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AASLD COVID-19 Working Group Presents

Clinical Insights: COVID-19 and the Liver – Antibody Testing and Treatment Recommendations

April 30, 2020
5-6 pm ET

Presenters:
Kimberly Ann Brown, MD, FAST, FAASLD, AGAF
Emmanuel Thomas, MD, PhD, FAASLD
Laura M. Kulik, MD

Moderator:
Brendan M. McGuire, MD

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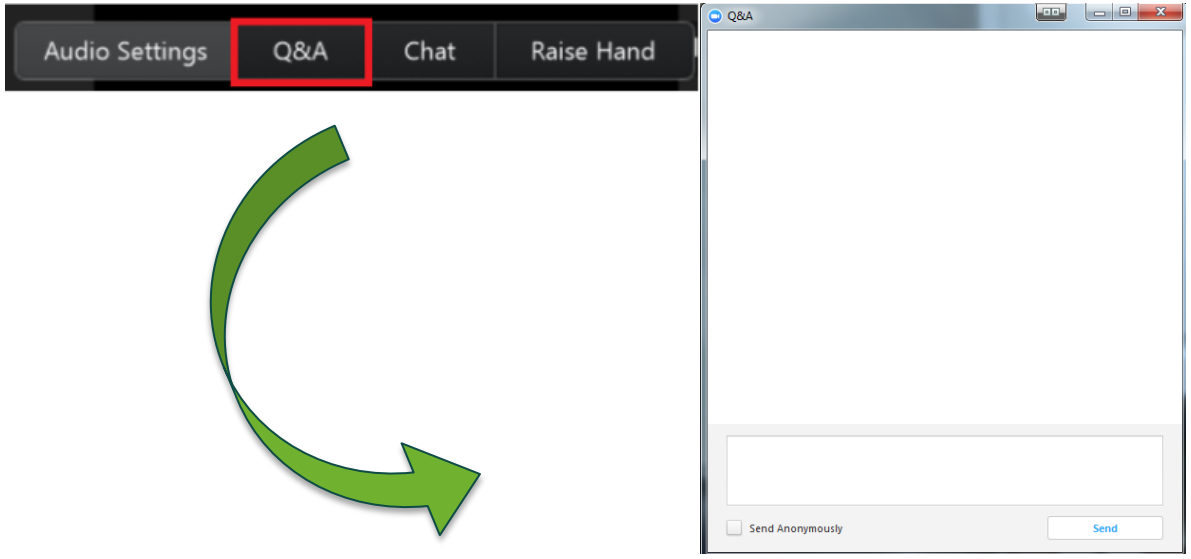
COVID-19 and the Liver – Antibody Testing and Treatment Recommendations

Webinar Series

Updates April 30, 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

Brendan M. McGuire, MD, MS

University of Alabama at Birmingham

Presenters

Kimberly Ann Brown, MD, FAST, FAASLD, AGAF

Henry Ford Health System

Emmanuel Thomas, MD, PhD, FAASLD

University of Miami School of Medicine

Laura M. Kulik, MD

Northwestern University Feinberg School of Medicine

Panelists

Jaime Chu, MD

Icahn School of Medicine at Mount Sinai

Oren K. Fix, MD, MSc, FAASLD

Swedish Medical Center

Patricia Harren, DNP

Columbia University Medical Center

David C. Mulligan, MD, FAASLD

Yale University

Daniel S. Pratt, MD, FAASLD

Massachusetts General Hospital

Elizabeth C. Verna, MD, MS

Columbia University Medical Center

AASLD COVID-19 Working Group	
K. Rajender Reddy, MD, FAASLD	University of Pennsylvania Medical Center
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Bilal Hameed, MD	University of California, San Francisco
Michael L. Schilsky, MD, FAASLD	Yale New-Haven Hospital
Mark W. Russo, MD, MPH, FAASLD	Carolinas Medical Center
Brendan M. McGuire, MD	University of Alabama at Birmingham
Robert J. Fontana, MD, FAASLD	University of Michigan Hospitals and Health
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Elizabeth C. Verna, MD, MS	Columbia University Medical Center
Jorge A. Bezerra, MD, FAASLD	Cincinnati Children's Hospital Medical Center
Raymond T. Chung, MD, FAASLD	Massachusetts General Hospital

- Welcome and Introduction
  - Brendan McGuire
- Antibody Tests for SARS-CoV-2/COVID-19: Everybody Wants to Know if They Have Been Infected and Are Protected
  - Emmanuel Thomas
- Treatment and NIH Guidance
  - Laura Kulik
- Case Presentation: Managing the Patient with Autoimmune Hepatitis and COVID-19
  - Kimberly Brown
- Q&A
- Closing

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Clinical Insights: COVID-19 and the Liver

Introduction

Brendan M. McGuire, MD, MS
Professor of Medicine
Medical Director of Liver Transplant
University of Alabama at Birmingham

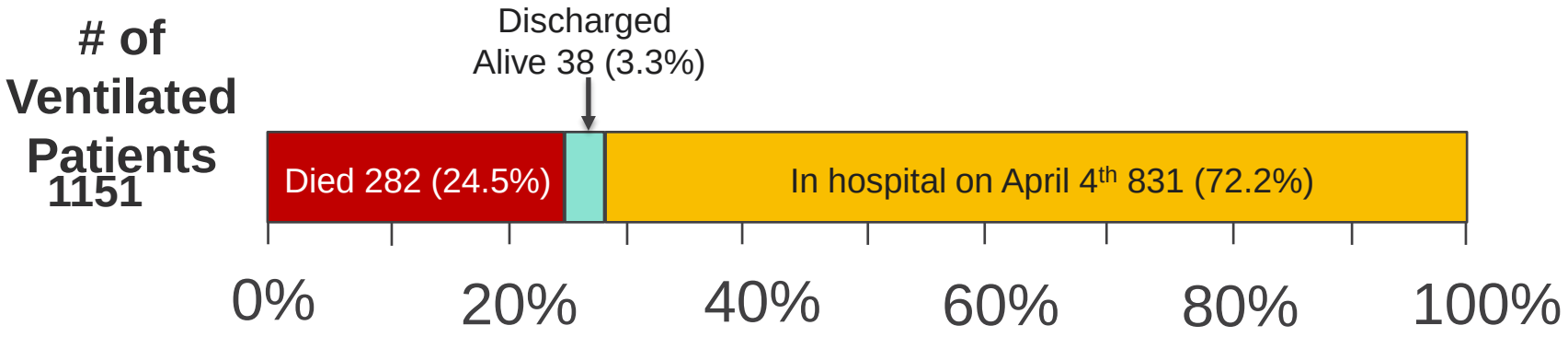
Presenting Characteristics, Comorbidities, & Outcomes Among 5,700 Patients Hospitalized with COVID-19 in the New York City Area

- Case series of 5,700 hospitalized patients confirmed + for the SARS-CoV-2 infection by PCR testing from nasopharyngeal samples, 3/1 – 4/4/20, from NY City area
- This study describes the demographics, baseline comorbidities, presenting clinical tests, and outcomes.

S. Richardson, et al. JAMA published 4/22/20. doi:10.1001/ja,a.2020.6775

“Mortality for those requiring mechanical ventilation was 88.1%.”

$$\frac{\text{\# of patients who died (N=282)}}{\text{\# discharged alive (N=38) + died (N=282)}} = 88.1\%$$



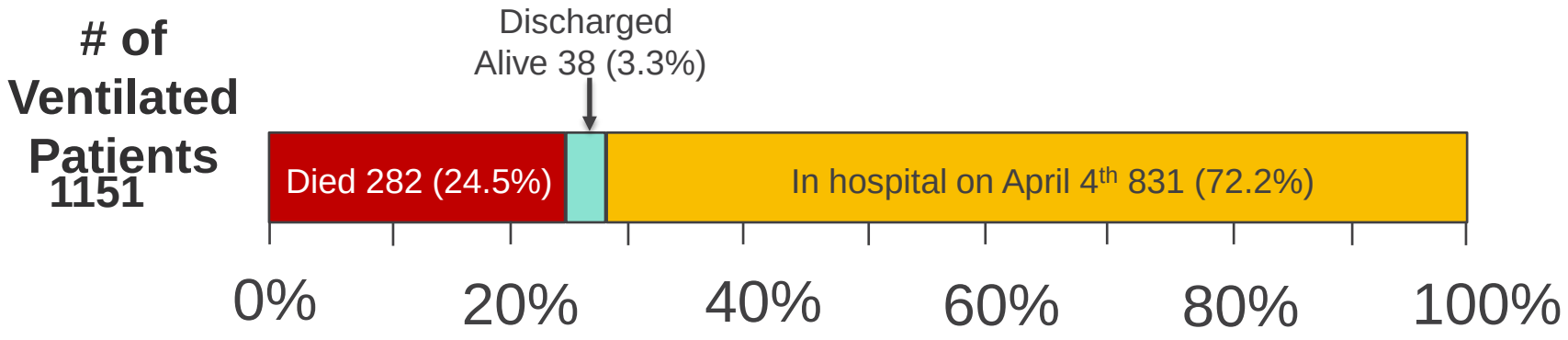
S. Richardson, et al. JAMA published 4/22/20. doi:10.1001/ja,a.2020.6775

