ASPR TRACIE Technical Assistance Request

Request Receipt Date (by ASPR TRACIE): 2 April 2020
Response Date: 28 April 2020
Updated Date: 10 March 2021
Type of TA Request: Complex

Request:

ASPR TRACIE received a request for information on clinical presentation, disease progression, and related information from clinicians in the field treating COVID-19 patients.

Response:

This document is a compilation of early reports and findings from published articles and clinical rounds presentations, webinars, and news articles through March 10, 2021.

Please refer to the Centers for Disease Control and Prevention’s Coronavirus Disease 2019 webpage for the most up-to-date information on COVID-19 outbreak management. Please refer to the National Institutes of Health COVID-19 Treatment Guidelines webpage for up to date clinical management information.

This technical assistance (TA) response documents findings and reports from clinicians treating COVID-19 patients in the U.S. We synthesized information on clinical presentation, disease progression, predictive findings, treatment pearls, and other clinical management practices that seemed consistent with other information available. It is important to note that there is only 1 year of data available on COVID-19 and new clinical patterns may emerge along with new prevention and treatment patterns and the pandemic continues.

Clinical Aspects/Clinical Progression

- Patients represent all age groups, ethnicities, and states of health. The CDC COVID-19 Data Tracker provides up to date COVID-19 demographics.
  - Cases by age:
    - Age 18-29 now has the highest case count at 22.5% of total cases.
    - Age 50-64 represents 20.6% of total cases.
    - Under 18 years of age accounts for 11.3% of cases (Updated March 10, 2021)
  - Fatalities by age group:
    - Age 85+ see the highest fatalities (32.4%) (Updated March 10, 2021)
    - 95.5% of fatalities occur in those over the age of 50
  - Cases & Facilities by gender
• More female cases than male. (52.2% compared to 47.8% respectively)
• More male deaths than female. (54.3% compared to 45.7% respectively)
• Between 5 and 25% of those admitted to the ICU die, with dramatically increased mortality with advanced age. Mortality rates have decreased substantially since spring of 2020 hospitalizations in NY City and Italy. (Updated March 10, 2021)
• A variety of comorbidities are correlated with negative outcomes, including hypertension, asthma, post-transplant, heart failure, coronary artery disease, morbid obesity, admission lab values with elevated inflammatory markers, troponin, and d-dimer

Presentation

• Approximately 40% of cases are thought to be asymptomatic and many symptomatic cases have mild symptoms for which they do not seek care. Approximately 80% of initially asymptomatic people with COVID-19 eventually develop some symptoms.
• Initially most patients presented to the emergency department or to emergency medical services (EMS) with fever, chills, headache, cough, shortness of breath. Over the course of the last few months, CDC has expanded the list of symptoms to also include presentation at primary care locations.
  o Fever or chills
  o Cough
  o Shortness of breath or difficulty breathing
  o Fatigue
  o Muscle or body aches
  o Headache
  o New loss of taste or smell
  o Sore throat
  o Congestion or runny nose
  o Nausea or vomiting
  o Diarrhea

The World Health Organization stratifies symptoms and notes that most infected people will develop mild to moderate illness and recover without hospitalization

  o Most common symptoms
    o Fever, dry cough, tiredness
  o Less common symptoms
    o Aches and pains, sore throat, diarrhea, conjunctivitis, headache, loss of taste and smell, rash or discoloration of fingers or toes
  o Serious symptoms
    o Difficulty breathing of shortness of breath chest pain or pressure, loss of speech or movement.
• Observational and published data indicate that nearly 50% of patients have taste /smell abnormality.  
  
1 COVID-19 and anosmia: A review based on up-to-date knowledge
2 Smell and Taste Dysfunction in Patients With COVID-19: A Systematic Review and Meta-analysis
• Patients often present with very low pulse oximetry readings (<80%), and are still conscious, coherent, and conversant (described colloquially as “happy hypoxia”). Deterioration in these patients can be swift. The majority of patients, however, do not present like this, so exertional pulse oximetry should be performed. This has occurred across all age groups.
• The presence of coagulopathy and renal failure is also a serious problem as described in Figure 3.

