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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More AASLD resources for COVID-19 and the Liver: https://www.aasld.org/about-aasld/covid-19-and-liver
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Overview and Rationale
Coronavirus disease 2019 (COVID-19), the illness caused by the SARS-CoV-2 virus, has impacted every aspect of life and health care in 2020 and for the foreseeable future. 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. 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 first version of this document was published online on March 23, 2020 and in print in Hepatology on April 16, 2020. This online document has been updated regularly to include rapid changes in information relevant for the hepatology workforce. 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.

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.\(^1,2\)
- ACE2 is present in biliary and liver epithelial cells; therefore, the liver is a potential target for infection.\(^3\)
  - Coronavirus particles have been identified in the cytoplasm of hepatocytes associated with typical histological evidence of viral infection.\(^4\)
- The incidence of elevated serum liver biochemistries in hospitalized patients with COVID-19 ranges from 14% to 83%.\(^5-14\)
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.11–13,15

Liver injury occurs more commonly in severe COVID-19 cases than in mild cases.10,12,16

Rare cases of severe acute hepatitis have been described in patients with COVID-19.6,11,12,17

Predictors of peak abnormal liver tests >5x ULN include age, male gender, body mass index, diabetes mellitus, medications (e.g., lopinavir/ritonavir, hydroxychloroquine, remdesivir, tocilizumab), and inflammatory markers (IL-6, ferritin).12,14

Liver injury in mild COVID-19 cases is usually transient and does not require specific treatment beyond supportive care.10

Low serum albumin on hospital admission is a marker of COVID-19 severity.9,12,18–20

AST is usually higher than ALT and is associated with severe COVID-19 and mortality, which may reflect non-hepatic injury.8,12,13,16

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).21,22

COVID-19 is linked with multisystem inflammatory syndrome in children (MIS-C), with overlapping features of Kawasaki disease and positive COVID-19 antibody testing suggesting a post-infectious entity.23

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.24–26

An American autopsy series demonstrated histologic findings of macrovesicular steatosis, mild acute hepatitis (lobular necroinflammation) and mild portal inflammation. In addition, SARS-CoV-2 viral RNA was detectable by PCR in 55% of liver samples that were interrogated.26

Elevated liver biochemistries may reflect a direct virus-induced cytopathic effect and/or immune damage from the provoked inflammatory response and cytokine release syndrome.7,27

Therapeutic agents used to manage symptomatic COVID-19 may be hepatotoxic but rarely lead to treatment discontinuation.10 These include remdesivir and tocilizumab.28–31

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.10

Patients with chronic lung disease including those with alpha-1 antitrypsin deficiency may be at increased risk of severe COVID-19.

COVID-19 may predispose patients to thromboembolic disease and anticoagulation may improve outcomes in hospitalized patients.32,33

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.34,35

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; and/or drug-induced liver injury.10,24

An approach to evaluating the patient with COVID-19 and elevated liver biochemistries is shown in Figure 1.
**Recommendations**

- 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.\(^\text{14}\)
- To limit unnecessary exposure to 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, 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.\(^\text{21}\)
- 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**

- 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.\(^\text{36}\)
  - 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.\(^\text{37–39}\)
- 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) (Table 1).\(^\text{40}\)
- 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.\(^\text{41}\)
- On August 15, 2020, the FDA issued an Emergency Use Authorization for a rapid saliva-based test for the detection of SARS-CoV-2.
  - The sensitivity of the saliva test in 70 COVID-19 patients was similar to a nasopharyngeal swab (81% vs. 71%).\(^\text{42}\)
- 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.\(^\text{43}\)
• Testing samples from multiple sites from the patient or repeated testing from one patient site may improve sensitivity and reduce false negative results.40
• Serological tests (antibody and antigen) hold promise as non-invasive, rapid, and convenient means of testing for current or past SARS-CoV-2 infection,44,45
  o SARS-CoV-2 antigen testing is less sensitive than PCR but with the advantage of more rapid results and potentially lower cost.45
  o Antibody testing may complement PCR testing to improve detection (IgM), detect subclinical infection (IgM or IgG) and identify individuals who have recovered (IgG).40
  o 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.
  o 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.46
  o Reinfection by a phylogenetically distinct strain of SARS-CoV-2 has been demonstrated in humans, suggesting that SARS-CoV-2 may continue to circulate despite herd immunity due to natural infection.47
  o 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.46

