COVID-19, SARS CoV-2

last updated Sep 8, 2021 9:05 PM

Coronavirus, SARS CoV-2, COVID-19

Management of COVID-19

- **Important Note August 2021**:
  - Other than hypertransmissibility and high peak viral loads, current understanding of SARS-CoV-2 infection with the currently predominant **Delta variant**, is very limited although improving daily. Delta has many unique properties. Most knowledge of clinical, epidemiologic, therapeutic, and diagnostic aspects of infection and COVID-19 are based on studies done in the **pre-Delta era and recommendations based on references that pre-date Delta should be interpreted in that context.** Of course, we will continue to update COVID-19 information and recommendations based on new developments.
- See COVID-19 Prevention for authorized vaccines and information.

Initial Clinical Evaluation

- Symptomatic person with positive test result (PCR or antigen)
- Initial clinical evaluation focuses on:
  - Risk factors
    - Age > 65 years, immune-compromised state, obesity (BMI ≥35), diabetes mellitus, chronic kidney disease
  - Potential treatment-limiting organ dysfunction (renal, hepatic)
  - **Date of onset of symptoms, not date of first positive test** (to determine duration of illness)
  - Severity of disease
  - Child or adolescent, see also MIS-C / MIS-A
- Refs: NIH COVID-19 Treatment Guidelines; N Engl J Med 2020;382:1708; Lancet 2020;395:497; JAMA 2020;323:1061; JAMA 2020;323:1239.

Severity of Disease

Severity	Indicators
Asymptomatic	No symptoms
Mild disease	Fever, cough, sore throat, N/V, diarrhea, loss of taste or smell but no dyspnea; normal O2 saturation and normal chest X-ray
Moderate disease	Symptoms of mild disease plus evidence of lower respiratory tract infection (exam and/or imaging), O2 saturation ≥94% on room air
Severe disease	Symptoms of moderate disease but O2 saturation <94%, PaO2/FiO2 <300 mmHg, respiratory frequency >30 breaths per minute, or lung infiltrates >50%
Critical disease	Symptoms of severe disease but intubated with respiratory failure, septic shock, and/or multiorgan dysfunction

Treatment

General Principles of Therapy

- Early diagnosis of COVID-19
- Important note: date of **onset of first symptoms** drives treatment decision making (**not** the date of first positive test).
- Two stages of disease:

- Day 1-10: **active viral replication**
  - Antiviral therapies most likely to be efficacious at this early stage
    - E.g., Remdesivir, anti-viral monoclonal antibodies and convalescent plasma
  - Not recommended: Systemic Corticosteroids and other immune modulators (e.g., IL-6 inhibitors)
    - Unlikely to be beneficial, may be harmful, may prolong the period of viral replication
- Day 8-14, or longer: **immune dysfunction** (e.g., respiratory compromise, other severe disease)
  - Antiviral therapies less effective, and maybe ineffective, in this stage of the disease
  - Corticosteroids and other immune modulators **likely to be beneficial for those with severe disease**

