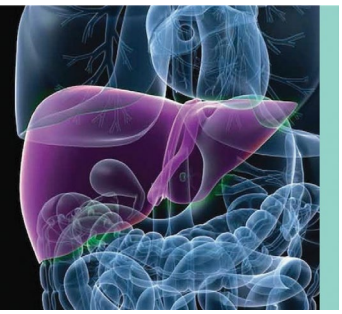

Synthesis of Liver Associations Recommendations for Hepatology and Liver Transplant Care During the COVID-19 Pandemic

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To navigate through the stormy unchartered ocean of SARS-coV-2 infections and coronavirus disease 2019 (COVID-19), all practicing hepatologists and other clinicians caring for patients with liver disease need guidance based on the best documented and rapidly evolving knowledge regarding SARS-CoV-2 infection and COVID-19. Prevention of SARS-CoV-2 transmission requires the redesign of patient workflow and other measures ensuring delivery of elective and emergency hepatology services without compromising the safety of patients and medical personnel.[1,2] Moreover, prevention of severe COVID-19 and related mortality requires updating management of persons with chronic liver disease (CLD) to diagnose COVID-19 and being vigilant for drug-drug interactions and other potential complications of COVID-19 in persons with CLD.[3] To respond to an urgent need for such information, the Asian Pacific Association for the Study of the Liver (APASL) recently published recommendations of an expert committee to guide infection control and clinical management of patients with CLD during the COVID-19 pandemic.[4] Previously, two other regional liver associations, American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL), convened expert panels with the same objectives.[5,6] This review summarizes the recommendations of the three liver associations for clinical practices to prevent SARS-CoV-2 transmission and protect persons with CLD from health risks posed by the emerging COVID-19 pandemic (Table 1).

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; APASL, Asian Pacific Association for the Study of the Liver; AST, aspartate aminotransferase; CHB, chronic hepatitis B; CHC, chronic hepatitis C; CLD, chronic liver disease; COVID-19, coronavirus disease 2019; EASL, European Association for the Study of the Liver; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HCW, health care worker; LT, liver transplantation; NAFLD, nonalcoholic fatty liver disease; NIH, National Institutes of Health; PPE, personal protective equipment; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; TKI, tyrosine kinase inhibitor; ULD, upper limit of normal.

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Potential conflict of interest: Nothing to report.

Received May 5, 2020; accepted May 8, 2020.

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TABLE 1. SELECTED AASLD, APASL, AND EASL RECOMMENDATIONS FOR LIVER DISEASE MANAGEMENT DURING THE COVID-19 PANDEMIC

