Covid-19 Management

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- Coronaviruses are RNA viruses that includes SARS-CoV-2 is related to bat coronaviruses and to SARS-CoV, the virus that causes SARS. Similar to SARS-CoV, SARS-CoV-2 enters human cells through the angiotensin-converting–enzyme 2 (ACE2) receptor.

- SARS-CoV-2 is primarily spread from person to person through respiratory particles, probably of varying sizes, which are released when an infected person coughs, sneezes, or speaks. Because both smaller particles (aerosols) and larger particles (droplets) are concentrated within a few meters, the likelihood of transmission decreases with physical distancing and increased ventilation.

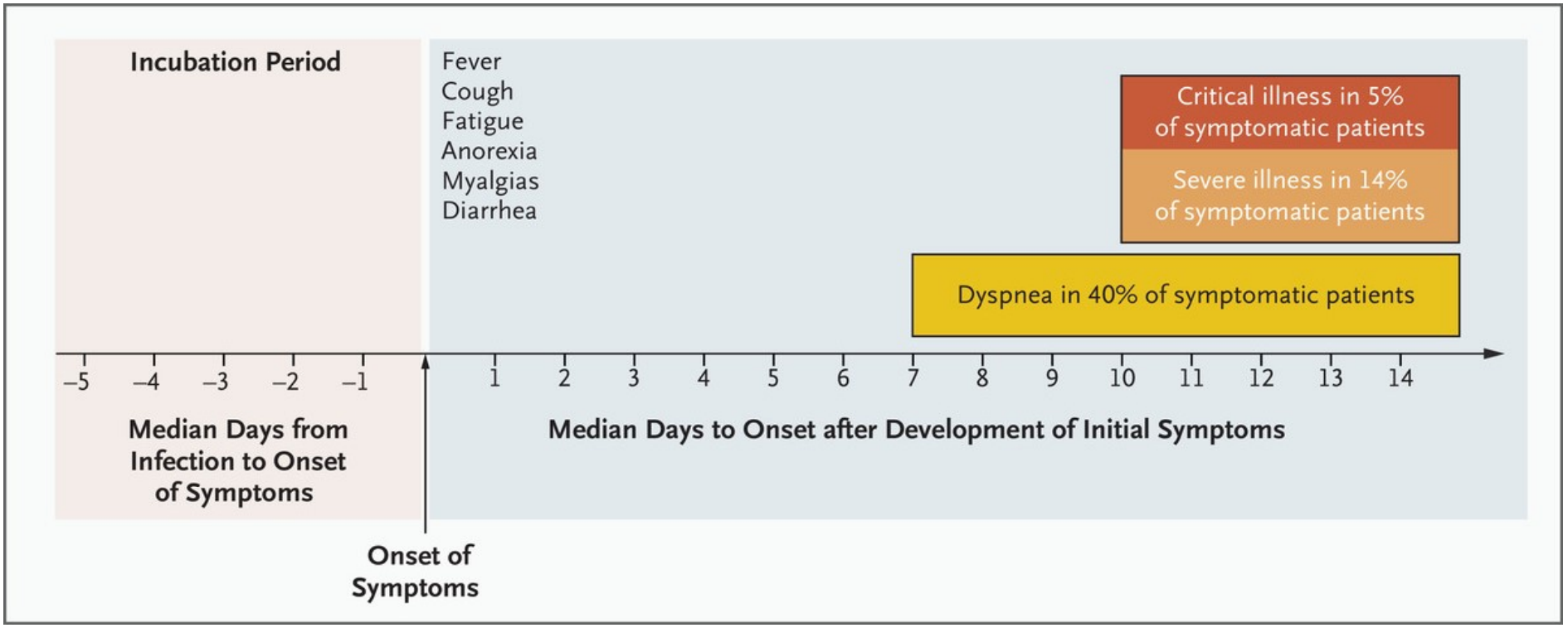
- Most SARS-CoV-2 infections are spread by respiratory-particle transmission within a short distance (when a person is <2 m from an infected person).

- SARS-CoV-2 RNA has been detected in blood and stool, although fecal–oral spread has not been documented. An environmental and epidemiologic study of a small cluster of cases suggested the possibility of fecal aerosol–associated airborne transmission after toilet flushing, but this is likely to be rare.

- Under laboratory conditions, SARS-CoV-2 may persist on cardboard, plastic, and stainless steel for days. Contamination of inanimate surfaces has been proposed to play a role in transmission, but its contribution is uncertain and may be relatively small.

- A major challenge to containing the spread of SARS-CoV-2 is that asymptomatic and presymptomatic people are infectious. Patients may be infectious 1 to 3 days before symptom onset, and up to 40 to 50% of cases may be attributable to transmission from asymptomatic or presymptomatic people. Just before and soon after symptom onset, patients have high nasopharyngeal viral levels, which then fall over a period of 1 to 2 weeks.

Timeline of Symptoms of Severe Corona virus Disease 2019 (Covid-19).



