Accepted Article

DR. OREN K FIX (Orcid ID : 0000-0002-8570-9646)
DR. JORGE A BEZERRA (Orcid ID : 0000-0001-9667-7742)

Article type : Original

Clinical Best Practice Advice for Hepatology and Liver Transplant Providers During the COVID-19 Pandemic: AASLD Expert Panel Consensus Statement

Oren K. Fix,[1] Bilal Hameed,[2] Robert J. Fontana,[3] Ryan M. Kwok,[4] Brendan M. McGuire,[5] David C. Mulligan,[6] Daniel S. Pratt,[7] Mark W. Russo,[8] Michael L. Schilsky,[6] Elizabeth C. Verna,[9] Rohit Loomba,[10] David E. Cohen,[11] Jorge A. Bezerra[12], K. Rajender Reddy,[13] Raymond T. Chung[7]

[1]Swedish Medical Center, Seattle, WA; [2]University of California San Francisco, San Francisco, CA; [3]University of Michigan, Ann Arbor, MI; [4]Uniformed Services University, Bethesda, MD; [5]University of Alabama, Birmingham, AL; [6]Yale University, New Haven, CT; [7]Massachusetts General Hospital, Boston, MA; [8]Carolinas Medical Center, Charlotte, NC; [9]Columbia University, New York, NY; [10]University of California San Diego, La Jolla, CA; [11]Weill Cornell Medicine, New York, NY; [12]Cincinnati Children's Hospital, Cincinnati, OH; [13]University of Pennsylvania, Philadelphia, PA

OKF: oren.fix@swedish.org
BH: bilal.hameed@ucsf.edu
RJF: rfontana@med.umich.edu
RMK: ryan.m.kwok.mil@mail.mil
BMM: bmcguire@uabmc.edu
DCM: david.mulligan@yale.edu
DSP: dspratt@mgh.harvard.edu
MWR: mark.russo@atriumhealth.org

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/HEP.31281

This article is protected by copyright. All rights reserved

MLS: michael.schilsky@yale.edu
ECV: ev77@cumc.columbia.edu
RL: roloomba@health.ucsd.edu
DEC: dcohen@med.cornell.edu
JAB: jorge.bezerra@cchmc.org
KRR: reddyr@pennmedicine.upenn.edu
RTC: chung.raymond@mgh.harvard.edu

Keywords: SARS-CoV-2, coronavirus, transplantation, cirrhosis, immunosuppression

Accepted Article

This article is protected by copyright. All rights reserved

Accepted Article

Contact Information:

Oren K. Fix, MD, MSc, FAASLD

Swedish Organ Transplant and Liver Center

1124 Columbia Street Suite 600

Seattle, WA 98104

Tel: (206) 386-3660

Fax: (206) 320-7431

oren.fix@swedish.org

K. Rajender Reddy, MD, FAASLD

Division of Gastroenterology and Hepatology

University of Pennsylvania

3400 Spruce Street

2 Dulles

Philadelphia, PA 19104

Tel: (215) 662-4276

Fax: (215) 349-5915

reddyr@pennmedicine.upenn.edu

Raymond T. Chung, MD, FAASLD

Liver Center, Gastrointestinal Division

Massachusetts General Hospital

55 Fruit Street

Boston, MA 02114

Tel: (617) 724-7562

Fax: (617) 643-0446

chung.raymond@mgh.harvard.edu

List of Abbreviations:

COVID-19 coronavirus disease 2019

This article is protected by copyright. All rights reserved

SARS	Severe Acute Respiratory Syndrome
CDC	Centers for Disease Control and Prevention
ICU	intensive care unit
MERS	Middle East Respiratory Syndrome
ACE	angiotensin converting enzyme
ULN	upper limit of normal
FDA	Food and Drug Administration
HCC	hepatocellular carcinoma
PPE	personal protective equipment
MELD	model for end-stage liver disease
CMS	Centers for Medicare and Medicaid Services
ARB	angiotensin receptor blocker

Financial Support:

OKF: None

BH: Research Support: Gilead, Intervept, Genfit, Salix; Advisory Boards: Gilead, Surrozen

RJF: Grant Funding: Abbvie, Gilead; Consulting Services: Sanofi

RMK: None

BMM: None

DCM: None

DSP: None

MWR: None

MLS: None

ECV: Advisory Boards: Gilead; Grant Support: Salix

RL: Consultant/Advisory Boards: 89bio, Alnylam, Arrowhead Pharmaceuticals, AstraZeneca, Boehringer Ingelheim, Bristol-Myer Squibb, Celgene, Cirius, CohBar, DiCerna, Galmed, Gemphire, Gilead, Glympse bio, Intercept, Ionis, Merck, Metacrine, NGM Biopharmaceuticals, Novo Nordisk, Pfizer, Sagimet, Viking Therapeutics; Grant Support (paid to UCSD): Allergan, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly and Company, Galmed Pharmaceuticals, Genfit, Gilead, Intercept, Janssen, Madrigal Pharmaceuticals, NGM Biopharmaceuticals, Novartis, Pfizer, pH Pharma, Siemens; Co-founder:

This article is protected by copyright. All rights reserved

Accepted Article

Liponexus, Inc; Funding Support: NIEHS (5P42ES010337), NCATS (5UL1TR001442), NIDDK (R01DK106419, 1R01DK121378, P30DK120515), and DOD PRCRP (CA170674P2)

