

AASLD COVID-19 Working Group Presents

Clinical Insights: COVID-19 and the Liver – Case Studies and Updates

April 7, 2020 5-6 pm ET

Presenters:

Oren K. Fix, MD, MSc, FAASLD Mark W. Russo, MD, MPH, FAASLD Elizabeth C. Verna, MD, MS

Moderator:

Robert J. Fontana, MD, FAASLD



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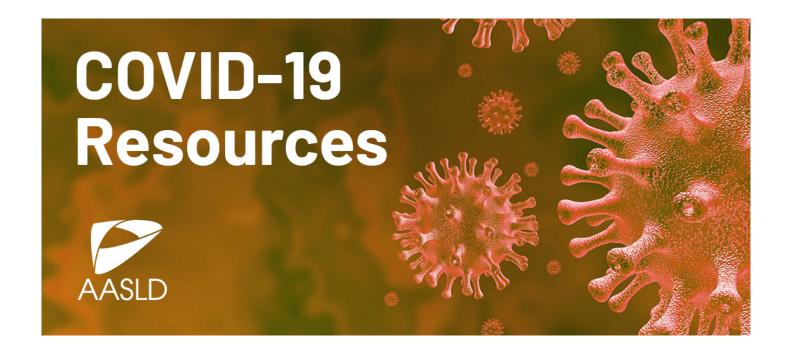


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For resources and updates on COVID-19 and the liver, visit aasld.org/COVID19



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Upcoming COVID-19 Webinar

Thursday, April 16, 2020 5-6pm Eastern

Clinical Insights: COVID-19 and the Liver – Case Studies and Updates

Presenters:

Bilal Hameed, MD Ryan Kwok, MD Michael Schilsky, MD, FAASLD

Moderator:

Brendan McGuire, MD

Registration: http://www.aasld.org/COVID19

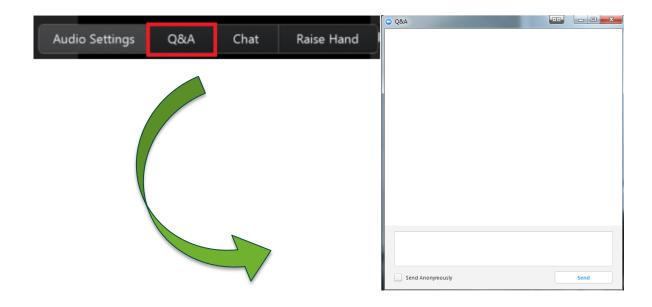


Clinical Insights: COVID-19 and the Liver

Case Studies and Updates
Webinar Series
Updates April 7, 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.



Moderator

Robert J. Fontana, MD, FAASLD University of Michigan Hospitals and Health





Presenters

Oren K. Fix, MD, MSc, **FAASLD**

Swedish Medical Center



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Mark W. Russo, MD, Elizabeth C. Verna, MD, MS

Columbia University **Medical Center**





AASLD COVID-19 Working Group

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Raymond T. Chung, MD, FAASLD	Massachusetts General Hospital



- Welcome and Introduction
 - Robert Fontana, MD, FAASLD
- Clinical Insights Updates
 - Oren K. Fix, MD, MSc, FAASLD
- Rapid Fire Journal Club
 - Mark W. Russo, MD, MPH, FAASLD
- Case Discussion
 - Elizabeth C. Verna, MD, MS
- o Q&A
- Closing



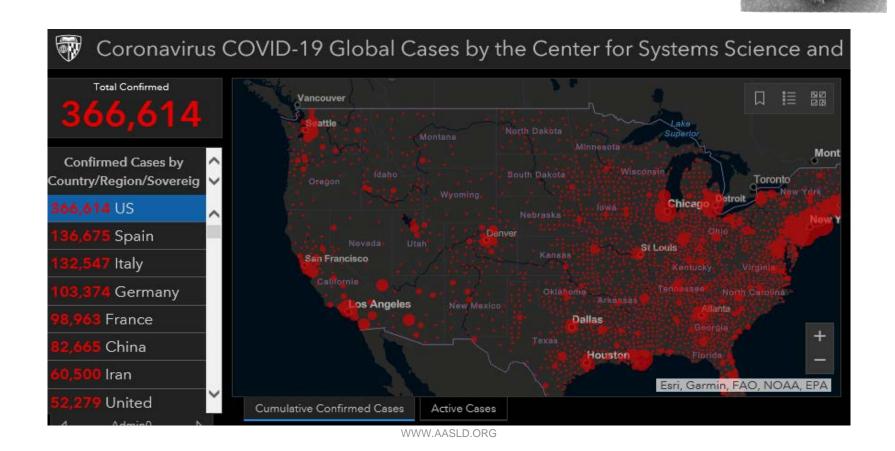
Introduction

Robert J. Fontana, MD, FAASLD University of Michigan Hospitals and Health

Coronavirus Disease- 2019 (COVID-19)



<u>Severe Acute Respiratory Syndrome CoronaVirus 2</u> (SARS-CoV-2)



COVID-19





ACE-2 is molecular target of SARS-CoV2

ACE-2 protein	% COVID-19 involvement
Lung	80-100%
Heart	10-20%
Gut	20-30%
Liver	15-40%
Kidney	10-20%

COVID-19





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CDC

The purpose of the Coronavirus Self-Checker is to help you make decisions about seeking appropriate medical care. This system is not intended for the diagnosis or treatment of disease or other conditions, including COVID-19. This system is intended only for people who are currently located in the United States.





