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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

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Major Changes and Updates

- Updated “[AASLD Expert Panel Consensus Statement: Vaccines to Prevent COVID-19 in Patients with Liver Disease](#)” available on [AASLD’s COVID-19 resource page](#)
- Revised section on “[Management of Chronic Liver Disease During the COVID-19 Pandemic](#)”, including data on post-COVID-19 cholangiopathy
- Revised section on “[Liver Transplantation, Resource Utilization, and Ethical Considerations](#)”, including guidance on evaluating and managing potential donors and recipients
- Updated information on [outpatient management of COVID-19 in patients with chronic liver disease and liver transplantation](#), including use of monoclonal antibodies for treatment and post-exposure prophylaxis, and preliminary information about Merck’s oral antiviral molnupiravir
- Updated list of “[COVID-19 Liver Disease and Transplant Registries](#)” and “[Helpful Resources](#)”
- Deleted Table 1 “[Diagnostic Methods for SARS-CoV-2 Detection](#)”
- Former Table 2 is now [Table 1: “Treatments for COVID-19”](#)

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 are 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 the rapidly evolving 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 occur 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 liver injury 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
- 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.²⁶
- 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), except if MIS-C is present.²⁷⁻²⁹

- 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.^{5,30,31}
- Several autopsy series have demonstrated SARS-CoV-2 within hepatocytes confirming that direct hepatic infection in COVID-19 occurs.⁴⁻⁶
 - 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.⁶ 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 and a rare cause of elevated liver biochemistries in some patients 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 (SSC-CIP) and cholangiopathy have been reported in patients with severe COVID-19 and during recovery.³⁸⁻⁴⁰
 - Typically, cholestasis is present early and cholangiopathy occurs later.
 - In a study of 2047 patients who were hospitalized for COVID-19, 12 patients developed a cholangiopathy characterized by cholestasis and biliary tract abnormalities.⁴¹ Imaging findings included beading, stricturing, and dilation of the biliary tree. Liver biopsy in 4 patients noted features of acute and/or chronic bile duct obstruction without ductopenia. One patient underwent liver transplantation.
 - The pathogenesis of this observation is currently unknown.
- 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.^{42,43}
 - Acute portal vein thrombosis has been reported in patients with COVID-19; however, a causal link to COVID-19 has not been definitively established.⁴⁴
 - 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 can 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.^{12,30}
- In a systematic review, chronic hepatitis and cholestatic liver injury were not reported as part of long-haul syndrome from COVID-19.⁴⁵
- 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
- **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 (SSC-CIP) 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.**²⁷
- **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.^{24,46–50}
 - 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).⁴⁶
 - A global meta-analysis with adjusted effect estimates that analyzed 90,095 COVID-19 patients showed that CLD patients had a higher tendency to develop severe outcomes (pooled effect size 1.52) and had an increased risk for mortality (pooled effect size 1.36).⁵¹
 - 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-19.⁴⁷

- 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).⁴⁸
- A French study of 15,476 COVID-19 patients with CLD demonstrated increased 30-day in-hospital mortality (adjusted OR 1.79).⁵²

Cirrhosis and Hepatic Decompensation

- 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, 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).⁴⁹
- Mortality from COVID-19 is higher in more advanced liver disease and strongly associated with hepatic decompensation.^{50,53}
 - 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.⁵⁰
 - 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.⁵³
 - In the above-mentioned French study, in-hospital mortality is increased in patients with decompensated cirrhosis (adjusted OR 1.38) but not compensated cirrhosis (adjusted OR 0.71).⁵²
 - This was hypothesized to be the result of limited access to care, particularly mechanical ventilation, in patients with more advanced liver disease.

Alcohol-Associated Liver Disease

- Alcohol-associated liver disease is a strong predictor of mortality in COVID-19.^{50,53}
- When compared to the pre-pandemic era, there has been a rapid increase in alcohol-associated liver disease as an indication for both liver transplant listing (+7.26%, $P < 0.001$) and liver transplantation (+10.67%, $P < 0.001$).⁵⁴
 - Listing for liver transplantation for alcohol-associated liver disease is currently more common than hepatitis C and nonalcoholic steatohepatitis combined.
 - Young adults accounted for over 35% of liver transplant listings in the COVID era.
 - Listing and liver transplantation for severe alcohol-associated hepatitis increased by over 50%.