April 24, 2020

CORRECTION

"For patients requiring mechanical ventilation (N=1151, 20.2%), 38 (3.3%) were discharged alive, 282 (24.5%) died, and 831 (72.2%) remained in hospital."

$$\frac{\text{\# of patients who died (N=282)}}{\text{\# discharged alive (N=38) + died (N=282) + still in hospital (N=831)}} = 24.5\%$$



S. Richardson, et al. JAMA published 4/22/20. doi:10.1001/ja,a.2020.6775

Demographic Information	Number
Age in years, median [IQR] {range}	63 [52-75] {0-107}
Sex, Male (%)	3437 (60.3)
Race (%)	
African American	(22.6)
Asian	(8.7)
White	(39.8)
Other/multiracial	(28.9)
Insurance (%)	
Commercial	(33.1)
Medicaid	(21.2)
Medicare	(42.4)
Self-pay	(1.7)
Other	(1.7)

IQR=Interquartile range

S. Richardson, et al. JAMA published 4/22/20. doi:10.1001/ja,a.2020.6775

Comorbidities	Number (%)
Liver disease	
Cirrhosis	19 (0.4)
Chronic HBV	8 (0.1)
Chronic HCV	3 (< 0.1)
Metabolic disease	
BMI ≥ 30	(41.7)
BMI ≥ 35	(19.0)
Diabetes	(33.8)
Hypertension	(56.6)
History of solid organ transplant	55 (1)

S. Richardson, et al. JAMA published 4/22/20. doi:10.1001/ja,a.2020.6775

Presentation Laboratory Results (reference range)	Median [IQR] (%)
WBC (3.8-10.5 x 10^9/L) Absolute neutrophil (1.8-7.4 x 10^9/L) Lymphocyte (1-3.3 x 10^9/L) Lymphocyte < 1 x 10^9/L	7.0 [5.2-9.5] 5.3 [3.7-7.7] 0.88 [0.6-1.2] (60)
AST (10-40 U/L) AST > 40 U/L	46 [31-71] (58.4)
ALT (10-45 U/L) ALT > 60 U/L	33 [21-55] (39)
Ferritin (15-400 ng/mL)	798 [411-1515]
D-dimer (0-229 ng/mL)	438 [262-872]

S. Richardson, et al. JAMA published 4/22/20. doi:10.1001/ja,a.2020.6775

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Lymphocyte < 1 x 10^9/L	(60)
AST (10-40 U/L) AST > 40 U/L	46 [31-71] (58.4)
ALT (10-45 U/L) ALT > 60 U/L	33 [21-55] (39)
Ferritin (15-400 ng/mL)	798 [411-1515]
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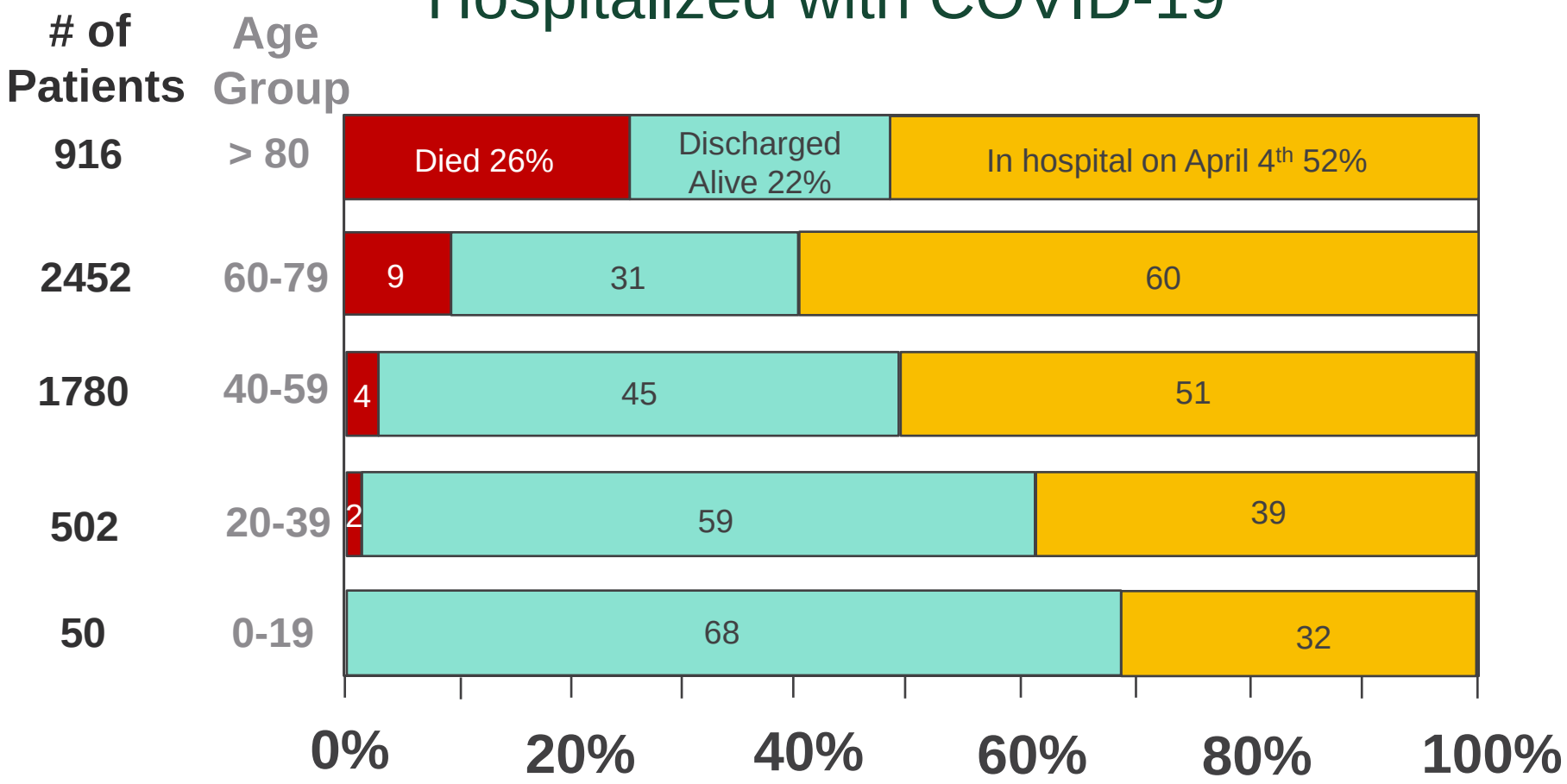
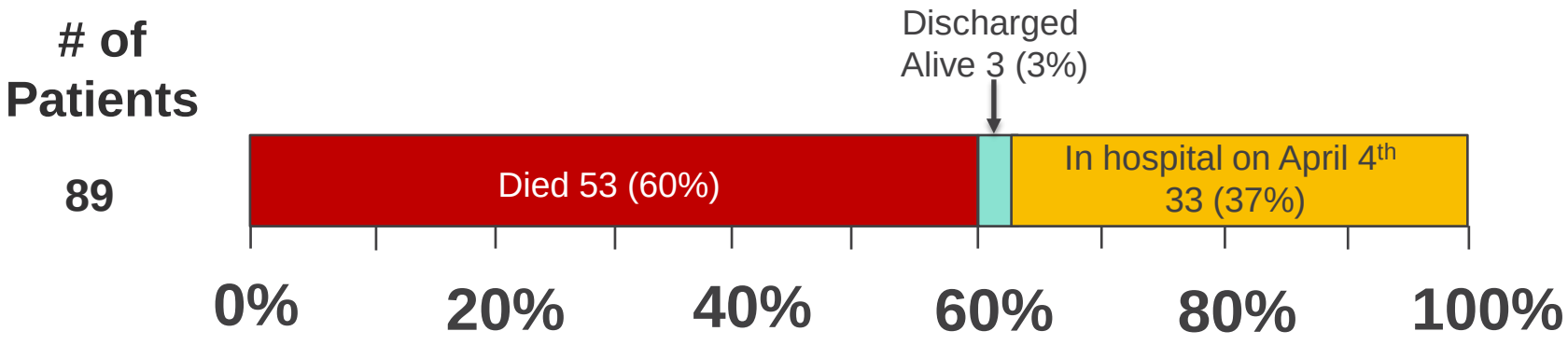
Disposition by 20 Year Age Intervals of Patients Hospitalized with COVID-19