Personal Protection Equipment





338 Clinical trials

Remdesivir
Favipiraivir
HCQ <u>+</u> Azithromycin
IL-6 receptor inhibitor

Diagnostics
RT-PCR
non-PCR
IgG, IgM serologies

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COVID-19 and the Liver: Case Studies and Updates

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Clinical Insights Document

- First published online
 March 23rd
- Update posted online this morning, April 7th



Released: April 7, 2020

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

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Clinical Insights Document Major Changes

- o New sections:
 - Diagnosis of SARS-CoV-2 Infection
 - COVID-19 Liver Disease/Transplant Registries
- New tables and figures
- Expanded "What We Know" sections
- Rearranged content for clarity



Table 1. Diagnostic Methods for SARS-CoV-2

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



Table 2. Investigational Treatments

	Agent (route/mechanism)	Target population	Safety issues	Efficacy Issues*
	Remdesivir	Moderate-	Nausea/vomiting	Investigational
	(IV/nucleotide	severe	Grade 1-2 ALT elevations	RCT vs placebo and
	analogue)		Drug vehicle accumulation	compassionate use protocols
			in acute kidney injury	Previously tested in Ebola
				Few DDIs anticipated
			Exclusions:	
			GFR < 30-50 m L/min	
			AST or ALT >5x ULN	
	Favipiravir	Early to		Investigational
	(oral/RNA	mild		Approved for influenza in Asia
	polymerase	disease		Tested with interferon-α
	inhibitor)			aerosol x 14 days
				Improved viral clearance
				compared to lopinavir-
				ritonavir(50)
	Lopinavir-ritonavir	Severe	CYP3A4 substrate	FDA-approved for HIV
	(oral/HIV protease		Severe DDI with CNI	No survival benefit in RCT vs
	inhibitor)		13% early discontinuation	standard of care x 14 days
			due to side effects	
#	Nitazoxanide	Moderate-	Similar to placebo in	FDA-approved for
8	(oral/host proteins)	severe	influenza trials	Crytosporidium/Giardia
₹.				In vitro activity against
픟				coronaviruses
Antiviral Agants	Hydroxychloroquine	Moderate-	QTc prolongation	FDA-approved for
•	(oral/host proteins)	severe	Nausea and vomiting	lupus/rheumatoid
				arthrtitis/malaria
			Exclusions:	Available as emergency use
			QTc >415 ms	May work by reducing ACE2
			Cardiomyopathy	receptor-mediated endocytosis
			G6PD deficiency	or inhibiting endosomal
	cu .		OT 1	acidification
	Chloroquine	Moderate-	QTc prolongation	FDA-approved for malaria
	(oral/host proteins)	severe	Nausea and vomiting	May work by reducing ACE2
			Exclusions:	receptor-mediated endocytosis or inhibiting endosomal
			OTc >415 ms	acidification
			4	
			Cardiomyopathy	Reduced progression of disease
	Azithromycin	Moderate-	G6PD deficiency CYP3A4 substrate	and symptom duration in China FDA-approved for bacterial
		severe	Moderate DDI with CNI	infections
	(oral/host proteins)	severe	Rare cholestatic hepatitis	Combined with
			nare cholestatic nepatitis	
			Exclusion:	hydroxychloroquine in only 6
			OTc >415 ms	patients
			QTC 2415 MS	

	Toclizumab (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	FDA-approved for RA 8 mg/kg dose
mmunomodulatory Agants	Sarilumab (SC/monoclonal antibody)	Severe (high IL-6 levels)	Exclusions: ANC <2,000/m³ Platelets <100,000/m³ ALT >5 xULN Grade 1-2 ALT 15%-25% Neutropenia 5% Thrombocytopenia 1% Exclusions: ANC <2,000/mm³ Platelets <150,000/m³ ALT >5 ULN	FDA-approved in RA Being tested as IV formulation
Immunor	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