Hepatocellular Carcinoma

- Hepatocellular carcinoma (HCC) is associated with increased all-cause mortality in patients with COVID-19.⁵³
- Primary liver cancer, with or without treatment, is associated with increased mortality in patients with COVID-19.⁵²

Viral Hepatitis

- Chronic hepatitis B or C have not been associated with mortality from COVID-19.⁵⁵

Autoimmune Hepatitis

- AIH has not been associated with severe COVID-19, hospitalization, or death from SARS-CoV-2 infection.⁵⁶ However, in multivariate analysis, cirrhosis is a strong predictor for severe COVID-19 (OR 17.46, P<0.001) in patients with AIH.
 - 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.
- Continuation of immunosuppression in patients with AIH is not associated with increased all-cause mortality or severe COVID-19.⁵⁷
- [Vaccination](#) may be less effective in patients on immunosuppressive medications.

Nonalcoholic Fatty 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.^{58,59}
 - NAFLD is associated with progressive COVID-19 and worse outcomes independent of obesity and comorbidities.^{58,60}
 - Studies of patients with COVID-19 demonstrated no increased mortality associated with NAFLD.^{53,61}
 - Data for severe COVID-19 in patients with NAFLD are conflicting, with some demonstrating no increased mortality risk⁵³ while others describe 2.6 to 4-fold increased risk.

Cholestatic Liver Disease

- Secondary sclerosing cholangitis, also known as post-COVID-19 cholangiopathy, occurs following recovery of COVID-19 in previously critically ill patients and may be mediated by perihilar biliary ischemia.⁶²
- Post-COVID-19 cholangiopathy may be difficult to distinguish from SSC-CIP or drug-induced liver injury.⁴⁰
- Severe cholestasis (total bilirubin $\geq 2x$ ULN) is associated with increased mortality when compared with patients without cholestasis.
- Liver transplantation has been successfully reported in these patients.^{40,63}

Liver Transplantation

- 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.⁶⁴

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.
- Patients who test positive for SARS-CoV-2 can be seen again in-person in clinic according to [CDC guidance regarding isolation](#): For most people, 10 days after symptom onset and after resolution of fever for at least 24 hours and improvement of other symptoms; for those with severe disease or immunocompromised, 20 days after symptom onset and after resolution of fever for at least 24 hours and improvement of other symptoms.⁶⁵
- 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.
- 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. 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.

Liver Transplantation, Resource Utilization, and Ethical Considerations

- Resource utilization and ethical considerations are inherently tied to liver transplantation. 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.

- 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 should establish its institutional capacity to perform liver transplantation and a process for determining whether or not to proceed when an organ is available. There is no over-arching policy that can or should be applied to every transplant center. Protocols and policies should be reviewed periodically considering new information on COVID-19 and transplant resources.
- 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. Liver transplant volumes in 2021 are on track to exceed 2019 volumes.

Evaluation of Potential Donors

- All Organ Procurement Organizations (OPOs) are testing donors for SARS-CoV-2 RNA using specimens obtained from nasopharyngeal swabs (and BAL if lung donation is being considered).
- SARS-CoV-2 donor testing status and results were added to DonorNet to help OPOs and transplant programs communicate this important information in a standard way.⁶⁶
- The vast majority of cases of donor-to-recipient transmission of respiratory viruses have occurred in lung recipients⁶⁷.
- To date, no proven or probable cases of donor-to-recipient SARS-CoV-2 transmission from non-lung donors have been reported in the medical literature or to the OPTN Disease Transmission Advisory Committee.⁶⁸
- Multiple case reports and case series have described the use of non-lung donors who tested positive for SARS-CoV-2 without transmission of SARS-CoV-2 to non-lung recipients.^{69–75}
- SARS-CoV-2 PCR may remain positive for months after resolution of infection and infectivity. Therefore in testing using nucleic acid amplification techniques, a high cycle threshold (Ct) for detection may help distinguish likely inactive from active infection.⁷⁶
 - A Ct value indicates the number of amplification cycles needed to achieve a positive result from a real-time PCR test. Low Ct values are generally considered to reflect a higher viral load, and high Ct values are generally considered to reflect a lower viral load.
- Incidental infection with SARS-CoV-2 in potential deceased donors hospitalized for other reasons may reflect ongoing shedding of non-viable virus or more recent infection. Distinction is not always possible with the information available at the time of the organ offer.

- Donors dying of COVID-19 may have other organ quality issues and may be at increased risk of transmitting SARS-CoV-2, but this has not been proven because these donors are not frequently used.
- It is possible but unproven that recipient immunity gained through vaccination or prior infection with SARS-CoV-2 will reduce the risk of donor-to-recipient transmission.

