



WGO GUIDANCE FOR PATIENTS WITH COVID-19 and LIVER DISEASE

(By members of the Hepatology Interest Group of WGO)

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I. Introduction and General Approach To The Patient With COVID-19 and Elevated Liver Enzymes

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The World Health Organization declared a global pandemic of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on March 11, 2020. To date, worldwide there have been approximately 5 million confirmed cases of coronavirus disease 2019 (COVID-19).

Worldwide, many of us are overwhelmed by the increased demands that this infection has put on our healthcare systems and our personal work. This document is to summarize what we believe is currently the best way forward realizing that, depending on local circumstances, some recommendations may be difficult or even impossible to implement.

Elevated liver biochemistries are common in COVID-19 infection with a reported incidence of 14 to 76%. Elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are the most commonly reported pattern of liver derangement with slight elevations of bilirubin seen in about 10 % of cases. Raised gamma-glutamyl transferase (GGT) levels are seen in up to 50% of cases, but alkaline phosphatase (ALP) is typically normal (1-3).

Significantly higher ALT and AST levels are reported in severe COVID-19. However, these increases in ALT and AST are usually quite mild and do not exceed 3 times the upper limit of normal (ULN). Serum AST was >40 IU/L in 52% of patients who died, but only in 16% patients who recovered (4). AST is more frequently elevated compared to ALT. Lower platelet counts and albumin levels are seen in those with more severe disease; 65% of deceased but only 14% of recovered patients had albumin levels <32g/L. However, low albumin levels are not linked to liver failure, which has not been reported so far in COVID-19. The virus *per se* is unlikely to cause primary liver injury (1-4) and is not clearly associated with flares or progression of chronic liver disease. Acute on chronic liver disease reported for the influenza virus (5) has, so far, not been reported for SARS-CoV-2 infection.

In the era of SARS-CoV-2 infection, atypical presentations can occur, requiring isolation and testing. Acute hepatitis as the presentation of COVID-19 with dark urine, AST of 1230 IU/L, ALT of 697 IU/L (normal range <50), low albumin and raised ferritin of 6606 ng/mL (N<150) is reported in a patient with HIV infection on therapy. Viral screen was negative and

previous liver tests were normal. Fever and chest X-ray changes were seen 18 hours after admission. An uneventful recovery occurred with normalisation of liver tests (6). Further data are required before recommending routine SARS-CoV-2 testing for SARS-CoV-2 as a potential cause of patients with acute hepatitis.

Pathogenesis of liver abnormalities in COVID-19 disease

The mechanisms of effects of SARS-CoV-2 on the liver are not well defined. Although direct viral cytopathic effects have been described with other coronaviruses (SARS, MERS), there was no data to support this in COVID-19. Findings on post mortem biopsies include moderate microvascular steatosis, and mild lobular and portal activity but no obvious inflammatory cell infiltration and/or typical liver cell necrosis were found (7). Liver biopsy in an infant who developed COVID-19 post-liver transplant showed moderate acute hepatitis with prominent clusters of apoptotic hepatocytes, lobular lymphohistiocytic inflammation, and mild steatosis in addition to mild to moderate features of acute cellular rejection (8). No viral inclusions were seen in any of the biopsy specimens. However, in a recent report, ultrastructural examination of liver tissues from 2 COVID-19 patients identified in the cytoplasm of hepatocytes typical coronavirus particles characterized by spike structure (9). Histologically, massive hepatic apoptosis and a certain binuclear hepatocytes were observed. Immunohistochemical results showed scanty CD4+ and CD8+ lymphocytes. These ultrastructural and histological changes were considered indicative of a typical viral infection lesion (9). A proposed mechanism of direct liver injury is by direct cytotoxicity from viral replication in liver cells. However, the cell entry receptor of SARS-CoV-2, angiotensin converting enzyme 2 receptor (ACE2) (10), which is highly expressed in alveolar epithelial cells of the lung, is expressed only in 2.6% of hepatocytes. In contrast, although ACE2 is expressed on 58% of bile duct cells (11); ALP, a marker of bile duct injury, appears to be the least-affected of the liver enzymes. Thus, it remains unclear whether SARS-CoV-2 plays a direct role, in producing liver injury (2-4).

ACE2 receptors are also expressed on vascular endothelial cells. One concern, therefore, may be that vascular diseases are increased in COVID-19 infection. An increase in peripheral arterial disease has been suggested (12). Furthermore, there are anecdotal reports of increased thromboembolism, particularly in critically-ill patients (13-16). However,

according to the American Society of Hematology, the incidence of venous thromboembolism in COVID-19 patients is not established. It remains to be seen if thromboembolic events are secondary to severe illness and associated co-morbidities or if there is a specific link between COVID-19 infection and thromboembolic events. The frequency of ACE2 receptor expression is reported to be low in the liver vascular endothelium and endothelitis has not been noted in post-mortem liver biopsies of COVID-19 patients (17).

Systemic viral infections can cause transient elevation in transaminases as a result of general immune activation due to circulating cytokines without significant liver injury even in the most severe cases (“bystander hepatitis”) (18). However, in the absence of obvious inflammatory cell infiltration and typical liver cell necrosis, it is hard to conclude that bystander hepatitis occurs in COVID-19 patients.

Based on a study of the immunological characteristics of severe COVID-19 patients, serum concentrations of both pro-inflammatory cytokines and anti-inflammatory cytokines, including IL-2R, IL-6, TNF- α and IL-10 were increased in most severe cases and were markedly higher than in moderate cases, suggesting that cytokine storms might be associated with disease severity (19). However, a relationship between cytokine changes and hepatic inflammation has not been confirmed, suggesting that other contributors to liver injury should also be considered, such as hypoxic ischemic organ damage.

Possible drug-induced liver injury (DILI) should always be considered; an association with lopinavir/ritonavir appears to have been consistently reported (2, 3). However, other drugs may also be associated with liver toxicity.

It is also possible that the raised transaminases may actually be due to myositis which have been commonly reported in COVID-19 infection, this should be considered if AST > ALT and if creatinine kinase (CK) is also elevated, as this is characteristic of myositis.

Transaminases > 3- 5 x ULN, and/or elevation of bilirubin > 3 x ULN are believed to be uncommon in COVID-19 patients and should lead to consideration of other causes (20). It is important to remember that intensive care unit (ICU) patients often suffer from multiple conditions, which could explain abnormal tests secondary to disease complications.

