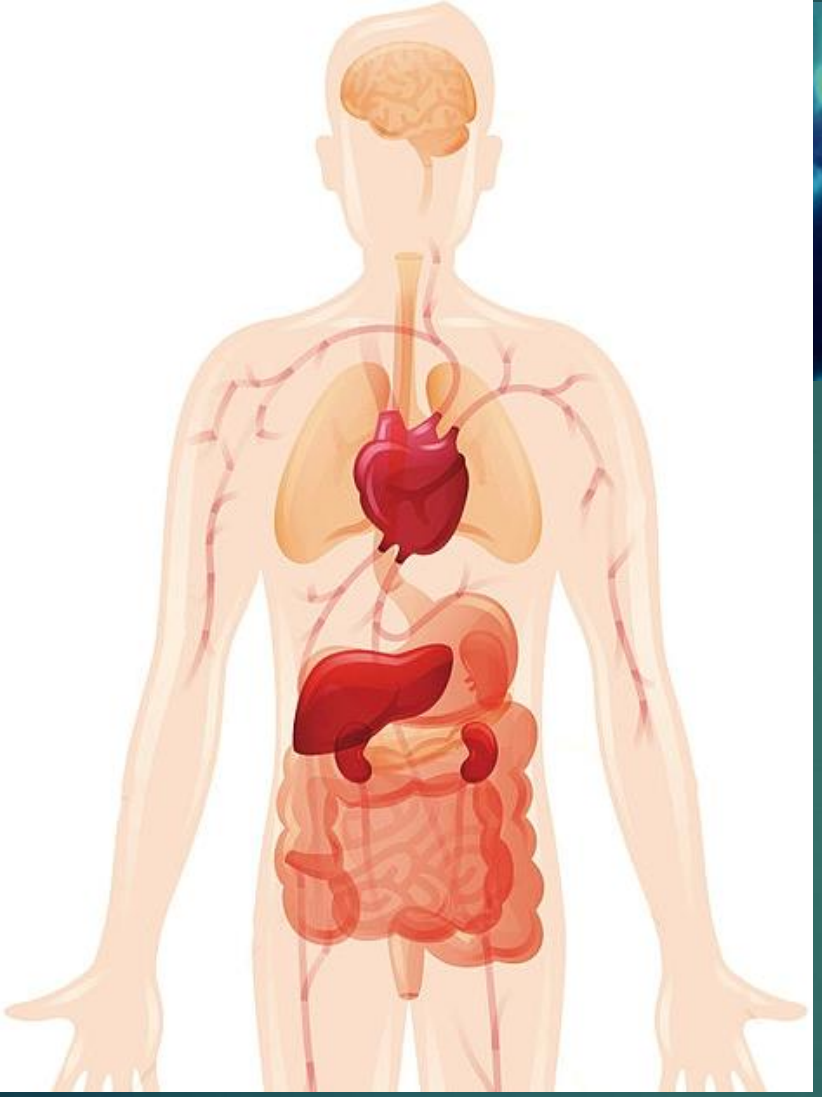
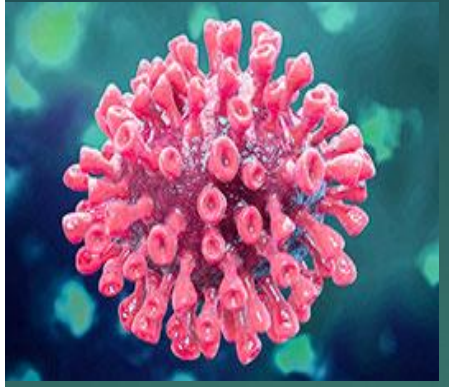

بسم الله الرحمن الرحيم


یا من اسمه دواء وذکره شفاء

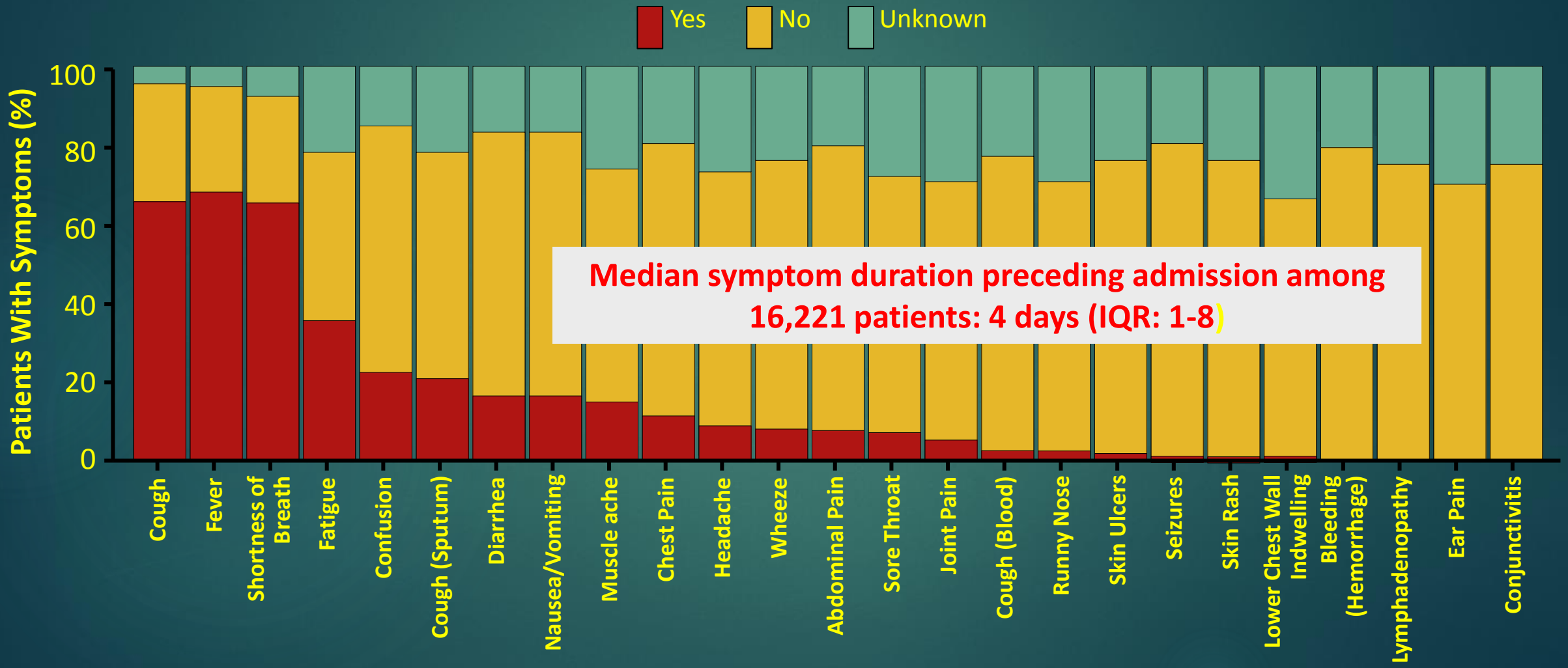




"Symptoms may appear **2-14 days after exposure** to the virus"

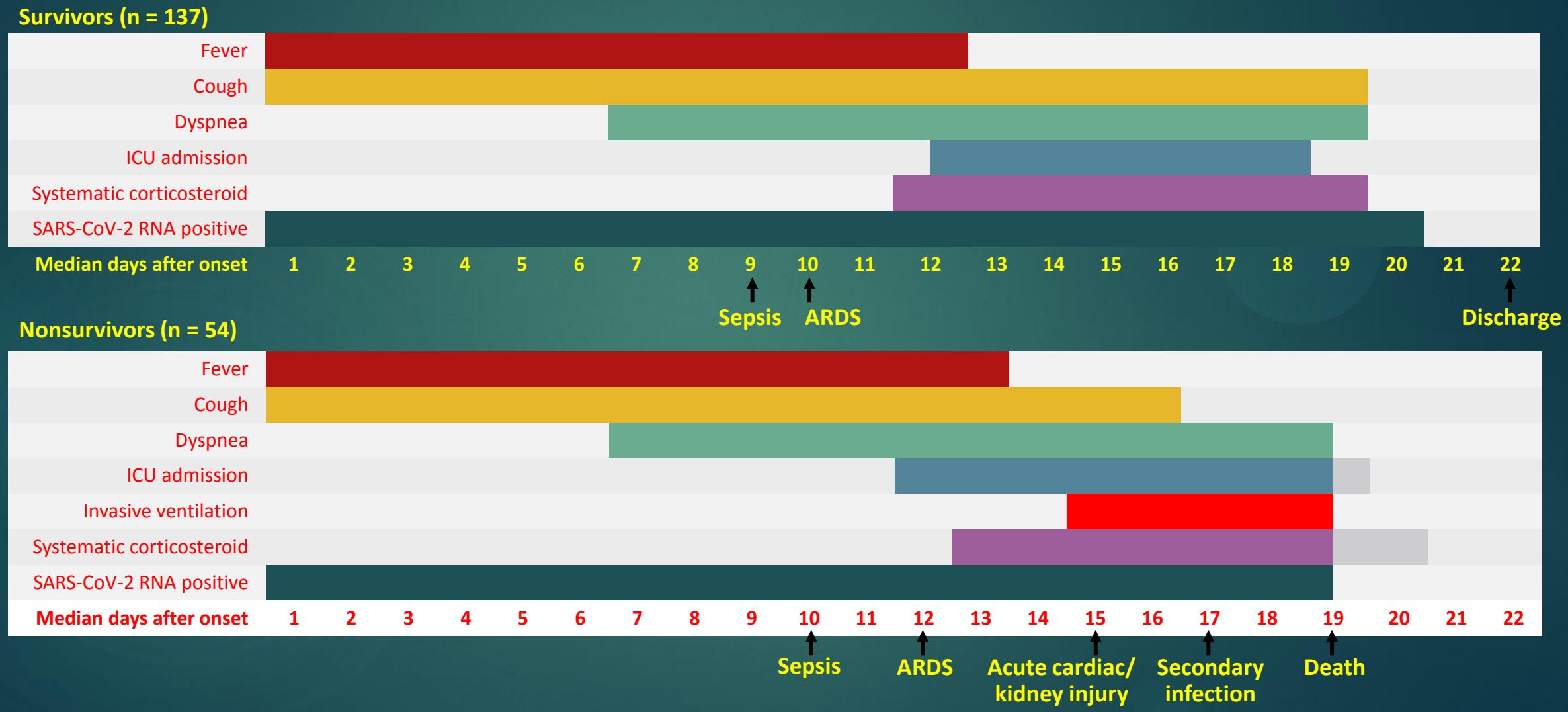
Guidance on Therapeutic Management

Frequency of Presenting Symptoms Among COVID-19–Positive Hospitalized Patients in the UK



Docherty. BMJ. 2020;369:m1985.