Recommendations	AASLD	APASL	EASL
Limit nosocomial transmission	• Prioritize patients to limit in-person care • On arrival, screen patients for COVID-19 symptoms, exposures; if suggestive of COVID-19, refer care per clinic's protocol for symptomatic patients • Use telemedicine alternatives for routine care • Reduce routine laboratory and imaging monitoring • Prescribe 90 days of medications • Cancel all elective/nonurgent endoscopic procedures and biopsies • Limit in-clinic evaluations for transplant • Limit clinical trial activity to essential clinical trials • Limit HCWs providing care or on patient rounds • HCWs follow recommendations for PPE	• Use telemedicine alternatives for routine care • Minimize number of HCWs caring for patients • Minimize number of HCWs on patient rounds • Cancel elective, nonurgent endoscopies and liver biopsies • HCWs follow recommendations for PPE	• Limit in-person care to urgent cases • Remodel clinic space for social distancing • Use telemedicine for routine care; postpone specialist visits • Reduce frequency of laboratory monitoring and obtain locally • HCWs follow recommendations for PPE
Evaluate and care for patients with COVID-19 for liver disease	• Prioritize for COVID-19 testing: (1) patients with cirrhosis, (2) patients with CLD receiving immunosuppressive medications, and (3) patients with new-onset encephalopathy or other acute decompensation • Regularly monitor liver biochemistries • Consider non-COVID-19 etiologies for liver disease: (1) exacerbation of preexisting CLD or (2) drug-induced hepatotoxicity • Use acetaminophen 2 g/day as preferred medication • Use nonsteroidal anti-inflammatory drugs as needed • Consult the University of Liverpool document to assess possible drug interactions	• Follow WHO guidelines for COVID-19 diagnosis • Consider NAFLD as a prognostic factor for severe COVID-19 • Screen patients for hepatitis B surface antigen • Consider HBV prophylaxis prior to use of anti-IL-6, other immunosuppressive therapy • Monitor liver function tests of patients with CLD • Be alert to possible drug hepatotoxicity • Decompensated CLD and ALT >5 times ULD contraindications for remdesivir therapy • Prioritize persons with CLD for clinical trials	• Test for COVID-19 patients with acute decompensation or acute-on-chronic liver and per institution's practices • Persons with NAFLD likely to have comorbidity risk factors for severe COVID-19 • Consider patients with CLD/COVID-19 for early admission and clinical trial • Use acetaminophen (2–3 g/day is generally safe) • Limit use of nonsteroidal anti-inflammatory drugs • Test for COVID-19 patients with acute decompensation or acute-on-chronic liver and per institution's practices • Persons with NAFLD likely to have comorbidity risk factors for severe COVID-19 • Consider patients with CLD/COVID-19 for early admission and clinical trial • Use acetaminophen (2–3 g/day is generally safe) • Limit use of nonsteroidal anti-inflammatory drugs
Manage hepatitis B; hepatitis C	• Continue HBV and HCV treatment of patients with COVID-19 • Proceed with HBV and HCV treatment in patients without COVID-19 as clinically warranted • Do not consider HBV treatment in patients with COVID-19 unless flare is suspected	• Continue HBV and HCV treatment of patients with COVID-19 • Proceed with HBV and HCV treatment in patients without COVID-19 as clinically warranted • Do not consider HBV treatment in patients with COVID-19 unless flare is suspected • Document discussion with patient regarding CLD diagnosis and management	
Manage patients with HCC	• Continue HCC surveillance schedule for high-risk subjects; 2-month delay is acceptable • Document discussion of risks and benefits of delaying surveillance with patient • Proceed with HCC treatments as appropriate	• Continue therapy for non-COVID-19 patients • For patients with HCC with COVID-19, postpone elective transplant and resection surgery, withhold immunotherapy	• Maintain care per guidelines • Admit early if COVID-19 is diagnosed • Consider postponing HCC therapies

TABLE 1. Continued

Recommendations	AASLD	APASL	EASL
Manage pretransplant and post-transplant patients	• Screen donors and recipient for COVID-19 • Do not postpone transplants (an essential medical service, CMS Tier 3b) • Notify patients of possible extended waiting times on transplant list • Have low threshold for admitting patients on transplant waiting list diagnosed with COVID-19 • For posttransplant patients with moderate COVID-19, consider reduction of immunosuppression therapy as appropriate • Do not reduce immunosuppressive therapy in patients with mild COVID-19 disease	• Test donors and recipient for COVID-19 • Limit transplant listing to emergency and urgent cases • Look for SARS-COV-2 prior to organ procurement; defer donors with evidence of infection • Consider specific COVD-19 consent for patients on transplant waiting list • For posttransplant patient with moderate COVID-19, consider reduction of immunosuppression therapy as appropriate • Do not reduce immunosuppressive therapy in patients with mild COVID-19 disease	• Maintain care per guidelines • Limit transplantation listings to patients with poor short-term prognosis • Vaccinate against pneumonia and flu • Avoid reductions in immunosuppressive therapy • Do not reduce immunosuppressive therapy in patients with mild COVID-19

HOW TO PROTECT MEDICAL PERSONNEL AND PATIENTS WITH LIVER DISEASES FROM SARS-COV-2 INFECTION?

To this end, all three associations recommend physical distancing by limiting face-to-face consultations to urgent situations, routine patient contact via telemedicine and phone visits, and use of local laboratories and pharmacies to reduce clinic and hospital visits and patient travel. AASLD guidance is most stringent by discouraging clinic entry of anyone with fever or other COVID-19 symptoms and SARS-CoV-2 testing of these patients. All recommend COVID-19 testing of liver transplant donors and recipients and patients with encephalopathy or acute decompensation. Recent data showed that many SARS-CoV-2–infected patients are asymptomatic, yet capable of transmitting the disease.[7] Ideally, all patients with a history of close contact with cases of possible or confirmed COVID-19 or from high-prevalence regions should be tested. APASL recommends SARS-CoV-2 testing based on clinical and epidemiological factors. EASL recommends following an institution's practice. AASLD and APASL describe the personal protective equipment (PPE) requirements for endoscopy and other procedures. Like SARS-CoV-2 testing, the limiting factor is the availability of PPE. Without adequate supply, many elective procedures will need to be canceled.

