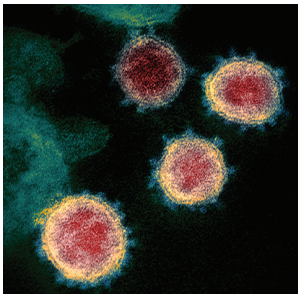
Diagnosis and Management of COVID-19 Disease

June 9, 2020 Update

SARS-CoV-2 is a novel coronavirus that was identified in late 2019 as the causative agent of COVID-19 (aka coronavirus disease 2019). On March 11, 2020, the World Health Organization (WHO) declared the world-wide outbreak of COVID-19 a pandemic. This document summarizes the most recent knowledge regarding the biology, epidemiology, diagnosis, and management of COVID-19.

Due to the rapidly evolving science on this novel disease, this information sheet should be considered a "living document" that may be updated on an as-needed basis. All previous versions are available in the supplemental materials tab so that interested readers may view this document's complete publication.



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Biology

- SARS-CoV-2 is single-stranded RNA, enveloped virus that likely spread to humans from a zoonotic source, possibly bats or pangolins.[1]
- It is believed to spread from **person to person** via **respiratory droplet nuclei**.[2]
- Other routes of infection (e.g. contact, enteric) are possible as the virus can persist on surfaces and is shed in feces, but it is unclear if these are significant means of spread.[2,3]
- There is evidence of transmission by asymptomatic individuals.[4]
- The virus binds to the ACE2 receptor on type II pneumocytes. However, the role of Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers (ARBs) as treatments or risk factors for disease is unclear.[5]
- The reported incubation time is 3-12 days with a median duration of viral shedding of 20 days.[6,7]
- There is evidence that the virus changes over time. There may be multiple strains of SARS-CoV-2 in circulation.[8]

Epidemiology

Characteristics such as the **attack rate** (% of individuals in an at-risk population who acquire the infection), **R0** (R naught, the expected number of cases directly generated by one case in a population where all individuals are susceptible to infection), and **case fatality rate** (CFR, % of infected individuals who die) are contextual. That is, they depend on factors such as testing rate, population density, and control strategies that vary from location to location. These factors may also change over time. Table 1 summarizes reported epidemiologic characteristics of SARS-CoV-2.[9]

Table 1: Reported epidemiologic characteristics of SARS-CoV-2

Attack rate:	30-40% (community, in China)
R0:	2-4 (lower with containment)
Case fatality rate	1.5% USA, 3.4% overall worldwide
Incubation time	3-14 days
Viral shedding	Median 20 days

Clinical Presentation

Symptoms may vary from mild cough to fulminant respiratory failure and ARDS. Many patients are asymptomatic. Table 2 lists the estimated frequency of symptoms observed to date.[10]

Table 2: Frequency of Common Symptoms in COVID-19

Symptom	Percent of patients with symptom
Cough	50-80%
Fever	85% (only 45% febrile on presentation)
Fatigue	69.6%
Dyspnea	20-40%
URI symptoms	15%
GI symptoms (nausea, vomiting, diarrhea)	10%
Loss of taste or smell, stroke, myalgias, headache, skin rash	variable

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Severe COVID-19

Severe COVID-19 may lead to multi-organ failures such as acute cardiac, kidney, liver injury, disorders of the central or peripheral nervous system, coagulopathy, cardiac arrhythmias, rhabdomyolysis and shock. It can be associated with a cytokine release syndrome characterized by high fevers, thrombocytopenia, hyperferritinemia, and elevation of other inflammatory markers.

Laboratory Findings

The following lab abnormalities have been observed in patients with COVID-19.[10]

- Complete blood count: normal WBC, leukopenia, lymphopenia (80%+), thrombocytopenia.
- Chemistries: elevated BUN/creatinine, elevated AST, ALT, and total bilirubin.
- Inflammatory markers: normal or low procalcitonin, elevated C-reactive protein and ferritin.
- Coagulation: elevated D-dimer and prothrombin time; PT INR can be normal.
- Miscellaneous: elevated interleukin-6, creatine kinase, troponin, and lactate dehydrogenase.

Imaging

Imaging findings are frequently absent on presentation and should not be used for diagnosis of COVID. Many patients have normal imaging at the time of presentation, but the following abnormalities have been reported (Figure 1).[10]

- Chest X-ray: bilateral, peripheral, patchy opacities.
- Chest CT scan: bilateral ground glass opacities, crazy paving, and consolidation. Not routinely recommended to avoid unnecessary exposure during transport.
- Point-of-care ultrasound: B-lines, pleural line thickening, consolidations with air bronchograms. Assessment of cardiac function is also useful.