Variation in Clinical Course and Outcome Among Patients Hospitalized With COVID-19 in Wuhan, China

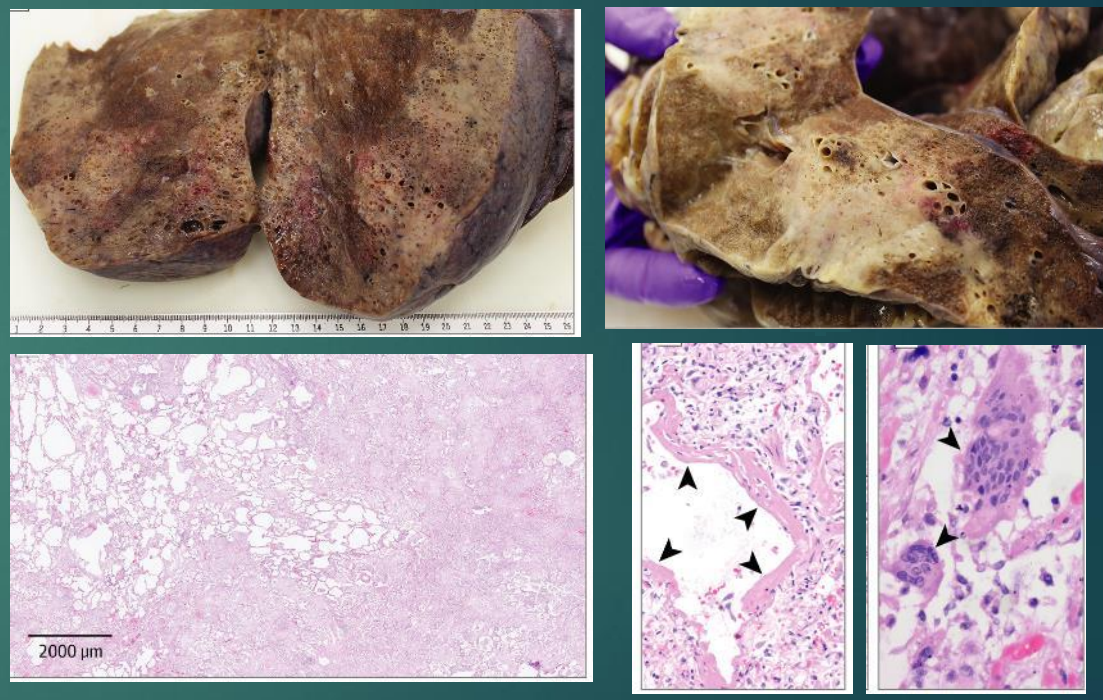


Zhou. Lancet. 2020;395:1054

Pulmonary Sequelae

- Diffuse alveolar damage noted in multiple, small postmortem studies of COVID-19
  - N = 38 from northern Italy[1]
  - N = 10 from Germany[2]
- Platelet–fibrin thrombi indicative of coagulopathy observed in small arterial vessels of some patients[1]

Macroscopic and Histologic Lung Findings[2]



1. Carsana. Lancet Infect Dis. 2020;20:1135. 2. Schaller. JAMA. 2020;323:2518.

Guidance on Therapeutic Management

شرایط بستری در بیمارستان

پس از ارجاع بیمار به بیمارستان، بر اساس معاینات بالینی و بررسی های انجام شده، برای بستری وی تصمیم گیری خواهد شد.

اندیکاسیون بستری

توجه به نکات زیر به منظور تصمیم گیری برای بستری بیماران در بیمارستان ضروری است:

۱. سطح اشباع اکسیژن کمتر از ۹۰ % (SpO2<۹۰%) و(نیاز به حمایت تنفسی شامل اکسیژن درمانی)

۲. کاهش سطح هشیاری،

۳. افت فشار خون (فشار سیستولیک کمتر از ۹۰mmHg،)

4. تداوم دهیدراتاسیون و عدم تحمل خوراکی پس از درمان های حمایتی

Visual summary of recommendation

Population

This recommendation applies only to people with these characteristics:

Disease severity

Non-severe	Severe	Critical
Absence of signs of severe or critical disease	SpO_2 <90% on room air	Requires life sustaining treatment
	Respiratory rate >30 in adults	Acute respiratory distress syndrome
	Raised respiratory rate in children	Sepsis
	Signs of severe respiratory distress	Septic shock
Recommendation 2	Recommendation 1	

فاکتورهای پیش بینی کننده پیشرفت بیماری در فرد بستری

آزمایش های روتین
روز اول بستری (درخواست این آزمایشات و تکرار آن می تواند بر اساس نیاز فرد و به صلاحدید پزشک و متناسب با بیماری زمینه ای فرد نیز باشد): • CBC • ESR • Quantitative CRP • BUN/Cr، ALP، SGPT،SGOT • ، K، Na، BS • LDH • Ferritin (در صورت دسترسی) • ECG (اولیه به عنوان پایه تا در مورد ادامه سیر بیماری یا عوارض دارویی بتوان قضاوت کرد- اندازهQT در پرونده بیمار ثبت شود)
آزمایشات زیر بر اساس شرایط بالینی بیمار (شدت بیماری) ممکن است درخواست و/یا تکرار شود:
• D-dimer ،LDH ،Ferritin ،CPK ،ABG ،Quantitative CRP ،Mg ،P ،Ca ،
در صورت بروز علائم نارسایی حاد کلیوی (**افزایش کراتینین سرم بیش از 0.3 از حد پایه**)
• U/A • BUN/Cr • Pr/Cr ادرار
آزمایشات زیر در صورت صلاحدید پزشک و امکان دسترسی ممکن است درخواست شود:
• Fibrinogen • IL6 • NT-proBNP • INR،PTT،PT
درصورت الزام بالینی
• کشت خون در صورت شک به عفونت باکتریال • Procalcitonin (شک به عفونت ثانویه باکتریال) • بتا HCG برای زنان در سنین باروری • تست های تشخیصی HBV،HCV

استفاده از داروهای ضد ویروسی در موارد بستری:

با توجه به **عدم** شواهد کافی پیرامون اثر بخشی داروهای ضد ویروسی در کاهش مورتالیتی کووید-۱۹، توصیه قطعی برای مصرف آن ها وجود ندارد، ولی در صورت صلاحدید پزشک معالج جهت استفاده از داروی آنتی وایرال، موارد زیر باید مد نظر قرار گیرد

-بیمار در فاز متوسط تا شدید بیماری باشد

-بیمار در شرایط بحرانی نبوده و نیاز به تهویه مکانیکی نداشته باشد.

در صورت مصرف هر یک از داروهای ضد ویرال، تمهیدات لازم در مورد نحوه تجویز و مانیتور بیمار باید رعایت شود

تأکید می شود برای بررسی اثربخشی این داروها، باید تجویز داروها در قالب کارآزمایی های بالینی باشد. بدیهی است که ثبت اطلاعات سیر بالینی بیمار در پرونده بیمارستانی در موارد استفاده از داروهای ضد ویروسی، الزامی بوده و باید با دقت کافی صورت گیرد

Interventions compared

Usual supportive care

No corticosteroids

Corticosteroids

Suggested regimen

Acceptable alternative regimens

Dexamethasone	Hydrocortisone	Methylprednisolone	Prednisone
6 mg	50 mg	10 mg	50 mg
Oral or intravenous	Intravenous	Intravenous	Oral
Daily for 7-10 days	Every 6 hours for 7-10 days	Every 6 hours for 7-10 days	Daily for 7-10 days

Key Therapeutic Classes Under Investigation for Treatment of COVID-19

Antivirals

Remdesivir
Interferon
Favipiravir
Convalescent plasma
Baloxivir
(Hydroxy)chloroquine
Nitazoxanide
Oseltamivir
RibavirinLopinavir/ritonavir

Immunomodulators

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

Barlow. Pharmacotherapy. 2020;40:416. McCreary. Open Forum Infect Dis. 2020;7:ofaa105. Sanders. JAMA. 2020;323:1824.

Ivermectin

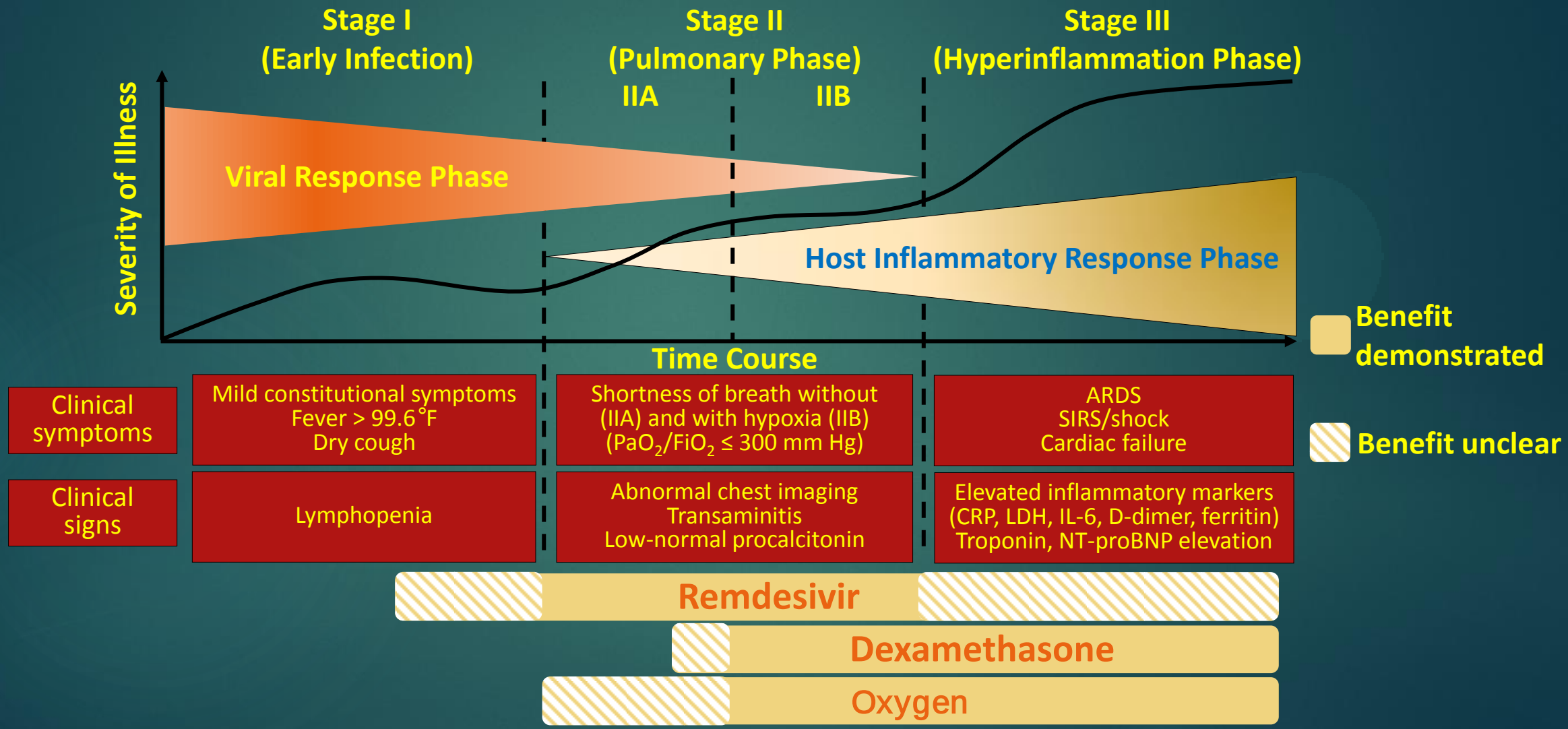
- Ivermectin inhibits the replication of SARS-CoV-2 in cell cultures
- Several randomized trials and retrospective cohort studies of ivermectin use in patients with COVID-19 have had mixed results
- Most studies had incomplete information and significant methodologic limitations

NIH Treatment Guidelines:

"**. . .** there are insufficient data to recommend either for or against the use of ivermectin for the treatment of COVID-19."

https://www.covid19treatmentguidelines.nih.gov/statement-on-ivermectin/ Updated: January 14, 2021.