Should all patients with COVID-19 get a set of liver tests done?

Outpatients with COVID-19 managed by home quarantine do not require routine liver tests. Patients admitted to hospital should have baseline liver tests, including ALT, AST, GGT, ALP and bilirubin. Liver enzymes should be monitored as COVID-19 progresses; if available, platelets, albumin, ferritin and CRP should also be monitored in severe cases.

Additional blood tests, including hepatitis B and C serology, should be considered to exclude other causes of liver disease, depending on the local context and available resources..

Imaging is not routinely recommended, unless it is likely to change the management of the patient.

New onset liver test abnormalities during admission in COVID-19 patients should be managed in the same way as in COVID-19 negative patients, with particular consideration for excluding DILI. Patients with abnormal liver tests should not be excluded from receiving investigational agents to treat COVID-19, but close monitoring is recommended. Routine liver biopsy is not recommended.

After analysis of findings, assessment should include the urgency of implementation of any recommendations (Table 1). Test results need to be interpreted in the context of the patient's illness (Table 2).

Table 1. A step-wise approach in COVID-19 patients suspected to have hepatobiliary disease

Determine Cause(s)

- COVID-19 infection *per se*
- Complication of COVID-19 or treatment
 - Sepsis
 - Hypoxic injury and/or ventilator complications
 - Drugs including antibiotics and experimental therapy
- Pre-existing liver disease that may not have been diagnosed (HAV, HBV, HCV, HEV, MAFLD, alcohol-related liver disease, auto-immune liver disease, other)
- Concomitant medical problems.

Examples: Common bile duct obstruction (stones)
 Malignancy of liver or biliary tract
 Ascites
 Thrombosis (Budd-Chiari, portal vein thrombosis)

- Exclude non-hepatic causes of abnormal liver tests

Determine need for further evaluation and urgency of intervention

- Conservative approach is the rule
 - No invasive procedure
 - Defer further imaging, use bedside ultra-sound if needed
- Exceptions
 - Findings that may determine disease outcome *and* if diagnosed/treated have major implications
 - Examples: Ascitic tap: decompensated cirrhosis vs malignancy and rule out Infection
 - Ultrasonography: Common bile duct obstruction stones vs mass
 - Liver biopsy: Autoimmune hepatitis? Can we treat without biopsy?
 - EGD for upper GI hemorrhage

Table 2. Interpretation of liver test results in COVID-19 patients

Test	Comments
Hypoalbuminemia	Common in patients with systemic inflammatory response, usually not an indicator of liver failure
Prolonged INR or thrombocytopenia	Spontaneous coagulopathy / disseminated intravascular coagulation (DIC) may be present in 1/3 of sick patients (15, 21) Thromboembolic events likely common
High transaminases or bilirubin (> 3 x ULN)	Not typical for COVID-19, consider other causes
Anemia	GI bleeding: ulcer? Variceal hemorrhage?
Imaging	Chest-CT often done in some places: Could it help to assess liver/biliary tract disease? If indicated do US but avoid unnecessary imaging including US. (Not formally investigated)
GI symptoms including diarrhea	Common

SUMMARY

- Most commonly reported liver test abnormalities are elevated ALT and AST (14-76% of patients) - more common in severe disease and associated with worse outcome.
- Bilirubin increase in about 10%, alkaline phosphatase elevation infrequent.
- Mechanism of liver test abnormalities unknown: ACE2 receptors on cholangiocytes, and to a lesser extent, on hepatocytes; direct injury plausible- recent data to support this.
- Possible mechanisms include drug induced liver injury (DILI), hypoxic hepatitis and an overactive immune-mediated pro-inflammatory response.
- Consider myositis when AST is higher than ALT and accompanied by creatinine kinase elevation.
- Prolonged INR and thrombocytopenia may be secondary to disseminated intravascular coagulation. Thromboembolic events are common in COVID-19.
- Hypoalbuminemia may develop as a consequence of severe inflammatory response and is not indicative of liver failure.
- When ALT and bilirubin is > 3 x ULN consider other causes.

WGO recommendations:

- In this COVID-19 era, routine outpatient testing is not recommended – this applies to developed as well as developing countries.
- In patients with elevated ALT or AST, check for viral hepatitis causes. In developing countries, this may be particularly important, as patient may not have been tested before.
- Monitor COVID-19 progression with platelets, albumin, ferritin and CRP in severe cases dependent on availability.
- Routine investigation to exclude other aetiologies should take into consideration local context and availability.
- Routine imaging is not recommended unless it will alter management.

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II. Liver co-morbidities and COVID-19:

A- Chronic hepatitis B and C

B- Metabolic dysfunction-associated fatty liver disease (MAFLD)

C- Autoimmune liver diseases

IIA. Chronic hepatitis B and C and COVID-19

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The COVID-19 pandemic has resulted in significant morbidity and mortality in the world since it began in late 2019. Mortality appears to be highest in persons with underlying chronic medical conditions. Currently, whether the novel coronavirus, SARS-CoV-2, causes direct liver injury is debated (1, 2). A more accepted concept is that the liver damage is collateral, caused by a cytokine storm induced by T cells and dysfunction of the innate immune response (2). However, three cases of viral hepatitis were found during the original SARS-1 outbreak early in this century (3). Thus, as more details on the pathogenicity of the SARS-CoV-2 coronavirus are uncovered, we may learn more about the virus's effect on hepatocytes.

Currently, little is known about the independent contribution of chronic viral hepatitis B (HBV), with or without hepatitis D, and chronic hepatitis C (HCV) to the overall outcome in those persons who are infected with SARS-CoV-2. A study conducted early in the COVID-19 epidemic in China where the prevalence of chronic HBV is high, found no evidence that underlying chronic HBV infection increased adverse outcomes in persons with COVID-19 (1). A recent report from the Centers for Disease Control and Prevention (CDC) in the US found that 1% of hospitalized persons with COVID-19 has underlying liver disease (4). However, the etiology of the underlying liver conditions in these patients was not included in this report. Nevertheless, it is highly likely that those persons with chronic HBV or HCV who have advanced fibrosis or cirrhosis would be at an increased risk of more adverse outcomes if they were to develop COVID-19 disease. However, we currently have no solid evidence

whether SARS-CoV-2 independently damages the liver in persons with underlying chronic hepatitis B, C or D.