Evaluation of Potential Recipients

- Successful living donor liver transplantation has been reported in recipients with COVID-19 after a minimum interval of 14 days from positive SARS-CoV-2 PCR.⁷⁵
- “Reactivation” of SARS-CoV-2 after solid organ transplantation has not been reported to date but has been observed in patients with other forms of immunosuppression.
- The CDC recommends isolating immunocompromised patients or those with severe infection with SARS-CoV-2 for 20 days.
- Immunocompetent patients with mild-to-moderate disease should be isolated for 10 days.
- There may be a significant increase in postoperative morbidity and mortality related to prior SARS-CoV-2 infection in symptomatic patients or for emergent surgery, particularly within 7 weeks of infection.^{77,78}
- The Scientific Registry of Transplant Recipients (SRTR) modified the evaluation metrics for transplant programs and organ procurement organizations (OPOs).⁷⁹ Evaluation cohorts will exclude transplants and follow-up time beyond March 12, 2020, the day before declaration of a national public health emergency.

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 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 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).⁸⁰**
- **The finding of incidental donor SARS-CoV-2 infection is not a contraindication to donation.**
- **Liver donation from potential donors with incidental findings of COVID-19 can be considered with recipient consent.**

- Findings that favor the safety of donation include lack of infiltrates consistent with COVID-19 on chest imaging and SARS-CoV-2 infection diagnosed in the previous 90 days, because this suggests ongoing shedding of viral nucleic acid often without viable virus.
- Higher cycle threshold (Ct) values (reflecting lower viral loads or non-infectious viral remains) also suggest decreased risk of donor-to-recipient transmission and may be requested to aid in overall risk assessment of donor-to-recipient SARS-CoV-2 transmission.
- Ideally, SARS-CoV-2-positive living donors can be considered following complete resolution of disease, expiration of isolation period, and either negative SARS-CoV-2 PCR or evaluation by an infectious disease specialist to determine if asymptomatic shedding is occurring.
- Urgency of recipient need for transplantation may also be factored into the decision to accept an organ from a SARS-CoV-2 positive donor.
- Donors dying because of COVID-19 should be evaluated as to organ quality; no recommendation regarding the risk of transmission of SARS-CoV-2 to the recipient can be made.
- Recipient pre-transplant COVID-19 vaccination is encouraged. While unproven, one benefit may be to reduce the risk of donor-to-recipient SARS-CoV-2 transmission.
- 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.
- Except in circumstances of extreme recipient need, patients with active COVID-19 should not undergo transplantation given concerns about intense immunosuppression worsening the course of the infection and the lack of highly effective antiviral therapy.
- The appropriate interval to wait before proceeding with transplantation after SARS-CoV-2 diagnosis is unknown. Repeat testing 14 or more days after diagnosis (or 21 days for those hospitalized for COVID-19 or immunocompromised individuals) is reasonable, and active listing can be considered if repeat testing is negative and symptoms have resolved.
- In many cases, SARS-CoV-2 PCR may continue to be positive and Ct values, clinical assessment, and consideration of recipient need can inform the decision to proceed with transplantation.
- Transplant centers should strongly encourage SARS-CoV-2 vaccination for all potential recipients and their close contacts prior to listing.

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; infectivity decreases to near-zero after about 10 days in mild-moderately ill patients and 20 days in severe-critically ill and immunocompromised patients.⁸¹
- The immune response may be the main driver for pulmonary injury attributable to COVID-19 and immunosuppression may be protective.^{10,28,82,83}

- Corticosteroids improve survival in critically ill patients with COVID-19 requiring supplemental oxygen.^{84,85}
- Baseline immunosuppression containing tacrolimus is associated with better survival in liver transplant recipients with COVID-19.⁸³
- Baseline immunosuppression containing mycophenolate is an independent predictor of severe COVID-19 in liver transplant recipients.⁸⁶
- 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.^{23,82,87}
- 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.⁸⁸
 - 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.⁸⁹
- The course of COVID-19 in patients with AIH on immunosuppression may be similar to non-immunosuppressed patients.⁸⁸
- 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.^{86,87,90,91}
- 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 PANDEMIC

Immunosuppressed patients (transplant recipients and patients with AIH on immunosuppressive medications) *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 [vaccination](#) with an initial 3-dose series of an mRNA COVID-19 vaccine (ideally at least 6 weeks post liver transplantation).⁹²**
- **Patients who received partial vaccination pre-transplantation should complete the vaccination series at least one month post-transplantation.**

Immunosuppressed patients (transplant recipients and patients with AIH on immunosuppressive medications) *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.**
- **Monitor kidney function and calcineurin inhibitor levels.**
- **Adjust immunosuppressive medications based on severity of COVID-19 (and risk of graft rejection and renal injury in transplant recipients).**

