COVID-19 Update May 10, 2021

464 Days Later!!!

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A guideline to limit indoor airborne transmission of COVID-19

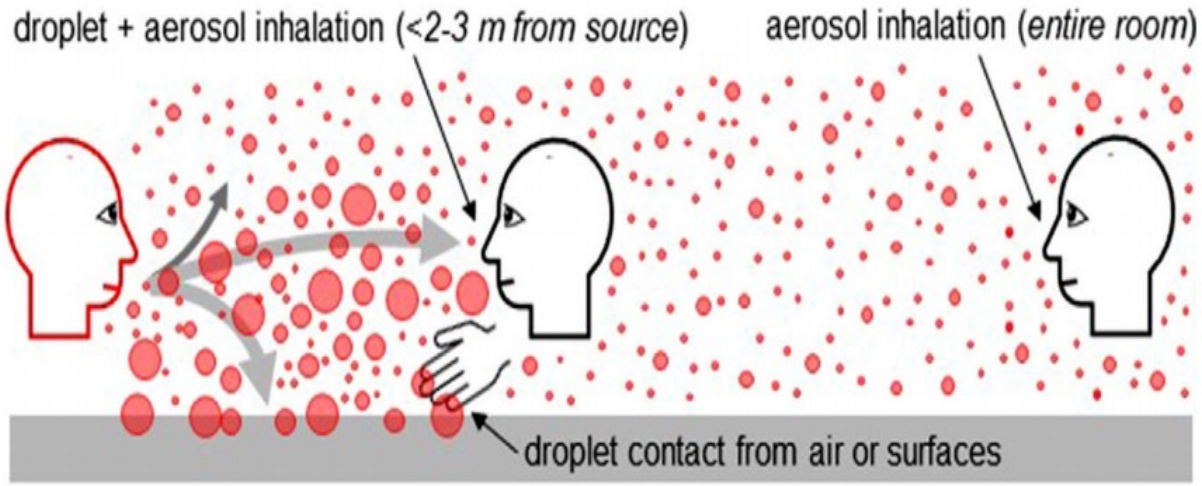
SARS-CoV-2 is known to be transported by respiratory droplets exhaled by an infected persons.

There are thought to be three possible routes of human-to-human transmission of COVID-19:

- Large droplets inhaled or auto inoculated
- Short range airborne transmitted aerosols
- Large range airborne transmitted aerosols

”The distinction between large-drop and airborne transmission is somewhat nebulous given the continuum of sizes of emitted droplets”

PNAS April 27, 2021, 118 (17) e2018995118



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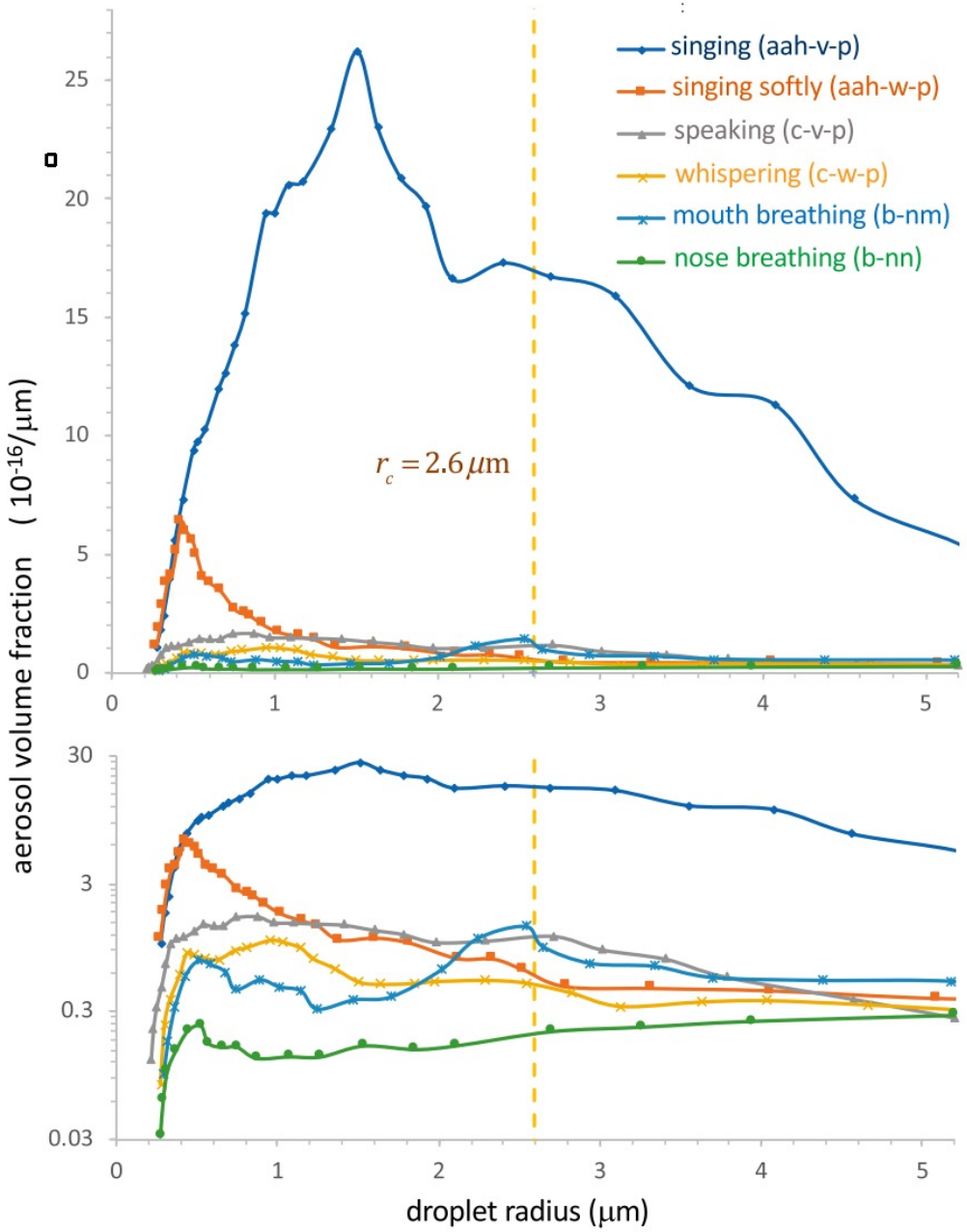
A guideline to limit indoor airborne transmission of COVID-19



