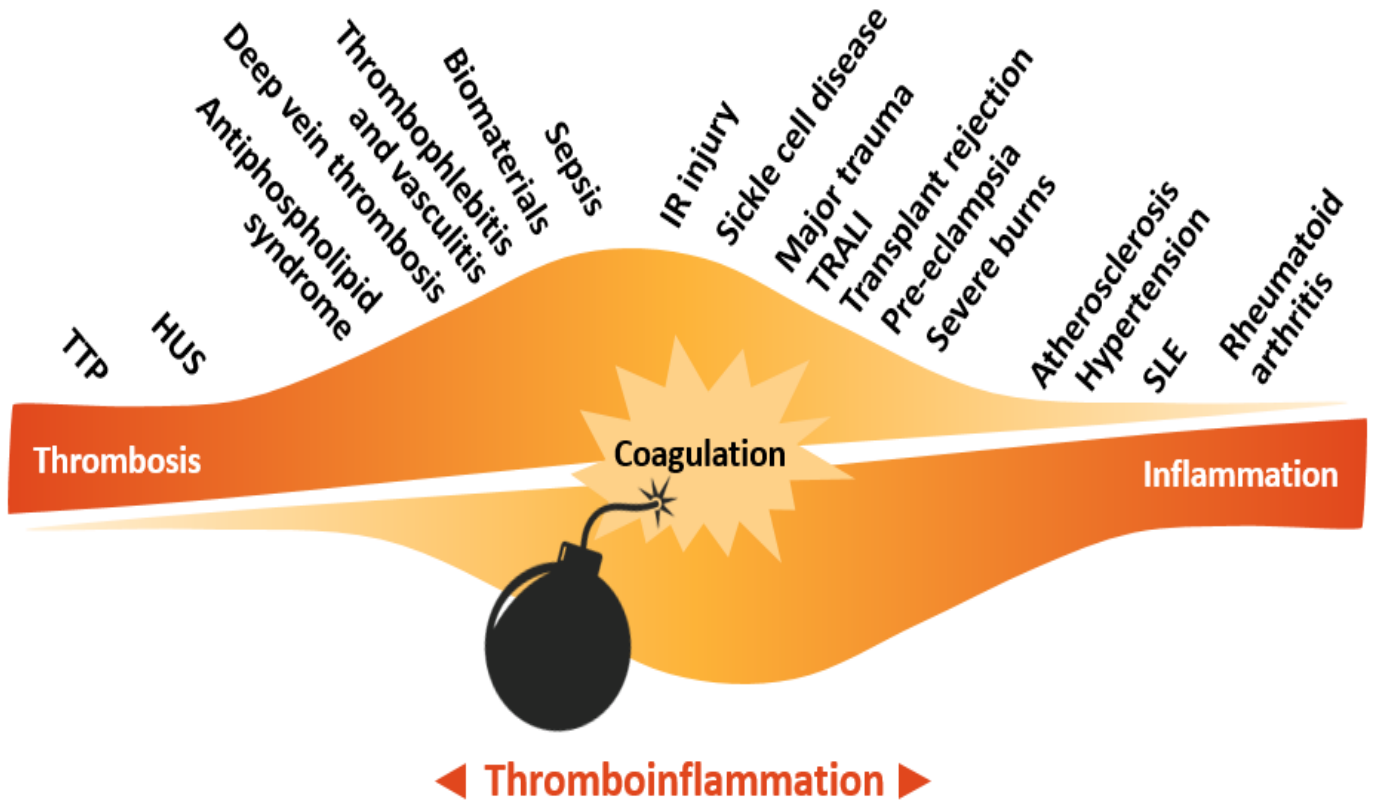
Sensory Deficits: Olfactory and Gustatory Dysfunction

