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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 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

Disclaimer

This document represents the collective opinion of its authors and approval of the AASLD Governing Board as of the date of publication. Its use is voluntary, and it is presented primarily for the purpose of providing information to hepatology and liver transplant care providers. This document is not a practice guideline and has not been subject to the methodical rigor of a practice guideline. There has not been a systematic evidence review as defined by the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine (formerly the Institute of Medicine), nor is the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach utilized. This document does not define a standard of practice or a standard of care. It should not be considered as inclusive of all proper treatments or methods of care, nor is it intended to substitute for the independent professional judgment of the treating provider. Hospitals, clinics and private practices should take into account local standards, practices, and environment.

Major Changes and Updates

- Sections removed: “Diagnosis of SARS-CoV-2”, “Medication Management of Patients with COVID-19 and Potential Drug-Drug Interactions”, “Procedures”, “Trainees”, “Telemedicine”, “Reentry and Return to Prepandemic State”, Figure 2: “Approach to Liver Transplant Organ Offers”, Figure 3: “Approach to the Liver Transplant Recipient with COVID-19”
- New section heading “Management of Chronic Liver Disease During the COVID-19 Pandemic” replaced “Stable Outpatients with Liver Disease and/or HCC” and “Patients with Decompensated Cirrhosis, Liver Transplant Evaluations, and Patients on the Liver Transplant Waiting List”
- New sections added: “Outpatient Management of COVID-19 in Patients with Liver Disease and Liver Transplantation”, “Inpatient Management of COVID-19 in Patients with Liver Disease and Liver Transplantation”
- Updated sections: “Effect of SARS-CoV-2 on the Liver and Evaluation of Patients with Elevated Liver Biochemistries”, “Liver Transplantation, Resource Utilization, and Ethical Considerations”, “Management of Post-Liver Transplant Patients and Patients on Immunosuppressive Agents During the COVID-19 Pandemic”
- Updated list of Helpful Resources
- Revised Table 1: “Diagnostic Methods for SARS-CoV-2 Detection”
- Revised Table 2: “Treatments for COVID-19”
- New document “AASLD Expert Panel Consensus Statement: Vaccines to Prevent COVID-19 in Patients with Liver Disease” available on AASLD’s COVID-19 resource page

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 2020-2021 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, and for providing 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

- 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.[4–6]
- The incidence of elevated serum liver biochemistries in hospitalized patients with COVID-19 ranges from 14% to 83%.[7–16]
    - 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.[13–15,17]
    - Elevations in alkaline phosphatase and gamma glutamyl transferase are seen in 6% and 21% of COVID-19 patients, respectively.[18]
    - Liver injury occurs more commonly in severe COVID-19 cases than in mild cases.[12,14,19]
    - Rare cases of severe acute hepatitis have been described in patients with COVID-19.[8,13,14,20]
        - 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).[14,16]
        - Acute liver failure secondary to Herpes Simplex Virus-1 has been reported in COVID-19 patients following tocilizumab and corticosteroid therapy.[21]

  - Liver injury in mild COVID-19 cases is usually transient and does not require specific treatment beyond supportive care.[12]
- Low serum albumin on hospital admission is a marker of COVID-19 severity.[11,14,22–24]
- AST is usually higher than ALT and is associated with severe COVID-19 and mortality, which may reflect non-hepatic injury.[10,14,15,19]
- Baseline liver test abnormalities are associated with risk of intensive care unit admission and tend to improve over time.[25]
- COVID-19 patients with elevated liver biochemistries are at increased risk of death and severe COVID-19 compared to COVID-19 patients without elevated liver biochemistries.[18]
- Alkaline phosphatase peak values are correlated with risk of death and may be predictive of a worse prognosis.[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).[26,27]
- 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.[28]
- 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.[5,29,30]
- Several autopsy series have demonstrated SARS-CoV-2 within hepatocytes confirming that direct hepatic infection in COVID-19 occurs.[4,5,31]
  - Typical histological evidence of viral infection in these hepatocytes has also been seen; however, the impact of direct SARS-CoV-2 hepatocyte infection on liver failure or the course of COVID-19 remains unclear.
  - 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.[5]
  - An Italian autopsy series showed minimal hepatic inflammation but extensive portal and sinusoidal thrombosis.[31] SARS-CoV-2 was found in 15 of 22 samples tested.
- Elevated liver biochemistries may reflect a direct virus-induced cytopathic effect and/or immune damage from the provoked inflammatory response and cytokine release syndrome.[9,32]
- Therapeutic agents used to manage symptomatic COVID-19 may be hepatotoxic but rarely lead to treatment discontinuation.[12] These include remdesivir and tocilizumab.[33–36]
- The pooled incidence of drug-induced liver injury in patients with COVID-19 is 25.4% (95% CI 14.2-41.4).[18]
- 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.[12]
- Cholestatic features including bile duct proliferation and canalicular/ductular bile plugs have been reported in post-mortem evaluations of COVID-19 patients.[5,37]
- Secondary sclerosing cholangitis of critically ill patients and cholangiopathy have been reported in patients with severe COVID-19 and during recovery.[38,39]