Since the global prevalence of chronic hepatitis B and C is high, though variable from country to country, we can make some generalized recommendations regarding approaches to persons with underlying chronic viral hepatitis who present with COVID-19 disease. First, all persons who are symptomatic with COVID-19 infection should have blood tests for AST, ALT, bilirubin and if any are elevated, they should be tested for hepatitis B surface antigen (HBsAg) and anti-hepatitis C antibody (reflexed to HCV RNA if positive). Those positive who have evidence of chronic viral hepatitis should have liver tests frequently monitored if they are hospitalized, as acute on chronic liver failure could be a theoretical risk as has been reported with influenza (5) but not so far with SARS-Cov-2. Furthermore, in patients with compensated liver disease non-invasive fibrosis markers may be used for assessment of advanced liver disease (fibrosis) or cirrhosis. Patients with decompensated cirrhosis should be further assessed with Child Pugh and MELD scores.

In persons with chronic viral hepatitis who have had a liver transplant and acquire COVID-19 disease, a flare of hepatitis could be related to the COVID-19 disease and not due to rejection of the transplanted liver, so clinicians should proceed with caution and thoroughly consider the aetiology of the rise in transaminases. Secondly, if persons with hepatitis B acquire COVID-19 and are on antiviral therapy, they should continue their medications. In these persons, an elevation of ALT/AST could be a direct result of the immunologic response to COVID-19 or a flare of their underlying HBV infection. An HBVDNA level should be done and if low (<2,000 IU/ml) or undetected, the cause of this flare could be considered a manifestation of the COVID-19 syndrome.

In the case of HCV infection, persons who are taking HCV direct acting antiviral medications (DAA) should continue these drugs and treatment should not be interrupted. In contrast, it would be prudent to stop interferon in persons receiving this medication to treat either HBV or HCV, as this could increase the severity of COVID-19, since severity appears to be associated, at least in part, with a cytokine storm response to the virus and interferon is a potent cytokine. Such patients should still be monitored carefully. Conversely, a prudent course of action would be to not start any patients with chronic HBV on interferon until this pandemic is over.

There is no evidence that HBV or HCV oral antiviral drugs have any additional adverse effects in persons with chronic viral hepatitis who acquire COVID-19 disease. However, for persons with active HCV infection who are not yet on DAA, it would be prudent to delay therapy until after their recovery from COVID-19 disease. While it is too early to tell, some HBV and HCV antiviral medications have recently been shown to bind to the SARS-CoV-2 RNA RdRp site on this virus, though the avidity of this binding appears to be less than, for example, sofosbuvir binding to HCV polymerase. Thus, it is conceivable that some medications for HCV and HBV, such as sofosbuvir, tenofovir and ribavirin may have some potential therapeutic activity against SARS-CoV-2 and clinical trials are underway.

In conclusion, more data are needed to determine if persons with chronic hepatitis B or C are at increased risk of adverse outcomes if they are infected with SARS-CoV-2, which causes COVID-19 disease. However, patients with chronic viral hepatitis who have advanced fibrosis or cirrhosis are, probably, at risk of more severe outcomes if infected with SARS-CoV-2 and they should, therefore, self-isolate to minimise the risk of developing COVID-19. Patients with chronic viral hepatitis should be counselled to wash their hands frequently, practise distancing, wear a facemask when going out and avoid crowds. It is also very important not to stop antiviral therapy in persons receiving DAA for hepatitis C or tenofovir or entecavir for HBV, as this could cause a viral rebound and subsequent flare of hepatitis. It is also important that patients with chronic HBV who are on oral antiviral medication have an adequate supply of their drugs, so they do not run out during the pandemic.

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SUMMARY

- It is unknown if patients with chronic hepatitis B and C, may be more susceptible to liver damage from SARS-CoV-2.
- It is not known whether patients with chronic HCV or HBV infection have a greater risk or not of severe disease after acquiring COVID-19.
- It is unknown whether patients on antiviral drugs for HCV or HBV are at less of a risk of severe outcomes after acquiring COVID-19.
- Some medication used to treat HBV or HCV such as sofosbuvir, tenofovir and ribavirin bind to the RdRp site on the CoV-SARS-2 virus and may have some potential therapeutic activity against SARS-CoV-2.

WGO Recommendations:

- In low income countries assessment for COVID-19 should include blood tests for AST, ALT, and if any are elevated, patients should be tested for HBsAg and anti-HCV (reflexed to HCV RNA if positive).
- In all patients with COVID-19 who are admitted to the hospital, test for hepatitis B and C: HBsAg and anti-HCV, with HCV RNA testing for those anti-HCV positive.
- Treat those diagnosed with HBV or HCV with DAAs, at least those with signs indicative of advanced liver disease.
- Do not stop antiviral medications for HBV or HCV in patients who present with COVID-19
- Avoid procedures during the COVID-19 illness that could put others at risk such as liver US or other advanced imaging unless there is a clinical suspicion.
- Provide 90-day supplies instead of 30-day supplies for HBV oral antiviral drugs and have a full course of DAA medications to complete HCV treatment if this has been started.

II.B. Metabolic dysfunction associated fatty liver disease (MAFLD) and COVID-19

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The diagnosis of metabolic dysfunction-associated fatty liver disease (MAFLD), formerly called non-alcoholic fatty liver disease (NAFLD), is based on evidence of hepatic steatosis, in addition to one of the following three criteria: overweight/obesity, presence of type 2 diabetes mellitus, or evidence of metabolic dysregulation (1). Untreated MAFLD may progress to steatohepatitis, development of fibrosis and cirrhosis and ultimately hepatic decompensation and hepatocellular carcinoma.

Many patients with MAFLD possess a number of risk factors such as obesity, which may translate to a greater risk from respiratory infections. A nested case control study among 561 patients with community acquired pneumonia found a MAFLD prevalence of 36%. Presence of MAFLD increased 30-day mortality from pneumonia to 17% compared to 5.8% among patients without MAFLD. This association was greater in patients with advanced hepatic fibrosis (2).

The interaction between MAFLD and respiratory infections begs the question whether (i) MAFLD patients are at a greater risk to acquire COVID-19 and (ii) whether MAFLD patients follow a different disease course. There are a number of small cohort studies that shed light on this issue.

i. Risk to acquire COVID-19

It is unknown whether MAFLD patients are at a higher risk of COVID-19. There is speculation that patients suffering from metabolic dysfunction-associated fatty liver disease may be especially vulnerable to COVID-19. SARS-CoV-2 enters the cell through the angiotensin converting enzyme (ACE) 2 receptor. Liver injury and MAFLD up-regulate ACE2 and it is possible that liver injury, treatment with ACE inhibitors and metabolic syndrome may increase susceptibility to COVID-19 (3).

