Released: June 25, 2020

CLINICAL BEST PRACTICE ADVICE FOR HEPATOLOGY AND LIVER TRANSPLANT PROVIDERS DURING THE COVID-19 PANDEMIC: AASLD EXPERT PANEL CONSENSUS STATEMENT

This is a “living” document that will continue to evolve and will be updated as new information becomes available.
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Overview and Rationale
Coronavirus disease 2019 (COVID-19), the illness caused by the SARS-CoV-2 virus, continues to spread rapidly throughout the world. In most of the United States, hospitals and health care providers are testing for and managing patients with COVID-19. Measures to reduce the community spread of SARS-CoV-2 have effectively been implemented in most areas where incidence is high. Better preparation and management are helping to keep the health care systems in areas with new outbreaks from becoming overwhelmed. However, these measures and patient and provider fear of infection have resulted in major disruptions to health care that may negatively impact the health of patients with liver disease. Nevertheless, we continue to manage the care of our patients with liver disease and our liver transplant recipients by adapting to the unique logistical and pharmacological issues caused by this crisis. Patients with chronic liver disease including cirrhosis may be at higher risk of death from COVID-19, but clinical risk factors in specific liver diseases, such as autoimmune hepatitis (AIH) or liver cancer, or in transplant recipients, are not clearly defined. Although many risks factors for severe COVID-19 are now known, it is unclear if patients on immunosuppressive medications are at increased risk for severe COVID-19. Given the extraordinary amount of rapidly emerging data on COVID-19, it is difficult for any single clinician to stay abreast of the latest information. The goals of this document are to provide data on what is currently known about COVID-19, and how it may impact hepatologists, liver transplant providers, and their patients. Our aim is to provide a template for developing clinical recommendations and policies to mitigate the impact of the COVID-19 pandemic on liver patients and health care providers. As some communities begin a gradual return toward a pre-pandemic state, we must adjust to the “new normal” and provide safe and optimal care in response to changes in our work and surrounding environment. We know that SARS-CoV-2 can be transmitted from asymptomatic individuals, including children, and can be detected in stool after viral clearance from pharyngeal samples. These recommendations have therefore been created to protect our patients, communities, and health care workers. During the initial phase of the pandemic in Italy, up to 20% of health care workers taking care of patients with COVID-19 became infected. The Centers for Disease Control and Prevention (CDC) has reported over 9200 COVID-19 cases in US health care workers, including some with severe outcomes including death. We must continue to work to contain the spread of SARS-CoV-2 to ensure the health of our patients with liver disease and the health care workers who care for them.

* Preprint article that has not been peer-reviewed
Effects of SARS-CoV-2 on the Liver and Evaluation of COVID-19 Patients with Elevated Liver Biochemistries

**What we know**

- The novel coronavirus SARS-CoV-2 is most similar to the beta-coronaviruses, SARS-CoV and MERS-CoV, the causative agents of the SARS outbreak in 2002-2003 and the MERS outbreak beginning in 2012, respectively.
- SARS-CoV-2 is a single, positive-stranded RNA virus that replicates using a virally-encoded RNA-dependent RNA polymerase.
- SARS-CoV-2 binds to and is internalized into target cells through angiotensin-converting enzyme 2 (ACE2), which acts as a functional receptor.13,14
- ACE2 is present in biliary and liver epithelial cells; therefore, the liver is a potential target for infection.15*
- The incidence of elevated serum liver biochemistries in hospitalized patients with COVID-19 ranges from 14% to 58%.1,16–23
  - Primarily elevated AST and ALT 1-2 times the upper limit of normal (ULN) and normal to modestly elevated total bilirubin early in the disease process.21–24
  - Liver injury occurs more commonly in severe COVID-19 cases than in mild cases.20,22,25
  - Rare cases of severe acute hepatitis have been described in patients with COVID-19.16,21,22,26
  - Liver injury in mild COVID-19 cases is usually transient and does not require specific treatment beyond supportive care.20
- Low serum albumin on hospital admission is a marker of COVID-19 severity.19,22,27–29
- AST is usually higher than ALT and is associated with severe COVID-19 and mortality, which may reflect immune-mediated inflammation or non-hepatic injury.18,22,23,25
- Severe liver injury in COVID-19 is uncommon in children; in the rare cases of severe pediatric COVID-19, increases in ALT or AST, when present, are usually mild (<2x ULN).30,31
- COVID-19 has recently been reported as possibly linked with a pediatric multisystem inflammatory syndrome disease with overlapping features of Kawasaki disease and positive COVID-19 antibody testing suggesting a post-infectious entity.
- Liver histologic assessment has been limited but thus far is nonspecific and ranges from moderate microvesicular steatosis with mild, mixed lobular and portal activity to focal necrosis.32,33
- An Italian autopsy series described focal portal and lobular lymphocytic infiltrates and changes suggestive of hepatic vascular involvement.34*
- Elevated liver biochemistries may reflect a direct virus-induced cytopathic effect and/or immune damage from the provoked inflammatory response and cytokine release syndrome.17,35
- Therapeutic agents used to manage symptomatic COVID-19 may be hepatotoxic but rarely lead to treatment discontinuation.20 These include remdesivir and tocilizumab.36
- It is unknown whether SARS-CoV-2 infection exacerbates cholestasis in those with underlying cholestatic liver disease such as primary biliary cholangitis or primary sclerosing cholangitis or with underlying cirrhosis.20
- Patients with chronic lung disease including those with alpha-1 antitrypsin deficiency may be at increased risk of severe COVID-19.

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Emerging data demonstrate that COVID-19 may predispose patients to thromboembolic disease and anticoagulation may improve outcomes in hospitalized patients.\textsuperscript{37,38} 
- An Italian autopsy series described diffuse intrahepatic vascular abnormalities, including partial or complete acute portal and sinusoidal thrombosis and chronic fibrous endothelial thickening, findings that may have contributed to liver injury in these patients.\textsuperscript{34} 
- An awareness of the high rate of thrombotic events in COVID-19 is necessary as this could potentially adversely impact the outcomes in those with chronic liver disease.

The impact of nonalcoholic fatty liver disease (NAFLD) on COVID-19 is controversial but metabolic risk factors such as obesity, diabetes mellitus, and hypertension are associated with COVID-19 severity.\textsuperscript{39,40}

It will be difficult to differentiate whether increases in liver biochemistries are due to SARS-CoV-2 infection itself; its complications, including myositis (particularly with AST>ALT), cytokine release syndrome, ischemia/hypotension; or a drug-induced liver injury.\textsuperscript{20,32}

An approach to evaluating the patient with COVID-19 and elevated liver biochemistries is shown in \textit{Figure 1}.

\textbf{Recommendations}

- Patients with cirrhosis or liver cancer are potentially at increased risk for severe COVID-19. Until further data become available, there should be a low threshold for testing these patients for SARS-CoV-2 if symptomatic.
- Consider etiologies unrelated to COVID-19, including other viruses such as hepatitis A, B and C, and drug-induced liver injury when assessing patients with COVID-19 and elevated liver biochemistries.
- To limit unnecessary transport of patients with COVID-19, ultrasound or other advanced imaging (e.g., MRI/MRCP) should be avoided unless it is likely to change management, e.g., clinical suspicion for biliary obstruction or hepatic/portal venous thrombosis.
- Consider other causes of elevated liver biochemistries, including myositis (particularly when AST>ALT), cardiac injury, ischemia, drug-induced liver injury, and cytokine release syndrome.
- The presence of abnormal liver biochemistries should not be a contraindication to using investigational or off-label therapeutics for COVID-19 (e.g., remdesivir, tocilizumab), although AST or ALT levels >5x ULN may exclude patients from consideration of some investigational agents.
- Regular monitoring of liver biochemistries should be performed in all hospitalized COVID-19 patients, particularly those treated with remdesivir or tocilizumab, regardless of baseline values.
- In patients with AIH or liver transplant recipients with active COVID-19 and elevated liver biochemistries, do not presume disease flare or acute cellular rejection without biopsy confirmation.
- Evaluate all children with elevated AST or ALT for underlying liver diseases and coexisting infections as COVID-19 is not commonly associated with abnormal liver biochemistries in children.\textsuperscript{30}
- Follow guidance in your clinical study protocol and/or by the Food and Drug Administration (FDA) for monitoring of liver biochemistries and discontinuation of study drug used to treat COVID-19.
Diagnosis of SARS-CoV-2 Infection

