COVID-19: Clinical Deep Dive into the Research – Part II

This meeting will be recorded and will be available at www.fmda.org/journalclub.php
Agenda

COVID 19 state of the state

COVID 19 Updates

Clinical Deep Dive

Open Discussion
Hospital Resource Use

- All beds needed (projected)
- ICU beds needed (projected)
- Invasive ventilators needed (projected)

All resources specific to COVID-19 patients.
Shaded areas indicate uncertainty.
Statement on the Reopening of Post-Acute & Long-Term Care Facilities

As states and local communities begin to reopen their retail stores, restaurants, offices, and other businesses, residents and employees of post-acute and long-term care facilities, along with their families, will wonder when they too will be able to end no-visitor policies, dine together again, and enjoy group activities and routine visits to the salon.

Residents of post-acute and long-term care (PALTC) facilities remain the most vulnerable population during this ongoing COVID-19 pandemic. While some areas in the country have seen a decline in hospital admissions and deaths from COVID-19, other areas continue to see a rise in cases, hospitalizations and deaths within PALTC. Of all deaths reported in the U.S., estimates suggest that some 46% to 56% are nursing home related.

Infectious disease experts warn that the country will experience a second wave of the virus this fall and it is unclear yet if we will be fully prepared for it. In addition, widespread, reliable testing is still not a reality for many PALTC communities, nor is a consistent supply of personal protective equipment for healthcare workers in long term care.

Given these factors, the decision to reopen or to relax social distancing efforts within PALTC communities must be made with great caution and on an individual basis, regardless of the status of the surrounding community. This critical decision rests with the people most familiar with residents, staff and resources—the clinical leaders managing the care of the patients and residents in these facilities. Medical directors, executive directors and directors of nursing, along with their regional leadership, should work in collaboration with their local health departments and hospital systems to determine the appropriate time to reopen their nursing homes and assisted living communities to visitors, to relax social distancing policies and personal protective equipment requirements.

Finally, we urge federal, state and local governments and health authorities to stipulate that, in the chain of events leading to reopening businesses and buildings, that PALTC facilities, where older adults most at risk of serious illness or death from COVID-19 reside, be the last to open to visitors and outside contractors and vendors.
Policy Statement: COVID-19 Testing Strategies Should Be Tailored to the Clinical Situation

May 18, 2020

Issue

There is a clear understanding that protecting our vulnerable post-acute and long-term care (PALTC) population is dependent on adequate access to testing. Testing must be readily accessible, completed in a timely manner by those with appropriate training, have low false negative or false positive rates, impose a low physical or emotional burden on the person being tested, and be appropriately reimbursed.

Many states, local health departments, facilities, and consumers are calling for “universal testing” of PALTC residents and staff. The underlying premises behind these calls are that tests would be available for all, would meet the criteria set forth above, result in better care being delivered to our PALTC residents, and save lives.
Clinical Deep Dive
“An Extraordinarily Efficient Virus”

Dr. Anthony Fauci - April 16, 2020
COVID 19: Unfortunately Efficient
Research Letter

April 27, 2020

Prevalence of SARS-CoV-2 Infection in Residents of a Large Homeless Shelter in Boston

Travis P. Baggett, MD, MPH\textsuperscript{1}; Harrison Keyes, MPAS, PA-C\textsuperscript{1}; Nora Sporn, MA, MPH\textsuperscript{2}; et al

Author Affiliations  |  Article Information

*JAMA*. Published online April 27, 2020. doi:10.1001/jama.2020.6887
Research Letter

May 18, 2020

Seroprevalence of SARS-CoV-2-Specific Antibodies Among Adults in Los Angeles County, California, on April 10-11, 2020

Neeraj Sood, PhD¹; Paul Simon, MD²; Peggy Ebner, BA³; et al

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JAMA. Published online May 18, 2020. doi:10.1001/jama.2020.8279
COVID 19 impact to Multiple organ system
BACKGROUND

Coronavirus disease 2019 (Covid-19) may disproportionately affect people with cardiovascular disease. Concern has been aroused regarding a potential harmful effect of angiotensin-converting–enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) in this clinical context.