- 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.[40,41]
    - Acute portal vein thrombosis has been reported in patients with COVID-19; however, a causal link to COVID-19 has not been definitively established.[42]
    - 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.
- 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.[12,29]
- An approach to evaluating the patient with COVID-19 and elevated liver biochemistries is shown in **Figure 1**.

GUIDANCE FOR EVALUATION OF COVID-19 PATIENTS WITH ELEVATED LIVER BIOCHEMISTRIES

- **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.**[16]
- **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.**
- **Consider cholangiopathy or secondary sclerosing cholangitis of critically ill patients in patients with severe COVID-19 with worsening cholestasis.**
- **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.**[26]
- **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.**

Management of Chronic Liver Disease During the COVID-19 Pandemic

- Chronic liver disease (CLD) is not more prevalent among hospitalized patients with COVID-19, but it is associated with severity of COVID-19 and mortality.[24,43–47]

- A meta-analysis that included 73 studies and 24,299 patients reported the prevalence of CLD was 3% among hospitalized COVID-19 patients, which was similar to the COVID-19-negative population. CLD was associated with COVID-19 severity (pooled OR 1.48) and mortality (pooled OR 1.78).[43]
- In a large cohort study of electronic health record data from over 17 million patients (>100,000 with CLD) in the United Kingdom, CLD was a risk factor for in-hospital death from COVID-19.[44]
- CLD was associated with significantly higher mortality (RR 2.8) in a cohort of 2780 US patients with COVID-19, and the mortality risk was higher in patients with cirrhosis (RR 4.6).[45]
- In a retrospective Italian study of 50 patients with COVID-19 and cirrhosis, patients with cirrhosis had a higher 30-day mortality rate compared to patients without cirrhosis (34% vs 18%).[24]
- In a multicenter study of inpatients with cirrhosis and COVID-19 compared with age/sex-matched patients with COVID-19 alone and cirrhosis alone, patient 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).[46]

- Mortality from COVID-19 is higher in more advanced liver disease and strongly associated with hepatic decompensation.[47,48]
  - In a large international registry study, patients with Child-Turcotte-Pugh class C cirrhosis and COVID-19 had a 4.6-fold increase in mortality compared to patients with Child-Turcotte-Pugh class A cirrhosis.[47]
  - Acute hepatic decompensation during COVID-19 was strongly associated with subsequent risk of death (44% with new decompensation died vs. 22% without decompensation).
  - 21% with acute hepatic decompensation had no respiratory symptoms at presentation.
  - Hepatic decompensation was an independent risk factor for mortality (HR 2.91) in a multicenter, observational US cohort of patients with COVID-19 and cirrhosis.[48]
- Alcohol-associated liver disease is a strong predictor of mortality in COVID-19.[47,48]
- Hepatocellular carcinoma (HCC) is associated with increased all-cause mortality in patients with COVID-19.[48]
- Chronic hepatitis B or C have not been associated with mortality from COVID-19.
- AIH has not been associated with hospitalization or death from SARS-CoV-2 infection.[49]
  - Among 932 patients with CLD and SARS-CoV-2 infection in an international registry study, including 70 patients with AIH, AIH was associated with increased risk of hospitalization but not ICU admission or death.
  - 83% of AIH subjects in this study were on one or more immunosuppressive drugs.
- 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.[50,51]
  - NAFLD is associated with progressive COVID-19 and worse outcomes independent of obesity and comorbidities.[50,52]
- The complex decision making involved in whether or not to proceed with transplantation has been more challenging because of the COVID-19 pandemic.
- COVID-19 has had a significant impact on the transplant waiting list and transplant center practice patterns.[53]

