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COVID–19
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EDUCATIONAL FORUM

Saliva is more sensitive for SARS-CoV-2 detection and has less variability over time than nasopharyngeal swabs

The current standard for COVID-19 diagnosis is nasopharyngeal swabbing which presents challenges due to high exposure risk to health care workers and swabs currently in global shortage. If saliva samples had comparable sensitivity, they could provide an important alternative. In contrast to nasopharyngeal swabs, saliva collection is minimally-invasive and can be self-collected. In a recent study,[1] investigators compared viral titers from matched nasopharyngeal and saliva samples, including some samples collected serially over time. Study participants included 44 inpatients with COVID-19 and 98 asymptomatic health care workers who were at risk of COVID-19 exposure (33 with matched samples). The inpatient cohort had a range of infection severity: 19 (43%) required ICU care; 10 (23%) required mechanical ventilation; and 2 (5%) died. The study showed that viral titers from saliva were significantly higher than titers from nasopharyngeal swabs when calculated from the entire study population and also when looking only at the inpatient samples. Virus was detected from saliva but not nasopharyngeal swabs in 8 matched samples and from nasopharyngeal swabs but not saliva in 3 matched samples. Longitudinal variability was measured from 22 study participants with multiple nasopharyngeal swabs and 12 participants with multiple saliva samples. Viral titers generally decreased over time in both sample types. There were 5 cases where a negative nasopharyngeal swab was followed by a positive swab, but no cases where a negative saliva sample was followed by a positive sample. Saliva samples demonstrated less variability in virus detection over time.

A smaller study confirmed that SARS-CoV-2 could be detected from saliva in 11 of 12 patients with positive nasopharyngeal swabs, and that positive detection continued for several days.[2] Three of the patients had positive viral cultures demonstrating that live virus was present in saliva. In contrast, nasopharyngeal swabs may have better diagnostic sensitivity than oropharyngeal swabs (not saliva). A retrospective review of 353 patients who provided both samples showed higher positive rates with nasopharyngeal swabs compared to oropharyngeal swabs for inpatients (32.9% versus 9.3%) and similar positive rates for outpatients (7.3% versus 6.3%).[3]

In summary, based on the totality of currently available data, we can now make recommendations on optimal PCR sample collection. Anterior nasal swabs and saliva should be the choices for sampling the majority of patients seen. This will balance a high sensitivity and improved safety for our health care providers.

Latest evidence on COVID-19 disease prevalence in different communities in the United States[4-9]

Several recent serology-based observations suggest population coronavirus exposure and potential immunity may already be substantial, especially in harder-hit areas. While serology surveys done early April in Santa Clara and LA counties, California implied seropositivity rates in the 2.5–5.6% range, those in the greater New York City area done mid-April implied rates in the 12–21% range. Another survey of 200 residents in Chelsea, MA collected on April 14 and 15 returned a positivity rate of 32%.

The table looks at serology, PCR and implied infection and mortality rate in two California counties, New York City, and Chelsea, MA.

	Population	Serology positive (%)	Implied infected	PCR positive	Ratio serology (+) to PCR (+)	Confirmed deaths	Implied mortality rate
LA County (CA)	10,400,000	2.8-5.6%	364,000	17,508	21	797	0.22%
Santa Clara County (CA)	1,928,000	2.5-4.2%	61,696	1,987	31	96	0.16%

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	Population	Serology positive (%)	Implied infected	PCR positive	Ratio serology (+) to PCR (+)	Confirmed deaths	Implied mortality rate
New York City (NY)	8,399,000	21%	1,763,790	145,855	12	10,889	0.62%
Nassau County (NY)	1,357,000	17%	226,619	32,124	7	1,813	0.80%
Suffolk County (NY)	1,477,000	17%	246,659	29,567	8	994	0.40%
Westchester County (NY)	967,506	12%	113,198	25,959	4	962	0.85%
Rockland County (NY)	325,789	12%	38,117	9,828	4	322	0.84%
Chelsea (MA)	40,000	32%	12,800	712	18	39	0.30%