Interestingly MAFLD increases viral shedding time (17.5 ± 5.2 days vs. 12.1 ± 4.4 days $p < 0.0001$) compared to patients without MAFLD. Thus MAFLD patients are infectious for ~5 days longer (4).

ii. Different COVID-19 prognosis

A Chinese cohort study selected 66 MAFLD patients and divided the cohort into obese (BMI > 25 kg/m²) and non-obese patients. Obesity (n=45) increased the risk of severe COVID-19 disease course substantially (unadjusted OR 5.77, 95% CI 1.19-27.91; p=0.029). The association with obesity and COVID-19 severity remained significant even after adjusting for age, sex, smoking, diabetes, hypertension and dyslipidaemia (5). A systematic review and meta-analysis from 20 articles (N=4062 participants) established that patients with a high BMI, and a combination of (metabolic) risk factors such as hypertension, diabetes and cardiovascular disease were more likely to develop critical illness. Diabetes mellitus increased the risk for severe disease by 3.04 (CI 2.01-4.60), hypertension by 2.31 (CI 1.68-3.18) and coronary heart disease by 2.76 (CI 1.39-5.45) (6). These data were confirmed by another study among 202 Chinese patients (MAFLD, n=76) (4). Patients with MAFLD had a higher risk of respiratory disease progression than those without MAFLD (44.7 vs. 6.6%), but also possessed a higher likelihood of abnormal liver biochemistry during admission (11.1% vs. 70%) (4). Another cohort study established that MAFLD patients with increased non-invasive liver fibrosis scores (FIB-4 score) are at higher likelihood of having severe COVID-19 illness, (7)

SUMMARY:

- Patients with MAFLD have a number of risk factors such as obesity which may translate to a higher mortality from respiratory illnesses, including COVID-19.
- It is unknown whether MAFLD patients are at a higher risk of acquiring SARS-CoV-2 infection.
- However, liver injury and MAFLD up-regulate ACE2 and it is possible that liver injury, treatment with ACE inhibitors and metabolic syndrome may increase susceptibility to COVID-19.
- Patients with MAFLD had a higher risk of respiratory disease progression than those without MAFLD (44.7 vs. 6.6%), but also possessed a higher likelihood of abnormal liver biochemistry during admission (11.1% vs. 70%).
- Shedding time of SARS-CoV-2 is longer in patients with MAFLD when compared to those without MAFLD.

WGO Recommendations:

- The identification and monitoring of patients with metabolic disease to identify MAFLD stage and grade is pivotal during and after the COVID-19 crisis.
- Counselling of MAFLD patients to change lifestyle with a focus to curtail risk factors (such as obesity) that predict for a poor prognosis of COVID-19 is encouraged.

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IIC. Autoimmune liver disease and COVID-19

Kelly W. Burak (Canada)

Patients with autoimmune liver diseases (autoimmune hepatitis, primary biliary cholangitis and primary sclerosing cholangitis), like all patients with chronic medical conditions, should avoid contact with anyone with symptoms, should respect physical distancing recommendations of public health officials and should wash their hands frequently to avoid contracting the virus. During the pandemic, follow-up of patients should be done with phone consultation or telehealth where available. Our usual practices for diagnosis and follow-up of these patients may be affected by limited access to outpatient laboratory, diagnostic imaging tests, endoscopic retrograde cholangiopancreatography (ERCP) and liver biopsy.

Autoimmune hepatitis

The diagnosis of autoimmune hepatitis (AIH) is typically confirmed with liver biopsy, but during the pandemic it is best to avoid invasive diagnostic procedures done within the hospital setting. Therefore, some experts have recommended starting empiric therapy (corticosteroids +/- azathioprine) for patients who present with elevated ALT, positive auto-antibodies and elevated immunoglobulin G levels, once other liver diseases have been excluded (1). Conversely, the AASLD expert panel warned against presuming that elevated liver tests in patients with AIH patients are due to a disease flare without biopsy confirmation (2).

AIH patients on immunosuppression may be at higher risk of acquiring infection and therefore should be prioritized for SARS-CoV-2 testing when presenting with fever, upper respiratory tract symptoms, other atypical symptoms (e.g. diarrhea or loss of smell and taste) (2,3). It is not recommended to lower immunosuppressive therapy in stable patients with AIH in an attempt to reduce the risk of contracting the infection, as this could result in disease flares that ultimately would require higher doses of corticosteroids to control (2,3). It is important that these patients receive pneumococcus and influenza vaccinations (3).

Early reports from the USA suggest that immune-compromised patients account for 6% of hospitalized patients and 9% of those admitted to ICU (4). From the emerging evidence, and from past experiences with other coronaviruses (SARS, MERS), it does not appear that

immunosuppressed patients with COVID-19 are at higher risk of severe pulmonary disease (5). Acute respiratory distress syndrome (ARDS) is a leading cause of mortality in patients admitted to ICU. These patients may develop a cytokines storm with hyper-inflammation (high ferritin, increased IL-6) that resembles hemophagocytic lymphohistiocytosis (HLH). A series of 150 cases from Wuhan, China suggests that corticosteroids might exacerbate COVID-19-associated lung injury, leading experts to recommend against their use (6).

Therefore, if AIH patients on corticosteroids develop COVID-19, high-doses of prednisone should be avoided, recognizing that critically ill patients may require stress doses to avoid adrenal insufficiency (2). Patients with COVID-19 can also develop lymphopenia due to the viral infection, and if this is associated with fever or worsening respiratory status, consideration should be given to lowering the doses of azathioprine or mycophenolate mofetil (2).

Cholestatic liver diseases

It is not clear if patients with primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC), without underlying cirrhosis, are at increased risk of COVID-19 or if the virus worsens chronic cholestatic liver disease (7). Patients with PBC should be continued on their usual treatment, including ursodeoxycholic acid, and second-line agents (e.g. obeticholic acid or bezafibrate). PBC patients with established cirrhosis could have their hepatocellular carcinoma (HCC) surveillance deferred for several months during the pandemic (2). PBC patients may have varices at early stages of disease, but endoscopic surveillance should also be deferred, with use of non-selective beta-blockers being a preferred strategy during the pandemic (8). Magnetic resonance cholangiopancreatography (MRCP) is best avoided in PSC patients unless it is likely to change management (e.g. suspected cholangiocarcinoma) (2). Although fever and worsening liver tests can be presentations of COVID-19, if this occurs in the setting of PSC, it is important to consider ascending cholangitis. These PSC patients should have blood cultures, be started on broad spectrum antibiotics, and ERCP may be indicated.