GUIDANCE FOR MANAGING CHRONIC LIVER DISEASE DURING THE COVID-19 PANDEMIC

- **See CDC Guidance for Healthcare Facilities.**
- **Optimize the use of telemedicine services for managing stable outpatients with CLD.**
- **Screen all patients for symptoms of COVID-19 or recent exposure 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.**
- **Patients with symptoms of COVID-19 should be rescheduled and tested for SARS-CoV-2.**
- **Follow CDC recommendations for PPE and social distancing in the clinic space, including waiting rooms.**
- **Patients, caregivers, and providers should wear masks while in the clinic.**
- **Consider limiting the number of visitors who accompany patients to their visits to at most one if necessary.**
- **Continue treatment for hepatitis B, hepatitis C, AIH, or primary biliary cholangitis (PBC) if already on treatment.**
- **There is no contraindication to initiating treatment of hepatitis B, hepatitis C, AIH, or PBC 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 or PBC in a patient *with* COVID-19 is not routinely warranted and can be deferred until recovered from COVID-19.**
- **Consider instructing patients to avoid attending in-person community recovery support meetings such as Alcoholics Anonymous and provide alternative telephone or online resources.**
- **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.**
- **Avoid HCC surveillance in patients with COVID-19 until infection is resolved.**
- **Proceed with liver cancer treatments or surgical resection when able rather than delaying them because of the pandemic.**
- **Have a low threshold for considering COVID-19 in patients with new complications for cirrhosis. Test patients with acute hepatic decompensation for SARS-CoV-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.[27,54] Nevertheless, immunosuppressed patients have higher viral titers and may be more infectious than immunocompetent individuals.[55]
- 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.[56]

Liver Transplantation, Resource Utilization, and Ethical Considerations

- 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.
- 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, with 8,896 liver transplants performed in 2019 and 8,908 in 2020. There were 524 living donor liver transplants in 2019 and 491 in 2020.
- All Organ Procurement Organizations are testing donors for SARS-CoV-2 RNA using specimens obtained from nasopharyngeal swabs, BAL, or both. See **Table 1**.
- 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 x-ray or noncontrast chest CT should be considered.[57]
- SARS-CoV-2 PCR may remain positive for months after resolution of infection and infectivity.
- Organs from donors with a prior history of COVID-19 but have recovered and are no longer shedding replication-competent virus may be suitable for donation.[58]
- "Reactivation" of SARS-CoV-2 after solid organ transplantation has not been reported to date.
- Transplantation in SARS-CoV-2-positive transplant candidates is currently not routinely recommended until at least 14 days after clinical recovery.
    - 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.
    - 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 national emergency on March 13, 2020.

GUIDANCE FOR LIVER TRANSPLANTATION DURING THE COVID-19 PANDEMIC

Transplant Programs

- **Develop a hospital-specific policy for organ acceptance.**
- **Remain aware of the status of COVID-19-free ICU beds for transplant recipients and supplies of platelets and other needed blood products to safely perform transplants and manage the early postoperative period.**
- **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.**
- **Notify patients that family and visitor access to them during their hospital stay may be limited or prohibited.**
- **Test all recipients and donors for SARS-CoV-2 before transplantation.**
- **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.**

Potential Donors

- **Screen potential donors for exposure and clinical symptoms/fever compatible with COVID-19 (regardless of test results or availability).**[59]
- **Organ donation from deceased donors who have recovered from COVID-19 can be considered if:**[60]
  - **Repeat SARS-CoV-2 RNA testing is negative.**
  - **SARS-CoV-2 RNA testing is positive, but patient is asymptomatic and the infection occurred between 21 to 90 days prior to donor evaluation.**
  - **The safety of deceased donors with a history of mild COVID-19 more than 10 and less than 21 days after disease onset and resolution of symptoms is unknown. These organs can be used on a case-by-case basis weighing the risks of undetected residual SARS-CoV-2 with continued waiting.**
- **Organ donation from deceased donors who have recovered from COVID-19 should not be considered if it is greater than 90 days from the donor's initial infection and repeat SARS-CoV-2 RNA testing is positive. This should be considered a true positive and reinfection of the donor.**[60]
- **Living donation from donors with mild or asymptomatic COVID-19 is likely safe 21-28 days after disease onset.**[60]
- **See the latest updates regarding COVID-19 related OPTN policy changes.**