DEC: Leadership in Related Society: Board, Committee, Journal: AASLD - editor; Data Safety Monitoring Board for Industry or Commercial Enterprise: Aegerion, Esperion, Alnylam; Scientific Consultant/Advisor to Industry or Commercial Enterprise, including Development of Educational Presentations: Relburn Metabolomics, Intercept, Surrozen

JAB: None

KRR: Advisory Boards: Mallinckrodt, Merck, Gilead; Research Support (paid to the University of Pennsylvania): Intercept, Bristol-Myer Squibb, Mallinckrodt, Exact Sciences, Grifols, Sequana; Data Safety Monitoring Board for Industry or Commercial Enterprise: Novartis

RTC: Grant Support (paid to MGH): Gilead, Merck, Bristol-Myers Squibb, Boehringer-Ingelheim, Janssen, Roche

Author Contributions:

OKF: Conceptualization, Project Administration, Visualization, Writing – original draft, Writing – review & editing

BH: Conceptualization, Writing – original draft, Writing – review & editing

RJF: Conceptualization, Writing – original draft, Writing – review & editing

RMK: Conceptualization, Writing – original draft, Writing – review & editing

BMM: Writing – original draft, Writing – review & editing

DCM: Writing – original draft, Writing – review & editing

DSP: Writing – original draft, Writing – review & editing

MWR: Writing – original draft, Writing – review & editing

MLS: Writing – original draft, Writing – review & editing

ECV: Writing – review & editing

RL: Writing – review & editing

DEC: Writing – review & editing

JAB: Conceptualization, Supervision, Writing – original draft, Writing – review & editing

KRR: Conceptualization, Supervision, Writing – original draft, Writing – review & editing

RTC: Conceptualization, Supervision, Writing – original draft, Writing – review & editing

Accepted Article

This article is protected by copyright. All rights reserved

Accepted Article

Acknowledgments: The authors would like to acknowledge the AASLD Governing Board for their contributions to and support of this paper: Jorge A. Bezerra, Cincinnati Children's Hospital; Raymond T. Chung, MD, FAASLD, Massachusetts General Hospital; Michael W. Fried, MD, FAASLD, University of North Carolina at Chapel Hill; Meena G. Bansal, MD, FAASLD, Icahn School of Medicine at Mount Sinai; Vijay H. Shah, MD, FAASLD, Mayo Clinic Rochester; Laurie D. DeLeve, MD, PhD, FAASLD, University of Southern California; Norah Terrault, MD, MPH, FAASLD, Keck Medical Center of University of Southern California; W. Ray Kim, MD, FAASLD, Stanford University Medical Center; John R. Lake, MD, FAASLD, University of Minnesota; Mary E. McCarthy Rinella, MD, FAASLD, Northwestern University Feinberg School of Medicine; David C. Mulligan, Yale University.

This article is protected by copyright. All rights reserved

Accepted Article

Abstract

Coronavirus disease 2019 (COVID-19), the illness caused by the SARS-CoV-2 virus, is rapidly spreading throughout the world. Hospitals and healthcare providers are preparing for the anticipated surge in critically ill patients but few are wholly equipped to manage this new disease. 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. 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.

This article is protected by copyright. All rights reserved

Accepted Article

An earlier version of this document was first posted online on March 23, 2020 at https://www.aasld.org/about-aasld/covid-19-resources and will continue to be updated.

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) If we do not contain the spread of SARS-CoV-2 quickly, our healthcare system's capacity will be overwhelmed, including insufficient availability of intensive care unit (ICU) beds, ventilators, and healthcare workers.

This article is protected by copyright. All rights reserved

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

The novel coronavirus SARS-CoV-2 is most similar to the beta-coronaviruses, SARS-CoV and MERS-CoV, the causative agents of the SARS outbreak in 2002-2003 and the MERS outbreak beginning in 2012, respectively. SARS-CoV-2 is a single, positive-stranded RNA virus that replicates using a virally encoded RNA-dependent RNA polymerase. SARS-CoV-2 binds to and is internalized into target cells through angiotensin-converting enzyme 2 (ACE2), which acts as a functional receptor.(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) AST and ALT are primarily elevated in COVID-19, generally 1-2 times the upper limit of normal (ULN), with normal to modestly elevated total bilirubin levels early in the disease process. Liver injury occurs more commonly in severe COVID-19 cases than in mild cases, and rare cases of severe acute hepatitis have been described.(11,15,16) Liver injury in mild COVID-19 cases is usually transient and does not require specific treatment.(15) In addition to other markers of disease severity such as lymphopenia and D-dimer, low serum albumin on hospital admission is a marker of COVID-19 severity.(14,17,18)

Severe COVID-19 is uncommon in children.(19,20) In the rare cases of severe pediatric COVID-19, increases in ALT or AST, when present, are usually mild (<2x ULN).(19) Data from Bergamo, a major site of COVID-19 in Italy, showed no increase in hospitalization among >300 children followed for liver transplantation, autoimmune hepatitis, or hepatoblastoma.(20) In this report, 3 of 13 hospitalized children following liver transplantation or receiving chemotherapy for hepatoblastoma tested positive for SARS-CoV-2 and none developed clinical pulmonary disease.(20)

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.(21,22) Elevated liver biochemistries may reflect a direct virus-induced cytopathic effect and/or immune damage from the provoked inflammatory response.(12,23) Therapeutic agents used to manage symptomatic COVID-19 may be hepatotoxic, including remdesivir and tocilizumab. Less common causes of elevated liver biochemistries include chloroquine, hydroxychloroquine, and azithromycin.