- Follow guidelines from the [NIH](#) for newly infected patients.⁸⁹

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 and Post-Exposure Prophylaxis of COVID-19 in Patients with Chronic Liver Disease and Liver Transplantation

Monoclonal Antibody Preparations for Treatment of Mild to Moderate COVID-19

- Three monoclonal antibodies that target the SARS-CoV-2 spike protein have received emergency use authorization (EUA) from the FDA for treatment of mild to moderate COVID-19.
 - [Casirivimab + imdevimab](#) (Regeneron).
 - [Sotrovimab](#) (Vir Biotechnology and GSK).
 - [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 (within 10 days of onset of symptoms but preferably earlier) monoclonal antibodies decrease the need for hospitalization and death (up to 85% reduction) and decrease viral load.^{93–96}

Monoclonal Antibody Preparations for Prevention of COVID-19 in High-Risk Exposed Individuals

- When given within 96 hours of index patient positive test, low doses of subcutaneous casirivimab and imdevimab (Regeneron) reduced the risk of symptomatic COVID-19 transmission to household contacts by 81% and reduced the mean duration of symptoms among infected persons.⁹⁷
- EUA was granted to casirivimab and imdevimab for post-exposure prophylaxis for high-risk individuals exposed to SARS-CoV-2 who are unvaccinated or not expected to reliably mount a response to vaccine.
- Other studies have demonstrated efficacy of monoclonal antibodies when given to institutionalized patients (e.g., nursing home residents) exposed to SAR-CoV-2 to prevent symptomatic or severe infection (not yet published).

Monoclonal Antibody Preparation for Treatment of Severe or Critical COVID-19

- Monoclonal antibodies appear to work best in those who have high viral loads and those who have not yet generated their own antibody response.⁹⁵

- Initial studies demonstrated that monoclonal antibodies lacked efficacy when given to patients hospitalized with severe COVID-19.⁹⁸
- One large study (RECOVERY) demonstrated a mortality benefit for seronegative hospitalized patients, but this study has not yet been peer-reviewed.⁹⁹
- While immunosuppressed patients may benefit from monoclonal antibodies even with severe disease given that they are less likely to generate their own anti-SARS-CoV-2 antibody, this has not been proven.
- Currently, the EUA does not allow the use of monoclonal antibodies for patients hospitalized for COVID-19 or those requiring oxygen for COVID-19.
- Long acting COVID-19 monoclonal antibodies are under investigation and may be particularly useful for immunosuppressed patients who do not respond to COVID-19 vaccines.

Other Outpatient Treatment

- Molnupiravir is an oral nucleoside analog developed by Merck and Ridgeback Biotherapeutics that inhibits replication of SARS-CoV-2.
 - In a press release on October 1, 2021, [Merck announced](#) that it was stopping its Phase 3 MOVE-OUT trial early because of positive results demonstrating a 50% reduction in hospitalization or death in patients who received molnupiravir compared to placebo (7.3% vs. 14.1%, P=0.0012).¹⁰⁰ These results have not yet been peer-reviewed.
 - Inclusion criteria for the MOVE-OUT trial included laboratory-confirmed mild to moderate COVID-19 with symptom onset within 5 days of randomization and at least one risk factor associated with poor disease outcome.
 - Merck submitted an [EUA application](#) on October 11, 2021.
- Other oral antiviral therapies for COVID-19 are in clinical trials, including an oral version of remdesivir.¹⁰¹
- Treatments that have been shown to be either ineffective or harmful include hydroxychloroquine (with or without azithromycin), azithromycin alone, and lopinavir/ritonavir.¹⁰²
- Corticosteroids have not been well studied in the outpatient setting and immune suppression may be harmful in the early stages of COVID-19.
- Ivermectin is unproven for the treatment or prevention of COVID-19 and should not be prescribed outside of a clinical trial.
- Fluvoxamine and inhaled corticosteroids may have promise in the treatment of mild to moderate COVID-19 but are not currently recommended for routine use.
- Many studies of convalescent plasma have been conducted, and overall consistent benefit has not been demonstrated. In the US, monoclonal antibodies are preferred in most situations where convalescent plasma might be of benefit. Guidelines recommend against the use of convalescent plasma in most situations.¹⁰³

See [Table 1](#) for additional details about COVID-19 treatments.