METHODS

Using an observational database from 169 hospitals in Asia, Europe, and North America, we evaluated the relationship of cardiovascular disease and drug therapy with in-hospital death among hospitalized patients with Covid-19 who were admitted between December 20, 2019, and March 15, 2020, and were recorded in the Surgical Outcomes Collaborative registry as having either died in the hospital or survived to discharge as of March 28, 2020.

RESULTS

Of the 8910 patients with Covid-19 for whom discharge status was available at the time of the analysis, a total of 515 died in the hospital (5.8%) and 8395 survived to discharge. The factors we found to be independently associated with an increased risk of in-hospital death were an age greater than 65 years (mortality of 10.0%, vs. 4.9% among those ≤65 years of age; odds ratio, 1.93; 95% confidence interval [CI], 1.60 to 2.41), coronary artery disease (10.2%, vs. 5.2% among those without disease; odds ratio, 2.70; 95% CI, 2.08 to 3.51), heart failure (15.3%, vs. 5.6% among those without heart failure; odds ratio, 2.48; 95% CI, 1.62 to 3.79), cardiac arrhythmia (11.5%, vs. 5.6% among those without arrhythmia; odds ratio, 1.95; 95% CI, 1.33 to 2.86), chronic obstructive pulmonary disease (14.2%, vs. 5.6% among those without disease; odds ratio, 2.96; 95% CI, 2.00 to 4.40), and current smoking (9.4%, vs. 5.6% among former smokers or nonsmokers; odds ratio, 1.79; 95% CI, 1.29 to 2.47). No increased risk of in-hospital death was found to be associated with the use of ACE inhibitors (2.1% vs. 6.1%; odds ratio, 0.33; 95% CI, 0.20 to 0.54) or the use of ARBs (6.8% vs. 5.7%; odds ratio, 1.23; 95% CI, 0.87 to 1.74).

CONCLUSIONS

Our study confirmed previous observations suggesting that underlying cardiovascular disease is associated with an increased risk of in-hospital death among patients hospitalized with Covid-19. Our results did not confirm previous concerns regarding a potential harmful association of ACE inhibitors or ARBs with in-hospital death in this clinical context. (Funded by the William Harvey Distinguished Chair in Advanced Cardiovascular Medicine at Brigham and Women’s Hospital.)
Cardiac injury is seen in about one-quarter of patients with coronavirus disease 2019 (COVID-19) who are admitted to hospital. Between 8% and 28% of inpatients have myocardial injury, troponin levels greater than the 99th centile of the upper limit of normal (ULN), from either indirect (e.g., owing to hypoxemia, sepsis or cytokine release) or direct myocardial damage. Higher rates are seen in patients requiring intensive care. Progressive elevation in troponin and natriuretic peptides (NPs) have been shown to parallel disease acuity, with peak levels about 2–3 weeks from symptom onset.

Cardiac biomarkers are useful for risk stratification in patients admitted to hospital, periodic measurement of troponin and NP levels may identify patients at increased risk of developing left ventricular dysfunction or arrhythmias. If levels are elevated, consider monitoring the patient in a higher-acuity setting. Consider assessment using cardiac point-of-care ultrasonography if moderate elevation (>3 times the ULN) or hemodynamic and/or electrical instability occur.

Myocardial infarction (MI) may occur without obstructive coronary artery disease (CAD). Patients may present with MI secondary to supply–demand mismatch or microvascular thrombosis. Myocarditis may mimic acute coronary syndrome, and these patients are at increased risk of cardiogenic shock. For patients with refractory or recurrent chest pain, moderate elevation of troponin level or focal electrocardiogram changes, consider performing cardiac point-of-care ultrasonography to assess for left ventricular dysfunction and coronary computed tomography (CT) angiography to rule out CAD.