Recommendations Based on Severity

Setting, disease severity, risk of progression	Therapy	Comments
Not hospitalized or hospitalized, asymptomatic	None recommended	Close clinical monitoring
Not hospitalized, mild-to-moderate disease, NOT at high risk of disease progression	None recommended. Dexamethasone NOT recommended	Close clinical monitoring
Not hospitalized, mild-to-severe disease, high risk of disease progression	Monoclonal antibody: (Casirivimab + Imdevimab) or Sotrovimab Alternative: convalescent plasma Dexamethasone NOT recommended (Bamlanivimab + Etesevimab) **retains ~full activity vs wild-type, alpha, and Delta variants.** It is not as active vs Beta, Gamma, Mu, and Delta-plus variants; (don't use in regions where these variants are > 5% of cases)	Monoclonal antibody strongly preferred over convalescent plasma. It should be administered as early as possible in the course of disease; not recommended after day 7- 9 of symptoms as unlikely to be effective. Sotrovimab is a single antibody preparation and may not have same coverage as other two monoclonal Ab preparations
Hospitalized, mild disease (no lower respiratory tract disease). Patient at high risk of disease progression	Monoclonal antibody if admitted for reason other than COVID-19 Alternative: convalescent plasma Dexamethasone NOT recommended Prophylactic anticoagulation (see below)	Monoclonal antibody strongly preferred over convalescent plasma. Should be administered as early as possible in the course of disease; do not give after day 7- 9 of symptoms.
Hospitalized, moderate disease (evidence of lower respiratory tract disease) with no supplemental O2 requirement. Patient at high risk of disease progression.	Remdesivir Dexamethasone NOT recommended Prophylactic anticoagulation (see below)	Can use convalescent plasma if ≤ 3 days of symptoms, but benefit unclear (see Comments below).
Hospitalized, severe disease (O2 saturation <94% and/or PaO2/FiO2 <300) requires supplemental O2.	Remdesivir + Dexamethasone ± Tocilizumab Consider therapeutic anticoagulation (see below)	In patients who are unable to receive dexamethasone, use as alternative Baricitinib (plus Remdesivir); see Notes on Recommended Regimens for use of Tocilizumab.
Hospitalized, critical disease -- requires mechanical ventilation or ECMO	Dexamethasone ± Remdesivir ± Tocilizumab Prophylactic anticoagulation (see below)	Benefit of Remdesivir unproven, but recommended by some authorities Consider IL-6 receptor blocker in the first 24 hours of ICU admission (ok to use with Remdesivir and dexamethasone, would not recommend in conjunction with Baricitinib) In patients who are unable to receive dexamethasone, consider Baricitinib. See Notes on Recommended Regimens for use of Tocilizumab.

- **In outpatient setting**: adjunctive therapy with acetaminophen, ibuprofen (or naproxen), guaifenesin, ondansetron, Imodium, inhaled albuterol, inhaled steroid, H2 blocker, and / or sleeping meds (e.g., melatonin) as needed prn
- Prophylactic dose anticoagulation with heparin is recommended for hospitalized patients with mild or moderate disease or for those with critical disease disease requiring mechanical ventilation or ECMO. Consider use of therapeutic anticoagulation with heparin for patients with severe disease requiring supplemental oxygen. See Comments.

Recommended Regimens, Dosing

Treatment	Type	Dose/duration	Indication	Comments
Remdesivir	Antiviral	Adult (wt > 40 kg): 200 mg IV loading dose on day 1, then 100 mg IV daily maintenance dose. Infuse each dose over 30-120 min. Pediatric (wt 3.5 - 40 kg): 5 mg/kg loading dose on day 1, then 2.5 mg/kg maintenance dose Duration: 5 days if not on ventilation/ECMO. If no clinical improvement at 5 days, extend to 10 days. 10 days for patients on mechanical ventilation/ECMO	Hospitalized patients with severe disease. Consider in patients with moderate and critical disease as well.	
Dexamethasone	Anti-inflammatory	6 mg once daily IV or po x 10 days for patients on supplemental oxygen or mechanical ventilation	Hospitalized patients with severe and critical disease	NOT RECOMMENDED unless patient on supplemental oxygen
Baricitinib	Anti-inflammatory (JAK inhibitor)	4 mg orally daily (for up to 14 days) + Remdesivir 200 mg on day 1, then 100 mg IV daily for up to 10 days.	Hospitalized patients with severe and critical disease who are unable to tolerate corticosteroids	Should only be used in the rare situation where corticosteroids cannot be used (see Comments)
Bamlanivimab + Etesevimab	Antiviral (monoclonal antibody)	(Bamlanivimab 700 mg + Etesevimab 1400 mg) co-administered as a single infusion in a healthcare setting.	Outpatients with mild-severe disease at high risk for progression to more severe disease and hospitalization	Benefit greatest if given early after onset of symptoms. **Do not use if Delta variant suspected**
Casirivimab + Imdevimab	Antiviral (monoclonal antibody)	Casirivimab + Imdevimab (Regeneron) combination 1,200 mg (casirivimab 600 mg + imdevimab 600 mg) single IV infusion	Outpatients with mild-severe disease at high risk for progression to more severe disease and hospitalization or death.	Benefit greatest if given early after onset of symptoms. Dose of each antibody lowered to 600 mg on June 3 2021.
Sotrovimab	Antiviral (monoclonal antibody)	Sotrovimab Administered as 500 mg IV over 30 minutes	Outpatients with mild-severe disease at high risk for progression to more severe disease and hospitalization	Benefit greatest if given early after onset of symptoms.
Convalescent plasma	Antiviral	Various: Single transfusion 250-700 mL or two transfusions of 200-500 mL given 24h apart	If used, for inpatients with mild-moderate disease at high risk for progression to more severe disease and not eligible for monoclonal antibody combinations	Use high antibody titer given within 72 hours of symptoms onset to maximize possible benefit (See Notes on Recommended Regimens).
Tocilizumab	Anti-inflammatory (Il-6 inhibitor)	8 mg/kg, actual body weight up to 800 mg, as a single IV infusion with a second dose 12-24h later if no improvement	Hospitalized patient with progressive severe or critical disease; RECOVERY trial included systemic inflammation, defined as CRP ≥ 75 mg/L, as a criterion	Benefit probably greatest if administered early, i.e., within 48h of hospitalization or < 24h after ICU admission. Possible increased risk of infection, especially is used in conjunction with corticosteroid: monitor clinically for secondary bacterial, fungal and other opportunistic infections.

