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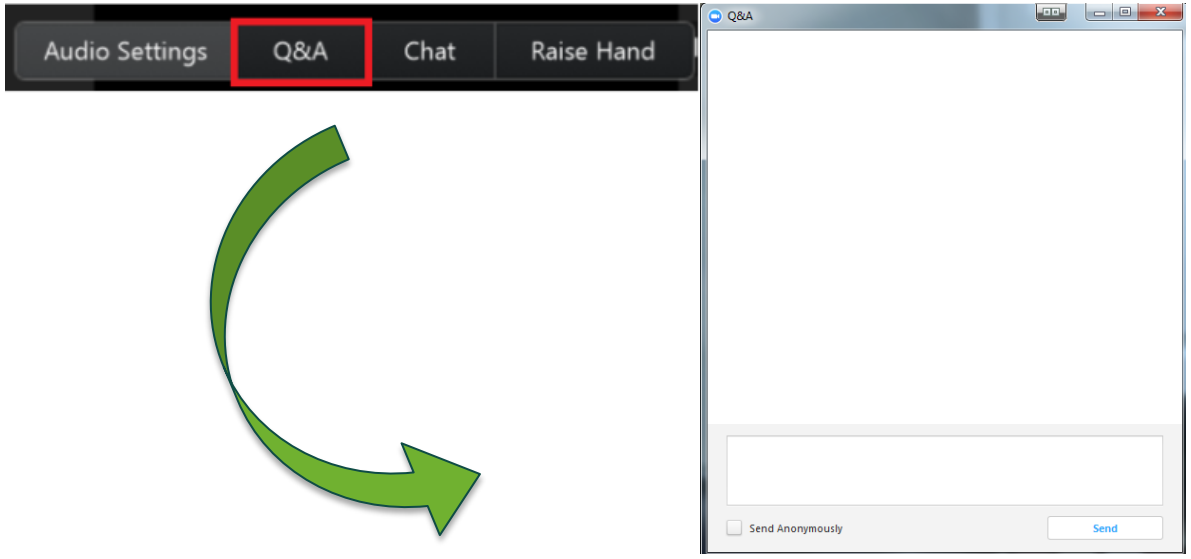
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

Clinical Insights: COVID-19 and the Liver

Highlights and Discussion of AASLD's paper "Clinical Insights for Hepatology and Liver Transplant Providers During the COVID-19 Pandemic"
Released March 23, 2020

Submit your questions in the Q&A box at the top or bottom of your screen.



Questions will be answered at the end of the presentation.

Moderators

Raymond T. Chung, MD, FAASLD
AASLD President-Elect

K. Rajender Reddy, MD, FAASLD

Presenters

Oren K. Fix, MD, MSc, FAASLD

Bilal Hameed, MD

- Welcome
  - Ray Chung, MD, FAASLD
- Introduction
  - Raj Reddy, MD, FAASLD
- Clinical Insights Debrief
  - Oren Fix, MD, FAASLD
  - Bilal Hameed, MD
- Questions and Answers
- Summary

o AASLD and COVID-19: rationale

- Potential for direct infection of the liver
- Elevated AST/ALT frequent
- Complications of ARDS and CRS → liver
- Hepatotoxic therapies
- Unique potential susceptibilities in CLD, post-transplant, AIH on immunosuppressives
- Risks of transplantation during COVID-19
- **Need for guidance for providers**

- AASLD COVID-19 Working Group
  - Raj Reddy
  - Oren Fix
  - Bilal Hameed
  - Michael Schilsky
  - Mark Russo
  - Brendan McGuire
  - Bob Fontana
  - Ryan Kwok
  - David Mulligan
  - Dan Pratt
  - Jorge Bezerra
  - Ray Chung

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Clinical Insights: COVID-19 and the Liver

