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CLINICAL INSIGHTS FOR HEPATOLOGY AND LIVER TRANSPLANT PROVIDERS DURING THE COVID-19 PANDEMIC

This is a "living" document that will continue to evolve and will be updated as new information becomes available.

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Overview and Rationale

Coronavirus disease 2019 (COVID-19), the illness caused by the SARS-CoV-2 virus, is rapidly spreading throughout the world.[1] Hospitals and healthcare providers across the United States are preparing for the anticipated surge in critically ill patients but few are wholly equipped to manage this new disease. Nonetheless, we all must do our part to prepare our patients, clinics, and hospitals for the drastic changes necessary to mitigate the spread of SARS-CoV-2 or we risk overwhelming the capacity of our healthcare system.[2] In addition, we must continue to manage the care of our patients with liver disease and our liver transplant recipients where unique logistical and pharmacological issues will arise. According to the Centers for Disease Control and Prevention (CDC), patients >65 years old, patients with cardiovascular disease, diabetes mellitus, morbid obesity, chronic obstructive pulmonary disease, or liver disease are at higher risk for severe COVID-19.[3] However while the CDC considers those with liver disease to be at increased risk, it is unclear if patients with cirrhosis, those with autoimmune hepatitis on immunosuppressive medications, and pretransplant and posttransplant patients on immunosuppressant therapy are at increased risk for severe COVID-19. 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 goals of this document are to provide data on what is currently known about COVID-19, and how it may impact hepatologists and liver transplant providers and their patients. Our aim is to provide a template for the development of clinical recommendations and policies to mitigate the impact of the COVID-19 pandemic on liver patients and healthcare providers. Considering that SARS-CoV-2 can be transmitted from asymptomatic individuals, including children, and it can be detected in stool after viral clearance from pharyngeal samples,[4–6] these recommendations have been created to protect our patients, communities, and healthcare workers. Data from China, Italy, and Spain are staggering with reports from Italy indicating that up to 20% of healthcare workers who are taking care of patients with COVID-19 may become infected.[7] We must work to contain the spread of SARS-CoV-2 quickly to ensure our healthcare system's capacity will be preserved, including the ability to test for the virus and maintain the availability of intensive care unit (ICU) beds, ventilators, and healthcare workers.

Effects of SARS-CoV-2 on the Liver and Evaluation of COVID-19 Patients with Elevated Liver Biochemistries

What we know

- The novel coronavirus SARS-CoV-2 is most similar to the beta-coronaviruses, SARS-CoV and MERS-CoV, the causative agents of the SARS outbreak in 2002-2003 and the MERS outbreak beginning in 2012, respectively.

- SARS-CoV-2 is a single, positive-stranded RNA virus that replicates using a virally-encoded RNA-dependent RNA polymerase.
- SARS-CoV-2 binds to and is internalized into target cells through angiotensin-converting enzyme 2 (ACE2), which acts as a functional receptor.[8,9]
- ACE2 is present in biliary and liver epithelial cells; therefore, the liver is a potential target for infection.[10]
- The incidence of elevated serum liver biochemistries in hospitalized patients with COVID-19 ranges from 14% to 53%.[1,11–15]
    - Primarily elevated AST and ALT 1-2 times the upper limit of normal (ULN) and normal to modestly elevated total bilirubin early in the disease process.
    - Liver injury occurs more commonly in severe COVID-19 cases than in mild cases.[15]
    - Rare cases of severe acute hepatitis have been described in patients with COVID-19.[11,16]
    - Liver injury in mild COVID-19 cases is usually transient and does not require specific treatment.[15]
- Low serum albumin on hospital admission is a marker of COVID-19 severity.[14,17]
- Severe 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).[18,19]
- 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.[20,21]
- Elevated liver biochemistries may reflect a direct virus-induced cytopathic effect and/or immune damage from the provoked inflammatory response.[12,22]
- Therapeutic agents used to manage symptomatic COVID-19 may be hepatotoxic. These include remdesivir and tocilizumab.
- Less common causes of elevated liver biochemistries include chloroquine, hydroxychloroquine, and azithromycin.
- It is unknown whether patients with chronic liver disease, especially viral hepatitis B and/or C, may be more susceptible to liver damage from SARS-CoV-2, as was the case with SARS-CoV.[14]
- It is also 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.[15]
- Patients with alpha-1 antitrypsin deficiency with lung disease may be at increased risk of severe COVID-19 due to their lung disease.
- Emerging data suggest that patients with nonalcoholic fatty liver disease (NAFLD) may be at higher risk for severe COVID-19.[23]
    - It is unclear if the risk is specific to NAFLD or to coexisting metabolic risk factors such as cardiovascular disease, diabetes mellitus, and obesity, which are known to be associated with COVID-19 severity.[24]
- It will be difficult to differentiate whether increases in liver biochemistries are due to SARS-CoV-2 infection itself; its complications, including myositis (particularly with AST>ALT), cytokine release syndrome, ischemia/hypotension; or a drug-induced liver injury.[15,20]
- An approach to evaluating the patient with COVID-19 and elevated liver biochemistries is shown in **Figure 1**.

Recommendations

- Patients with cirrhosis, those with autoimmune hepatitis on immunosuppressive medications, and posttransplant patients on immunosuppressant therapy are potentially at increased risk for severe COVID-19 and should be prioritized for testing until further data become available.
- Consider etiologies unrelated to COVID-19, including other viruses such as hepatitis A, B and C, when assessing patients with COVID-19 and elevated liver biochemistries.
- To limit unnecessary transport of patients with COVID-19, ultrasound or other advanced imaging (e.g., MRI/MRCP) should be avoided unless it is likely to change management, e.g., clinical suspicion for biliary obstruction or venous thrombosis.
- Consider other causes of elevated liver biochemistries, including myositis (particularly when AST>ALT), cardiac injury, ischemia, and cytokine release syndrome.
- The presence of abnormal liver biochemistries should not be a contraindication to using investigational or off-label therapeutics for COVID-19 (e.g., remdesivir, tocilizumab, chloroquine, hydroxychloroquine), 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 autoimmune hepatitis 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.[18]
- Follow guidance in your clinical study protocol and/or by the Food and Drug Administration (FDA) for monitoring of liver biochemistries and discontinuation of study drug used to treat COVID-19.

Diagnosis of SARS-CoV-2 Infection

What we know

- Routine labs including a complete blood count (CBC) with differential and platelets and comprehensive metabolic panel (CMP) can provide useful indirect evidence of infection.
    - Lymphopenia and thrombocytopenia are associated with a poorer prognosis (**Table 1**).
- Inflammatory markers including D-dimer, C-reactive protein, creatine phosphokinase, and ferritin are frequently elevated in hospitalized patients and should be followed over time.
- A chest computed tomography (CT) scan with bilateral ground glass opacities is highly sensitive for the detection of pneumonia due to COVID-19 but is non-specific.
    - The American College of Radiology recommends that chest CT should not be used as a first line screening test but rather to confirm the presence of pneumonia in selected hospitalized patients.[25–27]
- Accurate performance of real-time quantitative polymerase chain reaction (RT-PCR) testing for SARS-CoV-2 relies on sufficient amounts of replicating virus, optimal collection procedures and the collection site.[28]
- Nasopharyngeal swabs are more sensitive (63%) than oropharyngeal swabs (32%) while bronchoalveolar lavage (BAL) fluid specimens are the most sensitive (93%) using RT-PCR-based methods, although BAL poses a more significant risk of aerosolizing the virus.[29]
- Qualitative, isothermal, non-PCR nucleic acid amplification methods can deliver SARS-CoV-2 test results from a nasal or nasopharyngeal swab in <15 minutes.[30]

- Testing samples from multiple sites or repeat testing from one site may improve sensitivity and reduce false negative results.
- SARS-CoV-2 viral load may be low at early stages of disease but higher viral loads are detected soon after symptom onset and decline during the second week of illness.[28]
- Serological tests have now been developed, which hold promise as non-invasive, rapid, and convenient means of testing for current or past SARS-CoV-2 infection.[31]
    - They may complement PCR testing to improve detection (IgM), detect subclinical infection (IgM or IgG) and identify healthcare workers who have recovered (IgG) and may be less likely to become reinfected in the healthcare setting.[28]
    - Serological testing may also prove valuable in epidemiological studies and the development of SARS-CoV-2 vaccines and antiviral treatments.