- Systematic review and meta-analysis including 24 studies of confirmed COVID-19 (N = 8438)[1]
  - Pooled prevalence
    - Anosmia: 41.0%, ageusia: 38.2%
    - Decreased among older patients
- *"Not yet clear whether COVID-19–related OGDs are transient or permanent"*[1]
  - In one prospective cohort (N = 3191), resolution typical within 3 wks[2]

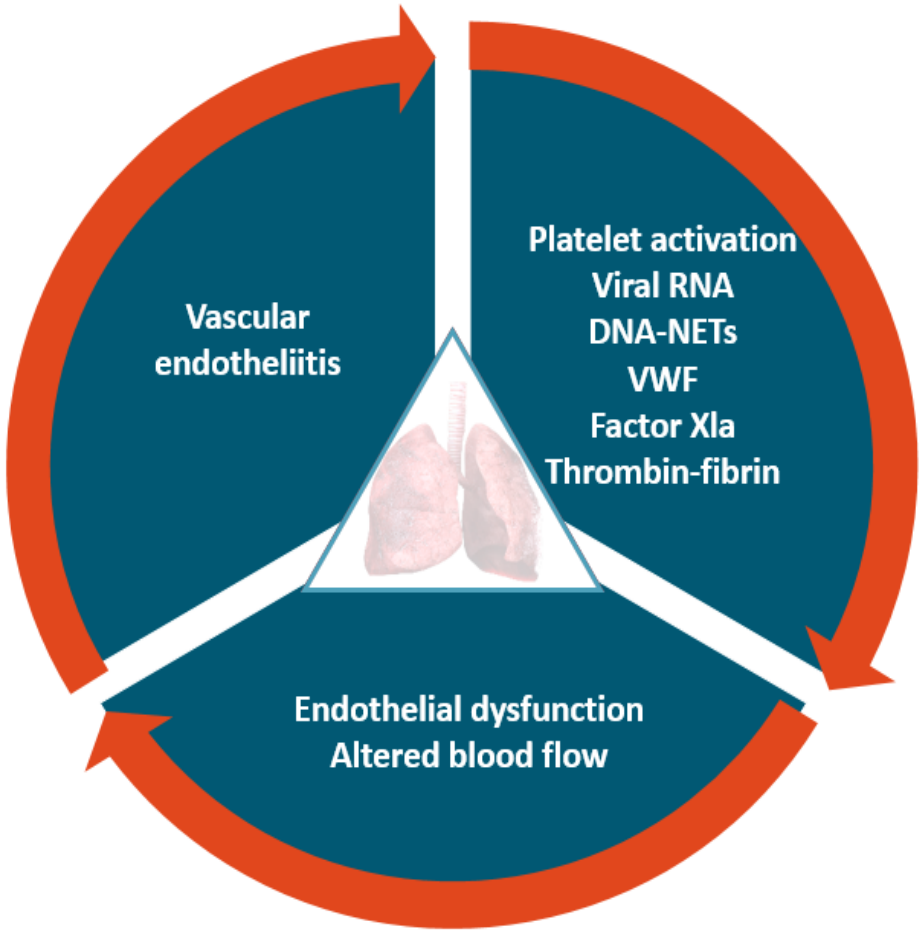
"Respiratory virus infections are associated with neurological and psychiatric sequelae, including Parkinsonism, dementia, depression, posttraumatic stress disorder, and anxiety . . . Significant long-term neurological and psychiatric sequelae have to be anticipated in COVID-19, especially in survivors of severe disease."[3]