SUMMARY:

- Our usual practices for diagnosis and follow-up of patients with AIH may be affected by limited access to outpatient laboratory, diagnostic imaging tests, ERCP) and liver biopsy.
- AIH patients on immunosuppression may be at higher risk of acquiring SARS-CoV-2 infection.
- It does not appear that immunosuppressed patients with COVID-19 are at higher risk of severe pulmonary disease.
- However, some reports suggest that corticosteroids might exacerbate COVID-19-associated lung injury.
- It is not clear if patients with PBC or PSC, without underlying cirrhosis, are at increased risk of COVID-19 or if the virus worsens their liver disease.

WGO Recommendations:

- During the pandemic, follow-up of stable patients with AIH should be done with phone consultation or tele-health where available.
- Patients with AIH should be prioritized for SARS-CoV-2 testing when presenting with symptoms.
- It is not recommended to lower immunosuppressive therapy in stable patients with AIH in an attempt to reduce the risk of contracting the infection.
- However, if patients with COVID-19 develop lymphopenia, consider lowering the doses of azathioprine or mycophenolate mofetil
- In new patients presenting with features of AIH, at first it appears better to avoid liver biopsy during the pandemic. However, starting empiric therapy cannot be recommended straight forward as concern exists that corticosteroids could be harmful to patients with COVID-19.
- If AIH patients on corticosteroids develop COVID-19, high-doses of prednisone should be avoided, keeping in mind that stress doses may be needed.

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III. Practical aspects to caring for chronic liver disease (CLD) patients during COVID-19

IIIA. How to follow CLD patients during COVID-19?**IIIB. Performing procedures during COVID-19****IIIC. Therapies under investigation for COVID-19 and potential hepatotoxicity****IIIA. How to follow chronic liver disease during COVID 19?**

Mario Reis Alvares-da-Silva (Brazil)

- Liver disease patients often need to consult, undergo laboratory and imaging routine tests, and therefore, make extensive use of the health system. However, during the pandemic, this population is paradoxically exposed to two risks: staying at home and suffering the consequences of not carrying out their exams and clinical reviews or attending hospitals and laboratories and running the risk of becoming infected with SARS-CoV-2.. Thus, some liver medical societies have tried to guide doctors on these issues, based on expert opinions, since knowledge about COVID-19 and the liver is still lacking^{1,2}. Probably, physicians will have to deal, in the future, with the varied consequences of COVID-19 in liver disease patients, balancing the risks of treatment in patients at risk of COVID-19, the risk of under treatment in patients with advanced or progressive liver disease and the risks of iatrogenic COVID-19 in patients exposed to the health care system³. Patients with stable, compensated liver diseases should postpone medical visits and routine labs. Telemedicine or phone visits should be encouraged in such cases ^{1,2,4,5}

Furthermore, self-isolation and distancing may lead to increased alcohol consumption, which may be associated with dreadful consequences in patients with alcohol-associated liver disease (ALD). Actually, it is speculated that patients with ALD may be amongst the populations that are most severely impacted during the COVID-19 era (6) for a couple of reasons: (i) they have a depressed immune system which make them susceptible to viral and bacterial infections (7); (ii) co-morbidities including obesity with metabolic syndrome are common; (iii) their inability to attend regular visits by providers and social isolation leads to psychological decompensation and increased drinking or relapse drinking; (iv) they are often smokers and have chronic respiratory disease. It is suggested that the reasons

mentioned above may put these patients at higher risk for severe COVID-19 infection (6). These patients may also be less willing to adopt suggested precautions for COVID-19 prevention.

Patients with severe alcoholic hepatitis probably should not receive standard corticosteroid treatment, in particular in areas where COVID-19 is frequent (6). One concern is that patients with ALD or alcoholic hepatitis will not seek medical care unless their situation is critical and that a substantial increase of patients with alcoholic decompensated cirrhosis will occur. Increase in alcohol consumption as well as alcohol relapse in patients with alcohol use disorder is expected to facilitate this trend. In the post COVID era liver transplantation centers may need to apply more flexible approaches to such patients. Finally and tragically, due to some terrible misunderstandings some people have started drinking alcohol to prevent COVID-19 (8). In Iran, some 180 people died after consuming 'moonshine' or industrial alcohol, including methanol, in March this year in the belief that it would protect them from the COVID-19 outbreak. This myth of alcohol being preventive against COVID-19 is by no means confined to Iran and has been observed in many geographical destinations ranging from Eastern Europe to the Far East.

SUMMARY:

- CLD patients are paradoxically exposed to two risks: staying at home and suffering the consequences of not carrying out their exams and clinical reviews or attending hospitals and laboratories and running the risk of acquiring nosocomial SARS-CoV-2.
- Staying at home is associated with increased alcohol drinking. In patients with ALD this may lead to hepatic decompensation.
- Patients with ALD may be prone to acquire SARS-CoV-2 and to go through a severe course of COVID-19.
- Given the nature of the pandemic, physicians and patients will have to deal with these risks for some time in the future.

WGO Recommendations

- Patients with stable, compensated liver diseases should postpone medical visits and routine labs. Telemedicine or phone visits should be encouraged in such cases
- In low-income countries, telemedicine or phone visits may not be possible. Outpatient visits may be used to differentiate patients with compensated vs. decompensated liver disease.
- Outpatient visits should be limited to those with high MELD scores.
- In persons with decompensated cirrhosis who have complications that need laboratory monitoring such as ascites management, visits for blood draw and clinical evaluation may be needed but should be kept to a minimum.
- Telemedicine approaches should take into account patients with alcohol use disorder and such patients should be approached.
- Routine prescriptions should be sent by mail and should be given to cover extended durations.
- Treatment of severe alcoholic hepatitis with corticosteroids should be decided and followed on a case-by-case basis, liberal use of high dose steroids should better be avoided, and whenever possible patients should be hospitalized.
- Liver biopsies should be restricted to cases in which it becomes unavoidable in order to make a definitive diagnosis
- Hospitalizations, if needed, should be as short as possible, preferably in private rooms: keep doors closed and windows open, limit medical and nursing staff
- Phone communication and tele-medicine is encouraged; limit imaging exams to those likely to change management
- SARS-CoV-2 testing should be done in patients who present with acute decompensation of CLD, or acute on chronic liver failure.