COVID-19 Therapies Predicted to Provide Benefit at Different Stages



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

IDSA Recommendations FOR Treatment of Patients With COVID-19

Updated

Overarching goal: recruit patients into ongoing trials to provide needed evidence regarding efficacy and safety of potential therapies

IDSA Guidance	Patient Population	Treatment
Recommends	▪ Hospitalized with critical* COVID-19	▪ Dexamethasone† vs none
Suggests	▪ Hospitalized with severe‡ COVID-19 ▪ Hospitalized with severe*‡ COVID-19 ▪ Hospitalized with severe‡ COVID-19 and corticosteroids contraindicated	▪ Dexamethasone† vs none ▪ Remdesivir§ vs no antiviral ▪ Baricitinib + remdesivir vs remdesivir alone
Recommends only in clinical trial	▪ Hospitalized with COVID-19 ▪ Hospitalized with COVID-19	▪ Convalescent plasma ▪ Baricitinib + remdesivir + corticosteroids

*Mechanical ventilation or ECMO. Includes end organ dysfunction (eg, ARDS). †If unavailable, methylprednisolone and prednisone acceptable at equivalent total daily doses. ‡$SpO_2 \leq 94\%$ on room air, including those on supplemental oxygen. §For patients on supplemental oxygen, 5 days suggested; for patients on mechanical ventilation or ECMO, 10 days.

IDSA. COVID-19 Guideline, Part 1: Treatment and Management. Version 3.6.0

IDSA Recommendations AGAINST Treatment of Patients With COVID-19

Updated

- Overarching goal: recruit patients into ongoing trials to provide needed evidence regarding efficacy and safety of potential therapies

IDSA Guidance	Patient Population	Treatment
Recommends against	▪ COVID-19 ▪ Hospitalized with COVID-19 ▪ Hospitalized with COVID-19	▪ (Hydroxy)chloroquine ▪ (Hydroxy)chloroquine + azithromycin ▪ Lopinavir/ritonavir
Suggests against	▪ Hospitalized with nonsevere* COVID-19 ▪ Hospitalized with COVID-19 ▪ Hospitalized with COVID-19* ▪ Ambulatory with COVID-19	▪ Glucocorticoids ▪ Routine tocilizumab ▪ Routine remdesivir ▪ Routine bamlanivimab
Suggests against outside clinical trial	▪ Hospitalized with severe COVID-19	▪ Famotidine

*SpO_2 > 94%, no supplemental oxygen.

IDSA. COVID-19 Guideline, Part 1: Treatment and Management. Version 3.6.0

NIH Guidelines: Therapeutic Management

Updated

Disease Severity	Recommendation
Not hospitalized, mild to moderate COVID-19	▪ ***Insufficient data*** to recommend for or against any specific antiviral or antibody ▪ **Bamlanivimab, casirivimab plus imdevimab *available through EUAs***, if high risk of disease progression ▪ ***Recommend against*** **dexamethasone**
Hospitalized but does not require supplemental oxygen	▪ ***Recommend against*** **dexamethasone** ▪ ***Insufficient data*** to recommend for or against **remdesivir**; may be appropriate if high risk of disease progression
Hospitalized and requires supplemental oxygen (but no high-flow oxygen, ventilation, or ECMO)	***Use 1 of the following:*** ▪ **Remdesivir** (eg, in case of minimal supplemental oxygen requirement) ▪ **Remdesivir** plus **dexamethasone** (eg, with increasing need for supplemental oxygen)* ▪ **Dexamethasone** (eg, if remdesivir cannot be used or is unavailable)
Hospitalized and requires high-flow oxygen or noninvasive ventilation	***Use 1 of the following:*** ▪ **Remdesivir** plus **dexamethasone*** ▪ **Dexamethasone**
Hospitalized and requires invasive mechanical ventilation or ECMO	▪ **Dexamethasone** ▪ ***For patients recently intubated,*** consider **remdesivir** plus **dexamethasone** (remdesivir alone not recommended)

*In rare case when corticosteroids cannot be used, *remdesivir* plus *baricitinib* available via EUA.

Remdesivir: 200 mg IV once, then 100 mg IV QD for 4 days or until discharge. Treatment may continue up to 10 days if no substantial clinical improvement by Day 5.
Dexamethasone: 6 mg IV or PO QD for 10 days or until discharge.
Baricitinib: 4 mg PO QD for 14 days or until discharge.

NIH COVID-19 Treatment Guidelines. Therapeutic management of patients with COVID-19. Last updated December 3, 2020.

NIH Guidelines: Investigational COVID-19 Treatments

Antivirals[1]

Guidance	Treatment
Recommends against	▪ High-dose chloroquine (600 mg BID for 10 days) ▪ (Hydroxy)chloroquine ± azithromycin in hospitalized patients
Recommends against except in a clinical trial	▪ (Hydroxy)chloroquine ± azithromycin in non-hospitalized patients ▪ Lopinavir/ritonavir or other HIV protease inhibitors ▪ Ivermectin

Immune-Based Therapies[2,3]

Guidance	Treatment
Insufficient data to recommend for or against	▪ IL-1 inhibitors ▪ IFN-β for early mild to moderate COVID-19 ▪ COVID-19 convalescent plasma or SARS-CoV-2 Ig
Recommends against except in a clinical trial	▪ IL-6/IL-6R inhibitors ▪ IFN-α/β for severe or critical COVID-19 ▪ BTK and JAK inhibitors ▪ Non-SARS-CoV-2–specific IVIG ▪ Mesenchymal stem cells

1. NIH COVID-19 Treatment Guidelines. Antiviral drugs that are approved or under evaluation for the treatment of COVID-19. Last updated November 3, 2020.
2. NIH COVID-19 Treatment Guidelines. Blood-derived products under evaluation for the treatment of COVID-19. Last updated July 17, 2020.
3. NIH COVID-19 Treatment Guidelines. Immunomodulators under evaluation for the treatment of COVID-19. Last updated November 3, 2020.

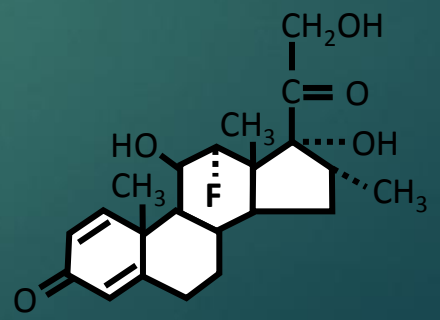
خاطر نشان می شود در حال حاضر هیچ مداخله درمانی و یا داروی
ضد ویروسی با اثرات ثابت شده قطعی
برای این بیماری وجود ندارد.

Corticosteroids

Dexamethasone

- Dexamethasone is a corticosteroid with anti-inflammatory effects that has been used to treat allergies, asthma, dermatitis, rheumatic disorders, MS, other autoimmune disorders, etc
- Can be administered IV or orally
- Contraindicated by FDA in patients with systemic fungal infections
- Pregnancy category C

- **Warnings:** can cause elevation in blood pressure, left ventricular free wall rupture in patients with recent MI, adrenocortical insufficiency, increased susceptibility to infection, and cataracts/glaucoma with possible damage to the optic nerve

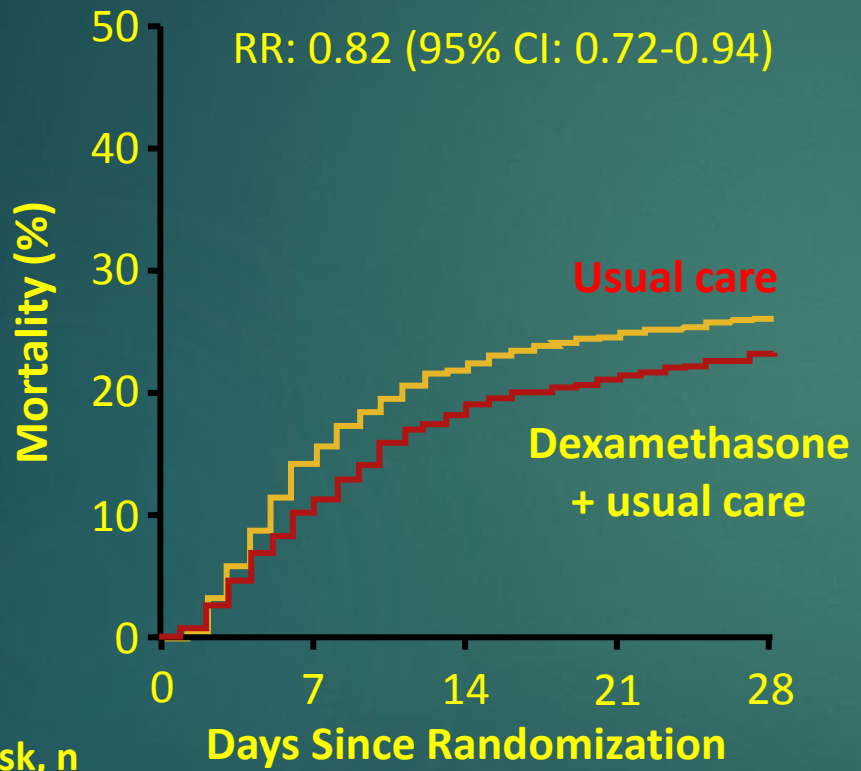


Dexamethasone PI. Dexamethasone sodium phosphate PI.