- Cognitive monitoring of recovered patients may be necessary

COVID-19 Coagulopathy: Thromboinflammation



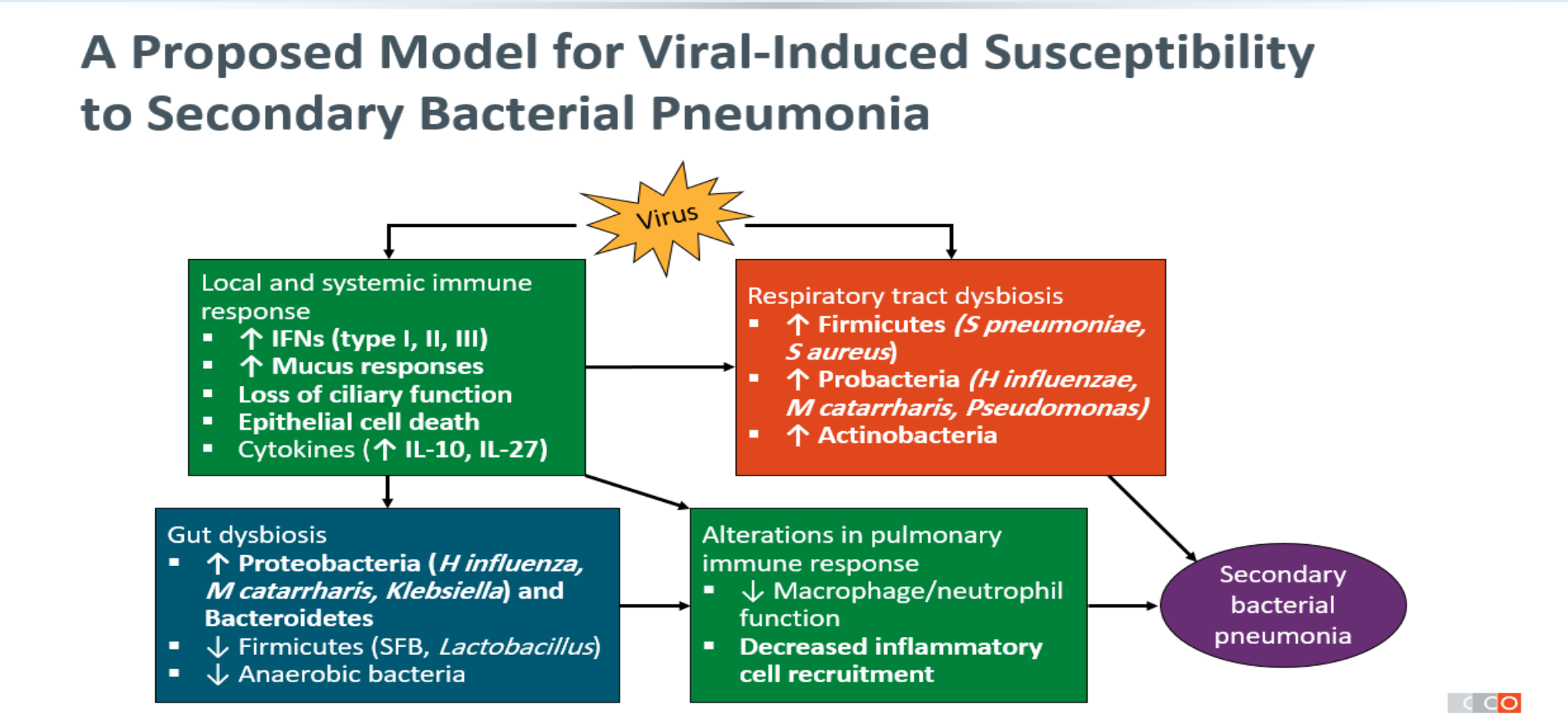
Virchow's Triad in COVID-19



Becker. J Thromb Thrombolysis. 2020;15:1.