Modifications of the practice of liver transplantation (LT) are recommended by all three associations. With the potential risks of SARS-CoV-2 transmission, aggravated by the limited supply of PPE and other resources, many governments have restricted elective medical procedures, including LT. However, in the United States, LTs are considered "high-acuity surgery" and can proceed as medically warranted.[8] All associations recommend limiting LT to patients with high Model for End-Stage Liver Disease scores, risk for decompensation, or hepatocellular carcinoma (HCC) progression.

SHOULD LT BE PERFORMED IN COVID-19 RECIPIENTS, AND SHOULD ONE USE ORGANS PROCURED FROM COVID-19 DONORS?

AASLD recommends against LT in patients with COVID-19. LT can proceed 21 days after symptom resolution and negative diagnostic tests in recipients. APASL suggests balancing risks of delaying LT against risks of

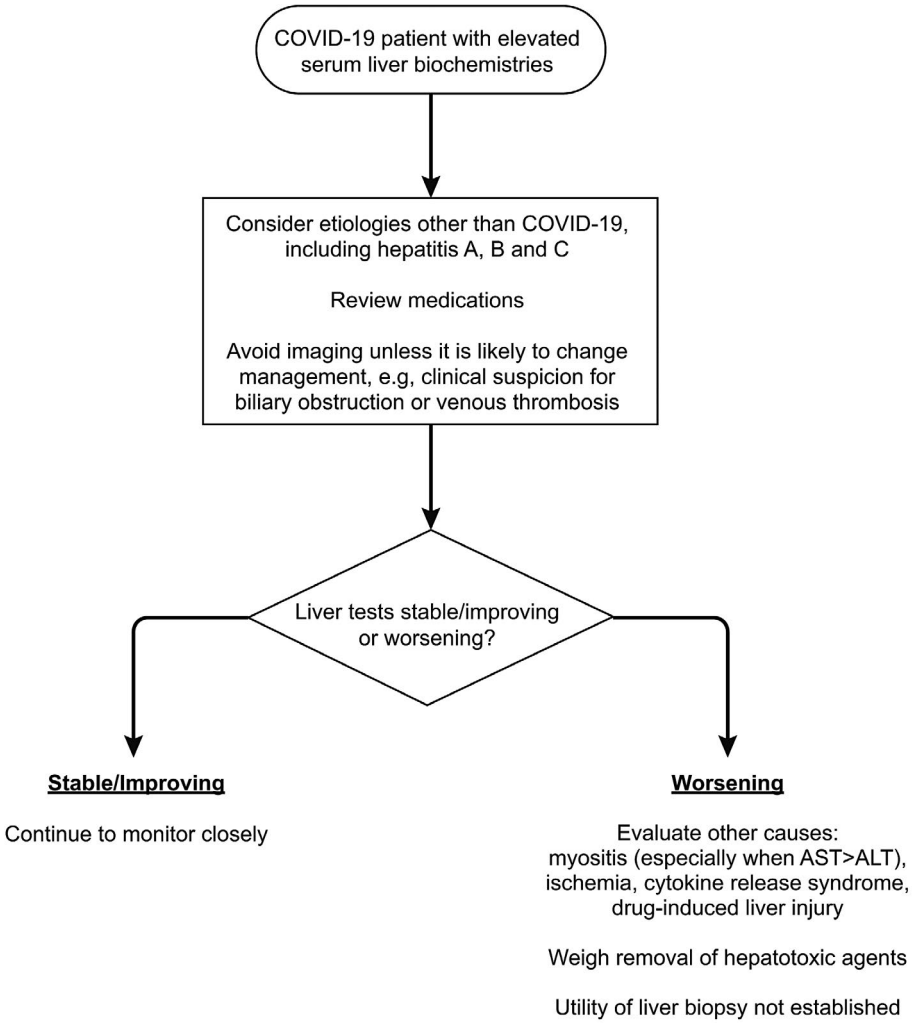

FIG 1 Approach to the patient with COVID-19 and elevated serum liver biochemistries. Reproduced with permission from *Hepatology*.[5] Copyright 2020, American Association for the Study of Liver Diseases.

transmission to health care workers (HCWs). EASL does not specifically address this issue. To minimize the risk to HCWs, APASL recommends LT be performed only in patients with COVID-19 with at least two consecutive negative SARS-CoV-2 nucleic acid results and the presence of antibodies. Finally, there is debate whether immunosuppression should be reduced during the COVID-19 pandemic. So far there are no data to suggest that post-transplant immunosuppression is a risk factor for severe COVID-19. In contrast, reducing immunosuppression may increase the risk for graft rejection. All three associations recommend against reducing immunosuppressive therapy in LT patients with mild COVID-19. The dose of azathioprine, mycophenolate, and calcineurin inhibitor may be reduced in the setting of severe lymphopenia or worsening pulmonary status.