Recommendations

- Check CBC with differential and platelets and CMP in all hospitalized patients with symptoms suggestive of COVID-19 as part of their initial evaluation, with the understanding that it is common for patients with chronic liver disease to have baseline leukopenia, thrombocytopenia, and hypoalbuminemia.
- Monitor systemic inflammatory markers, which may be useful in the assessment of the severity and response to treatment of COVID-19 in hospitalized patients.
- Test all patients with suspected COVID-19 with nasopharyngeal swab testing using RT-PCR or non-PCR methods.
- Consider retesting patients with a high clinical suspicion for COVID-19 and negative initial test results, as resources permit.
- Point-of-care oropharyngeal swabs can also be used to screen for and diagnose COVID-19, although this is not preferred due to low sensitivity.
- Reserve testing of BAL samples for intubated patients with high clinical suspicion for COVID-19 despite negative nasopharyngeal, oropharyngeal, or sputum testing.
- Use chest CT sparingly and only for hospitalized, symptomatic patients with specific clinical indications.
    - CT should not be used to screen for or as a first line test to diagnose COVID-19 due to its lower specificity compared to nasal swabs.

Stable Outpatients with Liver Disease and/or Hepatocellular Carcinoma

What we know

- Information is limited regarding the effects of SARS-CoV-2 infection in patients with chronic liver disease.
- Data from the CDC on 122,653 COVID-19 cases, including 7,162 (5.8%) with data on underlying conditions, showed that 1/3 of these patients (37.6%) had at least one underlying condition or risk factor for severe disease and poor outcomes.[32] Among these patients with underlying conditions, only 41 patients (0.6%) had chronic liver disease, including 7 who required ICU admission.[32]
- Both immunocompetent and immunosuppressed patients can contribute to SARS-CoV-2 spread even if they are asymptomatic.[33]
- Children are less likely to become ill from SARS-CoV-2 infection but can still contribute to spread of the virus.[18]

- There is no evidence that patients with stable chronic liver disease due to hepatitis B and/or C, or cholestatic syndromes such as primary biliary cholangitis or primary sclerosing cholangitis have increased susceptibility to SARS-CoV-2 infection.[15]
- It is unknown whether patients with hepatocellular carcinoma (HCC) are at increased risk for severe COVID-19 by virtue of their malignancy.
    - A case series reported an association between worse COVID-19 outcomes and a history of non-hepatic types of cancer.[34]
    - Those who underwent recent chemotherapy had an even higher risk of severe COVID-19, but the series also included those without recent chemotherapy.[34]
- The slow median doubling time of HCC supports a rationale of a short delay in radiological surveillance given the challenges many centers are currently facing with COVID-19.[35]

Recommendations

- Severely limit outpatient visits to only patients who must be seen in person, even in areas without significant COVID-19 community spread. (See CDC Interim Guidance for Healthcare Facilities.)
    - Consider seeing in person only new adult and pediatric patients with urgent issues and clinically significant liver disease (e.g., jaundice, elevated ALT or AST >500 U/L, recent onset of hepatic decompensation).
    - Follow CDC recommendations for personal protective equipment (PPE). If PPE is unavailable keep a distance of at least 6 feet from the patient.
    - Stagger patient arrival times, and if possible, room patients immediately on arrival to clinic to avoid patients congregating in the waiting area. If patients or caregivers are in the waiting area, appropriate distancing and decontamination of the waiting area should be practiced.
    - Limit the number of family members/friends who accompany patients to their visits. Have these persons wait outside the clinic unless their presence is required for clinical decision making. Enable critical caregivers to participate in the visit by phone or video if possible.
    - Strongly consider phone visits or telemedicine as appropriate and available to replace in-person visits.
- Screen all patients for symptoms of COVID-19 or recent exposure (i.e., fever, cough, shortness of breath, sore throat, diarrhea, new loss of sense of taste or smell,[36] contact with known COVID-19 patients, history of recent travel) before entry into the clinical space (e.g., phone call 24 hours prior to scheduled visit), and again at registration or as they enter the clinic.
- Check each patient's temperature when they arrive to the clinic or registration desk.
    - Patients with fever (>100 °F) should be referred to the hospital's protocol for symptomatic patients.
- Consider evaluating patients with COVID-19 symptoms or known exposure in an outpatient clinic or a site dedicated for this purpose. PPE should be prioritized to that site. Patients with COVID-19 symptoms or known exposure should not be evaluated in the hepatology/liver transplant clinic.
- Follow CDC recommendations for cleaning and disinfecting rooms or areas visited by individuals with suspected or confirmed COVID-19.
- Continue treatment for hepatitis B and hepatitis C if already on treatment.

- Proceed with treatment of hepatitis B and C in patients *without* COVID-19 as clinically warranted. The logistics of monitoring patients during the pandemic should be weighed against the urgency of treatment.
- Initiating treatment of hepatitis B in a patient *with* COVID-19 is not routinely warranted but should be considered if there is clinical suspicion of a hepatitis B flare or when initiating immunosuppressive therapy.
- Initiating treatment of hepatitis C in a patient *with* COVID-19 is not routinely warranted.
- Continue monitoring in those on or off therapy for HCC and continue surveillance in those at risk for HCC (cirrhosis, chronic hepatitis B) as close to schedule as circumstances allow, although an arbitrary delay of 2 months is reasonable.
    - Discuss the risks and benefits of delaying surveillance with the patient and document the discussion.
- Review images of new referrals for patients with liver masses in tumor board or with expert radiologists in virtual multidisciplinary conference prior to scheduling an in-person visit.
- Consider virtual visits to discuss diagnosis and management of HCC and other liver tumors.
- Proceed with HCC treatments when able rather than delaying them due to the pandemic.

Patients with Decompensated Cirrhosis, Liver Transplant Evaluations, and Patients on the Liver Transplant Waiting List

What we know

- Information is limited regarding the effects of SARS-CoV-2 infection in patients with decompensated cirrhosis or those awaiting liver transplantation.
- The complex decision making involved in whether or not to proceed with transplantation is now significantly more challenging due to the COVID-19 pandemic.
- It is essential that transplant centers continuously assess their local situation and its impact on patients awaiting transplantation.
- Some transplant centers may decide that individual candidates should not receive organ offers at this time.
- Special consideration could be given to wait-listed patients with high Model for End-stage Liver Disease (MELD) scores or HCC based on their risk of drop-out and disease progression.
- A reduction in organ recovery is expected because of COVID-19-related limitations on institutional resources and our evolving understanding of the risk of donor-derived disease transmission.
- These factors will have a significant impact on the transplant waiting list resulting in increased waiting times.
- Risk stratification is important to identify patients who need to be evaluated for transplantation or complete their evaluation during the COVID-19 pandemic, including patients with high MELD scores, risk of decompensation, or tumor progression.