Suggested Laboratory Evaluation, Inpatient

When	What to order

At hospital admission	• CBC with differential, troponin, LFTs, Chem 10, CPK
	• Ferritin, CRP, LDH, d-dimer, PT/PTT/fibrinog
	• For risk stratification (repeat if patient deteriorates clinically):
	  ◦ LDH (repeat daily if elevated)
	  ◦ Troponin
	  ◦ Baseline EKG
	• Viral serologies (unless checked recently):
	  ◦ HIV
	  ◦ HCV antibody
	  ◦ HBV surface antibody, core antibody and surface antigen
	• If clinically indicated:
	  ◦ Blood cultures x 2, sputum culture, UA with reflex to culture, and Urine strep/legionella antigen
	  ◦ β-HCG for women of childbearing age

Recommended daily labs (until stable)	• CBC with diff (esp. total lymphocyte count) • Complete metabolic panel • CPK (creatine kinase) • CRP first week of hospitalization; inflammatory markers hard to interpret beyond 1 week
Recommended every other day (daily if elevated or pt in ICU)	• PT/PTT/fibrinogen • D-dimer
Radiology	• Portable chest x-ray at admission; further imaging based on evaluation, concern for secondary bacterial infection, pulmonary embolism, etc.

Laboratory Predictors: Severe Disease, Poor Outcome

- Decreased absolute lymphocyte count
  - Ratio of absolute neutrophil count to absolute lymphocyte count > 3.5
- Elevated CPK, CRP, Ferritin, D-dimer, LDH, Troponin, PT
- Thrombocytopenia
- LFTs 5x upper limit of normal
- Acute kidney injury
- See Lancet 2020;395:1054.