Potential Recipients

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

- **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.**
- **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, clinical assessment including the presence of respiratory symptoms, time from initial diagnosis, severity of COVID-19 episode, and the risk of exposing transplant personnel to SARS-CoV-2.**

Management of Post-Liver Transplant Patients and Patients on Immunosuppressive Agents During the COVID-19 Pandemic

- SARS-CoV-2 is most infectious during the onset of symptoms and infectivity decreases to near-zero after about 10 days in mild-moderately ill patients and 20 days in severe-critically ill and immunocompromised patients.[61]
- The immune response may be the main driver for pulmonary injury attributable to COVID-19 and that immunosuppression may be protective.[10,27,62,63]
- Corticosteroids improve survival in critically ill patients with COVID-19 requiring supplemental oxygen.[64,65]
- Baseline immunosuppression containing tacrolimus was associated with better survival in liver transplant recipients with COVID-19.[63]
- Baseline immunosuppression containing mycophenolate was an independent predictor of severe COVID-19 in liver transplant recipients,[66]
- Lowering immunosuppression, primarily antimetabolites, in liver transplant recipients with COVID-19 during a period of active infection has not been shown to increase the risk of rejection as long as liver biochemistries are monitored.[23,62,67]
- Reducing the dosage or stopping immunosuppressants without monitoring liver biochemistries may cause a flare in a patient with AIH or precipitate acute rejection in a liver transplant recipient.[54]
    - 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.[68]
- The course of COVID-19 in patients with AIH on immunosuppression may be similar to non-immunosuppressed patients.[54]
- Liver transplant recipients, when adjusted for multiple risk factors, may not be at significantly increased risk of death compared to the general population with COVID-19.[66,67,69,70]
- Anti-IL-6 therapeutics have not been shown to increase the risk of acute cellular rejection.

GUIDANCE FOR MANAGING LIVER TRANSPLANT PATIENTS AND PATIENTS ON IMMUNOSUPPRESSIVE AGENTS DURING THE COVID-19 PANDEMICPost-transplant patients *without* COVID-19:

- **Optimize the use of telemedicine services for managing stable outpatients.**
- **Do not make anticipatory adjustments to current immunosuppressive drugs or dosages.**

- **Emphasize prevention measures to minimize the risk of acquiring SARS-CoV-2: frequent hand washing, cleaning frequently touched surfaces, staying away from large crowds, staying away from individuals who are ill, etc.**
- **Encourage COVID-19 vaccination of all liver transplant recipients (ideally at least 6 weeks post liver transplantation).[71]**

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.**
- **Monitor kidney function and calcineurin inhibitor levels.**
- **Adjust immunosuppressive medications based on severity of COVID-19 and risk of graft rejection and renal injury.**
- **Follow guidelines from the NIH.[68]**

Patients with AIH on immunosuppression *without* COVID-19:

- **Do not make anticipatory adjustments to current immunosuppressive drugs or dosages.**
- **Encourage all patients to be vaccinated against COVID-19.[71]**

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.**
- **Adjust immunosuppressive medications based on severity of COVID-19.**
- **Follow guidelines from the NIH.[68]**

Patients requiring initiation or modification of immunosuppressive therapy:

- **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).**

Outpatient Management of COVID-19 in Patients with Chronic Liver Disease and Liver Transplantation

Monoclonal Antibody Preparations

- Monoclonal antibodies that target the SARS-CoV-2 spike protein have received emergency use authorization (EUA) from the FDA.
    - Casirivimab + imdevimab (Regeneron).
    - Bamlanivimab alone and bamlanivimab + etesevimab (Eli Lilly).

- EUA criteria for treatment include the following:
    - Mild to moderate proven COVID-19.
    - Adult and pediatric patients age 12 years and older and weighing at least 40 kg.
    - At high risk for progressing to severe COVID-19 or hospitalization.
    - Not currently hospitalized for COVID-19 (allowed if hospitalized for another reason).
    - Not requiring oxygen therapy or increase in baseline oxygen therapy.
    - Must be administered in setting allowing treatment of infusion reactions,
- The totality of the data indicates that when given early in the course of COVID-19 (median 4 days after onset of symptoms in the bamlanivimab studies) monoclonal antibodies decrease the need for hospitalization and death (70% reduction) and decrease viral load.[72–74]
- Monoclonal antibodies appear to work best in those who have high viral loads.[74]
- Monoclonal antibodies have demonstrated lack of efficacy when given to patients hospitalized with severe COVID-19.[75]
- Emerging variants may reduce or eliminate the efficacy of monoclonal antibodies, particularly when only one antibody is used.[76]
- Monoclonal antibodies have been shown to be effective in preventing COVID-19 in exposed persons, but the FDA has not granted EUA for this indication