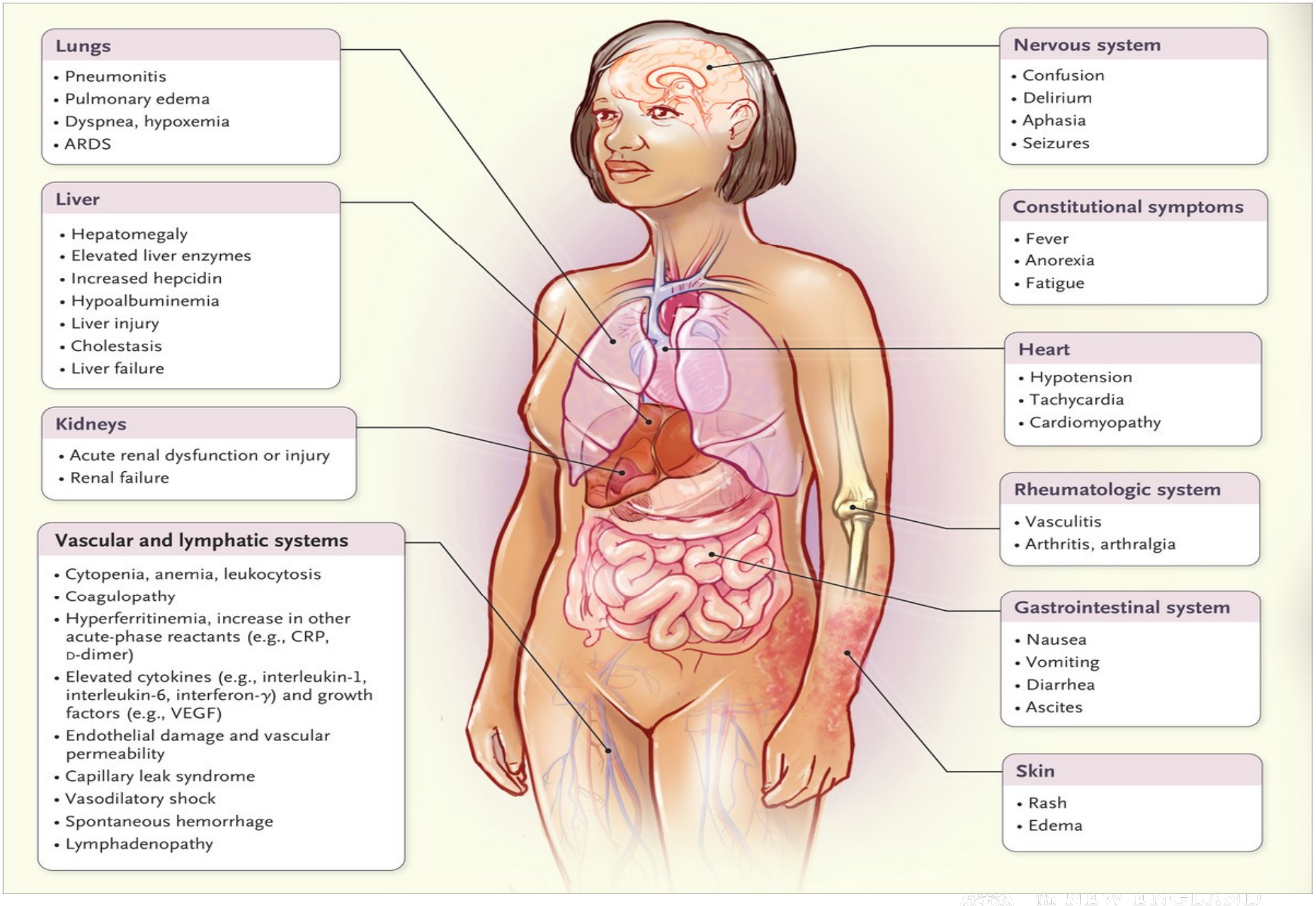
CLINICAL MANIFESTATIONS

- The clinical spectrum of SARS-CoV-2 infection ranges from asymptomatic infection to critical illness. Among patients who are symptomatic, the median incubation period is approximately 4 to 5 days, and 97.5% have symptoms within 11.5 days after infection.
- Covid-19, which is caused by SARS-CoV-2, is characterized by heterogeneous symptoms ranging from mild fatigue to life-threatening pneumonia, cytokine storm, and multiorgan failure
- Symptoms may include fever, cough, sore throat, malaise, and myalgia. Some patients have gastrointestinal symptoms, including anorexia, nausea, and diarrhea. Anosmia and Ageusia have been reported in up to 68% of patients and are more common in women than in men. In some series of hospitalized patients, shortness of breath developed a median of 5 to 8 days after initial symptom onset; its occurrence is suggestive of worsening disease.

- Cytokine storm was also reported in patients with SARS and was associated with poor outcomes. Although the mechanisms of lung injury and Multiorgan failure in Covid-19 are still under investigation, reports of Hemophagocytosis , elevated cytokine levels.
- Serum cytokine levels that are elevated in patients with Covid-19–associated cytokine storm include interleukin-1β, interleukin-6, IP-10, TNF, interferon-γ, macrophage inflammatory protein (MIP) 1α and 1β, and VEGF.Higher interleukin-6 levels are strongly associated with shorter survival.
- In addition to the elevated systemic cytokine levels and activated immune cells, several clinical and laboratory abnormalities, such as elevated CRP and D-dimer levels, hypoalbuminemia, renal dysfunction, and effusions, are also observed in Covid-19, as they are in cytokine storm disorders. Laboratory test results reflecting hyperinflammation and tissue damage were found to predict worsening outcomes in Covid-19.

- Thrombosis issues can occur across cytokine storm disorders, but thromboembolic events appear to be more frequent in Covid-19–associated cytokine storm.Levels of inflammatory mediators in pulmonary tissue during infection with SARS-CoV-2 remain unknown.

Clinical Presentation of Cytokine Storm



Risk Factors for Severe Covid-19.*

Table 1. Risk Factors for Severe Covid-19.*

Older age
Chronic obstructive pulmonary disease
Cardiovascular disease (e.g., heart failure, coronary artery disease, or cardiomyopathy)
Type 2 diabetes mellitus
Obesity (body-mass index, ≥30)
Sickle cell disease
Chronic kidney disease
Immunocompromised state from solid-organ transplantation
Cancer

* Data are adapted from the Centers for Disease Control and Prevention (CDC).[25] Of note, there has been a disproportionate burden of Covid-19 on racial and ethnic minorities and the poor. Studies indicate that the risk of severe disease increases with age. Male sex is not currently included on the CDC list of risk factors but has been noted in some reports to be associated with severe disease. Additional conditions that may confer an increased risk but for which the data are unclear include asthma (moderate to severe), cerebrovascular diseases, cystic fibrosis, hypertension, other immunocompromised states or use of immunosuppressive therapy, neurologic conditions such as dementia, liver disease, pregnancy, pulmonary fibrosis, smoking, thalassemia, and type 1 diabetes mellitus. The body-mass index is the weight in kilograms divided by the square of the height in meters.

RT Gandhi et al. N Engl J Med 2020;383:1757-1766.

The NEW ENGLAND JOURNAL of MEDICINE

Comorbidities the CDC classifies as risk factors for severe COVID-19* [1,2]

1. Established and probable risk factors (comorbidities that have been associated with severe COVID-19 in at least 1 meta-analysis or systematic review [starred conditions], or in observational studies)
   - Cancer*
   - Cerebrovascular disease*
   - Children with certain underlying conditions¶
   - Chronic kidney disease*
   - COPD* and other lung disease (including interstitial lung disease, pulmonary fibrosis, pulmonary hypertension)
   - Diabetes mellitus, type 1* and type 2*
   - Down syndrome
   - Heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies)*
   - HIV
   - Neurologic conditions, including dementia
   - Obesity* (BMI ≥30 kg/m^2) and overweight (BMI 25 to 29 kg/m^2)
   - Pregnancy*
   - Smoking* (current and former)
   - Sickle cell disease
   - Solid organ or blood stem cell transplantation
   - Substance use disorders
   - Use of corticosteroids or other immunosuppressive medications
2. Possible risk factors (supported by mostly case series, case reports, or, if other study design, the sample size is small)
   - Cystic fibrosis
   - Thalassemia
3. Possible risk factors but evidence is mixed (comorbidities have been associated with severe COVID-19 in at least 1 meta-analysis or systematic review, but other studies had reached different conclusions)
   - Asthma
   - Hypertension
   - Immune deficiencies
   - Liver disease

COVID-19: coronavirus disease 2019; CDC: Centers for Disease Control and Prevention; COPD: chronic obstructive pulmonary disease; BMI: body mass index.

* These comorbidities are associated with severe COVID-19 in adults of all ages. Risk of severe disease also rises steadily with age, with more than 80% of deaths occurring in adults older than age 65. People of color are also at increased risk of severe disease and death, often at a younger age, due to systemic health and social inequities.

¶ Underlying medical conditions are also associated with severe illness in children, but evidence implicating specific conditions is limited. Children with the following conditions might be at increased risk for severe illness: medical complexity; genetic, neurologic, or metabolic conditions; congenital heart disease; obesity; diabetes; asthma or other chronic lung disease; sickle cell disease; immunosuppression.