Recommendations
• 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.
• Point-of-care oropharyngeal swabs and saliva-based tests can also be used to screen for and diagnose COVID-19.
• 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.39,48
• 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 adults and children (who are less likely to become ill) with SARS-CoV-2 infection can contribute to the spread of the virus.21,49
• 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.50 Among these patients with underlying conditions, only 41 patients (0.6%) had chronic liver disease, including 7 who required ICU admission.50
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 (>100,000 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).\(^{51}\)
- 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.\(^{52}\)
  - The mortality risk was higher in patients with cirrhosis (RR 4.6, 95% CI 2.6-8.3).
  - 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.
- It is unclear if the association between nonalcoholic fatty liver disease and poor outcomes from COVID-19 is because of comorbidities associated with the metabolic syndrome, chronic inflammation, fibrosis, or a combination of factors.\(^{53}\)
- Despite the theoretical possibility that some hepatitis C and hepatitis B antiviral drugs (e.g., velpatasvir, ledipasvir, tenofovir) may have antiviral effects on SARS-CoV-2, there are insufficient data to conclude if these drugs are clinically effective against SARS-CoV-2.\(^{54}\)
- 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.\(^{10}\)
- 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.\(^{55}\)
  - Those who underwent recent chemotherapy had an even higher risk of severe COVID-19, but the series also included those without recent chemotherapy.\(^{55}\)
- The slow median doubling time of HCC supports a rationale of a short delay in radiological surveillance if necessary in areas of high SARS-CoV-2 prevalence.\(^{56}\)

**Recommendations**

- Consider limiting outpatient visits to only patients who must be seen in person when COVID-19 is prevalent in the community, per local guidance. (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 domestic or international 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 radiological 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 radiological surveillance with the patient and document the discussion.
  - These patients should be prioritized for imaging studies.
  - Avoid HCC surveillance in patients with COVID-19 until infection is resolved.
- 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**
- Mortality attributable to COVID-19 appears higher in patients with more advanced liver disease.20,51
• 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%.58
  o Cause of death in patients with cirrhosis was liver-related in 12.2%, compared to 78.7% pulmonary and 4.3% cardiac.
  o 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.
  o Hepatic decompensation during COVID-19 was strongly associated with subsequent risk of death (63.2% with new decompensation died vs. 26.2% without decompensation).
  o 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).20
  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%).
• In a multicenter study of inpatients with cirrhosis+COVID-19 compared with age/gender-matched patients with COVID-19 alone and cirrhosis alone, patients with cirrhosis and COVID-19 had a higher risk of death compared to patients with COVID-19 alone, but not significantly higher than the risk of death from cirrhosis alone without COVID-19.59
  o Patients with cirrhosis+COVID-19 had equivalent respiratory symptoms, chest findings, and rates of intensive care transfer and ventilation compared with patients with COVID-19 alone.
  o Patients with cirrhosis+COVID-19 were less likely to present with GI symptoms, while patients with cirrhosis alone were more likely to develop cirrhosis-related complications.
  o The only significant predictor of mortality was the Charlson Comorbidity Index.
• 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.
• COVID-19 has had a significant impact on the transplant waiting list and transplant center practice patterns.60
• 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**

- 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.
  - 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.
- 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.
- Consider telemedicine alternatives in place of outreach clinics.
- Obtain labs and imaging only as clinically necessary.
  - 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) 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 symptomatic with COVID-19.
- Test patients with new onset hepatic decompensation for SARS-CoV-2.