Recommendations

Outpatient management

- Limit the number of patients coming to clinic for transplant evaluations.
    - Consider evaluating only patients with HCC or those patients with severe disease and high MELD scores who are likely to benefit from immediate liver transplant listing.
- Develop a policy to decide which listed patients need to be seen in person.
- Consider telemedicine alternatives in place of outreach clinics.

- Obtain labs and imaging only as clinically necessary.
    - Patients should not be asked to update labs simply to update their MELD score. Recent Organ Procurement and Transplantation Network (OPTN) policy changes provide guidance on how to maintain candidate MELD when updated lab results are not obtained.
- Ensure that patients have refills available for essential medications. Provide prescriptions for 90-day supplies instead of 30-day supplies. Many insurance companies are waiving early medication refill limits.
- Consider instructing patients to avoid attending in-person community recovery support meetings such as Alcoholics Anonymous and provide alternative telephone or online resources.
- Advise patients not to travel during the COVID-19 pandemic.
- Consider providing documentation to patients, providers, and organ procurement teams to ease essential travel where travel restriction policies are in place.
- Have a low threshold for admitting patients on the transplant waiting list who are diagnosed with COVID-19.
- Consider using specific screening facilities and a "COVID-19-free" path through the hospital for transplantation candidates.

Patient transplant education and consultations

- Conduct patient transplant education and social work, dietitian, and financial consultations by video conference, telemedicine, or telephone whenever possible.
- Avoid multiple patients in one room for patient education.
    - Consider developing internet-based education sessions for patients and family members that can be deployed either by in-room computers or at home prior to patient evaluation.

Liver Transplantation, Resource Utilization, and Ethical Considerations

What we know

- Resource utilization and ethical considerations are inherently tied to liver transplantation. This is a critical and challenging area for which protocols and policies need to be carefully considered and developed. There is no over-arching policy that can or should be applied to every transplant center; these issues will need to be discussed and developed locally.
- Although the Centers for Medicare and Medicaid Services (CMS) recommends limiting all non-essential planned surgeries and procedures until further notice, they specifically exclude transplant surgery from this recommendation and categorize transplant surgery as Tier 3b ("do not postpone").
- Most Organ Procurement Organizations are testing donors for SARS-CoV-2 RNA, and those who test positive are medically ineligible for organ donation.
- The capacity to test recipients shortly before proceeding with transplant may be limited.
- There is a significant false negative rate and transplant programs should consider symptoms of COVID-19 to be strongly suggestive of infection despite negative testing.
- Transplantation in SARS-CoV-2-positive recipients is currently not recommended.

Recommendations

- Develop a hospital-specific policy for organ acceptance.

    - Ensure hospital administrators are aware of the CMS Tier 3b designation for transplant surgery ("Do not postpone").
    - Consider recipient age and comorbidities prior to organ acceptance.
    - Consider resource utilization including ICU beds, ventilators, PPE and supply of blood products (especially platelets and type-specific packed red cells) in the decision to proceed with liver transplantation.
    - Account for local COVID-19 prevalence data when considering suspension of transplantation.
- Consider notifying patients that the COVID-19 pandemic may impact their waiting time on the transplant list.
- Notify patients that family and visitor access to them during their hospital stay may be limited or prohibited.
- Screen potential donors for exposure and clinical symptoms/fever compatible with COVID-19 (regardless of test results or availability).[37]
    - Alternatives to PCR-based testing such as chest radiography may also be considered.
- Screen potential recipients with an acceptable organ offer for COVID-19 symptoms/fever before they are called in from home for transplantation.
- When an organ offer becomes available, call in to the hospital potential transplant recipients at the latest possible time to minimize exposure to the hospital environment.
- Consider accepting only grafts with a low risk of delayed graft function to minimize complications and postoperative lengths of stay.
- Consider testing of recipients and donors for SARS-CoV-2 before transplantation, if testing is available.
    - 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.
- Consider having backup transplant recipients wait at home or away from the transplant center.
- Consider suspending living donor liver transplant programs during the pandemic, except for pediatric patients with acute liver failure.[37]
- See the latest updates regarding COVID-19 related OPTN policy changes.
- An approach to liver transplant organ offers is shown in **Figure 2**.

Challenging Issues in Liver Transplantation During the COVID-19 Pandemic

- Should we decide who is more in need of limited resources, i.e., COVID-19 patients vs. patients in urgent need of liver transplantation? It is impossible to weigh the value of the life of a patient with COVID-19 against that of a patient in need of life-saving liver transplantation. We should not compound the pandemic by risking the lives of patients in need of liver transplantation and our goal should be to ensure that an ICU bed is available for every patient who requires one.
- An argument that has been advanced to justify deferring some transplants is a concern about immunosuppressing patients during the COVID-19 pandemic. However, it is possible that immunosuppressed patients may not be at increased risk for severe COVID-19.[19] Nevertheless, immunosuppressed patients have higher viral titers and may be more infectious than immunocompetent individuals.[37]
- CMS has 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.
- Is there a point at which we need to ration who will receive a liver transplant? If so, we may need to prioritize patients who are most likely to die on the waitlist and defer those who can wait longer.
- These issues are likely to arise in many transplant programs and predominantly center on the need for limited ICU beds, ventilators, and blood products. Each program will need to establish its institutional capacity to perform liver transplantation and a process for determining whether or not to proceed when an organ is available.
- These decisions should ideally be made in consultation with local medical ethics committees.[2]

Post-Liver-Transplant Patients

What we know

- Data suggest that the immune response may be the main driver for pulmonary injury due to COVID-19 and that immunosuppression may be protective.[13,19,38]
- Posttransplant immunosuppression was not a risk factor for mortality associated with SARS (2002-2003) or MERS (2012-present).[19]
- It is too early to know if posttransplant patients are at greater risk for more severe COVID-19; however, immunosuppressed patients are considered to be at higher risk for severe illness from COVID-19.
- Immunosuppression may prolong viral shedding in posttransplant patients with COVID-19.[37]

Recommendations

- Do not reduce immunosuppression or stop mycophenolate for asymptomatic posttransplant patients without known COVID-19.

- Emphasize prevention measures posttransplant patients already know well: frequent hand washing, cleaning frequently touched surfaces, staying away from large crowds, staying away from individuals who are ill, etc.
- Advise patients not to travel during the COVID-19 pandemic.[37]
- Minimize in-person visits for posttransplant patients by maximizing use of telemedicine.
- Consider advocating for telework options, appropriate excuses from work or leaves of absence for posttransplant patients and their primary caregivers.

Management of Patients on Immunosuppressive Agents

What we know

- The effects of immunosuppression on COVID-19 are not well established.
- Rapid pulmonary deterioration in COVID-19 is due to a systemic/ pulmonary inflammatory response associated with increased serum IL-6, IL-8 and TNF-α levels.[39]
- The potential role of corticosteroids for the prevention of progression of mild COVID-19 to severe pneumonia is unknown.
- The World Health Organization recommends avoiding corticosteroids for treatment of COVID-19 unless indicated for another therapeutic purpose.[40]
- Reducing the dosage or stopping immunosuppressants may cause a flare in a patient with autoimmune hepatitis or precipitate acute rejection in a liver transplant recipient.

Recommendations

- In immunosuppressed liver disease patients *without* COVID-19:
    - Do not make anticipatory adjustments to current immunosuppressive drugs or dosages.