Figure 1. Emory University Perspective of Disease Progression

This slide from Emory University’s (GA) presentation during Project ECHO COVID-19 clinical rounds, dated April 7, 2020, illustrates how they have “bucketed” their patients’ progression. The sudden cardiac failure can occur as patients improve or after discharge, however the rates of sudden cardiac death have decreased with anticoagulation.

Coagulopathy

Patients are developing hypercoagulability. Acute kidney injury is also occurring in many COVID-19 patients but appears to be as a result of the disease process. Very rarely large vessel strokes have occurred. Managing coagulopathy may be key to stopping cascading lung damage and multi organ system failure, but experts are not in agreement on a single treatment approach. Several approaches have emerged including use of therapeutic anticoagulation for all hospitalized patients, targeted use for those with higher d-dimer levels and/or confirmed thrombotic events, and lower-dose regimens. (Updated March 10, 2021)
• COVID-19 and Coagulopathy: Frequently Asked Questions
• COVID-19-Related Severe Hypercoagulability in Patients Admitted to Intensive Care Unit for Acute Respiratory Failure
• Current Overview on Hypercoagulability in COVID-19
• Coagulopathy in COVID-19: Review and Recommendations
• Full-dose blood thinners decreased need for life support and improved outcome in hospitalized COVID-19 patients
• Anticoagulation, Bleeding, Mortality, and Pathology in Hospitalized Patients With COVID-19
• Diagnosis, Management, and Pathophysiology of Arterial and Venous Thrombosis in COVID-19

Progression

ASPR TRACIE created this timeline of COVID-19 progression based on a review of multiple reports (e.g., anecdotal physician experiences, webinars, journal articles, and news articles).

Figure 5. Timeline of COVID-19 Disease Progression

This timeline shows an approximation of disease progression for COVID-19 patients who were admitted to the hospital between day 5 and 7. Patients with milder symptom presentation follow a similar path in terms of length of illness, but obviously do not progress to critical illness. COVID-19 patients can rapidly progress to death over several days versus weeks when placed on a ventilator. After initial infection subsides additional COVID associated syndromes have been identified that extend the length of recovery.
Associated Clinical Findings and COVID-19 related syndromes (Updated March 10, 2021)

Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with COVID-19
Clinicians are reporting cases of a syndrome similar to Kawasaki Disease affecting children who have had COVID-19 infection. From the CDC’s Health Alert Network Advisory, “patients presented with a persistent fever and a constellation of symptoms including hypotension, multiorgan (e.g., cardiac, gastrointestinal, renal, hematologic, dermatologic and neurologic) involvement, and elevated inflammatory markers. Respiratory symptoms were not present in all cases.” This ASPR TRACIE webinar on COVID-19 and the Effects of Secondary Disasters on Children addresses the management of MIS-C. As of March 6, 2021 there have been 2617 health department-reported cases and 33 deaths. Information on case definition, testing and treatment can be found by the CDC and the American Academy of Pediatrics.

COVID-19 Related Neurological Syndrome
Numerous case reports document a variety of pathologies, as outlined in this paper published in the journal Brain and in the Frontiers in Neurology journal. The neurological effects are bucketed into the following categories 1) encephalopathies, 2) inflammatory central nervous system syndromes, 3) ischemic strokes (discussed above), 4) peripheral neurological disorders, 5) and other neurological symptoms that don’t fit the previous categories, but are consistently present, such as cognitive clouding.

COVID-19 post-illness Syndrome
Numerous cases are being reported of persistent sequela in patients who have recovered from the initial COVID-19 infection, many confirmed with negative tests. Symptoms range from fatigue, dyspnea, joint pain, and chest pain. In an Italian study 87.4% of patients experienced at least one of those persistent symptoms up to 60 days post active infection. ASPR TRACIE developed a TA response addressing COVID-19 post-illness syndrome considerations. (Updated March 10, 2021)

Treatment Pearls for Hospitalized Patients (Updated March 10, 2021)
Please see the NIH COVID-19 Treatment Protocols for current recommendations for critical care/general supportive management, antiviral treatments, immune-based therapy, antithrombotic therapy, and concomitant medications.