References:

1. *Centers for Disease Control and Prevention. Underlying medical conditions associated with high risk for severe COVID-19: Information for healthcare providers. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html (Accessed on April 5, 2021).*
2. *Centers for Disease Control and Prevention. Science brief: Evidence used to update the list of underlying medical conditions that increase a person's risk of severe illness from COVID-19. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlying-evidence-table.html (Accessed on April 5, 2021).*

KEY CLINICAL POINTS
Mild or Moderate Covid-19

- Covid-19 has a range of clinical manifestations, including cough, fever, myalgia, gastrointestinal symptoms, and anosmia.
- Diagnosis of Covid-19 is commonly made through detection of SARS-CoV-2 RNA by PCR testing of a nasopharyngeal swab or other specimens, including saliva. Antigen tests are generally less sensitive than PCR tests but are less expensive and can be used at the point of care with rapid results.
- Evaluation and management of Covid-19 depend on the severity of the disease. Patients with mild disease usually recover at home, whereas patients with moderate disease should be monitored closely and sometimes hospitalized.
- Remdesivir and Dexamethasone have demonstrated benefits in hospitalized patients with severe Covid-19, but in patients with moderate disease, dexamethasone is not efficacious (and may be harmful) and data are insufficient to recommend for or against routine use of remdesivir.
- Infection control efforts center on personal protective equipment for health care workers, social distancing, and testing.

KEY CLINICAL POINTS
Evaluation and Management of Severe Covid-19

- Patients with severe coronavirus disease 2019 (Covid-19) may become critically ill with acute respiratory distress syndrome that typically begins approximately 1 week after the onset of symptoms.
- Deciding when a patient with severe Covid-19 should receive endotracheal intubation is an essential component of care.
- After intubation, patients should receive lung-protective ventilation with plateau pressure less than or equal to 30 cm of water and with tidal volumes based on the patient's height.
- Prone positioning is a potential treatment strategy for refractory hypoxemia.
- Thrombosis and renal failure are well-recognized complications of severe Covid-19.
- Dexamethasone has been shown to reduce mortality among hospitalized patients with Covid-19 who require oxygen, particularly those receiving mechanical ventilation.
- Remdesivir was recently approved by the Food and Drug Administration for the treatment of Covid-19 in hospitalized patients, on the basis of randomized trials showing that the drug reduces time to clinical recovery.

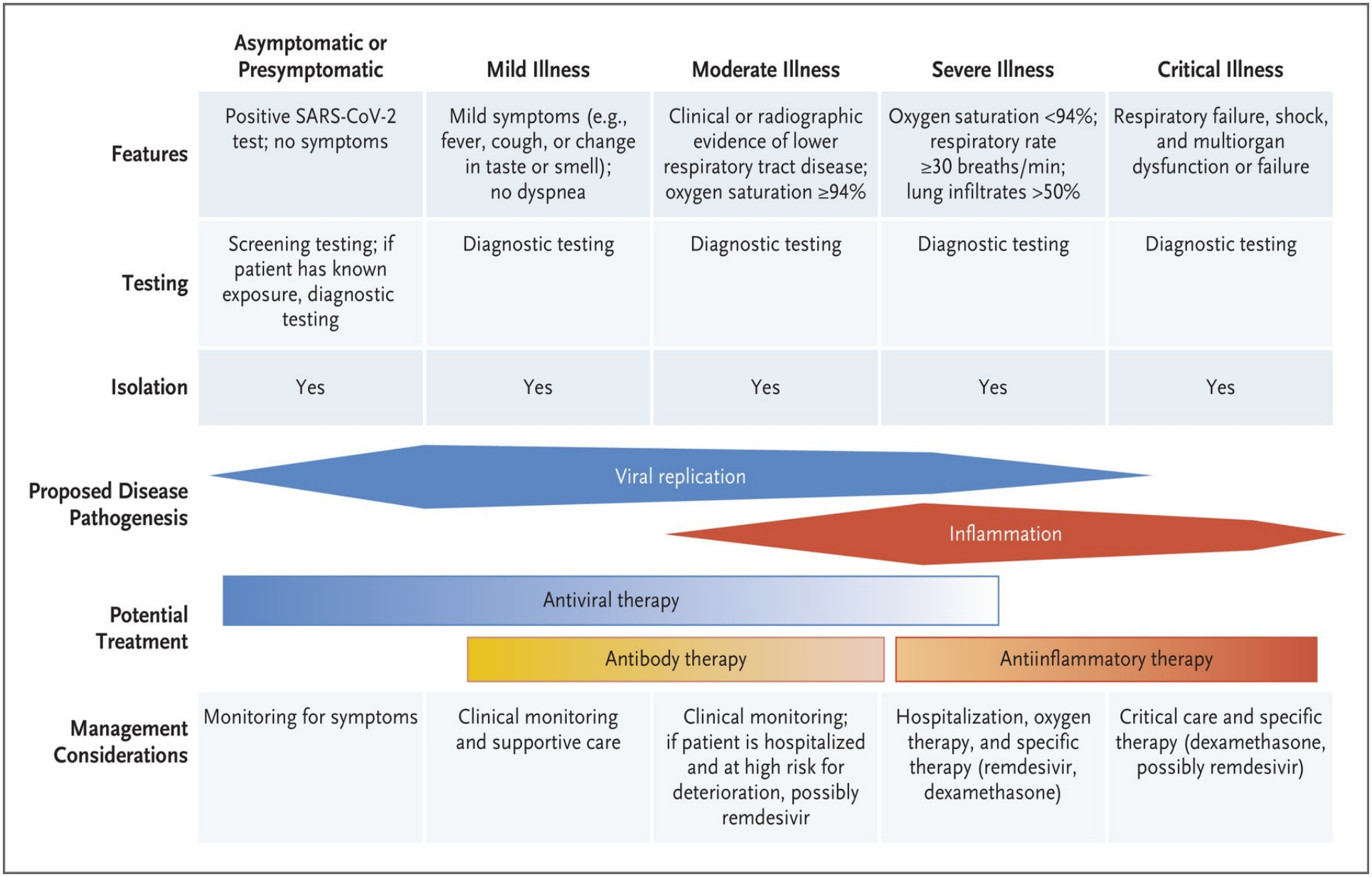


Figure . Characteristics, Diagnosis, and Management of Covid-19 According to Disease Stage or Severity

DIAGNOSIS

- Diagnostic testing to identify persons currently infected with SARS-CoV-2 usually involves the detection of SARS-CoV-2 nucleic acid by means of PCR assay. Just before and soon after symptom onset, the sensitivity of PCR testing of nasopharyngeal swabs is high. If testing is negative in a person who is suspected to have Covid-19, then repeat testing is recommended. The specificity of most SARS-CoV-2 PCR assays is nearly 100% as long as no cross-contamination occurs during specimen processing.
- Laboratory findings in hospitalized patients may include lymphopenia and elevated levels of D-dimer, lactate dehydrogenase, C-reactive protein, and ferritin. At presentation, the procalcitonin level is typically normal. Findings associated with poor outcomes include an increasing white-cell count with lymphopenia, prolonged prothrombin time, and elevated levels of liver enzymes, lactate dehydrogenase, D-dimer, interleukin-6, C-reactive protein, and procalcitonin. When abnormalities are present on imaging, typical findings are ground-glass opacifications or consolidation.