- In immunosuppressed liver disease patients *with* COVID-19:
    - Consider minimizing the dosage of high-dose prednisone but maintain a sufficient dosage to avoid adrenal insufficiency.
    - Consider reducing azathioprine or mycophenolate dosages, especially in the setting of lymphopenia, fever, or worsening pneumonia attributed to COVID-19.
    - Consider reducing but not stopping daily calcineurin inhibitor dosage, especially in the setting of lymphopenia, fever, or worsening pulmonary status attributed to COVID-19.
    - An approach to managing liver transplant recipients with COVID-19 is shown in **Figure 3**.
- Initiate immunosuppressive therapy in patients with liver disease with or without COVID-19 who have strong indications for treatment (e.g., autoimmune hepatitis, graft rejection).
- In patients with COVID-19, use caution in initiating prednisone, prednisolone, or other immunosuppressive therapy where the potential benefit might be outweighed by the risks (e.g., alcohol-associated hepatitis).

Inpatients

What we know

- Healthcare workers and other hospital staff are at risk for COVID-19.[7]
- Healthcare workers with SARS-CoV-2 may spread the virus to patients and to each other, and should remain away from in-person work until approved to return by local health authorities.

- Minimizing interactions among healthcare workers and between healthcare workers and patients is critical to reducing the spread of SARS-CoV-2.
- Minimizing the transport of patients within and between healthcare facilities could reduce the spread of SARS-CoV-2.

Recommendations

- Consider cohorting of inpatients with COVID-19 from other non-infected patients in the hospital.
- Consider equipping patient rooms with telemedicine equipment (e.g., tablet) to enable remote consultation and monitoring.
- Conduct medical and surgical transplant rounds with the minimum number of personnel needed to provide care at a given time.
- Limit the number of team members who enter a patient's room for patient examinations and encounters.
    - The same rule applies to inpatient consultations involving other medical or surgical services for the care of patients with liver disease or transplant evaluation. Limit the personnel permitted to enter patient rooms to the minimum needed for the performance of consultative care.
    - Consider conducting virtual visits for updates not requiring direct examination. This will reduce contact risks as well as unnecessary utilization of PPE thereby preserving hospital supplies for essential needs.
- Discourage in-person multidisciplinary rounds with dietary, pharmacy, social work, and care coordination staff.
    - Consider the use of virtual conferencing to reduce direct staff interactions.
- Consider restricting the direct patient care of providers at higher risk (age >65 years, serious underlying medical conditions, immunocompromised).
- Limit or even prohibit the presence of non-essential team members in the hospital (e.g., students, observers, research staff) to minimize exposure risk and prioritize the use of PPE.
- Consider use of telephone or virtual language translation services as needed to reduce contact with patients.
- Limit the number of visitors who may see inpatients.
    - Ideally, no visitors should be permitted in patient rooms except in specific circumstances such as hospice care or when a patient is being discharged following transplantation.
- Immediately identify caregivers and legal representatives (and collect their emergency contact information) to provide informed consent if a patient is impaired, and to enable provision of regular status updates to them while visitors are not permitted in patient rooms.
- Carefully consider and minimize all requests for imaging and procedures on patients, including blood draws. Order only studies essential for care to reduce institutional resource utilization, including patient transport between hospital locations.
- Consider developing a policy for review and triage of hospital inpatient transfers. For example, consider accepting for transfer only patients with acute liver failure or those in need of urgent liver transplant evaluation during their hospital stay.
    - Consider accepting for transfer only other liver patients with a unique need for inpatient interventions at the transplant center.
    - Avoid direct hospital admission for patients with fever and respiratory symptoms, particularly admission to a transplant unit.
- Consider evaluating patients with liver disease for COVID-19 if they develop new onset encephalopathy or other acute decompensation.

- Have a low threshold for aggressive airway management in COVID-19 patients with underlying pulmonary diseases such as hepatic hydrothorax, portopulmonary hypertension, or hepatopulmonary syndrome.
- Perform a needs assessment prior to patient discharge to determine whether the patient can have follow-up encounters by phone or telemedicine, and encourage early monitoring by these means to reduce early postdischarge, in-person visits.
    - Consider home health or visiting nurse services for frequent blood draws needed after posttransplant hospital discharge.
- Coordinate with outpatient services for admission and discharge planning to prevent unnecessary admissions and reduce unplanned re-admissions after discharge.
- Patients with active viral shedding on discharge should remain in isolation at home and appropriate precautions should be taken for caregivers or family members who live with the patient.
- Consider the capacity of local rehabilitation centers to accept complex patients as beds in those facilities may become limited during the COVID-19 pandemic.
    - Review the possibility of enhanced home services during the admission to expedite discharge.

Medication Management of Patients with COVID-19 and Potential Drug-Drug Interactions

What we know

- There currently are no FDA-approved therapies to prevent or treat COVID-19 infection.
- Many investigational or off-label therapeutics for COVID-19 may be hepatotoxic (**Table 2**).
- An open-label, randomized, controlled trial of lopinavir-ritonavir vs. standard of care in adults hospitalized with severe COVID-19 showed no clinical benefit.[41]
    - Treatment was stopped early in some patients taking lopinavir-ritonavir due to adverse events.
- Ritonavir is a potent inhibitor of CYP3A4, which is involved in the metabolism of calcineurin inhibitors, sirolimus, and everolimus.
    - The use of ritonavir requires a reduction in the tacrolimus dosage to 1/20-1/50 of baseline due to this drug-drug interaction.
- Remdesivir is a nucleotide analogue with demonstrated activity against SARS-CoV and MERS-CoV in cultured cells, mice and non-human primates, and more recently against SARS-CoV-2 in human cell lines.[42,43]
    - Remdesivir is being tested in hospitalized patients with moderate to severe COVID-19 in randomized controlled trials.[44] Data from compassionate use are encouraging but more data are needed.[45,46]
- Drugs that target the IL-6 receptor are being tested only in hospitalized patients with moderate to severe COVID-19.
- Hydroxychloroquine (an analogue of chloroquine with a better safety profile) has been shown to have anti-SARS-CoV-2 activity *in vitro*.[47]
    - A single-arm study from France of 20 patients with COVID-19 who were treated with hydroxychloroquine with or without azithromycin compared to 16 nonrandomized controls reported negative nasopharyngeal swabs for SARS-CoV-2 PCR in 70% of the treated group compared to 12.5% of the controls.[48]

    - A separate study from France reported that the combination of hydroxychloroquine and azithromycin was not associated with clinical recovery or viral clearance and 4 of the 11 patients discontinued therapy due to prolonged QT interval.[49]
    - The CDC recently issued a warning about the danger of using nonpharmaceutical chloroquine phosphate, a commercially available chemical for aquarium use, to treat or prevent COVID-19. One individual died after using nonpharmaceutical chloroquine and another became critically ill with gastrointestinal symptoms and cardiac conduction abnormalities.
- Convalescent plasma transfusion holds promise for treating critically ill patients with COVID-19.[50,51]
    - The FDA recently announced that it is facilitating access to convalescent plasma for patients with serious COVID-19 through its emergency Investigational New Drug application process.
- Treatment with ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) results in upregulation of ACE2, the target for SARS-CoV-2 entry into cells.[52]
    - Increased ACE2 expression *theoretically* facilitates infection with SARS-CoV-2.
    - Animal studies suggest that ACEIs and ARBs may protect against serious lung complications from SARS-Co-V, but to date there are no data in SARS-CoV-2 or in humans.[53]
    - The Council on Hypertension of the European Society of Cardiology highlighted the lack of evidence demonstrating harmful effects of ACEIs and ARBs in the setting of COVID-19 and recommends that patients should continue with their usual antihypertensive therapy, including ACEIs and ARBs.