CDC Update May 7,2021: SARS-CoV-2 and Aerosol Transmission

The principal mode by which people are infected with SARS-CoV-2 is through exposure to infectious respiratory fluids carrying infectious virus.

People release respiratory fluids during exhalation (e.g., quiet breathing, speaking, singing, exercise, coughing, sneezing) in the form of droplets across a spectrum of sizes.

- These droplets carry virus and transmit infection.
- The largest droplets settle out of the air rapidly, within seconds to minutes.
- The smallest very fine droplets, and aerosol particles formed when these fine droplets rapidly dry, are small enough that they can remain suspended in the air for minutes to hours.

Infectious exposures to respiratory fluids carrying SARS-CoV-2 occur in three principal ways (not mutually exclusive):

- **Inhalation** of air carrying very small fine droplets and aerosol particles that contain infectious virus. Risk of transmission is greatest within three to six feet of an infectious source where the concentration of these very fine droplets and particles is greatest.
- **Deposition** of virus carried in exhaled droplets and particles onto exposed mucous membranes (i.e., “splashes and sprays”, such as being coughed on). Risk of transmission is likewise greatest close to an infectious source where the concentration of these exhaled droplets and particles is greatest.
- **Touching** mucous membranes with hands soiled by exhaled respiratory fluids containing virus or from touching inanimate surfaces contaminated with virus.

https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/sars-cov-2-transmission.html

The risk of SARS-CoV-2 infection varies according to the amount of virus to which a person is exposed

Once infectious droplets and particles are exhaled, they move outward from the source.

The risk for infection decreases with increasing distance from the source and increasing time after exhalation.

Two principal processes determine the amount of virus to which a person is exposed in the air or by touching a surface contaminated by virus:

- **Decreasing concentration of virus in the air** as larger and heavier respiratory droplets containing virus fall to the ground or other surfaces under the force of gravity and the very fine droplets and aerosol particles that remain in the airstream progressively mix with, and become diluted within, the growing volume and streams of air they encounter. ***This mixing is not necessarily uniform and can be influenced by thermal layering and initial jetting of exhalations.***
- **Progressive loss of viral viability and infectiousness** over time influenced by environmental factors such as temperature, humidity, and ultraviolet radiation (e.g., sunlight).

https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/sars-cov-2-transmission.html

Transmission of SARS-CoV-2 from inhalation of virus in the air farther than six feet from an infectious source can occur

With increasing distance from the source, the role of inhalation likewise increases.