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

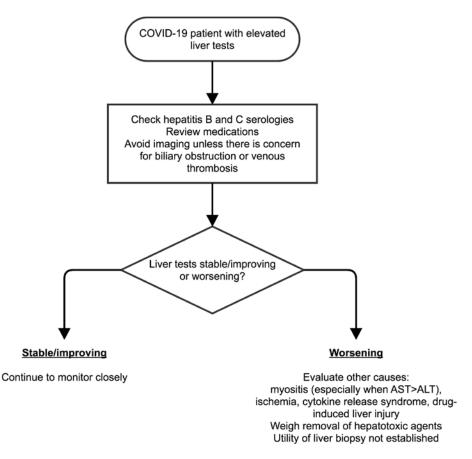
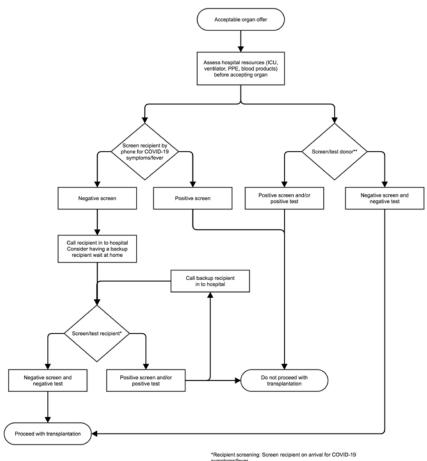




Fig 2. Approach to LT Organ Offers

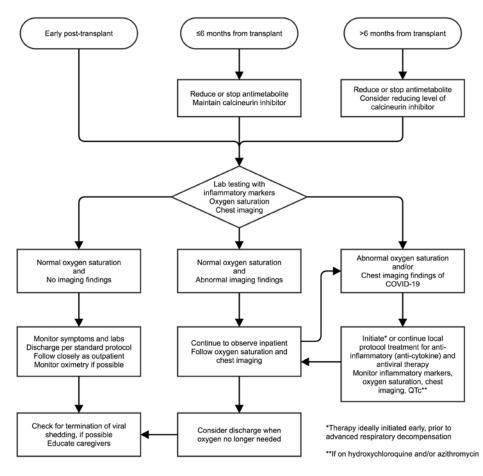


symptoms/fever Test recipient for SARS-Co-V-2, if available

**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



Fig 3. Approach to the LT Recipient with COVID-19





Major Changes: SARS-CoV-2

- Virology of SARS-CoV-2
- Liver histology in COVID-19
- Expanded COVID-19 symptoms for screening:
 - sore throat, diarrhea, new loss of sense of taste or smell
- Expanded COVID-19 complications when evaluating patients with elevated liver tests
 - myositis, cytokine release syndrome, ischemia/hypotension, DILI



Major Changes: Chronic Liver Disease

- Clarified recommendations for treatment of patients with liver disease
 - Continue treatment for HBV and HCV
 - Consider delaying initiation of HCV treatment
 - Removed specific 10 mg recommendation when tapering high-dose prednisone in patients with COVID-19
 - Recommend initiating immunosuppressive therapy in patients with liver disease who have strong indications for treatment (e.g., autoimmune hepatitis, graft rejection)



Major Changes: HCC

- Clarified recommendations for monitoring patients with HCC and surveillance of patients at risk for HCC
- Arbitrary delay of 2 months is reasonable based on tumor doubling time and COVID-19 circumstances



Major Changes: COVID-19 Treatment

- Expanded section on Medication Management to include new information about investigational agents
- Link to University of Liverpool Drug Interactions Group

Immunosuppressants

	ATV	LPV/r	RDV	FAVI	CLQ	HCLQ	RBV	TCZ	IFN-β
Adalimumab	\leftrightarrow								
Anti-thymocyte globulin	\leftrightarrow	\leftrightarrow	\leftrightarrow	\leftrightarrow	\leftrightarrow	\leftrightarrow	+	\leftrightarrow	\leftrightarrow
Azathioprine	\leftrightarrow	\leftrightarrow	\leftrightarrow	\leftrightarrow	\leftrightarrow	\leftrightarrow	↑	\leftrightarrow	\leftrightarrow
Basiliximab	\leftrightarrow								
Belatacept	\leftrightarrow								
Ciclosporin	↑	1	\leftrightarrow	\leftrightarrow	1	↑	\leftrightarrow	\	\leftrightarrow
Mycophenolate	\leftrightarrow	↑↓	\leftrightarrow						
Pirfenidone	\leftrightarrow	\	\leftrightarrow	\leftrightarrow	\leftrightarrow	\leftrightarrow	\leftrightarrow	\leftrightarrow	1
Sirolimus	↑	↑	\leftrightarrow	\leftrightarrow	1	↑	\leftrightarrow	\	\leftrightarrow
Tacrolimus	↑	1	\leftrightarrow	\leftrightarrow	↑	↑	\leftrightarrow	\	\leftrightarrow



Major Changes: Procedures

- Added transient elastography to list of elective/ non-urgent procedures
- Revised list of procedures that may need to be performed
- Revised PPE recommendations for endoscopic procedures to include N95 masks and double gloves



