COVID-19

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WHAT IS COVID -19

- COVID-19 is the disease caused by a new coronavirus called SARS-CoV-2. WHO first learned of this new virus on 31 December 2019, following a report of a cluster of cases of ‘viral pneumonia’ in Wuhan, People’s Republic of China.

SUSPICIOUS

- یافته های بالینی:

شروع ناگهانی تب و سرفه یا

شروع ناگهانی حداقل سه یا بیشتر از عالئمی چون تب، سرفه، ضعف عمومی/خستگی مفرط، سردرد، درد عضلانی، گلو درد، آبریزش بینی، تنگی نفس، بی اشتهایی/تهوع/استفراغ، اسهال، کاهش سطح هوشیاری +

اقامت، اشتغال یا مسافرت به مناطقی که احتمال چرخش ویروس وجود دارد)نظیر مراکز اقامتی ، محل های پرازدحام، همایش ها و مراسم ها، مراکز بهداشتی-درمانی و ...(در طی 14 روز گذشته)

POSSIBLE

- بیمار مشکوکی که در تماس با یک بیمار محتمل یا قطعی
- بیمار مشکوکی که یافته های تصویر برداری به نفع کووید-19 داشته باشد
- بیماری که بطور حاد دچار از دست دادن حس بویایی یا چشایی شده باشد
- مرگ در بیمار مشکوک به کووید که با دلیل دیگری توجیه نشود

DEFINITIVE

- فرد با تایید آزمایشگاهی ویروس ناشی از کووید-19 ،صرف نظر از وجود عالئم و نشانه های بالینی

- **Non-severe COVID-19** – Defined as absence of any criteria for severe or critical COVID-19

SEVERE COVID-19 – DEFINED BY ANY OF

- :
  - Oxygen saturation < 90% on room air;
  - in adults, signs of severe respiratory distress (accessory muscle use, inability to complete full sentences, respiratory rate > 30 breaths per minute), and, in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs (inability to breastfeed or drink, lethargy or reduced level of consciousness, convulsions) in addition to the signs of pneumonia.

CRITICAL COVID-19 – DEFINED BY

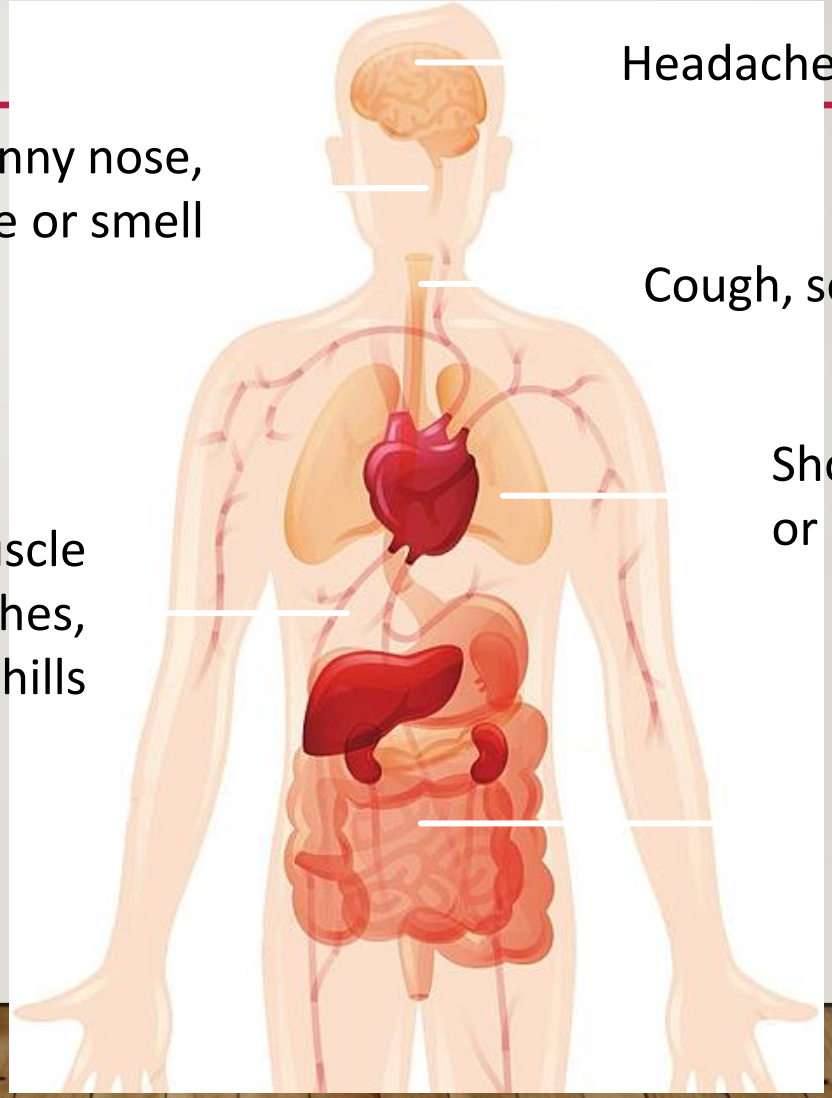
- the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions that would normally require the provision of life-sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.

CLINICAL PRESENTATION

- The incubation period for COVID-19 is thought to extend to 14 days, with a median time of 4-5 days from exposure to symptoms onset.[1-3] One study reported that 97.5% of people with COVID-19 who have symptoms will do so within 11.5 days of SARS-CoV-2 infection.