Although infections through inhalation at distances greater than six feet from an infectious source are less likely than at closer distances

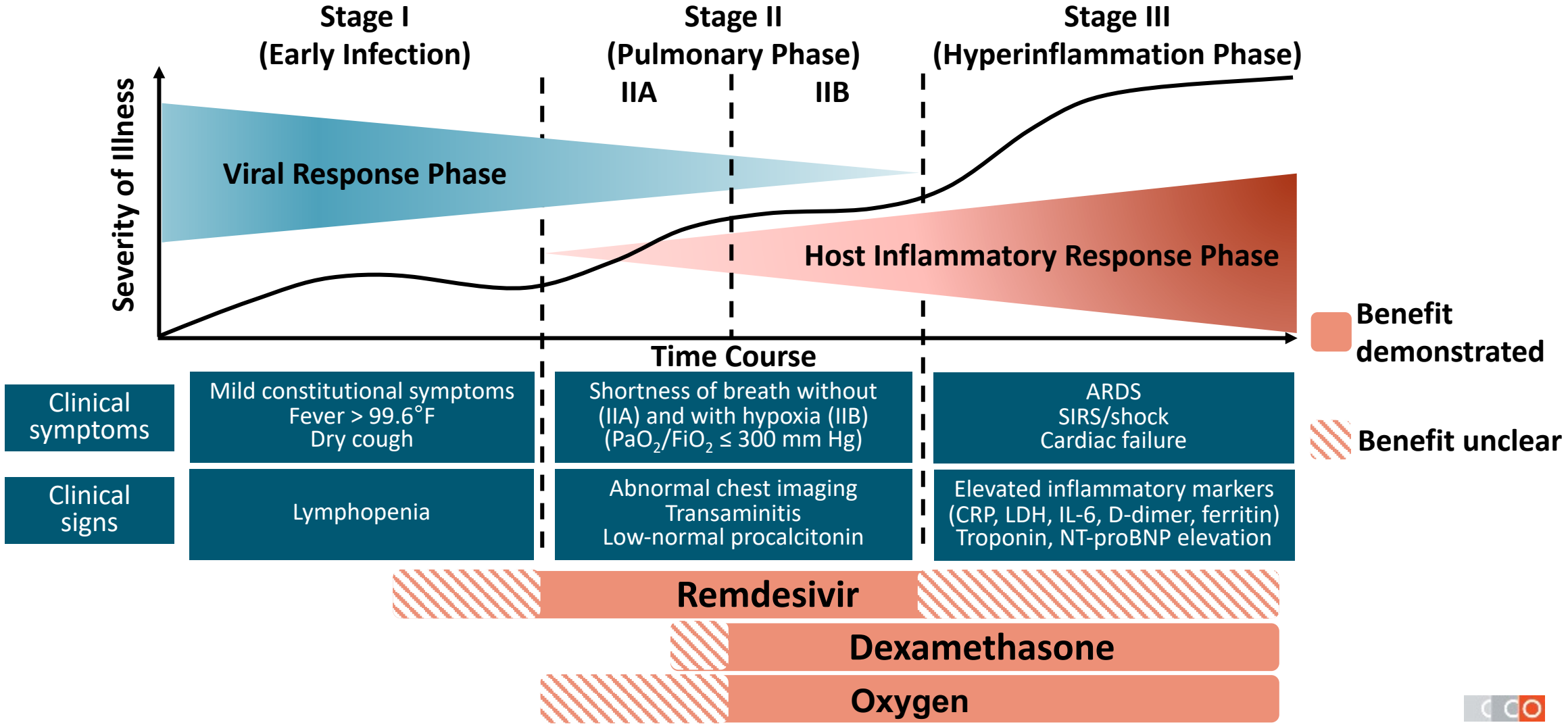
- The phenomenon has been repeatedly documented under certain preventable circumstances.
- These transmission events have involved the presence of an infectious person exhaling virus indoors for an extended time (more than 15 minutes and in some cases hours) leading to virus concentrations in the air space sufficient to transmit infections to people more than 6 feet away, **and in some cases to people who have passed through that space soon after the infectious person left.**

Per published reports, factors that increase the risk of SARS-CoV-2 infection under these circumstances include:

- **Enclosed spaces with inadequate ventilation or air handling** within which the concentration of exhaled respiratory fluids, especially very fine droplets and aerosol particles, can build-up in the air space.
- **Increased exhalation** of respiratory fluids if the infectious person is engaged in physical exertion or raises their voice (e.g., exercising, shouting, singing).
- **Prolonged exposure** to these conditions, typically more than 15 minutes.

https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/sars-cov-2-transmission.html

COVID-19 Therapies Predicted to Provide Benefit at Different Stages



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

Slide credit: clinicaloptions.com

NIH Guidelines: Therapeutic Management

Disease Severity	Recommendation
Not hospitalized, mild to moderate COVID-19	▪ **Bamlanivimab** plus **etesevimab** ***recommended*** if high risk of clinical progression as defined by EUA ▪ **Bamlanivimab** and **casirivimab plus imdevimab** ***available through EUAs*** if high risk of disease progression (***insufficient data*** to recommend for or against) ▪ ***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.