There are some differences in these surveys. The New York and Massachusetts surveys used convenience samples collected from people visiting public places, which is likely to yield an overestimate since it excludes people who avoid these sites. The California studies, by contrast, sought to enroll a more representative subset of people with internet-based advertisements. In March, universal PCR testing of all 3,300 residents of the Italian town of Vo, conducted at the time commenced when the very first infection had been detected, found 3% of the population testing positive at that moment in time. Also in March, seropositivity in the hard-hit German town of Gangelt was estimated from a 500-patient sample at 14%.

These data drive home the significance of spread by asymptomatic individuals and the likelihood of meaningful undetected spread in many municipalities. They also bring attention to the highly local area of transmission dynamics. New York has seen substantially wider spread than nearby Westchester County. Also relevant are the implied mortality estimates, which range between 0.40–0.85% in harder-hit areas and closer to 0.20% in lesser-affected ones. Given the timeframe of ~4–5 weeks to accumulate these cases, this implies during the peak of infection up to 5–8% of New Yorkers and up to 1–2% of Angelenos may have been infectious at any one time.

Two new studies for the use of hydroxychloroquine with COVID-19 infection[10-11]

We are still awaiting publication of several large randomized trials of hydroxychloroquine (HCQ) therapy currently ongoing in the United States. As noted in the past two COVID-19 Forum editions, both a large French observational trial looking at over 180 patients and a randomized trial from China looking at 150 patients failed to show a benefit of HCQ therapy.

In the French study, 10% of patients developed either prolongation of the QT interval or new heart block. Two new studies became available this week. The first was a randomized trial out of Brazil which compared high-dose HCQ (1200 mg daily for 10 days) to lower-dose HCQ (900 mg on day 1 followed by 450 mg daily days 2 through 5). The population was moderately severe inpatients, not on a ventilator. Importantly, all of the patients were also treated with azithromycin which may also have cardiac arrhythmogenic potential. The primary outcome was death and the secondary outcomes included recovery of viral DNA, intubation and ECG abnormalities. The intended sample was 220 patients in each group, but after enrolling only 81 patients the data safety monitoring board halted enrollment into the high-dose arm of the trial. By day 13 of enrollment, 6 of 40 patients (15.0%) in the low-dose group had died, compared with 16 of 41 patients (39.0%) in the high-dose group. Prolongation of QTc interval was observed in 4 of 36 patients (11.1%) in the low-dose group and 7 of 37 patients (18.9%) in the high-dose group. In addition, 2 patients in the high-dose group (2.7%) experienced ventricular tachycardia. Three of 5 patients (60.0%) in the high-dose group with underlying heart disease died. The low-dose arm of the trial is ongoing.

A second trial was published this week by the VA system. This was a retrospective analysis of all veterans treated for COVID-19 infection as of April 11. Three hundred sixty-eight patients were characterized by use of HCQ alone, HCQ plus azithromycin, or no HCQ. The endpoint was death or the need for mechanical ventilation. Rates of death in the HC, HC+AZ, and no HC groups were 27.8%, 22.1% and 11.4% respectively. Rates of ventilation in the HC, HC+AZ, and no HC groups were 13.3%, 6.9% and 14.1% respectively. Compared to the no-HC group, the risk of death from any cause was 260% higher in the HC group but not significantly higher in the HC+AZ group (adjusted hazard ratio, 1.14). The risk of ventilation was similar in the HC group and in the HC+AZ group compared to the no-HC group.

Due to the higher mortality in the HCQ-only group, the authors stated that these findings highlight the importance of awaiting the results of ongoing prospective, randomized and controlled studies before widespread adoption of HCQ use.