What we know

- Routine labs including a complete blood count (CBC) with differential and platelets and comprehensive metabolic panel (CMP) can provide useful indirect evidence of infection.
  - Lymphopenia, thrombocytopenia, and hypoalbuminemia are associated with a poorer prognosis (Table 1).
- Inflammatory markers including D-dimer, C-reactive protein, creatine phosphokinase, and ferritin are frequently elevated in hospitalized patients and may be followed over time.
- A chest computed tomography (CT) scan with bilateral ground glass opacities is highly sensitive for the detection of pneumonia caused by COVID-19 but is non-specific.41
  - The American College of Radiology recommends that chest CT should not be used as a first line screening test but rather to confirm the presence of pneumonia in selected hospitalized patients.42–44
- Accurate real-time quantitative polymerase chain reaction (RT-PCR) testing for SARS-CoV-2 relies on sufficient amounts of replicating virus, optimal collection procedures and the collection site (i.e., nasopharyngeal vs. oropharyngeal vs. lower respiratory tract).45
- Nasopharyngeal swabs are more sensitive (63%) than oropharyngeal swabs (32%) while bronchoalveolar lavage (BAL) fluid specimens are the most sensitive (93%) using RT-PCR-based methods, although BAL poses a more significant risk of aerosolizing the virus.46
- In early studies, saliva may be more sensitive and reliable for SARS-CoV-2 detection than nasopharyngeal samples in hospitalized patients and asymptomatic health care workers.47
- Qualitative, isothermal, non-PCR nucleic acid amplification methods can deliver SARS-CoV-2 test results from a nasal or nasopharyngeal swab in <15 minutes but with higher concern for false negatives.48
- Testing samples from multiple sites from the patient or repeated testing from one patient site may improve sensitivity and reduce false negative results.
- SARS-CoV-2 viral load may be low at early stages of disease but higher viral loads are detected soon after symptom onset and decline during the second week of illness.45
- Serological tests (antibody and antigen) have now been developed, which hold promise as non-invasive, rapid, and convenient means of testing for current or past SARS-CoV-2 infection.49,50
  - SARS-CoV-2 antigen testing is less sensitive than PCR but with the advantage of more rapid results and potentially lower cost.50
  - Antibody testing may complement PCR testing to improve detection (IgM), detect subclinical infection (IgM or IgG) and identify individuals who have recovered (IgG).45
  - Antibody testing may also prove valuable in epidemiological studies, identification of convalescent plasma donors, and in the ongoing development of SARS-CoV-2 vaccines and antiviral treatments.
  - Potential drawbacks of serological testing include false negative results early in the disease course, false positive results particularly with IgM testing and potential cross-reactivity with common cold coronaviruses.51
  - In a study of rhesus macaques, SARS-CoV-2 infection induced protective immunity against re-exposure, but it is not yet known if the same is true in humans.52
  - Per the Infectious Diseases Society of America (IDSA), antibody results should not be used to make staffing decision or decisions regarding the need for personal protective equipment (PPE) until more evidence is available.51

* Preprint article that has not been peer-reviewed
**Recommendations**

- Check CBC with differential and platelets and CMP in all hospitalized patients with symptoms suggestive of COVID-19 as part of their initial evaluation, with the understanding that it is common for patients with chronic liver disease to have baseline leukopenia, thrombocytopenia, and hypoalbuminemia.
- Monitoring systemic inflammatory markers may be useful in the assessment of the severity and response to treatment of COVID-19 in hospitalized patients.53*
- Test all patients with suspected COVID-19 with nasopharyngeal swab testing (or saliva if available) using RT-PCR or non-PCR methods.
- Consider retesting patients with a high clinical suspicion for COVID-19 and negative initial test results, as resources permit.
- Point-of-care oropharyngeal swabs can also be used to screen for and diagnose COVID-19, although this is not preferred because of low sensitivity.
- Reserve testing of BAL samples for intubated patients with high clinical suspicion for COVID-19 despite negative nasopharyngeal, oropharyngeal, or sputum testing.
- CT should not be used to screen for or as a first line test to diagnose COVID-19 because of its lower specificity compared to nasal swabs.44,54
- Antibody testing should not be used for the diagnosis of SARS-CoV-2 infection.
- Antibody testing results should not be used as the sole information necessary to make staffing decisions or decisions regarding the need for PPE.

**Stable Outpatients with Liver Disease and/or Hepatocellular Carcinoma**

**What we know**

- Asymptomatic patients and children (who are less likely to become ill from SARS-CoV-2) can contribute to the spread of the virus.30,55
- Information is accumulating regarding the effects of SARS-CoV-2 infection in patients with chronic liver disease.
- Preliminary data from the CDC on 122,653 COVID-19 cases, including 7,162 (5.8%) with data on underlying conditions, showed that 1/3 of these patients (37.6%) had at least one underlying condition or risk factor for severe disease and poor outcomes.56 Among these patients with underlying conditions, only 41 patients (0.6%) had chronic liver disease, including 7 who required ICU admission.56
  - These data are limited by small numbers and missing data (only 5.8% had available data on underlying conditions). Based on the known prevalence of NAFLD in the US population, the estimated prevalence of chronic liver disease in this study is likely underestimated.
- In a large cohort study of electronic health record data from over 17 million patients (>114,000 with chronic liver disease) in the United Kingdom, chronic liver disease was a risk factor for in-hospital death from COVID-19 (HR 1.61, 95% CI 1.33-1.95).5*
- Chronic liver disease was associated with significantly higher mortality (RR 2.8, 95% CI 1.9-4.0) in a cohort of 2780 US patients with COVID-19.57
  - The mortality risk was higher in patients with cirrhosis (RR 4.6, 95% CI 2.6-8.3).

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Fatty liver disease and nonalcoholic steatohepatitis were the most common etiologies in the liver disease group and the mortality risk was independent of risk factors such as body mass index, hypertension, and diabetes.

- There is no evidence that patients with stable chronic liver disease without advanced fibrosis/cirrhosis attributable to hepatitis B and/or C, or cholestatic syndromes such as primary biliary cholangitis or primary sclerosing cholangitis have increased susceptibility to SARS-CoV-2 infection.

- It is unknown whether patients with hepatocellular carcinoma (HCC) are at increased risk for severe COVID-19 by virtue of their malignancy or treatments.
  - A case series reported an association between worse COVID-19 outcomes and a history of non-hepatic types of cancer.
  - Those who underwent recent chemotherapy had an even higher risk of severe COVID-19, but the series also included those without recent chemotherapy.

- The slow median doubling time of HCC supports a rationale of a short delay in radiological surveillance given the challenges many centers are currently facing with COVID-19.

**Recommendations**

- When COVID-19 is prevalent in the community, severely limit outpatient visits to only patients who must be seen in person, even in areas without significant COVID-19 community spread. (See CDC Guidance for Healthcare Facilities.)
  - As clinical practices increase the volume of in-person visits, continue to prioritize new adult and pediatric patients with urgent issues and clinically significant liver disease (e.g., jaundice, elevated ALT or AST >500 U/L, recent onset of hepatic decompensation, selected patients with liver cancer, and selected patients for liver transplant evaluation).
  - Follow CDC recommendations for PPE. If PPE is unavailable keep a distance of at least 6 feet from the patient.
  - Patients, caregivers, and providers should wear masks while in the clinic. Masks should be provided and/or homemade cloth masks should be permitted.
  - Stagger patient arrival times, and if possible, room patients immediately on arrival to clinic to avoid patients congregating in the waiting area. If patients or caregivers are in the waiting area, maintain appropriate distancing and decontamination of the waiting area.
  - Limit the number of family members/friends who accompany patients to their visits. Have these persons wait outside the clinic unless their presence is required for clinical decision making. Enable critical caregivers to participate in the visit by phone or video if possible.
  - Continue to use phone visits or telemedicine as appropriate and available to replace in-person visits.

- Screen all patients for symptoms of COVID-19 or recent exposure (i.e., fever, cough, shortness of breath, sore throat, diarrhea, myalgias, new loss of sense of taste or smell, contact with known COVID-19 patients, history of recent travel) before entry into the clinical space (e.g., phone call 24 hours prior to scheduled visit), and again at registration or as they enter the clinic.

- Check each patient’s temperature and ask about symptoms when they arrive to the clinic or registration desk.
  - Patients with fever (>38 °C) or symptoms should be referred to the hospital’s protocol for symptomatic patients.
Consider evaluating patients with COVID-19 symptoms or known exposure in an outpatient clinic or a site dedicated for this purpose. PPE should be prioritized to that site. Patients with COVID-19 symptoms or known exposure should not be evaluated in the hepatology/liver transplant clinic.

Follow CDC recommendations for cleaning and disinfecting rooms or areas visited by individuals with suspected or confirmed COVID-19.

Continue treatment for hepatitis B and hepatitis C if already on treatment.

There is no contraindication to initiating treatment of hepatitis B and C in patients without COVID-19 as clinically warranted.

Initiating treatment of hepatitis B in a patient with COVID-19 is not contraindicated and should be considered if there is clinical suspicion of a hepatitis B flare or when initiating immunosuppressive therapy.

Initiating treatment of hepatitis C in a patient with COVID-19 is not routinely warranted and can be deferred until recovered from COVID-19.

Continue monitoring in those on or off therapy for HCC and continue surveillance in those at risk for HCC (cirrhosis, chronic hepatitis B) as close to schedule as circumstances allow, although an arbitrary delay of 2 months is reasonable.

- Discuss the risks and benefits of delaying surveillance with the patient and document the discussion.
- These patients should be prioritized for imaging studies as outpatient facilities start to re-open.
- Avoid HCC surveillance in patients with COVID-19 until infection is resolved.