Bamlanivimab: 700 mg IV once, as soon as possible after positive SARS-CoV-2 Ag test or NAAT and within 10 days of symptom onset.

Baricitinib: 4 mg PO QD for 14 days or until discharge.

Dexamethasone: 6 mg IV or PO QD for 10 days or until discharge.

Etesevimab: 1400 mg IV once, as soon as possible after positive SARS-CoV-2 Ag test or NAAT and within 10 days of symptom onset.

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.

NIH COVID-19 Treatment Guidelines. Therapeutic management of adults with COVID-19. Last updated February 11, 2021.
NIH COVID-19 Treatment Guidelines. Statement on bamlanivimab plus etesevimab EUA. Last updated March 2, 2021.

NIH Guidelines: Investigational COVID-19 Treatments

Antivirals[1]

Guidance	Treatment
Recommends against	▪ High-dose chloroquine (600 mg BID for 10 days) ▪ (Hydroxy)chloroquine ± azithromycin for hospitalized patients ▪ Lopinavir/ritonavir or other HIV protease inhibitors
Recommends against except in a clinical trial	▪ (Hydroxy)chloroquine ± azithromycin for non-hospitalized patients
Insufficient data to recommend for or against	▪ 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 ▪ Baricitinib + corticosteroids ▪ Baricitinib + remdesivir for hospitalized patients able to use corticosteroids
Recommends against except in a clinical trial	▪ Siltuximab ▪ Baricitinib without remdesivir ▪ IFN-α/β for severe or critical COVID-19 ▪ BTK and JAK inhibitors (not baricitinib) ▪ Non-SARS-CoV-2–specific IVIG

1. NIH COVID-19 Treatment Guidelines. Antiviral drugs that are approved or under evaluation for the treatment of COVID-19. Last updated February 11, 2021.
2. NIH COVID-19 Treatment Guidelines. Anti-SARS-CoV-2 antibody products. Last updated February 11, 2021.
3. NIH COVID-19 Treatment Guidelines. Immunomodulators under evaluation for the treatment of COVID-19. Last updated February 11, 2021.

Slide credit: clinicaloptions.com

Baricitinib

Preliminary results of this study suggest that baricitinib improves time to recovery in patients who require supplemental oxygen but not invasive mechanical ventilation.

However, a key limitation of the study is the inability to evaluate the treatment effect of Baricitinib in addition to, or in comparison to, corticosteroids used as standard treatment for severe or critical COVID-19 pneumonia

https://files.covid19treatmentguidelines.nih.gov/guidelines/section/section_36.pdf

NIH Guidelines on Baricitinib

Updated

- *"There are **insufficient data** for the COVID-19 Treatment Guidelines Panel (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, when corticosteroids can be used."*
- *In the rare circumstance where corticosteroids cannot be used, the Panel **recommends** baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized, non-intubated patients who require oxygen supplementation."*
- *"The Panel **recommends against** the use of baricitinib without remdesivir, except in a clinical trial."*

NIH COVID-19 Treatment Guidelines. Kinase inhibitors. Last updated February 11, 2021.

Slide credit: clinicaloptions.com

Post Covid-19

- Definitions
- Diagnosis
- Follow-up
- Evaluation
- Management

TERMINOLOGY AND STAGES OF RECOVERY

Acute COVID-19:

- Symptoms of COVID-19 for up to 4 weeks following the onset of illness

Ongoing symptomatic COVID-19:

- Symptoms of COVID-19 from 4 to 12 weeks following the onset of illness

Post-COVID-19:

- Symptoms that develop during or after COVID-19, continue for ≥ 12 weeks, not explained by an alternative diagnosis
- These stages reflect symptomatic recovery and are **not** related to active viral infection and infectivity.