**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 and local policies are evolving.
- Despite an initial decrease in liver transplantations at the onset of the COVID-19 pandemic, particularly in living donor liver transplantations, liver transplant volumes in the US have since rebounded to 2019 levels.
• All Organ Procurement Organizations are testing donors for SARS-CoV-2 RNA using
nasopharyngeal, BAL, or both, 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.
  o 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 routinely
recommended until at least 14 days after clinical recovery.
  o Limited data suggest there is a significant increase in postoperative morbidity and
  mortality related to SARS-CoV-2 infection, and for emergent surgery in particular.
  o The risks of emergent liver transplantation for patients with acute liver failure who test
  positive for SARS-CoV-2 are not known.
• The Scientific Registry of Transplant Recipients (SRTR) will be modifying the evaluation metrics
for transplant programs and organ procurement organizations (OPOs) and has recommended
to remove any patient and donor data from the performance metrics following the declaration of a

Recommendations
• Develop a hospital-specific policy for organ acceptance.
  o Ensure hospital administrators are aware of the CMS Tier 3b designation for transplant
  surgery (“Do not postpone”).
  o Consider resource utilization including ICU beds, operating rooms, ventilators,
  hemodialysis equipment, PPE and supply of blood products (especially platelets and
  type-specific packed red cells) in the decision to proceed with liver transplantation.
  o 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).61
  o 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.
• Test all recipients and donors for SARS-CoV-2 before transplantation, if testing is available.
  o Consider the risk of false negatives, disease prevalence, and testing turnaround time in
  your area.
  o 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.
• Ideally, transplantation in SARS-CoV-2-positive transplant candidates should be delayed for at
least 14-21 days after symptom resolution and 1 or 2 negative SARS-CoV-2 diagnostic tests.
  o The decision to proceed with transplantation in a SARS-CoV-2-positive candidate must
  be individualized based on several factors including the urgency of transplantation, the
presence of respiratory symptoms, and the risk of exposing transplant personnel to SARS-CoV-2.

- 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.
- These ethical 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.
- Posttransplant immunosuppression was not a risk factor for mortality associated with SARS (2002-2003) or MERS (2012-present).
- Several studies have shown a mortality benefit with the use of corticosteroids for the treatment of critically ill patients with COVID-19.
- Immunosuppression may prolong viral shedding in posttransplant patients with COVID-19.
• 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.62
  o 4 patients had cirrhosis, 1 who was decompensated (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 required 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.19
  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-19.64
  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.

• A prospective study of 111 liver transplant recipients with COVID-19 from Spain showed an increased risk of acquiring SARS-CoV-2 (almost double the rate in the age/gender matched general population) but lower mortality rates than the matched general population.67
  o Baseline immunosuppression containing mycophenolate, particularly doses >1000 mg/day, was an independent predictor of severe COVID-19 (RR 3.94, 95% CI 1.59-9.74, P=.003).

• 151 liver transplant recipients were described in an analysis of two combined international COVID-19 reporting registries (COVID-Hep and Secure-Cirrhosis).68
  o 124 (82%) were hospitalized, 47 (31%) required intensive care, and 28 (19%) died.
  o In propensity score-matched analysis comparing liver transplant recipients to non-transplant recipients (adjusting for age, sex, creatinine, obesity, hypertension, diabetes, and ethnicity), liver transplant status did not significantly increase the risk of death in patients with SARS-CoV-2 infection.
In multivariable logistic regression, age, creatinine, and non-liver cancer were significantly associated with risk of death among liver transplant recipients.

- Data have been reported from the first 103 patients of a European registry (ELITA/ELTR) of liver transplant recipients with COVID-19.69
  - 15 (15%) were admitted to intensive care, 68 (66%) were admitted to a general ward, and 20 (19%) were monitored at home.
  - 16 (16%) died, including 4 (44%) of the 9 who were on mechanical ventilation.
  - 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).

