August 28, 2020

COVID-19 - Safe Reopening of College, Frequency and Turnaround Time for Surveillance, Isolation Time, Predictive Cytokine Signature, Disease Outcomes Based on Sex Differences, and More

Today I have chosen a diverse group of topics. Given the controversy over testing, I went back and chose 2 articles looking at frequency, sensitivity, and TAT in preventing spread of SARS-CoV-2 infections. These articles do not apply to hospital settings.   The next article is the best review to date in my humble opinion on duration of infectivity and isolation from SARS-CoV-2. The next article looks at predictive biomarkers early in disease which might serve to inform healthcare allocation and prioritization of individuals at highest risk. The next article tries to explain why men have a higher risk of infection with SARS-CoV-2.   The next article raises the question of prophylactic AC versus therapeutic AC and outcomes from SARS-CoV-2 infection.   The last article reviews the ocular manifestation of SARS-CoV-2 in children.

Have a wonderful weekend

Ed

Assessment of SARS-CoV-2 Screening Strategies to Permit the Safe Reopening of College Campuses in the United States   JAMA Netw Open published online July 31, 2020

Test sensitivity is secondary to frequency and turnaround time for COVID-19 surveillance   MedRvix posted June 27, 2020

In the first study, the investigators modeled the cost-efficacy of routine screening using tests with sensitivities varying from 70% to 90%, and performed from once daily to once weekly, to prevent the spread of SARS-CoV-2 among 5000 college students, of whom 10 had initial SARS-CoV-2 infection. They included varying frequencies of exogenous infections introduced into the population and 3 different reproductive numbers (1.5, 2.5, and 3.5). They estimated a TAT of 8 hours with subsequent student

isolation and assumed that the cost of testing increased with increased sensitivity.   The model showed that over a 3 month semester, symptom-based screening would <u>not</u> control an outbreak; <u>test frequency was more important than test sensitivity</u> in decreasing the number of infections; and using a less expensive, less sensitive test was most cost-effective.

In the second study,[not peer reviewed] colleagues hypothesized that SARS-CoV-2 infectious particles are, at most, minimally present in samples with fewer than 10^6 RNA copies/mL, and that during the exponential growth of the virus in early infection, the increase from 10^3 and 10^5 RNA copies/mL likely occurs in less than a day. The investigators modelled the relative efficacy of preventing infection through surveillance and isolation using tests with levels of detection of 10^3 and 10^5 RNA copies/mL, analogous to highly sensitive NAATs and rapid antigen tests, respectively. The model showed minimal differences in averting secondary infections between the use of the different assays. However, there was a reduction in secondary infections of approximately 100%, 90%, 60%, and 40%, respectively, when testing daily, every third day, weekly, and biweekly. The effectiveness in reducing secondary infections decreased markedly as the test TAT increased from instantaneous to 1 to 2 days.

Comment: Given the recent controversy of the recent CDC revision on testing I went back and reviewed these 2 articles which may shed some light on testing strategies. Both studies show that our ability to
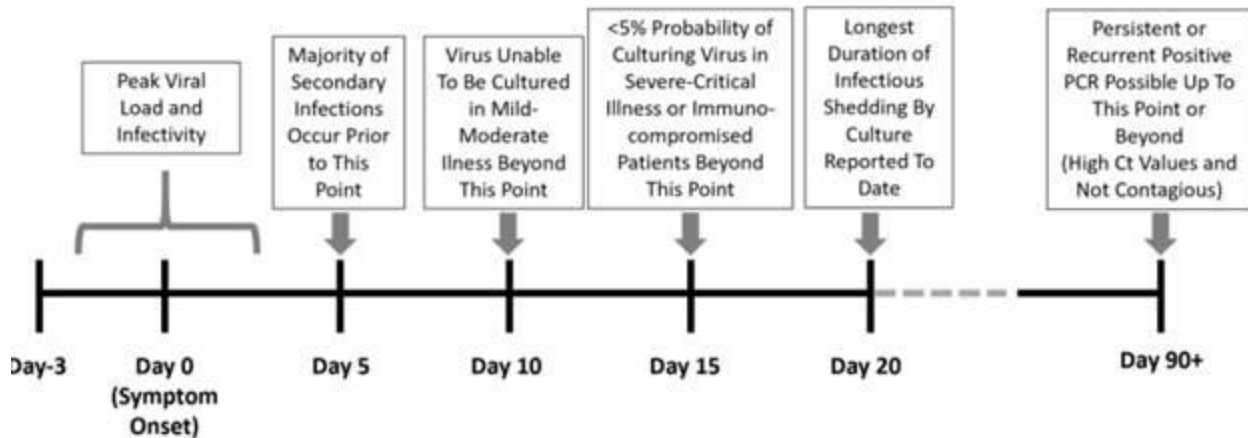
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control SARS-CoV-2 infections are less dependent on the sensitivity of assay used but rather the frequency of testing. The effect is magnified by TAT. So where do we go from here. Let me propose that we use frequent surveillance testing[at least weekly] in high-risk populations with rapid TAT. This strategy should enhance our ability to prevent spread of SARS-CoV-2 infections. The use of low-cost point of care testing with rapid TAT should be cost-effective.