This article is protected by copyright. All rights reserved

Accepted Article

It is unknown whether patients with chronic liver disease, especially viral hepatitis B and/or C, are 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) Emerging data suggest that patients with nonalcoholic fatty liver disease (NAFLD) may be at higher risk for severe COVID-19.(24) 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.(25)

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.(15,21) 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 should be considered to be 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.

Accepted Article

This article is protected by copyright. All rights reserved

- 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.(19)
- 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.

Stable Outpatients with Liver Disease and/or Hepatocellular Carcinoma

Information is limited regarding the effects of SARS-CoV-2 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 health conditions, showed that approximately one third of these patients (37.6%) had at least one underlying condition or risk factor for severe outcomes.(26) Among these patients with underlying conditions, only 41 patients (0.6%) had chronic liver disease, including 7 who required ICU admission.(26)

Both immunocompetent and immunosuppressed patients can contribute to SARS-CoV-2 spread even if they are asymptomatic.(27) Children are less likely to become ill from SARS-CoV-2 infection but can still contribute to spread of the virus.(19) 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)

The effect of COVID-19 in patients with hepatocellular carcinoma (HCC) is not known. A case series reported an association between worse COVID-19 outcomes and a history of non-hepatic types of cancer.(28) Those who underwent recent chemotherapy had an even higher risk of severe COVID-19, but the series also included those without recent chemotherapy.(28) It is unknown whether patients with HCC are at increased risk for severe COVID-19 by virtue of their malignancy. 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.(29)

Accepted Article

This article is protected by copyright. All rights reserved

Accepted Article

Recommendations

- The CDC has provided broad and comprehensive recommendations to limit face-to-face visits, optimize supply of personal protective equipment (PPE), clean and disinfect rooms or areas visited by individuals with suspected or confirmed COVID-19, and monitor healthcare workers for signs of illness.(3,30)
    - 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).
- 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.
- 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 patient 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

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

This article is protected by copyright. All rights reserved

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

- 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.(31)
- 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 using medication delivery services.
- 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.

Accepted Article

This article is protected by copyright. All rights reserved

- Consider using specific screening facilities and a "COVID-19-free" path through the hospital for transplantation candidates.
- 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

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 (**Table 1**). 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").(32)

Insufficient data regarding viral transmission of SARS-CoV-2 from organ donors are available at this time, but currently most Organ Procurement Organizations are testing donors for SARS-CoV-2 RNA, and those who test positive are medically ineligible for organ donation.(33) Based on center capability, testing for SARS-CoV-2 should be considered in all recipients prior to transplant; however, the capacity to test recipients shortly before proceeding with transplant may be limited and can add additional logistical hurdles. 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").(32)

This article is protected by copyright. All rights reserved

Accepted Article

Accepted Article

    - 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 may be limited or prohibited during their hospital stay.
- Screen potential donors for exposure and clinical symptoms/fever compatible with COVID-19 (regardless of test results or availability).(34)
    - 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 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.(34)
- See the latest updates regarding COVID-19 related OPTN policy changes.(31)
- An approach to liver transplant organ offers is shown in **Figure 2**.

This article is protected by copyright. All rights reserved

Accepted Article

Post-Liver-Transplant Patients

Data suggest that the immune response may be the main driver for pulmonary injury due to COVID-19 and that immunosuppression may be protective.(13,20) Posttransplant immunosuppression was not a risk factor for mortality associated with SARS (2002-2003) or MERS (2012-present).(20) 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.(25) Immunosuppression may prolong viral shedding in posttransplant patients with COVID-19.(34,35)

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.(34)
- Minimize in-person visits for posttransplant patients by more frequent telephone communication and 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

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.(36) 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.(37) 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.

This article is protected by copyright. All rights reserved

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

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

- 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.

Accepted Article

This article is protected by copyright. All rights reserved

Accepted Article

- Limit the personnel permitted to enter patient rooms to the minimum needed for the performance of consultative care.
- Discourage in-person multidisciplinary rounds with dietary, pharmacy, social work, and care coordination staff.
- 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.
- 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.

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

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.(38) 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.

This article is protected by copyright. All rights reserved

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.(39,40) Remdesivir is being tested in hospitalized patients with moderate to severe COVID-19 in randomized controlled trials and data from compassionate use have reported promising results.(41–43) 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*.(44) 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.(45) 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.(46)

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.(47) 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.(48,49) 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.(50)

Treatment with ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) results in upregulation of ACE2, the target for SARS-CoV-2 entry into cells.(51) 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-CoV, but to date there are no data in SARS-CoV-2 or in humans.(52) 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.(53)

This article is protected by copyright. All rights reserved

Accepted Article

Recommendations

- Monitor studies of antiviral and immunomodulatory approaches to COVID-19 at National Institutes of Health's (NIH) 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 ≤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.(54)
- Consult the University of Liverpool Drug Interactions Group document on Interactions with Experimental COVID-19 Therapies.(55)

Procedures

There is potential for fecal-oral SARS-CoV-2 transmission,(1,4,6,23,43) and the virus is detected in saliva.(1,23,56) Multiple societies have strongly recommended rescheduling non-urgent procedures. The Joint Gastroenterology Societies recommend to "strongly consider rescheduling non-urgent endoscopic procedures", and CMS, the US Surgeon General, and the American College of Surgeons recommend postponing elective surgeries.(32,57–59)

Endoscopic procedures should be considered aerosol-generating.(60) 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.(60) To further 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.(61,62)

Recommendations

- Cancel all elective/non-urgent procedures (e.g., endoscopy, liver biopsy, transient elastography).(60)

This article is protected by copyright. All rights reserved

- 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).