Diagnostic tests for COVID-19 [1,2]

Test category	Primary clinical use	Specimen type	Performance characteristics	Comments
NAATs (including RT-PCR)	Diagnosis of current infection	Respiratory tract specimens*	▪ High analytic sensitivity and specificity in ideal settings. ▪ Clinical performance depends on the type and quality of the specimen and the duration of illness at the time of testing. ▪ Reported false-negative rate ranges from <5 to 40%, depending on the test used.¶	▪ Time to perform the test ranges from 15 minutes to 8 hours.Δ ▪ Turnaround time is influenced by the test used and laboratory workflow. ▪ Some assays allow home collection of specimens that are mailed in.
Serology (antibody detection)	Diagnosis of prior infection (or infection of at least 3 to 4 weeks' duration)	Blood	▪ Sensitivity and specificity are highly variable. ▪ Detectable antibodies generally take several days to weeks to develop; IgG usually develops by 14 days after onset of symptoms. ▪ Cross-reactivity with other coronaviruses has been reported. ▪ Individual results should be interpreted with caution in settings of low seroprevalence; serologic tests that have high specificity still have a low positive predictive value.	▪ Time to perform the test ranges from 15 minutes to 2 hours. ▪ Turnaround time is influenced by the test used and laboratory workflow. ▪ It remains uncertain whether a positive antibody test indicates immunity against future infection.
Antigen tests	Diagnosis of current infection	Nasopharyngeal or nasal swabs	▪ Antigen tests are generally less sensitive than nucleic acid tests. ▪ Sensitivity is highest in symptomatic individuals within 5 to 7 days of symptom onset.	▪ Time to perform the test is <1 hour.

COVID-19: coronavirus disease 2019; NAAT: nucleic acid amplification test; RT-PCR: real-time polymerase chain reaction; IgG: immunoglobulin G; CDC: United States Centers for Disease Control and Prevention.

* Nasopharyngeal swabs, nasal swabs (from the mid-turbinate area or from both anterior nares), nasal or nasopharyngeal washes, oropharyngeal swabs, and saliva are recommended by the CDC. The Infectious Diseases Society of America suggests a nasopharyngeal swab, a mid-turbinate swab, an anterior nasal swab, saliva, or a combined anterior nasal/oropharyngeal swab rather than an oropharyngeal swab. Nasal swabs can be self-collected by the patient on-site or at home. Mid-turbinate swabs and saliva can be collected by the patient while supervised. Lower respiratory tract specimens can be collected in hospitalized patients with suspected lower respiratory tract infection if an upper respiratory tract specimen tests negative.

¶ A single positive test generally confirms the diagnosis. If initial testing is negative and clinical suspicion remains, performing a second test can enhance diagnostic yield.

Δ Low-complexity rapid tests can be performed at the point of care and provide results in less than 1 hour. Most moderate- to high-complexity laboratory-based tests result in several hours. However, the time for a clinician or patient to receive a result depends on how frequently the test is run and other processing factors.

References:

1. *Cheng MP, Papenburg J, Desjardins M, et al. Diagnostic Testing for Severe Acute Respiratory Syndrome-Related Coronavirus 2: A Narrative Review. Ann Intern Med 2020; 172:726.*
2. *Weissleder R, Lee H, Ko J, Pittet MJ. COVID-19 Diagnostics in Context. Sci Transl Med 2020; 12:eabc1931.*

Evaluation

- Evaluation of Covid-19 is guided by the severity of illness . According to data from China, 81% of people with Covid-19 had mild or moderate disease (including people without pneumonia and people with mild pneumonia), 14% had severe disease, and 5% had critical illness.
- Patients who have mild signs and symptoms generally do not need additional evaluation. However, some patients who have mild symptoms initially will subsequently have precipitous clinical deterioration that occurs approximately 1 week after symptom onset. In patients who have risk factors for severe disease , close monitoring for clinical progression is warranted, with a low threshold for additional evaluation.

- If new or worsening symptoms (e.g., dyspnea) develop in patients with initially mild illness, additional evaluation is warranted. Physical examination should be performed to assess for tachypnea, hypoxemia, and abnormal lung findings. In addition, testing for other pathogens (e.g., influenza virus, depending on the season, and other respiratory viruses) should be performed, if available, and chest imaging should be done.
- Hallmarks of moderate disease are the presence of clinical or radiographic evidence of lower respiratory tract disease but with a blood oxygen saturation of 94% or higher while the patient is breathing ambient air. Indicators of severe disease are marked tachypnea (respiratory rate, ≥30 breaths per minute), hypoxemia (oxygen saturation, ≤93%; ratio of partial pressure of arterial oxygen to fraction of inspired oxygen, <300), and lung infiltrates (>50% of the lung field involved within 24 to 48 hours).

- Laboratory testing in hospitalized patients should include a complete blood count and a comprehensive metabolic panel. In most instances, and especially if a medication that affects the corrected QT (QTc) interval is considered, a baseline electrocardiogram should be obtained.
- Chest radiography is usually the initial imaging method. Some centers also use lung ultrasonography. The American College of Radiology recommends against the use of computed tomography as a screening or initial imaging study to diagnose Covid-19, urging that it should be used “sparingly” and only in hospitalized patients when there are specific indications.
- Additional tests that are sometimes performed include coagulation studies (e.g., D-dimer measurement) and tests for inflammatory markers (e.g., C-reactive protein and ferritin), lactate dehydrogenase, creatine kinase, and procalcitonin.

MANAGEMENT OF COVID-19

- Patients who have mild illness usually recover at home, with supportive care and isolation. It may be useful for people who are at high risk for complications to have a pulse oximeter to self-monitor the oxygen saturation.
- Patients who have moderate disease should be monitored closely and sometimes hospitalized; those with severe disease should be hospitalized. If there is clinical evidence of bacterial pneumonia, empirical antibacterial therapy is reasonable but should be stopped as soon as possible. Empirical treatment for influenza may be considered when seasonal influenza transmission is occurring until results of specific testing are known.
- Treatment of Covid-19 depends on the stage and severity of disease , Because SARS-CoV-2 replication is greatest just before or soon after symptom onset, antiviral medications (e.g., remdesivir and antibody-based treatments) are likely to be most effective when used early. Later in the disease, a hyperinflammatory state and coagulopathy are thought to lead to clinical complications; in this stage, antiinflammatory medications, immunomodulators, anticoagulants, or a combination of these treatments may be more effective than antiviral agents. There are no approved treatments for Covid-19 but some medications have been shown to be beneficial.