- Data from the US multicenter COLD consortium of 112 liver transplant recipients were also recently reported.70
  - Overall, 25 (22.3%) died, 81 (72.3%) hospitalized, and 30 (26.8%) required ICU-level care.
  - In multivariable analysis, the strongest predictors of death were the presence of diabetes and the presence of acute liver injury.
  - The risk of death was not higher among liver transplant recipients compared to controls with chronic liver disease.

- Anti-IL-6 therapeutics have not been shown to increase the risk of acute cellular rejection.
- Reducing the dosage or stopping immunosuppressants may cause a flare in a patient with AIH or precipitate acute rejection in a liver transplant recipient.62
  - The NIH COVID-19 treatment guidelines recommend that oral corticosteroid therapy used prior to COVID-19 diagnosis for another underlying condition should not be discontinued.71

**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.61
  - 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).

Inpatients

*What we know*

- Health care workers and other hospital staff are at risk for COVID-19.72
- 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.
- Limit the number of team members who enter a patient’s room for patient examinations and encounters.
- 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.
- Depending on local prevalence of COVID-19, consider continuing to limit 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.
- 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.
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.

Screen and test all patients for SARS-CoV-2 prior to transfer or upon arrival if testing is not available at the transferring facility.

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 hepato-pulmonary 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.
  - Consider home health or visiting nurse services for frequent blood draws needed after posttransplant hospital 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 be limited during the COVID-19 pandemic.
  - Patients should have a negative SARS-CoV-2 test prior to discharge to a rehabilitation or skilled nursing facility.
  - 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*

- Remdesivir is currently the only FDA-approved therapy for the treatment of COVID-19.
  - Remdesivir is a nucleotide analogue with demonstrated activity against SARS-CoV-2 in human cell lines.73
  - The FDA approved remdesivir on October 22, 2020 for use in adult and pediatric patients >12 years of age and >40 kg with COVID-19 requiring hospitalization.
  - An Emergency Use Authorization for selected hospitalized pediatric patients <12 years of age and <40 kg remains in effect.
  - Patients should receive 200 mg IV on day 1 and 100 mg/day for up to 5 consecutive days.
  - Patients who are intubated or receiving ECMO may be treated for up to 10 days.
  - Liver biochemistries should be checked prior to starting remdesivir and during treatment.
  - Clinicians should consider stopping remdesivir if ALT >10x ULN.
  - Remdesivir should be discontinued in patients with ALT elevation and signs or symptoms of liver inflammation.
  - There are no studies of the pharmacokinetics of remdesivir in patients with hepatic impairment or cirrhosis.
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, \( P < .001 \)). 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.

- 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.

Elevated liver biochemistries have been commonly observed in the remdesivir clinical development program and in VigiBase, the World Health Organization’s safety reports database, rarely including elevations up to 10 times baseline values.

- The total number of patients treated with remdesivir with elevated serum aminotransferases was 32/532 (6%) vs. 55/516 (10%) with placebo.
- The incidence of hyperbilirubinemia with remdesivir was 2/532 (0.4%), which was similar in patients treated with placebo, 1/516 (0.2%).
- Investigational or off-label therapeutics for COVID-19 are infrequently discontinued because of hepatotoxicity (Table 2).

- 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, \( P < .001 \)).
  - 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, \( P = .14 \)).

