ASPR TRACIE Technical Assistance Request

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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 May 18, 2020.

Please refer to the Centers for Disease Control and Prevention’s Coronavirus Disease 2019 webpage for the most up-to-date clinical guidance on COVID-19 outbreak management.

This technical assistance 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.

Clinical Aspects/Clinical Progression

- Patients represented all age groups, ethnicities, and states of health
  - Many more young, healthy patients than anticipated, although “most” are still over the age of 40
  - More males than females
- Between 12 and 25% of COVID-19 hospital admissions progressed to the intensive care unit (ICU)
- Between 5 and 25% of those admitted to the ICU die
- 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 troponin and D-dimer
- Between 90 and 97% of ICU patients required intubation

Presentation

- Patients present with fever, chills, headache, cough, shortness of breath.
- Less frequent symptoms include loss of smell or taste, nausea, vomiting, diarrhea, runny nose, sore throat, and other symptoms. Observational data indicate that nearly 50% of patients have taste/smell abnormality. (ASPR TRACIE SME comment)

- Patients requiring ICU care are presenting with very, 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 must be performed. These patients can be fine at rest and while admitted to the floor, do not need ICU care, but can also suddenly deteriorate. This has occurred across all age groups.

- The presence of coagulopathy and renal failure is also serious problem as described in Figure 1.

Figure 1. Bellevue Perspective of Disease Progression

This slide from Bellevue’s (NY) presentation during Project ECHO COVID-19 clinical rounds, dated March 31, 2020, illustrates two general pathways for patients. They either come in mildly ill and progress to critical or they present critically ill. Patients in other facilities experienced a different pathway once admitted to the ICU; they experienced respiratory failure classified as either “typical ARDS” or a normal compliance severe viral pneumonia. (ASPR TRACIE SME Comment)
The Disease

- COVID waits for no one
- Slow, extended plateaus with rapid, unpredictable transitions over hours
  - Prodrome
    - Silent hypoxia (O2 2-8L, comfortable, floor phase)
    - Struggling (O2 10-15L, increasingly tachypneic +/- anxiety&SOB, worse CXR)
    - Increasing presentation, some recover from this phase but fewer, must be in ICU
  - Respiratory Failure (O2 > 15L)
    - HFNC or Intubation
  - Recovery or M0SF/sudden death
- Encephalopathy, atypical hypoxic failure (normal compliance, not really ARDS, mild AHI, variable but common AKI, hypercoagulability, difficult & occult secretions)
- Sudden death (hyperinflammatory/myocarditis picture) still appears uncommon
  - Seen a few, investigating currently

Recent Clinical Findings

Patients are developing hypercoagulability. The next two slides from Emory University’s presentation during Project ECHO COVID-19 clinical rounds, dated April 7, 2020, discuss these findings and their new treatment guidelines. Acute kidney injury is also occurring in many COVID-19 patients but appears to be as a result of the disease process. Managing coagulopathy may be key to stopping cascading lung damage and multi organ system failure, but full treatment with heparin is controversial.
Hypercoagulability

VTE and Prophylaxis Guidelines for COVID-19

Level 1: No VTE and D-dimer < 3,000
- LMWH 0.5mg/kg/day
- Dose adjustments for obesity and renal impairment +/- UFH
- Discharge with 7 days LMWH/DIAC

Level 2: No VTE and D-dimer ≥ 3,000
- LMWH 1mg/kg/day
- Heparin low-standard
- Discharge with 4-6 weeks LMWH/DIAC

Level 3: Known or suspected VTE*
- LMWH 1mg/kg/Q12
- Heparin high-standard
- Discharge with 3 months LMWH/DIAC

*Consider for unexplained increase in oxygen requirement, dead space, or organ failure (e.g., AKI, MOF).

Increasingly evident part of fundamental pathology of COVID
- Evidence: clotting lines, pulmonary deadspace, DVT, few PE
- Microvascular damage and thrombi
  - May be source cardiomyopathy and sudden death
  - May account for increased deadspace and MV requirements
- New protocol to address aggressively
Additional Clinical Findings (Added May 18, 2020)
Two additional clinical presentations have appeared within the last several weeks tied to COVID-19.

Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with COVID-19
A number of states in the United States and other countries 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.”

Large Vessel Stroke in Younger Patients
Possibly tied to the earlier discussion of hypercoagulability in COVID-19 patients, there have been recent studies published discussing large vessel strokes in younger patients1,2, for several of these patients, the stroke was the reason for seeking care and not previous COVID-19 symptoms.

Timeline of Disease 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 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.

Treatment Pearls for Hospitalized Patients

- Tachypnea may lead to hypoxic decompensation – growing pulmonary dead space
- There is disagreement as to a preference for early intubation
  - Some clinicians and healthcare facilities are still following protocols for early intubation on the assumption that patients decompensate very quickly.
  - Other facilities are trying to delay intubation by attempting high flow nasal cannula, continuous positive airway pressure (CPAP), and bilevel positive airway pressure (BiPAP). These measures are also being combined with awake proning and a process to teach patients to prone on their own, while conscious and physically capable.
- Proning patients (both conscious and alert patients and sedated patients) has been recognized as a method to increase patient oxygenation. Awake and alert patients can be guided to prone themselves and reminded, by use of bedside charts and verbal reminders, to change positions. Proning teams and proning protocols for intubated, sedated patients are also being put into place.
- Minimize patient-ventilator dyssynchrony with encephalopathy
  - Want patients to breathe variably at high flow rate
  - 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)
- Prepare protocols for anticoagulation, as appropriate.
  - At a minimum, consider initial prophylactic dosages for all patients and full anticoagulation protocols as clinically appropriate
- Consider IL-6 Antagonist, if IL-6 is elevated
- Lasix may be helpful for hypoxic normotensive patients
- Extracorporeal membrane oxygenation (ECMO) may be beneficial for selective patient population