General Treatment Pearls

- Tachypnea may lead to hypoxic decompensation – monitor patients carefully
  - There is now consensus to delay intubation by attempting high flow nasal cannula, continuous positive airway pressure (CPAP), and bilevel positive airway pressure (BiPAP).
- Proning patients (both conscious and alert patients and sedated patients) has been recognized as a method to increase patient oxygenation and reduce ventilator induced lung injury in patients with acute respiratory distress syndrome (ARDS). Awake and alert patients can be guided to prone themselves and reminded, by use of bedside charts and verbal reminders, to change positions. Prone positioning systems are available for use. Proning teams and proning protocols for
intubated, sedated patients have been helpful. The Society of Critical Care Medicine has developed a training video on Prone Positioning.

- Minimize patient-ventilator dyssynchrony with encephalopathy
  - Want patients to breathe variably at high flow rate when possible
  - Consider pressure-controlled ventilation (PCV) or airway pressure release ventilation (APRV), where can vary own flow rate and tidal volumes with higher positive end-expiratory pressure (PEEP)
- Protocol for anticoagulation.
  - At a minimum, consider initial prophylactic dosages for all patients and full anticoagulation protocols as clinically appropriate
- Consider IL-6 Antagonist, particularly if IL-6 is elevated or other indicators of systemic inflammatory response, tocilizumab shows survival benefit in critically ill patients
- Lasix may be helpful for hypoxic normotensive patients. Ultimately, COVID-19 patients who require fluid resuscitation or hemodynamic management of shock should be treated and managed identically to those with septic shock
- Prepare for acute kidney injury
- Extracorporeal membrane oxygenation (ECMO) may be beneficial for selective patient population
- On June 15, the FDA revoked the emergency use authorization for chloroquine and hydroxychloroquine. These medications are no longer recommended in the treatment of COVID-19 patients.
- On February 25, 2021 the NIH halted clinical trials of convalescent plasma use in emergency departments citing no harm, but no benefit. (updated March 10, 2021)
- Although supplements such as zinc, vitamin C, and vitamin D have been suggested for prevention or to reduce severity of disease, along with unusual approaches such as ivermectin there is no experimental data thus far to suggest benefit. A very small trial of the antidepressant fluvoxamine to prevent disease progression in outpatients appears promising; a larger trial is in process.

Steroid Therapy

- Based on the results of a clinical study, NIH is now recommending the following criteria for the use of dexamethasone:
  - The COVID-19 Treatment Guidelines Panel recommends using dexamethasone (at a dose of 6 mg per day for up to 10 days) in patients with COVID-19 who are mechanically ventilated (AI) and in patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated (BI).
  - The Panel recommends against using dexamethasone in patients with COVID-19 who do not require supplemental oxygen (AI).

Antiviral Therapy

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3 AKI in Hospitalized Patients with COVID-19
4 Acute kidney injury associated with COVID-19: A retrospective cohort study
5 Extracorporeal membrane oxygenation support in COVID-19: an international cohort study of the Extracorporeal Life Support Organization registry
6 Extracorporeal Membrane Oxygenation for Patients With COVID-19 in Severe Respiratory Failure
Based on current data, NIH recommends the following use of remdesivir under an emergency use authorization.

- **Recommendations for Hospitalized Patients with Severe COVID-19:**
  - The Panel recommends the investigational antiviral agent remdesivir for treatment of COVID-19 in hospitalized patients with SpO2 ≤94% on ambient air (at sea level) or those who require supplemental oxygen (AI).
  - The Panel recommends remdesivir for treatment of COVID-19 in patients who are on mechanical ventilation or extracorporeal membrane oxygenation (ECMO) (BI).

- **Recommendation for Duration of Therapy in Patients with Severe COVID-19 Who Are Not Intubated:**
  - The Panel recommends that hospitalized patients with severe COVID-19 who are not intubated receive 5 days of remdesivir (AI).

- **Recommendation for Duration of Therapy for Mechanically Ventilated Patients, Patients on ECMO, or Patients Who Have Not Shown Adequate Improvement After 5 Days of Therapy:**
  - There are insufficient data on the optimal duration of therapy for mechanically ventilated patients, patients on ECMO, or patients who have not shown adequate improvement after 5 days of therapy. In these groups, some experts extend the total remdesivir treatment duration to up to 10 days (CIII).