RECOVERY Trial:
Mortality in Patients on Oxygen or Mechanical Ventilation ± Dexamethasone

Oxygen Only (n = 3883)

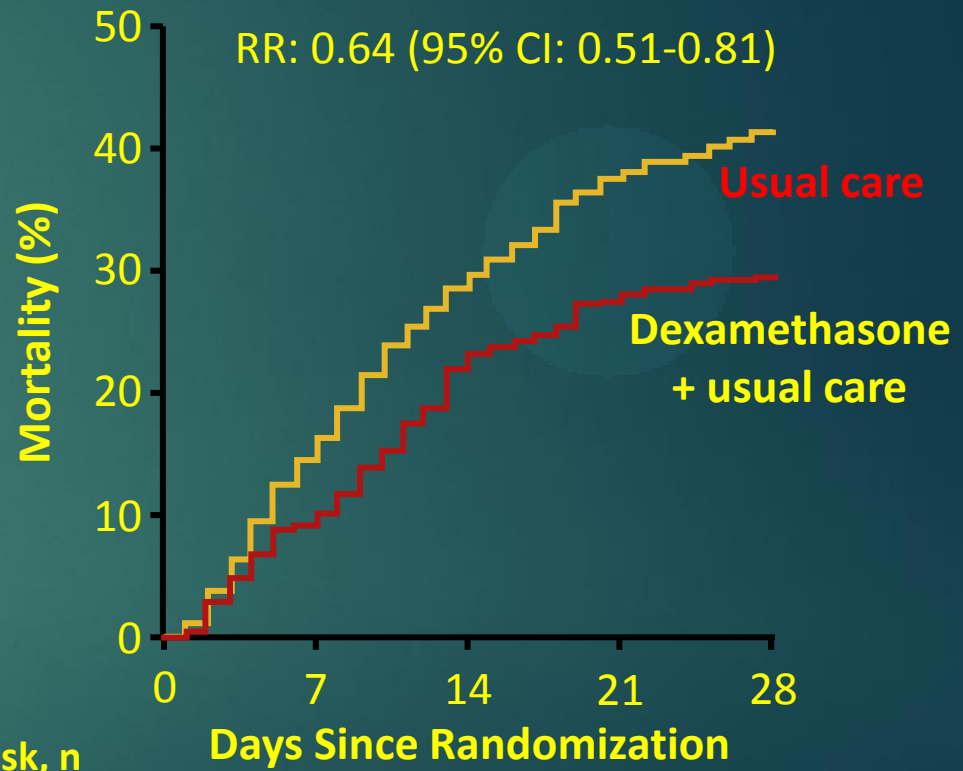
RR: 0.82 (95% CI: 0.72-0.94)



Patients at Risk, n					
Dexamethasone	1279	1135	1036	1006	981
Usual care	2604	2195	2018	1950	1916

Invasive Mechanical Ventilation (n = 1007)

RR: 0.64 (95% CI: 0.51-0.81)



Patients at Risk, n					
Dexamethasone	324	290	248	232	228
Usual care	683	572	481	424	400

- RECOVERY Collaborative Group. NEJM. 2020;[Epub].

WHO Living Guidance: Corticosteroids for COVID-19

Categories of Illness	Definition	Recommendation
Critical COVID-19	▪ ARDS, sepsis, septic shock ▪ Other conditions that would normally require life-sustaining therapies (mechanical ventilation) or vasopressor therapy	▪ Recommend systemic corticosteroids rather than no systemic corticosteroids
Severe COVID-19	Any of the following: ▪ 0_2 < 90% on room air* ▪ RR > 30 breaths/min in adults and children aged > 5 yrs; RR ≥ 40 in children aged 1-5 yrs; RR ≥ 50 in children aged 2-11 mos ▪ Signs of respiratory distress (accessory muscle use, inability to complete full sentences; in children very severe chest wall indrawing, grunting, central cyanosis, etc)	▪ Recommend systemic corticosteroids rather than no systemic corticosteroids
Non-severe COVID-19	▪ Absence of any signs of severe or critical COVID-19	▪ Suggest no corticosteroids

*Note that this threshold to define severe COVID-19 is arbitrary and should be interpreted cautiously when used for determining which patients should be offered systemic corticosteroids. Clinicians must use their judgement, and the panel suggests erring on the side of considering the illness as severe if there is any doubt.

WHO Living Guidance. Corticosteroids for COVID-19. September 2, 2020.

NIH/IDSA: Dexamethasone for Severe COVID-19

NIH[1]*

- For those **not hospitalized (AIII) or hospitalized but not requiring supplemental oxygen (AIIa)**, the Panel recommends against the use of dexamethasone
- For those **hospitalized and requiring supplemental oxygen**, the Panel recommends remdesivir alone (BIIa), remdesivir + dexamethasone (BIII), or dexamethasone alone (BI)
- For those **hospitalized and requiring high-flow oxygen or noninvasive ventilation**, the Panel recommends remdesivir + dexamethasone (BIII) or dexamethasone alone (AI)
- For those **hospitalized and requiring invasive mechanical ventilation or ECMO**, the Panel recommends dexamethasone (AI); for patients recently intubated, remdesivir + dexamethasone may be considered (CIII)
- **Dose**: Dexamethasone 6 mg IV or PO for 10 days or until discharge; equivalent corticosteroid dose (eg, prednisone, methylprednisolone, or hydrocortisone) may be used if dexamethasone unavailable

IDSA[2]

- For **hospitalized patients with critical† COVID-19**, the Panel recommends dexamethasone rather than no dexamethasone (Strong recommendation, Moderate certainty of evidence)
- For **hospitalized patients with severe‡ COVID-19**, the Panel suggests dexamethasone rather than no dexamethasone (Conditional recommendation, Moderate certainty of evidence)
- **Dose**: Dexamethasone 6 mg IV or PO for 10 days (or until discharge) or equivalent glucocorticoid dose (eg, methylprednisolone 32 mg, prednisone 40 mg) may be substituted if dexamethasone unavailable

*Recommendation rating: A = Strong; B = Moderate; C = Optional. Evidence rating: I = ≥ 1 randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion. †Mechanical ventilation or ECMO. ‡Patients with SpO_2 ≤ 94% on room air, including those who require supplemental oxygen.

1. NIH COVID-19 Treatment Guidelines. Therapeutic management of patients with COVID-19. Last updated December 3, 2020.
2. IDSA. COVID-19 Guideline, Part 1: Treatment and Management. Version 3.6.0.

NIH: Additional Considerations for Dexamethasone

Guidance
▪ Unknown if other corticosteroids will have a similar benefit. Of note: dose equivalencies for dexamethasone 6 mg daily = prednisone 40 mg, methylprednisolone 32 mg, and hydrocortisone 160 mg
▪ Patients should be closely monitored for adverse effects, including hyperglycemia and secondary infections
▪ Systemic corticosteroids may increase risk of reactivation of latent infections (HBV, herpes viruses, TB)
▪ Dexamethasone is a moderate CYP3A4 inducer, which may reduce the concentration and efficacy of some medications; clinicians should review current medications to assess potential interactions
▪ In other coronavirus outbreaks (MERS and SARS), corticosteroid use associated with delayed virus clearance

NIH COVID-19 Treatment Guidelines. Corticosteroids. Last updated November 3, 2020. RECOVERY Collaborative Group. NEJM. 2020;[Epub].

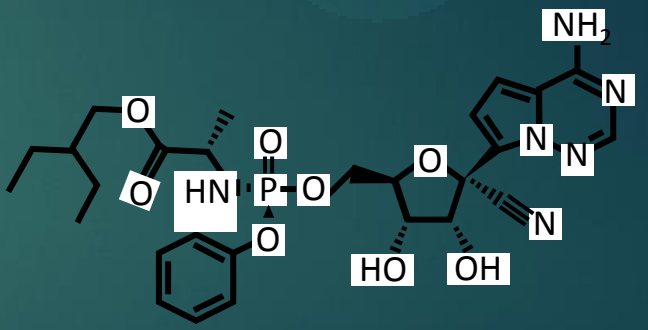
Remdesivir

FDA Approval: Remdesivir for Hospitalized Patients

- Remdesivir is a nucleoside analogue of ATP that inhibits SARS-CoV-2 RNA polymerase by competing with ATP for inclusion into nascent RNA→ delayed chain termination during viral RNA replication

FDA Indication

"…indicated for adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of coronavirus disease 2019 (COVID-19) requiring hospitalization. [Remdesivir] should only be administered in a hospital or healthcare setting capable of providing acute care comparable to inpatient hospital care."



Remdesivir PI.

FDA Approval for Remdesivir: Treatment Initiation and Dosing Regimens

Updated

- Treatment of hospitalized patients with suspected COVID-19 can be considered pending laboratory confirmation of SARS-CoV-2
- Treatment can be started any time after symptom onset
- All patients must have eGFR determined and hepatic laboratory testing before starting and while receiving remdesivir (as clinically appropriate)
- All patients must have prothrombin time determined before starting and while receiving remdesivir (as clinically appropriate)

IV Dosage Over 30-120 Mins		Patients Requiring Invasive Mechanical Ventilation and/or ECMO	Patients Not Requiring Invasive Mechanical Ventilation and/or ECMO
Adults and pediatric patients ≥ 40 kg	▪ Loading	200 mg on Day 1	200 mg on Day 1
	▪ Maintenance	100 mg on Days 2-10	100 mg on Days 2-5*

*Treatment may be increased to 10 days in patients not demonstrating clinical improvement at Day 5 of treatment.

Remdesivir PI

FDA Approval for Remdesivir: Safety Information and Warnings

- **Contraindicated in** patients with a history of clinically significant hypersensitivity reactions to remdesivir or any components
- **Not recommended** for patients with eGFR < 30 mL/min
- **Warnings and precautions:**
  - **Infusion-related reactions** have occurred in patients receiving remdesivir; immediately d/c if signs of clinically significant infusion reaction occurs
  - **Transaminase elevations** have occurred in healthy controls and patients with COVID-19 receiving remdesivir; consider discontinuing if ALT ≥ 10 x ULN

Remdesivir PI.

FDA Approval for Remdesivir: Use in Special Populations

Population	Recommendation
Pregnancy	No adequate and well-controlled studies
Nursing mothers	No information regarding remdesivir in human milk, effects on breastfed infants, or effects on milk production; in animal studies, remdesivir and metabolites are detected in the nursing pups of mothers given remdesivir, suggesting the presence of remdesivir in milk
Pediatric	Safety and efficacy for treating COVID-19 have not been assessed in pediatric patients younger than 12 yrs or weighing less than 40 kg; FDA EUA in effect for pediatric patients younger than 12 yrs or weighing less than 40 kg
Geriatric	Clinical experience has not identified differences in responses between elderly and younger patients; no dosage adjustment required; should be monitored closely for hepatic, renal, and cardiac function
Renal impairment	Remdesivir PK not evaluated in patients with renal impairment; not recommended patients with eGFR < 30 mL/min
Hepatic impairment	Remdesivir PK not evaluated in patients with hepatic impairment; perform hepatic testing prior to starting and while receiving remdesivir

Remdesivir PI

FDA EUA for Remdesivir in Pediatric Patients: Treatment Initiation and Dosing Regimens

Updated

- Treatment of hospitalized patients with suspected COVID-19 can be considered pending laboratory confirmation of SARS-CoV-2
- Treatment can be started any time after symptom onset
- Pediatric patients > 28-days old must have eGFR and full-term neonates (7-28 days old) must have serum creatinine determined prior to start
- Perform hepatic laboratory testing and determine prothrombin time in all patients prior to start

Dosage of Remdesivir for Injection (100 mg Lyophilized Powder)		Weighing 3.5 kg to < 40 kg	Weighing ≥ 40 kg
Pediatric patients < 12 yrs of age	▪ Loading (Day 1)	5 mg/kg	200 mg
	▪ Maintenance (Days 2-5)*	2.5 mg/kg	100 mg

*Treatment maybe increased to 10 days in patients not demonstrating clinical improvement at Day 5 of treatment.