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IIIB. Performing procedures during COVID 19

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The COVID-19 pandemic has created several challenges to healthcare services across the world, especially when caring for vulnerable patients. On the one hand, we should minimize physical contact between patients with chronic liver disease (CLD) and medical staff to reduce viral dissemination; on the other hand, we should continue to give the best medical care to these challenging patients.

Patients with CLD, particularly those with advanced or decompensated cirrhosis, often require therapeutic or prophylactic interventions. There is general agreement that procedures should not be performed in patients with CLD unless they are strictly necessary.

Endoscopy:

Human-to-human transmission occurs mainly through respiratory secretions and aerosols but the virus can, also, be transmitted via feces and contaminated environmental surfaces (1-3).

Endoscopy is a high-risk procedure as healthcare providers will be exposed to respiratory and/or gastrointestinal fluids (3). Thus, it is very important to strictly select the emergent procedures, and consider postponing other procedures to the end of the outbreak.

In order to minimize the risk of acquiring SARS-CoV-2 infection when performing endoscopic procedures, several measures should be taken: healthcare workers should always use personal protective equipment (PPE) which includes N95 masks, double gloves, hairnet, waterproof gowns and protective eyewear (4-6). Although not always available, if possible, procedures should be performed in negative pressure rooms on known COVID-19 positive patients (5).

Guidance regarding the use of PPE, particularly in resource restrained countries, is being issued by WGO.

Patients with CLD need to be protected against acquiring SARS-CoV-2 infection. Risk of infection to patients can be minimized by ensuring disinfection of equipment and the endoscopy room, minimizing exposure in waiting and recovery areas and triaging patients at entry to detect possible SARS-CoV-2 infection.

Portal hypertension:

In patients with liver cirrhosis we should use non-invasive risk assessment for the presence of varices in order to stratify patients, during the SARS-CoV-2 pandemic.

Pure screening of gastric and esophageal varices in patients with cirrhosis should be rescheduled as endoscopy is considered high-risk for the endoscopy team, because it is an aerosol-generating procedure. Therefore, it is of paramount importance to identify high-risk patients, in whom variceal banding should continue to be performed such as patients with large varices and red spots, recent variceal bleeding, signs of significant portal hypertension (large volume ascites, thrombocytopenia $< 100 \times 10^9/\text{mL}$) or with signs of active bleeding (hematemesis or melaena). (7, 8)

Endoscopic retrograde cholangiopancreatography (ERCP):

ERCP is also considered an aerosol-generating procedure. Consequently, all the procedures should be reviewed by experts and rescheduled after the outbreak if not urgent/essential.

ERCP should be performed in cases of cholangitis, acute biliary pancreatitis, sepsis or high suspicion of cholangiocarcinoma (4, 7-9).

Paracentesis:

Till now, there are no reports of the presence of SARS-CoV-2 in peritoneal fluid. Despite that, paracentesis should be performed with appropriate PPE and the patient should also wear a surgical mask.

In the vast majority of cases, there are few life-threatening situations where paracentesis is strictly necessary. Beyond cases of suspicion of spontaneous bacterial peritonitis, not only for the diagnosis but also to evaluate the response to the antibiotics at day 3, paracentesis should also be performed in cases of refractory large volume ascites.

Transjugular intrahepatic portosystemic shunt (TIPS):

There are no reported cases of TIPS insertion in COVID-19. As a risky and time-consuming procedure, which may also need admission to intermediate or intensive care units, TIPS insertion should only be performed in life-threatening cases of refractory variceal bleeding. (8)

SUMMARY:

- Endoscopy is a high-risk procedure as healthcare providers will be exposed to respiratory and/or gastrointestinal fluids.
- Patients with CLD also need to be protected against acquiring SARS-CoV-2 infection in the endoscopy unit.

WGO Recommendations:

- Interventional procedures, such as endoscopy and ERCP, should not be performed in patients with CLD unless they are strictly necessary, such as those with high risk varices or cholangitis.
- Pure screening of gastric and esophageal varices in patients with stable cirrhosis should be rescheduled.
- Endoscopy should always be performed using appropriate personal protective equipment (PPE). Please see recent WGO guidance on use appropriate use of PPE.

- Ensuring proper disinfection of equipment and the endoscopy room, minimize exposure in waiting and recovery areas and triage patients at entry, using well-trained staff.
- Clinicians should consider screening all patients undergoing endoscopy using a rapid COVID-19 test prior to the procedure
- TIPS insertion should only be performed in life-threatening cases of refractory variceal bleeding.

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IIIC. Therapies under investigation for COVID-19 and potential hepatotoxicity

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Currently there are no drugs approved for COVID-19, although several drugs have been tested and many of them are still under investigation. Regarding patients with chronic liver disease, possible adverse events have to be considered. Drug-drug interactions in liver transplant patients should be kept in mind with certain immunosuppressive therapies where drug levels of calcineurin inhibitors (cyclosporine or tacrolimus), and mTOR inhibitors (sirolimus or everolimus) will have to be closely monitored. Moreover, patients with impaired liver function, including patients with Child-Pugh B/C cirrhosis, are at high risk of drug toxicities (1).

Remdesivir is a nucleoside analogue (NUC) that is approved in the US for emergency use for COVID-19, acts as a viral RNA polymerase inhibitor. It inhibits SARS-CoV-2 *in vitro* (2) as well as in case reports of patients with COVID-19 (3). A recent double-blind placebo controlled randomized study in 1063 patients confirmed beneficial findings of case reports (4). There is no experience so far in patients with liver cirrhosis. However, based on experience with NUCs in chronic hepatitis B and C, it might be considered as a safer drug than other drug classes (1). Liver toxicity with ALT elevation is a possible adverse event. No relevant drug-drug interactions are expected (5).