COVID-19: Outpatient evaluation and management of acute illness in adults

- **Risk stratification** — Our patient-centered continuum of care management approach is based on stratification by risk for developing severe disease and close monitoring for respiratory decomposition. Patients without severe initial symptoms, who are deemed stable enough to not require immediate in-person evaluation, are risk stratified to determine the intensity (frequency and duration) of follow-up.
- **Assess risk for severe disease** — Older age and certain chronic medical conditions have been associated with more severe illness and higher mortality from COVID-19 . Specifically, in addition to increasing age, **established and probable** risk factors for severe disease in adults include:
- ●Cancer, Cerebrovascular disease, Chronic kidney disease
- ●Chronic obstructive pulmonary disease (COPD) and other lung disease (including interstitial lung disease, pulmonary fibrosis, pulmonary hypertension) ,Smoking, current and former
- ●Diabetes mellitus, type 1 and type 2,Down syndrome, Heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies),HIV
- ●Neurologic conditions, including dementia, Substance use disorders
- ●Overweight and obesity (BMI ≥30 kg/m^2),Pregnancy
- ●Sickle cell disease, Solid organ or blood stem cell transplantation
- ●Use of corticosteroids or other immunosuppressive medications
- In addition, **possible** risk factors for severe disease include:
- ●Cystic fibrosis,Thalassemia
- Additional possible risk factors for severe disease include hypertension, asthma, immune deficiencies, and liver disease, although there are fewer high-quality data to support an association with these conditions.

- **Dyspnea assessment** — Remote assessment of dyspnea should focus on the patient's subjective symptoms, as well as an objective assessment of breathing, including deterioration in respiratory function. We begin by asking if patients have developed any difficulty with their breathing, other than that associated with coughing. If yes, we ask the patient to describe the difficulty in their own words and assess the ease and comfort of their speech (eg, if they can speak comfortably in complete sentences).
- In addition, we ask questions that provide a more objective assessment of changes in respiratory status, including.
- ●“What activities that you could previously do without difficulty are now causing you to be out of breath?”
- ●"Has this gotten worse over the last one, two, or three days?"
- ●“Are you breathing harder or faster than usual when sitting still?”
- ●“Can you no longer do your usual household activities due to shortness of breath?”
- ●“Does walking cause you to feel dizzy?”

We use this assessment to categorize dyspnea by severity

- ●Mild dyspnea – Dyspnea that does not interfere with daily activities (eg, mild shortness of breath with activities such as climbing one to two flights of stairs or walking briskly).
- ●Moderate dyspnea – Dyspnea that creates limitations to activities of daily living (eg, shortness of breath that limits the ability to walk up one flight of stairs without needing to rest, or interferes with meal preparation and light housekeeping tasks).
- ●Severe dyspnea – Dyspnea that causes shortness of breath at rest, renders the patient unable to speak in complete sentences, and interferes with basic activities such as toileting and dressing.

- **Oxygenation assessment** — If a patient with COVID-19 already has access to a pulse oximeter at home, and can adequately measure and report the results to the clinician, we consider the oxygen saturation as an additional piece of information to assess their clinical status
- ●For any patient with an oxygen saturation of ≤94 percent on room air, in-person evaluation is warranted.
- ●For patients who have an oxygen saturation of ≥95 percent on room air, the decision on in-person evaluation depends on other clinical features such as severity of dyspnea, risk for severe disease, and assessment of overall acuity.

- **Assessment of overall acuity level** — In addition to evaluation of respiratory status, we assess the patient's overall acuity level by asking questions regarding orthostasis, dizziness, falls, hypotension (if home blood pressure measurement is available), mental status change (eg, lethargy, confusion, change in behavior, difficulty in rousing), observed cyanosis, and urine output..
- **Criteria for ED evaluation and likely hospital admission** — We typically refer patients with **one or more** of the following features to the ED for further management and likely hospital admission:
- ●Severe dyspnea (dyspnea at rest, and interfering with the ability to speak in complete sentences)
- ●Oxygen saturation on room air of ≤90 percent, regardless of severity of dyspnea
- ●Concerning alterations in mentation (eg, confusion, change in behavior, difficulty in rousing) or other signs and symptoms of hypoperfusion or hypoxia (eg, falls, hypotension, cyanosis, anuria, chest pain suggestive of acute coronary syndrome)

AIIMS/ ICMR-COVID-19 National Task Force/ Joint Monitoring Group (Dte.GHS)
Ministry of Health & Family Welfare, Government of India

CLINICAL GUIDANCE FOR MANAGEMENT OF ADULT COVID-19 PATIENTS

17th May 2021

COVID-19 patient

Mild disease

Upper respiratory tract symptoms (&/or fever) WITHOUT shortness of breath or hypoxia

Home Isolation & Care

MUST DOs
- ✓ Physical distancing, indoor mask use, strict hand hygiene.
- ✓ Symptomatic management (hydration, anti-pyretics, anti-tussive, multivitamins).
- ✓ Stay in contact with treating physician.
- ✓ Monitor temperature and oxygen saturation (by applying a SpO2 probe to fingers).

Seek immediate medical attention if:
- ○ Difficulty in breathing
- ○ High grade fever/severe cough, particularly if lasting for >5 days
- ○ A low threshold to be kept for those with any of the high-risk features*

MAY DOs

Therapies based on low certainty of evidence

- ➢ Tab Ivermectin (200 mcg/kg once a day for 3 days). Avoid in pregnant and lactating women.
  OR
- ➢ Tab HCQ (400 mg BD for 1 day f/b 400 mg OD for 4 days) unless contraindicated.
- ❖ Inhalational Budesonide (given via Metered dose inhaler/ Dry powder inhaler) at a dose of 800 mcg BD for 5 days) to be given if symptoms (fever and/or cough) are persistent beyond 5 days of disease onset.

*High-risk for severe disease or mortality
- ✓ Age > 60 years
- ✓ Cardiovascular disease, hypertension, and CAD
- ✓ DM (Diabetes mellitus) and other immunocompromised states
- ✓ Chronic lung/kidney/liver disease
- ✓ Cerebrovascular disease
- ✓ Obesity

Moderate disease

Any one of:
1. Respiratory rate ≥ 24/min, breathlessness
2. SpO2: 90% to ≤ 93% on room air

ADMIT IN WARD

Oxygen Support:
- ➢ Target SpO_2: 92-96% (88-92% in patients with COPD).
- ➢ Preferred devices for oxygenation: non-rebreathing face mask.
- ➢ Awake proning encouraged in all patients requiring supplemental oxygen therapy (sequential position changes every 2 hours).

Anti-inflammatory or immunomodulatory therapy
- ➢ Inj. Methylprednisolone 0.5 to 1 mg/kg in 2 divided doses (or an equivalent dose of dexamethasone) usually for a duration of 5 to 10 days.
- ➢ Patients may be initiated or switched to oral route if stable and/or improving.

Anticoagulation
- ➢ Conventional dose prophylactic unfractionated heparin or Low Molecular Weight Heparin (weight based e.g., enoxaparin 0.5mg/kg per day SC). There should be no contraindication or high risk of bleeding.

Monitoring
- ➢ Clinical Monitoring: Work of breathing, Hemodynamic instability, Change in oxygen requirement.
- ➢ Serial CXR; HRCT chest to be done ONLY if there is worsening.
- ➢ Lab monitoring: CRP and D-dimer 48 to 72 hrly; CBC, KFT, LFT 24 to 48 hrly; IL-6 levels to be done if deteriorating (subject to availability).

Severe disease

Any one of:
1. Respiratory rate >30/min, breathlessness
2. SpO2 < 90% on room air

ADMIT IN ICU

Respiratory support
- Consider use of NIV (Helmet or face mask interface depending on availability) in patients with increasing oxygen requirement, if work of breathing is LOW.
- Consider use of HFNC in patients with increasing oxygen requirement.
- Intubation should be prioritized in patients with high work of breathing /if NIV is not tolerated.
- Use conventional ARDSnet protocol for ventilatory management.