- In a prospective meta-analysis of 7 randomized trials that included 1703 patients, 28-day all-cause mortality was lower among patients who received corticosteroids (dexamethasone, hydrocortisone, or methylprednisolone) compared with those who received usual care or placebo (summary odds ratio 0.66).
- In a retrospective study from China of 20 patients with COVID-19 and untreated chronic hepatitis B, 3 patients who received corticosteroids or interferon alpha-1b experienced hepatitis B reactivation.
- The NIH recommends dexamethasone (or alternative corticosteroids) for the treatment of COVID-19 in patients who are mechanically ventilated and in patients who require supplemental oxygen.
- The Infectious Diseases Society of America (IDSA) recommends dexamethasone for hospitalized critically ill patients with COVID-19 or patients with severe, non-critical COVID-19.
• Drugs that target the IL-6 receptor (e.g., tocilizumab) are being tested only in hospitalized patients with moderate to severe COVID-19.
  o The IDSA and NIH recommend using tocilizumab only in the context of a clinical trial.78
  o A recently completed double-blind, placebo-controlled trial of a single dose of tocilizumab in 243 patients with severe COVID-19 failed to demonstrate any clinical or survival benefit.79
  o Sarulimab was not more effective than placebo in a recent randomized controlled trial and associated with more frequent AST and ALT elevations and is no longer under consideration for treatment of COVID-19.80
  o In the Phase 3 COVACTA trial, no differences in any primary or secondary outcomes were noted in 450 patients with severe COVID-19 who were randomized to tocilizumab vs. placebo.

• Cocktails of monoclonal antibodies targeting the receptor binding domain of the spike protein and viral binding to the ACE2 receptor are being developed to treat COVID-19.81
  o Preliminary results from an ongoing study in 799 treated patients demonstrated improvement in viral loads with different doses of the cocktail compared to placebo, particularly when given early to seronegative outpatients.

• Hydroxychloroquine (an analogue of chloroquine with a better safety profile) has been shown to have anti-SARS-CoV-2 activity in vitro.82
  o 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.83
  o The NIH recommends against the use of hydroxychloroquine plus azithromycin except in the context of a clinical trial because of the risk of QT prolongation.71
  o 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.

• Convalescent plasma transfusion was approved by the FDA under Emergency Use Authorization on August 23, 2020 for treating hospitalized patients with COVID-19.84–86
  o Antibody levels in currently available COVID-19 convalescent plasma are highly variable and assays to measure them remain limited.
  o PLACID was an open-label, randomized controlled trial of convalescent plasma vs. standard of care that demonstrated no difference in progression to severe disease or survival.87
  o Currently, the NIH and IDSA recommend that convalescent plasma should not be considered standard of care treatment for COVID-19 and that additional prospective, well-controlled, randomized trials are needed.

• The NIH recommends against the use of lopinavir-ritonavir for the treatment of COVID-19, except in the context of a clinical trial.71
  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.88 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.89
Ritonavir is a potent inhibitor of CYP3A4, which is involved in the metabolism of calcineurin inhibitors, sirolimus, and everolimus.

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.\(^9\)
  - Increased ACE2 expression theoretically facilitates infection with SARS-CoV-2.
  - Animal studies suggest that ACEIs and ARBs may protect against serious lung complications from SARS-Co-V, but to date there are no data in SARS-CoV-2 or in humans.\(^9\)
  - There is no evidence that ACEIs or ARBs are harmful in the setting of COVID-19.\(^7,92,93\)

**Recommendations**

- Monitor studies of antiviral and immunomodulatory approaches to COVID-19 at NIH’s [clinicaltrials.gov](https://clinicaltrials.gov).
- Remdesivir is recommended for the treatment of adult and pediatric patients >12 years of age who weigh >40 kg with COVID-19 requiring hospitalization.
  - Liver biochemistries should be checked in all patients prior to starting remdesivir and daily while receiving remdesivir.
  - Remdesivir should not be initiated in patients with ALT ≥5x ULN at baseline or in patients with an estimated glomerular filtration rate <30 mL/min.
  - Remdesivir should be discontinued in patients who develop ALT ≥10x ULN during treatment or ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR.
  - Remdesivir may be restarted when ALT is <5x ULN.
- On the basis of the preliminary report from the RECOVERY Trial, the NIH and IDSA recommend using dexamethasone 6 mg po or IV daily for 10 days in patients with moderate-to-severe COVID-19 requiring mechanical ventilation or supplemental oxygen.
  - If dexamethasone is not available, the NIH recommends using equivalent daily doses of prednisone (40 mg), methylprednisolone (32 mg), or hydrocortisone (160 mg).
  - Prolonged use of systemic corticosteroids may increase the risk of hepatitis B reactivation and other latent infections including herpesviruses, strongyloides, and tuberculosis, and therefore appropriate screening and monitoring should be undertaken.
  - Dexamethasone is a moderate CYP3A4 inducer and potential impact on other CYP3A4 substrates such as calcineurin inhibitors should be considered.
- The available evidence does not currently support the use of drugs targeting the IL-6 pathway outside of clinical trials.\(^7,8^0\)
- The available evidence does not currently support the use of lopinavir-ritonavir for the treatment of COVID-19.\(^7,8^8\)
- 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](https://www.liverdruginteractionchecker.com).
Procedures