Other drugs currently under evaluation include chloroquine and hydroxychloroquine that interfere with the cellular receptor ACE2 and act as an endosomal acidification fusion inhibitor. These drugs have long been used for treatment of malaria, amoebiasis and autoimmune conditions. Initial reports of hydroxychloroquine, in conjunction with azithromycin, leading to viral load reduction in COVID-19 patients have not been confirmed (6). Special consideration regarding those medications is to exclude G6PD deficiency before application, and to consider interactions with immunosuppressive drugs: close monitoring of drug levels is required for calcineurin or m-TOR inhibitors (5) and the risk of severe QT prolongation induced by the two drugs, more commonly seen with hydroxychloroquine,

should be considered. Hepatotoxicity due to hydroxychloroquine has been described but is rare (7)

Lopinavir/ritonavir are approved protease inhibitors (PIs) for second-line HIV treatment. Many centres have discontinued their experimental use as there is no proven efficacy *in vivo* in severe COVID-19 (8). Drug interactions with immunosuppressive drugs are well studied. Close monitoring for calcineurin inhibitor drug levels is recommended, while mTOR inhibitors should not be co-administered (5). Patients with decompensated cirrhosis should not be treated, based on the experience with PIs in HCV. The risk of lopinavir-associated hepatotoxicity in patients with very advanced liver disease is low (9).

Tocilizumab is a humanised mono-clonal antibody against interleukin-6 receptor that works by damping the cytokine release syndrome observed in COVID-19 patients. Liver toxicity in the form of ALT elevations is frequent but clinically apparent liver injury with jaundice seems to be rare (10). HBV reactivation is a considerable adverse event in case of its administration (11). Moreover, it should not be used in patients with decompensated cirrhosis (1).

Convalescent plasma shows a potential therapeutic effect and has low risk in the treatment of severe COVID-19 patients (112). There is no experience with convalescent plasma therapy in COVID-19 patients with chronic liver disease (1):

Favipiravir is a guanine analogue, that is an RNA-dependent RNA polymerase (RdRp)-inhibitor, approved for influenza in Japan. Studies have revealed that favipiravir showed better treatment outcomes in COVID-19 patients in terms of their disease progression and viral clearance (13). ALT and AST elevation is a possible side effect, while no data in cirrhosis are available (1).

The possibility of using sofosbuvir ± ribavirin in COVID-19 infection has been suggested. Sofosbuvir, a nucleotide analogue, was originally approved for the treatment of HCV infection. It inhibits HCV RdRp, which is essential for viral replication, and acts as a chain terminator (14). In the case of COVID-19, *in vitro* data also show binding to SARS-CoV-2 RdRp (15). It is safe, based on the experience of its use in patients with chronic hepatitis

including patients with decompensated cirrhosis. However, ribavirin should be used cautiously as it may cause severe haemolytic anaemia (1).

SUMMARY:

- Currently there are no drugs approved for COVID-19, although many are under investigation.
- Patients with impaired liver function are at high risk of drug toxicities, particularly patients with Child-Pugh B/C cirrhosis.
- Drug-drug interactions in liver transplant patients should always be kept in mind with certain immunosuppressive therapies.
- Remdesivir potentially reduces length of hospital stay and has received provisional fast-track approval from the US FDA. Liver toxicity with ALT elevation is a possible adverse event.
- Favourable data have been reported for favipiravir from Japan.
- Chloroquine and hydroxychloroquine, as well as lopinavir/ritonavir seem to have no role in COVID treatment.

WGO Recommendations:

- No recommendation can be currently made with regards to treatment of COVID-19.
- Evolving treatment data should be thoroughly evaluated by experts, bearing in mind issues of efficacy, safety, local access and affordability.
- Abnormal liver tests should not be a contraindication to using COVID-19 experimental therapies if needed.

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IV. Management of complications of liver disease:

IVA. Screening and treatment of HCC

IVB. Liver transplantation in the COVID-19 era

IVA. Screening and treatment of HCC

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The World Health Organization continues to report that hepatocellular carcinoma (HCC) is the fifth most common tumor, globally, and the second most common cause of cancer-related death (1). Although the incidence and mortality rates of most common cancers continue to decrease due to earlier diagnosis and marked advances in treatment, incidence and mortality rates from HCC continue to rise (2,3).

In patients with cirrhosis or high-risk HBV and MAFLD patients who are otherwise stable, routine HCC surveillance can be postponed for 2-3 months but probably no longer (4, 5).

Patients with cirrhosis and a suspect nodule, or an elevated AFP, should continue to undergo imaging exams to avoid missing HCC (6).

In the era of COVID-19, all patients being evaluated for the diagnosis and management of HCC must first be screened for COVID-19 (5, 6, 7). Those without COVID-19 should be treated according to local protocols, with added steps taken to limit risks of COVID-19 exposure during therapy. Use of telemedicine rather than in-person visits, choosing therapies that require minimal intervention or use of anesthesiologists, surgeons, interventional radiologists, or infusion therapies, in order to reduce risks to the patient and care givers whose efforts are focused on the severely-ill COVID-19 patients, are recommended (5,7).

If the patient is being referred from an outside institution or practitioner, the initial COVID-19 screen should be completed prior to the patient being seen. In addition, before an in-person evaluation, except for a very urgent presentation, a full review of all outside records and diagnostic imaging studies should be completed and, when possible, a visit by telemedicine or, minimally, by telephone interview, should be completed with a full review by a multidisciplinary team (MDT) at the recipient institution.

The standard of care for HCC patients is evaluation by a MDT comprised of transplant surgeons, hepatologists, oncologists, body image and interventional radiologists, pathologist, psychologist/psychiatrist, and social worker (5,7). In the era of COVID-19, the presence of infectious disease specialists and pulmonologists are especially critical, along with pharmacologists/pharmacists, in evaluating and making recommendations concerning the care of these very complex patients.

The following comments refer to patients found to be COVID-19 positive.

Except in the case of patients with extensive tumor burden and /or multiple lesions, it may be reasonable to allow one or two months of close monitoring of the HCC with AFP and imaging in order to provide time to determine the severity of the COVID-19 disease before initiating treatment. A high percentage of COVID-19 patients will resolve their infection in a matter of weeks. Data are insufficient to determine whether HCC increases the risk of COVID-19 severity or of effects of COVID-19 on HCC progression. The slow median doubling time of HCC supports a rationale for a short delay in initiating treatment for the HCC (8),

including a minor delay in radiological surveillance given the demands on many medical centers due to COVID-19 (5).

Non-surgical treatment approaches are recommended in most cases to reduce stress and risks to the patient as well as to other patients and staff in the OR and ICU (5, 7).