PRIMARY SYMPTOMS OF COVID-19

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



Li. J Med Virol. 2020;92:577.
https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html

Slide credit: clinicaloptions.com

SYMPTOM OF COVID -19

- The most common symptoms of COVID-19 are
- Fever
- Dry cough
- Fatigue

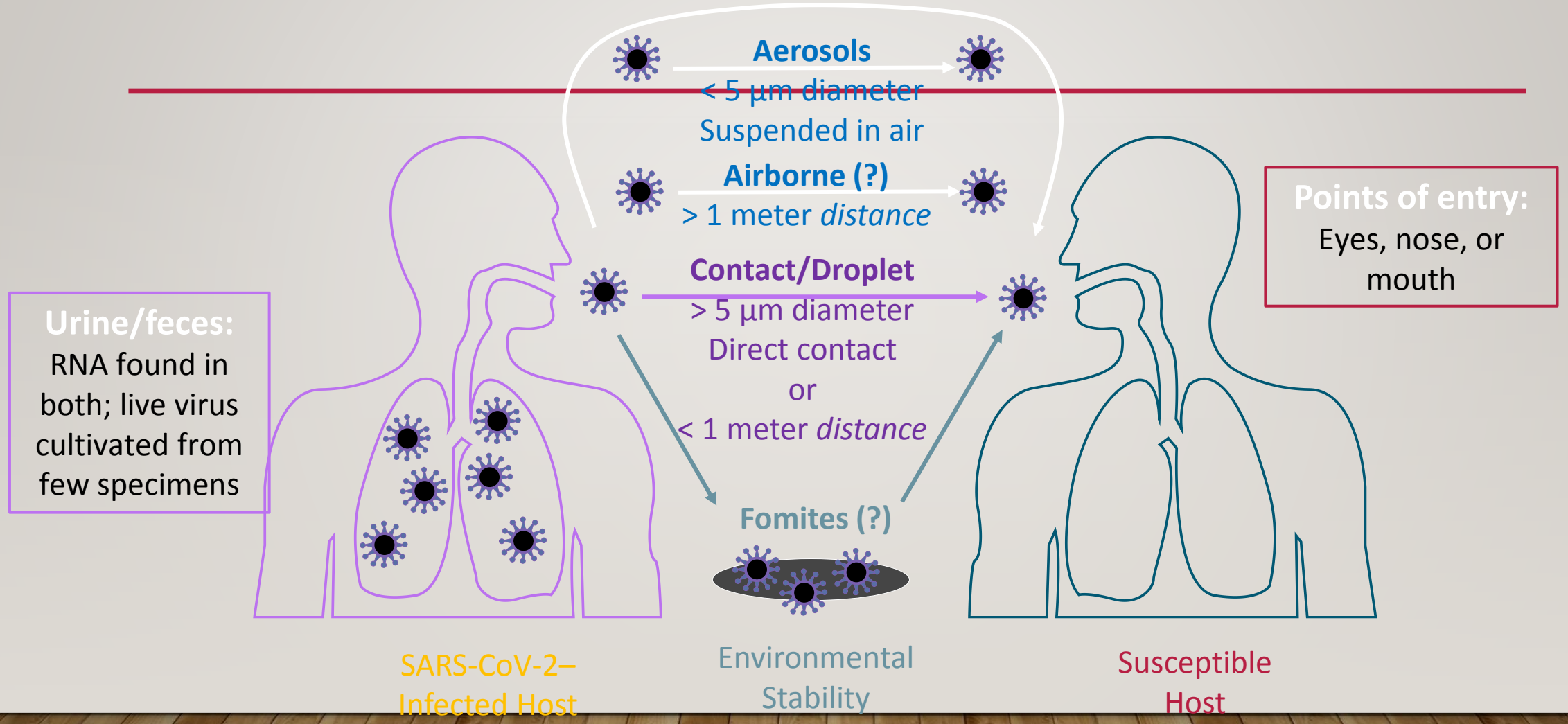
PRESENTATION

- Fever or chills
- Cough
- Shortness of breath or difficulty breathing
- Fatigue
- Muscle or body aches
- Headache

PRESENTATION

- New loss of taste or smell
- Sore throat
- Congestion or runny nose
- Nausea or vomiting
- Diarrhea

PROPOSED ROUTES OF SARS-COV-2 TRANSMISSION



Galbadage. Front Public Health. 2020;8:163. WHO. Scientific Brief. July 9, 2020.

Slide credit: clinicaloptions.com

اندیکاسیون ارجاع به بیمارستان

1- شروع علائم پنومونی یا هایپوکسی

2- احساس گیجی یا کاهش سطح هوشیاری

3- هموپیتیزی (خلط خونی)

4- اختلالات همودینامیک

COMMON COVID-19 DIAGNOSTIC METHODS: RNA

Viral Nucleic Acid Assays	
Typically indicate	▪ Current infection
Specimen sources	▪ Upper (eg, nasopharyngeal swabs or washes, oropharyngeal swabs, nasal aspirates) or lower (eg, sputum, bronchoalveolar lavage fluid, tracheal aspirates) respiratory tract
Considerations	▪ Primary method for COVID-19 diagnosis with multiple RT-PCR kits available ▪ False negatives may result from improper sampling or handling, low viral load, or viral mutations ▪ SARS-CoV-2 RNA undetectable by ~ Day 14 following onset of illness in some cases/samples

Udugama. ACS Nano. 2020;14:3822. Lee. Front Immunol. 2020;11:879.

FACTORS POTENTIALLY LEADING TO NEGATIVE RESULT IN AN INFECTED INDIVIDUAL

- Poor specimen quality
- Timing of specimen collection
- (very early or late in infection)
- Specimen was not handled appropriately
- Technical reasons inherent in test
- (virus mutation or PCR inhibition)

DIAGNOSTIC MEASURE

- Global covid -19 RT- PCR (recommended)
- Serologic test (not recommended)
- Chest CT scan

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

NIH COVID-19 Treatment Guidelines. Management of persons with COVID-19. Last updated June 11, 2020.

Slide credit: clinicaloptions.com

MILD ILLNESS

علائم خفیف بصورت تب کمتر از 38 درجه
گلودرد با یا بدون سرفه های خشک
لرز
سردرد
از دست دادن حس چشایی و بویایی
تهوع، استفراغ، بی اشتهایی، اسهال،
بدن درد
ضعف و خستگی مفرط است.

MILD ILLNESS

در این مرحله علائم حیاتی (نبض، فشارخون و تعداد تنفس) پایدار
SPO2بالای 93% است .