Research

During this unprecedented time, much of clinical and basic science research not directly related to COVID-19 has come to a standstill. Due to quarantine-related travel restrictions and potential supply chain interruptions, the FDA and NIH have posted guidance documents to advise on the conduct of clinical trials during the COVID-19 pandemic.(63,64)

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.

Accepted Article

This article is protected by copyright. All rights reserved

Accepted Article

- 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

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. The Accreditation Council for Graduate Medical Education has suspended some activities during the COVID-19 pandemic; however, requirements for adequate resources and training, adequate supervision, and work hour limitations have not changed.(65,66)

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.

This article is protected by copyright. All rights reserved

- 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.

Conclusion

The COVID-19 pandemic has profoundly strained healthcare resources around the world. Minimizing the risk of patient and healthcare worker exposure has been central to our efforts to mitigate the impact of the disease on our ability to continue to provide adequate care to our patients. Growing clinical experience with COVID-19 evaluation and management has identified subsets of patients who may be at higher risk for a more severe disease course. The pandemic has affected patients awaiting liver transplantation due to limited transplant center institutional resources and the possibility of donor-derived infection, which has resulted in longer waiting times. This article provides clinicians caring for patients with chronic liver disease with guidance for how to minimize the impact of the COVID-19 pandemic on their patients' care. The situation is evolving rapidly and these recommendations will need to evolve as well. As we learn more about how the COVID-19 pandemic impacts the care of patients with liver disease, we will update the online document available at https://www.aasld.org/about-aasld/covid-19-resources.

Accepted Article

This article is protected by copyright. All rights reserved

Accepted Article

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

This article is protected by copyright. All rights reserved

Accepted Article

References

1. Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020 February 28. doi: 10.1056/NEJMoa2002032. [Epub ahead of print]

2. Chopra V, Toner E, Waldhorn R, Washer L. How should U.S. hospitals prepare for Coronavirus Disease 2019 (COVID-19)? Ann Intern Med 2020 March 11. doi: 10.7326/M20-0907. [Epub ahead of print]

3. Centers for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19): Cleaning and disinfection for community facilities. Published February 11, 2020. https://www.cdc.gov/coronavirus/2019-ncov/community/organizations/cleaning-disinfection.html. Accessed April 2020.

4. Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for gastrointestinal infection of SARS-CoV-2. Gastroenterology 2020 April. doi: 10.1053/j.gastro.2020.02.055. [Epub ahead of print]

5. Wu Y, Guo C, Tang L, Hong Z, Zhou J, Dong X, et al. Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. Lancet Gastroenterol Hepatol 2020 March 19. doi: 10.1016/S2468-1253(20)30083-2. [Epub ahead of print]

6. Chen C, Gao G, Xu Y, Pu L, Wang Q, Wang L, et al. SARS-CoV-2-positive sputum and feces after conversion of pharyngeal samples in patients with COVID-19. Ann Intern Med 2020 March 30. doi: 10.7326/M20-0991. [Epub ahead of print]

7. Remuzzi A, Remuzzi G. COVID-19 and Italy: What next? Lancet 2020 March 13. doi: 10.1016/S0140-6736(20)30627-9. [Epub ahead of print]

8. Lan J, Ge J, Yu J, Shan S, Zhou H, Fan S, et al. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. Nature 2020 March 30. doi: 10.1038/s41586-020-2180-5. [Epub ahead of print]

9. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003 November 27;426:450–454.

This article is protected by copyright. All rights reserved

Accepted Article

10. Chai X, Hu L, Zhang Y, Han W, Lu Z, Ke A, et al. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. BioRxiv 2020 February 4. doi: 10.1101/2020.02.03.931766. [Epub ahead of print]

11. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet 2020 15;395:507–513.

12. Fan Z, Chen L, Li J, Tian C, Zhang Y, Huang S, et al. Clinical features of COVID-19 related liver damage. MedRxiv 2020 February 28. doi: 10.1101/2020.02.26.20026971. [Epub ahead of print]

13. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020 15;395:497–506.

14. Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. Liver Int 2020 March 14. doi: 10.1111/liv.14435. [Epub ahead of print]

15. Zhang C, Shi L, Wang F-S. Liver injury in COVID-19: Management and challenges. Lancet Gastroenterol Hepatol 2020 March 4. doi: 10.1016/S2468-1253(20)30057-1. [Epub ahead of print]

16. Wander P, Epstein M, Bernstein D. COVID-19 presenting as acute hepatitis. Am J Gastroenterol. Published April 2020. https://journals.lww.com/ajg/Documents/COVID19_Bernstein_et_al_AJG_Preproof.pdf. Accessed April 2020.

17. Liu W, Tao Z-W, Lei W, Ming-Li Y, Kui L, Ling Z, et al. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Chin Med J 2020 February 28. doi: 10.1097/CM9.0000000000000775. [Epub ahead of print]

18. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020 February 7. doi: 10.1001/jama.2020.1585. [Epub ahead of print]

19. Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al. SARS-CoV-2 infection in children. N Engl J Med 2020 March 18. doi: 10.1056/NEJMc2005073. [Epub ahead of print]

This article is protected by copyright. All rights reserved

Accepted Article

20. D'Antiga L. Coronaviruses and immunosuppressed patients. The facts during the third epidemic. Liver Transpl 2020 March 20. doi: 10.1002/lt.25756. [Epub ahead of print]

21. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020 April;8:420–422.