Depending on local capabilities, TACE/TARE, RFA or SBRT would be the first-line of therapy (5, 7). In those requiring urgent therapy, but with active COVID-19 infection, TARE may be preferable to reduce the risk of immunosuppressive effects of chemoembolization on COVID-19 recovery. Lacking the facilities to perform these therapies, ultrasound guided percutaneous ethanol injection (PEI) is an appropriate temporizing measure while hoping for improvement in the COVID-19 infection (9). A detailed discussion of approaches to HCC in localities with limited resources is contained in the World Gastroenterology Organization's Global Guideline "Hepatocellular Carcinoma (HCC): a global perspective".

There are no published reports at this time on the various chemotherapies and immunotherapies being used to prolong life in advanced HCC patients so no recommendations are possible. The International Liver Cancer Association (ILCA) suggests that in patients with advanced HCC who require systemic therapies, oral tyrosine kinase inhibitors may be preferred to minimize nosocomial exposures when receiving infusion regimens (7).

The ultimate therapy remains liver transplantation, when that option is available to the patient and they are otherwise an appropriate candidate. However, COVID-19 may reduce access to both deceased and live donor liver transplantation. Again, delaying transplant to allow the COVID-19 to resolve or improve is preferred as mild cases will often resolve in 2-3 weeks. Experience is very limited regarding transplantation in patients who have COVID-19. There are two reports of liver transplant in HCC patients, both of whom survived and recovered, although with prolonged post-op courses and infectious complications when immunosuppression had to be increased due to rejection episodes (5, 10). This remains a last choice until curative therapies for COVID-19 become available and should be made only after careful discussion by the MDT and with the patient and patient's family.

SUMMARY:

- The SARS-CoV-2 pandemic is likely to affect screening for HCC, and regular care of patients with already diagnosed HCC.
- Data are insufficient to determine whether HCC increases the risk of COVID-19 severity or whether COVID-19 affects HCC progression.
- In patients with concomitant COVID-19, the slow median doubling time supports a rationale for a short delay in initiating treatment for the HCC.
- Oral tyrosine kinase inhibitors may be preferred to minimize nosocomial exposures associated with receiving infusion regimens.
- Experience is very limited regarding transplantation in patients who have COVID-19.

WGO Recommendations:

- Routine HCC surveillance can be postponed for 2-3 months in patients who are otherwise stable.
- All patients being evaluated for the diagnosis and management of HCC must first be screened for COVID-19.
- Include ID specialists and pulmonologists in the MDT for HCC care.
- Non-surgical treatment approaches are recommended in most cases, depending on local availability. PEI can be a viable option in low and middle income countries, when other options are not available.
- Preferably use oral tyrosine kinase inhibitors to avoid nosocomial exposures associated with receiving infusion regimens.
- Delaying transplant to allow the COVID-19 to resolve is preferred if possible.

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IVB. Liver transplantation in the COVID-19 era

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Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 virus is impacting all aspects of hepatology, including the quality of our care (1). Liver transplantation is in the position where both donor and recipient risk must be considered. Developing hospital-specific policy for transplant can help with resource utilization while limiting risk to both patients and providers.

Pre-liver transplant

Patients with advanced liver disease are likely at higher risk for mortality if infected with SARS-CoV-2; however deferring management of complications of liver disease also places them at risk for severe consequences. Care should continue to follow clinical guidelines but it is important to limit contact with SARS-CoV-2 in all ways possible. Appointments should be conducted through virtual platforms when possible. Limit in-person visits to those with

urgent issues such as those with new symptoms of decompensation or those with high liver enzymes.

High MELD/Acute

Evaluation for liver transplantation is traditionally encouraged when patients either meet minimal listing criteria, or have uncontrollable symptoms of advanced liver disease or liver cancer within Milan criteria. However, the COVID-19 pandemic is expected to affect both organ availability as well as peri-transplant risk. Individuals with a poor short-term prognosis that are likely to be transplanted quickly should continue to be evaluated and listed, especially those with high MELD and acute hepatic failure. Transplant for other indications must be a balance between the necessity of testing and the risk of SARS-CoV-2 exposure. This is especially true for liver cancer patients for whom listing must occur to start to accrue time toward allocation of points to allow them to be more competitive for transplant. Recipient age and co-morbid conditions must be balanced against potential benefit of evaluation.

Elective procedures have been deferred which includes living donor liver transplantation (LDLT) for all but pediatric indications (2). However, in areas of the world where LDLT represents the majority of transplantations done, LDLT for patients with high MELD score and ALF in selected transplantation centers may be considered. Access to LDLT will need to be dynamically assessed as locations begin to reopen

There are few data to guide clinicians regarding transmission of SARS-CoV-2 through transplant. Testing organ donors for the presence of virus is recommended and those that are positive should be ineligible for donation (3, 4). Recipients should also be screened prior to transplant with rapid COVID-19 PCR testing; however, results could be misleading or contribute to delays. If a potential recipient has symptoms concerning for COVID-19, a CT chest without contrast can also be performed to look for opacities consistent with infection (4).

Post-liver transplant

Routine post-transplant monitoring should continue, but in-person visits should be minimized. Patients should be encouraged to practise social distancing which includes telework options.

Post-transplant immune suppression has not been shown to be a risk factor for mortality with SARS-CoV-2 although more data are needed. Prophylactic reduction in immunosuppression is not recommended but preventive measures (social distancing, hand washing etc.) should be strongly emphasized (5).

Immune suppressed patients infected with COVID-19 should have immunosuppression reduced to the lowest levels, especially if more than 6 months post-transplant (5)

SUMMARY:

- The COVID-19 pandemic is expected to affect both organ availability as well as peri-transplant risk.
- Elective procedures have been deferred which includes living donor liver transplantation (LDLT) for all but pediatric indications.
- There are few data to guide clinicians regarding transmission of SARS-CoV-2 through transplant.
- Post-transplant immune suppression has not been shown to be a risk factor for mortality with SARS-CoV-2, although more data are needed.

WGO recommendations:

- Listing for liver transplantation should be restricted to patients with a poor short-term prognosis such as patients with high MELD score, acute liver failure or liver cancer within Milan criteria.
- LDLT for patients with high MELD score and ALF may be considered in areas of the world where LDLT represents the majority of transplantations done. Access to LDLT will need to be dynamically assessed as locations begin to reopen
- Testing organ donors for the presence of virus is recommended, and those that are positive should be ineligible for donation.
- Recipients should also be screened for SARS-CoV-2 by rapid PCR testing. If found positive transplantation may be postponed until after recovery from SARS-CoV-2 infection.

- Post-transplantation immunosuppression (PTIS) regimens should not be changed. However, in patients diagnosed with COVID-19, reduction of PTIS should be considered.

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