LAB TESTMILD ILLNESS

- LYMPHOPENIA LOWER 1100
- MILD INCREASE :ESR ,CRP
- LUNG CT SCAN : NOT CHANGE
- INVOVEMENT OF MAXIMUM 2 LUNG LOBES (GGO , CONSOLIDATION , NODULE)

مرحله تنفسی

- فاز تنفسی شامل دوقسمت متوسط وشدید
- فاز متوسط : تنگی نفس ، احساس درد و فشار در قفسه سینه ، تب بیشتر از 38
- سطح اشباع اکسیژن بین 90 تا93%
- درگیری ریه کمتر از 50%

LAB TEST MODERATE PULMONARY PHASE

LYMPHOPENIA LOWER 1100

INCREASE : ESR ,CRP ,PT,PTT.

INCREASE : LDH

INCREASE : FERRITIN

INCREASE : D.DIMER

INCREASE THE NUMBER OF LOBES INVOLVED & ITS SIZE

SEVER PULMONARY PHASE

- AGGRAVATION OF SHORTNESS OF BREATH
- RR > 30
- SPO2< 90%
- PaO2/FIO2 >300
- CTSCAN : > 50% LUNG INVOLVEMENT

LAB TEST SEVER PULMONARY PHASE

- EXACERBATION OF LYMPHOPENIA
- PROGRESSIVE INCREASE D.DIMER
- LDH>245
- RISE AMINOTRANSFEREAS
- CRP>100
- INCREASE IL-6
- TROMBOCYTOPENIA

LAB TEST SEVER PULMONARY PHASE

- INCREASE TROPONIN
- CHEST CT SCAN : >50% OF LUNGS ARE INVOLVED . DIFFUSE & BILATERAL INFILTERATION

CRITICAL PHASE

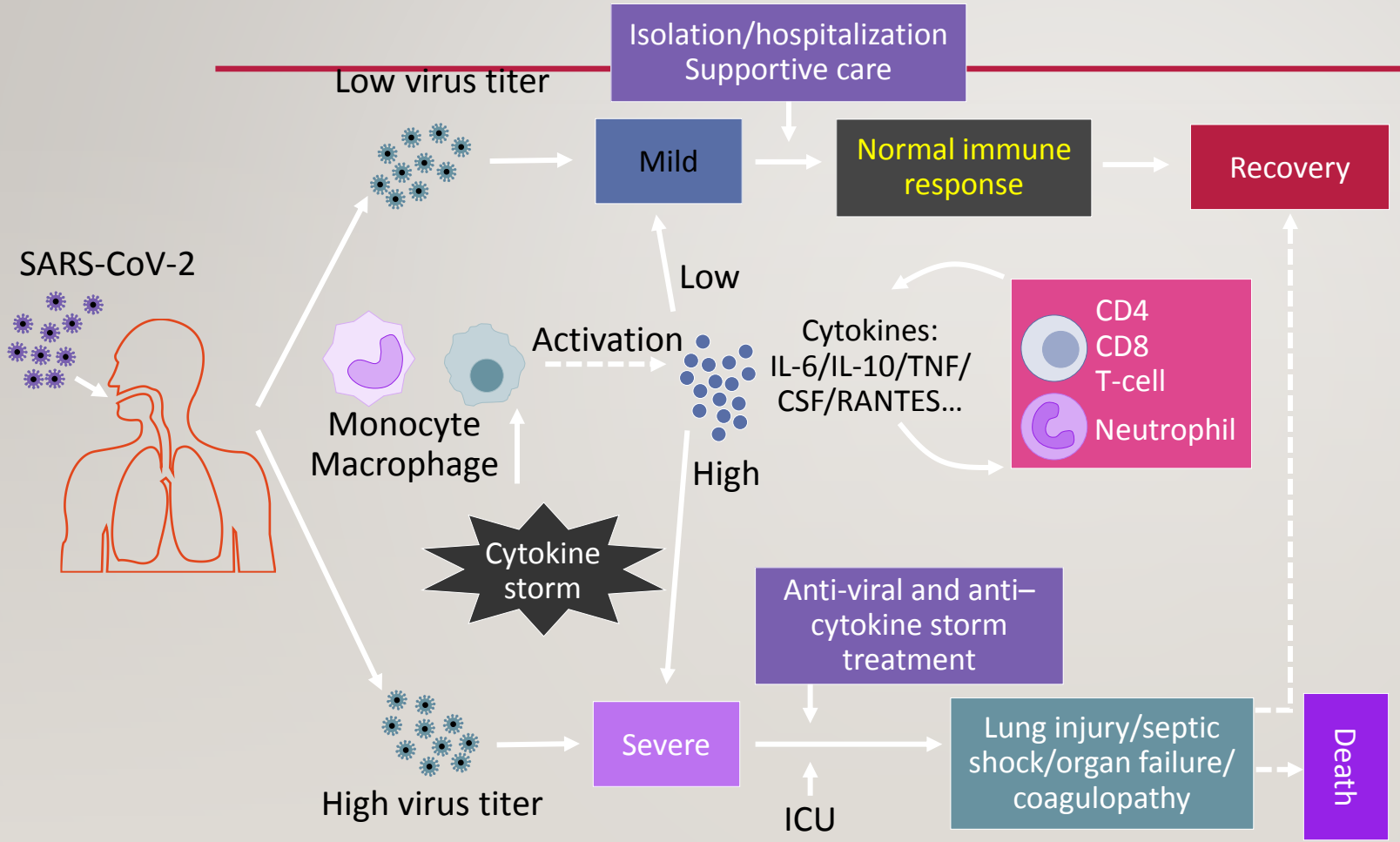
- RESPIRATORY FAILURE
- SPO2 < 88%
- SHOCK SYMPTOMS
- MULTI ORGAN FAILURE

LAB TEST CRITICAL PHASE

- EXACERBATION OF LYMPHOPENIA
- D.DIMER>1000
- FERRITIN > 1000
- AST/ALT>5 TIMES
- THROMBOCYTOPENIA
- RISE BUN/CR , COAGULATION DISORDER
- CHEST CT SCAN : ARDS , PLURAL EFFUSION,…
-