S. Richardson, et al. JAMA published 4/22/20. doi:10.1001/ja,a.2020.6775

Development of Acute Liver Injury (AST or ALT > 15 x ULN) – 1.5%



No patient under the age of 18 developed acute liver injury

S. Richardson, et al. JAMA published 4/22/20. doi:10.1001/ja,a.2020.6775

56 Patients who Developed Acute Liver Injury (AST or ALT > 15 x ULN with an Outcome - Discharged or Died

Outcome by Co-morbidity	Number (%)
Discharged Non-diabetic, N=1542 Diabetic, N=533	 1 (0.1%) 2 (0.4%)
Died Non-diabetic, N=327 Diabetic, N=224	 28 (8.6%) 25 (11.2%)
Discharged Non-HTN, N=1093 HTN, N=982	 1 (0.1%) 2 (0.2%)
Died Non-HTN, N=169 HTN, N=382	 27 (16.0%) 26 (6.8%)

S. Richardson, et al. JAMA published 4/22/20. doi:10.1001/ja,a.2020.6775

Summary

- This is the first large case series of sequentially hospitalized patients with COVID-19 in the US.
- Common co-morbidities included hypertension (56.6%), obesity (41.7%), and diabetes (33.8%).
- Only a few patients had underlying liver disease
  - 11 patients with chronic hepatitis B or C
  - 19 patients had cirrhosis
- Acute liver injury occurred in 1.5% of patients and was associated with worse outcomes
- No pediatric patient died or had an acute liver injury

S. Richardson, et al. JAMA published 4/22/20. doi:10.1001/ja,a.2020.6775

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Antibody Tests for SARS-CoV-2/COVID-19

Everybody Wants to Know if They Have Been Infected and Are Protected

Emmanuel Thomas M.D., Ph.D., FAASLD
Schiff Center for Liver Diseases
Department of Microbiology
University of Miami Miller School of Medicine

Coronavirus Background

- There have been 7 distinct coronaviruses discovered to date that infect humans and cause disease.
  - Mild Respiratory Illness
    - HCoV-229E
    - HCoV-OC43
    - HCoV-NL63 (2004-ACE2)
    - HCoV-HKU1
  - Severe Respiratory Illness
    - SARS-CoV-1 (2003-ACE2)
    - MERS-CoV (2012)
    - SARS-CoV-2 (2019 nCoV) *Disease named COVID-19*

Coronaviruses & Cross-Reactivity

- Details Pertaining to Coronaviruses That Cause Mild Respiratory Illness/Common Cold
  - Individuals usually exposed and seroconvert in childhood.
  - Reinfection with 229E and OC43 is common.
  - Evidence suggests that NL63 and HKU1 likely cause repeated infections also.
  - Cross-reactivity between SARS-COV-1 and 229E and OC43 has been reported but can be rectified by additional testing by western blot.
  - Pan-coronavirus tests that distinguish between exposure to multiple coronaviruses would increase specificity of tests.

Gaunt et al. Journal of Clinical Microbiology, Aug. 2010, p. 2940–2947.

Virus Testing

There are several approaches used to test for virus infection

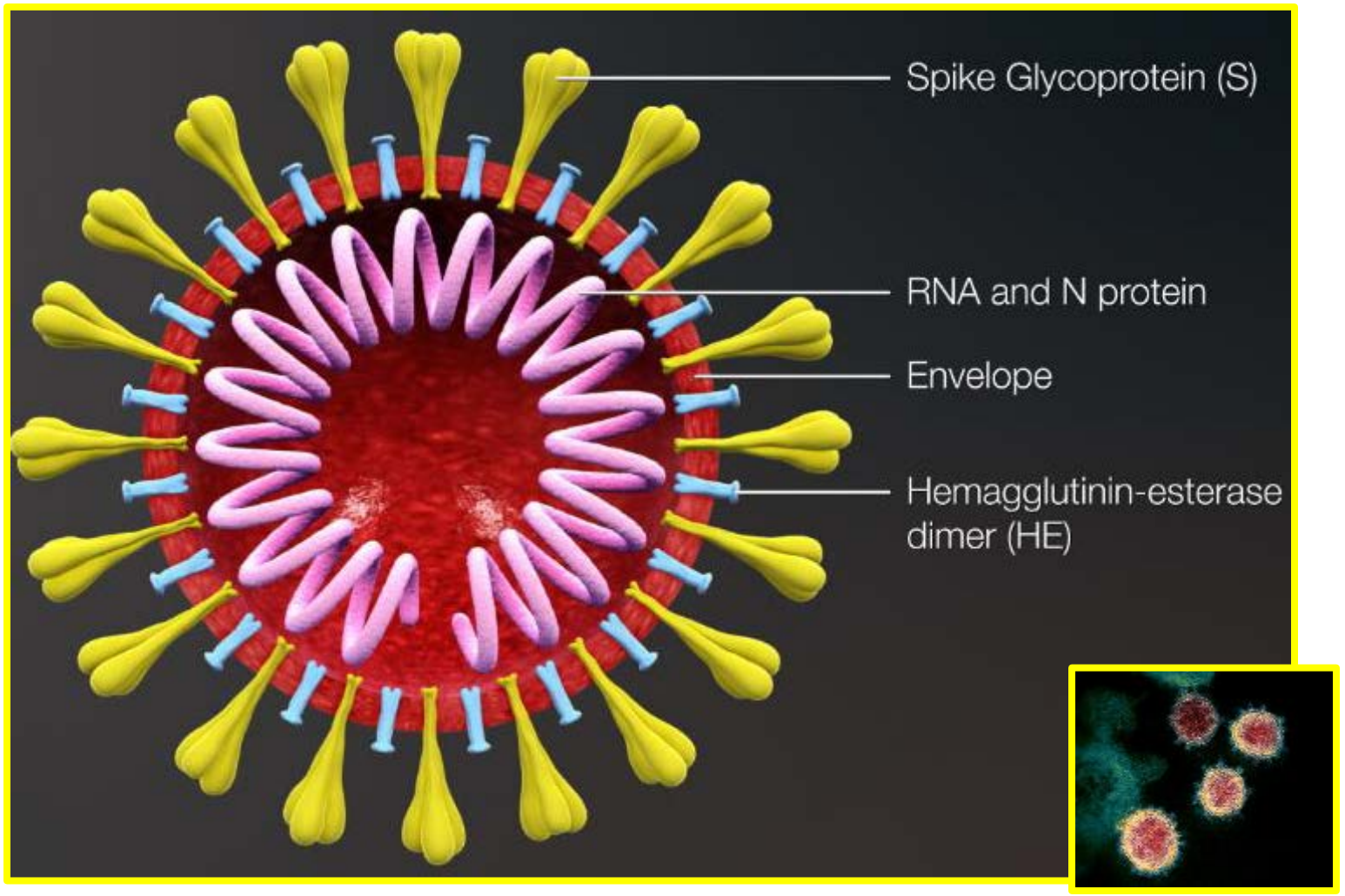
- Molecular (Nucleic Acid): Active Infection
  - PCR (Requires Temperature Variation)
  - Non-PCR Based Approaches
- Serology (Proteins)
  - Viral Antigens: Active Infection
  - Antibodies (e.g. IgM and IgG): Exposure