Duration of SARS-CoV-2 Infectivity: When is it Safe to Discontinue Isolation?   Clin Infect Dis published online August 25, 2020

This is an excellent review by my colleagues in Boston. Multiple studies have now shown that despite persistently positive PCRs,   it does not always correlate with replicating-competent virus. They review that the Ct value is inversely related to the amount of RNA present in a sample. Every increase in Ct value of ~3.3 there is a 10-fold reduction in amount of RNA. Most SARS-CoV-2 assays use a Ct cutoff of <40 for positivity. Some use 30. Patients in the early stages of disease have Ct values of <30. Ct values however do not reflect a true viral load. It is clear that persistent RNA detection does not necessarily mean viable virus. Ct values of 13-17 were all associated with positive viral cultures. No virus was successfully cultured from sample with Ct values >34 and some studies are unsuccessful with Ct values >30.   CDC has not been able to grow virus from patients after 8 days from symptom onset in non-severe disease. The probability of culturing SARS-CoV-2 is greatest between days 1-5 and peak at day 3 after symptoms onset. For severe disease and immunocompromised patients median interval of infectious shedding by culture was 8 days after symptom onset with the maximum up to 20 days.
The section on transmissibility is especially useful. We know that viral RNA is present 2-3 days before symptoms appear and peaks at symptom onset and declines over the next week.   They review several papers on secondary attack rates from different time intervals from symptom onset.   In one study the secondary attack rate was 0.7% within 5 days of symptom onset and zero for contacts > 5days.   In another study attacked rates were highest among household contacts and family contacts (~5%) and much lower in HCW (0.9%). A key observation was that close contacts to severely ill patients were 4X more likely to acquire infection compared to close contacts with mild disease. This observation mirrors the recent publication in AIM reviewed last week in the Daily Briefing which demonstrated secondary attack rates correlated with severity of disease and uncommon if asymptomatic. This supports the WHO claim that asymptomatic patients are less likely to transmit SARS-CoV-2.

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| Peak Viral Load and Infectivity | Majority of Secondary Infections Occur Prior to This Point | Virus Unable To Be Cultured in Mild-Moderate Ilness Beyond This Point | <5% Probability of Culturing Virus in Severe-Critical Illness or Immuno-compromised Patients Beyond This Point | Longest Duration of Infectious Shedding By Culture Reported To Date | Persistent or Recurrent Positive PCR Possible Up To This Point or Beyond (High Ct Values and Not Contagious) |

Day-3   Day 0 (Symptom Onset)   Day 5   Day 10   Day 15   Day 20   Day 90+

Comment: This is the best single review on this topic. Based on science, the WHO and CDC has modified guidance on duration of isolation shifting from test based to symptom based. Since acceptance, the first case of reinfection has been reported.

An inflammatory cytokine signature predicts COVID-19 severity and survival Nat Med published online August 24, 2020

Predictive biomarkers of pathogenic inflammation to help guide targetable immune pathways are critically lacking. The investigators implemented a rapid multiplex cytokine assay to measure serum interleukin (IL)-6, IL-8, tumor necrosis factor (TNF)-α and IL-1β in hospitalized patients with COVID-19 upon admission to the Mount Sinai Health System in New York. Patients ($n = 1,484$) were followed up to 41 d after admission (median, 8 d), and clinical information, laboratory test results and patient outcomes were collected.