IMMUNE RESPONSE TO SARS-COV-2

Immune Responses Leading to Recovery or Death[1]



Adequate immune responses[2]

- Timely innate/adaptive responses
- Quick type 1 IFN response
- Activation of efficient antiviral response (clearance by macrophages)
- Activation of Th1 cells and B-cells for production of neutralizing antibodies

Inadequate immune responses[2]

- Delayed/limited type 1 IFN
- Endothelial cell death
- Epithelial/endothelial leakage
- Overactivation/exhaustion T-cells and NK cells
- Accumulation of activated macrophages → cytokine storm

1. Wang. J Leukoc Biol. 2020;108:17. 2. Sokolowska. Allergy. 2020;75:2445.

Slide credit: clinicaloptions.com

RX MILD COVID-19

- 1st line : consider home isolation
- Plus : monitoring
- Plus : symptom management , supporting care
- Consider : antipyretic / analgesic
- Consider : experimental therapy

RX MODERATE COVID-19

- 1st consider home isolation or hospital admission
- plus monitoring
- plus symptom management and supportive care
- consider antipyretic/analgesic
- consider experimental therapies

SEVERE COVID-19

- 1st hospital admission
- plus consider oxygen therapy
- plus symptom management and supportive care
- plus venous thromboembolism prophylaxis
- plus monitoring

SEVERE COVID-19

- consider corticosteroid
- consider interleukin-6 (IL-6) inhibitor
- consider treatment of co-infections
- consider antipyretic/analgesic
- consider experimental therapies
- consider plan for discharge and rehabilitation
- consider palliative care

CRITICAL COVID-19

- 1st intensive/critical care unit admission
- plus symptom management and supportive care
- plus venous thromboembolism prophylaxis
- plus consider high-flow nasal oxygen or noninvasive ventilation
- plus consider invasive mechanical ventilation
- consider inhaled pulmonary vasodilator
- consider extracorporeal membrane oxygenation

CRITICAL COVID-19

- consider management of sepsis/septic shock
- consider corticosteroid
- consider interleukin-6 (IL-6) inhibitor
- consider treatment of co-infections
- consider experimental therapies
- consider plan for discharge and rehabilitation
- consider palliative care