https://www.nice.org.uk/guidance/ng188

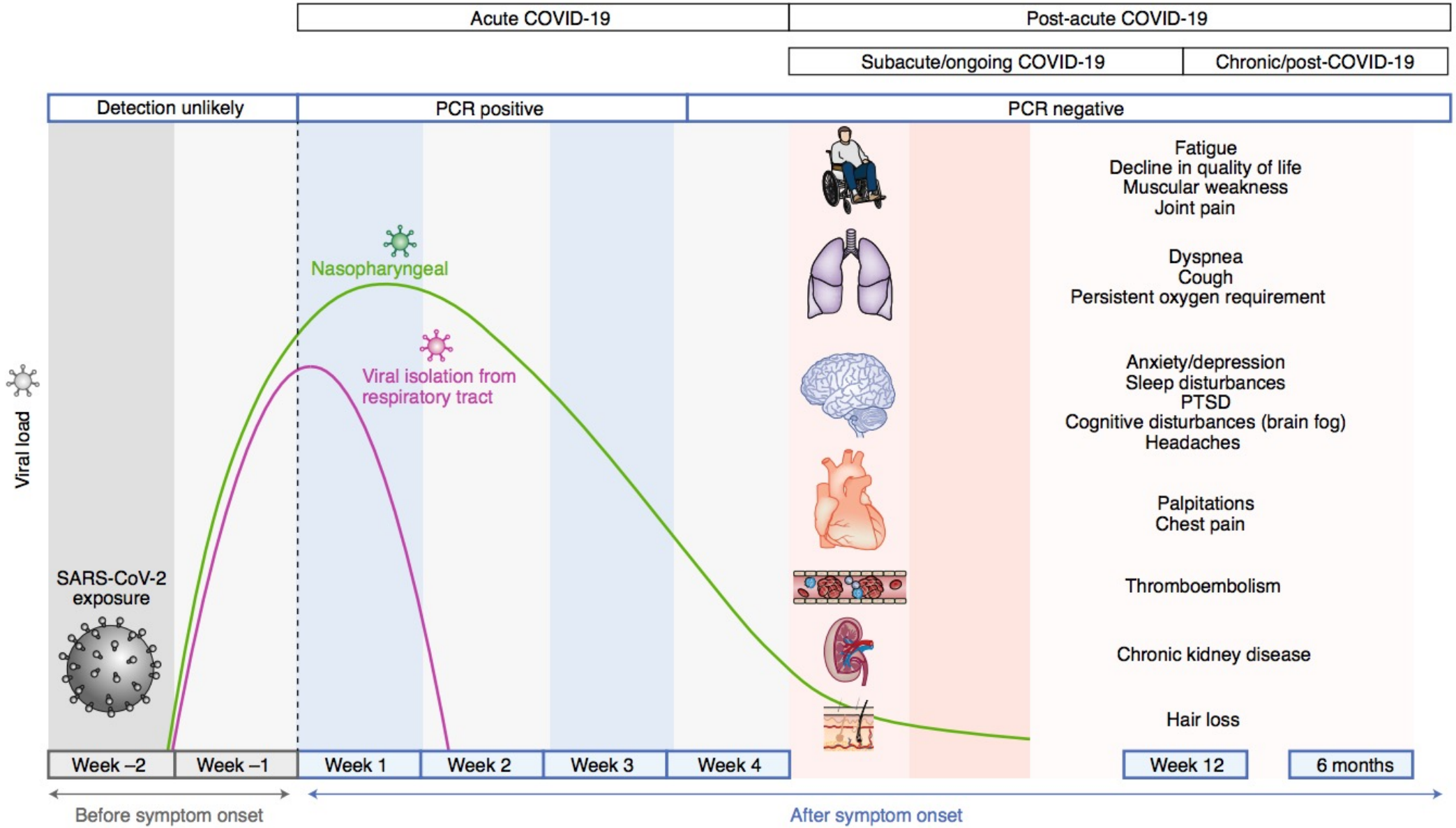
TERMINOLOGY AND STAGES OF RECOVERY

Other terms used for Post COVID-19 Syndrome:

- Long-COVID
- Post-acute sequelae of SARS-CoV-2 infection" (PASC)
- Post-acute COVID-19
- Chronic COVID-19
- Post-COVID syndrome

It is not known if these symptoms represents a new syndrome specific to COVID-19, or if there is overlap with the recovery from similar illnesses

https://www.nice.org.uk/guidance/ng188


Acute COVID-19
Post-acute COVID-19
Subacute/ongoing COVID-19
Chronic/post-COVID-19
Detection unlikely
PCR positive
PCR negative
Viral load
Nasopharyngeal
Viral isolation from respiratory tract
SARS-CoV-2 exposure
Fatigue
Decline in quality of life
Muscular weakness
Joint pain
Dyspnea
Cough
Persistent oxygen requirement
Anxiety/depression
Sleep disturbances
PTSD
Cognitive disturbances (brain fog)
Headaches
Palpitations
Chest pain
Thromboembolism
Chronic kidney disease
Hair loss
Week –2
Week –1
Week 1
Week 2
Week 3
Week 4
Week 12
6 months
Before symptom onset
After symptom onset