They found that high serum IL-6, IL-8 and TNF-α levels at the time of hospitalization were strong and independent predictors of patient survival ($P < 0.0001$, $P = 0.0205$ and $P = 0.0140$, respectively). Notably, when adjusting for disease severity, common laboratory inflammation markers, hypoxia and other vitals, demographics, and a range of comorbidities, IL-6 and TNF-α serum levels remained independent and significant predictors of disease severity and death. These findings were validated in a second cohort of patients ($n = 231$). Men had significantly higher levels of IL-6 than women ($P<0.0001$), but no sex differences were observed for the other three cytokines With increased age brackets (<50, 50–70 and >70 years old), levels of IL-6, IL-8 and TNF-α increased and the same was observed for age when assessed as a continuous variable. There was no association of any cytokine measured with body mass index (BMI) Using multivariable regression models, they confirmed that CKD was the only comorbidity significantly associated with elevated cytokine levels, whereas elevated TNF-α in patients with diabetes and hypertension were explained by other variables

Days from ELLA cytokine test to last follow-up
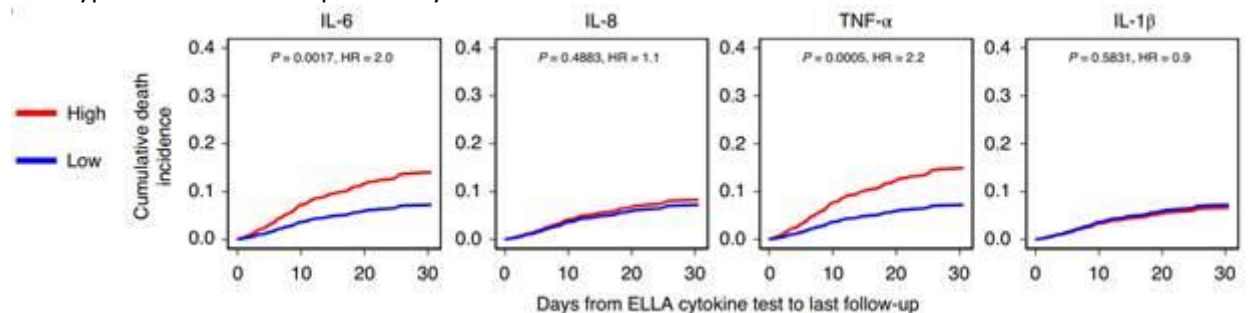
Comment: They propose that serum IL-6 and TNF-α levels should be considered in the management and treatment of patients with COVID-19 to stratify prospective clinical trials, guide resource allocation and inform therapeutic options. The predictive value of these cytokines might help inform therapeutic interventions to determine which individuals are likely to develop respiratory failure, end organ damage and death and to select optimal trial designs to disrupt the underlying inflammatory milieu. A prediction model built on cytokine levels early in disease might serve to inform healthcare allocation and prioritization of individuals at highest risk. This could help who would benefit from early remdesivir and convalescent plasma.

Sex differences in immune responses that underlie COVID-19 disease outcomes   Nature published online August 26, 2020
In this study, the investigators examined sex differences in viral loads, SARS-CoV-2-specific antibody titers, plasma cytokines, as well as blood cell phenotyping in COVID-19 patients. They focused on moderate disease who had not received immunomodulatory medications. Their results revealed that male patients had higher plasma levels of innate immune cytokines such as IL-8 and IL-18 along with more robust induction of non-classical monocytes. In contrast, female patients mounted significantly more robust T cell activation than male patients during SARS-CoV-2 infection, which was sustained in old age. Importantly, they found that a poor T cell response negatively correlated with patients' age and was associated with worse disease outcome in male patients, but not in female patients. Conversely, higher innate immune cytokines in female patients associated with worse disease progression, but not in male patients.
Comment: These findings may be a possible explanation underlying observed sex biases in COVID-19 and provide an important basis for the development of a sex-based approach to the treatment and care of men and women with COVID-19. Collectively, these data suggest that vaccines and therapies to elevate T cell immune response to SARS-CoV-2 might be warranted for male patients. Healthy HCWs used as the control population were not matched to patients based on age, BMI or underlying risk factors.