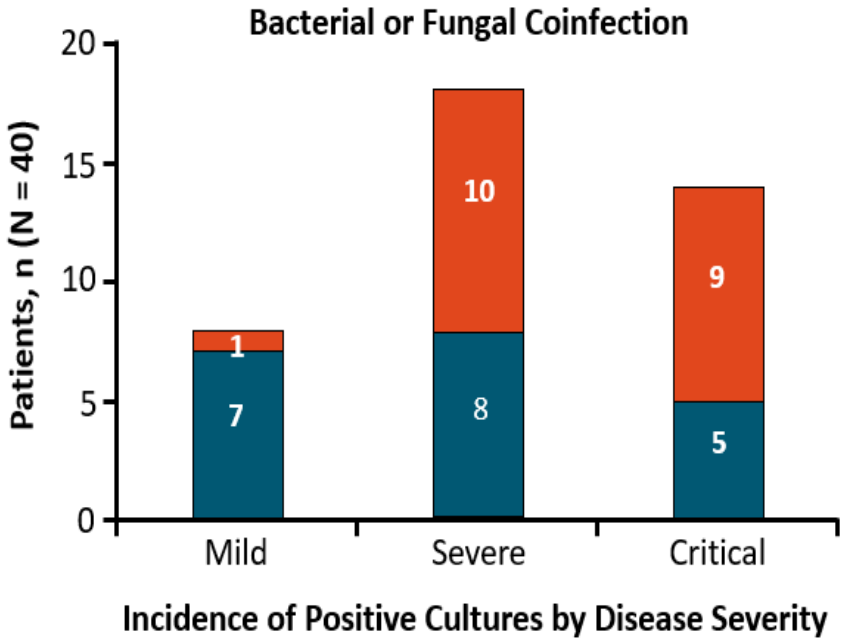
Slide credit: clinicaloptions.com

Coinfections and COVID-19



Incidence of Bacterial Coinfection in Patients With COVID-19: February 4-28, 2020, in Wuhan, China

- Retrospective, cohort study of 354 hospitalized patients with confirmed COVID-19; mean age: 62 yrs (range: 23-90)
- 116 patients tested for coinfection based on clinical suspicion:
  - 3 positive results for viral coinfection from 76 patients tested by sputum PCR
  - 20 positive results for bacterial or fungal coinfections from 40 patients tested by culture of BAL fluids or blood
- No distinction made between community-acquired and hospital-acquired coinfections



- **3 most prevalent pathogens: *A baumanii*, *E coli*, and *Candida albicans***

Bacterial Coinfection in SARS-CoV-2 vs Influenza A/B Cohorts: Retrospective Study in the UK, 2019-2020

- Blood culture positivity and bacteremia rates statistically similar between groups
  - **SARS-CoV-2 group:** 643/836 patients had blood cultures
    - **Blood culture positive: 9.3%** (60/643)
    - **True bacteremia: 3.3%** (21/643)
      - 2 respiratory, 3 central line, 16 unrelated nonrespiratory
  - **Influenza group:** 133/216 patients had blood cultures
    - **Blood culture positive: 6%** (8/133)
    - **True bacteremia: 1.5%** (2/133)

Blood Culture Results, n	SARS-CoV-2 (n = 643)		Influenza A/B (n = 133)	
	CA	HCAI	CA	HCAI
Respiratory bacteremias	1	1	2	0
Nonrespiratory bacteremias	11	8	0	0
No growth	583		133	
Contaminants*	36		6	

*Coagulase negative *Staphylococci.*

- **Among patients with SARS-CoV-2, relative risk of death with true pathogens in blood vs baseline admitted patients: 1.51 (*P* = .3543)**

Assessing Disease Severity and Risk Factors for Severe Disease

NIH Guidelines: Defining a COVID-19 Severity Spectrum

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

COVID-19 Severity in Mainland China

- Observational study of COVID-19 cases diagnosed in China's Infectious Disease Information System as of February 11, 2020 (N = 72,314)
  - No deaths among confirmed case patients with noncritical disease or who were ≤ 9 yrs of age

Disease Classification, %	Confirmed Cases* (n = 44,672)
Mild	**80.9**
Severe	13.8
Critical	4.7
Missing	0.6

Characteristic	Case-Fatality Rate, % (n/N)
All confirmed cases*	2.3 (1023/44,672)
▪ **Critical**	**49.0 (1023/2087)**
▪ ≥ 80 yrs of age	14.8 (208/1408)
▪ Cardiovascular disease	10.5 (92/873)
▪ 70-79 yrs of age	8.0 (312/3918)
▪ Diabetes	7.3 (80/1102)
▪ Chronic respiratory disease	6.3 (32/511)
▪ Hypertension	6.0 (161/2683)
▪ Cancer	5.6 (6/107)

*Positive for viral nucleic acid by throat swab.