Available Resources from AASLD

- Updated document available today at: https://www.aasld.org/about-aasld/covid-19-resources
- Spanish and Portuguese translations coming soon
- o Future updates planned
- Manuscript in preparation



RAPID FIRE JOURNAL CLUB

Mark W. Russo, MD, MPH, FAASLD



Clinical presentation

Study	Design	Presentation	Course			
Bhatraju PK et al, NEJM	Retrospective study 9 Seattle hospitals of 24 adult pts in ICU	Symptoms 1 wk prior to admission 54% contact with ill person 50% no fever 75% lymphopenia	Among 24 in ICU 75% ventilated 50% died, 70% men 62%>65 died 37%<65 died			
Onder G, et a. JAMA	Retrospective in Italy	Among fatalities 30% heart disease 35% diabetes 20% active cancer 2.7 preexisting diseases Per fatality	Fatality (%) age Italy China 60-69 3.5 3.6 70-79 12.8 8.0 80-89 20.2 14.8			
Lu X, et al NEJM Letter, pediatrics Wuhan Childrens hospital	Retrospective N=171 peds Median age 6.7 60% male	16% asymptomatic 65% pneumonia 3 pts in ICU & vent all had comorbidities	59% no fever 3.5% lymphopenia 149 discharged			



Commentary: Clinical Presentation

- Fever may not be present in 50% or more of adults or children
- Serious illness although uncommon in children, occurs and reported in those with comorbidities
- Lymphopenia common adults, not common in children
- Fatality rates are confounded by testing strategies, implicated causes of death
- Liver injury was not reported on initial studies of COVID-19
- Patients may present with GI symptoms (diarrhea, vomiting) (AJG)



Treatment

Study	Design &Treatment	Study population	Outcome
Cao, B NEJM Wunan	Lopinavir-ritonavir x 14d 99 treated vs 100 SOC Open label RCT	O2 sat<94% PAO2:FiO2<300 Excluded cirrhotics & ALT, AST >5XULN	No difference in clinical improvement btwn groups GI side fx with Lop/Rit
Gautret P, Int J Antimicro Agents France	Single arm n=36 Hydroxychloroquine+/- azithromycin Untreated controls n=16	Age >12 Excluded –retinopathy,G6PD def QT prolonged	Virologic cure day 6 70% treated group 12.5% controls p=0.001
Molina, et at Med Mal Infect France	11 patients, hydroxychlorquine+ azithromycin, same design as gautret	Mean age 58.7 (20-77) 8 patients had significant comorbidities	1 patient died 4 patients dc'd due to prolonged QT interval 8 pts remained PCR+
Chen, et al, MedRxiv Wuhan (not peer reviewed)	Prospective, multicenter open label RCT favipiravir n=116 vs arbidol (umifenovir) n=120	≥18 y/o, symptoms within 12 days and COVID pneumonia Excl AST/ALT>5xULN 3 groups: ordinary, DM+HTN, severe	7 day clinical recovery in "ordinary group" 56% arbidol group 71% favipravir group p=0.0199
Shen C JAMA 2020 Shenzhen	Convalescent plasma administered 10-22 after admission	5 critically ill patients with ARDS ventilated Age 36-65	4 pts resolution of ARDS 12 days post infusion,3 discharged



Commentary: Treatment

- Lopinavir-ritonavir was not associated with clinical improvement in clinical trial. May see studies in less ill populations or in combination with other antivirals
- Hydroxychloroquine +/- azithromycin with 1 positive and 2 negative trials. Larger, randomized studies with clinical outcomes awaited.
- Be aware of drug interactions with ritonavir, prolongation of QT interval with hydroxychloroquine, azithromycin
- Study from nonpeer reviewed article reported favipiravir led to improved clinical course compared to umifenovir in subgroup analysis of patients with mild disease. Results need to be reproduced.
- Convalescent plasma studied in small group that was severely ill with ARDS and ventilated and these patients were on multiple antivirals.
 Preliminary results encouraging but need validation.
- Data on remdesivir, tocilizumab, others eagerly awaited



Presents an algorithm for

dedicated transplant pathway

Liver related studies			
Study	Design	Findings	
Zhang Y et al. Liver Int Mar	N=115, COVID pts N=119 ComAcqPneum pts Retrospective.	No difference AST, ALT elevations btwn groups Albumin lower in COVID group	
Bangash MN, et al. Lancet GI Hep Mar	Correspondence -review of 7 studies	AST, ALT 1-2x ULN Most severe COVID cases AST, ALT 2x ULN, Elevations in CK	
Xiao, Y, et al Lancet GI Hep Mar	111 Decompensated cirrhosis enrolled in prevention study, WeChat messaging every 3 days total times	0 decomp cirrhosis had COVID symptoms at authors' hospital vs 17% decomp cirrhotics at other Wuhan hospitals	
Qin J et al. Hepatology 2020 Mar	Case report 37 y/o man OLT for HBV, HCC	Recovered, received oseltamivir and antivirals	
D'Antiga et al. Liver Transpl 2020	Bergamo - Peds, Transplant center experience	No sig. COVID disease among, 200 LT recipients,100 AIH pts, 3 recipients test positive	

