
2021
NCSCG
6TH ANNUAL VIRTUAL
LIVER SYMPOSIUM
January 7-28, 2021

Management of COVID-19 Patients on Immunosuppression

OREN FIX, MD, MSC, FACP, AGAF, FAASLD

Outline

- COVID-19 US timeline
- AASLD response to COVID-19
- Autoimmune hepatitis
- Transplant recipients
- COVID-19 vaccines and liver disease

COVID-19 US Timeline

January 20

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

First Case of 2019 Novel Coronavirus in the United States

Michelle L. Holshue, M.P.H., Chas DeBolt, M.P.H., Scott Lindquist, M.D., Kathy H. Lofy, M.D., John Wiesman, Dr.P.H., Hollianne Bruce, M.P.H., Christopher Spitters, M.D., Keith Ericson, P.A.-C., Sara Wilkerson, M.N., Ahmet Tural, M.D., George Diaz, M.D., Amanda Cohn, M.D., LeAnne Fox, M.D., Anita Patel, Pharm.D., Susan I. Gerber, M.D., Lindsay Kim, M.D., Suxiang Tong, Ph.D., Xiaoyan Lu, M.S., Steve Lindstrom, Ph.D., Mark A. Pallansch, Ph.D., William C. Weldon, Ph.D., Holly M. Biggs, M.D., Timothy M. Uyeki, M.D., and Satish K. Pillai, M.D., for the Washington State 2019-nCoV Case Investigation Team*

February 29

Public Health news and blog

First death due to novel coronavirus (COVID-19) in a resident of King County

February 29, 2020

Summary

Public Health – Seattle & King County and the Washington State Department of Health are announcing new cases of COVID-19, including one death. The individual who died was a man in his 50s with underlying health conditions who had no history of travel or contact with a known COVID-19 case. Public Health is also reporting two cases of COVID-19 virus connected to a long-term care facility in King County.