Box 1 | Summary of post-acute COVID-19 by organ system

Pulmonary

- Dyspnea, decreased exercise capacity and hypoxia are commonly persistent symptoms and signs
- Reduced diffusion capacity, restrictive pulmonary physiology, and ground-glass opacities and fibrotic changes on imaging have been noted at follow-up of COVID-19 survivors
- Assessment of progression or recovery of pulmonary disease and function may include home pulse oximetry, 6MWTs, PFTs, high-resolution computed tomography of the chest and computed tomography pulmonary angiogram as clinically appropriate

Hematologic

- Thromboembolic events have been noted to be <5% in post-acute COVID-19 in retrospective studies
- The duration of the hyperinflammatory state induced by infection with SARS-CoV-2 is unknown
- Direct oral anticoagulants and low-molecular-weight heparin may be considered for extended thromboprophylaxis after risk–benefit discussion in patients with predisposing risk factors for immobility, persistently elevated D-dimer levels (greater than twice the upper limit of normal) and other high-risk comorbidities such as cancer

Cardiovascular

- Persistent symptoms may include palpitations, dyspnea and chest pain
- Long-term sequelae may include increased cardiometabolic demand, myocardial fibrosis or scarring (detectable via cardiac MRI), arrhythmias, tachycardia and autonomic dysfunction
- Patients with cardiovascular complications during acute infection or those experiencing persistent cardiac symptoms may be monitored with serial clinical, echocardiogram and electrocardiogram follow-up

Neuropsychiatric

- Persistent abnormalities may include fatigue, myalgia, headache, dysautonomia and cognitive impairment (brain fog)
- Anxiety, depression, sleep disturbances and PTSD have been reported in 30–40% of COVID-19 survivors, similar to survivors of other pathogenic coronaviruses
- The pathophysiology of neuropsychiatric complications is mechanistically diverse and entails immune dysregulation, inflammation, microvascular thrombosis, iatrogenic effects of medications and psychosocial impacts of infection

Renal

- Resolution of AKI during acute COVID-19 occurs in the majority of patients; however, reduced eGFR has been reported at 6 months follow-up
- COVAN may be the predominant pattern of renal injury in individuals of African descent
- COVID-19 survivors with persistent impaired renal function may benefit from early and close follow-up in AKI survivor clinics

Endocrine

- Endocrine sequelae may include new or worsening control of existing diabetes mellitus, subacute thyroiditis and bone demineralization
- Patients with newly diagnosed diabetes in the absence of traditional risk factors for type 2 diabetes, suspected hypothalamic–pituitary–adrenal axis suppression or hyperthyroidism should undergo the appropriate laboratory testing and should be referred to endocrinology

Gastrointestinal and hepatobiliary

- Prolonged viral fecal shedding can occur in COVID-19 even after negative nasopharyngeal swab testing
- COVID-19 has the potential to alter the gut microbiome, including enrichment of opportunistic organisms and depletion of beneficial commensals

Dermatologic

- Hair loss is the predominant symptom and has been reported in approximately 20% of COVID-19 survivors

MIS-C

- Diagnostic criteria: <21 years old with fever, elevated inflammatory markers, multiple organ dysfunction, current or recent SARS-CoV-2 infection and exclusion of other plausible diagnoses
- Typically affects children >7 years and disproportionately of African, Afro-Caribbean or Hispanic origin
- Cardiovascular (coronary artery aneurysm) and neurologic (headache, encephalopathy, stroke and seizure) complications can occur

Nature Medicine
VOL 27, April 2021, 601–615
www.nature.com/naturemedicine

Pulmonary/cardiovascular

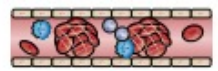
Symptom assessment through virtual/in-person follow-up at 4–6 weeks and at 12 weeks post-discharge

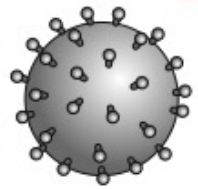
Dyspnea/persistent oxygen requirement

Consider 6MWT, PFT, chest X-ray, PE work up, echocardiogram and HRCT of the chest as indicated

Hematology

Consider extended thromboprophylaxis for high-risk survivors based on shared decision-making





Neuropsychiatry

Screening for anxiety, depression, PTSD, sleep disturbances and cognitive impairment

COVID-19 clinic

Renal

Early follow-up with nephrologists after discharge for patients with COVID-19 and AKI

Primary care

Consideration of early rehabilitation
Patient education
Consider enrollment in clinical research studies
Active engagment with patient advocacy groups

Persistent Physical and Psychological Symptoms following Acute COVID-19

Most Common Physical Symptoms (> 30 % of patients)

- **Fatigue** (15% - 87 %)
- **Dyspnea** (10% - 7%)
- **Chest pain/tightness** (12% - 44%)
- **Cough** (17% - 34%)