Notes on Recommended Regimens

- **Remdesivir**
  - **Efficacy demonstrated in hospitalized patients with respiratory disease: no benefit shown for those requiring high-flow oxygen, non-mechanical ventilation, mechanical ventilation, or extracorporeal membrane oxygenation**
    - Placebo-controlled randomized trial showing shortened time to recovery compared to standard care (N Engl J Med. 2020;383:1813-1826).
- **Dexamethasone**
  - **Efficacy demonstrated in hospitalized patients requiring supplemental oxygen**
    - The RECOVERY trial (see N Engl J Med. 2021; 394:755) found lower 28-day mortality in dexamethasone-treated patients compared to usual care. Dexamethasone reduced deaths in patients receiving invasive mechanical ventilation and in patients receiving supplemental oxygen without invasive mechanical ventilation, but no mortality benefit and possible harm in patients not receiving supplemental or other respiratory support at randomization.
    - Meta-analysis (JAMA 2020;324:1330) of seven recent randomized controlled trials of steroids (3 dexamethasone, 3 hydrocortisone, 1 methylprednisolone) for critically ill COVID-19 patients found improved 28-day survival in those treated with systemic corticosteroids. Survival benefit was driven largely by the dexamethasone.
- **Monoclonal Antibodies**
  - **Most likely to be efficacious in days 1-10 from onset of symptoms in outpatients**
  - Early Use Authorization by FDA for **outpatients only** who are defined as high risk of progression, defined as patients who meet at least one of the following criteria:
    - Body mass index (BMI) ≥35
    - Chronic kidney disease
    - Diabetes
    - Immunosuppressive disease
    - Age ≥65 years
    - Age ≥55 years and one of the following:
      - Cardiovascular disease
      - Hypertension
      - Chronic obstructive pulmonary disease/other chronic respiratory disease
    - Age 12-17 years and one of the following:

        - BMI ≥85th percentile for their age and gender based on CDC growth
        - Sickle cell disease
        - Congenital or acquired heart disease
        - Medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19)
        - Asthma, reactive airway or other chronic respiratory disease that requires daily medication for control
    - **Casirivimab + Imdevimab (Regeneron)**
        - Combination of two monoclonal antibodies (casirivimab and imdevimab) designed to specifically block two areas of the 'Spike Protein' of SARS-CoV-2 and, hence, infectivity of the virus
        - FDA issued an Emergency Use Authorization (EUA) letter on 21 Nov 2020 (see also: Medical Letter Dec 28, 2020), updated 3 June 2021.
        - Among seronegative patients, median time to symptom alleviation (defined as symptoms becoming mild or absent) was 13 days in placebo, 6-8 days with the monoclonal combination. Those with high viral loads at baseline had the most benefit in terms of time to symptom alleviation.
            - Serious adverse events occurred in 2 placebo patients, 1 low dose patient and no high dose patients. There were no deaths in the trial.
    - **Bamlanivimab + Etesevimab (Lilly)**
        - Monoclonal neutralizing IgG1 monoclonal antibodies that bind to distinct but overlapping epitopes within the receptor binding domain of the spike protein of SARS-CoV-2.
        - **Not active vs Delta variant.**
        - Early Use Authorization by FDA for outpatients issued 10 Nov 2020 for Bamlanivimab; (Prescribing information here; see also Medical Letter Nov 30, 2020) and for Etesevimab on 9 Feb 2021 (EUA and FDA fact sheet)
        - **Oupatient** clinical trial data
            - BLAZE-1: N Engl J Med. 2020 Oct 28;NEJMoa2029849: Reduction in hospitalizations and ER visits for the bamlanivimab treated subjects (e.g., 1.6% in bamlanivimab recipients vs 6.3% Placebo), more rapid improvement in symptoms with bamlanivimab and a favorable safety profile. There were no deaths in the trial.
            - No significant effect on viral load unless used in combination with a second monoclonal antibody, Etesevimab (JAMA. 2021 Jan 21;e210202).
        - **Hospitalized patients** (ACTIV-3: N Engl J Med. 2020 Published Online Dec 22; DOI: 10.1056/NEJMoa2033130): Study terminated on the recommendation of the data and safety monitoring board due to futility in meeting the primary efficacy outcomes of time to sustained recovery and ordinal outcome scores at 5 days.
    - **Sotrovimab (GSK)**
        - Monoclonal IgG1-kappa anti-SARS-CoV-2 antibody
        - Similar to Bamlanivimab + Etesevimab and Casirivimab + Imdevimab, but Sotrovimab is a single antibody preparation (not combination)
        - Early Use Authorization from the US FDA on 26 May 2021
        - Indications for use ~ identical to the other EUA antibodies above
        - Not indicated for Hospitalized patients