Milan- transplant center

experience

Andrea, et al AJT Mar



Commentary: Liver and Transplant

- Significant liver test abnormalities uncommon from COVID-19 disease
- If significant liver test elevations, evaluate for other causes including drugs, positive pressure ventilation-congestion, ischemia, myositis
- Increased morbidity and mortality from coronaviruses including SARS-CoV-2 has not been associated with immunosuppression in liver transplant recipients
- No evidence to support routinely reducing immunosuppression in uninfected liver transplant recipients, patients with autoimmune hepatitis



Case Discussion

Elizabeth C. Verna, MD, MS Columbia University Medical Center



52 year old woman with...

- Chief complaint: Subjective fever, cough, shortness of breath and headache
 - Onset of symptoms 7 days ago, initially with fever and headache, and now presents to the ER due to significant shortness of breath
 - No recent travel, husband also with about 10 days of fever and diarrhea
 - She and her husband were started on hydroxychloroquine empirically by her internist 4 days ago
 - They were not tested for COVID or other respiratory viruses
- Medical history: Hypothyroidism, stable on replacement therapy
- Surgical history: Cholecystectomy in 2011 for symptomatic cholelithiasis
- Social history: Works part time as a pharmacist, no alcohol or tobacco use, lives with husband and 34 year old son



At initial presentation:

• Vitals: Temperature 38.5 C, HR 111, BP 102/68, RR 28, O2 saturation 90% on RA at rest

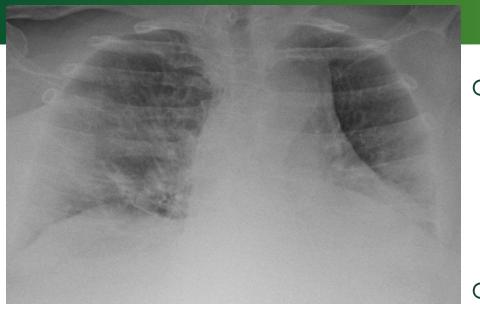
Physical Exam:

- Well nourished and well developed, moderate respiratory distress, difficulty speaking in full sentences
- Anicteric sclera
- Chest with mild diffuse crackles
- Tachycardia, regular rate and rhythm
- Abdomen soft, nontender, nondistended, no hepatosplenomegaly appreciated
- No edema, no cyanosis



- Initial diagnostic work up:
 - WBC: 4.1, 86% PMN, 7% lymphocytes
 - Hgb 13.4, platelets 167,000
 - Creatinine 1.37 mg/dl, eGFR 43ml/min
 - AST 266 U/L, ALT 234 U/L, TB 0.4 mg/dl
 - INR 1.1, Ddimer 0.5 ug/ml
 - CRP 99 mg/l, ESR 45
- Nasopharyngeal swab for SARS-CoV2 positive





- Chest x-ray: Bilateral patchy airspace opacities, no pleural effusion, normal cardiac silhouette
- EKG: Sinus tachycardia

Olinical course:

- Patient isolated and with mask upon initial ER intake assessment
- O2 saturation increased to 95% on 4L NC and more comfortable appearing



Initial treatment:

- Supplemental oxygen was slowly titrated up
- Continued hydroxychloroquine to complete 5 day course
- 5-day course of azithromycin started as well
- Evaluated for additional treatment options and clinical trials including:
 - Antivirals:
 - Remdesivir nucleotide analogue
 - <u>Immune modulation</u>:
 - IL-6 inhibitors Tocilizumab, Sarilumab
 - High dose steroids, IVIG



- Work up of elevated liver tests:
 - Liver tests had been normal 4 months ago
 - HCV Ab negative, HBsAg negative, HAV IgG positive
 - EBV and CMV negative
 - Ferritin 7800, CK 405
- Ultrasound deferred in order to minimal exposures



Preliminary analysis of <u>1076 patients</u> with confirmed COVID at CUIMC

	AST (U/L)	ALT (U/L)
Initial value, median (IQR)	37 (24, 60)	27 (18, 45)
> ULN, n (%)	353 (33%)	221 (21%)
>2x ULN, n (%)	107 (10%)	62 (5.8%)
>5x ULN, n (%)	26 (2.4%)	17 (1.6%)

- AST or ALT > ULN in 33%, >2x ULN in 10% and > 5x ULN in 2.4%
- AST elevation in more common than ALT and likely reflects contribution of AST sources outside the liver