**What we know**

- There is potential for fecal-oral SARS-CoV-2 transmission,$^{5,27,94,95}$ and the virus is detected in saliva.$^{5,27,42,96}$
- 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.$^{97}$
- Endoscopic procedures should be considered aerosol-generating.$^{98}$
- 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.$^{99}$

**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.$^{97}$
- 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.$^{97}$
- Regularly monitor state and local regulations and society guidance documents as the pandemic evolves.
- 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.¹⁰⁰
• Arrange for research medications to be sent to subjects by the study sponsor if the research pharmacy is unavailable.¹⁰⁰ 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.
• Our improved understanding of the epidemiology, pathogenesis, and transmission of SARS-CoV-2 allows us to continue to involve trainees in patient care with appropriate PPE and other safety considerations.
• 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).

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.
- Resume patient care and educational activities as appropriate based on local SARS-CoV-2 prevalence, PPE supplies, and training requirements.
  - Consider a phased approach to returning fellowship training to pre-pandemic practices.101
- Assign fellows only to participating sites that ensure the safety of patients and fellows.
- Ensure appropriate supervision of trainees if they are conducting remote patient care activities (telephone/telemedicine visits).
- Continue to hold virtual educational conferences as appropriate based on local SARS-CoV-2 prevalence.
- 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 conducting fellowship recruitment and interviews virtually.

**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.102–105
- 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.106
- 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 currently reimburses telephone and telemedicine visits for both new and established patients.
- 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).107
• 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.
• 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.108
• 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 CMS for general guidelines pertaining to reentry.
• Consult CDC guidelines for a reentry framework based on potential for patient harm and degree of community transmission.
• Continue 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.
• Providers, 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.109
• Establish criteria for reentering the mitigation phase if necessary based on increases in the local prevalence of SARS-CoV-2.109
• Continue to develop a telemedicine program to reduce contact between patients and health care workers.
• Consider the role of telemedicine in patient care during local changes in SARS-CoV-2 prevalence and beyond the COVID-19 pandemic.108
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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