- **Janus Kinase (JAK) Inhibitors**
    - **Baricitinib (Lilly)**
        - Specific JAK-1 and JAK-2 inhibitor.
        - EUA issued by US FDA on 19 Nov 2020 based on ACTT-2 trial that showed modest improvement when administered in combination with remdesivir in hospitalized adults and children aged ≥2 years with COVID-19 who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)
            - Recovery time was improved by 8 days in the subset of patients receiving non-invasive ventilation or high-flow oxygen devices at baseline (10 days versus 18 days).
            - Rate of progression to death or invasive ventilation was lower in the combination therapy group (12.2% vs. 17.2%; rate ratio, 0.69; 95% CI, 0.50 to 0.95).
            - Trend toward lower 28-day mortality in the combination therapy group.
            - **Patients were excluded from the trial if they were receiving corticosteroids:** Risks and benefits of baricitinib vis-a-vis dexamethasone are unknown and will require further study. Accordingly, remdesivir plus dexamethasone is preferred over baricitinib + remdesivir, which should be used only in situations where corticosteroids cannot be used

- **Convalescent plasma**
    - **Efficacy uncertain, most likely to be effective in patients with early stage of disease and at risk of progression to severe disease (**see Critical Care Medicine DOI: 10.1097/CCM.0000000000005068**). Monoclonal antibody, if available, preferred over convalescent plasma**
        - Lower rate of severe respiratory disease observed in older adults (age 75 and older and age 65 to 74 for those with a co-existing condition for progression to sever disease) with administration of high titer anti-SARS-CoV-2 antibody (anti-spike protein IgG titer > 1:1000) convalescent plasma within 3 days of symptom onset compared to placebo in one randomized trial (N Engl J Med. 2021; 384:610). An observational study (N Engl J Med 2021;384:1015) found similar results with improved mortality in patients treated with high titer anti-S antibody convalescent plasma within 3 days of diagnosis; no benefit in younger patients or those on mechanical ventilation.
        - Meta-analysis (JAMA 2021; 325:1185) of 1060 patients in 10 randomized trials found no benefit in all-cause mortality or other outcomes for convalescent plasma compared to placebo or standard care.

- **IL-6 receptor antagonists**
  - **Tocilizumab**
    - The most recent IDSA guidelines make a **conditional recommendation**, low certainty of evidence, for use of **Tocilizumab** in addition to standard of care, including corticosteroids, for progressive severe or critical disease in patients with COVID-19 pneumonia. (Link to most recently published IDSA review of IL-6 inhibitor studies here.) Revised NIH guidelines make similar recommendations. **Tocilizumab should be given only in combination with dexamethasone** (or another corticosteroid at an equivalent dose). Use of **Tocilizumab should be avoided in patients with any of the following**: (1) significant immunosuppression, particularly in those with a history of recent use of other biologic immunomodulating drugs; (2) alanine transaminase >5 times the upper limit of normal; (3) high risk for gastrointestinal perforation; (4) an uncontrolled, serious bacterial, fungal, or non-SARS-CoV-2 viral infection; (5) absolute neutrophil count <500 cells/μL; or (6) platelet count <50,000 cells/μL.
    - Clinical trial results:
      - Roche announced in a press release of that its phase III tocilizumab failed to meet its primary endpoint (7- category ordinal scale based on need for supplemental oxygen requirements, and intensive care and/or ventilator use) in hospitalized adult patients with severe COVID-19 associated pneumonia.
      - Phase III double-blind randomized trial (N Engl J Med. 2020; 383:2333) of tocilizumab compared to placebo for hospitalized, moderately ill patients with confirmed COVID-19 found no difference in intubation or death, worsening of disease; or time to discontinuation of supplemental oxygen.
      - Randomized controlled trial (N Engl J Med. 2021; 384:20) of tocilizumab versus placebo for hospitalized patients with COVID-19 pneumonia found that tocilizulmab reduced likelihood of progression to the composite outcome of mechanical ventilation or death, but did not improve survival.
      - Randomized ongoing international, multifactorial, adaptive platform trial (NEJM 2021, Feb 25; NEJMoa2100433. doi: 10.1056/NEJMoa2100433) of ICU patients receiving high-flow nasal cannula oxygen support, non-invasive or mechanical ventilation, or pressor support reported improved outcomes, including mortality with **Tocilizumab** (353 patients).
      - RECOVERY open-label trial (pre-print in medRxIV, not peer reviewed) of 2022 patients randomized to tocilizumab compared with 2094 patients randomized to usual care (82% of patients overall were taking a systemic corticosteroids) reported a mortality benefit at 28 days with tocilizumab , 596 deaths (29%) vs. 694 deaths (33%) (p=0·007). Tocilizumab also increased the probability of discharge alive within 28 days from 47% to 54% (p<0·0001). Trends toward benefit, not reaching statistical significance in most cases, were seen in several patient subgroups , including those requiring only supplemental oxygen and non-invasive ventilation, but not mechanical ventilation. Tocilizumab in combination with corticosteroids reduced mortality compared to those receiving corticosteroids and usual care 457/1664 (27%) vs. 565/1721 (33%), RR= 0.80 (95% CI 0.70–0.90)], but not in those not receiving corticosteroids).
  - **Sarilumab:** Regeneron Pharmaceuticals and Sanofi announced in a press release that the U.S. Phase 3 randomized controlled trial of sarilumab added to best supportive care compared to best supportive care alone (placebo) failed to meet its primary and secondary endpoints.