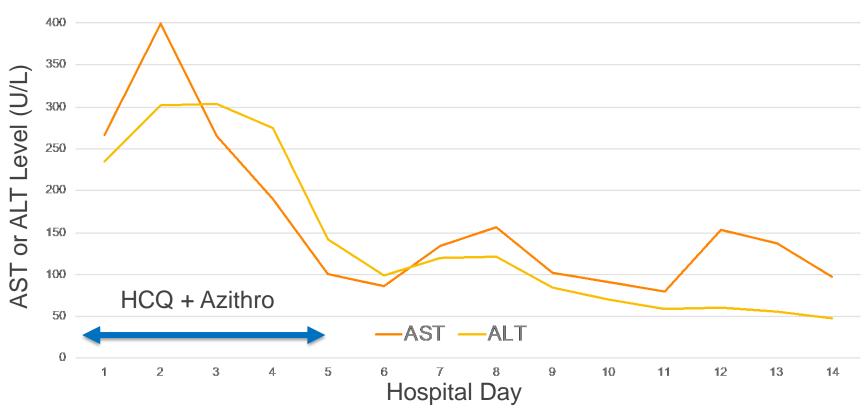


On first night of hospitalization:

- Progressive hypoxemic respiratory failure and increased work of breathing
- Placed on non-rebreather but with progressive decline in O2 saturation
- Ultimately intubated and moved to ICU on hospital day 2

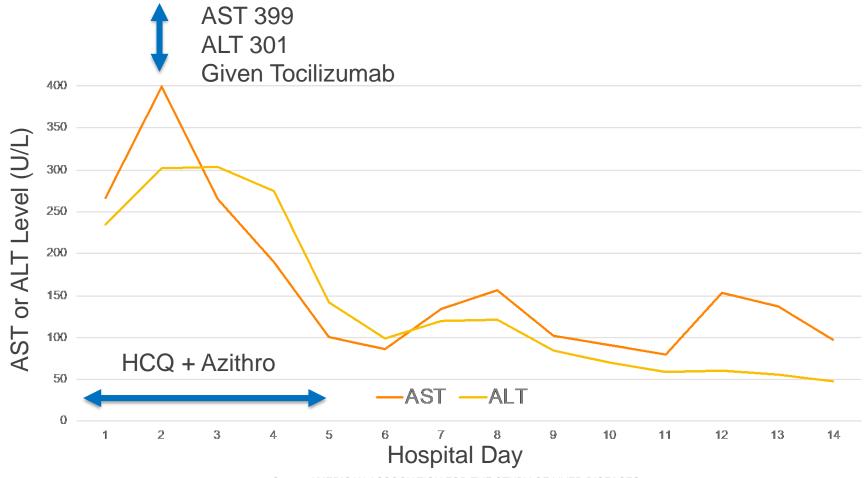


Trajectory of Liver Enzymes and Clinical Course

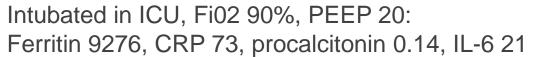


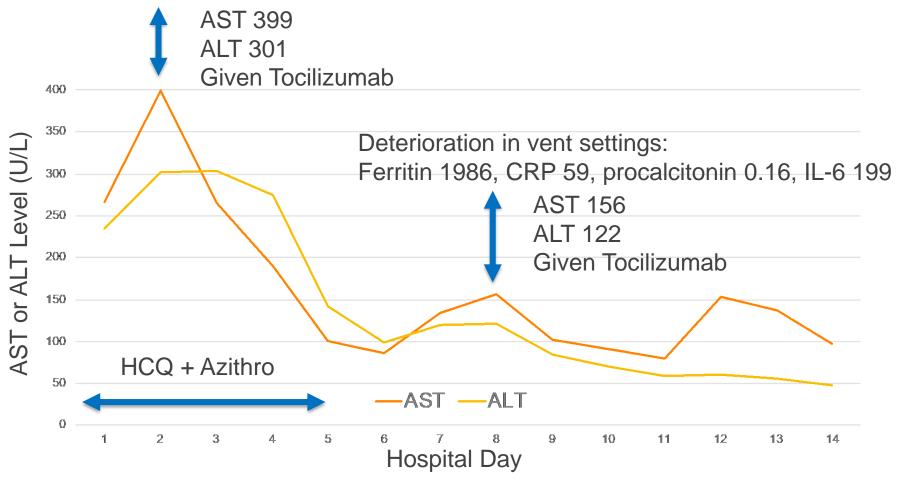


Intubated in ICU, Fi02 90%, PEEP 20: Ferritin 9276, CRP 73, procalcitonin 0.14, IL-6 21