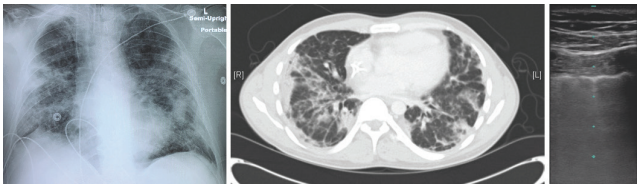

Figure 1: COVID-19 Imaging. (A) CXR showing bilateral peripheral opacities, (B) Chest CT showing diffuse ground glass with a peripheral predominance, (C) point of care lung ultrasound showing predominance of B-lines in patients with COVID-19. Images courtesy of Dr. Nick Mark.

Diagnostic Testing and Reporting

Lack of availability has hampered testing to date, but testing capacity is increasing quickly. The following recommendations have been made regarding diagnostic testing and reporting.[11,12]

- Send nasopharyngeal or oropharyngeal swab for SARS-CoV-2 polymerase chain reaction testing (RT-PCR). Check with your local facility regarding test characteristics, including sensitivity and specificity.
- Differentiating SARS-CoV-2 from other circulating respiratory viruses is important, particularly Influenza, therefore consider testing of usual respiratory pathogens. Co-infection has also been reported.
- Do not order sputum induction.
- Alternative respiratory collection in intubated patient can include tracheal aspirates and non-bronchoscopic alveolar lavage.
- Avoid bronchoscopy unless absolutely indicated.
  - If indicated, follow current recommendations for bronchoscopy in suspected COVID-19 patients as recommended by the American Association for Bronchology and Interventional Pulmonology.[13]
- PFTs or spirometry are not indicated in these patients. In addition, ATS and American College of Occupational and Environmental Medicine has recommended against doing routine outpatient PFTs for concerns of spread.
- Notify local health department of positive cases.

Isolation and Infection Control for Confirmed and Suspected Cases

Recommendations for isolation and infection control are evolving as more is learned about the SARS-CoV-2 virus. Current best practices include:

- Place all suspected patients in droplet masks during assessment and when in transit.
- If cohorting is required due to resource limitation, keep patients 2 meters apart in a single room.
- Restrict visitors.
- Try to avoid room entry unless essential; try to move equipment (e.g. IV pumps) out of the room.
- Hand hygiene: 20+ seconds with soap and or 60-95% alcohol containing hand gel.
- Use appropriate PPE in the correct sequence, including.[14]

- Standard precautions.
- Contact precautions.
- Droplet precautions with eye protection.
- PLUS airborne precautions for aerosolizing procedures such as intubation, extubation, non-invasive positive pressure ventilation (NIPPV), open circuit suctioning, bronchoscopy, and aerosol treatments.

- N95 masks must be fit tested.
- All healthcare professionals must be trained in how to properly don, use, and doff PPE in a manner to prevent self-contamination.
- If available, consider powered air-purifying respirator (PAPRs) or controlled air purifying respirators (CAPRs).
  - Use of tight-fitting respirators require fit testing, but use of loose-fitting respirators does not require fit testing.[15]

General Treatment Recommendations

The following treatment strategies are recommended based on experience to-date. Of note, these are *suggestions* and should not replace clinical judgement at the bedside.

- Fluid-sparing resuscitation.
- Empiric antibiotics if suspicion for secondary infection.
- Due to concerns for aerosol spread, nebulizers should be converted to Metered Dose Inhalation (MDIs).
- WHO has not recommended against the use of Non-steroidal anti-inflammatory agents. Clinicians should consider alternatives if concerns exist.
- Initiating or discontinuing ACE-I and ARBs have been an area of intense discussion. The American College of Cardiology, American Heart Association and Heart Failure Society of America's joint statement recommends against discontinuing ACE-I and ARBs in patients with COVID-19.
- Coagulation abnormalities leading to arterial and venous thromboembolism and clotting of hemodialysis catheters are increasingly identified. American Society of Hematology recommends anticoagulation prophylaxis in all hospitalized patients with low molecular weight heparin over unfractionated heparin to reduce contact, unless the risk of bleeding outweighs the risk of thrombosis.[16]
- Corticosteroids are not recommended except when required for other indications such as asthma or COPD exacerbations, refractory shock or evidence of cytokine storm.

Management of Hypoxemic Respiratory Failure

These are *suggestions* and should not replace clinical judgement at the bedside.

- Oxygen by nasal cannula OR simple mask OR non-rebreather masks (negative flow isolation where available)
- Recommend early use of oxygen by high flow nasal cannula in patients requiring more than standard nasal O_2 without indications for immediate intubation.
- Trial of non-invasive positive pressure ventilation (NIPPV) if high flow nasal cannula unavailable or concomitant COPD/CHF. Note that NIPPV is associated with a risk of aerosol generation and its benefit is unclear in COVID-19. If available, NIPPV via a Helmet may reduce aerosol dispersion compared with a full face mask.
- Trial awake proning with high flow nasal cannula or NIPPV, which are both aerosol generating and therefore negative flow isolation is recommended where available.
- Close monitoring and prompt intubation of patients deteriorating despite noninvasive support to avoid emergent intubations.
- Intubation should be performed by the most experienced operator using video laryngoscopy where available. Use of bag-valve mask may cause aerosol generation and should be limited and if used must have high efficiency particulate air (HEPA) filter.
- Connect suction and capnography in advance to avoid circuit breaks.
- Minimize circuit breaks and use high-efficiency particulate air (HEPA) filters between endotracheal tubes and CO_2 detectors.
- Use lung-protective ventilation strategies per ARDSnet protocol, along with targeting low Driving Pressure and early prone positioning. Neuromuscular blockade is recommended only in those with ventilator dyssynchrony despite adequate sedation and analgesia.[17]

