Hospital Operations Toolkit for COVID-19

Patient Care Policies/Processes:

Clinical Treatment of COVID-19

November 30, 2020

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UPDATE 2/3/2023: This document is based on information that was available as of October, 2021. Clinical treatment of COVID-19 continues to evolve. ASPR TRACIE recommends clinicians monitor the National Institutes of Health, Centers for Disease Control and Prevention, and other reliable sources of information. This section provides a summary of some current issues and treatment of COVID-19. The references included are representative or used as examples, but this document is not intended to be a comprehensive review nor be a source of clinical advice.

Clinical Presentation

- Estimations of hospitalized cases and those causing death are difficult due to the number of asymptomatic cases. Seroprevalence studies have suggested that approximately 30% of adults and 80% of children are asymptomatic. With the increase in vaccinations for those 12 years of age and older, seroprevalence studies have waned in some states. Notably, adults not vaccinated are about 5 times more likely to contract the highly contagious Delta variant and about 25 times more likely to die compared to vaccinated adults.
- Published hospitalization rates are around 8-20% for adults who develop symptoms (with risk markedly increased in those with underlying medical conditions), and about 1% for children; intensive care unit (ICU) hospitalization nationally is around 17% of cases. It is unclear if the Delta variant causes increased hospitalization rates though a study from Scotland suggests this may be the case (1.85 times). These rates seem to be fluctuating as the epidemic evolves, perhaps due to younger, healthier people being infected or unvaccinated compared to the initial phase of the pandemic. Other possibilities include viral mutation, improved treatments, vaccinations, or a combination of factors.
- Classic presentation has a wide range of symptoms that range from mild to severe and may include some of the following: fatigue, fever or chills, shortness of breath, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion, nausea or vomiting, diarrhea, and cough. Up to 40% of mild cases will not have fever.

- Symptoms may appear 2-14 days after exposure to the virus. Duration of symptoms is usually about one week to fourteen days for mild to moderate illness. More severe to critical illness or severe immunocompromise varies but can be for several weeks or longer.
- In the second week of illness, a minority of patients will experience worsening symptoms usually including hypoxia. Hypoxia can be clinically severe, but not be particularly bothersome to the patient (i.e., "happy hypoxia") where patients experience low oxygen saturation (S pO2<90%) but are not in respiratory distress and often appear clinically well. It can, however, progress to respiratory failure and this can occur rapidly.
- Anosmia or ageusia are frequently reported and can be the only symptoms experienced. Other gastrointestinal (GI) side effects are less common but can include anorexia, diarrhea, and more rarely vomiting. Anecdotally, changes to smell and taste may be less common with the Delta variant and congestion and sore throat more common.
- COVID-19 can present with isolated stroke and including ischemic stroke and cerebral venous thrombosis, though this seems rare. Encephalopathy and encephalitis may develop in intensive care patients and are likely related to hypoxic or metabolic changes produced by intense inflammatory response. The risk for stroke and myocardial infarction (heart attack) remains elevated for several weeks even after mild cases of illness.
- Dermatologic features can be seen in 20% of cases and are highly variable. Common manifestations include maculopapular rashes, urticaria, vesicles, petechiae, and less likely purpura, and occasional chilblains.
- Conjunctivitis can be seen in a minority of cases.
- Pediatric cases have increased due to the contagiousness of the Delta variant though the hospitalization rate is not necessarily changed. Patients seldom develop severe disease unless underlying health conditions (predominately diabetes and obesity) exist. Multisystem inflammatory syndrome may develop in a small number of pediatric patients and mimic Kawasaki disease in presentation. This usually responds well to treatment.
- Incidence of acute kidney injury (AKI) is estimated at 30-40% of hospitalized patients with about 9% requiring dialysis. Rhabdomyolysis is less common.
- Cardiac presentations of COVID-19 are uncommon, but evidence of myocardial inflammation is not uncommon on magnetic resonance imaging of patients and not correlated with disease severity – myocarditis is of unclear significance in asymptomatic patients and has not been shown to progress or be permanent. Most heart failure is due to right ventricular strain and diastolic dysfunction, though severe acute left ventricular dysfunction can occur.
- "Long-haul" symptoms are frequent. Many patients report symptoms continue at 60 days after onset of illness. This usually involves ongoing fatigue but can involve persisting fevers, dyspnea, and cognitive changes. Incidence has some correlation with disease severity – about half of patients hospitalized still had symptoms at one year in one study though another study found only 23% of patients were normal at one year with 56% of hospitalized patients continuing to

experience dyspnea. Antinuclear antibodies may have some correlation with cognitive changes. Persistent symptoms in children are rare and generally mild.