Introduction

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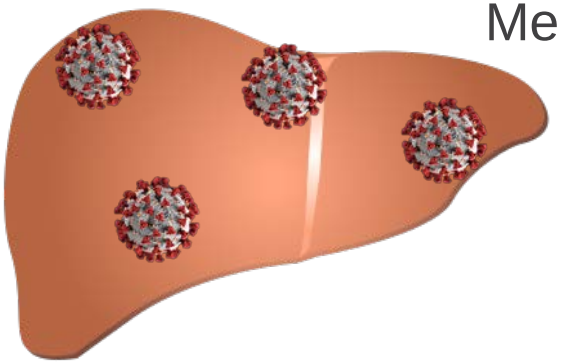
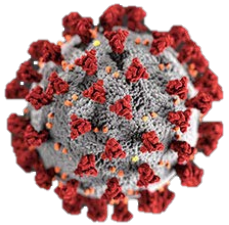
Ruimy Family President's Distinguished Professor in Medicine
Director of Hepatology
Medical Director, Liver Transplantation
University of Pennsylvania



What is SARS-CoV-2/COVID-19?

- SARS-CoV-2 is a novel enveloped RNA betacoronavirus first identified in Wuhan, China
  - Similar to SARS-CoV
  - Causes an infectious respiratory disease - COVID-19
  - Shown to be especially severe in older individuals and those with underlying medical problems[1]



Dec 30, 2019
Cluster of pneumonia cases with unknown origin reported to China NHC

Jan 7, 2020
Novel coronavirus isolated

Jan 11, 2019
First fatality reported

Jan 12, 2020
Named as 2019-nCoV; genome made publically available

Jan 13, 2020
First reported case outside China (Thailand)

Jan 20, 2020
First reported case in the U.S. (traveler from Wuhan)

Jan 30, 2020
W.H.O declares global health emergency

Feb 11, 2020
W.H.O names disease COVID-19

Feb 26, 2020
CDC confirms first possible instance of community spread in U.S.

Mar 11, 2020
W.H.O declares COVID-19 global pandemic

Mar 13, 2020
Europe becomes epicenter of the pandemic

Mar 16, 2020
President Trump issues guidelines urging social distancing and discouraging gatherings >10 people

https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen
https://www.cdc.gov/media/releases/2020/s0226-Covid-19-spread.html
https://www.nytimes.com/article/coronavirus-timeline.html

1.The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team 2020, 2(8): 113-122.

Symptoms & Clinical Presentation

An early study of 138 hospitalized patients with confirmed COVID-19 in Wuhan, China described the most common symptoms as[1]:

- **Fever (98.6%)**
- **Fatigue (69.6%)**
- **Dry cough (59.4%)**
- Anorexia (39.9%)
- Myalgia (34.8%)
- Dyspnea (31.2%)
- Expectoration (26.8%)
- Pharyngalgia (17.4%)
- Diarrhea (10.1%)
- Nausea (10.1%)

A larger study with 1099 patients with confirmed COVID-19 in 30 provinces in China[2] found:

- 43.8% had fever on admission but 88.7% had a fever during hospitalization
- Cough (67.8%)
- Fatigue (38.1%)
- Sputum production (33.7%)

The Chinese Center for Disease Control and Prevention reported[3]:

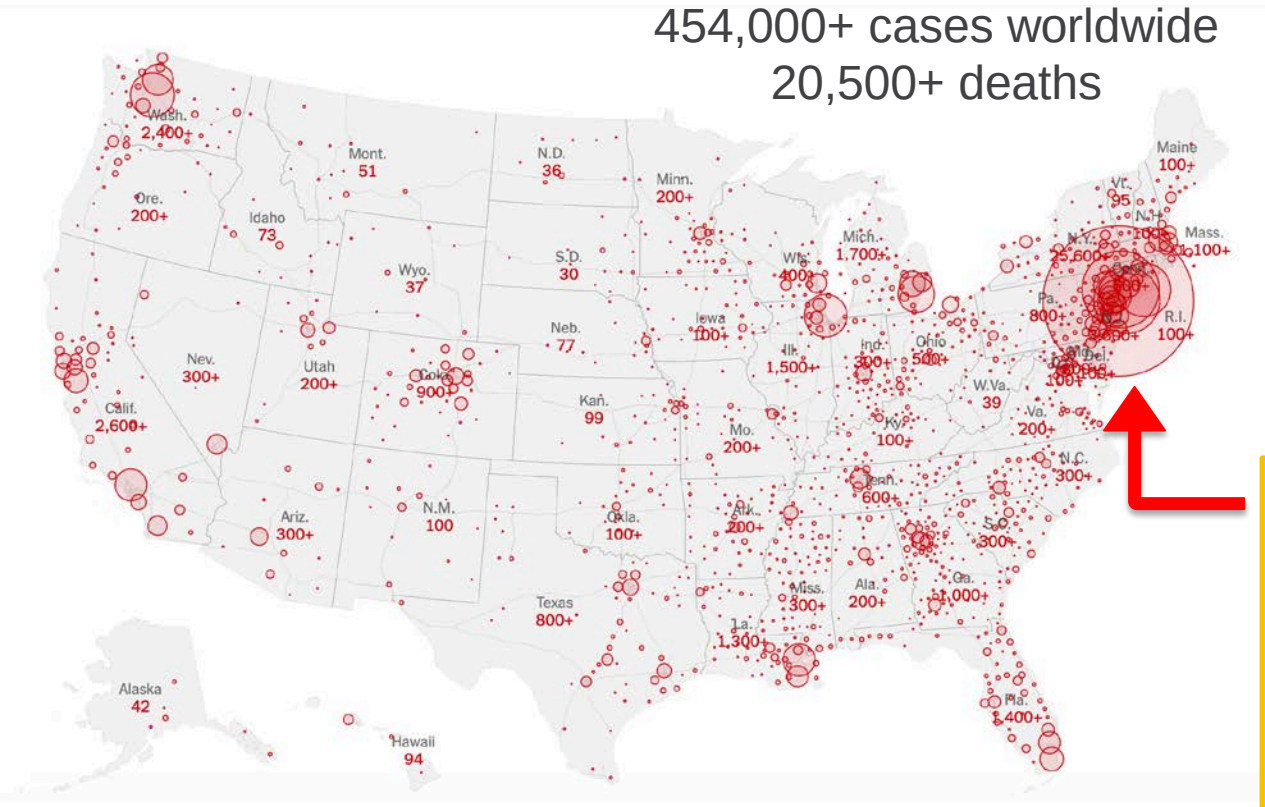
- **80.9% of cases were mild** (non-pneumonia and mild pneumonia cases)
- **13.8% of cases were severe** (dyspnea, respiratory frequency ≥ 30/minute, blood oxygen saturation ≤93%, PaO2/FiO2 ratio <300, and/or lung infiltrates >50% within 24–48 hours)
- **4.7% of cases were critical** (respiratory failure, septic shock, and/or multiple organ dysfunction/failure)

Incubation period average was 4-5 days (up to 14)[2,4]

1. Wang et al. JAMA, 2020;323(11):1061-1069. doi:10.1001/jama.2020.1585
2. Guan et al. NEJM, 2020. DOI: 10.1056/NEJMoa2002032
3. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team 2020, 2(8): 113-122.
4. Lauer et al. Ann Intern Med, 2020. https://doi.org/10.7326/M20-0504

World Wide Cases

454,000+ cases worldwide
20,500+ deaths

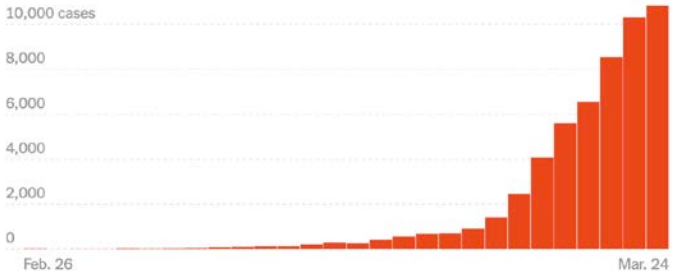


In the United States:

- 61,000+ cases
- 800+ deaths

New York is the new U.S. epicenter:

- 30,000+ cases in NY state
- 17,000+ cases in NYC



USA now has 10,000+ new cases per day

https://www.nytimes.com/news-event/coronavirus. Sources: State and local health agencies, hospitals, C.D.C. Data as of 9:49 a.m. E.T., Mar. 25
https://coronavirus.jhu.edu/map.html as of 3:30pm 3/25/2020

Populations at Risk

Early reports from China (cases reported to China's Infectious Disease Information System through Feb 11, 2020) show increased fatality rates for individuals who are older and with comorbid conditions[1]

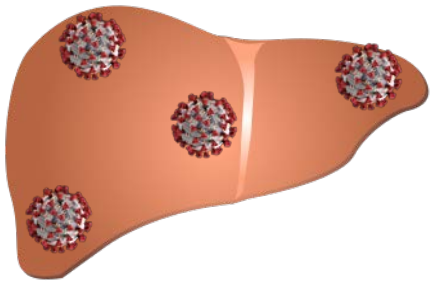
- **70-79: 8% fatality rate**
- **≥80: 14.8% fatality rate**

Preliminary reports by the CDC indicate in the US fatality is highest amount **individuals ≥85 (10-27%)[2]**

Comorbid Condition	Confirmed Cases	Deaths	Case Fatality Rate
Overall	44,672	1,023	2.3%
Hypertension	2,683	161	6%
Diabetes	1,102	80	7.3%
Cardiovascular Disease	873	92	10.5%
Chronic respiratory Disease	511	32	6.3%
Cancer (any)	107	6	5.6%
None	15,536	133	0.9%
Missing	23,690	617	2.6%

The Centers for Disease Control states individuals at higher risk for severe illness include:

- People aged 65 years and older
- People who live in a nursing home or long-term care facility
- Other high-risk conditions could include:
  - People with chronic lung disease or moderate to severe asthma
  - People who have serious heart conditions
  - People who are immunocompromised including cancer treatment
  - People of any age with severe obesity (body mass index [BMI] >40) or certain underlying medical conditions, particularly if not well controlled, such as those with diabetes, renal failure, or **<u>those with liver disease might also be at risk</u>**



https://www.cdc.gov/coronavirus/2019-ncov/specific-groups/people-at-higher-risk.html

1.The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team 2020, 2(8): 113-122.
2. CDC, 2020; MMWR Morb Mortal Wkly Rep. DOI: http://dx.doi.org/10.15585/mmwr.mm6912e2external icon.

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Clinical Insights: COVID-19 and the Liver

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Washington State University Elson S. Floyd College of Medicine

- Effects of SARS-CoV-2 on the Liver and Evaluation of COVID-19 Patients with Elevated Liver Biochemistries
- Stable Outpatients with Liver Disease or Hepatocellular Carcinoma
- Patients with Decompensated Cirrhosis, Liver Transplant Evaluations, and Patients on the Liver Transplant Waiting List
- Liver Transplantation, Resource Utilization, and Ethical Considerations

Effects of SARS-CoV-2 on the Liver

Evaluation of COVID-19 Patients with Elevated Liver Biochemistries

What we know:

- SARS-CoV-2 binds to ACE2 to gain entry into cells
  - Found on liver and biliary epithelial cells
- Incidence of elevated liver tests in hospitalized COVID-19 patients: 14%-53%, AST/ALT > bilirubin
- Liver injury more common in more severe COVID-19 cases than mild cases, rare cases of acute liver injury
- Severe COVID-19 is uncommon in children and less likely to be associated with elevated liver tests
- Low serum albumin is a marker of COVID-19 severity
- Liver histology ranges from moderate microvesicular steatosis + mild lobular/portal activity to focal necrosis

Xu L et al. Liver Int 2020
Zhang C et al. Lancet Gastroenterol Hepatol 2020
Lu X et al. N Engl J Med 2020
Zhe et al. Lancet Respir Med 2020
Yao XH et al. Chinese J Path 2020

What we don't know:

- Elevated liver tests in COVID-19: Direct viral effect *or* secondary to inflammatory/immune response *or* drug hepatotoxicity?
- Are patients with chronic liver disease (HBV, HCV, fatty liver) more susceptible to liver injury from SARS-CoV-2?
- Does SARS-CoV-2 exacerbate cholestasis in patients with PBC or PSC?