Treatment should be directed at specific causes of myocardial injury. Manage heart failure, ST-elevated MI and left ventricular dysfunction in a patient with COVID-19 as per protocol using appropriate personal protective equipment, including use of guideline-directed medical therapy. Invasive hemodynamic monitoring should be limited to patients whose volume status cannot be determined clinically.

Cardiac complications are associated with poor outcomes. Up to 40% of COVID-19 deaths may be at least partially attributed to heart failure. Among patients admitted to hospital who develop heart failure, mortality rates may be as high as 60%. Sustained ventricular tachycardia or ventricular fibrillation may occur in up to 17% of patients with cardiac injury and are more common among patients in intensive care.

References


Competing interests: None declared.

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To the Editor: Patients with coronavirus disease 2019 (Covid-19) have a profound hypercoagulable state, and complicating venous thrombotic events are common. Abnormalities in coagulation screening measures, including a prolonged activated partial-thromboplastin time (aPTT), have been reported in patients with Covid-19. This finding could be seen as a reason to avoid the use of anticoagulation at both therapeutic and prophylactic doses.

A prolonged aPTT may indicate a clotting-factor deficiency or the presence of an inhibitor of coagulation that is either specific (e.g., antibody to factor VIII) or nonspecific (e.g., lupus anticoagulant). Lupus anticoagulant can affect in vitro tests of blood coagulation but typically is not associated with bleeding. As part of the antiphospholipid syndrome, lupus anticoagulant is associated with a thrombotic risk.

We investigated the cause of prolonged aPTT in patients with Covid-19. Blood specimens obtained from 216 patients who were positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were received for coagulation screening, and 44 (20%) were found to have a prolonged aPTT. The specimens from 9 patients were excluded, and those from 35 patients were investigated further. (Details of the methods are provided in the Supplementary Appendix, available with the full text of this letter at NEJM.org.)

A summary of the results is provided in Table 1. The median age was 57 years, and 24 patients were male. Pulmonary embolism was confirmed in 1 patient, and clinically suspected thrombosis was present in 1 patient. No clinically significant bleeding or arterial thromboses were reported.

No patients were found to have deficiencies in factor VIII or factor IX. In 5 patients, marginal reductions in factor XI were found that were unlikely to be of clinical significance. The factor XII level was 50 IU per deciliter or lower in 16 patients. Lupus anticoagulant assays were performed in 34 patients, and 31 (91%) were positive. The presence of lupus anticoagulant was indicated by two assays (dilute Russell's viper-venom time [DRVVT] and lupus anticoagulant–sensitive aPTT) in 18 of 34 patients (53%), by DRVVT alone in 7 (21%), and by lupus anticoagulant–sensitive aPTT alone in 6 (18%). All lupus anticoagulant–positive specimens had a prolonged aPTT with a 50:50 mix (i.e., in a sample made up of 50% patient plasma and 50% normal plasma).

In a historical control cohort of 540 specimens received for lupus anticoagulant testing, 43 (8%) had an aPTT of 30 seconds or longer, and 11 of the 43 (26%) were positive for lupus anticoagulant. The percentage of specimens that were positive for lupus anticoagulant was significantly higher among the patients with Covid-19 than in the control cohort (P<0.001) (see the Supplementary Appendix).

In our study, most patients with Covid-19 who were admitted to the hospital with a prolonged aPTT were positive for lupus anticoagulant (91%) and often had an associated factor XII deficiency. It is important to note that neither observation is associated with a bleeding tendency; factor XII is not required for hemostasis, and the presence of lupus anticoagulant, if persistent, can be associated with a thrombotic tendency within the antiphospholipid syndrome. Further study is required to determine the role, if any, of lupus anticoagulant in the pathogenesis of Covid-19 thrombosis.