KEY THERAPEUTIC CLASSES UNDER INVESTIGATION FOR TREATMENT OF COVID-19

Antivirals

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

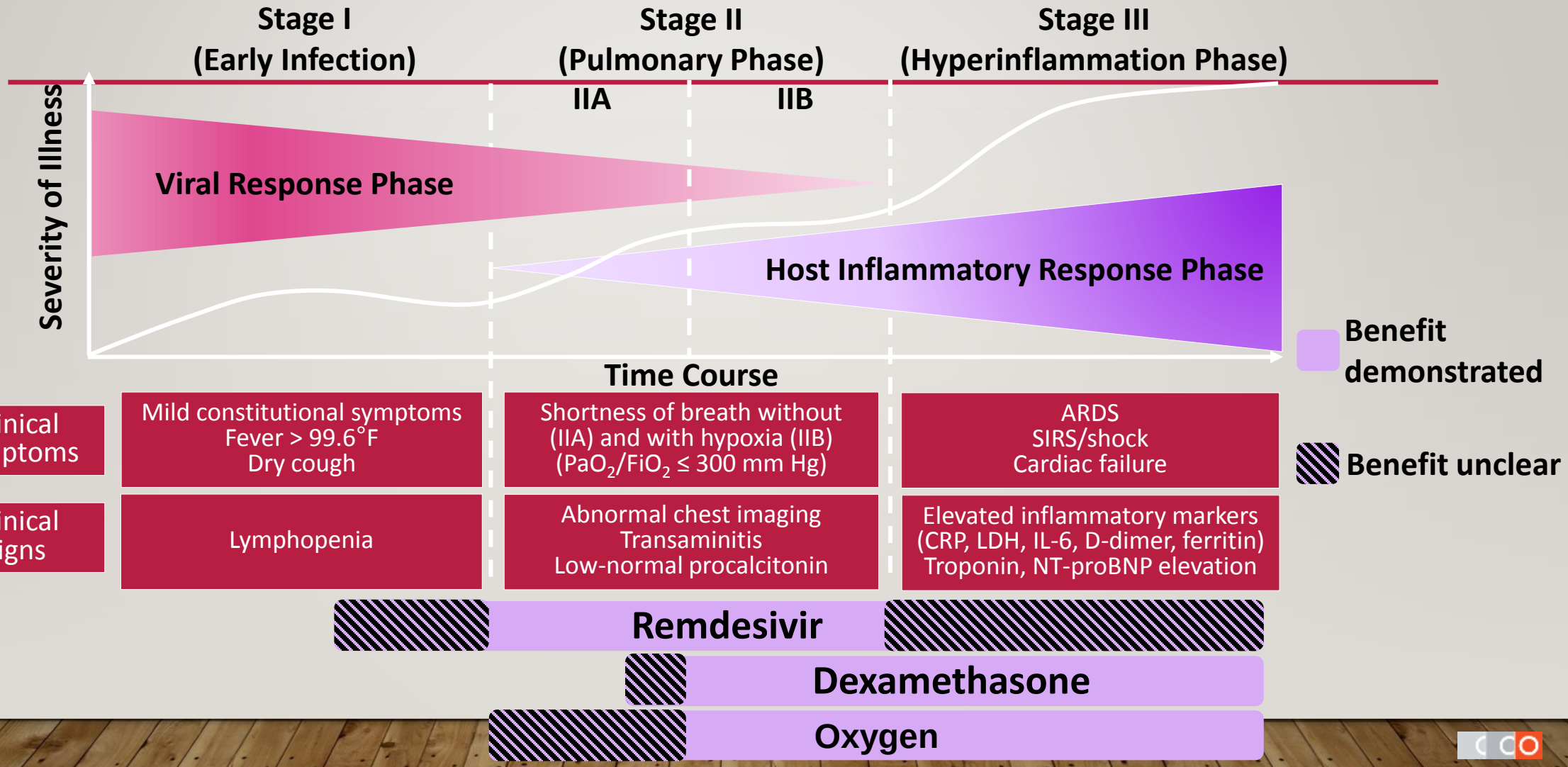
Immunomodulators

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

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

Slide credit: clinicaloptions.com

COVID-19 THERAPIES PREDICTED TO PROVIDE BENEFIT AT DIFFERENT STAGES



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

Slide credit: clinicaloptions.com

Updated

FDA APPROVAL FOR REMDESIVIR: SAFETY INFORMATION AND WARNINGS

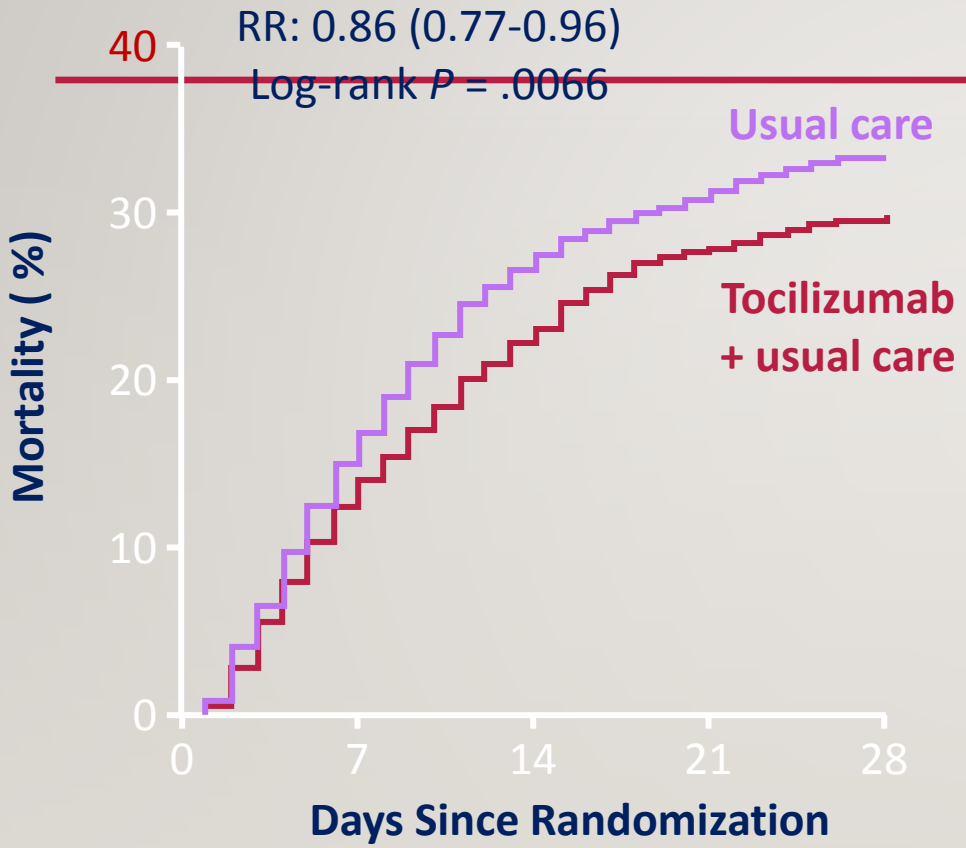
- **Contraindicated in** patients with a history of clinically significant hypersensitivity reactions to remdesivir or any components
- **Not recommended** for patients with eGFR < 30 mL/min
- **Warnings and precautions:**
  - **Hypersensitivity reactions** have occurred in patients receiving remdesivir; immediately discontinue if signs of a clinically significant reaction occur
  - **Transaminase elevations** have occurred in healthy volunteers and patients with COVID-19 receiving remdesivir; consider discontinuing if ALT > 10 x ULN

IL-6 RECEPTOR BLOCKERS

- treatment with IL-6 receptor blockers (tocilizumab or sarilumab) for patients with severe or critical COVID-19 infection.

RECOVERY: RESULTS FOR TOCILIZUMAB + USUAL CARE VS USUAL CARE ALONE

New



- Secondary endpoint:
  reduced receipt of mechanical ventilation in patients not receiving ventilation at time of randomization
  - 12% with tocilizumab vs 15% with usual care (RR: 0.81; 95% CI: 0.68-0.95)

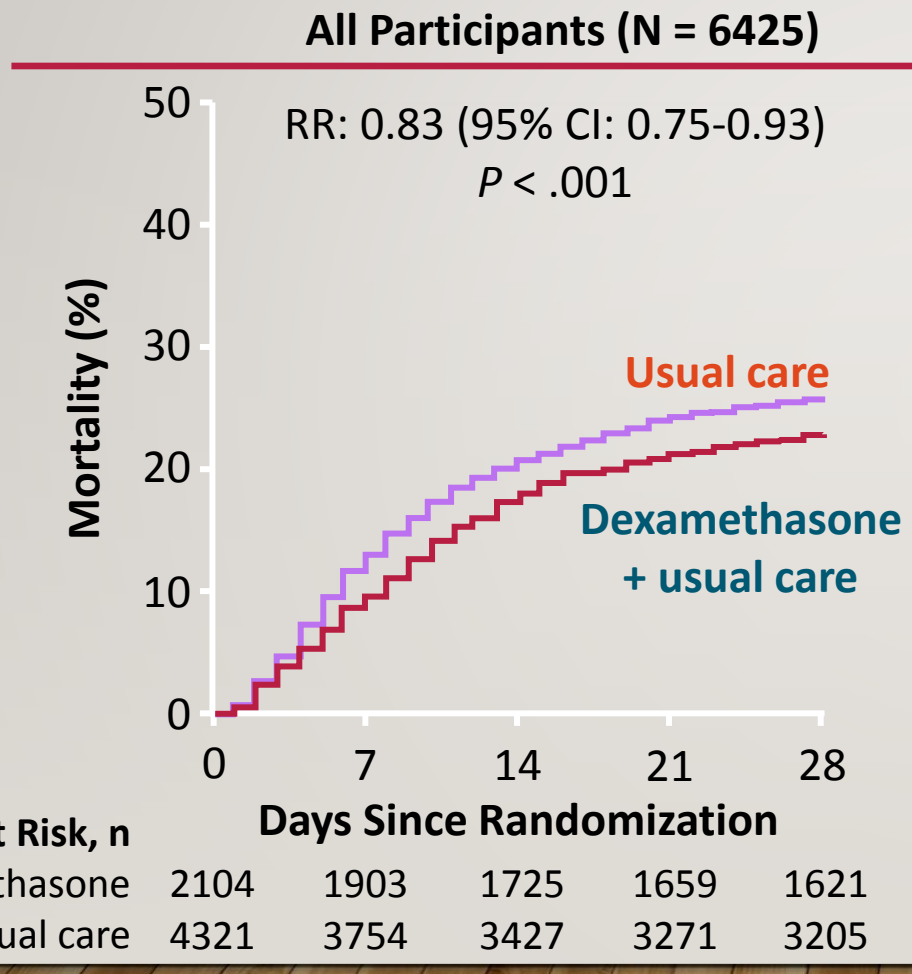
Recovery Collaborative Group. medRxiv. 2021;[Preprint]. Note: this study has not been peer reviewed.