22. Yao XH, Li TY, He ZC, Ping YF, Liu HW, Yu SC, et al. [A pathological report of three COVID-19 cases by minimally invasive autopsies]. Zhonghua Bing Li Xue Za Zhi 2020 March 15;49. doi: 10.3760/cma.j.cn112151-20200312-00193. [Epub ahead of print]

23. Gu J, Han B, Wang J. COVID-19: Gastrointestinal manifestations and potential fecal-oral transmission. Gastroenterology 2020 March 3. doi: 10.1053/j.gastro.2020.02.054. [Epub ahead of print]

24. Ji D, c E, Xu J, Zhang D, Cheng G, Wang Y, et al. Implication of non-alcoholic fatty liver diseases (NAFLD) in patients with COVID-19: A preliminary analysis. Journal of Hepatology 2020 April. doi: 10.1016/j.jhep.2020.03.044. [Epub ahead of print]

25. Centers for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19): Groups at higher risk for severe illness. Published February 11, 2020. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/groups-at-higher-risk.html. Accessed April 2020.

26. Centers for Disease Control and Prevention. Preliminary estimates of the prevalence of selected underlying health conditions among patients with Coronavirus Disease 2019 - United States, February 12–March 28, 2020. MMWR Morb Mortal Wkly Rep 2020 April 3;69:382–386.

27. Bai Y, Yao L, Wei T, Tian F, Jin D-Y, Chen L, et al. Presumed asymptomatic carrier transmission of COVID-19. JAMA 2020 February 21. doi: 10.1001/jama.2020.2565. [Epub ahead of print]

28. Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: A nationwide analysis in China. Lancet Oncol 2020 March;21:335–337.

29. Rich NE, John BV, Parikh ND, Rowe I, Mehta N, Khatri G, et al. Hepatocellular carcinoma demonstrates heterogeneous growth patterns in a multi-center cohort of patients with cirrhosis. Hepatology 2020 February 4. doi: 10.1002/hep.31159. [Epub ahead of print]

This article is protected by copyright. All rights reserved

Accepted Article

30. Centers for Disease Control and Prevention. Interim guidance for healthcare facilities: Preparing for community transmission of COVID-19 in the United States. Published February 11, 2020. https://www.cdc.gov/coronavirus/2019-ncov/healthcare-facilities/guidance-hcf.html. Accessed April 2020.

31. United Network for Organ Sharing. COVID-19 and solid organ transplant. https://unos.org/covid. Accessed April 2020.

32. Centers for Medicare and Medicaid Services. Non-emergent, elective medical services, and treatment recommendations. https://www.cms.gov/files/document/31820-cms-adult-elective-surgery-and-procedures-recommendations.pdf. Accessed April 2020.

33. Association of Organ Procurement Organizations. COVID-19 (coronavirus) bulletin. Published March 26, 2020. https://www.aopo.org/information-about-covid-19-coronavirus-is-being-released-rapidly-we-will-post-updates-as-we-receive-them. Accessed April 2020.

34. American Society of Transplantation. 2019-nCoV (Coronavirus): FAQs for organ donation and transplantation. Published March 20, 2020. https://www.myast.org/sites/default/files/COVID19%20FAQ%20Tx%20Centers%2003.20.2020-FINAL.pdf. Accessed April 2020.

35. Qin J, Wang H, Qin X, Zhang P, Zhu L, Cai J, et al. Perioperative presentation of COVID-19 disease in a liver transplant recipient. Hepatology 2020 March 27. doi: 10.1002/hep.31257. [Epub ahead of print]

36. Gong J, Dong H, Xia Q, Huang Z, Wang D, Zhao Y, et al. Correlation analysis between disease severity and inflammation-related parameters in patients with COVID-19 pneumonia. MedRxiv 2020 February 27. doi: 10.1101/2020.02.25.20025643. [Epub ahead of print]

37. World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: Interim guidance. Published March 13, 2020. https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected. Accessed April 2020.

This article is protected by copyright. All rights reserved

Accepted Article

38. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. N Engl J Med 2020 March 18. doi: 10.1056/NEJMoa2001282. [Epub ahead of print]

39. Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med 2017 June 28;9:eaal3653.

40. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020 March;30:269–271.

41. Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Discov 2020;19:149–150.

42. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate use of remdesivir for patients with severe Covid-19. N Engl J Med 2020 April 10. doi: 10.1056/NEJMoa2007016. [Epub ahead of print]

43. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med 2020 05;382:929–936.

44. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis 2020 March 9. doi: 10.1093/cid/ciaa237. [Epub ahead of print]

45. Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020 March 20. doi: 10.1016/j.ijantimicag.2020.105949. [Epub ahead of print]

46. Molina J, Delaugerre C, Goff J, Mela-Lima B, Ponscarme D, Goldwirt L, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. Med Mal Infect 2020 March 30. doi: 10.1016/j.medmal.2020.03.006. [Epub ahead of print]

This article is protected by copyright. All rights reserved

Accepted Article

47. Federal Laboratory Consortium. CDC warns against using nonpharmaceutical chloroquine phosphate. Published March 30, 2020. https://federallabs.org/news/cdc-warns-against-using-nonpharmaceutical-chloroquine-phosphate. Accessed April 2020.

48. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA 2020 March 27. doi: 10.1001/jama.2020.4783. [Epub ahead of print]

49. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci USA 2020 April 6. doi: 10.1073/pnas.2004168117. [Epub ahead of print]

50. US Food and Drug Administration. Revised information for investigational COVID-19 convalescent plasma. Published April 3, 2020. https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/revised-information-investigational-covid-19-convalescent-plasma. Accessed April 2020.

51. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med 2020 April;8:e21.

52. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med 2005 August;11:875–879.