Recommendations

- Monitor studies of antiviral and immunomodulatory approaches to COVID-19 at NIH's clinicaltrials.gov.
- The available evidence does not currently support the use of lopinavir-ritonavir for the treatment of COVID-19.
- Hydroxychloroquine with or without azithromycin is not routinely recommended and may be associated with serious adverse events such as prolongation of the QT interval.
- Patients receiving ACEIs and ARBs should remain on them even in the setting of COVID-19.
- Acetaminophen at a daily dosage of $\leq$2 g/d is the preferred analgesic and anti-pyretic for patients with known or suspected COVID-19.
- NSAIDS may also be used or continued as needed.
- Consult the University of Liverpool Drug Interactions Group document on Interactions with Experimental COVID-19 Therapies.

Procedures

What we know

- There is potential for fecal-oral SARS-CoV-2 transmission,[1,4,22,46] and the virus is detected in saliva.[1,22,54]
- Multiple societies have strongly recommended rescheduling non-urgent procedures.
- The Joint Gastroenterology Societies recommend to "strongly consider rescheduling non-urgent endoscopic procedures.

- CMS, the US Surgeon General and the American College of Surgeons recommend postponing elective surgeries.
- Endoscopic procedures should be considered aerosol-generating.[55]
- Non-urgent endoscopic procedures should be rescheduled to reduce the risk of disease transmission from asymptomatic patients, reduce the use of PPE, and reduce hospital admissions.[55]
- To limit disease transmission, the Joint Gastroenterology Societies and the American Gastroenterological Association recommend healthcare workers involved with endoscopy wear a full set of PPE, including N95 masks and double gloves.[56]

Recommendations

- Cancel all elective/non-urgent procedures (e.g., endoscopy, liver biopsy, transient elastography).[55]
- Consider, in the interim, primary prophylaxis with beta blocker therapy instead of screening endoscopy in patients with clinically significant portal hypertension or high risk of decompensation.
- Some procedures may need to be performed, e.g., liver biopsy to rule out rejection or diagnose autoimmune hepatitis, therapeutic paracentesis, transjugular intrahepatic portosystemic shunt and/or endoscopy for variceal bleeding, follow-up band ligation in those with recent variceal bleeding, urgent biliary procedures for symptomatic disease such as cholangitis and sepsis (interventional radiology or endoscopic).
- N95 masks (as opposed to surgical masks) and double gloves should be worn during upper and lower endoscopic procedures.[56]
    - N95 masks may need to be reused depending on the local situation.
    - Hats may be worn for the entire day unless visibly soiled.
    - Eyewear (personal or disposable) should be cleaned with an alcohol wipe between cases.
    - Disposable eyewear should be disposed of at the end of the day unless visibly soiled, in which case it should be immediately discarded.
- Consider limiting the involvement of fellows in endoscopies and other procedures to conserve PPE.[55]
- Follow CDC recommendations for cleaning and disinfecting rooms or areas visited by individuals with suspected or confirmed COVID-19.

Research

What we know

- Due to quarantine-related travel restrictions and potential supply chain interruptions, the FDA and NIH have posted guidance documents for the conduct of clinical trials during the COVID-19 pandemic.
- As the FDA states, protocol deviations may be necessary and will depend on many context-dependent factors related to the nature of the study, the patient population, and environmental circumstances.
- Patient safety is of utmost importance and should be used to guide decisions impacting the trial, including recruitment, continuation decisions, patient monitoring, delayed assessments, and investigational product dispensing.

- Evaluation of alternative visits, including virtual, phone, or remote contact, may be warranted if safety of the patient can be assured with the alternative approach.
- Protocol changes that reduce immediate danger or protect the well-being of the research participants may be implemented before Institutional Review Board (IRB) approval but must be subsequently reported.
- The NIH encourages grant recipients to discuss changes that prioritize patient and staff safety, including limiting study visits or conducting them virtually, suspending unnecessary travel, and increasing flexibility for laboratory testing and imaging with both the institution and the IRB.
- In an effort to ensure patient safety and maintain trial integrity, sponsors, investigators, and IRBs should document all such contingency measures and reasons for protocol deviations.

Recommendations

- Limit clinical trial activity to essential clinical trials, defined as those that enroll or follow patients with life-threatening or serious conditions for which participation in the clinical trial holds out the clear prospect of directly benefiting the patient. Patients already enrolled in clinical trials who are undergoing safety and efficacy assessments fall within this definition.
    - Continue in-person research visits for participants already enrolled in essential clinical trials if required for patient safety and/or participation in the clinical trial is an integral part of the patient's treatment plan.
    - The study physician – in consultation with the study team, the patient's physician, the patient, and the patient's family – should carefully assess the necessity and risks of an in-person visit.
- Do not initiate new clinical trials at this time unless meeting the definition of an essential clinical trial.
- Strongly consider not enrolling new research participants into existing clinical trials unless meeting the definition of an essential clinical trial.
    - Postpone all other in-person clinical research visits.
- Research staff should make efforts to use alternative methods to conduct research visits or perform testing such as check-ins with participants by phone and/or performing research-related lab testing at lab testing centers if feasible.
- Research staff should work remotely, unless their presence is required for the safe conduct of the trial.
- Discuss options for conducting telehealth study visits with clinical research organizations and study sponsors.
- Principal investigators should notify commercial sponsors that opening new nonessential clinical trials and enrolling subjects into ongoing "non-essential" clinical trials should be temporarily postponed.
- Arrange for research medications to be sent to subjects by the study sponsor if the research pharmacy is unavailable.
- Institutional policies on clinical research may be more restrictive and should supersede the recommendations contained here.
- Laboratory/basic science research may also need to be restricted based on local policies.

Trainees

What we know

- Although residents and fellows have much to learn from the diagnosis and management of COVID-19, there is widespread concern that the risks of exposing trainees to SARS-CoV-2 may outweigh the benefits.
- There is also concern about further reducing the already significant PPE shortages by involving trainees in direct patient care.
- In a Letter to the Community, the Accreditation Council for Graduate Medical Education (ACGME) announced it has suspended some activities during the COVID-19 pandemic, including self-studies, accreditation site visits, Clinical Learning Environment Review (CLER) program site visits, and resident/fellow/faculty surveys
- The ACGME issued new requirements to allow residents/fellows to participate in telemedicine.
- The ACGME requirements for adequate resources and training, adequate supervision, and work hour limitations have not changed.
- The ACGME has clarified the local circumstances in which fellows may function within their core specialty (i.e., act as attending physicians).
- Designated Institutional Officials (DIOs) may self-declare a Pandemic Emergency Status for all programs within the Sponsoring Institution, during which all Common Program Requirements and specialty-specific Program Requirements are suspended other than those outlined above (adequate resources and training, adequate supervision, work hour requirements, and fellows functioning in core specialty).
- See ACGME's response to the pandemic crisis for more details.

Recommendations

- Ensure adequate resources including PPE appropriate to the clinical setting for all trainees.
- Assign fellows only to participating sites that ensure the safety of patients and fellows.
- Ensure appropriate supervision of trainees working remotely if they are conducting patient care activities (telephone/telemedicine visits).
- Change all educational conferences to virtual conferences.
- Consider assigning fellows and other trainees to indirect patient care activities and/or telemedicine visits.
- Consider remote supervision of trainees by concurrently monitoring patient care through appropriate telecommunication technology.