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

- Clinicians should educate liver transplant recipients and those with chronic liver disease that early testing is indicated if signs or symptoms of COVID-19 develop because early use of monoclonal antibodies can be lifesaving.
- Liver disease clinics should be aware of local options for the administration of monoclonal antibodies.
- For those who test positive within 10 days of symptom onset, we recommend administration of EUA approved COVID-19 monoclonal antibodies.
- Patients with liver disease or a history of liver transplantation should receive COVID-19 monoclonal antibodies if there is significant exposure to SARS-CoV-2
- Except for supportive care, no other specific treatment targeting SARS-CoV-2 or the associated inflammatory response is currently 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.¹⁰⁴
- 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 extracorporeal membrane oxygenation (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.¹⁰⁵
- 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.⁸⁴
- 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.⁸⁴

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.¹⁰⁶
- Multiple 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 (e.g., CRP levels > 7.5mg/L).^{107,108}
- Tocilizumab is suggested for use in those not responding to steroids alone with high levels of inflammation (e.g., CRP >7.5 mg/L) and progressive oxygen requirements.¹⁰²
- Immunosuppressed patients who receive both corticosteroids and tocilizumab may be at increased risk for both routine and opportunistic infections and careful monitoring is required.
- Aminotransaminase elevations and drug-induced liver injury have been observed in patients treated with tocilizumab.¹⁰⁹

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, remdesivir + baricitinib was compared to remdesivir alone in hospitalized patients 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.¹¹⁰
- Baricitinab may also provide benefit when added to corticosteroids (although data have not yet been peer reviewed), but immunosuppressed patients may be at increased risk for opportunistic infections and careful monitoring is required.¹¹¹

See [Table 1](#) 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 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 40 mg), 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.
- Tocilizumab may benefit a subset of deteriorating critically ill patients already receiving corticosteroids and should be considered for patients with liver disease or solid organ transplantation with close monitoring for superinfection.
- 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 with close monitoring for superinfection. Further analysis of completed trials is needed to determine the benefit of baricitinab in patients already treated with corticosteroids.

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.
- 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, as dictated by the prevailing burden of COVID-19 in their area and institutional guidance, 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 may need to continue working 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.¹¹² 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-Liver](#): Endorsed by the AASLD. 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
- [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](#)
- [The Transplantation Society Guidance](#) on Coronavirus Disease 2019 (COVID-19) for Transplant Clinicians
- [OPTN Summary of current evidence and information: Donor SARS-CoV-2 testing and organ recovery from donors with a history of COVID-19](#)
- 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
- [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](#)

Table 1. 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 Hepatotoxicity rare	FDA-approved for multiple indications 6 mg daily up to 10 days
Combination monoclonal antibodies (IV/target SARS-CoV-2 proteins) Casirivimab + imdevimab (Regeneron) Sotrovimab (Vir Pharmaceuticals) 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 Casirivimab + imedvimab approved for post-exposure prophylaxis for those at high risk of progression with decreased vaccine response rates	Half-life of 18-21 days	Grade 3 or 4 adverse events similar in casirivimab + imdevimab group and placebo group, 1% each, not liver-related Hepatotoxicity not reported	Casirivimab + imedvimab and sotrovimab EUA for mild to moderate disease Only casirivimab + imedvimab approved for post-exposure prophylaxis
Remdesivir	Adults and pediatric patients ≥12 years old and weighing ≥40 kg requiring hospitalization for COVID-19	Hypersensitivity and infusion-related and anaphylactic reactions	5% grade 3 AST/ALT elevations 2% grade 4 AST/ALT elevations Consider stopping if ALT ≥10x ULN	FDA approved October 22, 2020 for hospitalized adults and pediatric patients ≥12 years old and weighing ≥40 kg

<p>IL-6 inhibitors (IV/monoclonal IL-6 receptor antagonists)</p> <p>Tocilizumab</p> <p>Sarilumab</p>	<p>Severe (high IL-6 levels)</p>	<p>Thrombocytopenia 2% Neutropenia 3% Opportunistic infections</p> <p><i>Exclusions:</i> ANC <2,000/m³ Platelets <100,000/m³ ALT >5x ULN</p>	<p>Grade 1-2 ALT 20%-40% Grade 3+ ALT 1%-2% Acute liver failure <1% Consider stopping if ALT or AST ≥5x ULN Incidence of AST and ALT elevations similar to placebo Risk of HBV flare/reactivation</p>	<p>FDA-approved for RA 8 mg/kg dose</p> <p>IDSA suggests consideration in those not responding to dexamethasone, needing supplemental oxygen, or critically ill with CRP >75 mg/dL¹⁰²</p>
<p>RNA nucleoside analogs (oral/nucleoside analog)</p> <p>Molnupiravir</p>	<p>Outpatients with mild-to-moderate COVID-19 with at least one risk factor associated with poor disease outcomes and symptom onset within 5 days of randomization</p>	<p>Unknown (full clinical trial results have not been released or peer reviewed)</p>		<p>EUA application submitted October 11, 2021</p>

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