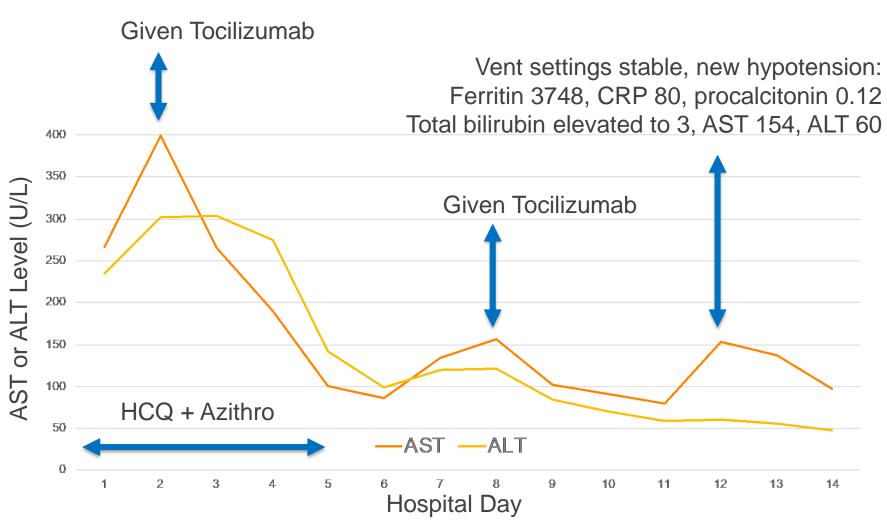














Olinical course continued:

- Abdominal ultrasound with heterogeneous appearing liver, normal bile ducts, no splenomegaly, no thrombosis
- Blood and urine cultures positive for E. Coli, started on antibiotics
- TTE with EF 65%, no significant valvular abnormalities

Hospital day 14:

- Off pressors, on antibiotics
- Improved vent settings: FiO2 40% with PEEP 15
- AST 98, ALT 48, total bilirubin 1.2

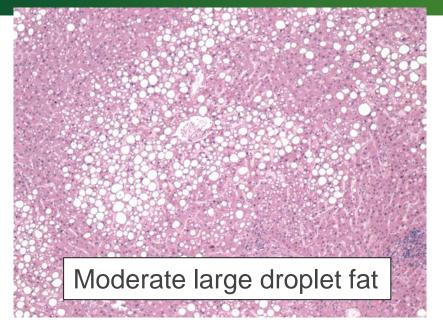


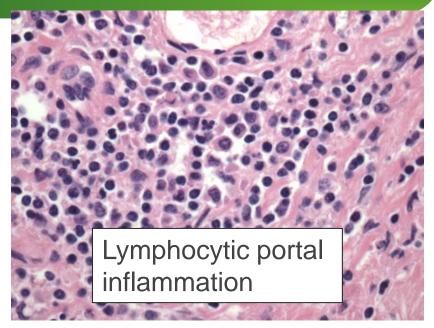
o Take away points:

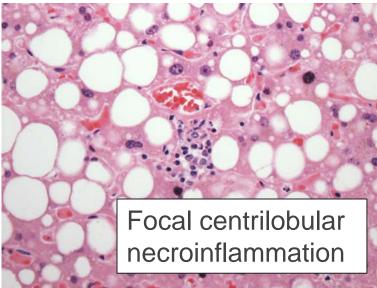
- Mild liver enzyme elevation is relatively common in COVID-19
- More severe elevations >5x ULN occur in <10% of patients and are more likely in severe disease
- Liver enzyme elevation may impact COVID-19 treatment strategies
- In critically ill patients, liver enzyme abnormalities are likely to be multifactorial
- Liver injury from COVID-19 likely reflects both direct viral-mediated injury as well as inflammatory response and may mimic the clinical course of the COVID-19 syndrome

Autopsy Histology: AST 48, ALT 23









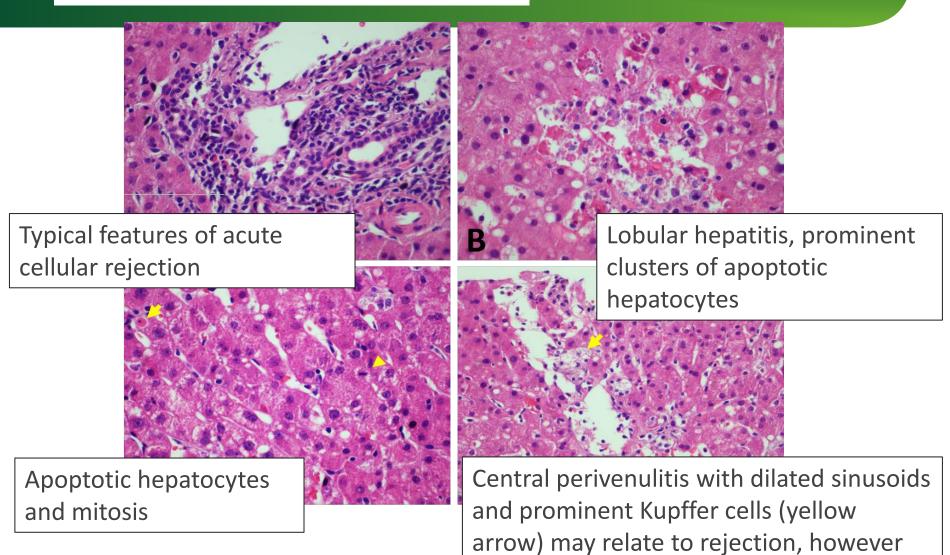
- Overall changes most consistent with NAFLD
- Uncertain whether any of these represent COVID-specific changes

DY OF LIVER DISEASES

Post-Liver Transplant: POD 7



such changes have also been described in



MERS hepatitis.