-Point of Care Screening

-Available from Quest and LabCorp

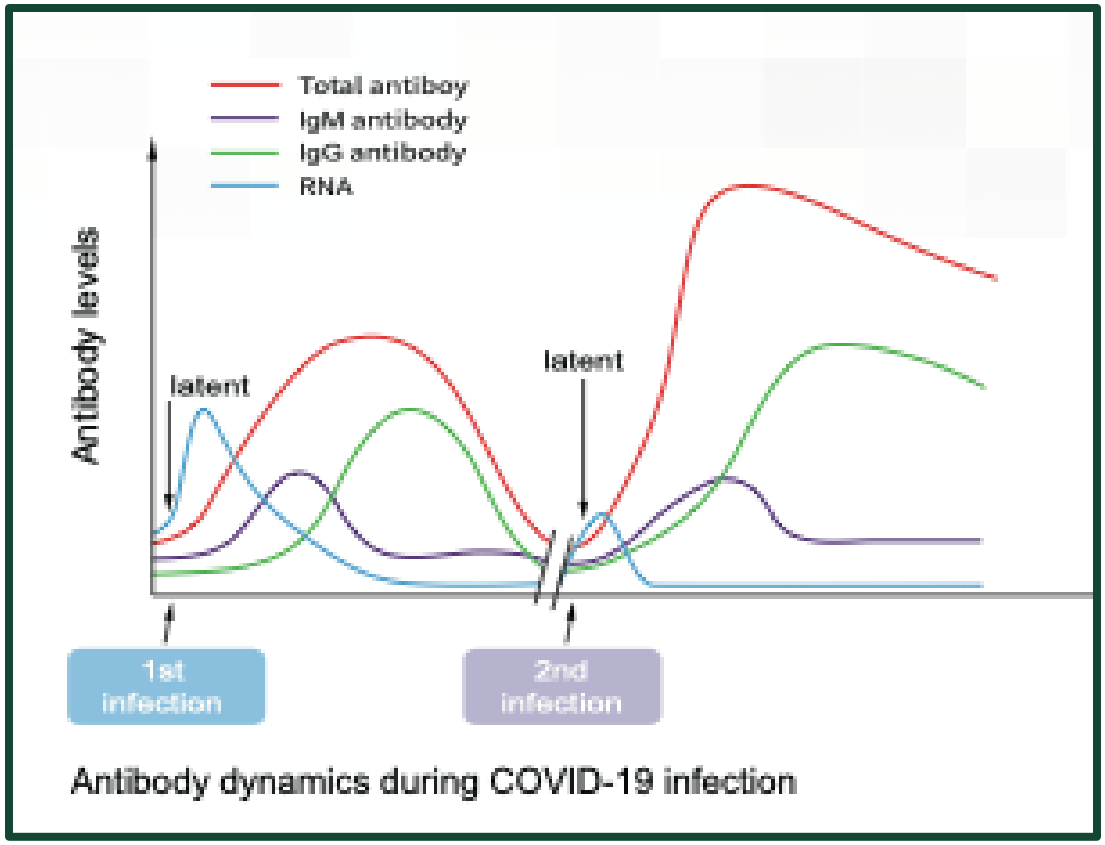
http://medmira.com/miriad-2/

SARS-CoV-2: Viral Structure



https://commons.wikimedia.org/wiki/File:3D_medical_animation_corona_virus.jpg

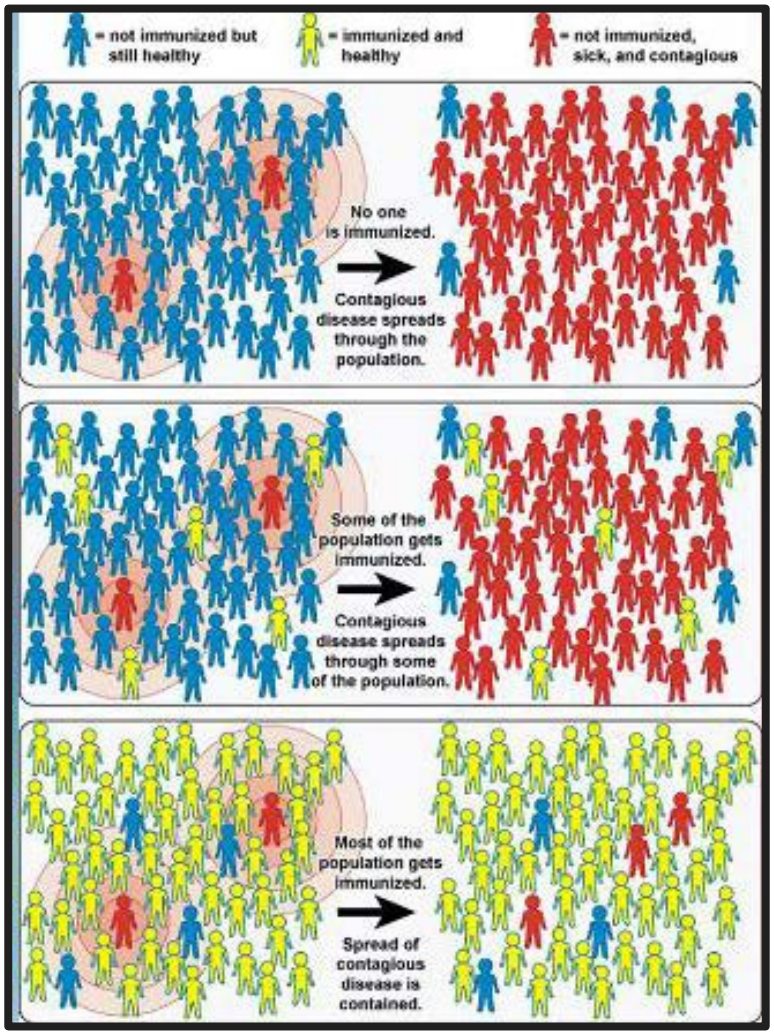
Theoretical Antibody Response Profile



Antibody dynamics during COVID-19 infection

Wantai Diagnostic Kits Product Information, Total Ab ELISA, IgM ELISA, Total Ab Rapid test.

Herd Immunity-Developing Neutralizing Antibody Responses & Vaccination

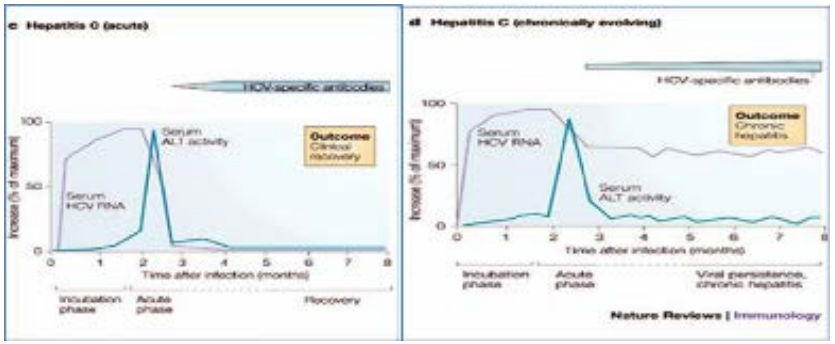


https://www.cnn.com/2020/04/23/health/coronavirus-herd-immunity-explainer-wellness-scn-trnd/index.html

Antibody Testing for SARS-CoV-2

General Comments:

- The antibody response in infected patients remains largely unknown, and the clinical values of antibody testing have not been fully demonstrated.
- Seroprevalence data will be important in understanding the scale of the pandemic and future vaccine utility.
- Correlates of Protection?
- Appropriate neutralization assays may require BSL3



B. Rehermann & M. Nascimbeni Nat. Rev. Imm. Vol. 5, pages215–229(2005)

Antibody Testing for SARS-CoV-2

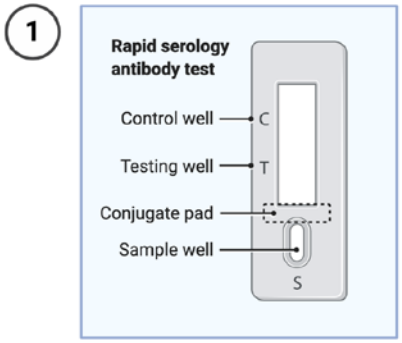
- Potential **utility** of serology in SARS-CoV-2:
  - Detection of PCR-negative cases, especially for patients who present late with a very low viral load below the detection limit of RT-PCR assays, or when lower respiratory tract sampling is not possible.
  - Identification of convalescent plasma donors
  - Verification of vaccine response once antibody correlate(s) protection are identified.
  - May support the identification of healthcare workers that can have some protection from future infection.
  - Can support the identification of patients that may have exacerbation of comorbid illnesses following exposure to SARS-CoV-2.

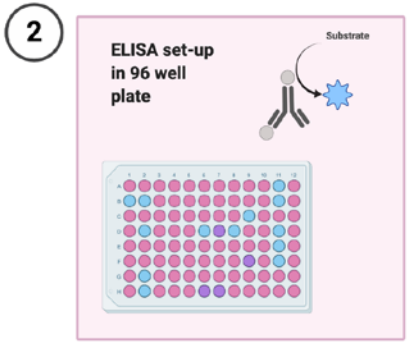
Antibody Testing for SARS-CoV-2

- Potential **drawbacks** if serological assays are not well-validated:
  - False negative risks if performed early in disease course, especially in mild disease.
  - False positive risks, particularly with tests for Immunoglobulin M (IgM) and potential cross-reactivity with common cold coronaviruses (e.g. HKU1, NL63, OC43, 229E).
  - If SARS-CoV-2 spike protein is going to be used in vaccines, will need to test for nucleocapsid or other viral protein in the future.
  - Inaccuracy of proposed “Immunity Passports”
  - Many companies have created assays that are desperately needed but few with a track record in the virology space
  - *https://covidtestingproject.org*

