Major Updates to COVID-19 Expert Panel Consensus Statement

11/9/2020

- Coronavirus particles have been identified in the cytoplasm of hepatocytes associated with typical histological evidence of viral infection.
- An American autopsy series demonstrated histologic findings of macrovesicular steatosis, mild acute hepatitis (lobular necroinflammation) and mild portal inflammation. In addition, SARS-CoV-2 viral RNA was detectable by PCR in 55% of liver samples that were interrogated.
- On August 15, 2020, the FDA issued an Emergency Use Authorization for a rapid saliva-based test for the detection of SARS-CoV-2.
- Reinfection by a phylogenetically distinct strain of SARS-CoV-2 has been demonstrated in humans, suggesting that SARS-CoV-2 may continue to circulate despite herd immunity due to natural infection.
- In a multicenter study of inpatients with cirrhosis+COVID-19 compared with age/gender-matched patients with COVID-19 alone and cirrhosis alone, patients with cirrhosis and COVID-19 had a higher risk of death compared to patients with COVID-19 alone, but not significantly higher than the risk of death from cirrhosis alone without COVID-19.
- Despite an initial decrease in liver transplantations at the onset of the COVID-19 pandemic, particularly in living donor liver transplantations, liver transplant volumes in the US have since rebounded to 2019 levels.
- Transplantation in SARS-CoV-2-positive transplant candidates is currently not routinely recommended until at least 14 days after clinical recovery.
  - Limited data suggest there is a significant increase in postoperative morbidity and mortality related to SARS-CoV-2 infection, and for emergent surgery in particular.
  - The risks of emergent liver transplantation for patients with acute liver failure who test positive for SARS-CoV-2 are not known.
  - Ideally, transplantation in SARS-CoV-2-positive transplant candidates should be delayed for at least 14-21 days after symptom resolution and 1 or 2 negative SARS-CoV-2 diagnostic tests.
  - The decision to proceed with transplantation in a SARS-CoV-2-positive candidate must be individualized based on several factors including the urgency of transplantation, the presence of respiratory symptoms, and the risk of exposing transplant personnel to SARS-CoV-2.
- The Scientific Registry of Transplant Recipients (SRTR) will be modifying the evaluation metrics for transplant programs and organ procurement organizations (OPOs) and has recommended to remove any patient and donor data from the performance metrics following the declaration of a national emergency on March 13, 2020.
- Several studies have shown a mortality benefit with the use of corticosteroids for the treatment of critically ill patients with COVID-19.
• A prospective study of 111 liver transplant recipients with COVID-19 from Spain showed an increased risk of acquiring SARS-CoV-2 (almost double the rate in the age/gender matched general population) but lower mortality rates than the matched general population.

• 151 liver transplant recipients were described in an analysis of two combined international COVID-19 reporting registries (COVID-Hep and Secure-Cirrhosis).
  
  o In propensity score-matched analysis comparing liver transplant recipients to non-transplant recipients, liver transplant status did not significantly increase the risk of death in patients with SARS-CoV-2 infection.

• Data from the US multicenter COLD consortium of 112 liver transplant recipients were also recently reported.
  
  o The risk of death was not higher among liver transplant recipients compared to controls with chronic liver disease.

• The NIH COVID-19 treatment guidelines recommend that oral corticosteroid therapy used prior to COVID-19 diagnosis for another underlying condition should not be discontinued.

• Remdesivir is currently the only FDA-approved therapy for the treatment of COVID-19.
  
  o The FDA approved remdesivir on October 22, 2020 for use in adult and pediatric patients >12 years of age and >40 kg with COVID-19 requiring hospitalization.
  
  o An Emergency Use Authorization for selected hospitalized pediatric patients <12 years of age and <40 kg remains in effect.
  
  o Remdesivir is recommended for the treatment of adult and pediatric patients >12 years of age who weigh >40 kg with COVID-19 requiring hospitalization.
  
  o Liver biochemistries should be checked in all patients prior to starting remdesivir and daily while receiving remdesivir.
  
  o Remdesivir should not be initiated in patients with ALT ≥5x ULN at baseline or in patients with an estimated glomerular filtration rate <30 mL/min.
  
  o Remdesivir should be discontinued in patients who develop ALT ≥10x ULN during treatment or ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR.
  
  o Remdesivir may be restarted when ALT is <5x ULN.
  
  o There are no studies of the pharmacokinetics of remdesivir in patients with hepatic impairment or cirrhosis.