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o Take away points:

- There is not yet a complete description of liver histological changes with COVID-19
- Underlying liver disease will impact liver enzyme and liver histology abnormalities
- Liver biopsy is not indicated unless there is a strong suspicion for additional pathology that will influence urgent treatment decisions (i.e. allograft rejection)



Panel Discussion

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





Upcoming COVID-19 Webinar

Thursday, April 16, 2020 5-6pm Eastern

Clinical Insights: COVID-19 and the Liver – Case Studies and Updates

Presenters:

Bilal Hameed, MD Ryan Kwok, MD Michael Schilsky, MD, FAASLD

Moderator:

Brendan McGuire, MD

Registration: http://www.aasld.org/COVID19



COVID-19 websites

- CDC https://www.cdc.gov/coronavirus/2019
- NIH https://clinicaltrials.gov/
- FDA https://www.fda.gov/emergency-preparedness
- AASLD http://www.aasld.org/COVID19
- Endoscopy
 https://www.aasld.org/sites/default/files/2020-04/JointSocietyMessage-ProceduresInTimeOfCOVID19-FINAL.pdf
- UNOS https://unos.org/covid/
- UW Transplant registry



AASLD's COVID-19 Resources

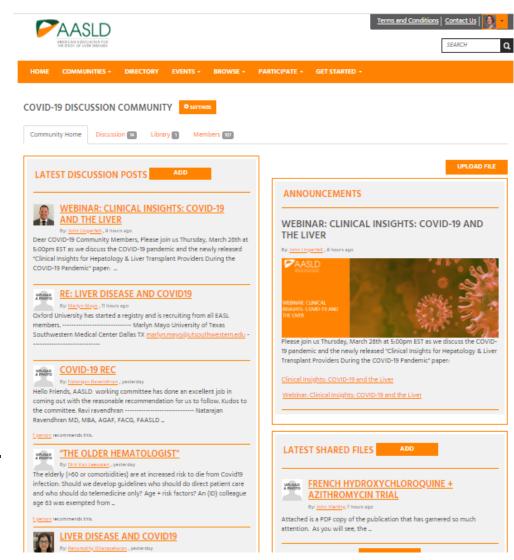
Follow/Share: COVID-19

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 COVID19 original articles, case
reports





References

Bhatraju PK, et al.. Covid-19 in Critically III Patients in the Seattle Region - Case Series. N Engl J Med. 2020 Mar 30. Epub ahead of print. PMID: 32227758.

Onder G, et al. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. JAMA. 2020 Mar 23.. PMID: 32203977.

Lu, X et al. SARS-CoV-2 Infection in Children. N Engl J Med. 2020 Mar 18.

Cao, B et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020 Mar 18

Gautret P, et al. Hydroxychloroquine and Azithromycin as a Treatment of COVID-19: Results of an Open-Label Non-Randomize Clinical Trial 2020 Mar Int J Antimicrobial Agents

Molina, et al. No evidence of Rapid Antiviral Clearance or Clinical Benefit with the Combination of Hydroxychloroquine and Azithromyicn in paitents with severe COVID-19 Infection Med Mal Infect 2020 Mar.

Chen C, et al. Favipiravir versus Arbidol for COVID-19: A randocmized Clinic Trial.medRxiv preprint doi: https://doi.org/10.1101/2020.03.17.20037432

Shen C, et al. Treatment of 5 Critically III Patients with COVID-19 with Convalescent Plasma. JAMA 2020 Mar.

Zhang Y, et al. Liver Impairment in COVID-19 Patients: a Retrospective Analysis of 115 cases from a Single Center in Wuhan city, China. Liver Int. 2020 Apr 2..

Bangash MN, et al. COVID-19 and the Liver: Little Cause for Concern. Lancet Gastroenterol Hepatol 2020 Mar.

Xiao Y, et al. Prevention of SARS-CoV-2 infection in patients with decompensated cirrhosis. Lancet Gastroenterol Hepatol. 2020 Mar 17.

.Qin J, et al Perioperative Presentation of COVID-19 Disease in a Liver Transplant Recipient. Hepatology. 2020 Mar 27. doi: 10.1002/hep.31257. Epub ahead of print. PMID: 32220017.

D'Antiga L. Coronaviruses and imm@n@suppressed patients! The facts dufing the third epidemic. Liver Transpl. 2020 Mar 20. Andrea G, et al. Coronoa Disease 2019 and Transplantation: a view from the inside. Am J Transpl 2020.