Zhang C et al. Lancet Gastroenterol Hepatol 2020
Xu Z et al. Lancet Respir Med 2020

Recommendations:

- Test for HBV and HCV in patients with COVID-19 and elevated liver tests
- Avoid unnecessary imaging unless there is a clinical suspicion for biliary obstruction, cholangitis, etc.
- Patients with COVID-19 and elevated liver tests should still be considered for investigational/off-label therapeutics
- Monitor liver tests in all COVID-19 patients, especially if treated with remdesivir or tocilizumab
- Don’t assume AIH flare or rejection in patients with elevated liver tests and COVID-19
- Evaluate children with COVID-19 and elevated liver tests for underlying liver disease: Do not assume COVID-19

Stable Outpatients with Liver Disease or Hepatocellular Carcinoma

What we know:

- Asymptomatic patients can contribute to SARS-CoV-2 spread (immunocompetent and immunosuppressed)
- Children less likely to become ill but can still be infectious

What we don't know:

- Are patients with HCC at increased risk for severe COVID-19?

Bai Y et al. JAMA 2020
Lu X et al. N Engl J Med 2020
Liang W et al. Lancet Oncol 2020

Recommendations:

- Severely limit outpatient visits to urgent issues and clinically significant liver disease (e.g., jaundice, ALT or AST >500, recent decompensation)
- Stagger patient arrival times, room patients immediately
- Limit family/friends who accompany patients
- Use phone visits or telemedicine
- Screen all patients for symptoms/fever or recent exposure before entry to clinic space
- Check each patient's temperature when they arrive
- Consider cohorting patients with COVID-19 symptoms
- Do not evaluate patients with COVID-19 symptoms/fever in the hepatology/liver transplant clinic

https://www.cdc.gov/coronavirus/2019-ncov/healthcare-facilities/guidance-hcf.html

Recommendations (HCC):

- Consider reviewing images of new referral for liver masses in tumor board or with expert radiologists before scheduling in-person visit
- Continue usual surveillance imaging in patients with cirrhosis, HBV or HCC
  - An arbitrary delay of 2 months is reasonable and may be necessary
- Proceed with HCC treatments

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

What we know:

- Nearly all OPOs now test for SARS-CoV-2 RNA
- Test performance is not perfect:
  - Sensitivity: nasal (63%), pharyngeal (32%), BAL (93%)
- Capacity for testing may be limited
- Moving target: rapid tests including antibody tests being developed

What we don't know:

- What are the effects of SARS-CoV-2 in patients with chronic liver disease, decompensated cirrhosis or those awaiting liver transplantation?

Wang W et al. JAMA 2020

Recommendations:

- Limit the number of patients coming to clinic for transplant evaluations
- Use telemedicine/telephone: patient education, social work/dietitian/financial consults, outreach clinics
- Avoid multiple patients in one room for patient education
- Obtain labs and imaging only as clinically necessary
  - Know recent OPTN policy changes
- Ensure patients have adequate supplies of medications
  - 90-day supplies instead of 30-day supplies
- Instruct patients to avoid community recovery support meetings (e.g., AA): Provide telephone/online resources
- Instruct patients not to travel

https://unos.org/covid/

Liver Transplantation, Resource Utilization, and Ethical Considerations

What we know:

- Resource utilization and ethical considerations:

  We've got this

- CMS includes transplant surgery in Tier 3b:
  "Do not postpone"
- People who test positive for SARS-CoV-2 are medically ineligible for organ donation

https://www.cms.gov/files/document/31820-cms-adult-elective-surgery-and-procedures-recommendations.pdf

https://www.aopo.org/information-about-covid-19-coronavirus-is-being-released-rapidly-we-will-post-updates-as-we-receive-them/

What we don't know:

- Which life is more valuable and in need of limited resources: COVID-19 patient or patient with urgent need of liver transplantation?
- Is it ethical to start a patient on immunosuppression now?
- Are immunosuppressed patients at higher risk of severe COVID-19?
- Will we need to ration transplants? How do we prioritize?