53. de Simone G. Position statement of the ESC Council on Hypertension on ACE-inhibitors and angiotensin receptor blockers. Published March 13, 2020. https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang. Accessed April 2020.

54. AFP. Updated: WHO now doesn't recommend avoiding ibuprofen for COVID-19 symptoms. Published March 18, 2020. https://www.sciencealert.com/who-recommends-to-avoid-taking-ibuprofen-for-covid-19-symptoms/amp. Accessed April 2020.

55. Liverpool Drug Interaction Group. Liverpool COVID-19 interactions. Published April 3, 2020. https://www.covid19-druginteractions.org. Accessed April 2020.

This article is protected by copyright. All rights reserved

Accepted Article

56. To KK-W, Tsang OT-Y, Chik-Yan Yip C, Chan K-H, Wu T-C, Chan JMC, et al. Consistent detection of 2019 novel coronavirus in saliva. Clin Infect Dis 2020 February 12. doi: 10.1093/cid/ciaa149. [Epub ahead of print]

57. Joint Gastroenterology Societies. Joint GI Society message: COVID-19 clinical insights for our community of gastroenterologists and gastroenterology care providers. Published March 15, 2020. https://www.aasld.org/about-aasld/media/joint-gi-society-message-covid-19-clinical-insights-our-community. Accessed April 2020.

58. Luthi S. Surgeon General advises hospitals to cancel elective surgeries. Politico. Published March 14, 2020. https://www.politico.com/news/2020/03/14/surgeon-general-elective-surgeries-coronavirus-129405. Accessed April 2020.

59. American College of Surgeons. COVID-19: Recommendations for management of elective surgical procedures. Published March 13, 2020. https://www.facs.org/covid-19/clinical-guidance/elective-surgery. Accessed April 2020.

60. Soetikno R, Teoh AYB, Kaltenbach T, Lau JYW, Asokkumar R, Cabral-Prodigalidad P, et al. Considerations in performing endoscopy during the COVID-19 pandemic. Gastrointest Endosc 2020 March 27. doi: 10.1016/j.gie.2020.03.3758. [Epub ahead of print]

61. Sultan S, Lim J, Altayar O, Davitkov P, Feuerstein J, Siddique S, et al. AGA Institute rapid recommendations for gastrointestinal procedures during the COVID-19 pandemic. Gastroenterology 2020 March 31. doi: 10.1053/j.gastro.2020.03.072. [Epub ahead of print]

62. Joint Gastroenterology Societies. Joint Gastroenterology Society message: COVID-19 use of personal protective equipment in GI endoscopy. https://www.aasld.org/sites/default/files/2020-04/JointSocietyMessage-PersonalProtectiveEquipmentInGIEndoscopy.pdf. Accessed April 2020.

63. Food and Drug Administration. FDA guidance on conduct of clinical trials of medical products during COVID-19 pandemic: Guidance for industry, investigators, and institutional review boards. Published April 2, 2020. https://www.fda.gov/media/136238/download. Accessed April 2020.

This article is protected by copyright. All rights reserved

Accepted Article

64. National Institutes of Health. Guidance for NIH-funded clinical trials and human subjects studies affected by COVID-19. Published March 16, 2020. https://grants.nih.gov/grants/guide/notice-files/NOT-OD-20-087.html. Accessed April 2020.

65. Nasca TJ. ACGME response to the coronavirus (COVID-19). Published March 18, 2020. https://acgme.org/Newsroom/Newsroom-Details/ArticleID/10111/ACGME-Response-to-the-Coronavirus-COVID-19. Accessed April 2020.

66. Accreditation Council for Graduate Medical Education. ACGME response to pandemic crisis. https://acgme.org/COVID-19. Accessed April 2020.

This article is protected by copyright. All rights reserved

Figure Legends

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

Figure 2. Approach to Liver Transplant Organ Offers.

ICU, intensive care unit; PPE, personal protective equipment.

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

Accepted Article

This article is protected by copyright. All rights reserved

Table 1. 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.(20) Nevertheless, immunosuppressed patients have higher viral titers and may be more infectious than immunocompetent individuals.(34)
- CMS has clarified that transplants fall into Tier 3b and should not be postponed.(32)
- 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)

Accepted Article

This article is protected by copyright. All rights reserved

Accepted Article

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:*	FDA-approved for lupus/rheumatoid arthritis/malaria Available as emergency use

This article is protected by copyright. All rights reserved

Accepted Article

			QTc >415 ms Cardiomyopathy G6PD deficiency	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