Anti-inflammatory or immunomodulatory therapy
- Inj Methylprednisolone 1 to 2mg/kg IV in 2 divided doses (or an equivalent dose of dexamethasone) usually for a duration 5 to 10 days.

Anticoagulation
- Weight based intermediate dose prophylactic unfractionated heparin or Low Molecular Weight Heparin (e.g., Enoxaparin 0.5mg/kg per dose SC BD). There should be no contraindication or high risk of bleeding.

Supportive measures
- Maintain euvolemia (if available, use dynamic measures for assessing fluid responsiveness).
- If sepsis/septic shock: manage as per existing protocol and local antibiogram.

Monitoring
- Serial CXR; HRCT chest to be done ONLY if there is worsening.
- Lab monitoring: CRP and D-dimer 24-48 hourly; CBC, KFT, LFT daily; IL-6 to be done if deteriorating (subject to availability).

After clinical improvement, discharge as per revised discharge criteria.

EUA/Off label use (based on limited available evidence and only in specific circumstances):
- ➢ Remdesivir (EUA) may be considered ONLY in patients with
  - ○ Moderate to severe disease (requiring SUPPLEMENTAL OXYGEN), AND
  - ○ No renal or hepatic dysfunction (eGFR <30 ml/min/m2; AST/ALT >5 times ULN (Not an absolute contradiction), AND
  - ○ Who are within 10 days of onset of symptom/s.
    - ❖ Recommended dose: 200 mg IV on day 1 f/b 100 mg IV OD for next 4 days.
  - ○ Not to be used in patients who are NOT on oxygen support or in home setting.
- ➢ Tocilizumab (Off-label) may be considered when ALL OF THE BELOW CRITERIA ARE MET
  - ○ Presence of severe disease (preferably within 24 to 48 hours of onset of severe disease/ICU admission).
  - ○ Significantly raised inflammatory markers (CRP &/or IL-6).
  - ○ Not improving despite use of steroids.
  - ○ No active bacterial/fungal/tubercular infection.
    - ❖ Recommended single dose: 4 to 6 mg/kg (400 mg in 60kg adult) in 100 ml NS over 1 hour.

COVID-19 specific therapy
Monoclonal antibody therapy

- Monoclonal antibodies that target severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continue to be evaluated in outpatients with mild to moderate disease, and trial results suggest a benefit from these agents . The FDA EUAs for bamlanivimab-etesevimab, casirivimab-imdevimab, and sotrovimab are for **non-hospitalized** COVID-19 patients with mild to moderate illness (eg, not requiring supplemental oxygen or, if on chronic supplemental oxygen, without an increased oxygen requirement) who have certain risk factors for severe disease .])

- These risk factors for adults (≥18 years) include any of the following:
- Older age (≥65 years),Body mass index (BMI) ≥25 kg/m^2,Pregnancy,Chronic kidney disease
- •Immunosuppression (immunosuppressive disease or treatment), Diabetes mellitus
- •Cardiovascular disease (including congenital heart disease) or hypertension, Sickle cell disease
- •Chronic lung disease (eg, chronic obstructive pulmonary disease [COPD], asthma [moderate to severe], interstitial lung disease, cystic fibrosis, pulmonary hypertension)
- •Neurodevelopmental disorders (eg, cerebral palsy) or other medically complex conditions (eg, genetic or metabolic syndromes and severe congenital anomalies)
- •Dependence on a medical-related technology (eg, tracheostomy, gastrostomy, or positive pressure ventilation [unrelated to COVID-19

Casirivimab-imdevimab

- In preliminary results of a phase 3 randomized controlled trial including 4057 non-hospitalized adults with mild to moderate COVID-19 and one or more risk factors for severe disease, combination casirivimab-imdevimab, at two different doses (1200 and 2400 mg total doses) administered intravenously within seven days of symptom onset was compared with placebo .
- Treatment with IV casirivimab-imdevimab was associated with rare infusion-related reaction events of moderate severity, including fever, chills, urticaria, pruritus, abdominal pain, and flushing. A single episode of anaphylaxis was also reported . Subcutaneous administration was associated with greater local injection site reactions compared with placebo (12 versus 4 percent) .
- The EUA for casirivimab-imdevimab is for the combined 1200 mg dose, administered IV (preferred) or subcutaneous if IV administration is not feasible or would delay treatment . There are no outcomes data regarding subcutaneous administration; dosing is based upon safety and pharmacokinetic data in healthy subjects.

Limited role for other investigational outpatient therapies

- **Ivermectin** – Ivermectin is being evaluated as a potential therapy for early treatment in outpatients with nonsevere disease. However, there is a lack of high-quality data to support its efficacy in these patients .
- ●**Inhaled corticosteroids** – Inhaled corticosteroids budesonide 800 mcg twice daily (an average of seven days) may be of some benefit in the treatment of mild, early, COVID-19. However, additional randomized controlled trials are necessary to determine the efficacy of inhaled corticosteroids for early, mild, COVID-19
- **Avoiding nebulized medications** — Inhaled medications should be administered by metered dose inhaler, whenever possible, rather than through a nebulizer, to avoid the risk of aerosolization of SARS-CoV-2 through nebulization.
- Hydroxychloroquine and azithromycin have received attention as agents with possible antiviral activity, but trials have not suggested a clinical benefit for patients with COVID-19, including those managed in the outpatient setting.
- The potential toxicity of hydroxychloroquine , including QTc prolongation ,arrhythmias,and gastrointestinal symptoms.

- ●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.
- 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. Another trial in Iran suggested no benefit with favipiravir for severe COVID-19 .
- **Interferons** – Interferons modulate immune responses and may have antiviral effects. Overall, clinical data do not indicate a clear benefit of interferon beta for severe COVID-19 and no difference in 28-day mortality with subcutaneous or intravenous interferon beta compared with standard of care.

Others treatment

- Other treatments are being evaluated in outpatients with mild to moderate illness, including vitamin C, vitamin D, and zinc supplementation. Limited observational data suggest a possible association between certain vitamin and mineral deficiencies and more severe disease . However, there are no high-quality data that supplementation with vitamin C, vitamin D, or zinc reduces the severity of COVID-19 in non-hospitalized patients.

Remdesivir (RNA-dependent RNA polymerase)

- ACTT-1, a multinational, randomized, placebo-controlled trial of remdesivir (given for up to 10 days or until death or discharge) evidence of lung involvement; 85 percent had severe disease and 27 percent were receiving invasive mechanical ventilation or ECMO at baseline .
- Remdesivir resulted in a faster time to recovery, defined as discharge from the hospital or continued hospitalization without need for supplemental oxygen or ongoing medical care).
- Remdesivir reduced time to recovery whether patients were randomized within or after 10 days of symptom onset. However, in subgroup analysis, the reduced time to recovery was only statistically significant among patients who were on low-flow oxygen at baseline.