Other Outpatient Treatment

- Treatments that have been shown to be either ineffective or harmful include hydroxychloroquine (with or without azithromycin), azithromycin alone, or lopinavir/ritonavir.[77]
- Corticosteroids have not been well studied in the outpatient setting and immune suppression may be harmful in the early stages of COVID-19.
- One study demonstrated a benefit of high-titer convalescent plasma if given very early (within 72 hours of symptom onset) to high-risk elderly patients with mild COVID-19.[78]
    - In the United States, monoclonal antibodies are typically used in this circumstance and outpatient use of convalescent plasma is not covered in the current EUA.

See **Table 2** for additional details about COVID-19 treatments.

GUIDANCE FOR OUTPATIENT MANAGEMENT OF COVID-19 IN PATIENTS WITH CHRONIC LIVER DISEASE AND LIVER TRANSPLANTATION

- **Patients with liver disease and those who have received a liver transplant should be offered monoclonal antibody treatment if EUA criteria are met (see above) and monoclonal antibody is available.**
- **Among monoclonal antibody preparations currently available under EUA, we do not recommend one product in preference to another; however this may change as variant strains emerge.**
- **Except for supportive care, no other specific treatment targeting SARS-CoV-2 or the associated inflammatory response is recommended in the outpatient setting.**
- **The use of new or increased doses of corticosteroids should be avoided in the outpatient setting.**

- **It is unclear if NSAIDS are detrimental in patients in with COVID-19; however, in the absence of contraindications, acetaminophen-based analgesics are preferred.**

Inpatient Management of COVID-19 in Patients with Chronic Liver Disease and Liver Transplantation

- SARS-CoV-2 infection includes an early phase of viral replication followed in some patients by an inflammatory phase. Thus, the precise timing of treatments appears to be critical to efficacy.

Remdesivir

- Remdesivir is a nucleotide analogue with demonstrated activity against SARS-CoV-2 in human cell lines.[79]
- 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.
- No mortality benefit has been demonstrated, but remdesivir shortens duration of illness and hospitalization and appears to be most effective when given to patients on supplemental oxygen within 10 days of symptom onset.[35]
- No benefit observed in those requiring high-flow oxygen, non-invasive ventilation, mechanical ventilation, or ECMO.[35]
- No efficacy of treatment duration beyond 5 days has been observed.[33]
- Elevations in aminotransaminase levels have been observed in patients and healthy volunteers treated with remdesivir, although in clinical trials aminotransaminase elevations did not occur more frequently in patients on remdesivir compared to placebo.[80]
    - Cases of hepatocellular injury with jaundice have not been reported due to short-term treatment with remdesivir for COVID-19.

Dexamethasone

- Dexamethasone given at 6 mg daily for up to 10 days decreases mortality in hospitalized patients with COVID-19 requiring supplemental oxygen.[64]
    - The greatest benefit was seen in patients requiring mechanical ventilation, a trend toward harm was observed in patients who did not require supplemental oxygen, and no benefit was seen in those more than 7 days from onset of symptoms.
- Very few patients with severe liver disease were included in the RECOVERY trial (<3%) and the number of solid organ transplant patients included is not reported.[64]

IL-6 inhibitors (e.g., tocilizumab, sarilumab)

- Tocilizumab and sarilumab are IL-6 inhibitors approved by the FDA for treatment of autoimmune diseases (e.g., rheumatoid arthritis) and chimeric antigen receptor T cell (CAR-T) induced cytokine release syndrome.
- Early in the COVID-19 pandemic, case series suggested that IL-6 inhibition of the inflammatory state occurring in some patients with COVID-19 might improve outcomes.[81]

- Seven randomized trials have been reported with mixed results. Overall, when added to dexamethasone, tocilizumab (less data available for sarilumab), may improve mortality and the duration of critical illness and need for mechanical ventilation in patients with recent (24 hours) or impending need for mechanical ventilation and elevated markers of inflammation (CRP levels > 75mg/L).[82,83]
- Tocilizumab is suggested for use in those not responding to steroids alone with high levels of inflammation.[77]
- Aminotransaminase elevations and drug-induced liver injury have been observed in patients treated with tocilizumab.[84]