- **Recommendation for Patients with Mild or Moderate COVID-19:**
  - There are insufficient data for the Panel to recommend for or against remdesivir for the treatment of patients with mild or moderate COVID-19.

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**Outpatient Antibody Therapy** *(Updated March 10, 2021)*

The anti-SARS-CoV-2 monoclonal antibodies bamlanivimab, bamlanivimab and etesevimab, and casirivimab plus imdevimab are available through Emergency Use Authorizations issued by the FDA for outpatients adults and children 12 years weighing at least 40kg in the first 10 days of mild to moderate illness who are at high risk for disease progression based on age, body mass index, and/or underlying medical conditions. Limited data is currently available but suggests reductions in hospitalization with early treatment (example BLAZE-1 for bamlanivimab). ASPR TRACIE has developed a Tip Sheet on Planning Considerations for Monoclonal Antibody Administration. Note that these medications require intravenous infusion over 16-60 minutes with a one hour observation period afterwards to monitor for potential allergic symptoms. The CDC also offers information on other common over the counter therapies to treat symptoms of COVID-19.

**Predictive Labs**

Taken from What’s Working for COVID-19 Patients, NIH Clinical Treatment Protocols: Laboratory Diagnosis, and validated by numerous subject matter experts, articles, and presentations:
• **CBC with differential:** The white blood count is usually normal in the absence of superinfection/sepsis, lymphopenia is very frequent, and mild thrombocytopenia is common. (https://bit.ly/2UQO8CT)

• **CMP with magnesium and phosphorus:** Liver function tests (ALT, AST) commonly elevated. Creatinine elevations common.

• **Coagulation studies with D-dimer:** PT/PTT/INR is usually normal on initial presentation. Some develop DIC. The D-dimer is commonly elevated and severe elevations are associated with poor outcomes.

• **COVID PCR:** (Respiratory Viral Panel if you suspect alternate viral etiology, coinfection is possible.) False-negative COVID testing found in 10-30% percent of cases (especially if samples are collected too early or inappropriately and are reported higher in rapid antigen testing over molecular testing).78

• **Procalcitonin:** Not increased with COVID-19. If elevated, it may indicate an alternate diagnosis or superimposed bacterial infection. Procalcitonin is not routinely elevated higher than 0.5 ng/mL (https://bit.ly/3bDobxu). It may increase as disease progresses. An elevated procalcitonin in the emergency department should lead you to consider an alternative or additional diagnosis.

• **CRP (ESR similar profile):** Often elevated in COVID-19 patients, and may trend upward with the progression of the disease. It may have some negative prognostic correlation.

• **Troponin:** High correlation with severe disease and complications.

• **CPK, LDH, ferritin, urine legionella, blood cultures, lactate, CK, ABG, and consider G6PD:** Chloroquine may cause hemolytic anemia in G6PD. These labs are helpful for inpatient teams as well.

**COVID-19 Laboratory Testing (updated 5.18.20)**

The FDA has published updated information on all the tests available for COVID-19 diagnostics. The FDA has provided a list of available serological tests along with their expected performance and accuracy.

**Poor Prognostic Factors**

- Absolute lymphocyte count <0.8
- LDH >245 U/L
- Ferritin >300 ug/L
- CRP >100 mg/L
- D-dimer >1000 ng/mL. (https://bit.ly/3bIGQYT)
- Rising troponin, not attributed to renal insufficiency and especially associated with abnormal echo (JAMA, March 2020 and JACC, October 26)

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7 False negative rate of COVID-19 PCR testing: a discordant testing analysis
8 False Negative Tests for SARS-CoV-2 Infection — Challenges and Implications
Clinical Operations Pearls