- AASLD Patient Flyers can be found on the [AASLD COVID-19 and the Liver website](https://www.aasld.org)
- [Asian Pacific Association for the Study of the Liver (APASL)](https://www.apasl.org)
- [American Society of Transplantation (AST) COVID-19 Information for Transplant Community](https://www.ast.org)
- [European Association for the Study of the Liver (EASL)](https://www.easlhepatology.org)
  - CDC [recommendations](https://www.cdc.gov/coronavirus/2019-ncov/index.html) for cleaning and disinfecting rooms or areas visited by individuals with suspected or confirmed COVID-19
- [The Transplantation Society Guidance](https://www.transplantjournal.org) on Coronavirus Disease 2019 (COVID-19) for Transplant Clinicians
- [Association of Organ Procurement Organizations COVID-19 Bulletin](https://www.aoporg.org)
- [FDA Guidance](https://www.fda.gov) on Conduct of Clinical Trials of Medical Products During COVID-19 Pandemic
- [Medicare Telemedicine](https://www.cms.gov) Health Care Provider Fact Sheet
- [CMS Flexibilities to Fight COVID-19](https://www.cms.gov)
- [ACGME's Response](https://www.acgme.org) to the Coronavirus (COVID-19)
- [Joint GI Society](https://www.jointgicare.org) Message for Gastroenterologists and Gastroenterology Care Providers
- [ASGE guidance](https://www.asge.org) 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](https://www.liverpool.ac.uk)
### 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>
</table>
| CBC with differential & platelets                                           | <1               | NA           | Lymphopenia frequently identified at presentation and associated with poor prognosis  
Elevated WBC and thrombocytopenia indicate poor prognosis                                                |
| Comprehensive metabolic panel                                               | <1               | NA           | Abnormal aminotransferases are common but usually 1-2x ULN  
Alkaline phosphatase usually normal  
Acute kidney injury indicates poor prognosis                                                           |
| LDH, D-dimer, CRP, INR, CPK, ferritin                                        | <1               | NA           | Elevated inflammatory markers associated with poorer outcomes                                                                         |
| Chest CT                                                                     | <1               | 80%-90%      | Bilateral ground glass opacities (lower lobe and peripheral) seen in >90% of hospitalized cases confirmed by RT-PCR  
Specificity only 25%                                                                                   |
| Nasopharyngeal swab (RT-PCR)                                                 | 2-48             | 40%-80%      | Peak shedding 12-14 days after infection; Nasopharyngeal higher yield than oropharyngeal  
Requires frozen transport media if >24 hours  
False negative common in early in disease                                                               |
| Qualitative nasopharyngeal swab (non-PCR)                                    | <1               | 80%-90%      | Point of care qualitative test using isothermal detection methods  
Results in 15 minutes                                                                                   |
| Saliva (RT-PCR)                                                              | 2-48             | 80%          | FDA emergency approval for simplified tests with self-collection                                                                      |
| Sputum (RT-PCR)                                                              | 2-48             | 60%-80%      | Should be spontaneous expectorant  
Do not induce                                                                                           |
| Bronchoalveolar lavage (RT-PCR)                                              | 2-48             | 95%          | Recommended only for intubated patients with negative nasopharyngeal swab                                                               |
| Plasma serology (IgG, IgM, IgA)                                              | 1-2              | 70%-90%      | 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                         |
| Nasopharyngeal swab (CRISPR)                                                 | 1-2              | NA           | Colorimetric dipstick in development                                                                                                   |
| Blood (RT-PCR)                                                               | 24               | 15%          | May be present in more severe cases                                                                                                      |
| Stool (RT-PCR)                                                               | 24               | 30%          | May be detectable throughout disease phase                                                                                              |
| Cell culture                                                                 | >24 (days)       | NA           | For research purposes only  
Requires high level safety lab  
Used for vaccine and antiviral testing                                                                          |

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 2. Investigational Treatments for COVID-19