Story

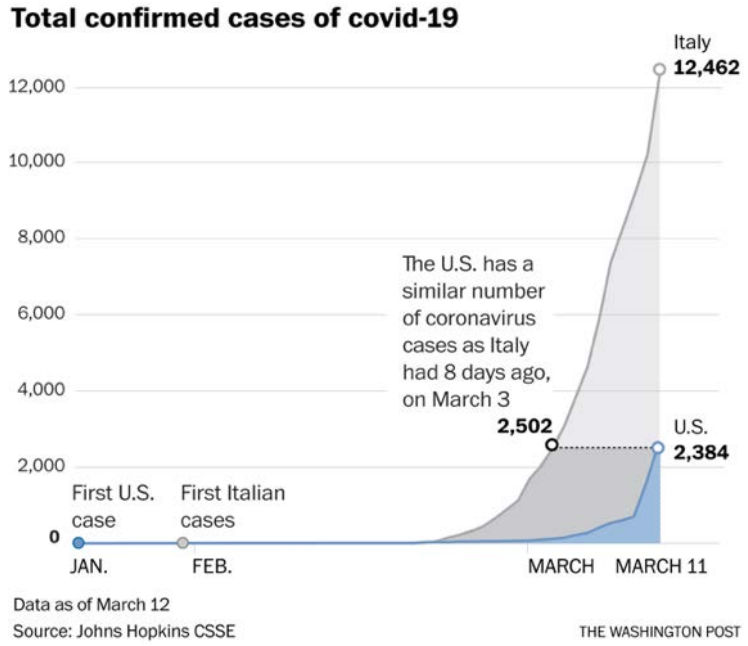
Public Health Seattle & King County

Washington State Department of Health

CDC

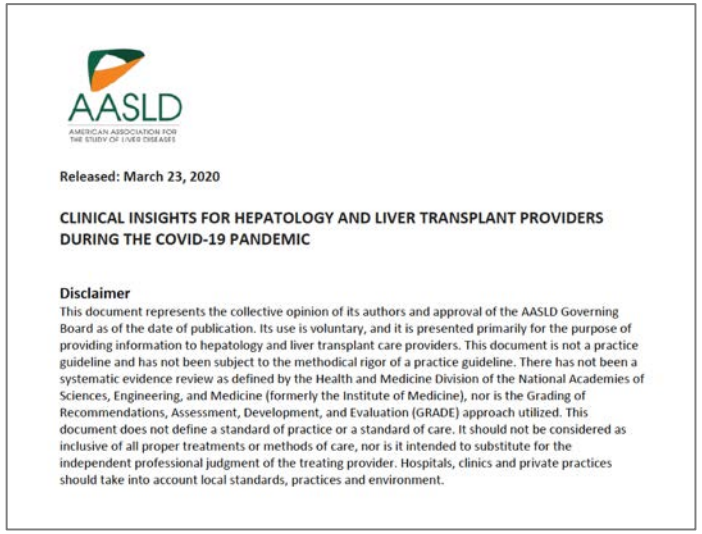
COVID-19 US Timeline

March 11



AASLD Response

March 23



AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

Released: March 23, 2020

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

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.

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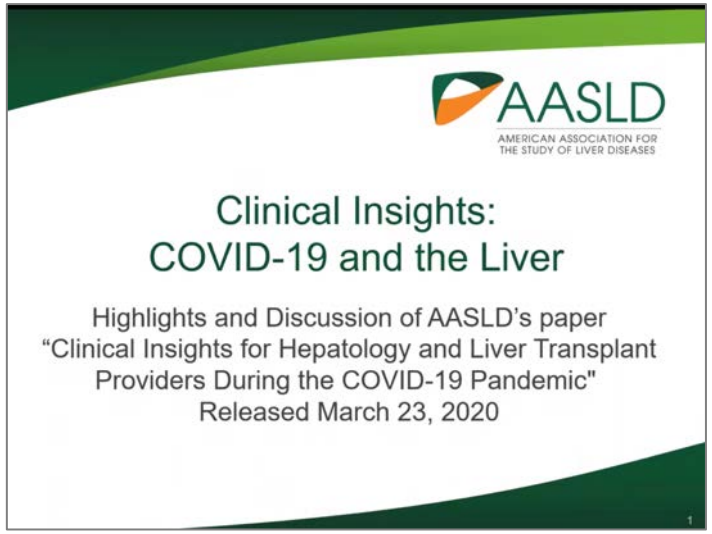
Translated into
Spanish and Portuguese

March 26



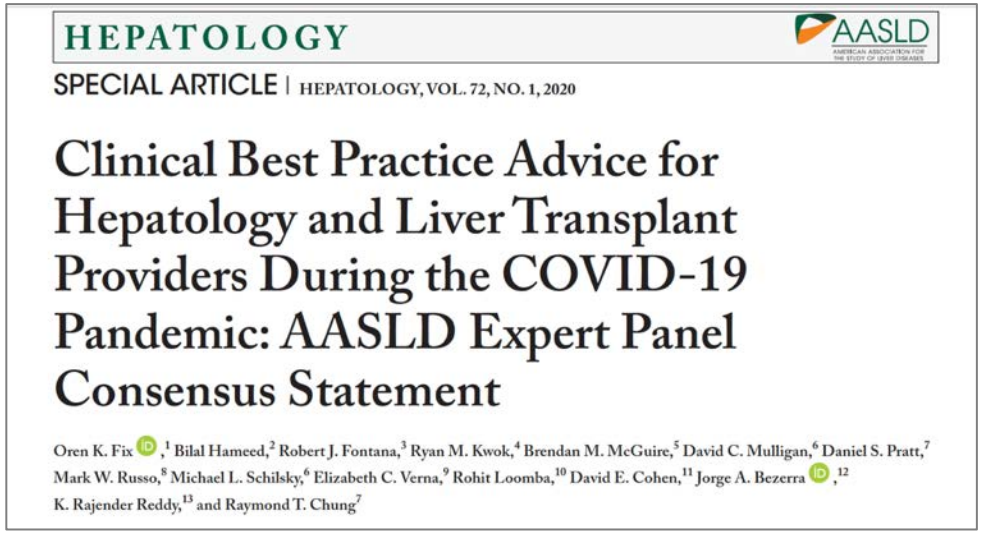
AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

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

16 webinars
Viewed >379,000 times

April 16



HEPATOLOGY
AASLD

SPECIAL ARTICLE | HEPATOLOGY, VOL. 72, NO. 1, 2020

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] and Raymond T. Chung[7]