Slide credit: clinicaloptions.com

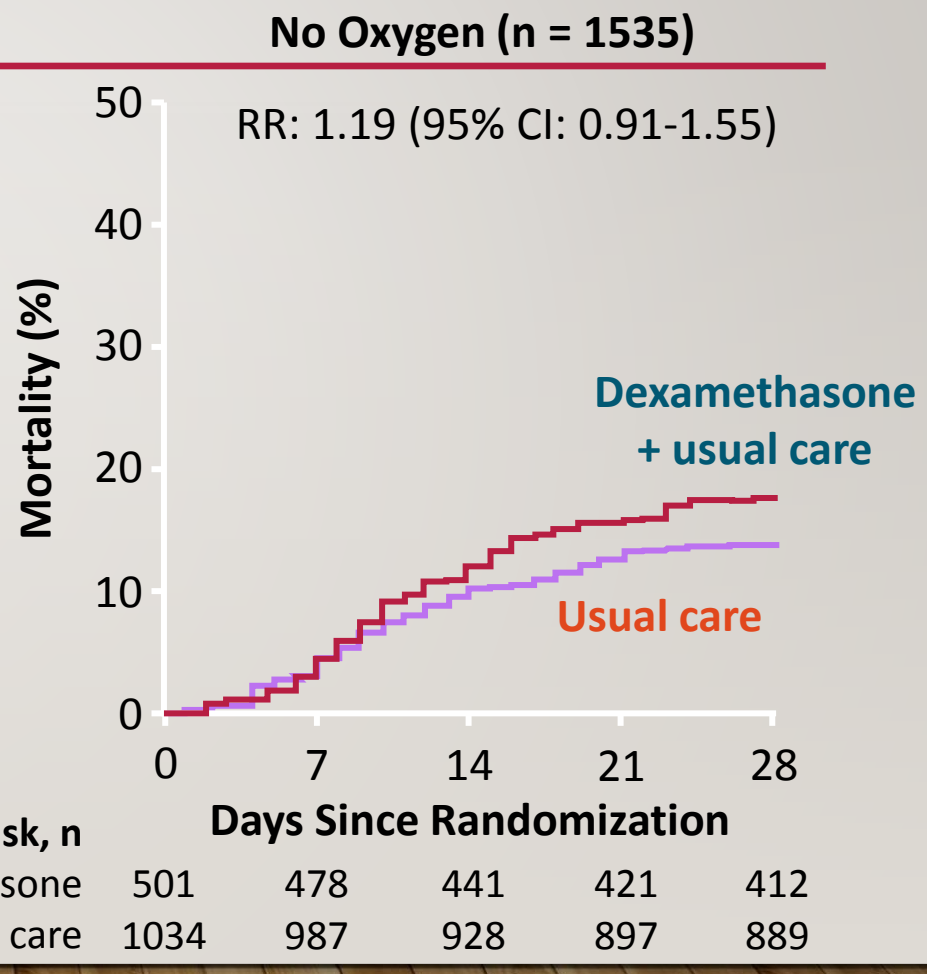
SYSTEMIC CORTICOSTEROIDS

- Corticosteroid regimens included: methylprednisolone 40 mg every 12 hours for 3 days and then 20 mg every 12 hours for 3 days (GLUCOCOVID) [76]; dexamethasone 20 mg daily for 5 days followed by 10 mg daily for 5 days (two trials, DEXA-COVID19, CoDEX) [77][78]; hydrocortisone 200 mg daily for 4 to 7 days followed by 100 mg daily for 2 to 4 days and then 50 mg daily for 2 to 3 days (one trial, CAPE-COVID)