Key Therapeutic Classes Under Investigation for Treatment of COVID-19

Antivirals
Baloxivir
Convalescent plasma
Favipiravir
(Hydroxy)chloroquine
Interferon
Lopinavir/ritonavir
Nitazoxanide
Oseltamivir
Remdesivir
Ribavirin

Immunomodulators
Corticosteroids (eg, dexamethasone)
IL-1 inhibitors (eg, anakinra)
IL-6 inhibitors (eg, tocilizumab)
Intravenous immunoglobulin
JAK inhibitors (eg, baricitinib)

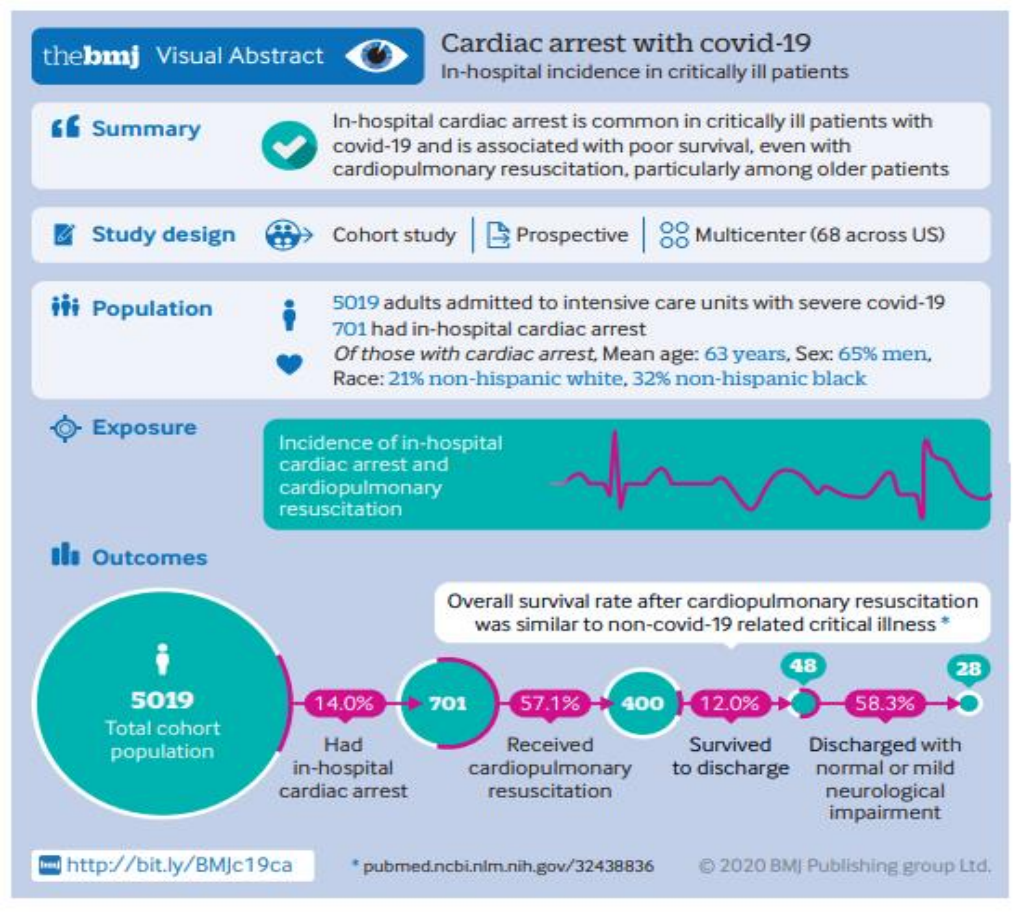
Cardio pulmonary resusitation in covid 19