Antibody Testing for SARS-CoV-2

Comparison of main types of COVID-19 tests

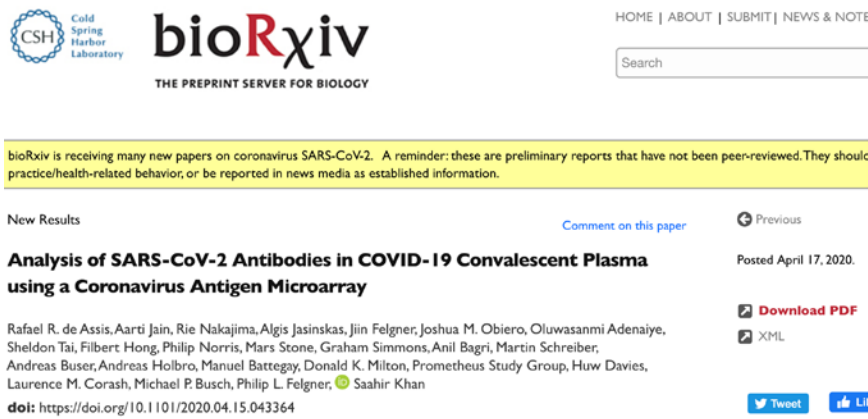




	Rapid serology antibody test	ELISA
Sample input	**Serum** or **plasma** sample (whole blood or finger prick also possible)	**Serum** or **plasma** sample
Result output	Detection of **IgM/IgG antibodies** via color change of strip in lateral flow assay	Detection of **IgM/IgG** or RBD IgG **antibodies**, via colorimetric assay
Strengths	**Very low relative cost**, can be conducted at **point-of-care** or at **home**, ease-of-use, **fast results** (5-15 min, highly accurate detection of IgM/IgG **several days after onset**	**Robust detection of seroconversion** status in a laboratory setting, can detect IgM/IgG highly accurately **several days after onset or sooner**
Limitations	Requires rigorous testing of **cross-reactivity** with other immune response, **variation of test specificity & sensitivity** among manufacturers	Requires rigorous testing of **cross-reactivity** with other immune response, requires **laboratory setting**

https://covidtestingproject.org/faq.html

Neutralizing Ab for SARS-CoV-2



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bioRxiv is receiving many new papers on coronavirus SARS-CoV-2. A reminder: these are preliminary reports that have not been peer-reviewed. They should practice/health-related behavior, or be reported in news media as established information.

New Results

Comment on this paper

Previous

Analysis of SARS-CoV-2 Antibodies in COVID-19 Convalescent Plasma using a Coronavirus Antigen Microarray

Posted April 17, 2020.

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XML

Rafael R. de Assis, Aarti Jain, Rie Nakajima, Algis Jasinskas, Jiin Felgner, Joshua M. Obiero, Oluwasanmi Adenaiye, Sheldon Tai, Filbert Hong, Philip Norris, Mars Stone, Graham Simmons, Anil Bagri, Martin Schreiber, Andreas Buser, Andreas Holbro, Manuel Battegay, Donald K. Milton, Prometheus Study Group, Huw Davies, Laurence M. Corash, Michael P. Busch, Philip L. Felgner, Saahir Khan

doi: https://doi.org/10.1101/2020.04.15.043364

Tweet

- Utilized Pseudotyped Lentivirus (BSL2):
  - Detected neutralizing antibodies from the sera of COVID-19 convalescent patients.
  - Using linear peptides and functional assays, they identified two regions on the spike glycoprotein that were highly recognized by neutralizing antibodies in sera.
  - One target was highly specific to SARS-CoV-2 while the other is a possible pan-coronavirus target.
  - Using 25 patient samples, found 6 patients with good neutralizing activity.

Antibody Testing and Immune Responses in Immunocompromised Individuals

- The antibody response is impaired in older PLWH, and other immunocompromised individuals.
- Both B and T cells compartments are affected in these individuals.
- Testing several weeks after an initial negative test may be needed to confirm.
- Multiple testing approaches will most probably be needed to appropriately characterize immune responses in these individuals.

Conclusions

- The antibody response in infected patients remains largely uncharacterized for breadth and potency.
- Differences in the generation of neutralizing antibodies against SARS-CoV2 between individuals have been observed and is likely important.
- False positives/negatives remain a concern.
- Serology test development from established companies are underway.
- Appropriate neutralization assays with SARS-CoV2 are underway but necessitate BSL3 facilities.

Update on Clinical Trials in COVID-19

Laura Kulik MD
Professor of Medicine, Transplant Surgery and Interventional Radiology
Northwestern University, Chicago, Il.

April 3, 2020

This EUA is for the unapproved use of hydroxychloroquine sulfate supplied from the Strategic National Stockpile (SNS) to treat adults and adolescents who weigh 50 kg or more and are hospitalized with COVID-19 for whom a clinical trial is not available, or participation is not feasible.

Hydroxychloroquine sulfate must be administered orally

To request hydroxychloroquine sulfate under Emergency Use Authorization (EUA):
Contact your Local or State Health Department

Health care providers must submit a report on all medication errors and **ALL SERIOUS ADVERSE EVENTS** and **CLINICAL OUTCOMES** related to hydroxychloroquine sulfate.
See specific reporting instructions below.

The optimal dosing and duration of treatment is unknown.

- 2 recent studies reported results of Chloroquine & Hydroxychloroquine in COVID-19
  - 1 RCT: Brazil
  - 1 Retrospective US

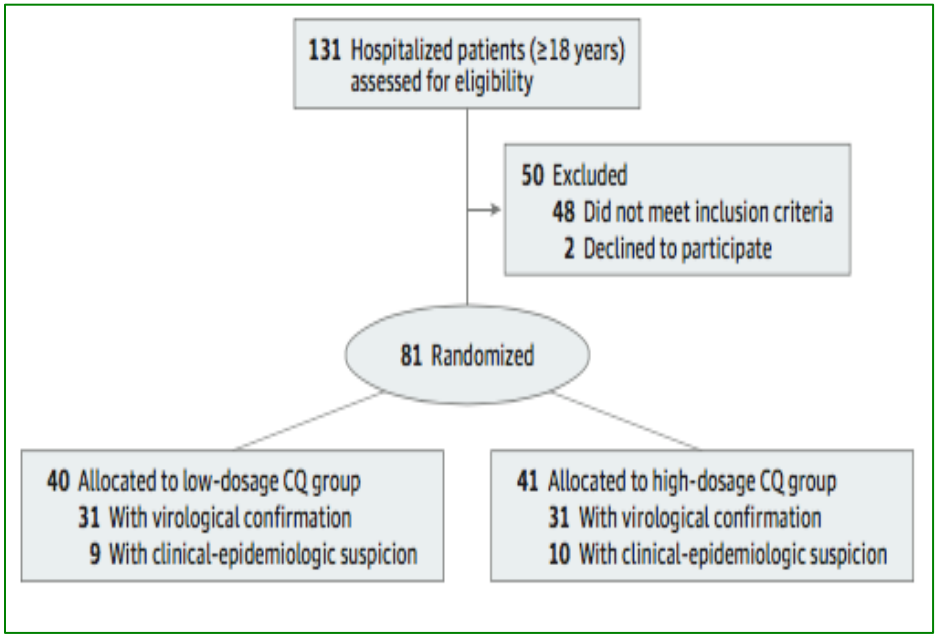
Original Investigation | Infectious Diseases

Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection A Randomized Clinical Trial

Mayla Gabriela Silva Borba, MD; Fernando Fonseca Almeida Val, PhD; Vanderson Souza Sampaio, PhD; Marcia Almeida Araújo Alexandre, MD; Gisely Cardoso Melo, PhD; Marcelo Brito, MSc; Maria Paula Gomes Mourão, MD; José Diego Brito-Sousa, MSc; Djane Baía-da-Silva, PhD; Marcus Vinitius Farias Guerra, MD; Ludhmila Abrahão Hajjar, MD; Rosemary Costa Pinto, BSc; Antonio Alcirley Silva Balieiro, MSc; Antônio Guilherme Fonseca Pacheco, MD; James Dean Oliveira Santos Jr, PhD; Felipe Gomes Naveca, PhD; Mariana Simão Xavier, MSc; André Machado Siqueira, MD; Alexandre Schwarzbold, MD; Júlio Croda, MD; Maurício Lacerda Nogueira, MD; Gustavo Adolfo Sierra Romero, MD; Quique Bassat, MD; Cor Jesus Fontes, MD; Bernardino Cláudio Albuquerque, MD; Cláudio-Tadeu Daniel-Ribeiro, MD; Wuelton Marcelo Monteiro, PhD; Marcus Vinícius Guimarães Lacerda, MD; for the CloroCovid-19 Team

- Phase IIb double blind RCT of hospitalized patients with severe ARDS due to COVID -19
- High dose Chloroquine (600 mg BID x 10 d) vs. Low dose CQ (450 mg BID on D1, followed by QD x 4 d)
- 1° outcome: decrease in mortality by ≥ 50% in the high dose group by D28
  - Unplanned interim analysis performed due to safety concerns raised by DSMB

  - Predefined sample size: 440 pts.
  - 2° endpoints: mortality at D13, clinical status, duration of ventilation, supplementary O2, EKG @ D13 and D28 & viral RNA @ D0 & 4