Recommendations:

- Start thinking about these challenging issues now and develop a policy in your program
- Ensure your administrators are aware of the CMS Tier 3b designation
- Consider resource utilization in the decision to proceed with liver transplantation (ICU beds, ventilators, PPE, blood)
- COVID-19 prevalence and resources vary across the country

https://www.cms.gov/files/document/31820-cms-adult-elective-surgery-and-procedures-recommendations.pdf

Recommendations:

- Screen potential donors for exposure and COVID-19 symptoms/fever (regardless of test results or test availability)
- Screen recipients for COVID-19 symptoms/fever and exposure before they are called in from home for transplantation
- Consider testing asymptomatic recipients and donors for SARS-CoV-2 before transplantation, if available
- Consider suspending living donor liver transplant programs (exceptions: pediatric patients with ALF)
- Consult local medical ethics committees
- See AASLD's COVID-19 Clinical Insights document

https://www.aasld.org/sites/default/files/2020-03/AASLD-COVID19-ClinicalInsights-3.23.2020-FINAL-v2.pdf

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Clinical Insights: COVID-19 and the Liver

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University of California San Francisco, CA

- Post-Liver-Transplant Patients
- Management of Patients on Immunosuppressive Agents
- Inpatients
- Medication Management of Patients with COVID-19
- Procedures

Post-Liver-Transplant Patients

Post Liver Transplant Patients

What we know:

- Post-transplant recipients aged >60 years and immunosuppressed patients are more likely to acquire SARS-CoV-2 infection.
- Too early to know if immunosuppressed patients are at greater risk for severe COVID-19.
- Immunosuppression may prolong viral shedding.

Recommendations:

- Emphasize prevention measures.
- Minimize in-person visits for post-transplant patients by maximizing use of telemedicine.
- Advise against travel.
- Consider advocating for telework or excuses from work for transplant patients and their primary care givers.

1.D'Antiga, L. Liver Transpl 2020 [Epub ahead of print].

Management of Patients on Immunosuppressive Agents

Management on Immunosuppressive Agents

What we know:

- The effects of immunosuppression on COVID-19 are not well established.
- Reducing or stopping immunosuppressants may cause a flare of autoimmune hepatitis or precipitate acute rejection.
- The WHO recommends avoiding corticosteroids for treatment of COVID-19 unless indicated for another therapeutic purpose.

Recommendations:

Patients without COVID-19:

- Not to routinely reduce immunosuppression.

Patients with COVID-19:

- Consider minimizing the dosage of high-dose prednisone but maintain a dosage to avoid adrenal insufficiency.
- Consider reducing but not stopping calcineurin inhibitor or mycophenolate, especially in the setting of lymphopenia, fever or pneumonia attributed to COVID-19.
- Use caution in initiating prednisone or immunosuppressive therapy where the potential benefit might be outweighed by the risks (e.g alcoholic hepatitis).

1.World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: interim guidance, 13 March 2020.

Inpatients

Inpatients

What we know:

- Healthcare workers are at risk for COVID-19.
- Minimizing interactions among healthcare workers and between patients and healthcare workers is critical to reducing the spread of SARS-CoV-2.
- Minimizing the transport of patients within facilities could reduce the spread of SARS-CoV-2.

Recommendations:

- Consider developing a policy for review and triage of hospital inpatient transfers.
- Avoid direct admission for patients with fever or respiratory symptoms.
- Consider COVID-19 in patients with new onset HE.
- Aggressive airway management in COVID-19 patients with liver-related pulmonary disease (e.g., hydrothorax, PoPH, HPS).

Remuzzi A et al. Lancet. 2020 Mar 13. doi: 10.1016/S0140-6736(20)30627-9.