This article is protected by copyright. All rights reserved

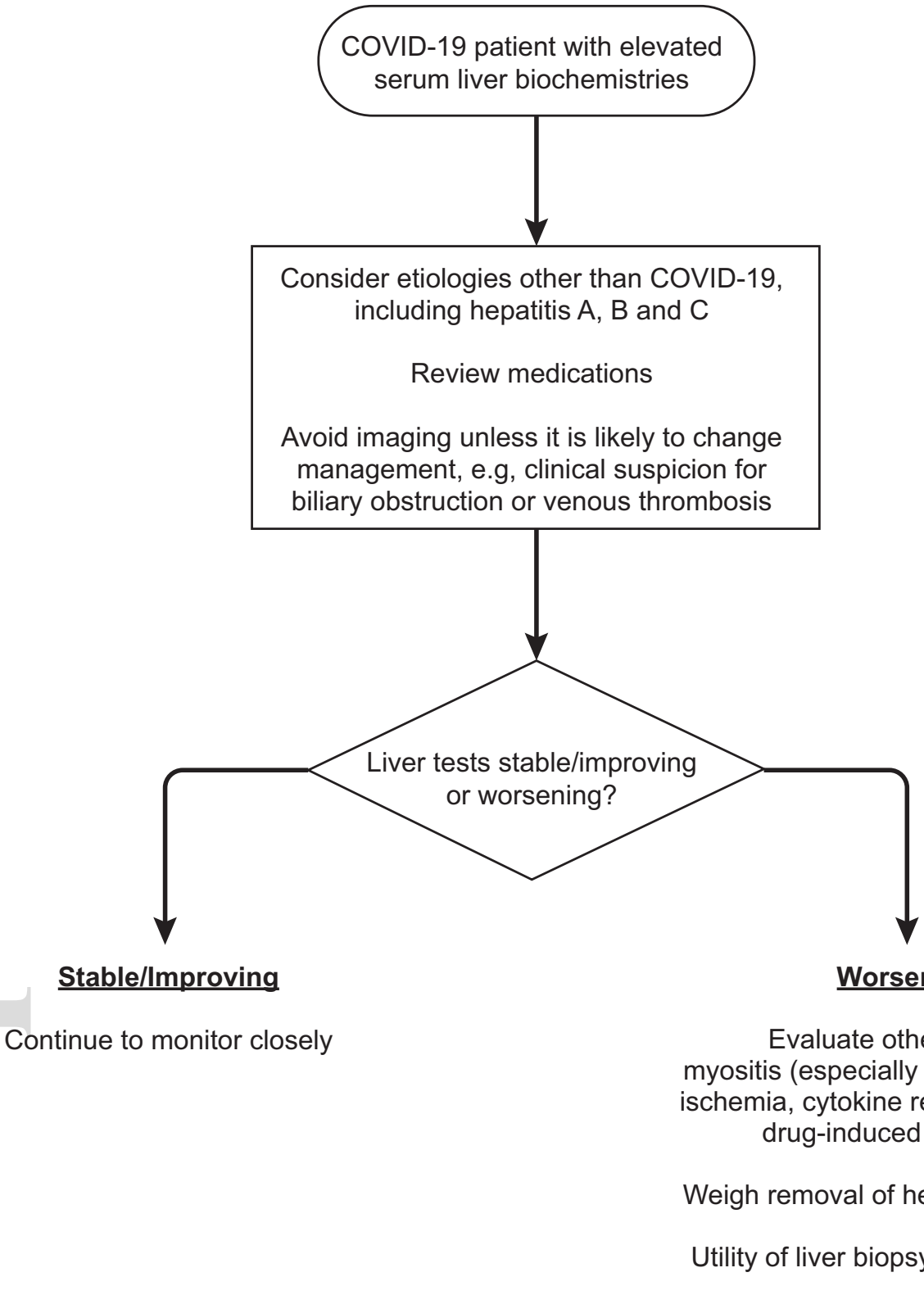
Accepted Article

	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

This article is protected by copyright. All rights reserved

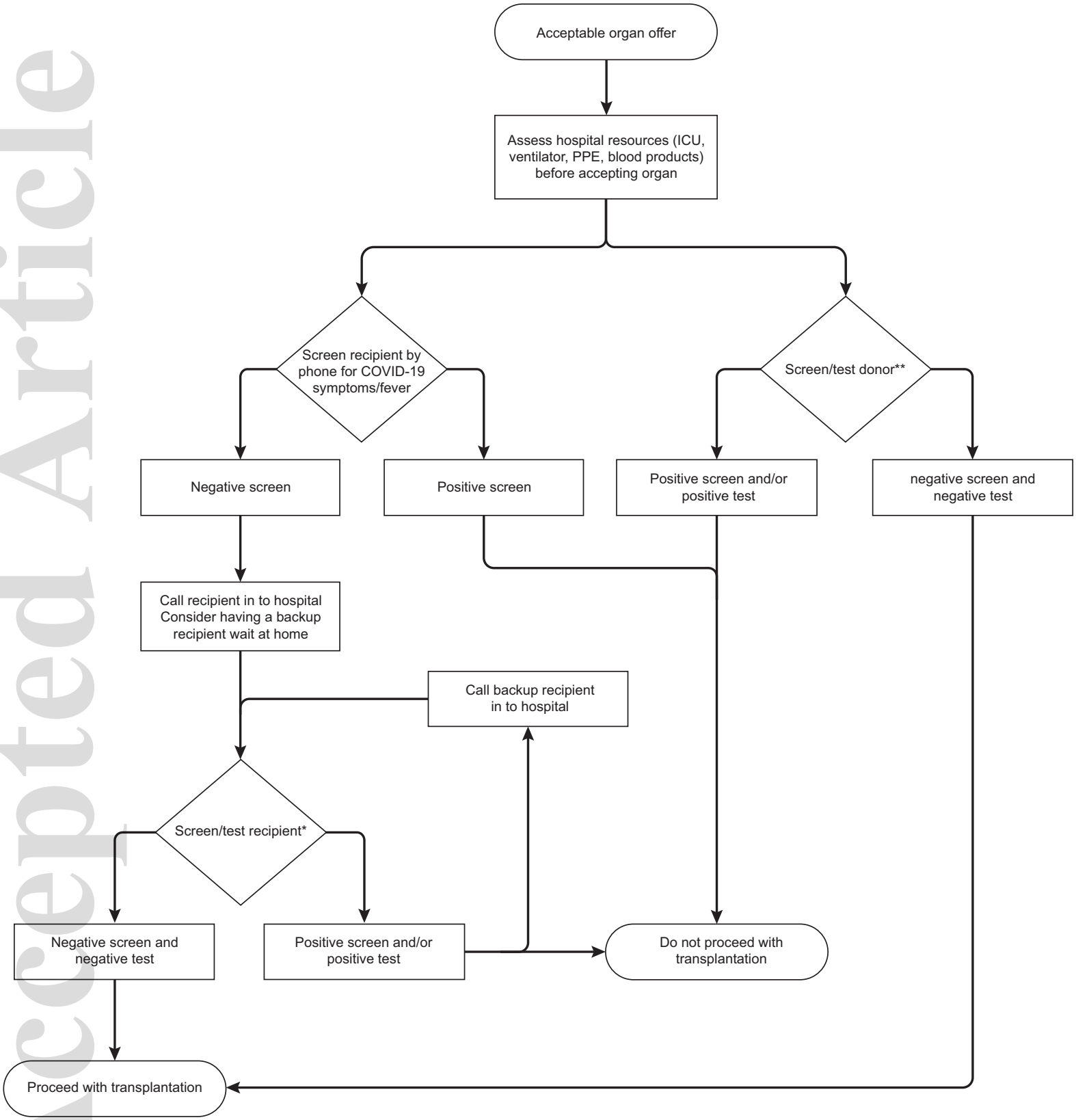
Accepted Article



hep_31281_f1.eps

This article is protected by copyright. All rights reserved

Accepted Article