Cited >114 times

https://www.aasld.org/covid19

COVID-19 and Immunosuppression

- The immune response may be the main driver for pulmonary injury attributable to COVID-19
- Posttransplant immunosuppression was not a risk factor for mortality associated with SARS (2002-2003) or MERS (2012-present)
- **Immunosuppression may be protective**
- Several studies have shown a mortality benefit with the use of corticosteroids for the treatment of critically ill patients with COVID-19
- NIH and IDSA recommend dexamethasone for hospitalized COVID-19 patients requiring mechanical ventilation or supplemental oxygen

Huang C et al Lancet 2020; D'Antiga L Liver Transpl 2020; Bhoori S et al Lancet Gastroenterol Hepatol 2020; Horby P et al N Engl J Med 2020; Sterne JAC et al JAMA 2020; NIH COVID-19 treatment guidelines www.covid19treatmentguidelines.nih.gov; IDSA www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management

Autoimmune Hepatitis

- Retrospective report from Italy of 10 pts with AIH on immunosuppression + COVID-19
  - 4 had cirrhosis, 1 decompensated (the only one who died)
  - 2 on high-dose corticosteroids for treatment of acute onset of AIH
  - 6 were hospitalized, including 5 with pneumonia and 3 who required non-invasive ventilation
  - Liver biochemistries remained normal in all hospitalized patients except the 2 on high-dose steroids for treatment of acute AIH
- **Course of COVID-19 in AIH may be similar to non-immunosuppressed patients**