- In an interim report of the WHO-sponsored, multinational SOLIDARITY trial of patients hospitalized with COVID-19, there was no difference in overall 28-day mortality between the 2750 patients randomly assigned to open-label remdesivir and the 2708 patients assigned to standard care.
- From SOLIDARITY there appeared to be a trend toward lower mortality with remdesivir among those who were not on mechanical ventilation at baseline, but this did not reach statistical significance . There was no mortality benefit among those on ventilation at baseline .
- The suggested adult dose is 200 mg intravenously on day 1 followed by 100 mg daily for 5 days total (with extension to 10 days if there is no clinical improvement and in patients on mechanical ventilation or ECMO).

- **Severe COVID-19** – Overall, data from randomized trials do not demonstrate a clear, major clinical benefit with remdesivir among hospitalized patients .
- Among patients with severe disease, we prioritize remdesivir for those requiring low-flow supplemental oxygen because it may also reduce mortality in this population.
- **Nonsevere COVID-19** – Among hospitalized patients with nonsevere disease, remdesivir may have a modest benefit, but the clinical significance of the benefit is uncertain.
- Although discharge rates by day 14 were higher with remdesivir (76 percent in each of the remdesivir groups versus 67 percent with standard of care), these differences were not statistically significant. Interpretation of this trial is limited by the open-label design and an imbalance in co-therapies.
- Reported side effects include nausea, vomiting, and transaminase elevations. In one trial, the most common adverse events were anemia, acute kidney injury, fever, hyperglycemia, and transaminase elevations; the rates of these were overall similar between remdesivir and placebo .

ORIGINAL ARTICLE

Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19

List of authors

The REMAP-CAP Investigators

- We found that in critically ill patients with Covid-19, the interleukin-6 receptor antagonists tocilizumab and sarilumab were both effective as compared with the current standard of care, which included glucocorticoids in the majority of patients (>80%)
- We saw both a shorter time to clinical improvement and lower mortality with tocilizumab and with sarilumab than with control. It is therefore possible that the maximum clinical benefit from interleukin-6 inhibition (i.e., improved survival) is seen in the most severely ill patients with Covid-19, who are at the highest risk for death. which included glucocorticoids in the majority of patients (>80%).

- The EMPACTA (Evaluating Minority Patients with Actemra) trial showed that patients who received tocilizumab were less likely than those who received placebo to undergo mechanical ventilation or to die by day 28 , although no substantial difference in overall mortality was noted .
- The COVACTA trial, in which approximately 38% of the patients were mechanically ventilated, showed no significant difference between the tocilizumab and placebo groups with respect to clinical status or mortality at day 28, although the time to hospital discharge was shorter with tocilizumab .
- In the safety population, serious adverse events occurred in 103 of 295 patients (34.9%) in the tocilizumab group and in 55 of 143 patients (38.5%) in the placebo group. Mortality at day 28 was 19.7% in the tocilizumab group and 19.4% in the placebo group .

ORIGINAL ARTICLE

Dexamethasone in Hospitalized Patients with Covid-19

The RECOVERY Collaborative Group

- A total of 2104 patients were assigned to receive dexamethasone and 4321 to receive usual care. Overall, 482 patients (22.9%) in the dexamethasone group and 1110 patients (25.7%) in the usual care group died within 28 days after randomization .
- In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%;) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%;) **but not among those who were receiving no respiratory support at randomization (17.8% vs. 14.0%;).**
- However, there was no evidence that dexamethasone provided any benefit among patients who were not receiving respiratory support at randomization, and the results were consistent with possible harm in this subgroup.

- It is likely that the beneficial effect of glucocorticoids in severe viral respiratory infections is dependent on the selection of the right dose, at the right time, in the right patient.
- High doses may be more harmful than helpful, as may such treatment given at a time when control of viral replication is paramount and inflammation is minimal.
- The RECOVERY trial provides evidence that treatment with dexamethasone at a dose of 6 mg once daily for up to 10 days reduces 28-day mortality in patients with Covid-19 who are receiving respiratory support. We found no benefit (and the possibility of harm) among patients who did not require oxygen.
- If dexamethasone is not available, it is reasonable to use other glucocorticoids at equivalent doses (eg, total daily doses of hydrocortisone 150 mg, methylprednisolone 32 mg, or prednisone 40 mg), although data supporting use of these alternatives are more limited than those for dexamethasone.

ORIGINAL ARTICLE

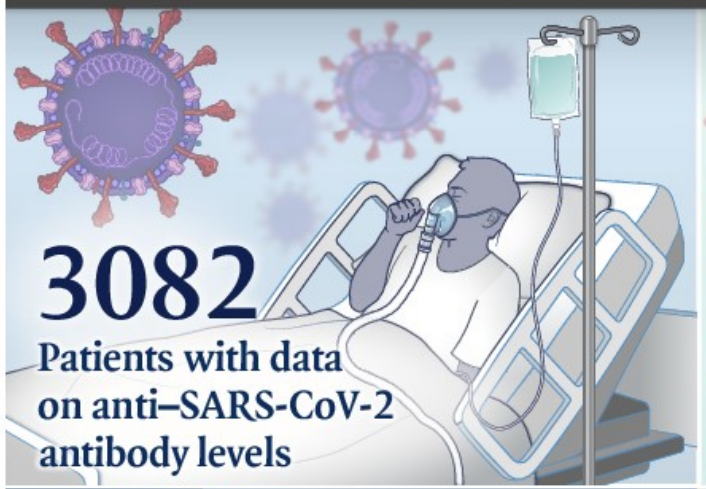
Convalescent Plasma Antibody Levels and the Risk of Death from Covid-19

- Our analyses show that among patients with Covid-19 who were not receiving mechanical ventilation, the transfusion of plasma with high antibody levels was associated with a lower risk of death than the transfusion of plasma with low antibody levels.
- In addition, patients who received plasma within 3 days after the diagnosis of Covid-19 had a lower risk of death than those who received a transfusion later in the disease course.
- The association of anti–SARS-CoV-2 antibody levels with the risk of death from Covid-19 was moderated by mechanical ventilation status.
- A lower risk of death within 30 days in the high-titer group than in the low-titer group was observed among patients who had not received mechanical ventilation before transfusion and no effect on the risk of death was observed among patients who had received mechanical ventilation .

The NEW ENGLAND JOURNAL of MEDICINE

Convalescent Plasma Antibody Levels and Covid-19 Mortality

RETROSPECTIVE STUDY BASED ON A U.S. NATIONAL REGISTRY



3082
Patients with data on anti–SARS-CoV-2 antibody levels

	High Antibody Level	Medium Antibody Level	Low Antibody Level
	N=515	N=2006	N=561
Death within 30 days after plasma transfusion	22.3% (115 patients)	27.4% (549 patients)	29.6% (166 patients)

Relative risk (high vs. low), 0.66; 95% CI, 0.48 to 0.91

In patients not receiving mechanical ventilation, transfusion of plasma with higher antibody levels was associated with a lower risk of death.

M.J. Joyner et al. 10.1056/NEJMoa2031893

Imatinib in patients with severe COVID-19: a randomised, double-blind, placebo-controlled, clinical trial

- The observed effects on survival and duration of mechanical ventilation suggest that imatinib might confer clinical benefit in hospitalised patients with COVID-19, but further studies are required to validate these findings.
- **Baricitinib** - is a Janus kinase inhibitor used for treatment of rheumatoid arthritis,but also it is thought to have potential antiviral effects through interference with viral entry. Baricitinib is given at 4 mg orally once daily for up to 14 days.
- We suggest baricitinib as an option for patients requiring high-flow oxygen or noninvasive ventilation and for select patients who are on low-flow oxygen but are progressing toward needing higher levels of respiratory support despite initiation of dexamethasone.
- We do not use baricitinib in patients who have also received an IL-6 pathway inhibitor and if the estimated glomerular filtration rate (eGFR) is <15 mL/min .

Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial

- The ACTION trial, which had an elevated D-dimer to receive therapeutic dose anticoagulation (mostly rivaroxaban 15 or 20 mg once daily) or prophylactic dose anticoagulation (mostly prophylactic LMW heparin), found no major differences in efficacy between therapeutic and prophylactic dosing .
- Use of therapeutic-dose rivaroxaban, and other direct oral anticoagulants, should be avoided in these patients in the absence of an evidence-based indication for oral anticoagulation.
- Severe COVID-19 therapeutic-dose anticoagulation (enoxaparin, 1 mg/kg twice daily) or prophylactic-dose anticoagulation (enoxaparin, 40 mg once daily or unfractionated heparin, 5000 units three times daily) .
- **Dosing** — Prophylactic dosing (rather than higher-intensity dosing) is appropriate for patients hospitalized for COVID-19, including those in the intensive care unit (ICU). patients with creatinine clearance (CrCl) >30 mL/min, 40 mg once daily; for CrCl 15 to 30 mL/min, 30 mg once daily.

- Three randomized trials (REMAP-CAP, ACTIV-4a, ATTACC, reported in a not-yet-peer-reviewed preprint) that included 1074 people hospitalized with severe COVID-19 who were randomly assigned to therapeutic-dose anticoagulation or standard prophylactic dosing, found that hospital survival was comparable between groups (64.3 versus 65.3 percent)
- The rate of major thrombotic events was lower in the therapeutic dosing group (5.3 percent, versus 10.7 percent with prophylactic dosing). Major bleeding was seen in 3.1 percent of patients assigned to therapeutic dosing and 2.4 percent of those assigned to standard prophylaxis, a difference that did not reach statistical significance..

USE OF CONCOMITANT MEDICATIONS IN PEOPLE WITH COVID-19

- **ACE inhibitors/ARBs** — Patients receiving angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) should continue treatment with these agents if there is no other reason for discontinuation (eg, hypotension, acute kidney injury).
- SARS-CoV-2 enters human cells through the ACE2 receptor, questions were raised regarding ,whether the use of ACE inhibitors or angiotensin-receptor blockers (ARBs) which may increase ACE2 levels.
- **NSAID use** — As with the general approach to fever reduction in adults, we use acetaminophen as the preferred antipyretic agent in patients with COVID-19 and use the lowest effective dose to minimize common adverse effects.
- We do not discontinue NSAIDs in patients who are on them chronically for other conditions, unless there are other reasons to stop them (eg, renal injury, gastrointestinal bleeding).

- **Statins and aspirin** — We make a point of continuing statins in hospitalized patients with COVID-19 who are already taking them. We also continue aspirin unless there are concerns about bleeding risk. A high proportion of patients with severe COVID-19 have underlying cardiovascular disease, diabetes mellitus, and other indications for use of statins and aspirin.
- **Immunomodulatory agents** — Use of immunosuppressing agents has been associated with increased risk for severe disease with other respiratory viruses, and the decision to discontinue prednisone, biologics, or other immunosuppressive drugs in the setting of COVID-19 must be determined on a case-by-case basis.

Empiric treatment for bacterial pneumonia in select patients

- Since the clinical features of COVID-19 may be difficult to distinguish from bacterial pneumonia, empiric treatment for community-acquired pneumonia is reasonable when the diagnosis is uncertain.
- Empiric treatment for bacterial pneumonia may also be reasonable in patients with documented COVID-19 if there is clinical suspicion for it (eg, new fever after defervescence with new consolidation on chest imaging).
- If empiric antibiotic therapy is initiated, we attempt to make a microbial diagnosis (eg, through sputum Gram stain and culture, urinary antigen testing) and reevaluate the need to continue antibiotic therapy daily.
- In such settings, a low procalcitonin may be helpful to suggest against a bacterial pneumonia; however, elevated procalcitonin has been described in COVID-19, particularly late in the course of illness, and does not necessarily indicate bacterial infection .

SARS-CoV-2 Variants and Vaccines

Table 2. Key Spike Protein Mutations in Five SARS-CoV-2 Variants.

Variant	Phenotypic Change	Amino Acid Position in Prototype Virus and Proposed Effect of Changing It*						
		Δ69–70 Increase transmission	K417 Decrease neutralization	L452 Decrease neutralization	E484 Decrease neutralization	N501 Increase transmission	D614 Increase transmission	P681 Increase transmission
B.1.1.7 (or alpha)	Increase transmission	69–70 deleted			K (later change)	Y	G	H
B.1.351 (or beta)	Increase transmission and virulence		N		K	Y	G	
B.1.1.28.1 (or gamma or P.1)	Increase transmission and virulence, decrease neutralization		N/T		K	Y	G	
B.1.617.2 (or delta)	Increase transmission, decrease neutralization			R			R	R
B.1.617.1 (or kappa)	Increase transmission, decrease virulence			R	Q		G	R

* Single letter codes of amino acid changes at specified positions for the listed variants are shown.

For The ENSEMBLE Study Group
Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant

- New SARS-CoV-2 virus lineages have emerged, with mutations in the N-terminal and receptor-binding domains of the spike protein that are known targets for neutralizing antibodies; in particular, the E484K mutation is associated with reduced neutralization sensitivity.
- Of main concern are variants that were first identified in Brazil, South Africa, and the United Kingdom.In our trial, 95% of the Covid-19 cases in South Africa in which SARS-CoV-2 was sequenced were caused by the 20H/501Y.V2 variant, whereas a variant from the P.2 lineage carrying the E484K mutation was identified in 69% of the cases in Brazil with a sequenced sample.
- However, despite the high prevalence of SARS-CoV-2 variants of concern, vaccine efficacy remained high. This finding shows that a Covid-19 vaccine that was based on the original Wuhan-Hu-1 strain can elicit cross-protective efficacy against new variants in South Africa and Brazil.

Reduced neutralization of SARS-CoV-2 B.1.617 by vaccine and convalescent serum

- •Vaccine/convalescent sera show reduced neutralization of B.1.617.1 and B.1.617.2
- •Sera from B.1.351and P.1 show markedly reduced neutralization of B.1.617.2
- •B.1.351, P.1 and B.1.617.2 are antigenically divergent
- •Vaccines based on B.1.1.7 may broadly protect against current variants
- SARS-CoV-2 has undergone progressive change with variants conferring advantage rapidly becoming dominant lineages e.g. B.1.617.
- With apparent increased transmissibility variant B.1.617.2 has contributed to the current wave of infection ravaging the Indian subcontinent and has been designated a variant of concern in the UK.
- However, B.1.351 and P.1 sera showed markedly more reduction in neutralization of B.1.617.2 suggesting that individuals previously infected by these variants may be more susceptible to reinfection by B.1.617.2.

Thank you