Stewardship Considerations:

- Concomitant bacterial pneumonia is **uncommon**. Hence, routine coverage for bacterial co-infection is not recommended
- **Hospitalized patients** with COVID-19 pneumonia may develop bacterial and fungal pneumonia **in the health care setting**
  - Overall bacterial infection rate of 7.1% with 3.5% of patients infected at presentation and with 15.5% of patients developing secondary bacterial infections over the course of illness (Clin Microbiol Infect 220; Jul 22;S1198-743X(20)30423-7)
  - Single center study of 4267 hospitalized patients in New York City between 3/1/20 to 4/28/20 (Infect Control Hosp Epidemiol 2020; Jul 24, 1-13. doi: 10.1017/ice.2020.368) found overall bacterial and fungal infection rate of 3.6% with respiratory only infection in 46%, blood only in 40%, both in 14%. 95% of patients with positive respiratory cultures were intubated. Similar findings in a second multicenter study (Open Forum Infect Dis. 2020 Dec 21;8(1):ofaa578).

Comments

Anticoagulation

- **Rapidly evolving area**
  - Two randomized controlled trials, one in non-critically ill patients (N Engl J Med. 2021;385:790-802) and the other in critically ill patients requiring ICU-level care (N Engl J Med. 2021;:777-789), compared outcomes with therapeutic anticoagulation with heparin to usual care in hospitalized patients with COVID-19.
    - **In non-critically ill patients**, there was a 4% difference (80.2% vs 76.4%) in survival without receipt of organ support in the therapeutic anticoagulation group compared to usual care (98.6% probability of superiority); the difference in hospital survival until discharge was not statistically significantly different.
    - I**n critically ill patients requiring ICU-level care**, therapeutic anticogaulation compared to usual care did not result in improved survival or in fewer days of cardiovascular or respiratory organ support.

Other Therapies Under Study

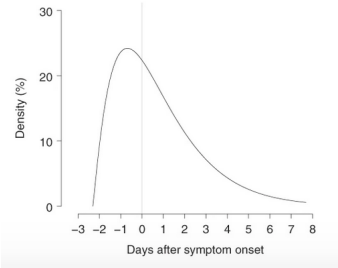
- **Colchicine: Efficacy unproven**
  - Randomized placebo controlled trial (not peer reviewed, pre-print in medRXiv) of non-hospitalized patients with proven or suspected COVID-19 found no statistically significant difference in the primary efficacy composite endpoint of death or hospitalization for COVID-19 in the primary analysis population, with possible benefit (4.6% vs. 6%) in a subpopulation analysis of those who tested PCR-positive for COVID-19.
- **Interferon beta 1-a**: **Efficacy unknown, not recommended outside of a clinical trial.**
  - Press release on July 20 from Synairgen announced positive results of a phase II placebo controlled trial of inhaled interferon-beta.
- **Ivermectin: Efficacy unproven: not recommended outside of a clinical trial.**
  - Limited data, mostly unpublished and not peer-reviewed.
  - Manufacturing company (Merck) recommends against using ivermectin for treatment of COVID-19 disease
- **IL-1 inhibitors: Efficacy unproven, not recommended outside of a clinical trial.**