Psychological Symptoms

- **Anxiety** (most common)
- **Depression**
- **PTSD**
- **Cognitive symptoms**

1. Ann Intern Med. 2021;174(3):316. Epub 2020 Nov 24 2. Stavem K, Ghanima W, Olsen MK, Gilboe HM, Einvik G. Thorax. 2020 Dec 3;76(4):405–7. 3. Haverall S, Rosell A, Phillpson M et al. JAMA 2021

Persistent Symptoms and Functional Impairment following Acute COVID-19

Less common symptoms include:	Post-intensive care syndrome (PICS) is not uncommon and includes:	Functional impairment reported in over 40 % of patients
• Headache, • Anosmia/dysgeusia • Arthralgias/myalgias • Dizziness • Alopecia • sweating • Diarrhea	• Anxiety (most common) • Depression • PTSD • Cognitive symptoms	• Only 40% independent in all activities at 1 month • Only 60% returned to normal activities at 2 months • Over 50 % had abnormal Short Physical Performance Battery (SPPB and 2-minute walking test) at 4 months

1. Ann Intern Med. 2021;174(3):316. Epub 2020 Nov 24 2. Stavem K, Ghanima W, Olsen MK, Gilboe HM, Einvik G. Thorax. 2020 Dec 3;76(4):405–7. 3. Haverall S, Rosell A, Phillpson M et al. JAMA 2021

Time to Symptom Resolution

Determined by:

- Premorbid risk factors, severity of the acute illness and spectrum of symptoms experienced by the patient

Has wide variability in time to resolution

- Regardless of severity of illness

Is longer in certain groups of patients such as:

- Patients requiring hospitalization
- Older patients with preexisting comorbidities
- Those who experienced medical complications
- Those who suffered a prolonged hospital or ICU stay

Patients with less severe disease are not spared from Post COVID-19

- Patients who were never hospitalized have often reported prolonged and persistent symptoms

Time to Symptom Resolution

Symptoms that usually resolve within 2-4 weeks:	Symptoms that may last for 2-6 months
• Fever • Chills • Olfactory/gustatory symptoms	• Fatigue • Dyspnea • Cough • Chest tightness • Cognitive deficits • Psychological effects

Risk Factors for Hospital Readmission

- Age ≥65 years
- Discharge to SNF or with home health services
- Comorbidities
  - COPD
  - CHF
  - DM with complications
  - CKD
  - BMI > 30 kg/m²
- PCS with :
  - Functional dependency, cognitive impairment or daily Pain
- Gender and race
  - Greater in males and white individuals

Approximately 10 to 20 percent require rehospitalization within 30 and 60 days

1. Bowles KH, McDonald M, Barrón Y, Kennedy E, O'Connor M, Mikkelsen M. Ann Intern Med. 2021 Mar;174(3):316-325. , 2. Ayoubkhani D, Khunti K, Nafilyan V, et al. BMJ. 2021 Mar 31;372:n693. 3. Chopra V, Flanders SA, O'Malley M, et al. Ann Intern Med. 2021 Apr;174(4):576-578. 4. Lavery AM, Preston LE, Ko JY, et al. March-August 2020. MMWR Morb Mortal Wkly Rep. 2020 Nov 13;69(45):1695-1699. 5. Anesi GL, Jablonski J, Harhay MO, et al. . Ann Intern Med. 2021 Jan 19:M20-5327.

Readmission

Common readmission diagnoses were

- COVID-19 (30 percent)
- Sepsis (8.5 percent)
- Pneumonia (3.1 percent)
- Heart failure (3.1 percent).

Over 20 percent required ICU readmission, mortality was 9 percent

- Rates of readmission or death were highest during the first 10 days following discharge.

In a UK study of ~ 50,000 patients discharged after COVID-19

- ~ 30 percent were readmitted, and 10 percent died after discharge
- There were higher rates of respiratory disease, diabetes, and cardiovascular disease in patients discharged following COVID-19 compared with patients discharged with non-COVID diagnoses.

Ayoubkhani D, Khunti K, Nafilyan V, et al. BMJ. 2021 Mar 31;372:n693.

Follow-up

Follow-up

For the evaluation and treatment of persistent symptoms after recovery from the acute COVID-19

Range

Mild illness does not require medical attention

Those with severe illness may require prolonged critical care support.

The optimal timing and location of follow-up evaluation are Unknown and depends upon several factors

Severity of acute illness

Current symptomatology

Patient's age

Risk factors for severe illness

Resources

Timing of Follow-up:
For Patients That Did Not Require Hospitalization

In a healthy young patient with mild disease who is improving

- No need for a scheduled follow-up

In a healthy young patient with mild disease that requests to be seen or has persistent, progressive, or new symptoms.