Remdesivir EUA Provider Fact Sheet. Updated October 2020

FDA EUA for Remdesivir in Pediatric Patients: Safety Information and Warnings

Updated

"There are limited data available for [remdesivir] in patients weighing 2.5 kg to less than 40 kg or patients less than 12 years of age weighing at least 40 kg. Serious and unexpected adverse events may occur that have not been previously reported…"

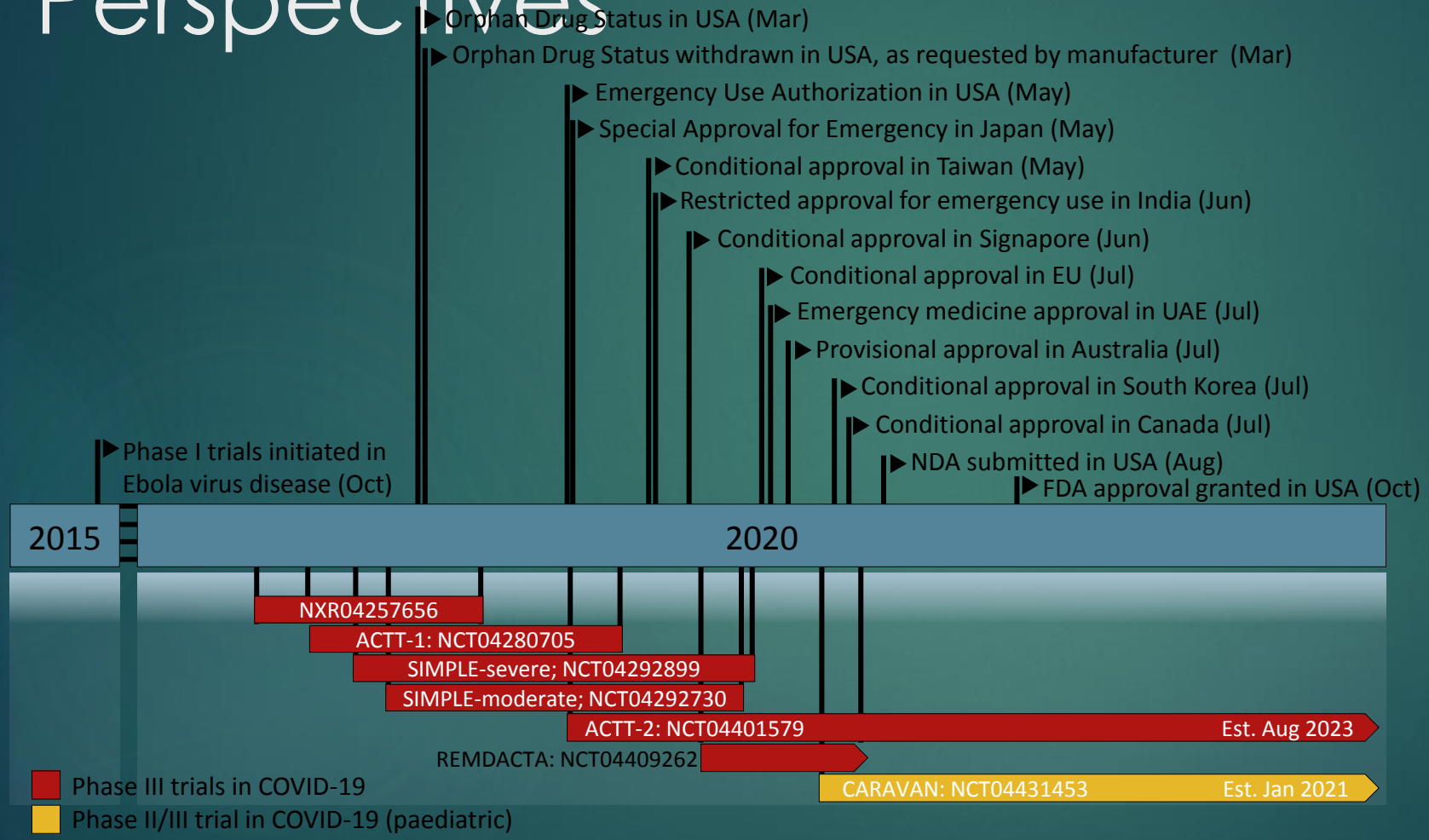
- Recommended monitoring
  - Serum chemistries, hematology
  - ALT, AST, renal function tests, bilirubin, ALP

- Infusion-related reactions have occurred in patients receiving remdesivir; immediately D/C if signs of clinically significant infusion reaction occurs
- Transaminase elevations have occurred in healthy controls and patients with COVID-19 receiving remdesivir
  - Consider discontinuing if ALT ≥ 10 x ULN

Remdesivir EUA Provider Fact Sheet. Updated October 2020.

Remdesivir: Snapshot on Global Perspectives

Updated



"Remdesivir has been approved or authorized for temporary use as a COVID-19 treatment in approximately 50 countries worldwide."

Lamb. Drugs. 2020;80:1355. https://www.gilead.com/news-and-press/press-room/press-releases/2020/10/us-food-and-drug-administration-approves-gileads-antiviral-veklury-remdesivir-for-treatment-of-covid19.

Remdesivir EMA Conditional Marketing Authorization

Therapeutic Indication

"…is indicated for treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen…"

- Recommended dose/duration:
  - Day 1: single 200 mg IV dose
  - Day 2 onwards: 100 mg IV once daily
  - Total treatment duration should be 5-10 days
- Contraindicated in patients with hypersensitivity to remdesivir or excipients

- Warnings:
  - Hypersensitivity reactions and transaminase elevations have been observed
  - Should not be used in patients with eGFR < 30 mL/min
  - Risk of reduced antiviral activity when administered with chloroquine or HCQ

Remdesivir EMA PI.

Convalescent Plasma

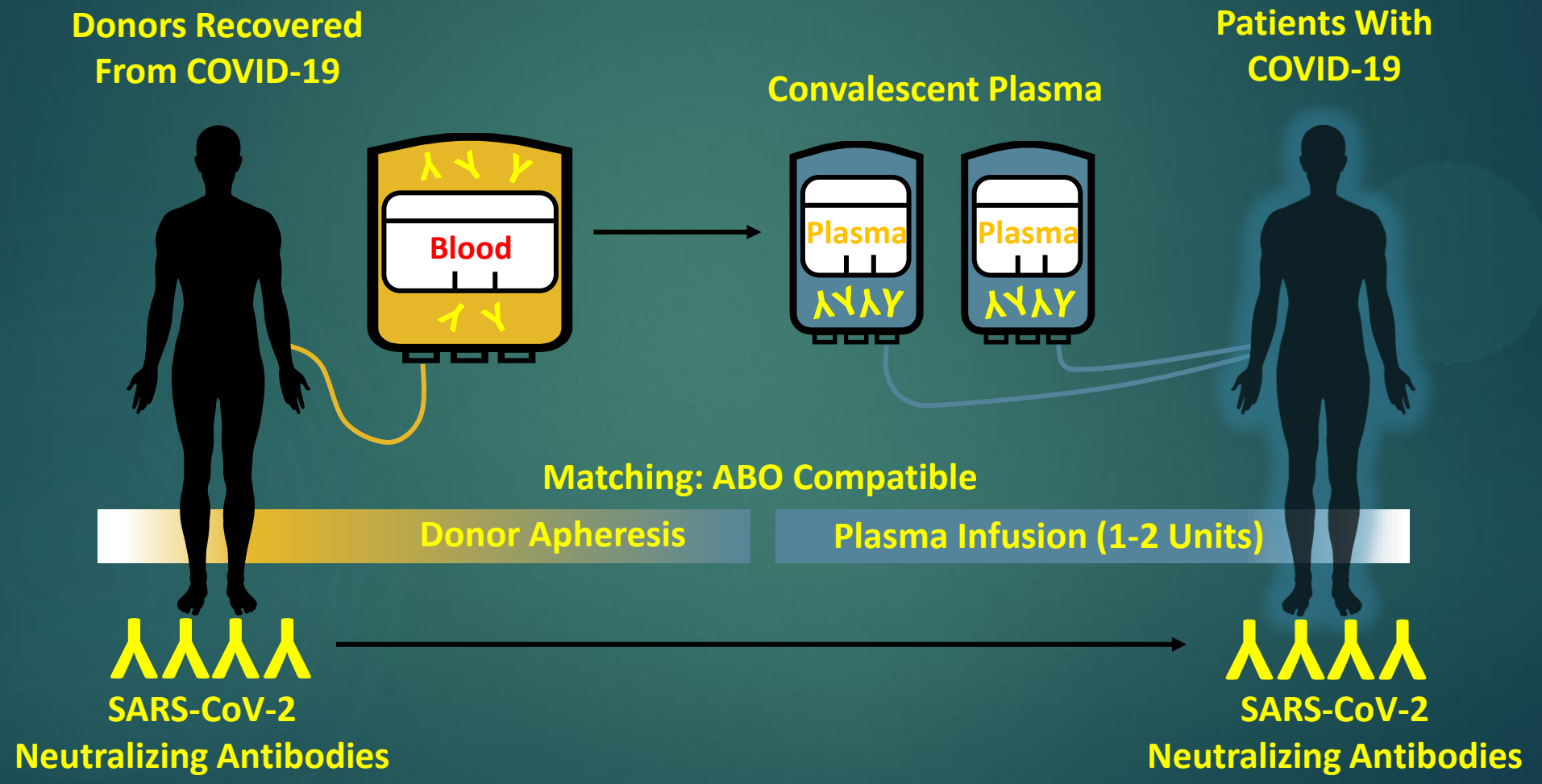
Background: Passive Immunization

Multiple ways to infuse neutralizing antibodies ▶

Monoclonal Antibodies[1]	Hyperimmune Immunoglobulins[2]	Convalescent Plasma[1,2]
▪ Produced in laboratories ▪ Scalable ▪ Genetic modification of Fc domain can reduce the risk of ADE and extend half-life	▪ Derived from plasma ▪ Standardized product	▪ Plasma from recovered individuals ▪ Batch-to-batch variability ▪ Requires blood-type matching

1. Abraham. Nat Rev Immun. 2020;20:401. 2. Piechotta. Cochrane Database Syst Rev. 2020;7:CD013600.

Theory of Using Convalescent Plasma to Treat COVID-19



IDEA. COVID-19 Tx. https://covid.idea.medicine.uw.edu/page/treatment/drugs/human-coronavirus-immune-plasma-hcip

FDA EUA for COVID-19 Convalescent Plasma: Clinical Evidence

- ***"Convalescent plasma should not be considered a new standard of care for the treatment of patients with COVID-19"***
- *"Given that the clinical evidence supporting this EUA was not obtained from prospective, well-controlled randomized clinical trials (RCTs), additional RCTs are needed"*
- *"Ongoing clinical trials of convalescent plasma should not be amended based on the issuance of the EUA. Providers are encouraged to enroll patients in those ongoing clinical trials"*

Convalescent Plasma EUA Fact Sheet for Healthcare Providers.

FDA EUA for COVID-19 Convalescent Plasma: Safety Information and Warnings

Potential Adverse Events

- Transfusion-transmitted infections (ie, HIV, HBV, HCV)
- Allergic or anaphylactic reactions
- Hemolytic reactions
- Febrile nonhemolytic reactions
- TRALI
- TACO
- Hypothermia
- Metabolic complications
- Posttransfusion purpura

Convalescent Plasma EUA Fact Sheet for Healthcare Providers.