Review images of new referrals for patients with liver masses in tumor board or with expert radiologists in virtual multidisciplinary conference prior to scheduling an in-person visit.

Consider virtual visits to discuss diagnosis and management of HCC and other liver tumors.

Proceed with liver cancer treatments or surgical resection when able rather than delaying them because of the pandemic.

Patients with Decompensated Cirrhosis, Liver Transplant Evaluations, and Patients on the Liver Transplant Waiting List

**What we know**

- Information is growing regarding the effects of SARS-CoV-2 infection in patients with decompensated cirrhosis and those awaiting liver transplantation.29
- Mortality attributable to COVID-19 appears higher in patients with more advanced liver disease.5,29
- Preliminary data from two combined international reporting registries (COVID-Hep and Secure-Cirrhosis) of the first 152 consecutive submissions of COVID-19 patients with chronic liver disease show a high mortality rate of 39.8%.61
  
  - Cause of death in patients with cirrhosis was liver-related in 12.2%, compared to 78.7% pulmonary and 4.3% cardiac.
  - Mortality strongly correlated with Child-Turcotte-Pugh (CTP) class: 12.2% without cirrhosis, 23.9% CTP class A, 43.4% CTP class B, 63.0% CTP class C died.
  - Hepatic decompensation during COVID-19 was strongly associated with subsequent risk of death (63.2% with new decompensation died vs. 26.2% without decompensation).
  - 24.3% with new hepatic decompensation had no respiratory symptoms of COVID-19 at the time of diagnosis.
• A retrospective Italian study of 50 patients with COVID-19 and cirrhosis reported a high rate of hospitalization (96%) and high mortality rate (35% of hospitalized patients).29
  o The most common cause of death was respiratory failure (71%); however, end-stage liver disease (with hypoxemic respiratory failure) was the cause of death in 29% of patients.
  o Overall, liver function worsened and 46% decompensated during the course of their COVID-19 illness.
  o 12% of patients were asymptomatic at presentation and were tested as part of a protocol for contact with positive patients.
  o Compared to patients without cirrhosis hospitalized with COVID-19 during the study period, patients with cirrhosis had a higher 30-day mortality rate (18% vs. 34%) and a lower median age at death (80 vs. 70).
  o Compared to historical controls (cirrhotic patients hospitalized for acute decompensation because of bacterial infection), patients with COVID-19 were older with lower MELD and CTP scores and a higher 30-day mortality rate (17% vs 34%).
• Although it seems clear that patients with cirrhosis and COVID-19 have a higher risk of death compared to patients with COVID-19 alone, emerging data using matched controls suggest that inpatient mortality in patients with cirrhosis and COVID-19 may be similar to the mortality of patients with cirrhosis alone without COVID-19.62
• The complex decision making involved in whether or not to proceed with transplantation has been more challenging because of the COVID-19 pandemic.
• It is essential that transplant centers continuously assess their local situation and its impact on patients awaiting transplantation.
• Some transplant centers restricted or paused their transplant programs because of the pandemic.63
• A reduction in organ recovery occurred because of COVID-19-related limitations on institutional resources and staff involved in organ recovery and our evolving understanding of the risk of donor-derived disease transmission.64
• These factors have had a significant impact on the transplant waiting list and transplant center practice patterns.64
• Risk stratification continues to be important to identify patients who need to be evaluated for transplantation or complete their evaluation during the COVID-19 pandemic, including patients with high MELD scores, risk of decompensation, or tumor progression.

**Recommendations**

**Outpatient management**

• Continue to prioritize patients coming to clinic for transplant evaluations who have HCC or those patients with severe disease and high MELD scores who are likely to benefit from immediate liver transplant listing.
  o Telemedicine can continue to be used to evaluate less urgent patients.
• Continue to assess which listed patients need to be seen in person based on local prevalence of SARS-CoV-2 and individual patient factors such as MELD.
• Consider telemedicine alternatives in place of outreach clinics.
• Obtain labs and imaging only as clinically necessary.
  o Patients should not be asked to update labs or imaging simply to update or maintain their MELD score. Recent [Organ Procurement and Transplantation Network (OPTN)](https://optn.transplant.hrsa.gov)
**Policy changes** provide guidance on how to maintain candidate MELD when updated clinical data are not obtained.

- Ensure that patients have refills available for essential medications. Provide prescriptions for 90-day supplies instead of 30-day supplies. Many insurance companies are waiving early medication refill limits.
- Consider instructing patients to avoid attending in-person community recovery support meetings such as Alcoholics Anonymous and provide alternative telephone or online resources.
- Advise patients to limit travel during the COVID-19 pandemic.
- Consider providing documentation to patients, providers, and organ procurement teams to ease essential travel where travel restriction policies are in place.
- Have a low threshold for admitting to the hospital patients on the transplant waiting list who are diagnosed with COVID-19.
- Test patients with new onset hepatic decompensation for SARS-CoV-2.
- Consider using specific screening facilities and a “COVID-19-free” path through the hospital for transplantation candidates.
  - Recognizing the current limitations with testing of patients and staff, these pathways might be described as “COVID-19-minimal” rather than “COVID-19-free”.

**Patient transplant education and consultations**

- Conduct patient transplant education and social work, dietitian, and financial consultations by video conference, telemedicine, or telephone whenever possible.
- Avoid multiple patients in one room for patient education.
  - Consider developing internet-based education sessions for patients and family members that can be deployed either by in-room computers or at home prior to patient evaluation.

**Liver Transplantation, Resource Utilization, and Ethical Considerations**

**What we know**

- Resource utilization and ethical considerations are inherently tied to liver transplantation. This is a critical and challenging area for which protocols and policies need to be carefully considered and developed. There is no over-arching policy that can or should be applied to every transplant center; these issues will need to be discussed and developed locally.
- Although the Centers for Medicare and Medicaid Services (CMS) recommended limiting all non-essential planned surgeries and procedures, they specifically excluded transplant surgery from this recommendation and categorize transplant surgery as Tier 3b (“do not postpone”).
  - The status of medical and surgical procedures is changing as state executive orders are expiring.
- Most Organ Procurement Organizations are testing donors for SARS-CoV-2 RNA, and those who test positive are medically ineligible for organ donation.
- There is a significant false negative testing rate and transplant programs should consider symptoms of COVID-19 in a potential donor or recipient to be strongly suggestive of infection despite negative testing.
  - Additional data including chest imaging and inflammatory markers (e.g., C-reactive protein, ferritin, IL-6) should be considered.
- Transplantation in SARS-CoV-2-positive transplant candidates is currently not recommended.
**Recommendations**

- Develop a hospital-specific policy for organ acceptance.
  - Ensure hospital administrators are aware of the CMS Tier 3b designation for transplant surgery (“Do not postpone”).
  - Consider resource utilization including ICU beds, ventilators, PPE and supply of blood products (especially platelets and type-specific packed red cells) in the decision to proceed with liver transplantation.
  - Consider changes in local COVID-19 prevalence data to determine if transplantation should be restricted/suspended.

- Consider notifying patients that the COVID-19 pandemic may impact their waiting time on the transplant list.

- Notify patients that family and visitor access to them during their hospital stay may be limited or prohibited.

- Screen potential donors for exposure and clinical symptoms/fever compatible with COVID-19 (regardless of test results or availability).65
  - Alternatives to PCR-based testing such as chest radiography may also be considered.

- Screen potential recipients with an acceptable organ offer for COVID-19 symptoms/fever before they are called in from home for transplantation.

- Consider accepting only grafts with a low risk of delayed graft function to minimize complications and prolonged ICU and hospital lengths of stay.

- Test all recipients and donors for SARS-CoV-2 before transplantation, if testing is available.
  - Consider the risk of false negatives, disease prevalence, and testing turnaround time in your area.
  - Review as much donor history as possible for fever, respiratory symptoms and radiographic findings.

- Consider having backup transplant recipients wait at home or away from the transplant center.

- Consider resuming living donor liver transplant programs that were suspended because of the pandemic.

- SARS-CoV-2-positive transplant candidates may be considered for transplantation at least 14-21 days after symptom resolution and 1 or 2 negative SARS-CoV-2 diagnostic tests.

- See the latest updates regarding COVID-19 related OPTN policy changes.