RECOVERY TRIAL: MORTALITY WITH DEXAMETHASONE + USUAL CARE VS USUAL CARE ALONE

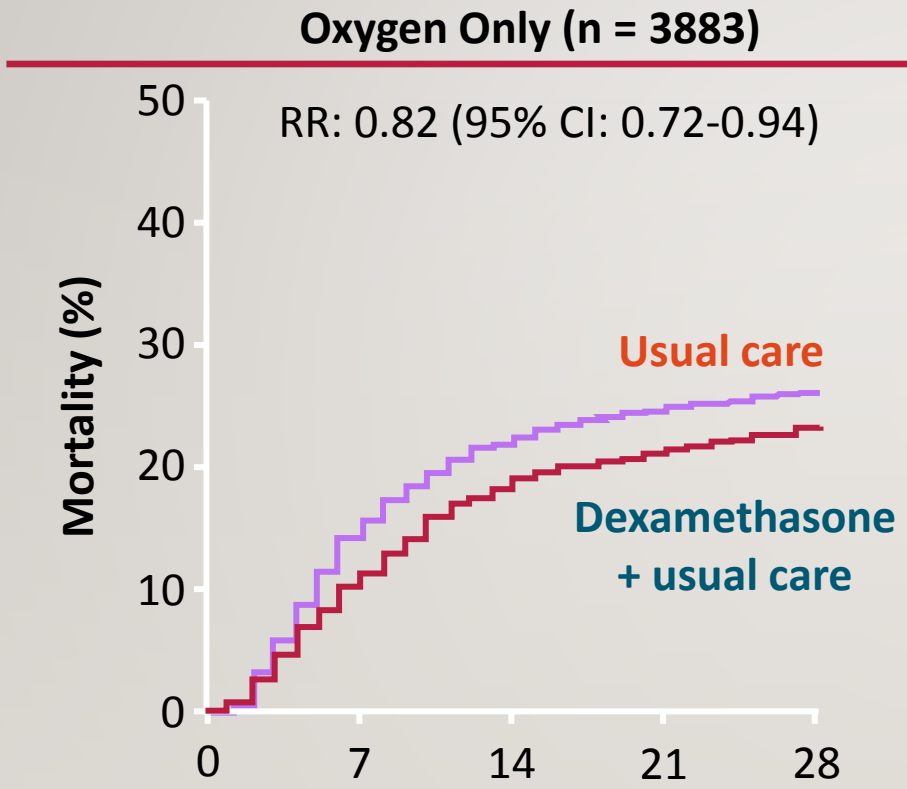


Patients at Risk, n					
Dexamethasone	2104	1903	1725	1659	1621
Usual care	4321	3754	3427	3271	3205

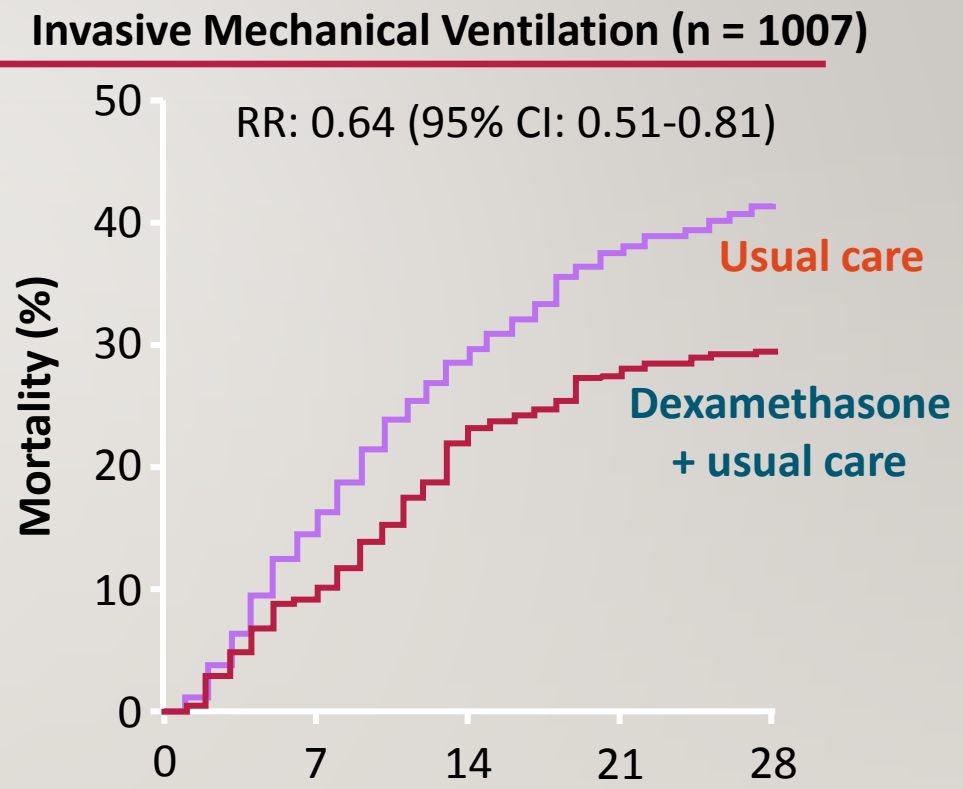


Patients at Risk, n					
Dexamethasone	501	478	441	421	412
Usual care	1034	987	928	897	889

RECOVERY TRIAL: MORTALITY IN PATIENTS ON OXYGEN OR MECHANICAL VENTILATION ± DEXAMETHASONE



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



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

RECOVERY Collaborative Group. NEJM. 2021;384:693.

Slide credit: clinicaloptions.com

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
Nonsevere 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.

CASIRIVIMAB AND IMDEVIMAB (NEUTRALIZING MONOCLONAL ANTIBODIES)

- treatment with casirivimab and imdevimab, conditional to those at highest risk of hospitalization
- typical characteristics of people at highest risk include lack of vaccination, older people, or those with immunodeficiencies and/or chronic diseases (e.g. diabetes).

FDA EUA FOR CASIRIVIMAB + IMDEVIMAB

" . . . permit the emergency use of the unapproved product, casirivimab with imdevimab to be administered together, for the treatment of mild to moderate COVID-19 in adults and pediatric patients (≥ 12 yrs of age weighing ≥ 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are ***at high risk for progressing to severe COVID-19 and/or hospitalization****."*

- Must be administered by single IV infusion (1200 mg casirivimab + 1200 mg imdevimab over ≥ 60 mins) following dilution
- Should be given as soon as possible after positive SARS-CoV-2 viral test, within 10 days of symptom onset
- No recommended dose adjustments for pregnant or lactating women, patients with renal impairment

Casirivimab With Imdevimab. EUA Fact Sheet for Healthcare Providers. Last updated February 2021.