Baricitinab

- Kinase inhibitors reduce inflammation that may worsen organ damage in patients with COVID-19 and may have direct antiviral properties.
- Baricitinab is FDA approved for the treatment of refractory rheumatoid arthritis.
- In the ACTT-2 trial, baricitinib + remdesiver was compared to baricitinib alone in hospitalized patinets with COVID-19. Patients randomized to the baricitinib arm recovered more quickly with the greatest benefit seen in those on high-flow oxygen or non-invasive ventilation. Mortality overall was low and no mortality benefit was seen.[85]
- Whether or not baricitinab provides additional benefit in patients receiving corticosteroids is unknown.

Convalescent Plasma

- Plasma obtained from patients recovered from SARS-CoV-2 infection contains polyclonal antibodies (and perhaps other factors) that might benefit COVID-19 patients.
- The FDA issued an EUA for convalescent plasma on August 23, 2020 for hospitalized patients with COVID-19, and revised the EUA on February 3, 2021 to exclude the use of low-titer plasma.
- Currently, many units of available plasma do not have antibody titers measured.
- The totality of the data suggests that high-titer convalescent plasma given very early (i.e., within 72 hours) after onset of symptoms may reduce the risk of progression to more severe disease in high-risk individuals with mild disease, but little benefit is seen in patients with severe disease.[78,86,87]
- The benefit of convalescent plasma remains unknown and theoretical in immunosuppressed patients with severe or prolonged COVID-19 who do not generate an adequate humoral response.
    - Repeated treatment raises concerns of favoring the development of resistant variants.

See **Table 2** for additional details about COVID-19 treatments.

GUIDANCE FOR OUTPATIENT MANAGEMENT OF COVID-19 IN PATIENTS WITH CHRONIC LIVER DISEASE AND LIVER TRANSPLANTATION

- **Remdesivir should be offered for a 5-day duration to hospitalized patients with liver disease or liver transplant recipients hospitalized with COVID-19 and requiring supplemental oxygen.**
- **In patients who require high-flow oxygen or non-invasive mechanical ventilation, remdesivir should be considered.**

- **Remdesivir should not be used in patients with liver disease or liver transplantation requiring mechanical ventilation.**
- **Baseline testing of liver biochemistries should be performed prior to initiating remdesivir and testing should be repeated frequently during treatment with drug discontinuation for elevations >10x ULN or signs or symptoms of liver inflammation.**
- **While a large, reported experience in patients with liver disease or post-liver transplantation is not available, these groups of patients hospitalized with COVID-19 and requiring supplemental oxygen or mechanical ventilation should receive dexamethasone 6 mg daily for up to 10 days if there is no contraindication (e.g., severe non-SARS-CoV-2 infection, uncontrolled hyperglycemia).**
- **If already receiving corticosteroids at lower than an equivalent dose of 6 mg daily of dexamethasone (prednisone 40mg), dose should be increased to equivalent of 6 mg daily of dexamethasone.**
- **If dexamethasone is not available, an alternative corticosteroid at equivalent doses may be substituted.**
- **While tocilizumab may benefit a subset of deteriorating critically ill patients already receiving corticosteroids, no recommendation about use in patients with liver disease or solid organ transplantation can be made based on currently available data.**
- **Baricitinab could be considered in patients with liver disease or in transplant recipients who are unable to tolerate corticosteroids and who otherwise meet indications for corticosteroids.**
- **In most situations, convalescent plasma is not indicated for hospitalized patients with liver disease or liver transplant recipients. However, patients with recent onset of symptoms (within 72 hours) and mild disease with risk factors for progression may benefit from high-titer plasma.**
- **The role of high-titer convalescent plasma in immunosuppressed patients unable to generate an adequate immune response remains unknown. One risk of this approach is the generation of immune escape variants.**

Research

- 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 carefully documented and subsequently reported.