Theoretical Risks

- Antibody-dependent enhancement of infection
- Attenuation of immune response leading to increased susceptibility to reinfection

Provider Role

- Maintain records
- Conduct thorough investigation of posttransfusion adverse reactions
- Report transfusion-related fatalities

NIH Guidance on Use of Convalescent Plasma

Updated

"There are insufficient data to recommend either for or against the use of convalescent plasma for the treatment of COVID-19"

"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"

NIH COVID-19 Treatment Guidelines. Convalescent plasma. Last updated October 9, 2020.

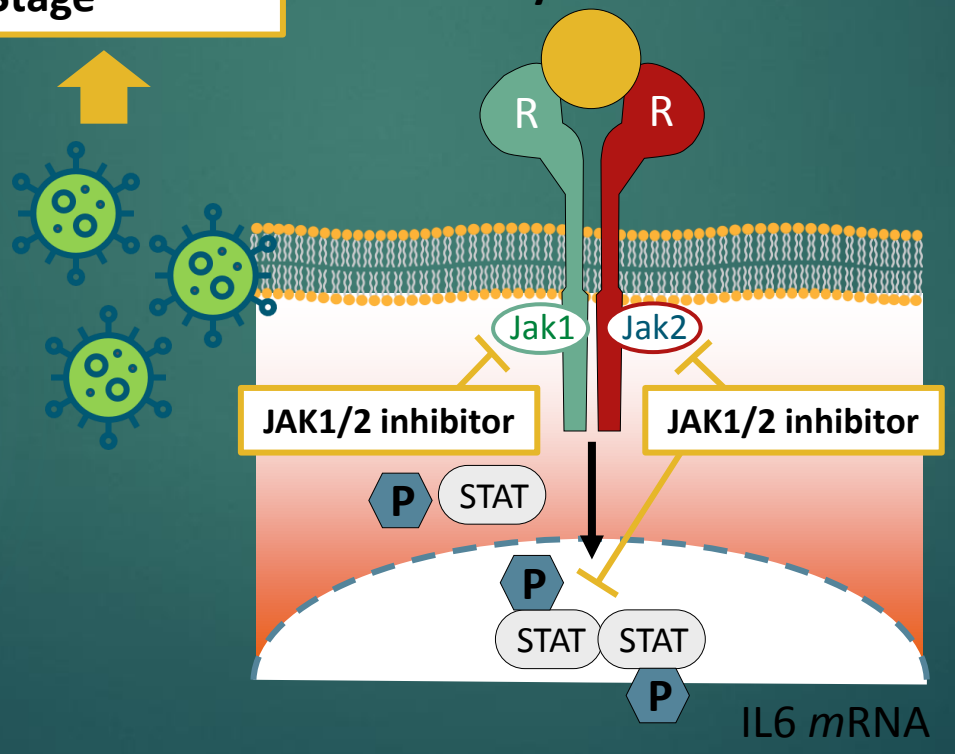
JAK Inhibitors

JANUS KINASE INHIBITOR

JAK1/2 Inhibitors

Elevated in blood
IL-1b, IL-2, IL-6, IL-7, IL-8,
IL-9, IL-10, IL-17, G-CSF, GM-CSF,
IFNα, IFNγ, TNF-α, IP10, MCP1,
MIP1A, MIP1B

Hyperinflammatory Stage



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

Baricitinib

Baricitinib may have mechanisms of action within both infected cells and immune responder cells

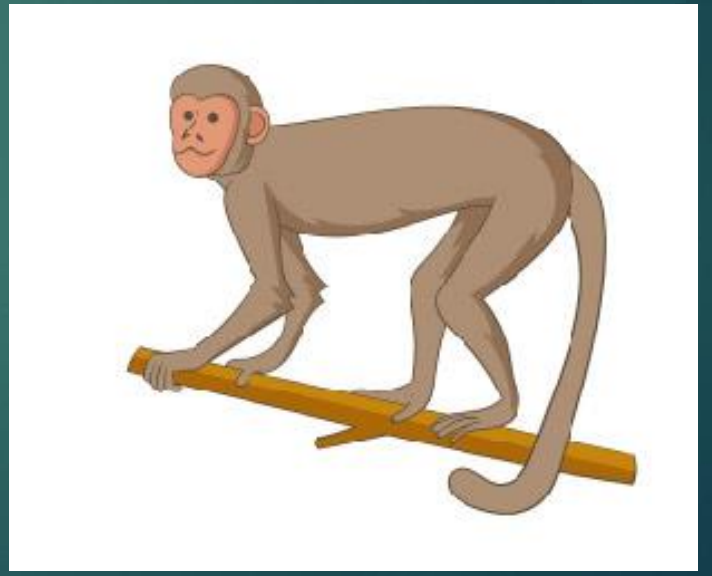
- Janus kinase inhibitor approved as a DMARD for rheumatoid arthritis
- Identified as a therapeutic candidate by artificial intelligence for both immunomodulatory and potential antiviral properties
- Inhibits host proteins (P2-associated kinase 1 AAK1 and the cyclin G–associated kinase GAK(
- May inhibit virus entry into cells and reduce inflammatory responses

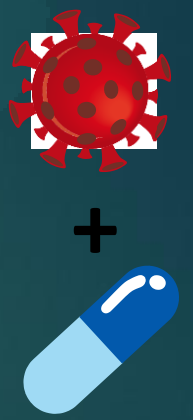
Stebbing. Sci Adv 2020;7:eabe4724.

Baricitinib in Rhesus Macaque Model of SARS-CoV-2 Infection

- SARS-CoV-2–infected rhesus macaques mimic signatures of inflammation seen in COVID-19 patients

Baricitinib Treatment Results
↓ Inflammatory cytokines and chemokines
↓ Neutrophil and macrophage recruitment
↓ NETosis activity
↓ Activated T-cells
Preserved innate viral responses
No change in viral shedding





SARS-CoV-2 + Baricitinib

Hoang. Cell. 2020;10:S0092-8674(20)31466-5.

NIH Guidelines on Baricitinib

" There are insufficient data for the Panel to recommend either for or against the use of baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized patients in cases where corticosteroids can be used instead.

In the rare circumstances where corticosteroids cannot be used, the Panel recommends using baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized, nonintubated patients who require oxygen supplementation."

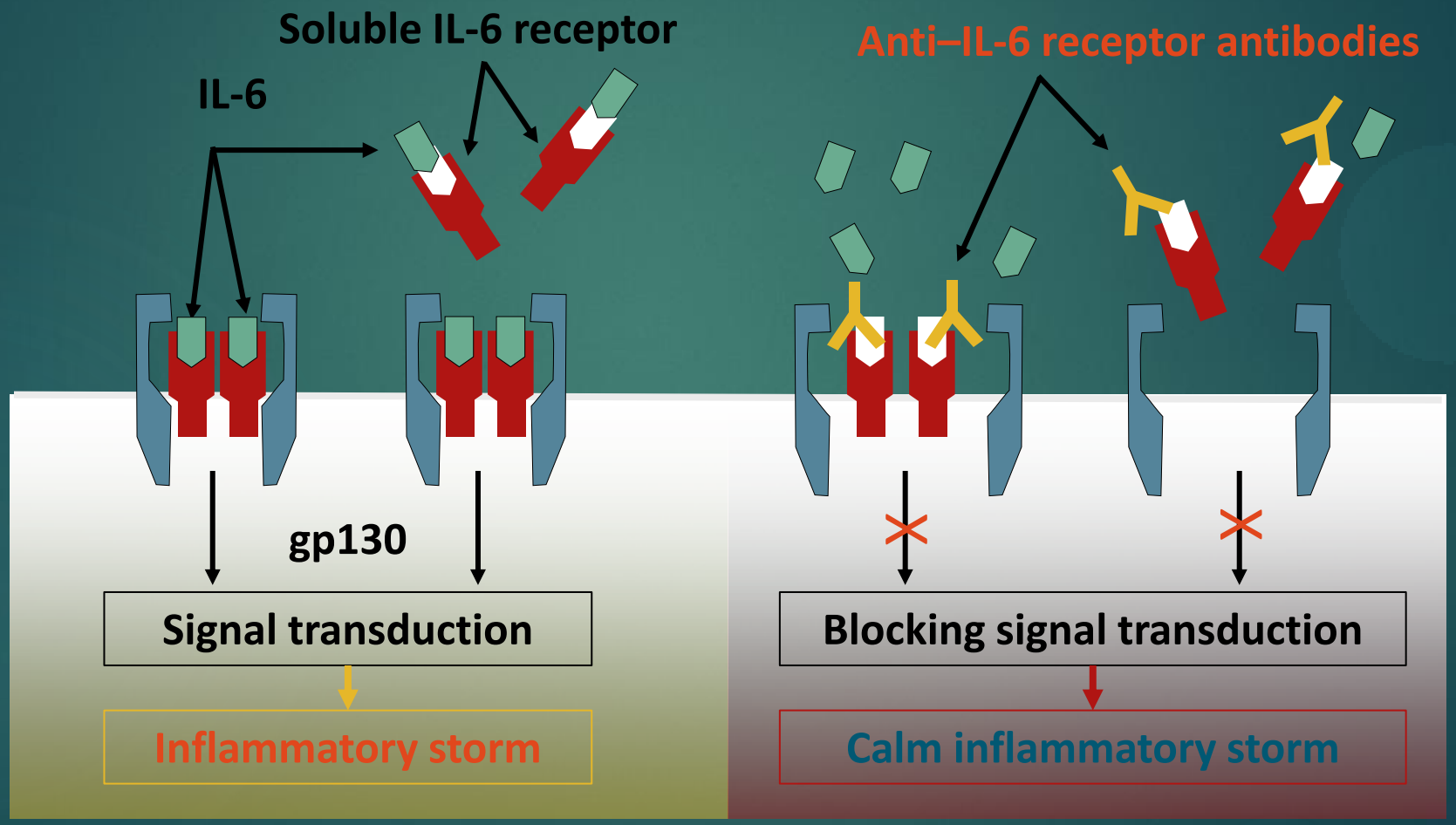
baricitinib (4 mg orally once daily for up to 14 days)

For the rare patients who have contraindications to glucocorticoids and are starting remdesivir, adding baricitinib is a reasonable approach. ***Baricitinib should not be used without remdesivir***.

https://www.covid19treatmentguidelines.nih.gov/statement-on-baricitinib-eua/

Immunomodulatory Therapies

Anti–IL-6 Receptor Antibodies
IL-6 pathway inhibitors (eg, tocilizumab)