Protecting Healthcare Workers and Workforce Utilization

What we know

- The SARS-CoV-2 infection rate of healthcare workers may be up to 20%, as reported in Italy.[7]
- In addition to protecting our patients, healthcare workers must take action to prevent infection within and outside patient care settings.
- We must endeavor to avoid the loss of healthcare workers to illness or quarantine, but plans must be developed to mitigate the effects of workforce shortages during the pandemic.
- Given the potential for SARS-CoV-2 to spread via aerosol as well as droplet, the use of N95 masks or other respirators are essential when caring for patients with known or suspected COVID-19.[57] It is not known whether surgical masks protect the wearer from infection, but data suggest that a surgical mask worn by infected individuals may reduce the risk of transmission

(source control).[58] It is unknown whether surgical masks reduce the risk of transmission from asymptomatic healthcare workers to patients or other healthcare workers.

Recommendations

- Cancel all in-person meetings (even small meetings) and change to virtual meetings.
- Practice social distancing even in meetings, e.g., keep an empty chair between each person.
- Consider staggering work shifts for physicians, providers, nurses, and staff.
- Create a backup schedule for physicians and surgeons in the event of quarantine or illness.
- Consider assigning backup personnel for providers in leadership positions.
- Consider checking temperatures of all providers and staff as they arrive to the office or clinic. There should be a zero-tolerance policy for presenting to work with fever or symptoms of COVID-19.
- All healthcare workers should wear a surgical mask in patient care settings.

Telemedicine

What we know

- Telemedicine can mitigate the exposure of patients and healthcare workers to COVID-19 and has potential to change healthcare delivery now and after the COVID-19 pandemic.[59–61]
- Emergency funding legislation HB 6074 waived many of the long-standing restrictions to the use of telehealth for Medicare recipients, including: rural area requirements for originating sites (i.e., patient location); allowing a patient's home to be an eligible originating site; allowing phones with two-way, real-time interactive audio and visual capabilities to be used; and allowing the provider to conduct a telemedicine encounter from their home.[62]
- The Department of Health and Human Services Office of Civil Rights announced that it would not impose penalties for the good faith provision of telemedicine during the COVID-19 public health emergency, even if remote communication technologies used for such services may not fully comply with the requirements of the Health Insurance Portability and Accountability Act (HIPAA) Rules.
- Medicare will currently reimburse telephone and telemedicine visits for both new and established patients.
- Providers can bill for telemedicine visits at the same rate as in-person visits
- CMS has temporarily waived the Medicare and Medicaid requirements that physicians and non-physician practitioners be licensed in the state where they are providing services.
- Telemedicine limitations include patient access to the electronic health record patient portal; access to a computer, phone, or tablet with video/audio capabilities; and ability to manage the technology.
- See the Joint Gastroenterology Societies' message about telehealth.

Recommendations

- Consider phone visits or telemedicine as appropriate and available to replace in-person visits.
- Conduct patient education and social work, dietitian, and financial consultations by video conference, telemedicine or telephone for liver transplant evaluations.
- Consider telemedicine alternatives in place of outreach clinics.
- Minimize in-person visits for posttransplant patients by maximizing use of telemedicine.

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COVID-19 Liver Disease and Transplant Registries

- SECURE-Cirrhosis (COVID-19 in patients with cirrhosis and liver transplant recipients, "PHI-free")
- University of Washington (COVID-19 in solid organ transplant recipients, "PHI-free")
- COVID-LT Consortium (COVID-19 in patients with cirrhosis and liver transplant recipients)

Helpful Resources

- Centers for Disease Control and Prevention, COVID-19 Website
    - CDC recommendations for cleaning and disinfecting rooms or areas visited by individuals with suspected or confirmed COVID-19
- The Transplantation Society Guidance on Coronavirus Disease 2019 (COVID-19) for Transplant Clinicians
- Association of Organ Procurement Organizations COVID-19 Bulletin
- FDA Guidance on Conduct of Clinical Trials of Medical Products During COVID-19 Pandemic
- Guidance for NIH-funded Clinical Trials and Human Subjects Studies Affected By COVID-19
- Medicare Telemedicine Health Care Provider Fact Sheet
- CMS Flexibilities to Fight COVID-19
- ACGME's Response to the Coronavirus (COVID-19)
- CMS Adult Elective Surgery and Procedures Recommendations:
- Joint GI Society Message for Gastroenterologists and Gastroenterology Care Providers
- Joint GI Society Message about Telehealth
- University of Liverpool Drug Interactions Group document on Interactions with Experimental COVID-19 Therapies

Tables

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

	Test (method)	Turn around (hrs)	Sensitivity	Comments
Routine Bloodwork and Imaging	CBC with differential & platelets	<1	NA	Lymphopenia frequently identified at presentation and associated with poor prognosis Elevated WBC and thrombocytopenia indicate poor prognosis
	Comprehensive metabolic panel	<1	NA	Abnormal aminotransferases are common but usually 1-2x ULN Alkaline phosphatase usually normal Acute kidney injury indicates poor prognosis
	LDH, D-dimer, CRP, INR, CPK, ferritin	<1	NA	Elevated inflammatory markers associated with poorer outcomes
	Chest CT	<1	80%-90%	Bilateral ground glass opacities (lower lobe and peripheral) seen in >90% of hospitalized cases confirmed by RT-PCR Specificity only 25%
Commercially Available Diagnostics	Nasopharyngeal swab (RT-PCR)	2-48	40%-80%	Peak shedding 12-14 days after infection; Nasopharyngeal higher yield than oropharyngeal Requires frozen transport media if >24 hours False negative common in early in disease
	Qualitative nasopharyngeal swab (non-PCR)	<1	80%-90%	Point of care qualitative test using isothermal detection methods Results in 15 minutes
	Sputum (RT-PCR)	2-48	60%-80%	Should be spontaneous expectorant Do not induce
	Bronchoalveolar lavage (RT-PCR)	2-48	95%	Recommended only for intubated patients with negative nasopharyngeal swab
	Plasma serology (IgG, IgM, IgA)	1-2	70%-90%	Indicative of prior exposure False negative early in disease False positive due to lack of SARS-CoV-2 specificity IgA/IgM positive at 3-6 days after symptom onset May be useful in healthcare workers, close contacts, and epidemiological studies
Investigational Diagnostics	Nasopharyngeal swab (CRISPR)	1-2	NA	Colorometric dipstick in development
	Blood (RT-PCR)	24	15%	May be present in more severe cases
	Stool (RT-PCR)	24	30%	May be detectable throughout disease phase
	Cell culture	>24 (days)	NA	For research purposes only Requires high level safety lab Used for vaccine and antiviral testing

CBC, complete blood count; CPK, creatine phosphokinase; CRISPR, clusters of regularly interspaced short palindromic repeats; CRP, C-reactive protein; CT, computed tomography; INR, international normalized ratio; LDH, lactate dehydrogenase; RT-PCT, real-time polymerase chain reaction; ULN, upper limit of normal