GUIDANCE FOR RESEARCH DURING THE COVID-19 PANDEMIC

- **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.**
- **Arrange for research medications to be sent to subjects by the study sponsor if the research pharmacy is unavailable.[88] Dispensing Investigational Product on site can be gradually scaled up based on allowed visits to sites by research patients.**
- **Institutional policies on clinical and laboratory research may be more restrictive and should supersede the recommendations contained here.**

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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
- 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 health care providers.
    - 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 Clinical Trial Conduct During the COVID-19 Pandemic
- Guidance for NIH-funded Clinical Trials and Human Subjects Studies Affected By COVID-19
- NIH Extended Guidance for Applicants Preparing Applications During the COVID-19 Pandemic
- Medicare Telemedicine Health Care Provider Fact Sheet
- CMS Flexibilities to Fight COVID-19
- ACGME Response to Pandemic Crisis
- Joint GI Society Message for Gastroenterologists and Gastroenterology Care Providers
- ASGE COVID-19 Resources
- ASGE guidance for resuming GI endoscopy and practice operations after the COVID-19 pandemic
- Joint GI Society Message about Telehealth
- Joint GI Society Virtual Physical Exam Tips
- University of Liverpool Drug Interactions Group COVID-19 Drug Interaction Checker

Tables

Table 1. Diagnostic Methods for SARS-CoV-2 Detection

Assay type	Specimen	Advantages	Limitations
PCR	Nasopharyngeal or nasal/throat swab, saliva, BAL fluid	Gold standard for diagnosis of active disease	Positive results may persist after resolution of active/communicable infection May require hospital laboratory although simpler platforms available False negatives may occur; sensitivity falls as time from infection increases
RT-LAMP	Nasopharyngeal or nasal/throat swab, saliva, BAL fluid	Simple to perform Performance similar to PCR At home kit FDA cleared (Lucira)	Positive results may persist after resolution of active/communicable infection
Antigen	Nasopharyngeal or nasal/throat swab, saliva BAL fluid	Simple to perform Useful as part of large screening programs Rapid and inexpensive At home kits FDA cleared (Ellume, BinaxNOW)	Reduced sensitivity compared to PCR and negative tests may need confirmation in symptomatic individuals
Serology	Blood	Determines past infection using IgG or IgM antibodies to the nucleocapsid protein and/or spike glycoprotein May be useful aid for diagnosis 14-21 days after symptom onset in select PCR-negative cases; IgG antibodies may become undetectable within 6 to 12 months of infection Useful for sero-epidemiological studies	Negative early after infection Seroconversion rates in immunocompromised persons may be lower Positive results may not indicate protection from reinfection Should not be used to assess response to vaccine.

Table 2. Treatments for COVID-19

Agent (route/mechanism)	Target population	Safety issues	Issues related to liver disease	Approval status
Dexamethasone (oral or IV/anti-inflammatory)	Hospitalized patients requiring supplemental oxygen	Potential for hyperglycemia and reactivation of latent hepatitis B, tuberculosis, herpes	Hepatitis B reactivation may occur within 1 week of hospitalization	FDA-approved for multiple indications 6 mg daily up to 10 days
Combination monoclonal antibodies (IV/target SARS-CoV-2 proteins) casirivimab+imdevimab (Regeneron) bamlanivimab, bamlanivimab+etesevimab (Eli Lilly)	Mild to moderate disease, outpatients Adult and pediatric patients age 12 years and older At risk for progressing to severe COVID-19 or hospitalization, not currently hospitalized for COVID-19 disease Not requiring oxygen therapy or increase in baseline oxygen therapy Must be administered in a setting to monitor for infusion reactions	Half-life of 18-21 days Decreases hospitalization and death	Grade 3 or 4 adverse events similar in Casirivimab+imdevimab group and placebo group, 1% each, not liver-related	Received FDA EUA 11/21/2020
IL-6 inhibitors (IV/monoclonal IL-6 receptor antagonists) tocilizumab and sarilumab	Severe (high IL-6 levels)	Grade 1-2 ALT 20%-40% Grade 3+ ALT 1%-2% Acute liver failure <1% Neutropenia 3% Thrombocytopenia 2% Opportunistic infections *Exclusions:* ANC <2,000/m^3 Platelets <100,000/m^3 ALT >5 xULN	Incidence of AST and ALT elevations similar to placebo	FDA-approved for RA 8 mg/kg dose IDSA suggests consideration in those not responding to dexamethasone, needing supplemental oxygen, or critically ill with CRP >75 mg/dL[77]
Convalescent plasma (IV/neutralizing antibodies)	Hospitalized patients	Potential TRALI/ anaphylaxis ICU monitoring needed Must screen donor for other transmissible pathogens		FDA revised EUA 2/3/2021 to exclude the use of low-titer plasma

Figures

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