WHAT ARE THE ROLES OF A HEPATOLOGIST IN THE MANAGEMENT OF A PATIENT WITH COVID-19?

Elevation of serum transaminase levels is commonly observed in patients with COVID-19, and a hepatologist might therefore be consulted. All of the guidance suggests that the underlying cause of liver injury may be related to SARS-CoV-2 infections, exacerbation of preexisting CLD, or drug-induced hepatotoxicity. AASLD and APASL provide an algorithm to clinical evaluations (Fig. 1). A key question is whether patients with CLD have a higher risk for severe COVID-19. AASLD and APASL suggest nonalcoholic fatty liver disease (NAFLD) as an independent prognostic factor, and patients with CLD should be prioritized as candidates for COVID-19 drug trials. EASL and AASLD mention that patients with NAFLD are more likely than others to

have other comorbidity risks for severe COVID-19. To date, there is no evidence that patients with stable CLD due to chronic hepatitis B (CHB) or chronic hepatitis C (CHC) have increased susceptibility to SARS-CoV-2 infection. It is controversial whether there is an increased risk for flare-up of CHB or CHC during COVID-19 and whether prophylactic therapy should be started. Both AASLD and APASL recommend continuing treatment for CHB or CHC in patients with COVID-19. APASL recommends prophylactic hepatitis B therapy for those planned for anti-IL-6 or other immunosuppressive therapy. Initiating prophylactic hepatitis C therapy is not recommended. If there is any suggestion of a flare-up, therapy should be initiated in patients who are not already receiving hepatitis B or hepatitis C treatment.

On May 1, 2020, remdesivir, a nucleotide RNA polymerase inhibitor, was authorized by the US Food and Drug Administration under Emergency Use Authorization for treatment of those patients hospitalized with severe COVID-19.[9] APASL and AASLD recommend close monitoring of liver function in patients, especially those with CLD, who are treated with remdesivir. Patients with decompensated CLD and those with alanine aminotransferase (ALT) >5 times upper limit of normal should not be treated with remdesivir.

HOW SHOULD WE MODIFY MANAGEMENT OF PATIENTS WITH HCC?

To avoid SARS-CoV-2 exposures, all associations recommend reducing patient visits and a delay in HCC ultrasound surveillance. It is uncertain whether HCC treatment should be deferred or started as usual in patients with COVID-19 with newly diagnosed HCC, and whether tyrosine kinase inhibitors (TKIs) or checkpoint inhibitors should be stopped in patients with COVID-19 who are already receiving such therapy. Delaying or withdrawing treatment increases the risk for HCC progression with detrimental outcomes, whereas surgical resection may increase risk for transmission to health care personnel, and checkpoint inhibitors might worsen COVID-19 by exacerbating a cytokine storm. AASLD recommends HCC treatments should proceed. EASL recommends locoregional therapies should be postponed whenever possible and immune-checkpoint inhibitor therapy be temporarily withdrawn. TKI in nonsevere COVID-19 should be taken on a case-by-case basis. APASL recommends postponing elective transplant/resection surgery, whereas radiofrequency ablation, transcatheter arterial chemoembolization, TKI, or immunotherapy can be initiated with change of immunotherapy schedules to every 4 to 6 weeks.

HOW TO CONDUCT CLINICAL TRIALS?

Both APASL and AASLD recommend using alternative physical distancing processes for study assessments to reduce SARS-CoV-2 exposure. APASL specifically recommends seeking local regulators and institutional review board approval of the contingency measures during the COVID-19 pandemic, obtaining trial participant's consent, and documentation of all deviations from the contingency measures. These recommendations align with US National Institutes of Health (NIH) revised guidance for NIH-supported clinical research.[10]

SUMMARY

APASL, AASLD, and EASL strongly recommend changes in patient workflow and clinical procedures to protect HCWs and patients from SARS-CoV-2 infection. Similarly, the associations generally agree on approaches to evaluation and treatment of patients with COVID-19 for liver disease, and management of patients with HCC and post–liver transplant patients with slight differences in the populations targeted for SARS-CoV-2 testing. These recommendations will evolve with further clinical experience and data from randomized controlled trials. For now, the liver associations provide the best available advice for the management of CLD during the COVID-19 pandemic.

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