- An approach to liver transplant organ offers is shown in Figure 2.
Challenging Issues in Liver Transplantation During the COVID-19 Pandemic

- Should we decide who is more in need of limited resources, i.e., COVID-19 patients vs. patients in urgent need of liver transplantation? It is impossible to weigh the value of the life of a patient with COVID-19 against that of a patient in need of life-saving liver transplantation. We should not compound the negative impact of the pandemic by risking the lives of patients in need of liver transplantation. Our goal is to ensure that an appropriately staffed ICU bed is available for every patient who requires one.
- An argument that has been advanced to justify deferring some transplants is a concern about immunosuppressing patients during the COVID-19 pandemic. However, immunosuppressed patients may not be at increased risk for severe COVID-19. Nevertheless, immunosuppressed patients have higher viral titers and may be more infectious than immunocompetent individuals.
- CMS clarified that transplants fall into Tier 3b and should not be postponed.
- Other issues to consider in hospitals with a high prevalence of COVID-19 include the risk of nosocomial transmission during the transplant admission, difficulty obtaining procedures or other resources when complications arise, and limitations on family/caregiver visitation for a postoperative period that often relies on the engagement of caregivers.
- Is there a point at which we will need to ration who will receive a liver transplant? If so, we may need to prioritize patients who are most likely to die on the waitlist and defer those who can wait longer.
- These issues may arise in transplant programs when the community incidence of infection is high and hospitalized COVID-19 patients utilize more resources, and predominantly center on the need for limited ICU beds, ventilators, and blood products. Each program will need to establish its institutional capacity to perform liver transplantation and a process for determining whether or not to proceed when an organ is available.
- These decisions should ideally be made in consultation with local medical ethics committees.

Post-Liver-Transplant Patients and Management of Patients on Immunosuppressive Agents

**What we know**

- Data suggest that the immune response may be the main driver for pulmonary injury attributable to COVID-19 and that immunosuppression may be protective. Rapid pulmonary deterioration in COVID-19 is due to a systemic/pulmonary inflammatory response associated with increased serum IL-6, IL-8 and TNF-α levels.
- Posttransplant immunosuppression was not a risk factor for mortality associated with SARS (2002-2003) or MERS (2012-present).
- The effects of immunosuppression on COVID-19 are not well established.
- Immunosuppression may prolong viral shedding in posttransplant patients with COVID-19.

* Preprint article that has not been peer-reviewed
• A retrospective report from Italy of 10 patients with AIH on immunosuppression and with COVID-19 suggests that the course of COVID-19 may be similar to non-immunosuppressed patients.6
  o 4 patients had cirrhosis, 1 who was decompensated. This decompensated patient was the only one who died.
  o 2 patients were on high-dose corticosteroids for treatment of acute onset of AIH.
  o Prednisone was increased in 2 patients, decreased in 3 patients, and 1 patient stopped taking prednisone.
  o 6 patients were hospitalized, including 5 with pneumonia and 3 requiring non-invasive ventilation.
  o Liver biochemistries remained normal in all hospitalized patients except the 2 on high-dose steroids for treatment of acute AIH (liver biochemistries improved in these 2 patients).
  o The authors suggested that pre-emptive reduction in immunosuppression during COVID-19 can be potentially harmful.

• A retrospective report described the outcomes of 90 solid organ transplant recipients with COVID-19 treated as outpatients or inpatients in New York City.28
  o The report included 13 liver transplant recipients (9 with mild/moderate COVID-19 and 4 with severe disease).
  o Nosocomial transmission was suspected in 3 patients including 1 liver transplant recipient who was undergoing inpatient treatment for refractory rejection.
  o Immunosuppressive medications were reduced in most hospitalized patients: Antimetabolite decreased or held in 88%, steroids decreased or held in 7%, and calcineurin inhibitor decreased or held in 18%.
  o 34% required ICU admission, 35% required mechanical ventilation, 24% died (52% of the ICU patients), and 54% were discharged at the time of publication.
  o There was no reported acute cellular rejection.

• A group from Lombardy, Italy described 6 liver transplant recipients from their program who were diagnosed with COVID-19.66
  o 3 long-term liver transplant recipients died of COVID-19-related pneumonia and ARDS.
  o All were >65 years with hypertension, obesity, diabetes, and hyperlipidemia.
  o 3 recently transplanted (<2 years) patients had mild COVID-19 and did not require hospitalization.

• 39 liver transplant recipients were described in a preliminary analysis of two combined international reporting registries (COVID-Hep and Secure-Cirrhosis).67
  o 9 (23%) died of respiratory failure and 30 survived.
  o 4 of the deaths were in patients transplanted within 2 years.
  o Comorbidities (such as diabetes, hypertension, and obesity) and immunosuppression were not significantly associated with mortality.

• Data have been reported from the first 103 patients of a European registry (ELITA/ELTR) of liver transplant recipients with COVID-19.68
  o 15 (15%) were admitted to intensive care, 68 (66%) were admitted to a general ward, and 20 (19%) were monitored at home.
  o 16 (16%) died, including 4 (44%) of the 9 who were on mechanical ventilation.
  o No patients <60 years old died.
More patients who were transplanted at least 2 years ago died than did those transplanted within the last 2 years (not statistically significant).

- Although the World Health Organization and the NIH continue to recommend avoiding corticosteroids for treatment of COVID-19, these recommendations have not been updated since new data recently emerged about the benefit of dexamethasone in patients with COVID-19 requiring mechanical ventilation or supplemental oxygen.69–71*

- Anti-IL-6 therapeutics have not been shown to increase the risk of acute cellular rejection.

- It is too early to know if posttransplant patients are at greater risk for more severe COVID-19.

- Reducing the dosage or stopping immunosuppressants may cause a flare in a patient with AIH or precipitate acute rejection in a liver transplant recipient.6

**Recommendations**

- **In post-transplant patients without COVID-19:**
  - Do not make anticipatory adjustments to current immunosuppressive drugs or dosages.
  - Emphasize prevention measures posttransplant patients already know well: frequent hand washing, cleaning frequently touched surfaces, staying away from large crowds, staying away from individuals who are ill, etc.
  - Advise patients not to travel during the COVID-19 pandemic.65
  - Minimize in-person visits for posttransplant patients by maximizing use of telemedicine.
  - Consider advocating for telework options, appropriate excuses from work or leaves of absence for posttransplant patients and their primary caregivers.

- **In post-transplant patients with COVID-19:**
  - Consider lowering the overall level of immunosuppression, particularly anti-metabolite dosages (e.g., azathioprine or mycophenolate) based on general principles for managing infections in transplant recipients and to decrease the risk of superinfection.
  - Consider the risk of kidney injury in COVID-19 and monitor calcineurin inhibitor levels.
  - Adjustment of immunosuppressive medications must be individualized based on severity of COVID-19 and risk of graft rejection.
  - An approach to managing liver transplant recipients with COVID-19 is shown in Figure 3.

- **In patients with AIH on immunosuppression without COVID-19:**
  - Do not make anticipatory adjustments to current immunosuppressive drugs or dosages.

- **In patients with AIH on immunosuppression with COVID-19:**
  - Consider lowering the overall level of immunosuppression, particularly anti-metabolite dosages (e.g., azathioprine or mycophenolate) based on general principles for managing infections in immunosuppressed patients and to decrease the risk of superinfection.
  - Adjustment of immunosuppressive medications must be individualized based on severity of COVID-19.

- Initiate immunosuppressive therapy in patients with liver disease with or without COVID-19 who have strong indications for treatment (e.g., AIH, graft rejection).

- In patients with COVID-19, use caution in initiating prednisone, prednisolone, or other immunosuppressive therapy where the potential benefit might be outweighed by the risks (e.g., alcohol-associated hepatitis).

* Preprint article that has not been peer-reviewed
Inpatients

**What we know**

- Health care workers and other hospital staff are at risk for COVID-19.¹¹
- Health care workers with SARS-CoV-2 may spread the virus to patients and to each other and should remain away from in-person work until approved to return by local health authorities.
- Minimizing interactions among health care workers and between health care workers and patients is critical to reducing the spread of SARS-CoV-2.
- Minimizing the transport of patients within and between health care facilities could reduce the spread of SARS-CoV-2.