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Further evidence on hypercoagulability due to COVID-19 infection

As discussed in the COVID-19 Forum Special Edition 4, patients with severe COVID-19 infection can develop a coagulopathy meeting criteria for disseminated intravascular coagulation (DIC), with fulminant activation of coagulation, resulting in widespread microvascular thrombosis and consumption of coagulation factors. There is new evidence[12] of direct invasion of the vascular endothelium by SARS-CoV-2. Involved vascular beds develop lymphocytic inflammation which may lead to thrombosis, and this may contribute to the microthromboses seen in the pulmonary vasculature and elsewhere. This may in part account for the hypoxia seen in those patients whose lung mechanics don't suggest typical ARDS. There are also early data suggesting an increased risk of large vessel thrombosis, and we don't yet understand if this endothelial inflammation is playing a role here. In a Dutch study[13] of 184 patients admitted with severe COVID-19 disease, investigators evaluated incidence of the composite outcome of symptomatic acute PE, DVT, ischemic stroke, MI or systemic arterial embolism of COVID-19 patients admitted to the ICU. All patients received at least standard doses of thromboprophylaxis. The cumulative incidence of thrombosis was 31%. Three patients had ischemic stroke and the rest were pulmonary emboli or lower extremity DVT. Another study out of Wuhan[14] looked at 81 patients hospitalized with severe disease who were screened for DVT/PE. Twenty-five percent of patients tested positive and a significantly elevated D-dimer had a PPV of 85% and a NPV of 95%. Additionally, there is increasing recognition of a hypercoagulable state which may predate severe infection. In a study under review, neurologists at Thomas Jefferson University Hospitals found that 12 of their patients treated for large vessel occlusive stroke over a three-week period during the pandemic tested positive for COVID-19. Forty percent were under 50, and they had few or no risk factors. In a letter to be published in the New England Journal of Medicine next week, the Mount Sinai team detailed five case studies of young patients, ages 33–49, who associated with COVID-19 infection, had strokes over a two-week period. Anecdotally, there are case reports of higher than average clotting of dialysis catheters and spontaneous mesenteric ischemia. Inpatient management of COVID-19 infection now includes routine use of prophylactic anticoagulation. There are protocols at some institutions which up titrate to intermediate or full anticoagulation based upon rising D-dimer levels, although there is not yet an evidence base to support this approach. How should this information be applied to the outpatient treatment of COVID-19 infection? For patients with advanced age or comorbidities in the setting of moderately severe COVID-19 infection, there are consensus statements[15] suggesting a role for prophylactic doses of anticoagulants, however again without a firm evidence base to support this practice.

ACEi and ARB medications may lower mortality risk among hospitalized patients with hypertension and COVID-19[16]

Hypertension has been associated with an increased mortality risk with COVID-19 infections. Angiotensin-converting enzyme inhibitor (ACEi) and angiotensin II receptor blocker (ARB) medications are considered first-line treatments for many patients with hypertension. But controversy about their use with COVID-19 infections stems from animal studies that show increased expression of ACE2 receptors, the cellular receptor and entry site for SARS-CoV-2. ACE2 is downregulated following SARS infection, and ACEi/ARB medications block downregulation. It is not known whether ACEi/ARB medications have beneficial or harmful effects with COVID-19 infection. Using a retrospective, multi-center design, a recent study compared mortality rates between 1128 hospitalized patients with hypertension and COVID-19 infection. One hundred eighty-eight patients were taking ACEi/ARB therapy and 940 were not. Age and sex distributions did not differ between cohorts. The unadjusted mortality rate was lower in the ACEi/ARB group compared to the non-ACEi/ARB group (3.7% versus 9.8%). In a mixed-effect model that adjusted for age, sex, comorbidities and other in-hospital medications, mortality remained lower in the ACEi/ARB group. Further analyses comparing use of ACEi/ARB to use of other antihypertensive drugs continued to demonstrate decreased mortality in the ACEi/ARB group.

Overall, the study suggests a beneficial effect — lower mortality risk — among hospitalized patients with hypertension and COVID-19 who use ACEi/ARB.