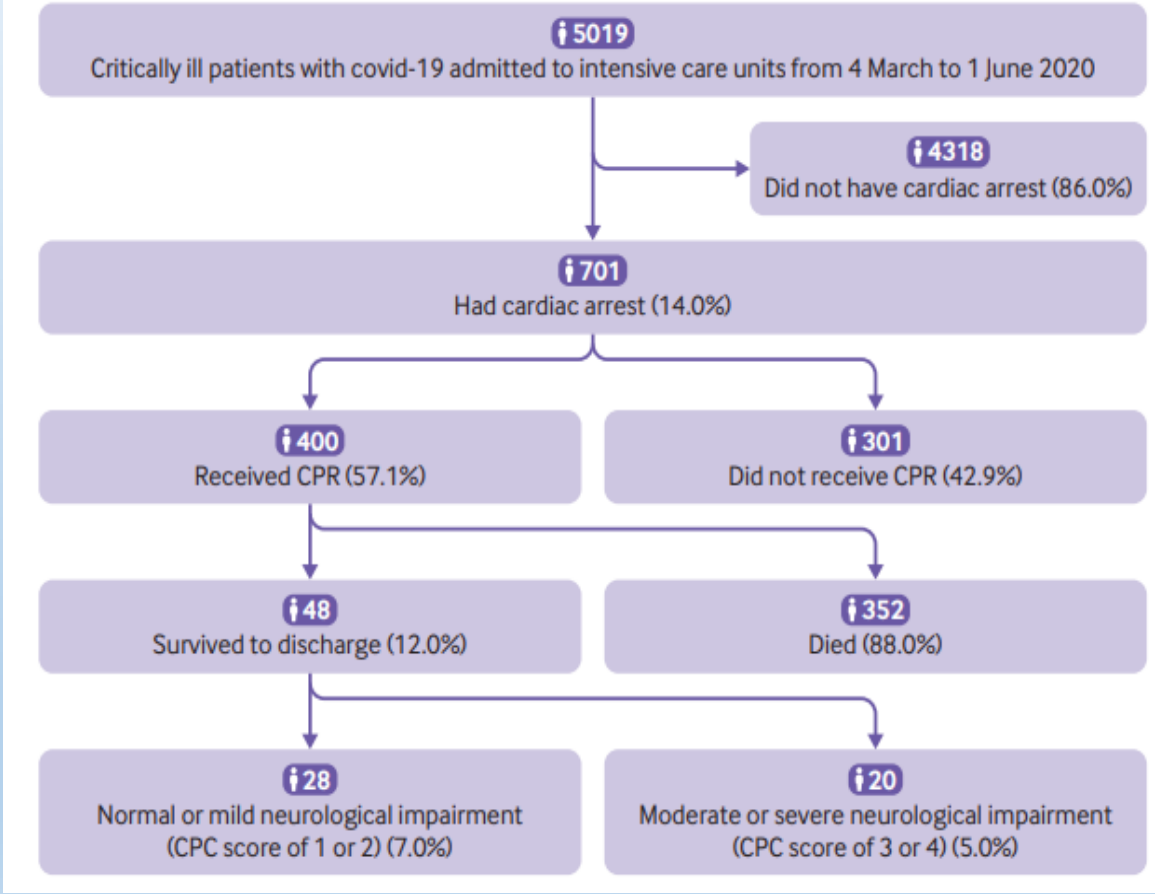
Cardiopulmonary resusitation

- In-hospital cardiac arrest in critically ill patients with covid-19: multicenter cohort study

- Conclusions Cardiac arrest is common in critically ill patients with covid-19 and is associated with poor survival, particularly among older patients

Cardiopulmonary resusitation






اگر از سر بریده می ترسید
در محفل عاشقان نمی رقصیدید