- Ensure patient’s end of life wishes are known including the desire for prolonged intensive care, prolonged intubation/ventilation, and use of dialysis. Discuss relative prognosis and potential ICU course with family based on known risk factors / current condition and update information as clinical picture evolves.
- Engage palliative team early to work with providers and families assuring adequate symptom control for all patients; consider establishing palliative care unit for patients that are receiving limited interventions.
- Cohort patients to floors or units to restrict personal protective equipment (PPE) use and optimize staff utilization and safety.
- Move IV pumps, continuous veno-venous hemofiltration (CVVH) machines, and all other equipment outside patient rooms to reduce the number of times staff need to enter the room. This enables staff to silence a pump or monitor dialysis from outside the room. Place the patient bed as close to the door/window as possible to facilitate this and determine how to increase line lengths where possible (e.g., IV line) so equipment can be kept outside patient room and managed. Lines and equipment MUST be kept off the floor, however, to decrease the risk of infection. (This would work differently in a cohort area where staff is wearing the same PPE between rooms.)
- Provide phones or tablets to patients and communicate via phone call for awake, alert, and oriented patients; focus on patient self-care.
- Reduce the items that need to be disinfected after being brought into a room. Use pre-made intubation kits in plastic bags, rather than existing boxes, because they are easier to clean and include mostly disposable items.
- Perform CPR with a Lucas or similar device to avoid providers performing compressions.
- Use a “Butterfly” or similar device for in-room sonography, since it can be easily disinfected.
- Patients may require high levels of sedation to prevent self-extubating. It takes between 5 and 7 minutes to get into full PPE; keeping the patient more heavily sedated decreases the risk of in-room issues for patients (although may prolong recovery).
- Central venous access is important for medication administration.
- Plan for unanticipated shortages
  - IV pumps and tubing
  - Cooling blankets
  - CVVH machines
  - Medications
    - Fentanyl, cisatracurium, and other sedatives and paralytics
COVID-19 Staffing Considerations

Figure 4. Tiered Staffing Strategy (Society of Critical Care Medicine)

This graphic is from the Society of Critical Care Medicine publication United States Resource Availability for COVID-19. This plan is for one physician for 96 patients, which is designed for an extremely resource constrained environment. Ideally, the ratio of critical care physician to patients is 1:24.

Using Staff

- Consider using non-ICU trained clinical staff to augment and “stretch” the ICU staff.
- Non-traditional personnel (e.g. orthopedic and neurosurgeons, PT) can be part of proning teams, as they lift and prone patients frequently for their surgeries and know how to do it.
- Outpatient nurse practitioners can help support patients on CVVH.
- Anesthesia staff can be part of procedure team (airways, CVL, A-line, HD Line, OG tubes) and support respiratory therapy.
- Ventilator management team may be helpful (pulmonary critical care, RT, anesthesia, others).
- Ear/Nose/Throat and Interventional Pulmonologists can be part of the tracheostomy team as well as other surgeons.
- Use behavioral health and palliative care for case management and family support.
- Redeployment strategies should look at creating/supplementing COVID clinics/ICU/MICU expansion and other units with higher than normal census/daily intensity.
- Have medical students and scribes collect and document information to share this information with clinicians and assist with data sharing and peer-reviewed articles for publication.
Supporting Staff (ASPR TRACIE Subject Matter Experts)

- Have PPE safety officers (e.g., non-clinical nurse educators, administrative staff) round regularly to instruct/supervise safe PPE use. Assign “doff-icers” to ensure PPE is doffed correctly.
- Care for the caregiver is immeasurably important. Ensure staff have access to mental health support and are given information on self-care in disasters.
- Be prepared to implement “Line of Duty Death” or “Helping Healers Heal” plan when needed—can help ease the loss for family and colleagues.
- Internal communication should occur regularly and take many forms (e.g., emails, rounding, virtual town halls). Ensure engagement and duplicate messaging with all staff and shifts.
- Tracking absenteeism, quarantines, and required isolation can help with staffing plans.
- Promoting effective technology-based patient /family interface can help alleviate stress on all parties and contribute to sense of satisfaction for staff.
- Consider allowing family members to visit critically ill or dying patients – establish policy and safe process for entry, PPE use, exit, supervised donning/doffing.
- Ensure healthcare facilities are practicing social distancing policies for staff not wearing PPE or not working in clinical areas of the facility.