Presenting characteristics and outcomes of 5,700 hospitalized patients with COVID-19[17]

A recent case series characterized patient demographics, baseline comorbidities and outcomes of 5700 sequentially hospitalized patients with COVID-19 in the New York City area. Clinical outcomes were monitored until April 4, 2020. The median age of the cohort was 63 years; 39.7% were female. The median Charlson Comorbidity Index score was 4 points, reflecting a substantial comorbidity burden. The most common comorbidities included hypertension (56.6%), obesity (41.7%) and diabetes (33.8%). Fever was present on presentation in 30.7%, and 27.8% required supplemental oxygen.

Upon study completion, outcomes (discharge or death) were available for 2,634 patients: 14.2% were treated in the ICU; 12.2% received mechanical ventilation; 3.2% were treated with kidney replacement therapy; and 21% died. Among patients who received mechanical ventilation, 88.1% died. Deaths were reported by age: 38.3% of patients over 65 years; 8.9% of patients 18-65 years; and none of the 32 patients under 18 years. Death rates were stratified by sex and age (see table below), and men appear to have higher rates than women in every age category, but statistical comparisons were not performed. Patients with diabetes were more likely to receive mechanical ventilation or ICU care than patients without diabetes. Only 436 patients were younger than 50 years old and had a Charlson Comorbidity Index of zero; 9 (2.1%) of these patients died. The unadjusted mortality rate for patients with hypertension, but not taking an ACEi or ARB antihypertensive medicine was 26.7%; unadjusted mortality rates for patients taking an ACEi or an ARB were 32.7% and 30.6%, respectively. Given the study design, further analyses related to the possible adverse (or protective) effects of ACEi and ARB medicines were not performed.

In the largest case series to date, age, diabetes and male sex appear to be strong risk factors for poor outcomes among patients with COVID-19 infections who were sick enough to be hospitalized. Other recent research suggests a beneficial effect from ACEi/ARB use among inpatients with

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hypertension and COVID-19 (see Forum article above, as ACEi and ARB medications appear to lower mortality risk among hospitalized patients with hypertension and COVID-19).

Discharge Disposition by 10-Year Age Intervals of Patients Hospitalized With COVID-19[17]

	Patients discharged alive or dead at study end point						Patients in hospital at study end point	
	Died, No./No. (%)		Length of stay among those who died, median (IQR), d[a]	Discharged alive, No./No. (%)		Length of stay among those discharged alive, median (IQR), d[a]	No./No. (%)	Length of stay, median (IQR), d[a]
	Male	Female		Male	Female			
Age intervals, y								
0-9	0/13	0/13	NA	13/13 (100)	13/13 (100)	2.0 (1.7-2.7)	7/33 (21.2)	4.3 (3.1-12.5)
10-19	0/1	0/7	NA	1/1 (100)	7/7 (100)	1.8 (1.0-3.1)	9/17 (52.9)	3.3 (2.8-4.3)
20-29	3/42 (7.1)	1/55 (1.8)	4.0 (0.8-7.4)	39/42 (92.9)	54/55 (98.2)	2.5 (1.8-4.0)	52/149 (34.9)	3.2 (1.9-6.4)
30-39	6/130 (4.6)	2/81 (2.5)	2.8 (2.4-3.6)	124/130 (95.4)	79/81 (97.5)	3.7 (2.0-5.8)	142/353 (40.2)	5.1 (2.5-9.0)
40-49	19/233 (8.2)	3/119 (2.5)	5.6 (3.0-8.4)	214/233 (91.8)	116/119 (97.5)	3.9 (2.3-6.1)	319/671 (47.5)	4.9 (2.9-8.2)
50-59	40/327 (12.2)	13/188 (6.9)	5.9 (3.1-9.5)	287/327 (87.8)	175/188 (93.1)	3.8 (2.5-6.7)	594/1109 (53.6)	4.9 (2.8-8.0)
60-69	56/300 (18.7)	28/233 (12.0)	5.7 (2.6-8.2)	244/300 (81.3)	205/233 (88.0)	4.3 (2.5-6.8)	771/1304 (59.1)	5.0 (2.4-8.2)
70-79	91/254 (35.8)	54/197 (27.4)	5.0 (2.7-7.8)	163/254 (64.2)	143/197 (72.6)	4.6 (2.8-7.8)	697/1148 (60.7)	4.5 (2.3-8.2)
80-89	94/155 (60.6)	76/158 (48.1)	3.9 (2.1-6.5)	61/155 (39.4)	82/158 (51.9)	4.4 (2.7-7.7)	369/682 (54.1)	4.1 (2.1-7.4)
≥90	28/44 (63.6)	39/84 (46.4)	3.0 (0.7-5.5)	16/44 (36.4)	45/84 (53.6)	4.8 (2.8-8.4)	106/234 (45.3)	3.2 (1.5-6.4)

Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range; NA, not applicable.

[a] Length of stay begins with admission time and ends with discharge time, time at death, or midnight on the last day of data collection for the study. It does not include time in the emergency department.

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Dr. Kenneth Cohen is an experienced physician leader, practicing internist, and researcher who has attained national recognition for health care quality improvement. He has successfully developed and reported numerous clinical quality studies in primary care, including tobacco cessation, osteoporosis, asthma, diabetes, hypertension, and ischemic vascular disease. He was one of the founding physicians of New West Physicians, which is the largest primary care group practice in Colorado and now part of OptumCare. He has served as Chief Medical Officer since 1995. Dr. Cohen has received awards of recognition and distinction for teaching, including the Lutheran Medical Center Physician of the Year award in 2011. Under his stewardship New West Physicians was awarded the AMGA Acclaim award in 2015 and the Million Hearts Hypertension Champion Award in 2017. He is a Clinical Associate Professor of Medicine and Pharmacy at the University of Colorado School of Medicine. Dr. Cohen holds degrees from Dickinson College and Hahnemann University. He is a Fellow of the American College of Physicians and a member of the Phi Beta Kappa and Alpha Omega Alpha honor societies.

John Hitt, MD, MBA | *Senior Medical Director*

Dr. Hitt has been a physician executive for more than 25 years. Most recently he was the CMO of Ativa Medical a medical device startup company and an independent health care consultant. Previously, he was CMO at Maricopa Integrated Health System (MIHS) and a key member of the senior leadership team having responsibility for Medical Staff Services, Grants and Research, Academic Affairs, Risk Management, physician contracted services and the activity of Residency Program Directors, Clinical Department Chairs, and Medical Staff.

Dr. Hitt has over 25 years of experience in quality and performance improvement, clinical integration, academic and medical staff affairs. He served as the Chief Medical Quality Officer for Hennepin Health System, a premier Level 1 Adult and Pediatric Trauma Center. He was a physician leader for VHA (now Vizient). He was the national Medical Director for Disease Management at Caremark International and the VP of Medical Affairs at the University of Minnesota Hospital.

Dr. Hitt is a graduate of the University of Virginia where he played Division 1 soccer. He received his Medical Doctorate from the Medical College of Georgia in 1984 (AOA honors) and completed his Internal Medicine and Infectious Disease Fellowship training at the University of Minnesota Hospital and Clinics. Dr. Hitt completed his MBA at the Carlson School of Management at the University of Minnesota in 2003. He is the proud father of seven children.

Geoffrey Heyer, MD | *Senior Clinical Practice Performance Consultant*

Dr. Heyer is board certified in neurology with special certification in child neurology and in headache medicine. Prior to joining our team, Dr. Heyer was an associate professor of neurology and pediatrics at The Ohio State University and Columbia University Medical Center, specializing in autonomic disorders, headache, and pain management. He has published over 50 peer-reviewed research papers and numerous editorials, clinical reviews, and textbook chapters. He also co-authored a textbook on childhood stroke and cerebrovascular disorders.

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