• In a prospective meta-analysis of 7 randomized trials that included 1703 patients, 28-day all-cause mortality was lower among patients who received corticosteroids (dexamethasone, hydrocortisone, or methylprednisolone) compared with those who received usual care or placebo (summary odds ratio 0.66).
  
  o In a retrospective study from China of 20 patients with COVID-19 and untreated chronic hepatitis B, 3 patients who received corticosteroids or interferon alpha-1b experienced hepatitis B reactivation.
  
  o On the basis of the preliminary report from the RECOVERY Trial, the NIH and IDSA recommend using dexamethasone 6 mg po or IV daily for 10 days in patients with moderate-to-severe COVID-19 requiring mechanical ventilation or supplemental oxygen.
  
  o If dexamethasone is not available, the NIH recommends using equivalent daily doses of prednisone (40 mg), methylprednisolone (32 mg), or hydrocortisone (160 mg).
  
  o Prolonged use of systemic corticosteroids may increase the risk of hepatitis B reactivation and other latent infections including herpesviruses, strongyloides, and tuberculosis, and therefore appropriate screening and monitoring should be undertaken.
Dexamethasone is a moderate CYP3A4 inducer and potential impact on other CYP3A4 substrates such as calcineurin inhibitors should be considered.

- The IDSA and NIH recommend using tocilizumab only in the context of a clinical trial.
- A recently completed double-blind, placebo-controlled trial of a single dose of tocilizumab in 243 patients with severe COVID-19 failed to demonstrate any clinical or survival benefit.
- Sarulimab was not more effective than placebo in a recent randomized controlled trial and associated with more frequent AST and ALT elevations and is no longer under consideration for treatment of COVID-19.
- In the Phase 3 COVACTA trial, no differences in any primary or secondary outcomes were noted in 450 patients with severe COVID-19 who were randomized to tocilizumab vs. placebo.
- The available evidence does not currently support the use of drugs targeting the IL-6 pathway outside of clinical trials.
- Cocktails of monoclonal antibodies targeting the receptor binding domain of the spike protein and viral binding to the ACE2 receptor are being developed to treat COVID-19.
  - Preliminary results from an ongoing study in 799 treated patients demonstrated improvement in viral loads with different doses of the cocktail compared to placebo, particularly when given early to seronegative outpatients.
- Convalescent plasma transfusion was approved by the FDA under Emergency Use Authorization on August 23, 2020 for treating hospitalized patients with COVID-19.
  - Antibody levels in currently available COVID-19 convalescent plasma are highly variable and assays to measure them remain limited.
  - PLACID was an open-label, randomized controlled trial of convalescent plasma vs. standard of care that demonstrated no difference in progression to severe disease or survival.
  - Currently, the NIH and IDSA recommend that convalescent plasma should not be considered standard of care treatment for COVID-19 and that additional prospective, well-controlled, randomized trials are needed.
- Added a link to AASLD Patient Flyers under the Helpful Resources section.
- Updated Tables 1 and 2.

6/25/2020

- Additional changes reflecting the ramping up of routine and in-person clinical care, procedures, and clinical research
- A retrospective Italian study showing a high mortality rate (35%) in hospitalized patients with cirrhosis and COVID-19
- Inpatient mortality in patients with cirrhosis and COVID-19 may be similar to the mortality of patients with cirrhosis alone without COVID-19
- Another retrospective Italian report of 10 patients with autoimmune hepatitis on immunosuppression and with COVID-19 that suggests the course of COVID-19 may be similar to non-immunosuppressed patients
- Single-center and registry data of liver transplant recipients with COVID-19 suggesting that mortality may be associated with comorbidities and not to immunosuppression
- Results of the RECOVERY trial that demonstrated a significant mortality benefit from dexamethasone in patients receiving invasive mechanical ventilation or oxygen without invasive mechanical ventilation
• The FDA revoked the Emergency Use Authorization for chloroquine and hydroxychloroquine after determining they are unlikely to be effective in treating COVID-19
• Clearly identified preprint articles that have not been peer-reviewed