**Recommendations**

- Consider cohorting of inpatients with COVID-19 from other non-infected patients in the hospital.
- Consider equipping patient rooms with telemedicine equipment (e.g., tablet) to enable remote consultation and monitoring.
- Conduct medical and surgical transplant rounds with the minimum number of personnel needed to provide care at a given time.
- Limit the number of team members who enter a patient’s room for patient examinations and encounters.
  - The same rule applies to inpatient consultations involving other medical or surgical services for the care of patients with liver disease or transplant evaluation. Limit the personnel permitted to enter patient rooms to the minimum needed for the performance of consultative care.
  - Consider conducting virtual visits for updates not requiring direct examination. This will reduce contact risks as well as unnecessary utilization of PPE thereby preserving hospital supplies for essential needs.
- Discourage in-person multidisciplinary rounds with dietary, pharmacy, social work, and care coordination staff.
  - Consider the use of virtual conferencing to reduce direct staff interactions.
- Consider restricting the direct patient care of providers at higher risk (age >65 years, serious underlying medical conditions, immunocompromised).
- Limit or even prohibit the presence of non-essential team members in the hospital (e.g., students, observers, research staff) to minimize exposure risk and prioritize the use of PPE.
- Consider use of telephone or virtual language translation services as needed to reduce contact with patients.
- Patients and visitors (if permitted) should wear masks while in the hospital. Masks should be provided to those without and/or homemade cloth masks should be permitted to preserve PPE resources.
- Limit the number of visitors who may see inpatients.
- Immediately identify caregivers and legal representatives (and collect their emergency contact information) to provide informed consent if a patient is impaired, and to enable provision of regular status updates to them while visitors are not permitted in patient rooms.
- Carefully consider and minimize all requests for imaging and procedures on patients, including blood draws. Order only studies essential for care to reduce institutional resource utilization, including patient transport between hospital locations.
- Consider developing a policy for review and triage of hospital inpatient transfers. For example, when ICU capacity is limited or when risk of nosocomial transmission is high, consider accepting
for transfer only patients with acute liver failure or those in need of urgent liver transplant evaluation during their hospital stay.
  o Depending on local prevalence of SARS-CoV-2, consider accepting for transfer only other liver patients with a unique need for inpatient interventions at the transplant center.
  o Screen and test all patients for SARS-CoV-2 prior to transfer or upon arrival if testing is not available at the transferring facility.
  o Avoid direct hospital admission for patients with fever and respiratory symptoms, particularly admission to a transplant unit.
• Consider evaluating patients with liver disease for COVID-19 if they develop new onset encephalopathy or another acute decompensation.
• Have a low threshold for aggressive airway management in COVID-19 patients with underlying pulmonary diseases such as hepatic hydrothorax, portopulmonary hypertension, or hepatopulmonary syndrome.
• Perform a needs assessment prior to patient discharge to determine whether the patient can have follow-up encounters by phone or telemedicine and encourage early monitoring by these means to reduce early postdischarge, in-person visits.
  o Consider home health or visiting nurse services for frequent blood draws needed after posttransplant hospital discharge.
• Coordinate with outpatient services for admission and discharge planning to prevent unnecessary admissions and reduce unplanned re-admissions after discharge.
• Patients with active viral shedding on discharge should remain in isolation at home and appropriate precautions should be taken for caregivers or family members who live with the patient.
• Consider the capacity of local rehabilitation centers to accept complex patients as beds in those facilities may become limited during the COVID-19 pandemic.
  o Patients should have a negative SARS-CoV-2 test prior to discharge to a rehabilitation or skilled nursing facility.
  o Review the possibility of enhanced home services during the admission to expedite discharge.

Medication Management of Patients with COVID-19 and Potential Drug-Drug Interactions

What we know
• There currently are no FDA-approved therapies to prevent or treat COVID-19 infection.
• The frequency of discontinuation of investigational or off-label therapeutics for COVID-19 because of hepatotoxicity is low (Table 2).
• Remdesivir is a nucleotide analogue with demonstrated activity against SARS-CoV and MERS-CoV in cultured cells, mice and non-human primates, and more recently against SARS-CoV-2 in human cell lines.72,73
• Remdesivir is being tested in hospitalized patients with moderate to severe COVID-19 in randomized controlled trials.74
  o On May 1, 2020, the FDA issued an Emergency Use Authorization (EUA) for remdesivir for the treatment of hospitalized patients with severe COVID-19, allowing patients to be treated while further studies are being conducted.
  o Interim analysis of the NIH-sponsored Adaptive COVID-19 Treatment Trial (ACTT) showed that remdesivir significantly accelerates time to recovery to hospital discharge
or return to normal activity level compared to placebo (mean of 11 days vs. 15 days, P<.001).\textsuperscript{75}

- Remdesivir may also have a survival benefit compared to placebo, but the difference was not statistically significant (14-day mortality rate of 7.1% vs. 11.9%, HR 0.70, 95% CI 0.47-1.04).
  - A Phase 3 trial of remdesivir showed similar efficacy between a 5-day course and a 10-day course in patients with severe COVID-19 who did not require mechanical ventilation at baseline.\textsuperscript{36}
    - There was a trend toward better outcomes (discharge rates and death) in patients treated with a 5-day course than in those treated for 10 days. This trend may be because the 10-day group included a higher percentage of patients who went on to require invasive mechanical ventilation and high-flow oxygen and a higher proportion of men.
    - Patients who progress to mechanical ventilation may benefit from 10 days of remdesivir.
  - 2.5% (5-day group) and 3.6% (10-day group) discontinued treatment because of aminotransferase elevations.

- An under-enrolled, randomized, double-blind, placebo-controlled trial of remdesivir from Wuhan, China showed no significant difference in time to clinical improvement (median 21 days vs 23 days) or 28-day mortality (14% vs 13%).\textsuperscript{76}
  - Remdesivir was stopped early in 12% or subjects because of adverse events.
  - Elevated liver biochemistries have been commonly observed in the remdesivir clinical development program, rarely including elevations up to 10 times baseline values.

- The RECOVERY trial of dexamethasone 6 mg oral or IV daily for up to 10 days demonstrated a significant mortality benefit in the dexamethasone arm (RR 0.83, 95% CI 0.74-0.92, P<.001).\textsuperscript{71}\textsuperscript{*}
  - Dexamethasone reduced deaths by 35% in patients receiving invasive mechanical ventilation (RR 0.65, 95% CI 0.51-0.82, P<.001) and by 20% in patients receiving oxygen without invasive mechanical ventilation (RR 0.80, 95% CI 0.70-0.92, P=.002).
  - There was no benefit (and possible harm) from dexamethasone in patients who did not require respiratory support (RR 1.22, 95% CI 0.93-1.61, P=.14).

- Drugs that target the IL-6 receptor (e.g., tocilizumab) are being tested only in hospitalized patients with moderate to severe COVID-19.
  - The IDSA recommends using tocilizumab only in the context of a clinical trial.\textsuperscript{77}
- Hydroxychloroquine (an analogue of chloroquine with a better safety profile) has been shown to have anti-SARS-CoV-2 activity \textit{in vitro}.\textsuperscript{78}
  - The FDA revoked the Emergency Use Authorization for chloroquine and hydroxychloroquine after determining they are unlikely to be effective in treating COVID-19 and risks of cardiac adverse effects may outweigh potential benefits.\textsuperscript{79}
  - The NIH\textsuperscript{70} recommends against the use of hydroxychloroquine plus azithromycin except in the context of a clinical trial because of the risk of QT prolongation.
  - The CDC issued a warning about the danger of using nonpharmaceutical chloroquine phosphate, a commercially available chemical for aquarium use, to treat or prevent COVID-19. One individual died after using nonpharmaceutical chloroquine and another became critically ill with gastrointestinal symptoms and cardiac conduction abnormalities.

\textsuperscript{*} Preprint article that has not been peer-reviewed
• Convalescent plasma transfusion is under investigation for treating critically ill patients with COVID-19.80,81
  o The FDA is facilitating access to convalescent plasma for patients with serious COVID-19 through its emergency Investigational New Drug application process.
• The NIH recommends against the use of lopinavir-ritonavir for the treatment of COVID-19, except in the context of a clinical trial.70
  o An open-label, randomized, controlled trial of lopinavir-ritonavir vs. standard of care in adults hospitalized with severe COVID-19 showed no clinical benefit.82 Treatment was stopped early in some patients taking lopinavir-ritonavir because of adverse events.
  o Lopinavir-ritonavir combined with ribavirin and interferon-beta-1b showed more rapid viral clearance by nasopharyngeal swab compared to lopinavir-ritonavir alone in a phase 2, open-label, randomized trial.83
  o Ritonavir is a potent inhibitor of CYP3A4, which is involved in the metabolism of calcineurin inhibitors, sirolimus, and everolimus.
  o The use of ritonavir requires a reduction in the tacrolimus dosage to 1/20-1/50 of baseline because of this drug-drug interaction.
• Treatment with ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) results in upregulation of ACE2, the target for SARS-CoV-2 entry into cells.84
  o Increased ACE2 expression theoretically facilitates infection with SARS-CoV-2.
  o Animal studies suggest that ACEIs and ARBs may protect against serious lung complications from SARS-CoV-V, but to date there are no data in SARS-CoV-2 or in humans.85
  o There is no evidence that ACEIs or ARBs are harmful in the setting of COVID-19.70,86,87

Recommendations
• Monitor studies of antiviral and immunomodulatory approaches to COVID-19 at NIH’s clinicaltrials.gov.
• Consider remdesivir for the treatment of hospitalized patients with severe COVID-19 under the FDA’s EUA.
  o According to the FDA, liver biochemistries should be checked in all patients prior to starting remdesivir and daily while receiving remdesivir.
  o Remdesivir should not be initiated in patients with ALT ≥5x ULN at baseline
  o Remdesivir should be discontinued in patients who develop ALT ≥5x ULN during treatment or ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR.
  o Remdesivir may be restarted when ALT is <5x ULN.
• Consider dexamethasone 6 mg po or IV daily for 10 days in patients with COVID-19 requiring mechanical ventilation or supplemental oxygen.
• The available evidence does not currently support the use of lopinavir-ritonavir for the treatment of COVID-19.70,82
• Hydroxychloroquine with or without azithromycin is not routinely recommended and may be associated with serious adverse events such as prolongation of the QT interval.
• Patients receiving ACEIs and ARBs should remain on them even in the setting of COVID-19.
• Acetaminophen at a daily dosage of ≤2 g/d is the preferred analgesic and anti-pyretic for patients with known or suspected COVID-19.
• NSAIDS may also be used or continued as needed.
• Consult the University of Liverpool Drug Interactions Group COVID-19 Drug Interaction Checker.
Procedures