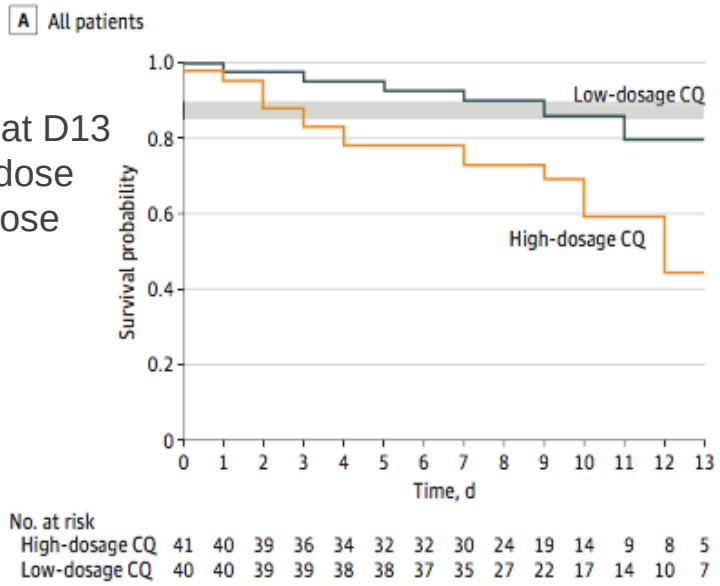


-All patients treated with IV ceftriaxone, 1 g bid x 7 d + azithromycin, 500 qd x 5 d.
- Oseltamivir, 75 mg bid x 5 d given if flu suspected

Age for entire cohort: Mean 51.1 yrs.
-Low dose CQ 47.7 vs. high dose 54.7 yrs.
Heart disease:
-Low dose CQ 0% vs. high dose CQ 17.9%
2/81 had liver disease

Results:

Lethality: 27.2% at D13
- 39.0% high dose
- 15.0% low dose



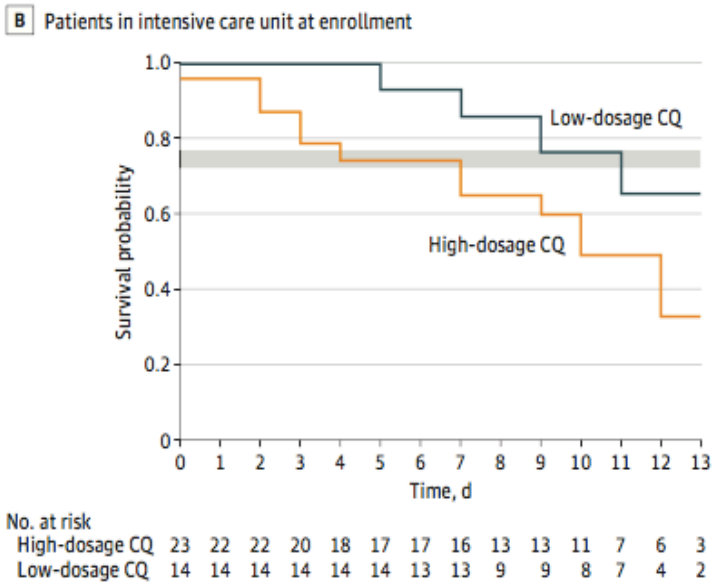


Table 2. Safety Outcomes in the Intention-to-Treat Population Until Day 13[a]

	No/ total No. (%)					
	All patients			COVID-19 confirmed cases		
Variable	Total	Low-dosage group[b]	High-dosage group[c]	Total	Low-dosage group[b]	High-dosage group[c]
Hemoglobin decreased[d]	11/42 (26.2)	4/18 (22.2)	7/24 (19.2)	7/29 (24.1)	3/11 (27.3)	4/18 (22.2)
Creatinine increased[e]	16/38 (42.1)	7/15 (46.7)	9/23 (39.1)	13/27 (48.1)	5/9 (55.6)	8/18 (44.4)
CK increased	13/33 (39.4)	6/19 (31.6)	7/14 (50.0)	9/24 (37.5)	3/15 (20.0)	6/9 (66.7)
CKMB increased	10/26 (38.4)	3/13 (23.1)	7/13 (53.8)	7/22 (31.8)	3/13 (23.1)	4/9 (44.4)
QTcF >500 ms[f]	11/73 (15.1)	4/36 (11.1)	7/37 (18.9)	8/57 (14.0)	1/27 (3.6)	7/29 (24.1)
Ventricular tachycardia	2/73 (2.7)	0/36	2/37 (2.7)	2/62 (3.2)	0/31	2/31 (6.5)

Results:

- High dose group OR: 3.6; 95% CI (1.2 – 10.6)
- After adjusting for AGE, high dose CQ was no longer associated with mortality
  - OR 2.8; 95% CI (0.9 -8.5)
- 60% mortality in 5 pts. with cardiac disease
- 12 pts. had prolonged cQT > 500 milliseconds and/or VT
  - Cumulative dosages of CQ were not higher in those who died
- RNA at D4 was negative in 22.2%

CONCLUSIONS: The preliminary findings of this study suggest that the higher CQ dosage should NOT be recommended for critically ill patients with CO VID-19 because of its potential safety hazards, especially when taken concurrently with azithromycin and oseltamivir. These findings cannot be extrapolated to patients with non-severe COVID-19.

- Single center
- No placebo arm
- Small sample size
- No exclusion based on baseline EKG
- Inability to perform per protocol analysis

Chloroquine Diphosphate in the Prevention of SARS in Covid-19 Infection (CloroCOVID19II)

NCT04342650

- Phase IIb Study: Double-blind RCT
- Aim: to evaluate the efficacy and safety of Chloroquine in patients with COVID-19 ***with comorbidities, without SARS***
- CQ 450 mg bid D1, followed by CQ 450mg qd on D2 to D5 vs. placebo
- 1° endpoint: proportion that develop SARS within 7 d of randomization
- Exclusion: patients on chronic drugs that prolong QT

Hydroxychloroquine in VA population with COVID-19

Posted 04/21/20

- National retrospective analysis of 368 patients with laboratory confirmation of COVID-19
  - HC, n=97; HC+AZ, n=113; no HC, n=158
  - Index hospitalization 03/09/20 – 04/11/20

- Study outcomes:
  - Discharge or death
  - Ventilation needed: Yes/No
  - Result of hospitalization in patients requiring ventilation

- Propensity scoring adjustment was used which included all baseline covariates:
  - Age, race, sex, BMI, co-morbidities
  - Vital signs: HR, pulse ox, temperature, RR, BP on admission and prior to ventilation
  - Labs: LFTs, renal function, ESR, WBC, Platelets, Hct, CRP, Procalcitonin, ESR

Magagnoli J et al. MedRxiv 2020

Outcomes based on treatment exposure

Outcome	HC N=97	HC+AZ N=113	No HC N=158	P value
Death – no. (%)	27 (27.8)	25 (22.1)	18 (11.4)	0.003
Discharge – no. (%)	70 (72.2)	88 (77.9)	140 (88.6)	

Outcomes based on pre-ventilation treatment

Outcome	Pre-Ventilation Treatment – N (%)			
	HC N=90	HC+AZ N=101	No HC N=177	P value
Ventilation – no. (%)	12 (13.3)	7 (6.9)	25 (14.1)	0.547
Death without ventilation – no. (%)	9 (10)	11 (10.9)	15 (8.4)	
Discharge without ventilation – no. (%)	69 (76.7)	83 (82.2)	137 (77.4)	

- *"Propensity scores based on all baseline characteristics*
- *Models analyzing the outcome of death took into account the competing risk of discharge.*
- *Models analyzing the outcome of ventilation took into account the competing risks of discharge and death prior to ventilation"*

Adjusted Hazard Ratio (95% Confidence Interval)

		Ventilation	Death	Death after ventilation
HC	vs. No HC	1.43 (0.53-3.79)	2.61 (1.10-6.17)	4.08 (0.77-21.70)
HC+AZ		0.43 (0.16-1.12)	1.14 (0.56-2.32)	1.20 (0.25-5.77)

- Retrospective
- Population: all male, median age > 65
- No data on dose of medications received
- Missing data for many of the variables
- No reported side effects

CONCLUSIONS:

In this study, we found no evidence that use of hydroxychloroquine, either with or without azithromycin, reduced the risk of mechanical ventilation in patients hospitalized with Covid-19. **An association of increased overall mortality was identified in patients treated with hydroxychloroquine alone.** These findings highlight the importance of awaiting the results of ongoing prospective, randomized, controlled studies before widespread adoption of these drugs.