6/4/2020
• Data from two international registries showing that patients with chronic liver disease have a high mortality rate and mortality is associated with liver disease severity
• Revised recommendations for management of immunosuppression in patients with COVID-19
• Revised Procedures section to address reopening endoscopy centers to elective/non-urgent cases

5/14/2020
• Acknowledgement of possible link between COVID-19 and Kawasaki-like pediatric multisystem inflammatory syndrome
• Italian autopsy series describing involvement of hepatic vasculature including acute portal and sinusoidal thrombosis
• Introduction of SARS-CoV-2 antigen testing in addition to increasing availability of antibody testing
• OpenSAFELY study from the UK showing chronic liver disease is a risk factor for in-hospital death from COVID-19
• Large US study also showed that chronic liver disease and cirrhosis are associated with higher COVID-19 mortality
• Clarification that treatment of hepatitis B is not contraindicated in patients with or without COVID-19
• Recommendations regarding use of masks for patients and caregivers as well as providers in the clinic or hospital setting
• Evolving data on hydroxychloroquine suggesting it should no longer be used outside RCTs
• New data on triple therapy with lopinavir-ritonavir, ribavirin and interferon-beta-1b showing more rapid viral clearance compared to lopinavir-ritonavir (phase 2 RCT)
• Expanded section on reentry

5/4/2020
• Changed the title to match the Hepatology manuscript
• Edited the Overview and Rationale to acknowledge that the US is reaching the peak or past the peak in many communities
• Added to data on serological testing
• Briefly described a recent publication from the American Journal of Transplantation about 90 solid organ transplant recipients with COVID-19
• Included recommendations from the recent NIH COVID-19 Treatment Guidelines
• Discussed recently released results of trials and the FDA’s Emergency Use Authorization of remdesivir
• Added a new section titled "Reentry and Return to a Pre-Pandemic State" – this section will be further developed in future updates
4/16/2020

- Emerging data suggest that patients with NAFLD may be at higher risk for COVID-19
- Patients with chronic liver disease and transplant recipients are potentially at increased risk for severe COVID-19 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
  - Updated Figure 1
- Proceed with treatment of hepatitis B and C in patients without COVID-19 as clinically warranted
- 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
- Consider the following issues in hospitals with a high prevalence of COVID-19:
  - The risk of nosocomial transmission during the transplant admission
  - Difficulty obtaining procedures or other resources when complications arise
  - Limitations on family/caregiver visitation for a postoperative period that often relies on the engagement of caregivers
- Due to cancelations of elective/non-urgent endoscopy:
  - Consider, in the interim, primary prophylaxis with beta blocker therapy for patients with clinically significant portal hypertension or high risk of decompensation
- Data suggest that a surgical mask worn by infected individuals may reduce the risk of transmission (source control)
  - All healthcare workers should wear a surgical mask in patient care settings

4/7/2020

- New sections
  - Diagnosis of SARS-CoV-2 Infection
  - COVID-19 Liver Disease/Transplant Registries
- New tables
  - Diagnostic Methods for SARS-CoV-2 Detection
  - Investigational Treatments for COVID-19
- New figures
  - Approach to the Patient with COVID-19 and Elevated Serum Liver Biochemistries
  - Approach to Liver Transplant Organ Offers
  - Approach to the Liver Transplant Recipient with COVID-19
- Expanded “What We Know” sections
- Added virology of SARS-CoV-2
- Added liver histology in COVID-19
- Expanded COVID-19 symptoms for screening: sore throat, diarrhea, new loss of sense of taste or smell
- Expanded complications of COVID-19 complications when evaluating patients with elevated liver tests: myositis, cytokine release syndrome, ischemia/hypotension, DILI
- Clarified recommendations for treatment of patients with liver disease
- Recommend continue treatment for hepatitis B or C
- Consider delaying initiation of hepatitis C treatment
- Removed specific prednisone 10 mg recommendation to avoid confusion when tapering high-dose prednisone in patients with COVID-19
- Recommend initiating immunosuppressive therapy in patients with liver disease with or without COVID-19 who have strong indications for treatment (e.g., autoimmune hepatitis, graft rejection)
  - Clarified recommendations for monitoring patients with HCC and surveillance of patients at risk for HCC
  - Expanded section on Medication Management of Patients with COVID-19 to include new information about investigational agents
  - Revised PPE recommendations for endoscopic procedures to include N95 masks