What we know

- There is potential for fecal-oral SARS-CoV-2 transmission,\textsuperscript{1,7,35,88} and the virus is detected in saliva.\textsuperscript{1,35,47,89}
- The decision to reopen endoscopic facilities ultimately rests with state and local authorities based upon criteria in the White House guidance document.
- The American Society of Gastrointestinal Endoscopy (ASGE) provides guidance for practices in endoscopy centers.\textsuperscript{90}
- Endoscopic procedures should be considered aerosol-generating.\textsuperscript{91}
- To limit disease transmission, the Joint Gastroenterology Societies and the American Gastroenterological Association recommend health care workers involved with endoscopy wear a full set of PPE, including N95 masks and double gloves.\textsuperscript{92}

Recommendations

- Consult state guidelines and local regulatory authorities to determine if hospitals and endoscopy centers can schedule elective procedures.
- The ASGE guidance document should be consulted for areas that allow elective/non-urgent procedures.\textsuperscript{90}
- Consider, in the interim, primary prophylaxis with beta blocker therapy instead of screening endoscopy in patients with clinically significant portal hypertension or high risk of decompensation.
- Some procedures should continue to be performed in areas that are limiting elective/non-urgent procedures, e.g., liver biopsy to rule out rejection or diagnose AIH, therapeutic paracentesis, transjugular intrahepatic portosystemic shunt and/or endoscopy for variceal bleeding, follow-up band ligation in those with recent variceal bleeding, urgent biliary procedures for symptomatic disease such as cholangitis and sepsis (interventional radiology or endoscopic).
- Follow ASGE recommendations for patient and staff screening procedures and PPE use in the endoscopy suite.\textsuperscript{90}
- Regularly monitor state and local regulations and society guidance documents as the pandemic evolves.
- Consider limiting the involvement of fellows in endoscopies and other procedures to conserve PPE.\textsuperscript{91}
- Follow CDC recommendations for cleaning and disinfecting rooms or areas visited by individuals with suspected or confirmed COVID-19.

Research

What we know

- Because of quarantine-related travel restrictions and potential supply chain interruptions, the FDA and NIH have posted guidance documents for the conduct of clinical trials during the COVID-19 pandemic.
- As the FDA states, protocol deviations may be necessary and will depend on many context-dependent factors related to the nature of the study, the patient population, and environmental circumstances.
• Patient safety is of utmost importance and should be used to guide decisions impacting the trial, including recruitment, continuation decisions, patient monitoring, delayed assessments, and investigational product dispensing.
• Evaluation of alternative visits, including virtual, phone, or remote contact, may be warranted if safety of the patient can be assured with the alternative approach.
• Protocol changes that reduce immediate danger or protect the well-being of the research participants may be implemented before Institutional Review Board (IRB) approval but must be subsequently reported.
• The NIH encourages grant recipients to discuss changes that prioritize patient and staff safety, including limiting study visits or conducting them virtually, suspending unnecessary travel, and increasing flexibility for laboratory testing and imaging with both the institution and the IRB.
• In an effort to ensure patient safety and maintain trial integrity, sponsors, investigators, and IRBs should document all such contingency measures and reasons for protocol deviations.

**Recommendations**

• Resume suspended or delayed clinical trials as able based on local SARS-CoV-2 prevalence and local/institutional policies.
• The study physician – in consultation with the study team, the patient’s physician, the patient, and the patient’s family – should continue to carefully assess the necessity and risks of in-person study visits.
• Research staff should continue efforts to use alternative methods to conduct research visits or perform testing such as check-ins with participants by phone and/or performing research-related lab testing at lab testing centers if feasible.
• Research staff should continue to work remotely while following site/institutional guidance for working on site when necessary and allowed. Presence on site is necessary for certain study-related procedures such as collection of liver biopsies, and specimen processing and shipping to central laboratories.
• Discuss options for conducting telehealth study visits with clinical research organizations and study sponsors.
• Arrange for research medications to be sent to subjects by the study sponsor if the research pharmacy is unavailable. Dispensing Investigational Product on site can be gradually scaled up based on allowed visits to sites by research patients.
• Institutional policies on clinical research may be more restrictive and should supersede the recommendations contained here.
• Laboratory/basic science research may also be restricted based on local policies.

**Trainees**

**What we know**

• Although residents and fellows have much to learn from the diagnosis and management of COVID-19, the risks of exposing trainees to SARS-CoV-2 may outweigh the benefits in areas with ongoing SARS-CoV-2 community spread.
• There has also been concern about further reducing the already significant PPE shortages by involving trainees in direct patient care.
• In a Letter to the Community, the Accreditation Council for Graduate Medical Education (ACGME) announced it has suspended some activities during the COVID-19 pandemic, including
self-studies, accreditation site visits, Clinical Learning Environment Review (CLER) program site visits, and resident/fellow/faculty surveys

- The ACGME issued new requirements to allow residents/fellows to participate in telemedicine.
- The ACGME requirements for adequate resources and training, adequate supervision, and work hour limitations have not changed.
- The ACGME has clarified the local circumstances in which fellows may function within their core specialty (i.e., act as attending physicians).
- Designated Institutional Officials (DIOs) may self-declare a Pandemic Emergency Status for all programs within the Sponsoring Institution, during which all Common Program Requirements and specialty-specific Program Requirements are suspended other than those outlined above (adequate resources and training, adequate supervision, work hour requirements, and fellows functioning in core specialty).
- See ACGME’s response to the pandemic crisis for more details.

**Recommendations**

- Ensure adequate resources including PPE appropriate to the clinical setting for all trainees.
- Assign fellows only to participating sites that ensure the safety of patients and fellows.
- Ensure appropriate supervision of trainees working remotely if they are conducting patient care activities (telephone/telemedicine visits).
- Change all educational conferences to virtual conferences.
- Consider assigning fellows and other trainees to indirect patient care activities and/or telemedicine visits.
- Consider remote supervision of trainees by concurrently monitoring patient care through appropriate telecommunication technology.
- Consider the potential impact of COVID-19 on new fellow orientation, fellowship recruitment, and interviews and develop contingencies for conducting these activities by virtual means.

**Protecting Health Care Workers and Workforce Utilization**

**What we know**

- The SARS-CoV-2 infection rate of health care workers may be up to 20%, as reported in Italy.\(^{11}\)
- The CDC has reported over 9200 COVID-19 cases in US health care workers, including some with severe outcomes including death.\(^{12}\)
  - This is an underestimate because health care worker status was only available for 16% of reported cases.
- In addition to protecting our patients, health care workers must take action to prevent infection within and outside patient care settings.
- We must endeavor to avoid the loss of health care workers to illness or quarantine, but plans must be developed to mitigate the effects of workforce shortages during the pandemic.
- Given the potential for SARS-CoV-2 to spread via aerosol as well as droplet, the use of N95 masks or other respirators are essential when caring for patients with known or suspected COVID-19.\(^{93}\) It is not known whether surgical masks protect the wearer from infection, but data suggest that a surgical mask worn by infected individuals may reduce the risk of transmission (source control).\(^{94}\) It is unknown whether surgical masks reduce the risk of transmission from asymptomatic health care workers to patients or other health care workers.

* Preprint article that has not been peer-reviewed
**Recommendations**

- Continue to limit in-person meetings (even small meetings) and change to virtual meetings when possible.
- Maintain physical distancing even in meetings, e.g., keep an empty chair between each person, and have each individual wear a mask.
- Consider staggering work shifts for physicians, providers, nurses, and staff.
- Create a backup schedule for physicians and surgeons in the event of quarantine or illness.
- Consider assigning backup personnel for providers in leadership positions.
- Consider checking temperatures of all providers and staff as they arrive to the office or clinic. There should be a zero-tolerance policy for presenting to work with fever or symptoms of COVID-19.
- All health care workers should wear a surgical mask for performance of standard duties in patient care settings but utilize a higher level of PPE when there are concerns for contact with patients with suspicious symptoms or known COVID-19.
- These recommendations should continue to be followed even as states begin to loosen restrictions.

**Telemedicine**

**What we know**

- Telemedicine can mitigate the exposure of patients and health care workers to COVID-19 and has potential to change health care delivery now and after the COVID-19 pandemic.95–98
- Emergency funding legislation HB 6074 waived many of the long-standing restrictions to the use of telehealth for Medicare recipients, including: rural area requirements for originating sites (i.e., patient location); allowing a patient’s home to be an eligible originating site; allowing phones with two-way, real-time interactive audio and visual capabilities to be used; and allowing the provider to conduct a telemedicine encounter from their home.99
- The Department of Health and Human Services Office of Civil Rights announced that it would not impose penalties for the good faith provision of telemedicine during the COVID-19 public health emergency, even if remote communication technologies used for such services may not fully comply with the requirements of the Health Insurance Portability and Accountability Act (HIPAA) Rules.
- Medicare will currently reimburse telephone and telemedicine visits for both new and established patients.
- Providers can bill for telemedicine visits at the same rate as in-person visits.
- Audio-only telephone calls that are used as a replacement for care that would otherwise be billed as in-person or telehealth will be paid the equivalent of in-person visits.
- Telemedicine limitations include patient access to the electronic health record patient portal; access to a computer, phone, or tablet with video/audio capabilities; and ability to manage the technology.
- See the Joint Gastroenterology Societies’ message about telehealth.