Predictive Labs

Taken from What’s Working for COVID-19 Patients, and validated by numerous subject matter experts, articles, and presentations:

- **CBC with differential**: The white blood count is usually normal, lymphopenia is very frequent, and mild thrombocytopenia is common. [https://bit.ly/2UQO8CT](https://bit.ly/2UQO8CT)
- **CMP with magnesium and phosphorus**: Liver function tests (ALT, AST) commonly elevated
- **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**: (RVP if you suspect alternate viral etiology, though coinfection is possible.) False-negative COVID testing found in 10-30% percent of cases (especially if samples are collected too early or inappropriately).
- **Procalcitonin**: This is usually 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 in these patients (https://bit.ly/3bDobxu). It does seem to increase as disease progresses. An elevated procalcitonin in the emergency department should lead you to consider an alternative or additional diagnosis more strongly.

- **CRP** (sometimes ESR too, but difficult for some because it is often performed manually): This is elevated in COVID-19 patients, and it seems to trend upward with the progression of the disease. It may have some prognostic correlation.
- **CPK, LDH, ferritin, urine legionella, blood cultures, lactate, troponin, CK, CKMB, ABG, and G6PD**: Chloroquine causes hemolytic anemia in G6PD; these labs are helpful for inpatient teams as well.

**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 (JAMA. March 2020)

**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.

**Clinical Operations Pearls**

- Ensure patient’s end of life wishes are known relative to prolonged intensive care and discuss relative prognosis with family.
- 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. (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 device, versus sparing a staff member for compressions.
- Use a “Butterfly” or similar device for in-room sonography, since it can be easily disinfected
- Patients are requiring higher 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).
- Prepare to treat cytokine storm – watch for high CRP, high LDL, high IL-6, high ferritin
- Central venous access is important for medication administration.
- Consider ECMO for refractory hypoxia in otherwise previously healthy patients.
- Need to plan for end of life care and reassess patient progress and prognosis regularly. Engage palliative team early; consider establishing palliative care unit.
- 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.
- Orthopedic surgeons and neurosurgeons can be part of proning teams, as they prone patients frequently for their surgeries and know how to do it. Physical therapy and Occupational therapy personnel can support respiratory therapy involvement for intubated patients.
- 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).
- Ear/Nose/Throat and Intervention Pulmonologists can be part of the tracheostomy team.
- Use behavioral health and palliative care on the family contact team.
- 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 collect and document information to share this information with clinicians and submit 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” 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, town halls). Ensure engagement and duplicate messaging with all staff and shifts.
- Tracking absenteeism can help with staff planning.
- Promoting effective technology-based patient /family interface can help alleviate stress on all parties and contribute to sense of satisfaction for staff.
- Ensure healthcare facilities are practicing social distance policies for staff not wearing PPE or not working in clinical areas of the facility.

Sources (updated May 18, 2020)

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
• Guidance for Certifying Deaths Due to Coronavirus Disease 2019 (COVID-19)
• COVID-19 in the United States: Insights from Healthcare Systems
• Clinical Management of Critically Ill Adults with COVID-19
• Underlying Medical Conditions and People at Higher Risk for Coronavirus Disease 2019 (COVID-19)
• COVID-19 Update: Optimization Strategies for Healthcare Personal Protective Equipment (PPE)
• Coronavirus Disease 2019 (COVID-19) Update and Information for Long-term Care Facilities
• Coronavirus Disease 2019 (COVID-19) Update and Infection Prevention and Control Recommendations
• Coronavirus Disease 2019 (COVID-19) Update—Information for Clinicians Caring for Children and Pregnant Women
• Coronavirus Disease 2019 (COVID-19) Update—What Clinicians Need to Know to Prepare for COVID-19 in the United States
• Outbreak of 2019 Novel Coronavirus (2019-nCoV)—Interim Guidance for Clinicians

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


Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19) (updated May 15, 2020)

JAMA Network: COVID-19

Massachusetts General Hospital COVID-19 Treatment Guidance (Page 2 Labs)

New England Journal of Medicine COVID-19 Free Resources

Project ECHO COVID-19 Clinical Rounds: Critical Care Resources

April 21
• Sinai-Grace/Detroit Presentation
• Atlantic Health Systems Presentation
• Session Recording

April 14
• Bellevue Presentation
• University of Munich Presentation
• Session Recording

April 10 - Ventilation Support
• Providence Presentation
• LSU Presentation
• Session Recording

April 7
• Bellevue Update
• University of Minnesota Update
• Emory Update
• Session Recording

April 2, 2020
• Video: https://youtu.be/xB1-mE40eJQ

March 31
• Bellevue Presentation
• NCID Singapore Presentation
• NCID Singapore Pt 2 Presentation
• Session Recording

March 24
• University of Minnesota Presentation
• Emory University Presentation
• Session Recording

Project ECHO COVID-19 Clinical Rounds: Emergency Department Resources

April 23
• LSU Medical Presentation
• Inova Fairfax Presentation
• Session Recording

April 16
• University of Maryland Presentation
• NYC Health + Hospitals Presentation
• Session Recording

April 9
Severe COVID-19

The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application

Towards an Artificial Intelligence Framework for Data-Driven Prediction of Coronavirus Clinical Severity

What’s Working for COVID-19 Patients