Although we detected heparin in 28 of the 35 specimens, the DRVVT assay contains heparinase, which neutralizes any heparin effect that might lead to false positive detection of lupus anticoagulant. An association between lupus anticoagulants and acquired factor XII deficiency secondary to...
Coagulopathy associated with COVID-19

Stephanie G. Lee MD MSc, Michael Fralick MD PhD, Michelle Sholzberg MDCM MSc


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Keywords: COVID-19, gastrointestinal and liver manifestations

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Conflict of interest disclosure: All members were required to complete the disclosure statement. These statements are maintained at the American Gastroenterological Association.
Renal Involvement and Early Prognosis in Patients with COVID-19 Pneumonia

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Renin–Angiotensin–Aldosterone System Inhibitors in Patients with Covid-19

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The renin–angiotensin–aldosterone system (RAAS) is an elegant cascade of vasoactive peptides that orchestrate key processes in human physiology. Severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and SARS-CoV-2, which have been responsible for the SARS epidemic in 2002 to 2004 and for the more recent coronavirus disease 2019 (Covid-19) pandemic, respectively, interface with the RAAS through angiotensin-converting enzyme 2 (ACE2), an enzyme that physiologically counters RAAS activation but also functions as a receptor for both SARS viruses.1,2 The interaction between the SARS viruses and ACE2 has been proposed as a potential factor in their infectivity,3,4 and there are concerns about the use of RAAS inhibitors that may alter ACE2 and whether variation in ACE2 expression may be in part responsible for disease virulence in the ongoing Covid-19 pandemic.5-8

Indeed, some media sources and health systems have recently called for the discontinuation of ACE inhibitors and angiotensin-receptor blockers (ARBs), both prophylactically and in the context of suspected Covid-19.

Given the common use of ACE inhibitors and ARBs worldwide, guidance on the use of these drugs in patients with Covid-19 is urgently needed. Here, we highlight that the data in humans are too limited to support or refute these hypotheses and concerns. Specifically, we discuss the uncertain effects of RAAS blockers on ACE2 levels and activity in humans, and we propose an alternative hypothesis that ACE2 may be beneficial rather than harmful in patients with lung injury. We also explicitly raise the concern that withdrawal of RAAS inhibitors may be harmful in certain high-risk patients with known or suspected Covid-19.

Covid-19 and Older Adults with Coexisting Conditions

Initial reports5-8 have called attention to the potential overrepresentation of hypertension among patients with Covid-19. In the largest of several case series from China that have been released during the Covid-19 pandemic (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org), hypertension was the most frequent coexisting condition in 1099 patients, with an estimated prevalence of 15%;9 however, this estimate appears to be lower than the estimated prevalence of hypertension seen with other viral infections10 and in the general population in China.11,12

Coexisting conditions, including hypertension, have consistently been reported to be more common among patients with Covid-19 who have had severe illness, been admitted to the intensive care unit, received mechanical ventilation, or died than among patients who have had mild illness. There are concerns that medical management of these coexisting conditions, including the use of RAAS inhibitors, may have contributed to the adverse health outcomes observed. However, these conditions appear to track closely with advancing age,13 which is emerging as the strongest predictor of Covid-19–related death.14 Unfortunately, reports to date have not rigorously accounted for age or other key factors that contribute to health as potential confounders in risk prediction. With other infective illnesses, coexisting conditions such as hypertension have been key prognostic determinants,10 and this also appears to be the case with Covid-19.15

It is important to note that, despite inferences...
response to therapies within a given drug class. It is important to note that the plasma ACE2 level may not be a reliable indicator of the activity of the full-length membrane-bound form, in part because ACE2 is shed from the membrane, a process that appears to be separately regulated by an endogenous inhibitor. In addition to the degree of expression, the biologic relevance of ACE2 may vary according to tissue and clinical state. Unfortunately, data showing the effects of ACE inhibitors, ARBs, and other RAAS inhibitors on lung-specific expression of ACE2 in experimental animal models and in humans are lacking. Furthermore, even if RAAS inhibitors modify ACE2 levels or activity (or both) in target tissue beds, clinical data are lacking to indicate whether this would in turn facilitate greater engagement and entry of SARS-CoV-2 spike protein. Further mechanistic studies in humans are needed to better define the unique interplay between SARS-CoV-2 and the RAAS network.