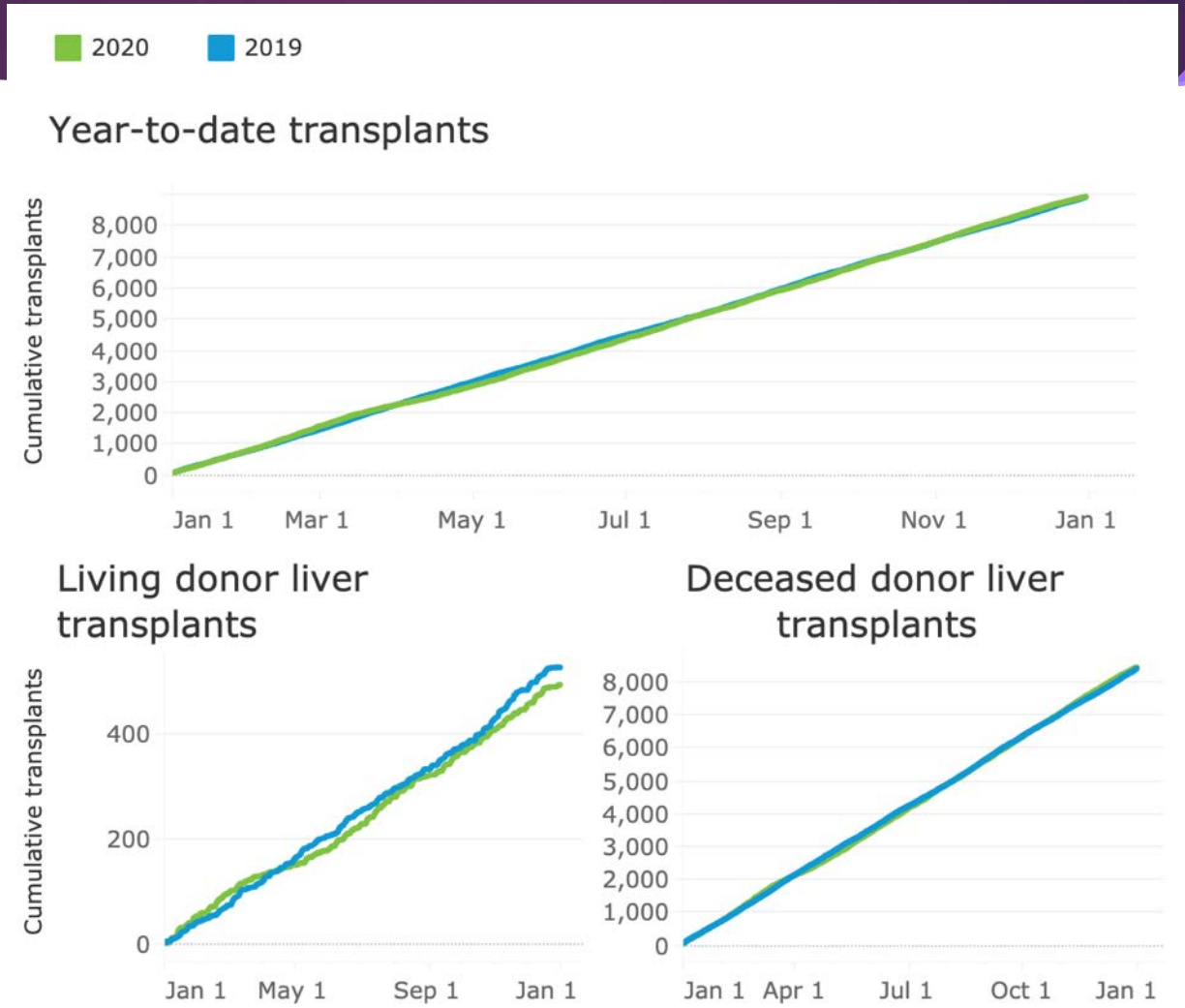
Gerussi A et al Hepatol Comm 2020

Autoimmune Hepatitis

- **Pre-emptive reduction in immunosuppression during COVID-19 can be potentially harmful**
- NIH COVID-19 treatment guidelines recommend that oral corticosteroid therapy used prior to COVID-19 diagnosis for another underlying condition should not be discontinued
- Initiate immunosuppressive therapy in patients with liver disease with or without COVID-19 who have strong indications for treatment

NIH COVID-19 treatment guidelines https://www.covid19treatmentguidelines.nih.gov; Fix O et al Hepatology 2020

US Liver Transplant Volume



Liver Transplant Recipients in Italy

- Group from Lombardy, Italy described 6 LT recipients from their program diagnosed with COVID-19
  - 3 long-term LT recipients died of COVID-19-related pneumonia, ARDS
  - All were >65 years with hypertension, obesity, diabetes, hyperlipidemia
  - 3 recently transplanted (<2 years) patients had mild COVID-19 and did not require hospitalization

Bhoori S et al Lancet Gastroenterol Hepatol 2020

Liver Transplant Recipients in NYC

- Retrospective report of 90 solid organ transplant recipients with COVID-19 treated as outpatients or inpatients in New York City
  - Included 13 LT recipients (9 with mild/moderate COVID-19, 4 w/severe COVID-19)
  - **Immunosuppressive medications reduced in most hospitalized patients**: antimetabolite decreased or held in 88%, steroids decreased or held in 7%, calcineurin inhibitor decreased or held in 18%
  - 34% required ICU admission, 35% required mechanical ventilation, 24% died (52% of the ICU patients), 54% discharged at time of publication
  - No reported acute cellular rejection

Pereira MR et al Am J Transplant 2020

Liver Transplant Recipients in US

- COVID-19 in chronic Liver Disease (COLD) consortium:
  112 LT recipients with COVID-19 at 15 US medical centers
  - Median age = 61; 55% male; median time from LT = 4 years
  - **Immunosuppression was changed in half the patients during COVID-19, more often in those with severe disease** (ICU admission, vasopressors, mechanical ventilation)
  - Most common change: holding mycophenolate (33%), followed by decrease in tacrolimus dose (26%), holding tacrolimus (5%)
  - 1 patient had acute cellular rejection after reducing tacrolimus dose
  - Reduction in immunosuppression was not associated with liver injury or mortality

Rabiee A et al Hepatology 2020

AASLD Recommendations

- In post-transplant patients ***without*** COVID-19:
  - Do not make anticipatory adjustments to current immunosuppressive drugs or dosages
- In post-transplant patients ***with*** COVID-19:
  - Consider lowering the overall level of immunosuppression, particularly anti-metabolite dosages (e.g., azathioprine or mycophenolate) based on general principles for managing infections in transplant recipients and to decrease the risk of superinfection
  - Consider the risk of kidney injury in COVID-19 and monitor CNI levels
  - Adjustment of immunosuppressive medications must be individualized based on severity of COVID-19 and risk of graft rejection