Table 2. Investigational Treatments for COVID-19

	Agent (route/mechanism)	Target population	Safety issues	Efficacy Issues*
Antiviral Agents	Remdesivir (IV/nucleotide analogue)	Moderate-severe	Nausea/vomiting Grade 1-2 ALT elevations Drug vehicle accumulation in acute kidney injury *Exclusions:* GFR <30-50 mL/min AST or ALT >5x ULN	Investigational RCT vs placebo and compassionate use protocols Previously tested in Ebola Few DDIs anticipated
	Favipiravir (oral/RNA polymerase inhibitor)	Early to mild disease		Investigational Approved for influenza in Asia Tested with interferon-α aerosol x 14 days
	Lopinavir-ritonavir (oral/HIV protease inhibitor)	Severe	CYP3A4 substrate Severe DDI with CNI 13% early discontinuation due to side effects	FDA-approved for HIV No survival benefit in RCT vs standard of care x 14 days
	Nitazoxanide (oral/host proteins)	Moderate-severe	Similar to placebo in influenza trials	FDA-approved for Cryptosporidium/Giardia In vitro activity against coronaviruses
	Hydroxychloroquine (oral/host proteins)	Moderate-severe	QTc prolongation Nausea and vomiting *Exclusions:* QTc >415 ms Cardiomyopathy G6PD deficiency	FDA-approved for lupus/rheumatoid arthritis/malaria Available as emergency use May work by reducing ACE2 receptor-mediated endocytosis or inhibiting endosomal acidification
	Chloroquine (oral/host proteins)	Moderate-severe	QTc prolongation Nausea and vomiting *Exclusions:* QTc >415 ms Cardiomyopathy G6PD deficiency	FDA-approved for malaria May work by reducing ACE2 receptor-mediated endocytosis or inhibiting endosomal acidification Reduced progression of disease and symptom duration in China
	Azithromycin (oral/host proteins)	Moderate-severe	CYP3A4 substrate Moderate DDI with CNI Rare cholestatic hepatitis *Exclusion:* QTc >415 ms	FDA-approved for bacterial infections Combined with hydroxychloroquine in limited number of patients

Immunomodulatory Agents	Tocilizumab (IV/monoclonal IL-6 receptor antagonist)	Severe (high IL-6 levels)	Grade 1-2 ALT 20%-40% Grade 3+ ALT 1%-2%. Acute liver failure <1% Neutropenia 3% Thrombocytopenia 2% Opportunistic infections *Exclusions:* ANC <2,000/m^3 Platelets <100,000/m^3 ALT >5 xULN	FDA-approved for RA 8 mg/kg dose
	Sarilumab (SC/monoclonal antibody)	Severe (high IL-6 levels)	Grade 1-2 ALT 15%-25% Neutropenia 5% Thrombocytopenia 1% *Exclusions:* ANC <2,000/mm^3 Platelets <150,000/m^3 ALT >5 ULN	FDA-approved in RA Being tested as IV formulation
	Siltuximab (IV/monoclonal antibody)	Severe (high IL-6)	Grade 1-2 ALT Rash 30% Thrombocytopenia 9% *Exclusions:* ALT >5x ULN	FDA-approved in Castleman's disease
	Convalescent plasma (IV/neutralizing antibodies)	Severe or life-threatening pneumonia	Potential TRALI/ anaphylaxis ICU monitoring needed Must screen donor for other transmissible pathogens	Investigational Open label 400 mL plasma infusion in 5 patients and 200 mL plasma infusion in 10 patients Finding donors with neutralizing IgG activity not well established Reserved for severe/life threatening cases

ACE2, angiotensin converting enzyme 2; ANC, absolute neutrophil count; CNI, calcineurin inhibitor; DDI, drug-drug interaction; G6PD, glucose-6-phosphate dehydrogenase; GFR, glomerular filtration rate; HIV, human immunodeficiency virus; ICU, intensive care unit; IV, intravenous; RA, rheumatoid arthritis; RCT, randomized controlled trial; SC, subcutaneous; TRALI, transfusion-related acute lung injury; ULN, upper limit of normal

Figures

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

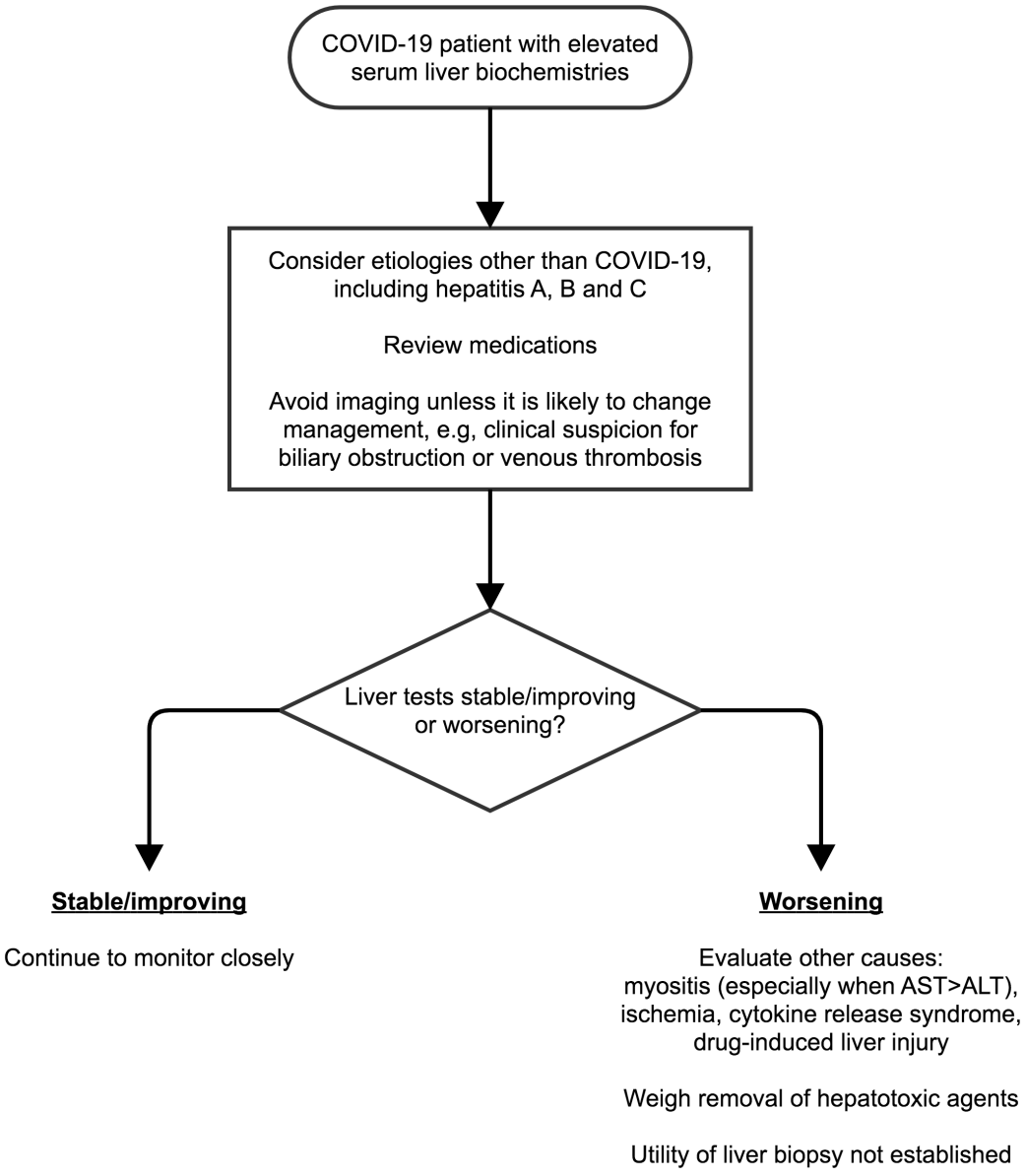
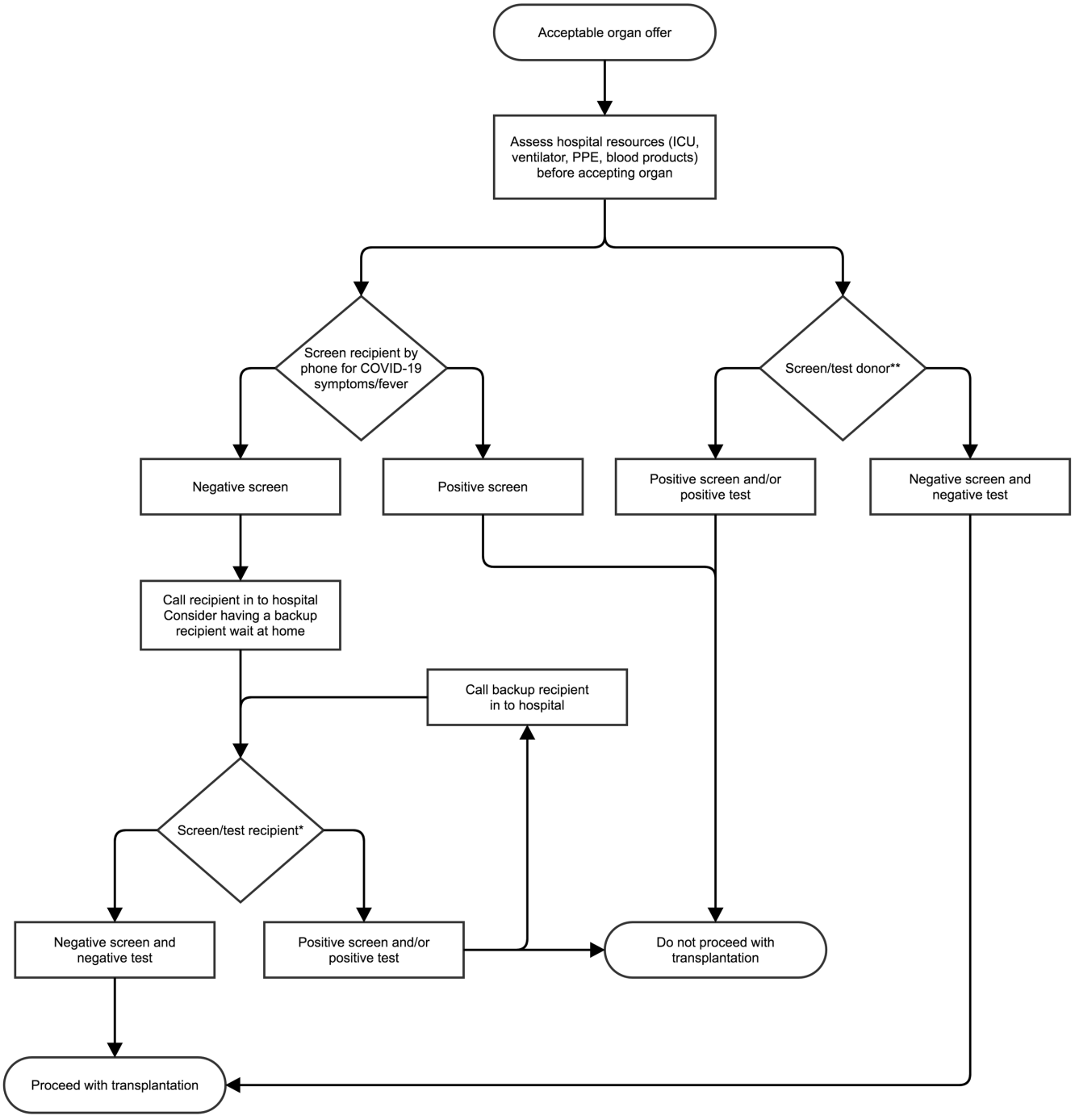