### Potential for Benefit Rather Than Harm of RAAS Blockers in Covid-19

SARS-CoV-2 appears not only to gain initial entry through ACE2 but also to subsequently down-regulate ACE2 expression such that the enzyme is unable to exert protective effects in organs. It has been postulated but unproven that unabated angiotensin II activity may be in part responsible for organ injury in Covid-19. After the initial engagement of SARS-CoV-2 spike protein, there is subsequent down-regulation of ACE2 abundance.
Altered Mental Status & COVID 19
Brief Report

Altered Mental Status as a Novel Initial Clinical Presentation for COVID-19 Infection in the Elderly

Christine F. Ward D.O. 1, Gary S. Figiel M.D. 1, William M. McDonald M.D. 2
Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic

Jonathan P Rogers, MRCPsych † Edward Chesney, MRCPsych † Dominic Oliver, MSc
Thomas A Pollak, PhD • Prof Philip McGuire, FMedSci • Paolo Fusar-Poli, PhD • et al.  Show all authors

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Searching for a Treatment
WHO Launches Global Solidarity Project To Ramp Up Clinical Trials For Coronavirus Drugs

“Multiple small trials with different methodologies may not give us the clear strong evidence we need about which treatments help to save lives,” said WHO Director-General Tedros Adhanom Ghebreyesus. Scientists around the world have been racing around the clock to come up with treatments, even as a promising drug fails to show results. Meanwhile, President Donald Trump considered an executive order to expand the use of drugs in coronavirus patients, but FDA scientists objected over safety concerns. And health officials push back on rumors the ibuprofen could worsen the symptoms.
By Robert Nellis

Early indicators: Investigational convalescent plasma is safe for patients with COVID-19

May 14, 2020

- Mayo Clinic & collaborators reported safety data on the first 5,000 hospitalized patients transfused
- As of May 11th
  - 14,000 patients enrolled
  - 8,900 patients infused with Convalescent plasma
Adaptive COVID-19 Treatment Trial (ACTT)
Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial

Prof Ivan Fan-Ngai Hung, MD • Kwok-Cheung Lung, FRCP • Eugene Yuk-Keung Tso, FRCP • Raymond Liu, FRCP • Tom Wai-Hin Chung, MRCP • Man-Yee Chu, MRCP • et al. Show all authors

Published: May 08, 2020 • DOI: https://doi.org/10.1016/S0140-6736(20)31042-4 •
The Race for a Vaccine
Moderna Announces Positive Interim Phase 1 Data for its mRNA Vaccine (mRNA-1273) Against Novel Coronavirus

May 18, 2020 at 7:30 AM EDT
Inovio commences Phase I trial of DNA vaccine for Covid-1
Where are the NON-COVID 19 patients?
Debra Malina, Ph.D., Editor

The Untold Toll — The Pandemic’s Effects on Patients without Covid-19

Lisa Rosenbaum, M.D.
US hospitals are seeing fewer patients without Covid-19. (And that could be a problem.)

April 22, 2020
Ongoing Preparedness
Commentary

Unprecedented solutions for extraordinary times: Helping long-term care settings deal with the COVID-19 pandemic

Swati Gaur MD, MBA1, Ghinwa Dumyati MD2, David A. Nace MD, MPH3 and Robin L. P. Jump MD, PhD4,5

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COVID-19 IN THE LONG-TERM CARE SETTING: THE CMS PERSPECTIVE

Alan F. Levitt M.D. 🌱, Shari M. Ling M.D.

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"The breaking of a wave cannot explain the whole sea."
by Vladimir Nabokov
Open Discussion
Questions & Comments

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This meeting has been recorded and will be available at www.fmda.org/journalclub.php