**Recommendations**

- Consider phone visits or telemedicine as appropriate and available to replace in-person visits.
• Consider ways to mitigate disparities in access to care delivered through telemedicine (e.g., rural populations, older adults, racial/ethnic minorities, low socioeconomic status, limited health literacy, limited English proficiency).100
• Conduct patient education and social work, dietitian, and financial consultations by video conference, telemedicine or telephone for liver transplant evaluations.
• Consider telemedicine alternatives in place of outreach clinics.
• Minimize in-person visits for posttransplant patients by maximizing use of telemedicine.

Reentry and Return to a Pre-Pandemic State

What we know
• The necessary prioritization of the acute care of patients with COVID-19 and implementation of strategies to minimize risk of disease transmission has resulted in a delay of elective procedures, routine care, and clinical research.
• Many hospitals that are seeing a decline in COVID-19 cases are beginning the process of reentry.
• It has been suggested that a backlog of routine procedures and clinic visits could result in an increase in hepatic decompensating events and morbidity in patients with liver disease.3
• Patient perspectives and comfort level about in-person clinic visits, hospital-based procedures, laboratory testing, and imaging studies may influence their willingness to comply with standard recommendations and impact their quality of care.

Recommendations
• Develop policies and processes for reentry to gradually ramp up clinical operations and clinical research with pathways for minimizing SARS-CoV-2 transmission and for care of patients who develop COVID-19.
• Consult the CDC and CMS for general guidelines pertaining to reentry.
• Identify patient characteristics (e.g., MELD, recent decompensation, etc.) that help prioritize who will first be reintroduced into the clinical environment. Use a staged approach appropriate for local conditions.
• As the COVID-19 prevalence declines in geographic areas, each transplant center should have plans in place for careful reentry into standard brain-dead deceased donor liver transplants; followed by acceptable, DCD donor transplants <50 years old; and finally, once COVID-19 risks are minimized within the health care environment and well-controlled in the community, living donor liver transplants.
• Consult CDC guidelines for a reentry framework based on potential for patient harm and degree of community transmission.
• Consider how to prioritize patients who need to be seen in person, such as those with decompensated cirrhosis with high MELD scores.
• Schedule patients with sufficient time to minimize patient and staff interactions and screen for fever or COVID-19 symptoms before clinic visits.
• Avoid patients congregating in the waiting area.
• Patients and caregivers (if caregivers are permitted) should wear a mask in the clinic area.
• Remain aware of SARS-CoV-2 prevalence, incidence, and diagnostic testing availability in your community.101
• Consider the risk of a “second wave” of COVID-19 and establish criteria for reentering the mitigation phase if necessary.101
• Continue to develop a telemedicine program to reduce contact between patients and healthcare workers during the reentry phase and consider the role of telemedicine in patient care beyond the COVID-19 pandemic.³
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COVID-19 Liver Disease and Transplant Registries

- **SECURE-Cirrhosis** (COVID-19 in patients with cirrhosis and liver transplant recipients, “PHI-free”, North or South America, China/Japan/Korea)
- **COVID-Hep** (COVID-19 in patients with cirrhosis and liver transplant recipients, “PHI-free”, for cases outside North or South America, China/Japan/Korea)
- **University of Washington** (COVID-19 in solid organ transplant recipients, “PHI-free”)
- **COVID-LT Consortium** (COVID-19 in patients with cirrhosis and liver transplant recipients)
- **NASPGHAN and SPLIT-TTS- COVID-19 Pediatric Registry** (pre- and post-liver and intestine patients, 0-21 years, “PHI-free”)

Helpful Resources

- **Asian Pacific Association for the Study of the Liver (APASL)**
- **American Society of Transplantation (AST) COVID-19 Information for Transplant Community**
- **European Association for the Study of the Liver (EASL)**
- Centers for Disease Control and Prevention, **COVID-19 Website**
  - CDC **recommendations** for cleaning and disinfecting rooms or areas visited by individuals with suspected or confirmed COVID-19
- **The Transplantation Society Guidance** on Coronavirus Disease 2019 (COVID-19) for Transplant Clinicians
- Association of Organ Procurement Organizations **COVID-19 Bulletin**
- **FDA Guidance** on Conduct of Clinical Trials of Medical Products During COVID-19 Pandemic
- **Guidance for NIH-funded** Clinical Trials and Human Subjects Studies Affected By COVID-19
- **Medicare Telemedicine** Health Care Provider Fact Sheet
- **CMS Flexibilities to Fight COVID-19**
- **ACGME’s Response** to the Coronavirus (COVID-19)
- **Joint GI Society** Message for Gastroenterologists and Gastroenterology Care Providers
- **ASGE guidance** for resuming GI endoscopy and practice operations after the COVID-19 pandemic
- Joint GI Society Message about **Telehealth**
- University of Liverpool Drug Interactions Group **COVID-19 Drug Interaction Checker**
### Table 1. Diagnostic Methods for SARS-CoV-2 Detection

<table>
<thead>
<tr>
<th>Test (method)</th>
<th>Turn around (hrs)</th>
<th>Sensitivity</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC with differential &amp; platelets</td>
<td>&lt;1</td>
<td>NA</td>
<td>Lymphopenia frequently identified at presentation and associated with poor prognosis. Elevated WBC and thrombocytopenia indicate poor prognosis.</td>
</tr>
<tr>
<td>Comprehensive metabolic panel</td>
<td>&lt;1</td>
<td>NA</td>
<td>Abnormal aminotransferases are common but usually 1-2x ULN. Alkaline phosphatase usually normal. Acute kidney injury indicates poor prognosis.</td>
</tr>
<tr>
<td>LDH, D-dimer, CRP, INR, CPK, ferritin</td>
<td>&lt;1</td>
<td>NA</td>
<td>Elevated inflammatory markers associated with poorer outcomes.</td>
</tr>
<tr>
<td>Chest CT</td>
<td>&lt;1</td>
<td>80%-90%</td>
<td>Bilateral ground glass opacities (lower lobe and peripheral) seen in &gt;90% of hospitalized cases confirmed by RT-PCR. Specificity only 25%.</td>
</tr>
<tr>
<td>Nasopharyngeal swab (RT-PCR)</td>
<td>2-48</td>
<td>40%-80%</td>
<td>Peak shedding 12-14 days after infection; Nasopharyngeal higher yield than oropharyngeal. Requires frozen transport media if &gt;24 hours. False negative common in early in disease.</td>
</tr>
<tr>
<td>Qualitative nasopharyngeal swab (non-PCR)</td>
<td>&lt;1</td>
<td>80%-90%</td>
<td>Point of care qualitative test using isothermal detection methods. Results in 15 minutes.</td>
</tr>
<tr>
<td>Sputum (RT-PCR)</td>
<td>2-48</td>
<td>60%-80%</td>
<td>Should be spontaneous expectorant. Do not induce.</td>
</tr>
<tr>
<td>Bronchoalveolar lavage (RT-PCR)</td>
<td>2-48</td>
<td>95%</td>
<td>Recommended only for intubated patients with negative nasopharyngeal swab.</td>
</tr>
<tr>
<td>Plasma serology (IgG, IgM, IgA)</td>
<td>1-2</td>
<td>70%-90%</td>
<td>Indicative of prior exposure. False negative early in disease. False positive because of lack of SARS-CoV-2 specificity. IgA/IgM positive at 3-6 days after symptom onset. May be useful in health care workers, close contacts, and epidemiological studies.</td>
</tr>
<tr>
<td>Saliva (RT-PCR)</td>
<td>NA</td>
<td>NA</td>
<td>May be more sensitive and reliable than nasopharyngeal samples from hospitalized patients and asymptomatic health care workers.</td>
</tr>
<tr>
<td>Nasopharyngeal swab (CRISPR)</td>
<td>1-2</td>
<td>NA</td>
<td>Colorimetric dipstick in development.</td>
</tr>
<tr>
<td>Blood (RT-PCR)</td>
<td>24</td>
<td>15%</td>
<td>May be present in more severe cases.</td>
</tr>
<tr>
<td>Stool (RT-PCR)</td>
<td>24</td>
<td>30%</td>
<td>May be detectable throughout disease phase.</td>
</tr>
<tr>
<td>Cell culture</td>
<td>&gt;24 (days)</td>
<td>NA</td>
<td>For research purposes only. Requires high level safety lab. Used for vaccine and antiviral testing.</td>
</tr>
</tbody>
</table>