Fix O et al Hepatology 2020

Liver Transplant Recipients in Spain

- Prospective study from Spain of 111 LT recipients w/COVID-19
  - Increased risk of acquiring SARS-CoV-2 (almost double the rate in the age/gender matched general population)
  - **Lower mortality rates than the matched general population**
  - Baseline immunosuppression containing **mycophenolate**, particularly doses >1000 mg/day, was an **independent predictor of severe COVID-19** (RR 3.94, 95% CI 1.59-9.74, *P*=.003)

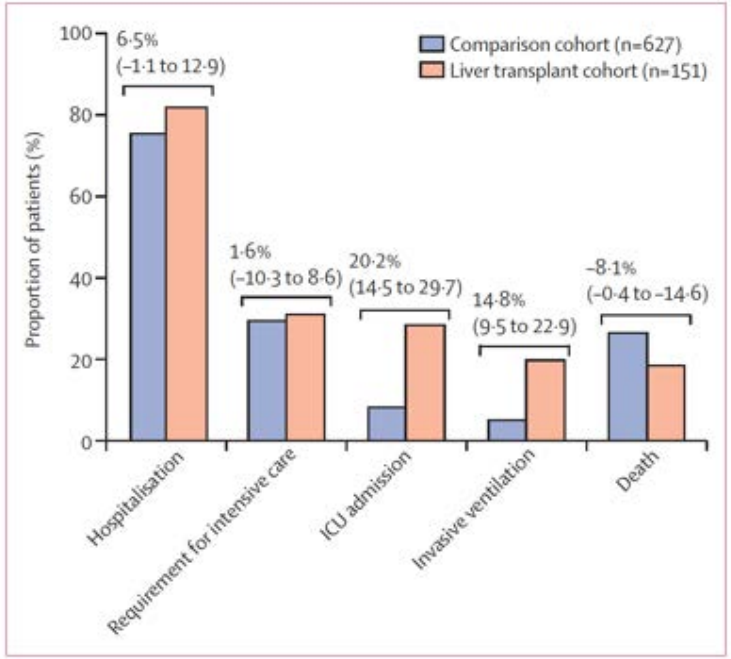
Colmenero J et al J Hepatol 2020

International Liver Transplant Registries

- International registry data of 151 liver transplant recipients with COVID-19
  - 124 (82%) were hospitalized, 47 (31%) required intensive care, and 28 (19%) died
  - Liver transplant status did not significantly increase the risk of death in patients with COVID-19 in a propensity score matched analysis
- **Liver transplant recipients are probably not at increased risk of severe COVID-19**

SECURE-Cirrhosis REGISTRY
Surveillance Epidemiology of Coronavirus (COVID-19) Under Research Exclusion

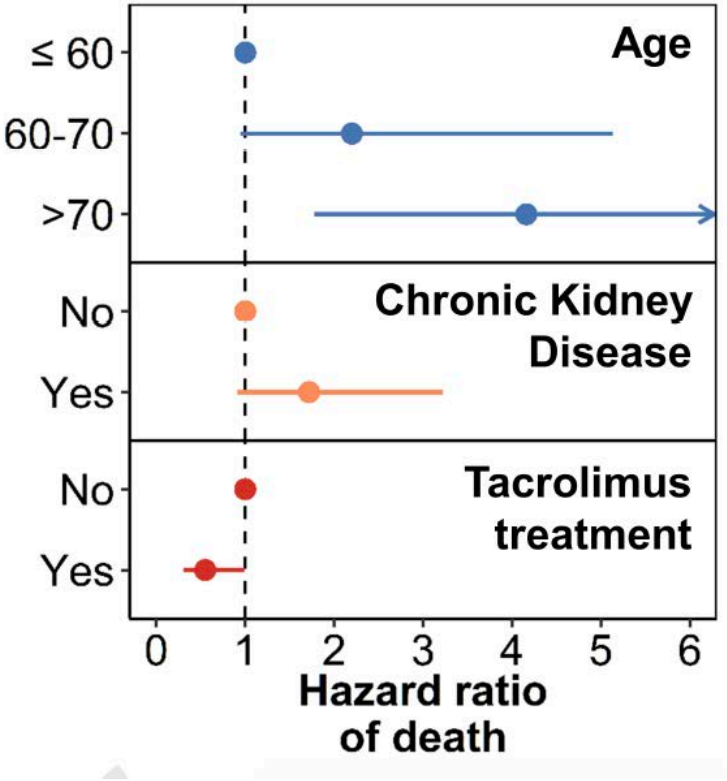
EASL
COVID-HEP REGISTRY
COVID-19 in Patients with Liver Disease or Transplantation