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

Potential Treatment Regimens

NO APPROVED DRUGS

Possible role

- Remdesivir*
- IL-6 receptor blockers (e.g. tocilizumab)*
- (Hydroxy)chloroquine and azithromycin
- Darunavir/Cobicistat
- Convalescent plasma
- Favipiravir

No role (except specific other need)

- Lopinavir/ritonavir
- Steroids
- ACE-inhibitors
- Oseltamivir

Concern for drug-drug interactions and safety

* ALT/AST >5xULN, exclusion or stopping criteria

Medication Management of Patients with COVID-19

What we know:

- RCT of lopinavir-ritonavir in severe COVID-19 showed no clinical benefit.
- Lopinavir-ritonavir are potent inhibitors of CYP3A4.
- The European Society of Cardiology recommends continuation of usual antihypertensive therapy, including ACEIs and ARBs.

Recommendations:

- The evidence does not support the use of lopinavir-ritonavir for COVID-19.
- Patients on chronic ACEIs/ARBs should remain on them even in the setting of COVID-19.
- Acetaminophen ≤2 g/d is the preferred analgesic and anti-pyretic.
- Monitor liver chemistries in all COVID-19 patients, especially if treated with remdesivir or tocilizumab.

1. *B Cao et al. N Engl J Med 2020. DOI: 10.1056/NEJMoa2001282.*

Potential Drug-Drug Interactions

Liverpool Drug Interactions Group

Interactions with Experimental COVID-19 Therapies

Charts updated 20 March 2020

Please check www.covid19-druginteractions.org for updates.

Please note that if a drug is not listed it cannot automatically be assumed it is safe to coadminister. No recommendation to use experimental therapy for COVID-19 is made. Drug interaction data for many agents are limited or absent; therefore, risk-benefit assessment for any individual patient rests with prescribers.

Immunosuppressants

	ATV	LPV/r	RDV	FAVI	CLQ	HCLQ	NITAZ	RBV	TCZ
Adalimumab	↔	↔	↔	↔	↔	↔	↔	↔	↔
Anti-thymocyte globulin	↔	↔	↔	↔	↔	↔	↔	↔	↔
Azathioprine	↔	↔	↔	↔	↔	↔	↔	↑	↔
Basiliximab	↔	↔	↔	↔	↔	↔	↔	↔	↔
Belatacept	↔	↔	↔	↔	↔	↔	↔	↔	↔
Ciclosporin	↑	↑	↔	↔	↑	↑	↔	↔	↓
Mycophenolate	↔	↑↓	↔	↔	↔	↔	↔	↔	↔
Sirolimus	↑	↑	↔	↔	↑	↑	↔	↔	↓
Tacrolimus	↑	↑	↔	↔	↑	↑	↔	↔	↓

Procedures

Procedures

What we know:

- Endoscopic procedures should be considered aerosol-generating.
- Potential for fecal-oral SARS-CoV-2 transmission and the virus is detected in saliva.
- The joint GI societies recommend to "strongly consider rescheduling non-urgent endoscopic procedures."

Recommendations:

- Cancel all elective/non-urgent procedures (e.g., endoscopy, liver biopsy and fibroscan).
- Procedures can be performed
  1. Liver biopsy (rejection or AIH).
  2. Therapeutic paracentesis.
  3. TIPS.
  4. Endoscopy for variceal bleeding,or secondary prophylaxis
  5. Biliary procedures.
- Use appropriate personal protective equipment (PPE)
- Consider limiting the involvement of fellows in endoscopies.

1.Soetikno R, Teoh AYB et al. Gastrointest Endosc 2020.
2. Xiao F, Tang M et al. Gastroenterology 2020.
3. Gu J, Han B et al. Gastroenterology 2020.

Questions?

Please submit your questions to the Q&A Chat now.

AASLD's COVID-19 Resources

Follow/Share: COVID-19 Resources Webpage: https://www.aasld.org/about-aasld/covid-19-resources

Join/Engage: COVID-19 Care Community on AASLD's online community, Engage. Open to all members. Log in to Engage with your AASLD user name and password.

Submit: *Hepatology, Liver Transplantation, Hep Commun* all accepting and fast tracking review of COVID-19 original articles, case reports