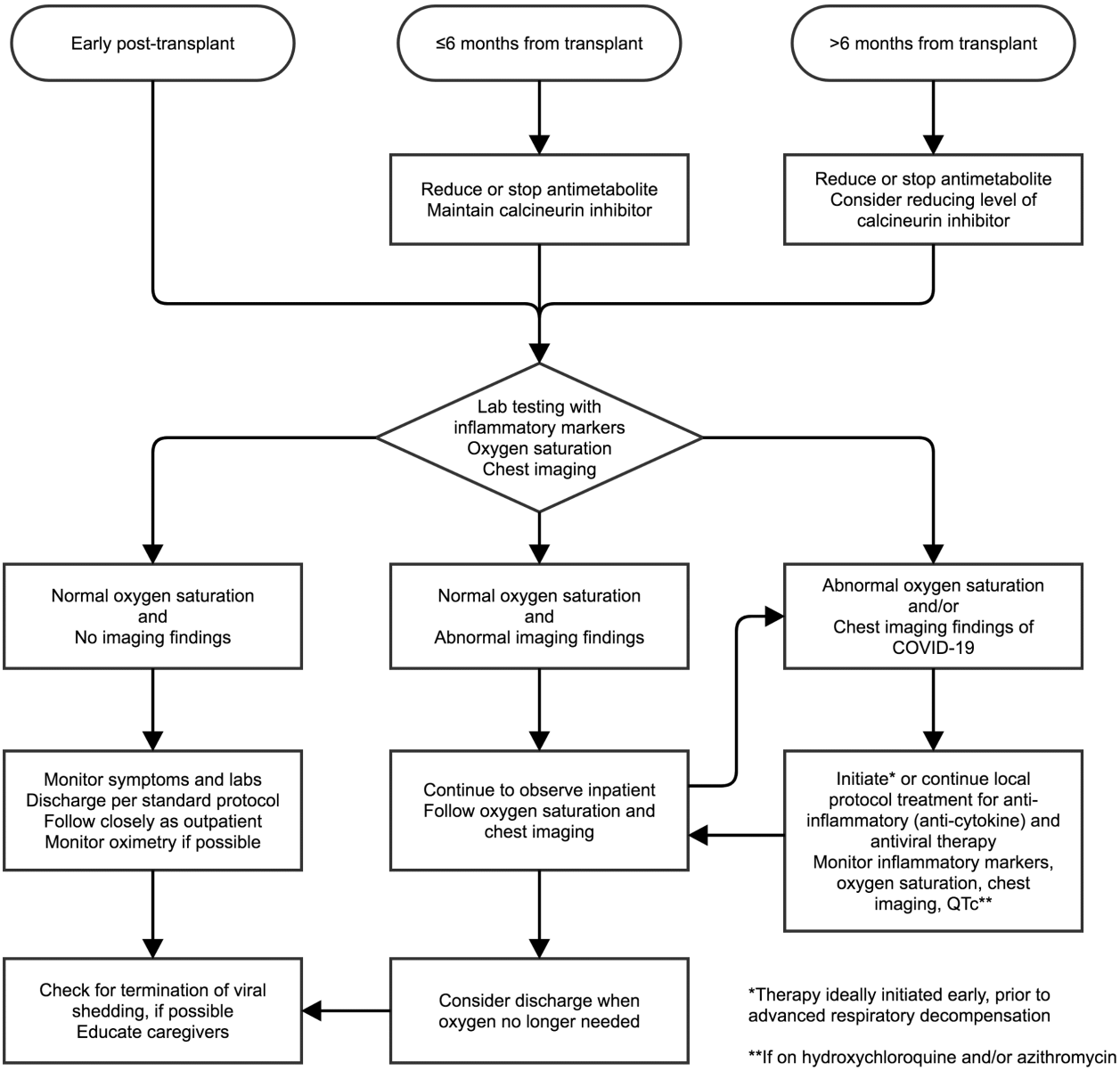
Figure 2. Approach to Liver Transplant Organ Offers



*Recipient screening: Screen recipient on arrival for COVID-19 symptoms/fever
Test recipient for SARS-CoV-2, if available

**Donor screening: Screen donor history for possible COVID-19 exposure or clinical symptoms, fever, or chest imaging compatible with COVID-19
Test donor for SARS-CoV-2, if available

Figure 3. Approach to the Liver Transplant Recipient with COVID-19



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