Webb G et al Lancet Gastroenterol Hepatol 2020

Tacrolimus May Be Protective

- Large European registry of 243 LT recipients with COVID-19
  - In multivariable analysis, **tacrolimus was associated with decreased mortality compared to other immunosuppressive agents** (cyclosporine, mycophenolate, mTOR inhibitors): HR 0.55, 95% CI 0.31-0.99
  - Age, diabetes, CKD also independent risk factors for death from COVID-19
  - Is the protective mechanism of tacrolimus related to its immunomodulatory effect or a potential direct antiviral effect?



Belli LS et al Gastroenterology 2020; Pearson MM et al Gastroenterology 2020; Carbajo-Lozoya J et al Virus Res 2012

COVID-19 Vaccines and Liver Disease

- **Pfizer-BioNTech**
  - Phase 2/3 study included participants with stable chronic liver disease
  - Excluded treatment with immunosuppressive therapy or diagnosis of an immunocompromising condition
  - **214 (0.6%) participants had liver disease**: 124 BNT162b2, 90 placebo
  - Vaccine Efficacy (VE) was 95.3% in participants with comorbidities, which included liver disease
- **Moderna**
  - Phase 3 trial included participants with liver disease
  - Excluded patients with immunosuppressive state or recent use of immunosuppressant drugs
  - **196 (0.6%) participants had liver disease**: 100 mRNA-1273, 96 placebo
  - No participants with liver disease developed COVID-19, VE cannot be determined

Pfizer and BioNTech FDA Briefing Document www.fda.gov/media/144245/download;
Moderna FDA Briefing Document www.fda.gov/media/144434/download

COVID-19 Vaccines and Liver Disease

- Transplant recipients may have lower antibody responses and waning titers compared to those without transplants
- Patients vaccinated pre-transplant may have reduced protection post-transplant, especially if B-cell depleting therapies are used
- **Benefits of vaccination in transplant recipients likely outweigh the risks**
- While awaiting data on vaccine safety and efficacy in transplant recipients, AST recommends that they receive the mRNA vaccines when available, ideally pre-transplant

Phase 1a
Healthcare personnel Residents of long-term care facilities
Phase 1b
Frontline essential workers People aged ≥75 years
Phase 1c
People aged 65-74 years **People aged 16-64 years with underlying medical conditions** Other essential workers

CDC www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations.html;
AST COVID-19 Vaccine FAQ Sheet www.myast.org/covid-19-vaccine-faq-sheet;
Marjot T et al Lancet Gastroenterol Hep 2020

Summary

- Immunosuppression may be protective against severe COVID-19
- LT recipients may not be at increased risk for severe COVID-19 and may have lower mortality rates than the general population
- High doses of mycophenolate may be associated with severe COVID-19, while tacrolimus may be associated with decreased mortality compared to other immunosuppressants
- Pre-emptive reduction in immunosuppression during COVID-19 can be potentially harmful
- In hospitalized patients with COVID-19, consider lowering the overall level of immunosuppression, particularly anti-metabolite dosages
- mRNA vaccine trials have had few participants with liver disease and none who were immunosuppressed
- Benefits of vaccination in transplant recipients likely outweigh the risks and LT recipients should receive the vaccines when available, ideally pre-transplant

COVID-19 Clinical Oversight Committee

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AASLD COVID-19 Webinar

- **COVID-19 Vaccination in Patients with Liver Disease**
  - Thursday, January 28, 2021
  - 1:00-2:00 PM PST
  - Free to register
  - www.aasld.org/event/webinar-covid-19-vaccination-patients-liver-disease

Thank you!