FDA warns about hydroxychloroquine, chloroquine for COVID-19

Filed Under: COVID-19; Malaria

Chris Dall | News Reporter | CIDRAP News | Apr 24, 2020

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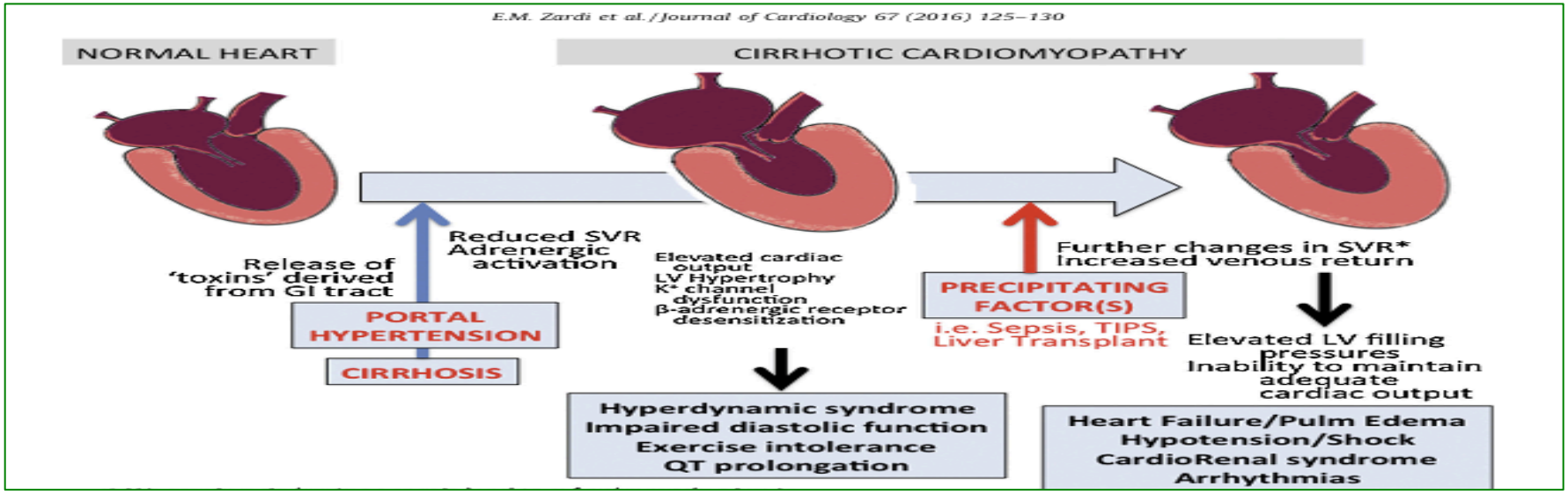
The Food and Drug Administration (FDA) today issued a warning on the use of the antimalaria drugs hydroxychloroquine and chloroquine for treating COVID-19.

The warning is related to the potential for the drugs to prolong the QT interval—a cardiogram measurement used to assess some of the electrical properties of the heart—and cause abnormal heart rhythms, particularly in patients with cardiac conditions. Those risks may increase when the drugs are combined with the antibiotic azithromycin, which can further increase the risk for sudden cardiac arrest.

Marcelo Ricardo Daros / iStock

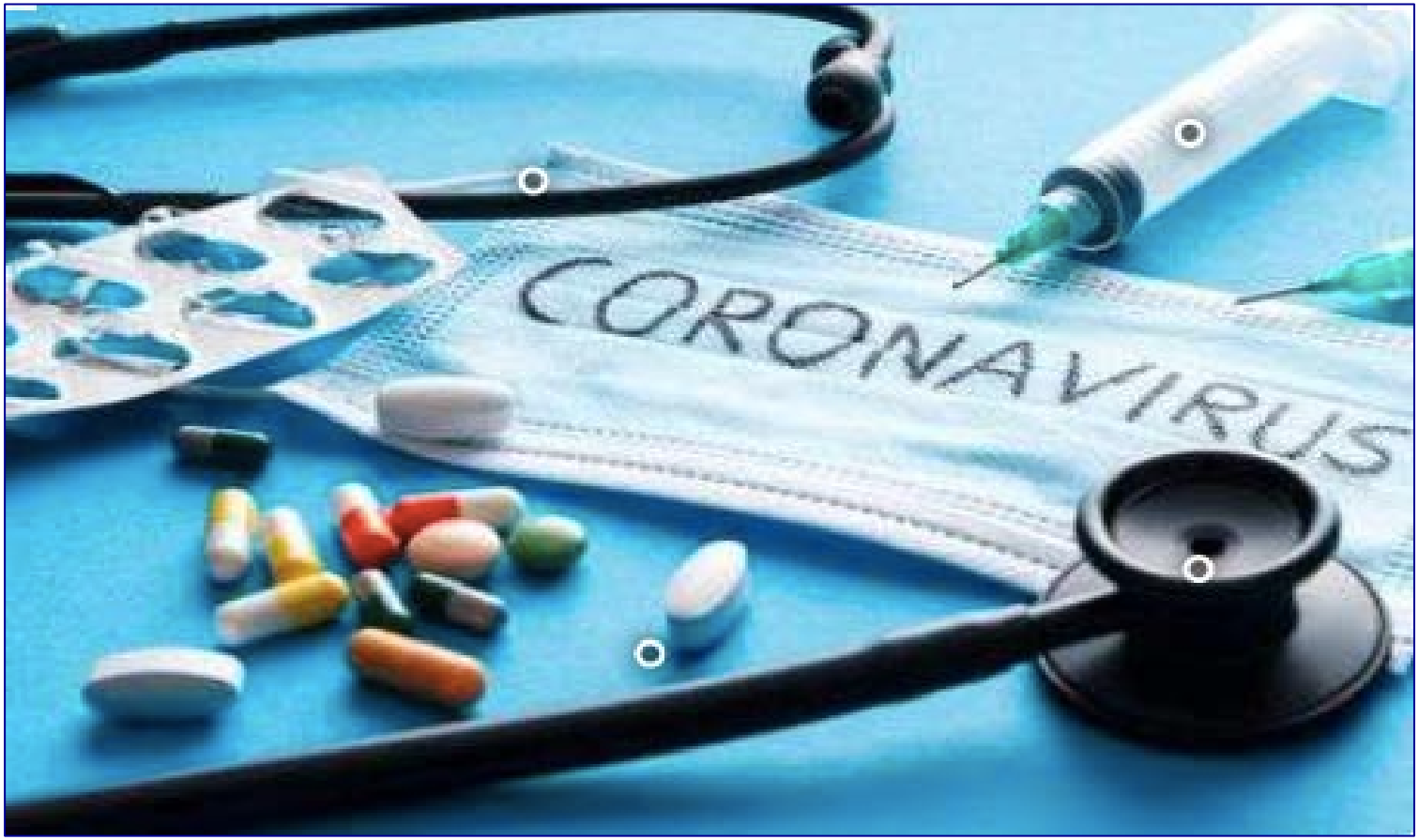
Prolonged QT Interval

- record an electrocardiogram before treatment initiation if possible. If rate-corrected QT (QTc, by Bazett's formula, or preferably using the Fridericia formula) is > 500 ms (higher values may be considered if treatment is deemed life-saving in desperate cases), or if the patient is known to have had torsades de pointes or has the congenital long QT syndrome, do not start the drugs;
- avoid any other concomitant non-essential drugs known to prolong QT;
- supplement potassium to > 4 mmol/L;
- if QTc is long (> 480 ms) at baseline, obtain an electrocardiogram again 2—4 hours after the initial dose, and if possible, monitor heart rhythm. Consider stopping therapy if QTc > 520 ms is documented;
- continue to monitor the electrocardiogram as appropriate during treatment (e.g. every other day).



Funck-Brentanoc et al. Arch Cardiovasc Dis. 2020 Apr 15

Other Agents…



New York hospitals are studying a common heartburn drug as treatment for Covid-19

By **Elizabeth Cohen**, Senior Medical Correspondent

Updated 6:50 AM ET, Mon April 27, 2020

- 

- Study began 04/07/20: critically ill COVID- 19 patients
    - High dose Famotidine IV + hydroxychloroquine vs. hydroxychloroquine

- Goal is to enroll 1174 patients

- As of 04/25/20: 187 enrolled

- Possible action: Viral protein, papainlike protease associated with replication may be inhibited

- Dose reduction required in renal dysfunction therefore such patients not included

04/01/20

U.S. FOOD & DRUG ADMINISTRATION

Home / News & Events / FDA Newsroom / Press Announcements / FDA Requests Removal of All Ranitidine Products (Zantac) from the Market

FDA NEWS RELEASE

FDA Requests Removal of All Ranitidine Products (Zantac) from the Market

FDA Advises Consumers, Patients and Health Care Professionals After New FDA Studies Show Risk to Public Health

Journal of Gastroenterology and Hepatology
JGHF
Meta-Analysys and Systematic Review

Acid-suppressive therapy is associated with spontaneous bacterial peritonitis in cirrhotic patients: A meta-analysis

Abhishek Deshpande, Vinay Pasupuleti, Priyaleela Thota, Chaitanya Pant, Sulaiman Mapara, Sohaib Hassan, David D K Rolston, Thomas J Sferra, Adrian V Hernandez