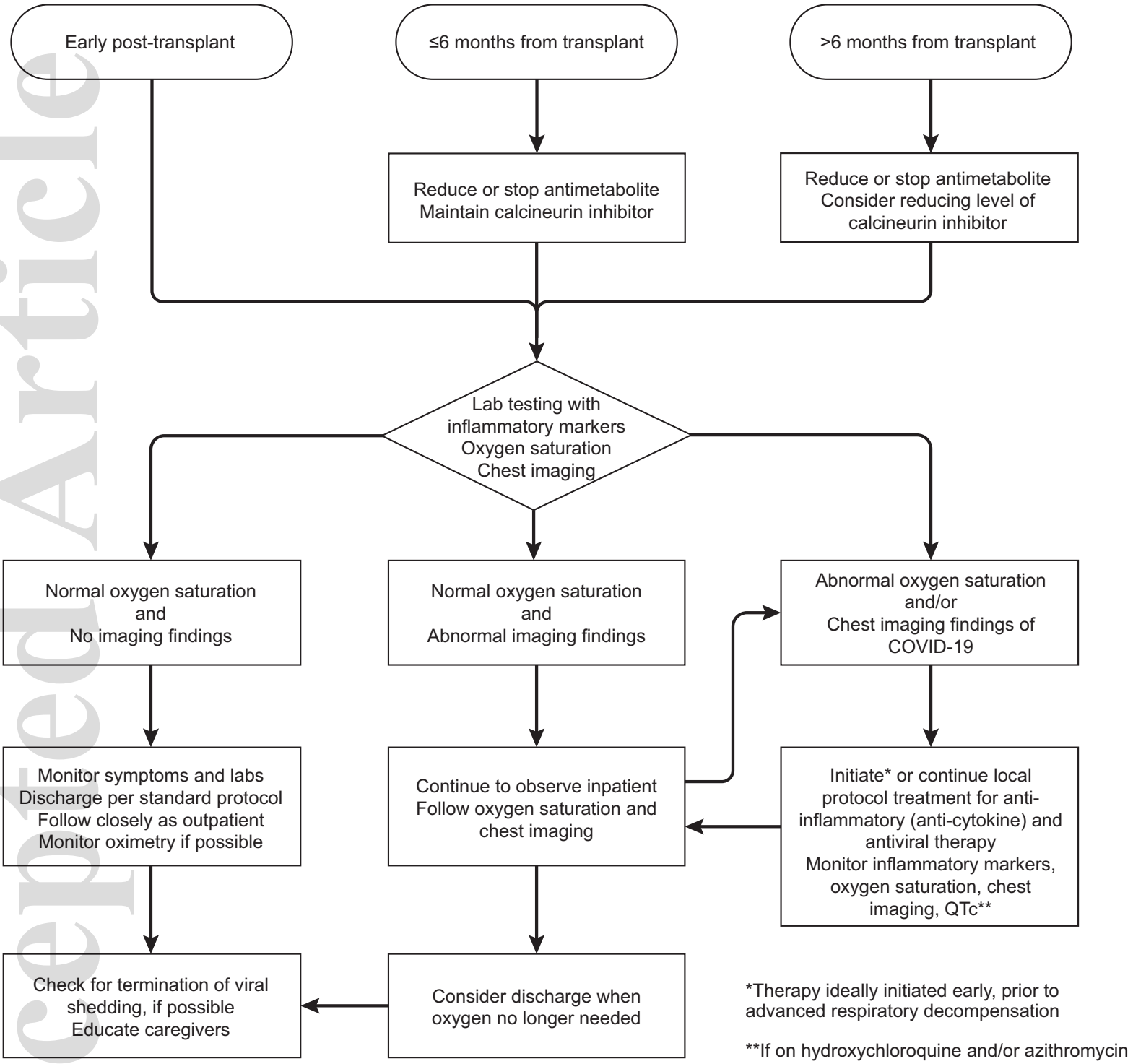
*Recipient screening: Screen recipient on arrival for COVID-19 symptoms/fever
Test recipient for SARS-CoV-2, if available

**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

This article is protected by copyright. All rights reserved

hep_31281_f2.eps

Accepted Article



hep_31281_f3.eps

This article is protected by copyright. All rights reserved