- Avoidance of hypervolemia and dry lung strategy is recommended.
- If patient develops shock, the vasopressor of choice is norepinephrine to keep mean arterial pressure (MAP) to 60-65 mm Hg.[18] Unexplained hemodynamic instability should also prompt investigation of myocardial ischemia, myocarditis and pulmonary embolism.
- Patients who require intubation will likely require a prolonged duration of mechanical ventilation.
- Consider venous thromboembolism in patients with rapid respiratory deterioration and high D-dimer concentrations. When diagnostic testing is not possible and patient has low bleeding risk, consider therapeutic anticoagulation.[19]
- Extracorporeal Membrane Oxygenation (ECMO) can be considered but is associated with a high mortality rate[20] based on reports from China. In the U.S. ECMO is being offered to highly selective patients with refractory hypoxemia despite optimization of ventilator strategies and adjunctive therapies. There are multiple NIH clinical trials evaluating its efficacy in COVID-19 population.
- Monitor for and treat cardiomyopathy and cardiogenic shock which have been reported as a late complication of COVID-19. Point-of-care ultrasound as well as BNP levels may be useful in identifying patients with this complication.
  - In a recent case series from Washington, 33% of patients developed cardiomyopathy.[21]
- If critical illness polyneuropathy and/or myopathy is suspected, high flow nasal cannula and/or NIPPV may be useful following extubation.
- Tracheostomy may be considered in those with prolonged mechanical ventilation beyond 21 days, who are otherwise without significant comorbidities and would be expected to have good prognosis if recovery is achieved.[22]

Due to high risk of complications and mortality in patients with severe COVID-19, early discussions on goals of care with patients and families and palliative care consultation (when available) is highly advisable for all hospitalized patients.

Investigational Therapies

Information on registered clinical trials for COVID-19 in the United States is available at: https://clinicaltrials.gov/.[23]

Antiviral agents with in-vitro activity against SARS CoV-2:

- Remdesivir is granted FDA emergency-use authorization for hospitalized patients with severe Covid-19; compassionate-use program for pregnant women and children with severe Covid-19; and expanded-access program for persons unable to participate in clinical trials (ClinicalTrials.gov number, NCT04323761).
- Chloroquine or hydroxychloroquine—blocks viral entry into the endosome; early in vitro data suggested some utility, but data from recent RCTs are either equivocal or shows more risk than benefit.[24] FDA has granted emergency-use authorization from Strategic National Stockpile for certain hospitalized patients with Covid-19.
- Lopinavir/ritonavir—anti-viral protease inhibitors; recent negative RCT Covid-19.[25]

Investigational Immunomodulatory agents:

- Convalescent plasma from COVID-19 recovered donors: may have a role due to the presence of neutralizing antibodies. FDA single-patient emergency IND; expanded-access program for persons ineligible for or unable to participate in clinical trials. randomized control trials in progress.[26]
- These are FDA approved therapies for autoimmune, rheumatological and hematological disorders which are under intense investigation via clinical trials for the treatment of COVID-19.
  - Interleukin-6 inhibitors (sarilumab, siltuximab, tocilizumab): activity in cytokine release syndrome.
  - BTK inhibitors (acalabrutinib, ibrutinib, rilzabrutinib): targets cytokines.
  - Interleukin-1 inhibitors (anakinra, canakinumab) mmunomodulation; activity in macrophage activation syndrome.
  - JAK inhibitors (baricitinib, ruxolitinib): Broad immunomodulation.

Prognosis

Based on experience in China, 80% of patients have mild symptoms, 15% moderate, and 5% severe (requiring mechanical ventilation). Most patients deteriorate gradually with a median of 9 days from symptom onset to ICU admission. Pregnant women and children appear to have a better prognosis.

The following factors have been associated with worse outcomes:

- Increasing age.
- Comorbidities including diabetes, cardiovascular disease (including hypertension), and chronic lung disease.
- Coagulopathy.
- Higher admission sequential organ failure assessment (SOFA) score.
- Laboratory abnormalities: elevated D-dimer, lactate dehydrogenase; ferritin, and troponin, thrombocytopenia and neutrophilia.

Control Strategies

The following strategies are recommended to slow the rate of SARS-CoV-2 spread:

- Contact tracing.
- Social/physical distancing.
- Wearing mask covering nose and mouth in public.
- Hand hygiene.
- Quarantine of suspected cases and exposed individuals.
- Travel restrictions.

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