AASLD

- 8 trials of 3815 hospitalized cirrhotic patients

- Risk of SBP with acid suppression:

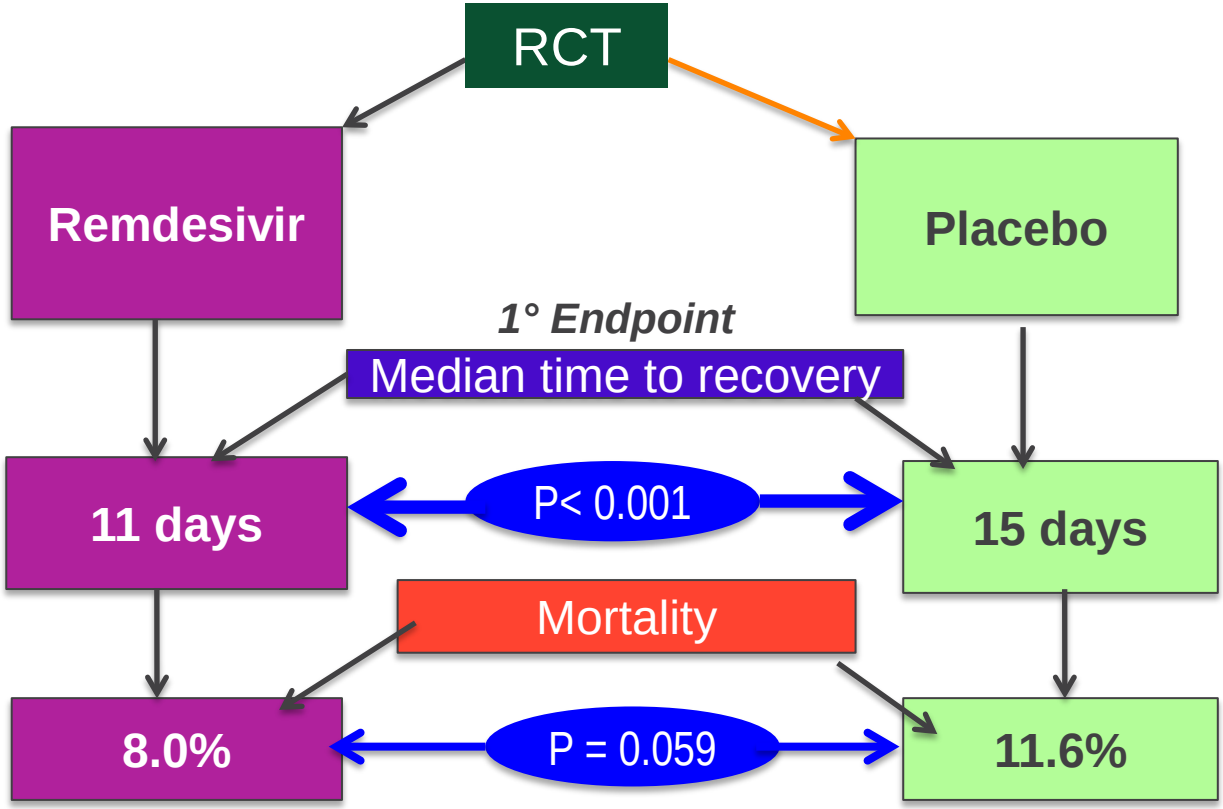
Proton pump inhibitor (N = 3815)	**OR = 3.15; 95% CI 2.09 – 4.74**
H2 blocker (N = 562)	OR = 1.71; 95% CI 0.97 – 3.01

NIH Clinical Trial Shows Remdesivir Accelerates Recovery from Advanced COVID-19

April 29, 2020

Adaptive COVID-19 Treatment Trial

- Hospitalized pts. with COVID-19 & lung involvement; N = 1063
  - 68 sites: 47 USA, 21 Europe& Asia



Tuesday, April 21, 2020

Expert U.S. panel develops NIH treatment guidelines for COVID-19

"Living document" expected to be updated often as new clinical data accrue.

At present, no drug has been proven to be safe and effective for treating COVID-19.

https://www.nih.gov/coronavirus

Antivirals:

- There are insufficient clinical data to recommend either for or against using **chloroquine** or **hydroxychloroquine** for the treatment of COVID-19 (AIII).
  - If chloroquine or hydroxychloroquine is used, clinicians should monitor the patient for adverse effects, especially prolonged QTc interval (AIII).
- There are insufficient clinical data to recommend either for or against using the investigational antiviral drug **remdesivir** for the treatment of COVID-19 (AIII).

Remdesivir as a treatment for COVID-19 is currently being investigated in clinical trials and is also available through expanded access and compassionate use mechanisms for certain patient populations.

- Except in the context of a clinical trial, the COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of the following drugs for the treatment of COVID-19:

The combination of **hydroxychloroquine plus azithromycin** (AIII)because of the potential for toxicities.

Lopinavir/ritonavir (AI) or other HIV **protease inhibitors** (AIII) because of unfavorable pharmacodynamics and negative clinical trial data.

Host Modifiers/Immunotherapy:

- There are insufficient clinical data to recommend either for or against the use of **convalescent plasma** or **hyperimmune immunoglobulin** for the treatment of COVID-19 (AIII).
- There are insufficient clinical data to recommend either for or against the use of the following agents for the treatment of COVID-19 (AIII):
  - **Interleukin-6 inhibitors** (e.g., sarilumab, siltuximab, tocilizumab)
  - **Interleukin-1 inhibitors** (e.g., anakinra)
- Except in the context of a clinical trial, the Panel **recommends against**the use of other immunomodulators, such as:

Interferons (AIII), because of lack of efficacy in treatment of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) and toxicity.

Janus kinase inhibitors (e.g., baricitinib) (AIII), because of their broad immunosuppressive effect.

Case Presentation: Managing the Patient with Autoimmune Hepatitis and COVID-19

Kimberly Brown, MD, FAST, FAASLD, AGAF
Professor of Medicine Wayne State University
Chief, Gastroenterology and Hepatology
Associate Medical Director, Henry Ford Hospital Transplant Institute
Henry Ford Hospital

o Case 1

- 64 yo AA woman with CAD, Hyperlipidemia, HTN, and DM who was diagnosed with AIH in 2018 by biopsy.
- Biopsy at that time showed bridging septa and few nodule formation
- She was maintained on Azathioprine 100 mg daily with normal liver tests
- January 21, 2020 routine labs showed an AST of 110 and ALT 86
- Prednisone 40 mg daily po was added to AZA

- On 3/16/20 ALT had returned to normal and Prednisone was decreased to 30 mg daily with AZA 100 mg daily
- 3/26/20 she presented to the ER with nausea, diarrhea, cough, sob, weakness, wheezing, HA, anorexia, myalgias and blurred vision for 4 days with an episode of syncope the day of presentation
- In the ER O2 Sat was 88% which improved to 96% on 2 L
- Temperature was 99.8
- CXR showed RLL infiltrate
- COVID test was sent and was positive

- Medications as an outpatient included chlorthalidone, losartan, ASA, atorvastatin, carvedilol and dulaglutide.
- Chlorthalidone and carvedilol were held due to initial hypotension
- She was started on cefriaxone, doxycycline, hydroxychloroquine 400mg bid for 2 doses and then 200 mg bid to complete 5 days
- Oral prednisone was held and methylprednisolone 40 mg iv q 12 hours were begun

- Labs on admission showed AST 29, ALT 22, Bili 0.6, ferritin 754, CRP 3.3, CPK 103, platelet 198, absolute lymphocyte count 0.7
- On 3/29, losartan was restarted due to hypertension
- On 3/31/20 the patient was moved to the ICU for desaturation to 82% requiring a non-rebreather
- On 4/1/20 the patients was intubated and hepatology was consulted
- At that time the patient had completed hydroxychloroquine and pulse steroids and was receiving 30 mg prednisone and AZA 100 mg daily.
- Hepatology recommended discontinuing AZA and continuing prednisone 30 mg daily

- The patient was extubated 4/7/20
- She remained hospitalized requiring O2
- Labs on 4/15/20 showed an AST of 25, ALT 26, Bili 0.4, CRP 0.1, Ferritin 239, CPK 84, absolute lymphocyte count 3.4
- COVID testing 4/11 was negative
- COVID testing 4/16 and 4/17 were both positive
- The patient was discharged home on 4/20 with O2 and 40 mg prednisone daily with followup
- LFTs at discharge remained normal

o Questions

- Are patients receiving baseline Immunosuppression at increased risk of infection or severity of infection?
- Do ACE inhibitors or ARBs play a role in the severity of infection?
- Should losartan have been held and should it have been resumed?
- What should our approach have been to managing AZA and prednisone during this event?
- What risk does hydroxychloroquine pose to a patient with underlying liver disease?
- If anti-IL6 had been recommended, what would be the risk given the history of AIH/liver disease?

Panel Discussion

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