- Follow-up in 2-3 weeks from onset of illness, Telemedicine/Face to Face

In a patient age > 65 or with comorbidities

- Follow-up in 2-3 after onset of illness. Telemedicine/Face to Face

Timing of Follow-up:
For Patients Requiring Hospitalization or With Persistent Symptoms

For patients that required hospitalization with or without post-acute care placement	For all patients with persistent symptoms lasting more than 12 weeks Regardless of Hospitalization
• Follow-up within one week of facility discharge • Face to face Preferred	• Refer to a specialized outpatient COVID-19 recovery clinic or • Refer to subspecialty clinic relevant to the patient's specific symptoms • Face to face visit preferred

Post COVID-19
Evaluation and Management

- **General evaluation**
- **Cardiopulmonary evaluation**
- **Fatigue and functional assessment**
- **Neuropsychiatric evaluation**
- **Olfactory/gustatory evaluation**
- Miscellaneous
  - Liver injury, kidney injury, dermatologic, gastrointestinal and other

Initial Follow-up Visit: General Evaluation

Evaluation for need of removing infectious precautions

Comprehensive history of acute illness including

- COVID-19 testing
- Duration of illness
- Severity of symptoms
- If hospitalized, types and severity of complications (eg, VTE, AKI, O_2 requirements, noninvasive or invasive ventilation requirements, etc.)
- Cardiac complications
- Delirium
- Treatments implemented

VTE: Venous Thromboembolism, AKI: Acute Kidney Injury

Laboratory Testing

For most patients who have recovered from mild acute COVID-19, laboratory testing is not necessary.

On whom t obtain laboratory testing?

- Patients recovering from more severe illness
- Patients with identified laboratory abnormalities
- Patients who were discharged from hospital or an inpatient rehabilitation facility
- Patients with unexplained continuing symptoms

What tests are reasonable to obtain?

- Complete blood count
- Comprehensive metabolic panel (Electrolytes, BUN, creatinine, liver function studies and albumin

Additional laboratory tests that might be appropriate for select patients include:

- BNP and troponin in patients whose course was complicated by CHF or myocarditis, or in those with possible cardiac symptoms from underlying myocarditis (eg, dyspnea, chest discomfort, edema).
- D-dimer in patients with unexplained persistent or new dyspnea, or in any patient in whom there is a concern for thromboembolic disease.
- Thyroid studies in those with unexplained fatigue or weakness.
- Antinuclear antibody and creatinine kinase in patients with arthralgias, myalgias, or other symptoms concerning for rheumatologic disorders.

BUN: Blood urea nitrogen, BNP: Brain natriuretic peptide, CHF: Congestive Heart Failure

Laboratory Testing

There is no data to support monitoring coagulation parameters or inflammatory markers to resolution.

There is no clinical utility in obtaining SARS-CoV-2 serology (antibodies) in patients who had their acute infection documented by a molecular test

- For patients with prior COVID-19 based upon symptoms, but without a documented positive molecular antigen test, the value of obtaining SARS-CoV-2 serology is unclear

Cardiopulmonary testing in Patients with Cardiopulmonary symptoms

Only to be performed in Patients

- With symptoms
- As follow-up of previous documented imaging abnormality

What type of tests:

- Chest imaging and electrocardiography (ECG) will suffice for the majority of patients
- Additional tests (echocardiography, Holter monitoring, PFT's) may be necessary in select patients.

Chest Imaging necessary for

- All patients who had an abnormality identified on imaging obtained during COVID-19 illness,
- In any patient with new or worsening respiratory symptoms or an abnormal cardiopulmonary physical examination

Cardiopulmonary testing in Patients with Cardiopulmonary symptoms

Type of imaging

- For most patients, chest radiography is sufficient. Chest CT when you are suspecting PTE or pulmonary fibrosis

Timing

- Have a high index of suspicion for VTE
- Resolution may require 12 weeks or longer
- Lung abnormalities may persist on chest CT for six months or longer in 50 percent of previously hospitalized patients, even among those with non-severe respiratory disease
- Earlier imaging may be needed in patients with worsening or new respiratory symptoms, or complicating pathology is suspected

Pulmonary/cardiovascular

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Dyspnea/persistent oxygen requirement

Consider 6MWT, PFT, chest X-ray, PE work up, echocardiogram and HRCT of the chest as indicated

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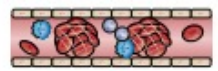

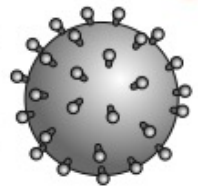

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