Slide credit: clinicaloptions.com

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

FDA EUA FOR BARICITINIB

". . . permit the emergency use of ***baricitinib, in combination with remdesivir,*** *for treatment of suspected or laboratory confirmed COVID-19 in hospitalized adults and pediatric patients ≥ 2 yrs of age requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)."*

- **Recommended dosage under EUA:**
  - Adults and pediatric patients ≥ 9 yrs of age: 4 mg orally once daily
  - Pediatric patients 2 yrs to < 9 yrs of age: 2 mg orally once daily
  - Optimal duration of treatment unknown; 14 days or until hospital discharge (if first) recommended
- eGFR, aminotransferase levels, and CBC with differential must be determined before first dose

Baricitinib. EUA Fact Sheet for Healthcare Providers. Last updated November 2020.

Slide credit: clinicaloptions.com

BARICITINIB EUA: CONTRAINDICATIONS AND WARNINGS

- **No known contraindications**
- **Hypersensitivity:**
  - If serious hypersensitivity occurs, discontinue baricitinib
- **Serious infections:**
  - Serious infections have occurred in patients receiving baricitinib
  - Avoid use in cases of known active tuberculosis
  - Weigh potential benefits vs risks in situations with active coinfections other than COVID-19
- **Thrombosis:**
  - In hospitalized patients with COVID-19, VTE prophylaxis recommended, unless contraindicated
- **Vaccinations:**
  - Avoid use of live vaccines with baricitinib
- **Abnormal laboratory values:**
  - Evaluate at baseline and thereafter according to management practice
  - Dose adjustments for patients with abnormal renal, hepatic, and hematologic values

Baricitinib. EUA Fact Sheet for Healthcare Providers. Last updated November 2020.

Slide credit: clinicaloptions.com

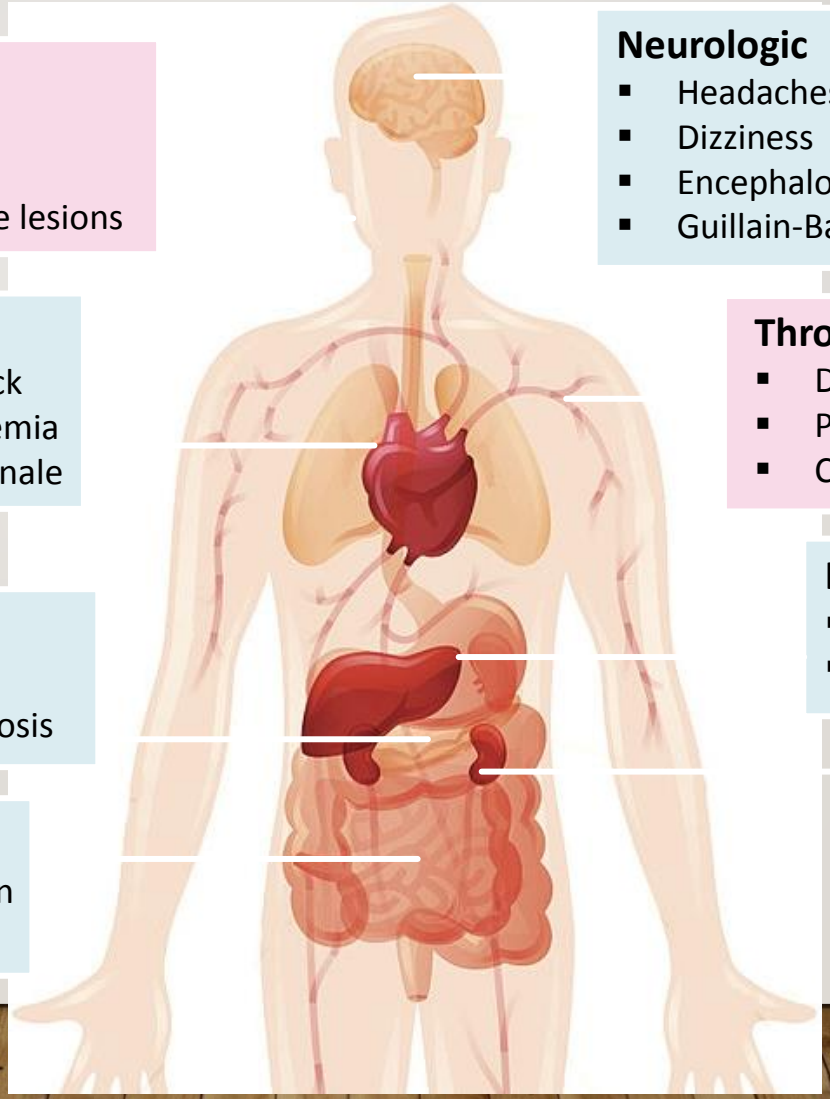
EXTRAPULMONARY MANIFESTATIONS

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



Endocrine
- Hyperglycemia
- Diabetic ketoacidosis

Hepatic
- Elevated ALT/AST
- Elevated bilirubin

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

Renal
- Acute kidney injury
- Proteinuria
- Hematuria

Gupta. Nat Med. 2020;26:1017.

Slide credit: clinicaloptions.com

CDC: DISCONTINUATION OF TRANSMISSION-BASED PRECAUTIONS FOR PATIENTS WITH CONFIRMED SARS-COV-2

Updated

Symptom-Based Strategy*

≥ 24 hrs since resolution
of fever, last antipyretics

And

Improvement in symptoms
(eg, cough, shortness of breath)

And

≥ 10 days since symptom onset
for mild to moderate illness,
10-20 days for severe to critical illness
or those severely immunocompromised

Test-Based Strategy

Not generally recommended because *"in the majority of cases, it results in prolonged isolation of patients who continue to shed detectable SARS-CoV-2 RNA but are no longer infectious"*

*If patient is asymptomatic, not severely immunocompromised, precautions may be discontinued ≥ 10 days after positive viral test.

https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-hospitalized-patients.html

Slide credit: clinicaloptions.com

DISCHARGE

- 1- بهترشدن حال عمومی ، افزایش اشباع سطح اکسیژن ، بدون دیسترس تنفسی
- 2- نداشتن تب به مدت 3 روز
- 3- -decease ESR , CRP ,increase lymphocyte (helper)

THANKS FOR ATTENTION