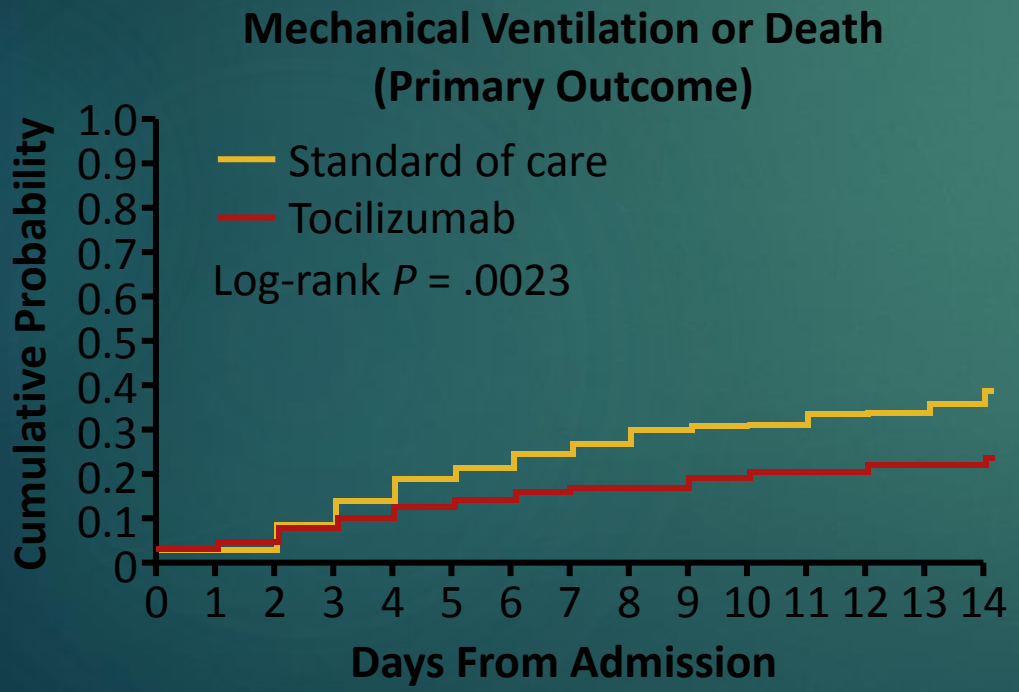


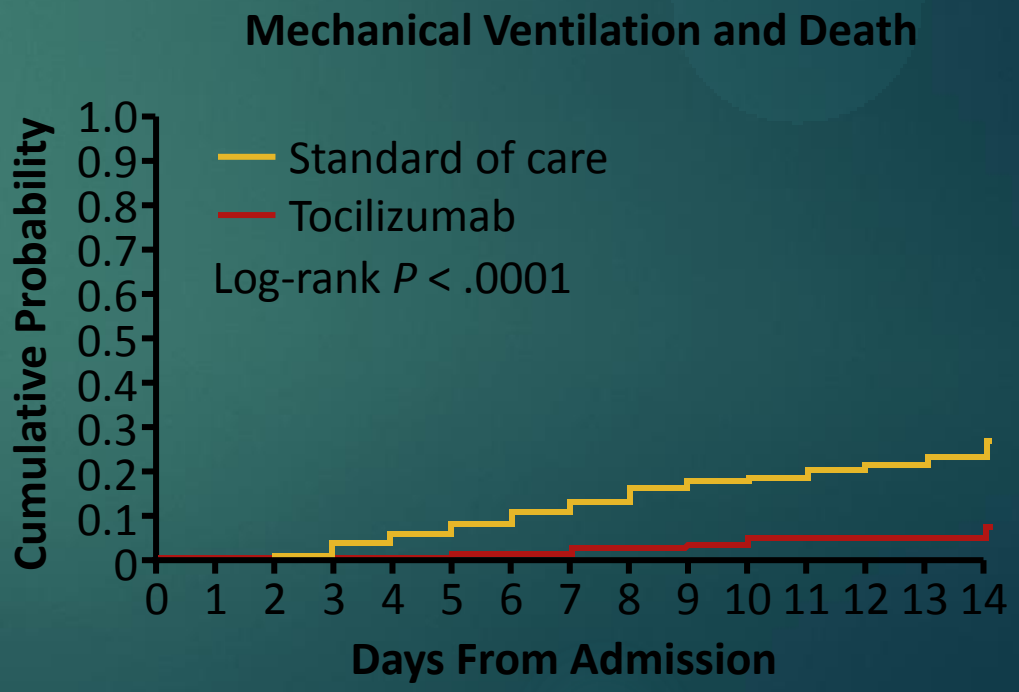
Fu. J Translational Medicine. 2020;18:164.

Slide credit: clinicaloptions.com

TESEO Cohort: Tocilizumab to Treat Severe COVID-19 in Italy

- Retrospective, observational, cohort study of adults with severe COVID-19 pneumonia admitted to tertiary care centers in Italy between February and March 2020 who received tocilizumab plus standard of care (n = 179) vs standard of care alone (n = 365)
  - ***Tocilizumab: 8 mg/kg via 2 infusions 12 hrs apart or 162 mg SQ in each thigh (324 mg total) when IV formulation unavailable***





Guarlandi. Lancet Rheumatology. 2020;20:30173.

Enrollment at 113 Sites in 6 Countries

- Primary outcome: respiratory and cardiovascular organ support-free days, up to Day 21

Critically ill adults with suspected or confirmed severe COVID-19 admitted to ICU and receiving organ support, Apr 19 - Nov 19, 2020

(N = 895)

Tocilizumab 8 mg/kg (max 800 mg) IV x 1 or 2 doses
(n = 350; 366 randomized, 13 withdrew consent, 3 - outcome not available)

Sarilumab† 400 mg IV x 1 dose
(n = 45; 48 randomized, 3 - outcome not available)

Control (current standard of care)
(n = 397; 412 randomized, 10 withdrew consent, 5 - outcome not available)

Anakinra or interferon beta 1a
(n = 61; 69 randomized, 7 withdrew consent, 1 - outcome not available)

*Tocilizumab met statistical trigger for efficacy by interim analysis on Oct 28, 2020; subsequent interim analysis revealed that sarilumab had also met statistical trigger for efficacy. †Fewer enrollees in sarilumab arm because it opened later than tocilizumab arm.

Gordon. medRXiv [preprint]. https://www.medrxiv.org/content/10.1101/2021.01.07.21249390v1.full.pdf.

Key RCT Data For Other Investigational Agents

Agent	N	Population	Comparator	Primary Outcome
Lopinavir/ritonavir[1]	199	Adults, severe	SOC alone	▪ No difference in time to clinical improvement
Lopinavir/ritonavir[2]	86	Adults, mild-to-moderate	Umifenovir or no antiviral	▪ No difference in rate of positive-to-negative conversion of SARS-CoV-2 nucleic acid
Lopinavir/ritonavir + ribavirin + IFNβ1b[3]	127	Adults, hospitalized	LPV/RTV	▪ Significantly shorter median time from start of study treatment to negative nasopharyngeal swab for combination treatment
Lopinavir/ritonavir[4]	5040	Hospitalized	SOC alone	▪ No difference in 28-day mortality
Favipiravir[5]	240	Adults, pneumonia	Umifenovir	▪ No difference in clinical recovery rate of Day 7
IFNκ + TFF2[6]	80	Adults, moderate	SOC alone	▪ Shortened mean time to viral RNA negative conversion (3.8 vs 7.4 days, *P* = .031)

1. Cao. NEJM. 2020;382:1787. 2. Li. Med (NY). 2020;1:105. 3. Hung. Lancet. 2020;395:1695. 4. RECOVERY Collaborative Group. Lancet. 2020;396:1345. 5. Chen. medRxiv. 2020;[Preprint]. Note: This paper has not been peer reviewed. 6. Fu. EClinicalMedicine. 2020;[Epub].

Key RCT Data For OtherInvestigational Agents(Cont.)

Updated

Agent	N	Population	Comparator	Primary Outcome
Hydroxychloroquine[1]	150	Adults, mild-to-moderate	SOC alone	▪ No difference in negative conversion of SARS-CoV-2 by Day 28
Hydroxychloroquine[2]	4716	Hospitalized	SOC alone	▪ No difference in 28-day mortality
Hydroxychloroquine as post-exposure prophylaxis[3]	821	Asymptomatic adults with known COVID-19 exposure	Placebo	▪ No difference in incidence of COVID-19 within 14 days
Hydroxychloroquine ± azithromycin[4]	504	Hospitalized adults, mild-to-moderate	SOC alone	▪ No difference in clinical status by 7-level ordinal scale at Day 15
Azithromycin[5]	397*	Hospitalized adults, severe	SOC alone	▪ No difference in clinical status by 6-point ordinal scale at Day 15

*All patients received hydroxychloroquine, as it was considered standard care for severe COVID-19 in Brazil.

1. Tang. BMJ. 2020;369:m1849. 2. RECOVERY Collaborative Group. NEJM. 2020;383:2030.
3. Boulware. NEJM. 2020;383:517. 4. Cavalcanti. NEJM. 2020;383:2041. 5. Furtado. Lancet. 2020;396:959

Key RCT Data For Other Investigational Agents

Agent	N	Population	Comparator	Primary Outcome
Tocilizumab[1,2]	129	Moderate or severe pneumonia	Standard care alone	▪ Improvement in composite endpoint of death or need for ventilation at Day 14 with tocilizumab vs standard care
Sarilumab (200 or 400 mg)[3,4]	457	Severe or critical	Placebo	▪ CRP decline: 77% and 79% vs 21% ▪ IDMC recommended continuing phase III only in critical subgroup with 400 mg sarilumab vs placebo

1. https://www.aphp.fr/contenu/tocilizumab-improves-significantly-clinical-outcomes-patients-moderate-or-severe-covid-19
2. NCT04331808. 3. NCT04315298. 4. https://newsroom.regeneron.com/news-releases/news-release-details/regeneron-and-sanofi-provide-update-us-phase-23-adaptive

New

WHO SOLIDARITY: Summary of Findings

- No study drug improved 28-day mortality overall, or when stratified by age group, ventilation at entry, geographic region, or corticosteroid use
- No study drug reduced initiation of ventilation for those not already ventilated
- Proportion of patients remaining hospitalized on Day 7 was similarly increased for each study drug vs its respective SoC group
  - Might reflect the practice of keeping patients on a study drug in the open-label trial setting when they may otherwise be fit for discharge
  - Given the increases were similar across all 3 study drugs administered past Day 7 (remdesivir, HCQ, and LPV/RTV), investigators concluded that none of the 3 drugs accelerated recovery

WHO Solidarity Trial Consortium. NEJM. 2020;[Epub].

New

DDRI: SOF/DCV + LPV/RTV vs LPV/RTV for Severe COVID-19

- Sofosbuvir and daclatasvir: anti-HCV direct-acting antivirals, with in vitro activity against SARS-CoV-2 cell lines; DCV EC50 estimates for SARS-CoV-2 within PK exposure levels at standard dosing[1]
- DDRI: open-label, randomized, controlled trial at 4 university hospitals in Iran[2]

Adults hospitalized with fever and ≥ 1 of:
respiratory rate > 24/min, O_2 saturation < 94%, or PaO_2/FiO_2 ratio < 300;
PCR confirmed SARS-CoV-2; and
diagnostic chest CT scan
(N = 66)

→ **SOF/DCV + LPV/RTV** (n = 33)

→ **LPV/RTV** (n = 33)

- Primary endpoint: clinical recovery (composite) within 14 days from study treatment initiation until: fever normalization, respiratory rate ≤ 24/min on room air, O_2saturation
  ≥ 94% on room air sustained for ≥ 24 hrs

1. Sacramento. bioRxiv. 2020;[Preprint]. Note: This paper has not been peer reviewed. 2. Sadeghi. IAS COVID-19. Abstr 11125.

Interferons

- Interferons modulate immune responses and may have antiviral effects. Interferon beta, specifically, has been reported to inhibit SARS-CoV-2 replication in vitro [111]. Defects in production of type 1 interferons (which include interferon beta), as well as autoantibodies that neutralize type 1 interferons, have been identified in patients with severe COVID-19.