Other Therapies Studied: Efficacy Not Shown

- **Chloroquine or Hydroxychloroquine ± Azithromycin: Not recommended** in any setting due to lack of efficacy and risk of serious, potentially fatal cardiac arrhythmia
- **HIV protease inhibitors: Not recommended**, clinical benefit not demonstrated
- **Vitamin supplements (B, C or D) or zinc**: No conclusive evidence supporting benefit

Transmission

- Predominantly droplet, less commonly airborne; asymptomatic persons can transmit infection
  - Transmission through contact with contaminated surfaces or objects (fomites) is low (generally 1:10,000) according to CDC Guidance 5 Apr 2021
- **Maximum viral shedding begins prior to onset of symptoms**, see figure below (He et al, Nature on line, 15 Apr 2020 (Figure 1c excerpt used with permission)



- **Mean incubation time is estimated to be ~5 days after exposure** (range 4.1 - 7.0 days, but as short as 36 hours.
- **Viral shedding** (References: Nature. 2020;581(7809):465-469; Lancet Infect Dis. 2020;20(5):565-574; Nat Commun. 2021 Jan 11;12(1):267, N Engl J Med . 2021 Jan 27. doi: 10.1056/NEJMc2027040):
  - Infectious virus unlikely to be isolated after the first week from onset of symptoms, falling to below 5% after 2 weeks.
  - Shedding of viral RNA assayed by RT-PCR from saliva and nasopharyngeal secretions remains high for approximately 6 days, declines significantly in the second week of illness, and usually ceases after 2-3 weeks.
- **Emerging SARS CoV-2 variants**
  - See CDC for current information on emerging variants and implications for vaccine efficacy and possibility of re-infection.
  - Alpha and Beta variants are ~ 50 - 60% more infectious than the original wide-type strain
  - Delta variant is ~60% more infectious and transmissible than the alpha strain (and by extension, ~ 90% more infectious than the original wild-type strain)
- **Re-infection**
  - Re-infection accounts for <1% COVID-19 cases. An observational cohort study (The Lancet, published online March 17, 2021) conducted in Denmark estimated the protective immunity of prior COVID-19 infection to be ~80% overall and ~47% in persons age 65 years and older. The protective effect was durable with protection out to 7 months and longer.

Mitigation / Quarantine / Isolation

- **Masks Work:** Reduction in transmission documented in multiple studies, summarized here (JAMA, Feb 2021; MMWR March 5, 2021)
- Interim CDC guidance (updated 29 July 2021) on how **fully vaccinated persons** do not need to quarantine if asymptomatic, but should be tested at day 3 - 5 after exposure and wear a mask until their test is negative.
  - Resume activities outdoors without wearing masks or physically distancing, except in health care, long-term care, and correctional facilities; in homeless shelters; or as mandated for public transportation.
    - Immunocompromised persons who have been fully vaccinated should consult their physicians before relinquishing a face mask.
  - Resume domestic travel and refrain from testing before or after travel or self-quarantine after travel
  - Refrain from testing before leaving the United States for international travel (unless required by the destination) and refrain from self-quarantine after arriving back in the United States
  - Refrain from quarantine following a known exposure if asymptomatic
  - Refrain from routine screening testing if feasible