CBC, complete blood count; CPK, creatine phosphokinase; CRISPR, clusters of regularly interspaced short palindromic repeats; CRP, C-reactive protein; CT, computed tomography; INR, international normalized ratio; LDH, lactate dehydrogenase; RT-PCR, real-time polymerase chain reaction; ULN, upper limit of normal.
<table>
<thead>
<tr>
<th>Agent (route/mechanism)</th>
<th>Target population</th>
<th>Safety issues</th>
<th>Approval Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiviral Agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remdesivir (IV/nucleotide analogue)</td>
<td>Moderate-severe</td>
<td>Nausea/vomiting Grade 1-2 ALT elevations Drug vehicle accumulation in acute kidney injury <em>Exclusions:</em> GFR &lt;30-50 mL/min AST or ALT &gt;5x ULN</td>
<td>Available in the US under FDA EUA but remains under study Approved for COVID-19 in Japan</td>
</tr>
<tr>
<td>Favipiravir (oral/RNA polymerase inhibitor)</td>
<td>Early to mild disease</td>
<td></td>
<td>Investigational Approved for influenza in Asia Tested with interferon-α aerosol x 14 days</td>
</tr>
<tr>
<td>Lopinavir-ritonavir (oral/HIV protease inhibitor)</td>
<td>Moderate-severe</td>
<td>CYP3A4 substrate Severe DDI with CNI 13% early discontinuation because of side effects</td>
<td>FDA-approved for HIV No survival benefit in RCT vs standard of care x 14 days Shorter time to viral clearance when combined with ribavirin and interferon-beta-1b in a phase 2, open-label, randomized trial§3</td>
</tr>
<tr>
<td>Nitazoxanide (oral/host proteins)</td>
<td>Moderate-severe</td>
<td>Similar to placebo in influenza trials</td>
<td>FDA-approved for Cryptosporidium/Giardia In vitro activity against coronaviruses</td>
</tr>
<tr>
<td>Hydroxychloroquine (oral/host proteins)</td>
<td>Moderate-severe</td>
<td>QTc prolongation Nausea and vomiting <em>Exclusions:</em> QTc &gt;415 ms Cardiomyopathy G6PD deficiency</td>
<td>FDA revoked EUA after determining it is unlikely to be effective in treating COVID-19 FDA-approved for lupus/rheumatoid arthritis/malaria</td>
</tr>
<tr>
<td>Chloroquine (oral/host proteins)</td>
<td>Moderate-severe</td>
<td>QTc prolongation Nausea and vomiting <em>Exclusions:</em> QTc &gt;415 ms Cardiomyopathy G6PD deficiency</td>
<td>FDA revoked EUA after determining it is unlikely to be effective in treating COVID-19 FDA-approved for malaria Reduced progression of disease and symptom duration in China</td>
</tr>
<tr>
<td>Azithromycin (oral/host proteins)</td>
<td>Moderate-severe</td>
<td>CYP3A4 substrate Moderate DDI with CNI Rare cholestatic hepatitis <em>Exclusion:</em> QTc &gt;415 ms</td>
<td>FDA-approved for bacterial infections Should only be combined with hydroxychloroquine in clinical trials because of risk of QT prolongation</td>
</tr>
<tr>
<td>Famotidine (oral or IV/protease inhibitor)</td>
<td>All</td>
<td>None significant</td>
<td>FDA-approved for other indications Retrospective data only, RCTs ongoing102*</td>
</tr>
</tbody>
</table>

* Preprint article that has not been peer-reviewed
<table>
<thead>
<tr>
<th>Immunomodulatory Agents</th>
<th>Tocilizumab (IV/monoclonal IL-6 receptor antagonist)</th>
<th>Severe (high IL-6 levels)</th>
<th>Grade 1-2 ALT 20%-40% Grade 3+ ALT 1%-2%. Acute liver failure &lt;1% Neutropenia 3% Thrombocytopenia 2% Opportunistic infections</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>Exclusions:</em> ANC &lt;2,000/m³ Platelets &lt;100,000/m³ ALT &gt;5 xULN</td>
</tr>
<tr>
<td></td>
<td>FDA-approved for RA 8 mg/kg dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarilumab (SC/monoclonal antibody)</td>
<td>Severe (high IL-6 levels)</td>
<td>Grade 1-2 ALT 15%-25% Neutropenia 5% Thrombocytopenia 1%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>Exclusions:</em> ANC &lt;2,000/mm³ Platelets &lt;150,000/m³ ALT &gt;5 ULN</td>
</tr>
<tr>
<td></td>
<td>FDA-approved in RA Being tested as IV formulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Siltuximab (IV/monoclonal antibody)</td>
<td>Severe (high IL-6)</td>
<td>Grade 1-2 ALT Rash 30% Thrombocytopenia 9%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>Exclusions:</em> ALT &gt;5x ULN</td>
</tr>
<tr>
<td></td>
<td>FDA-approved in Castleman’s disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Convalescent plasma (IV/neutralizing antibodies)</td>
<td>Severe or life-threatening pneumonia</td>
<td>Potential TRALI/ anaphylaxis ICU monitoring needed Must screen donor for other transmissible pathogens</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Investigational Open label 400 mL plasma infusion in 5 patients and 200 mL plasma infusion in 10 patients Finding donors with neutralizing IgG activity not well established Reserved for severe/life threatening cases</td>
</tr>
<tr>
<td>Dexamethasone (oral or IV/anti-inflammatory)</td>
<td>Moderate-severe</td>
<td></td>
<td>FDA-approved for multiple indications</td>
</tr>
</tbody>
</table>

ACE2, angiotensin converting enzyme 2; ANC, absolute neutrophil count; CNI, calcineurin inhibitor; DDI, drug-drug interaction; EUA, Emergency Use Authorization; G6PD, glucose-6-phosphate dehydrogenase; GFR, glomerular filtration rate; HIV, human immunodeficiency virus; ICU, intensive care unit; IV, intravenous; RA, rheumatoid arthritis; RCT, randomized controlled trial; SC, subcutaneous; TRALI, transfusion-related acute lung injury; ULN, upper limit of normal
Figures

Figure 1. Approach to the Patient with COVID-19 and Elevated Serum Liver Biochemistries

COVID-19 patient with elevated serum liver biochemistries

Consider etiologies other than COVID-19, including hepatitis A, B and C
- Review medications
- Avoid imaging unless it is likely to change management, e.g., clinical suspicion for biliary obstruction or venous thrombosis

Liver tests stable/improving or worsening?

**Stable/improving**
- Continue to monitor closely

**Worsening**
- Evaluate other causes: myositis (especially when AST>ALT), ischemia, cytokine release syndrome, drug-induced liver injury
- Weigh removal of hepatotoxic agents
- Utility of liver biopsy not established
Figure 2. Approach to Liver Transplant Organ Offers

Acceptable organ offer

Assess hospital resources (ICU, ventilator, PPE, blood products) before accepting organ

Screen recipient by phone for COVID-19 symptoms/fever

- Negative screen
  - Call recipient in to hospital
    - Consider having a backup recipient wait at home
- Positive screen
  - Call backup recipient in to hospital

Screen/test recipient*

- Negative screen and negative test
- Positive screen and/or positive test

Screen/test donor**

- Positive screen and/or positive test
  - Do not proceed with transplantation
- Negative screen and negative test

Proceed with transplantation

*Recipient screening: Screen recipient on arrival for COVID-19 symptoms/fever
  Test recipient for SARS-CoV-2, if available

**Donor screening: Screen donor history for possible COVID-19 exposure or clinical symptoms, fever, or chest imaging compatible with COVID-19
  Test donor for SARS-CoV-2, if available
Figure 3. Approach to the Liver Transplant Recipient with COVID-19

Early post-transplant

≤6 months from transplant
- Reduce or stop antimitabolite
- Maintain calcineurin inhibitor

>6 months from transplant
- Reduce or stop antimitabolite
- Consider reducing level of calcineurin inhibitor

Lab testing with inflammatory markers
- Oxygen saturation
- Chest imaging

Normal oxygen saturation and no imaging findings
- Monitor symptoms and labs
  - Discharge per standard protocol
  - Follow closely as outpatient
  - Monitor oximetry if possible
- Check for termination of viral shedding, if possible
  - Educate caregivers

Normal oxygen saturation and abnormal imaging findings^
- Continue to observe inpatient
  - Follow oxygen saturation and chest imaging

Abnormal oxygen saturation and/or chest imaging findings of COVID-19
- Initiate* or continue local protocol treatment for anti-inflammatory (anti-cytokine) and antiviral therapy
  - Monitor inflammatory markers, oxygen saturation, chest imaging, QTc**

Consider discharge when oxygen no longer needed

*Therapy ideally initiated early, prior to advanced respiratory decompensation

**If on hydroxychloroquine and/or azithromycin

^Abnormal imaging may not be due to COVID-19; other infections or sequelae of organ failure should be considered and addressed independently of COVID-19-related treatment
References


93. Santarpia JL, Rivera DN, Herrera V, Morwitzer MJ, Creager H, Santarpia GW, et al. Transmission potential of SARS-CoV-2 in viral shedding observed at the University of Nebraska Medical Center. MedRxiv 2020 March 26. doi: 10.1101/2020.03.23.20039446. [Preprint article that has not been peer-reviewed]