Resources Related to Clinical Presentation

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- American Society of Nephrology. (2020). COVID-19 Toolkit for Nephrology Clinicians: Preparing for a Surge.
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Risk Factors and Predictors of Severe Disease

- Older age – Data from U.S. intensive care patients indicates that the odds ratio (OR) for death is 11.5 when comparing patients age 80 to those age 40. The OR is 7.45 for patients age 70 versus younger patients.
- Elevated d-dimer

- Elevated troponin, particularly when associated with new evidence of heart failure
- Underlying conditions, especially diabetes, new renal failure, obesity (OR 1.6-3), and heart disease (including hypertension and heart failure)

A predictive calculator for severe disease incorporating several of these variables is available with higher scores portending poor outcomes

Resources Related to Risk Factors

- American College of Emergency Physicians. (2020). ACEP COVID-19 Field Guide.
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Treatment

Available treatments and the data supporting their use changes rapidly. Please do *not* use this guide to inform direct medical care of patients. Multiple new treatments are available under emergency use authorization (EUA). NIH has comprehensive guidance available – particularly helpful are Figures 1 and 2 under the Clinical Management Summary section

Outpatient care

- Supportive care
- Antipyresis – early concerns about ibuprofen were not confirmed.
- Monoclonal antibody therapies for prophylaxis and early treatment currently have emergency use authorization (EUA) from the U.S. Food and Drug Administration for treatment of mild to moderate COVID-19 in non-hospitalized patients with laboratory confirmed SARS-CoV-2 infection who are at high risk for progressing to severe disease and/or hospitalization. Evidence suggests significant prevention of disease progression when given early in the course of illness to at-risk patients. Administration is primarily Intravenous (IV) with subcutaneous (SQ) injections approved for post-exposure prophylaxis. As of September 2021, casirivimab + imdevimab

(REGEN-COV) is recommended with sotrovimab as alternate therapy; the efficacy of bamlinivimab + etesevimab against some variants is questionable.

- Inhaled steroids were beneficial in one study in reducing progression of disease and shortening the course of illness (NNT = 8 to prevent repeat acute care visit/hospitalization).

Hospitalized patients

- Monoclonal antibody treatment for hospitalized patients – tocilizumab (and similar agents inhibiting IL-6) and baricitinab (and similar JAK inhibitors) show beneficial effect in patients preventing disease progression in hospitalized patients with severe illness
- Steroids – dexamethasone 6mg x 10 days indicated for patients requiring supplemental oxygen
- Prone positioning as tolerated for hypoxia
- Oxygen – including use of high-flow nasal cannula when available. Intubation if required, use lung protective strategies as per usual acute respiratory distress syndrome (ARDS) care.
- Fluid management strategies are controversial. Generally, in patients with evolving respiratory pathology a fluid-limited strategy may be best consistent with ARDS guidelines. However, in patients with normal lung compliance more aggressive hydration may be appropriate if early evidence of AKI or elevated lactate is present.
- Anticoagulation at prophylactic doses for all admitted patients, escalating to therapeutic for evidence of pulmonary embolism (PE) or deep venous thrombosis (DVT) is recommended. Up to 50% mortality benefit in hospitalized patients versus no anticoagulation and 30% reduction in intubation rate in one study. At present, insufficient information is available to recommend therapeutic anticoagulation for patients without evidence of DVT/PE.
- Remdesivir – probable modest mortality benefit in 5-day course, particularly for patients with severe disease (e.g., hospitalized with oxygen requirement). Patients well enough for discharge should not continue to receive treatment.
- Convalescent plasma – NIH study shows no significant benefit of convalescent plasma for COVID-19 outpatients with early symptoms or for hospitalized patients.
- Statins have been widely reported to exert antiviral activity against many enveloped viruses by inhibiting the cholesterol biosynthesis and decreasing inflammatory response to viral infections – significant reductions (30-40%) in deaths when on statin in two major retrospective analyses. Acute initiation of statins has not been studied.
- Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) – there is conclusive evidence of benefit to remain on these medications if currently using. Data for acute initiation as therapy to prevent severe pulmonary disease is not supported by a recent large study.
- Ivermectin – no current data to support use. Many examples of harm from ingestion of high doses and/or veterinary or topical preparations. Data from outpatients with COVID-19 does not support ivermectin shortening illness course or moderating severity. Larger trials are ongoing.

One of the key articles showing benefit was withdrawn from pre-print status owing to concerns about integrity of the data.

- Azithromycin – single dose treatment has no effect on disease course. Not recommended by current guidelines.
- Extracorporeal membrane oxygenation (ECMO) has been shown to benefit selected COVID-19 patients with refractory hypoxia despite mechanical ventilation. However, mortality benefit is lower than in usual ARDS cases likely related to other organ damage.
- Pulmonary vasodilators such as nitric oxide or epoprostenol (Flolan) may be initiated per usual guidelines and have been beneficial according to anecdotal accounts and small case series. These should be offered when available and appropriate but specific data on outcomes in COVID-19 are lacking at this time (though studies are underway).
- Hospitals should develop multispecialty, multidisciplinary guidelines that offer the most up to date information on supportive care and treatment of patients with COVID-19. The guidelines can help to standardize the use of scarce resources such as critical care beds, therapeutics, and life sustaining measures including continuous renal replacement therapy and hemodialysis.

Resources Related to Treatment

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- American Society of Hematology. (2021). COVID-19 and VTE/Anticoagulation: Frequently Asked Questions.
- American Society of Nephrology. (2020). Overcoming Challenges to the Provision of Acute Dialysis for COVID-19 Positive Patients.
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