- **CDC Federal mask mandate for conveyances and transportation hubs** (expires 13 Sep 2021).
- **Quarantine following exposure to COVID-19**
    - Updated CDC Guidance (2 Dec 2020) here.
        - 10 days without testing and no symptoms
        - 7 days with negative test result (within 48 hrs of intended discontinuance) and no symptoms
        - Fully vaccinated people with no COVID-like symptoms do not need to quarantine following an exposure to someone with suspected or confirmed COVID-19; they should be tested 3- 5 days after exposure (as above).
        - Fully vaccinated people should still monitor for symptoms of COVID-19 for 14 days following an exposure. If they experience symptoms, they should isolate themselves from others, be clinically evaluated for COVID-19, including SARS-CoV-2 testing, if indicated.
- **Isolation following positive test ± symptoms**. See CDC Clinical Care Interim Guidance 20 Jul 2020.
    - For persons who are COVID-19 positive **and** symptomatic who were directed to self-care at home (or hotel, dormitory), isolation may be discontinued:
        - After 10 days from symptom onset **and** after 24 hours from fever resolution (without use of fever-reducing medication) **and** other symptoms have improved
    - For persons who remain asymptomatic after a positive RT-PCR for SARS CoV-2:
        - After 10 days from date of positive test
    - Test-based strategy no longer recommended to determine when to end home isolation (except in specific situations, i.e., immunocompromised)
- **Return to work for Healthcare providers** after COVID-19: see CDC guidance.
    - Mild / moderate illness: 10 days from symptom onset + 24 hours from resolution of fever (without fever-reducing meds) + improved symptoms
    - Severe illness: 20 days from symptom onset + 24 hours from resolution of fever (without fever-reducing meds) + improved symptoms

Testing / Diagnostics

- **Testing Recommendations**: see https://www.cdc.gov/coronavirus/2019-ncov/hcp/testing-overview.html.
    - Asymptomatic individuals with recent known or suspected exposure to SARS-CoV-2 to control transmission.
    - Individuals with signs or symptoms consistent with COVID-19
    - Asymptomatic individuals without known or suspected exposure to SARS CoV-2 in special settings that can lead to rapid spread (e.g., long-term care facilities, correctional/detention facilities, homeless shelters, congregate work or living settings)
    - Selected individuals being tested to determine resolution of infection (e.g., test-based strategy for early return to work for healthcare providers, immunocompromised patients)
    - Individuals being tested for purposes of public health surveillance for SARS-CoV-2
- **RT-PCR and nucleic acid amplification tests**
    - For diagnosis of active COVID-19 infection (See IDSA Guidelines at https://www.idsociety.org/practice-guideline/covid-19-guideline-diagnostics; excellent review of current state of diagnostic testing in Ann Intern Med 2020;172:726;
    - **Specimen**: upper respiratory nasopharyngeal (NP) swab preferred (see CDC interim guidelines (above) and JAMA 2020 Mar 11. doi: 10.1001/jama.2020.3786 for yields of different specimen types).
    - **Test kits**: The U.S. FDA has issued Emergency Use Application (EUA) letters for a growing list of SARS CoV-2 / COVID-19 diagnostic tests. Accuracy and/or reliability remains highly variable. See FDA for current details: https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations
- **Antigen tests** (See CDC guidance and FDA website for details)
    - Antigen tests detect viral protein fragments of proteins from samples collected from the nasal cavity using swabs.
    - Anitigen tests, performed on nasal or nasopharyngeal swab specimens are relatively inexpensive, rapid, point-of-care tests that can be useful for screening in high risk congregant settings, in diagnosis of infection in those exposed to a known case of COVID-19, and in diagnosis of infection in symptomatic patients. Sensitivity is less than RT-PCR; specificity is high. Rapid antigen tests are most sensitive in individuals who are tested during early stages of infection when viral load is generally highest.
- **Serological (Antibody) testing** (See FDA website for details)
    - IDSA Guidelines on COVID-19 serological testing here.
    - Cochrane review of serological testing here.

References

- NIH COVID-19 Treatment Guidelines.
- IDSA Guidelines on Treatment and Management of Patients with COVID-19
- WHO Clinical Management Guidelines (January 25, 2021) and WHO Therapeutics Review
- CDC Coronavirus information
- WHO Coronavirus information