- Overall, clinical data do not indicate a clear benefit of interferon beta for severe COVID-19. Interim results of a large multinational trial of patients hospitalized with COVID-19 showed no difference in 28-day mortality with subcutaneous or intravenous interferon beta compared with standard of care (2703 patients in each group; RR 1.16, 95% CI 0.96-1.39) [52]. Although some smaller trials had suggested clinical improvement, faster time to hospital discharge, and a potential mortality benefit with interferon beta, methodologic limitations reduce confidence in those findings [114].

- Inhaled interferon beta, an investigational formulation of the drug delivered by nebulizer, is also being evaluated. In a randomized trial of 101 patients hospitalized with COVID-19, inhaled interferon beta increased the likelihood of recovery by day 15 compared with placebo (OR 3.19, 95% CI 1.24-8.24); a reduction in the likelihood of severe disease or death was not statistically significant [115].

Favipiravir

Favipiravir is an RNA polymerase inhibitor available in some Asian countries for treatment of influenza and available in India for treatment of mild COVID-19, and it is being evaluated in clinical trials for treatment of COVID-19 in the United States and elsewhere. Early trials in Russia and China suggested some benefit, but since other therapies (eg, immunomodulatory agents) were administered in these studies, the results should be interpreted with caution given potential confounders.

Contraindicated in pregnancy due to early embryonic death and teratogenicity observed in animal studies.

Ivermectin

Ivermectin has also been proposed as a potential therapy based on in vitro activity against SARS-CoV-2, but the drug levels used in vitro far exceed those achieved in vivo with safe drug doses.

Mechanism of Action:

Ivermectin inhibits the host alpha/beta-1 nuclear transport proteins, which are a part of a key intracellular transport process that viruses use to enhance infection by suppressing the host antiviral response.

In a retrospective review of 280 patients hospitalized with COVID-19, receipt of ivermectin was associated with a lower mortality rate; however, patients who received ivermectin were also more likely to receive corticosteroids, highlighting the potential for confounders to impact the findings of nonrandomized studies .Various clinical trials of ivermectin are underway, but the only results available thus far are from low-quality unpublished trials. As with other interventions that are not supported by high-quality data, we do not use ivermectin outside of clinical trials.

Colchicine

- Anti-inflammatory Agent
- Rationale for Use: Cytokine release syndrome may be a component of severe disease in COVID-19 patients•

Mechanism of Action: Colchicine downregulates multiple pro-inflammatory pathways and increases levels of anti-inflammatory mediators. It also prevents microtubule assembly and thereby disrupts inflammasome activation, microtubule-based inflammatory cell chemotaxis, phagocytosis, and generation of leukotrienes and cytokines (including interleukin-1 beta). Consequently, colchicine prevents the activation, degranulation, and migration of neutrophils.

- Evidence / Experience

o Gastrointestinal reactions (abdominal pain, diarrhea, nausea, and vomiting)

o Neuromuscular toxicity and rhabdomyolysis

o Caution in patients with bone marrow suppression

o Caution in patients with renal or hepatic impairment

“Pulmonary interstitial damage and functional decline caused by SARS mostly recovered, with a greater extent of recovery within 2 yrs after rehabilitation. Femoral head necrosis induced by large doses of steroid pulse therapy in SARS patients was not progressive and was partially reversible.”

Zhang. Bone Res. 2020;8:8

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]

1. Puntmann. AMA Cardiol. 2020;[Epub]. 2. Mitrani. Heart Rhythm. 2020 [Epub].

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

1. Agyeman. Mayo Clin Proc. 2020;95:1621. 2. Lee. J Korean Med Sci. 2020;35:e174. 3. Iadecola. Cell. 2020;[Epub].

Slide credit: clinicaloptions.com

درمان ضد انعقاد

- درمان پیشگیرانه ضد انعقادی در بیماران بستری به شرح زیر توصیه می شود:
- Heparin 5000IU SC TDS
- BMI≥40: Heparin 7500 IU SC TDS o
- یا
- Enoxaparin 40 mg SC once daily
- BMI ≥ 40: Enoxaparin 40 mg SC BID o

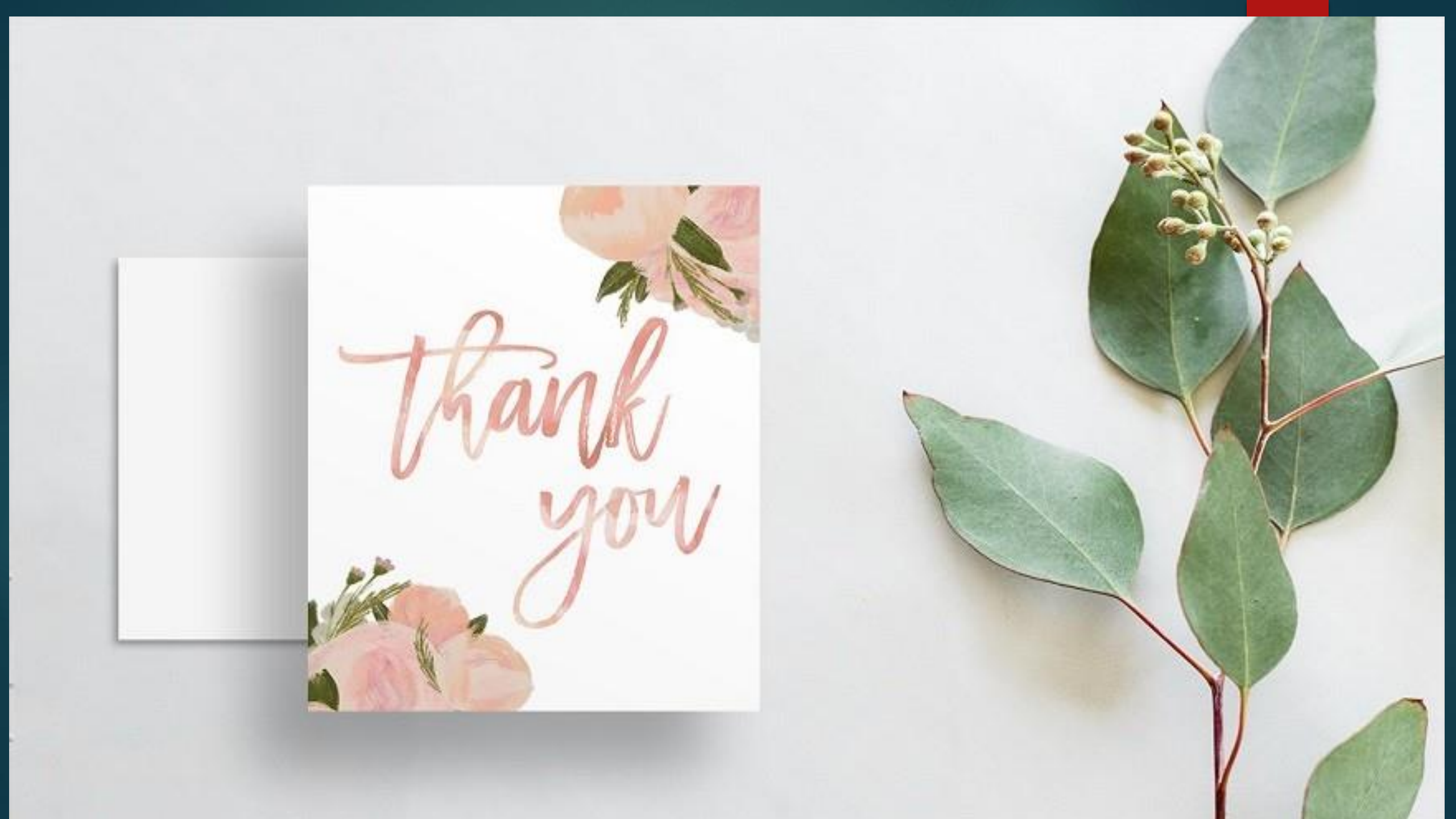
- In patients who are *not* bleeding, there is no evidence that correction of laboratory parameters with blood products improves outcomes. Replacement might worsen disseminated thrombosis and further deplete scarce blood products. In a patient who is experiencing clinically relevant bleeding, transfuse platelets (one adult dose) if the platelet count is less than 50 x 10^9/L, give plasma (4 units) if the INR is above 1.8 and order fibrinogen concentrate (4 grams) or cryoprecipitate (10 units) if the fibrinogen level is less than 1.5 g/L. For patients with severe coagulopathy and bleeding, consider 4F-PCC (e.g. 25 Units/kg) instead of plasma, as volume status appears to be a significant factor associated with respiratory compromise. The hemostatic effectiveness of tranexamic acid (TXA) is unknown in this setting.

معیارهای زیر در صورت دسترسی به تصمیم گیری بهتر برای ترخیص می تواند کمک کند:

- CBCقبل از ترخیص رو به طبیعی شدن باشد, CRPحداقل ۵۰ %و ESRحداقل ۲۰ %نسبت به قبل افت کرده باشد
- در مواردی که به دلیل شدت عالئم در خواست scan CT/CXRشده است, کاهش یافته های قبلی درتصویربرداری دیده شده و ضایعه جدیدی ایجاد نشده باشد
- بیمار نیاز به درمان داخل وریدی نداشته و تحمل خوراکی داشته باشد
- ***در حال حاضر انجام PCR-RTجزو معیارهای پیش نیاز ترخیص نمی باشد ولی در موارد زیر و متناسب باامکانات و شرایط بیمار و محل نگهداری پس از ترخیص, ممکن است توصیه شود:***
- بیماران با نقص ایمنی زمینه ای
- بیمارانی که قرار است به واحد های مراکز مراقبت درازمدت منتقل شوند الزام است همه بیماران و افراد خانواده آنها قبل از ترخیص آموزش های الزم در مورد تداوم پیشگیری از انتشار ویروس و جداسازی, خود ارزیابی و خود مراقبتی را دریافت کرده و با علائم هشدار برگشت بیماری آشنا شده باشند.

معیار های ترخیص

- همواره دید و تصمیم بالینی پزشک , مهمترین تعیین کننده زمان ترخیص بیماران خواهد بود. توجه به نکات زیرکمک کننده خواهد بود:
- برای ترخیص بیماران بستری در بیمارستان, باید معیار های زیر وجود داشته باشد:
- حداقل به مدت ۴۸-۲۴ ساعت تب بدون استفاده از تب بر قطع شده باشد و
- علائم تنفسی نظیر سرفه , در حال بهبودی باشد)قطع سرفه پایدار(و تنگی نفس نداشته باشد و
- SpO2 ≤۹۳%بدون ونتیلاتور در هوای اتاق بوده و یا در صورت پایین بودن آن, ضمن داشتن سایرکرایتریای
- ترخیص, باید طی دو تا سه روز متوالی سطح اشباع اکسیژن در حد قابل قبولی تثبیت شده)SpO2 ≤۹۰%(
- و افت پیدا نکند)
- در افراد با بیماری تنفسی زمینه ای می توان بر اساس قضاوت بالینی پزشک, SpO2<۸۸%را برای تثبیت می تواند در نظر گرفته شود
- سایر علائم حیاتی بیمار به تشخیص پزشک معالج پایدار شده باشد


thank
you