Sources (Updated March 10, 2021)

ASPR TRACIE Subject Matter Expert Reviewers

Craig DeAtley, PA-C, John Hick, MD, and Richard Hunt, MD

American Association of Critical-Care Nurses COVID-19 Update

Association of American Medical Colleges (AAMC) COVID-19 Clinical Guidance Repository

Care for Critically Ill Patients With COVID-19

CDC COCA Calls - all 2020 and 2021 calls indexed

Clinical Characteristics and Outcomes of Patients Undergoing Surgeries During the Incubation Period of COVID-19 Infection

Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China

Coronavirus disease 2019 (COVID-19): Critical care issues

COVID-19 in Critically Ill Patients in the Seattle Region — Case Series


This web page provides links to free e-learning modules relevant to COVID-19, including: Acute Respiratory Distress Syndrome (ARDS), Hypoxemic Respiratory Failure, Pneumonia, and COVID-19 Rx: Treatment Simulations.

ASPR TRACIE. (2020). COVID-19 Clinical Experiences from the Field.

This ASPR TRACIE Technical Assistance response is a compilation of early reports and findings from published articles and clinical rounds presentations, webinars, and news articles on COVID-19.


During a pandemic or other emergency, healthcare facilities face significant challenges to quickly onboard additional healthcare providers when hospital admissions and ICU occupancy increase rapidly. This onboarding checklist can ensure new employees are compliant with administrative requirements, familiar with the mission and culture of the hospital, and understand expectations.


This web app provides guidance, algorithms for triage, treatment, and updated resource protocols related to COVID-19.


This series of videos provides training to non-respiratory therapists on basic respiratory care and ventilator management to increase healthcare surge capacity during a mass casualty incident. The videos cover topics including infection control, terms and definitions, manual and mechanical ventilation, and airway maintenance and suctioning. The training is intended for non-respiratory health care providers to be cross-trained as extenders delivering care to adult patients.


This document describes a project to cross-train non-respiratory therapists to provide basic respiratory care and ventilator management to provide surge staffing capacity during mass casualty incidents. The authors reviewed the literature and legal and regulatory requirements, identified competencies, developed a curriculum, pilot tested the training, conducted exercises, and provided recommendations.


This online course prepares licensed non-intensive care unit clinicians to support hospital critical care teams. The course covers: principles and physiology of mechanical ventilation, initial ventilator setting and adjustments, troubleshooting the ventilator, and ventilating patients in special circumstances.
This 5 part “train the trainer” series is based on military expertise in addressing trauma, stress, resilience, and wellness adapted to support the mental health of frontline workers affected by the COVID-19 pandemic.


These guidelines reflect the best information available to guide decision making in the management of COVID-19 patients. Included is information on screening and triage, infection prevention, specimen collection, clinical management, treatment options, telemedicine, emergency medical services, and ethical considerations. It also includes appendices with checklists, supply lists, algorithms, and other tools.


This collection of resources provides training and job aids for numerous critical care and infectious disease management skills that may be new or require refresher training for healthcare providers.


This toolkit provides resources to surge critical care skills to respond to COVID-19 via a team-based care approach.


This resource page includes several editable airway management infographics, a training video on tracheal intubation, and a consensus statement on airway management and tracheal intubation of adult COVID-19 patients.


These free, online modules provide training for non-intensive care unit clinicians to provide care during a surge of critically ill patients. **NOTE:** The next course is not offered until August 12, 2020, but you can register for the listserv to be notified of new offerings.


This web page includes several disaster/ emergency resources specifically for clinicians responding to disasters to include COVID-19.

This one-page flyer provides information on the Extension for Community Health Outcomes (known as Project ECHO). HHS ASPR, in collaboration with the National Ebola and Special Pathogens Training and Education Centers (NETEC), and Project ECHO, launched a series of three COVID-19 Clinical Rounds: 1) Critical Care: Lifesaving Treatment and Clinical Operations; 2) Emergency Department: Patient Care and Clinical Operations; and 3) EMS: Patient Care and Operations. The intent of the initiative is to create peer-to-peer learning networks where clinicians who have more experience treating patients with COVID-19 can share their challenges and successes with clinicians across the U.S. and the world. NOTE: A link to listen to previous Clinical Rounds is located at the bottom of the flyer. In particular, the Critical Care series may be useful. Our COVID-19 Critical Care Surge Resources page also links directly to the videos to these Clinical Rounds.


This resource compilation includes information from various sources for clinicians looking for COVID-19 clinical data.