<table>
<thead>
<tr>
<th>Agent (route/mechanism)</th>
<th>Target population</th>
<th>Safety issues</th>
<th>Issues related to liver disease</th>
<th>Approval status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiviral Agents</strong></td>
<td></td>
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</tr>
<tr>
<td>Remdesivir (IV/nucleotide analogue)</td>
<td>Moderate-severe</td>
<td>Nausea/vomiting Drug vehicle accumulation in acute kidney injury (Exclusions:) GFR &lt;30 mL/min AST or ALT &gt;5x ULN</td>
<td>Incidence of AST, ALT, bilirubin elevations similar to placebo Consider stopping drug if ALT &gt;10x ULN Stop drug if symptoms of hepatitis</td>
<td>FDA approved for patients &gt;12 years and &gt;40 kg EUA for patients &lt;12 years or &lt;40 kg</td>
</tr>
<tr>
<td>Favipiravir (oral/RNA polymerase inhibitor)</td>
<td>Early to mild disease</td>
<td></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>Use with caution in patients with hepatic impairment</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[^89]</td>
</tr>
<tr>
<td>Nitazoxanide (oral/host proteins)</td>
<td>Moderate-severe</td>
<td>Similar to placebo in influenza trials</td>
<td></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 (Exclusions:) QTc &gt;415 ms Cardiomyopathy G6PD deficiency</td>
<td></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 (Exclusions:) QTc &gt;415 ms Cardiomyopathy G6PD deficiency</td>
<td></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>Immunomodulatory Agents</td>
<td>Azithromycin (oral/host proteins)</td>
<td>Moderate-severe</td>
<td>CYP3A4 substrate Moderate DDI with CNI Rare cholestatic hepatitis Exclusion: QTc &gt;415 ms</td>
<td>Can rarely cause cholestatic hepatitis</td>
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<tr>
<td>Famotidine (oral or IV/protease inhibitor)</td>
<td>All</td>
<td>None significant</td>
<td>FDA-approved for other indications A retrospective study demonstrated famotidine was associated with lower in-hospital mortality (OR 0.37, 95% CI 0.16-0.86)(^{110}) In a propensity score-matched analysis, famotidine was associated with a reduced risk of death or intubation (adjusted HR 0.42, 95% CI 0.21-0.85)(^{111})</td>
<td></td>
</tr>
<tr>
<td>Combination monoclonal antibodies (IV/target SARS-CoV-2 proteins)</td>
<td>All</td>
<td>Half-life of 18-21 days Placebo studies ongoing</td>
<td>Submitted to FDA for EUA on 10/8/2020</td>
<td></td>
</tr>
<tr>
<td>Tocilizumab (IV/monoclonal IL-6 receptor antagonist)</td>
<td>Severe (high IL-6 levels)</td>
<td>Grade 1-2 ALT 20%-40% Grade 3+ ALT 1%-2%. Acute liver failure &lt;1% Neutropenia 3% Thrombocytopenia 2% Opportunistic infections Exclusions: ANC &lt;2,000/m(^3) Platelets &lt;100,000/m(^3) ALT &gt;5 xULN</td>
<td>Incidence of AST and ALT elevations similar to placebo Only recommended for COVID-19 in a clinical trial RCT in 243 patients showed no clinical benefit compared to placebo FDA-approved for RA 8 mg/kg dose</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% Exclusions: ALT &gt;5 x ULN</td>
<td>No published data in COVID-19 yet available FDA-approved in Castleman’s disease Only recommended for COVID-19 in clinical trial</td>
<td></td>
</tr>
<tr>
<td>Convalescent plasma (IV/neutralizing antibodies)</td>
<td>Severe or life-threatening</td>
<td>Potential TRALI/anaphylaxis ICU monitoring needed</td>
<td>Available in US under FDA EUA Investigational</td>
<td></td>
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<tr>
<td>Condition</td>
<td>Screening/Precautions</td>
<td>Dexamethasone (oral or IV/anti-inflammatory)</td>
<td></td>
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<tr>
<td>Threatening pneumonia</td>
<td>Must screen donor for other transmissible pathogens</td>
<td>Moderate-severe</td>
<td></td>
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<tr>
<td></td>
<td>Recommended only for intubated patients or those needing supplemental oxygen</td>
<td>Potential for hyperglycemia and reactivation of latent hepatitis B, tuberculosis, herpes</td>
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<tr>
<td></td>
<td>Finding donors with neutralizing IgG activity not well established</td>
<td>Hepatitis B reactivation may occur within 1 week of hospitalization</td>
<td></td>
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<tr>
<td></td>
<td>Reserved for severe/life threatening cases</td>
<td>FDA-approved for multiple indications</td>
<td></td>
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</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
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

Screen/test recipient*

Negative screen and negative test

Positive screen and/or positive test

Proceed with transplantation

Positive screen

Call backup recipient in to hospital

Screen/test recipient*

Negative screen and negative test

Positive screen and/or positive test

Do not proceed with transplantation

Positive screen and/or positive test

Screen/test donor**

Negative screen and negative test

*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

Consider discharge when
oxygen no longer needed

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**

*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