Anticoagulation, Mortality, Bleeding and Pathology Among Patients Hospitalized with COVID-19: A Single Health System Study J Am Coll Cardiol published online August 25, 2020

Observational analyses have suggested potential benefit for in-hospital use anticoagulation (AC) in COVID-19 treatment. In a preliminary analysis of 2700 patients admitted to the Mount Sinai Health System (MSHS) in New York, the authors found an association between in-hospital therapeutic AC and lower mortality compared to patients on no/prophylactic AC. [J Am Coll Cardiol published May 10, 2020]The present analysis expands upon those results in a larger cohort to explore the impact of therapeutic versus prophylactic AC, as well as choice of agent, on survival, intubation, and major bleeding compared to no AC.

Of nearly 4400 adults admitted to MSHS with COVID-19, 45% received prophylactic anticoagulation, 21% received therapeutic anticoagulation, and the remainder received none. Overall, 24% of the patients died in the hospital. After multivariable adjustment, prophylactic and therapeutic treatment were each associated with roughly a 50% reduction in mortality, relative to no anticoagulation. Rates of major bleeding were low (2%–3%). In addition, of 26 autopsies performed, thromboembolic disease was found in 42%; most of these patients had not received therapeutic anticoagulation.
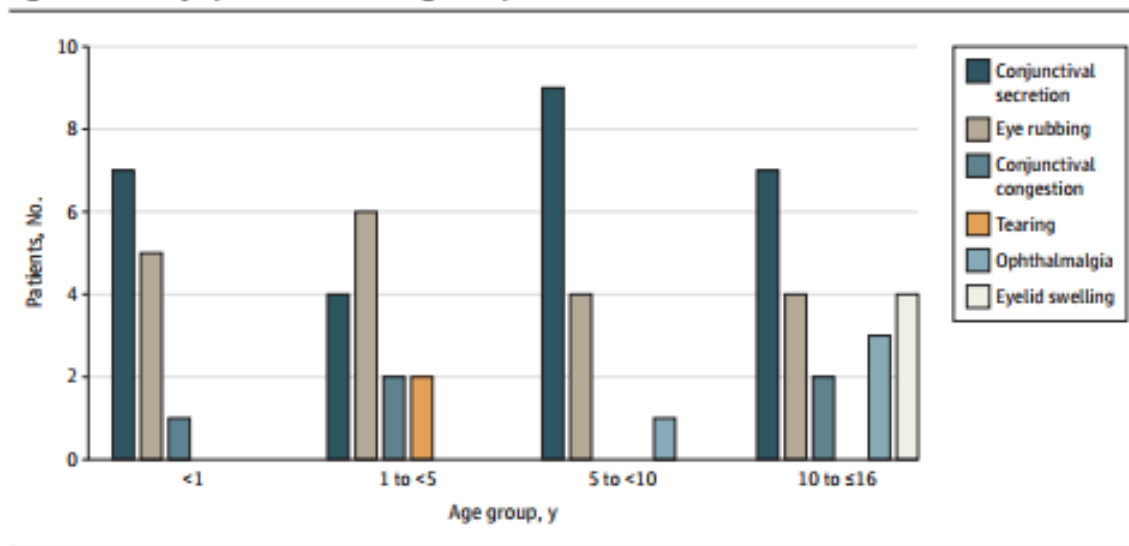
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Comment: . Compared to prophylactic AC, therapeutic AC was associated with lower mortality, though not statistically significant. Autopsies revealed frequent thromboembolic disease. Many facilities call for therapeutic AC only in patients with high D-dimer (>3). The data presented in this article may stimulate trials to determine optimal AC regimens. The generalizability of the autopsy data may be limited due to small sample. Since this was an observational study, there may have been confounders leading to differences in the outcomes for the treatment groups despite efforts to minimize their potential impact through IPTW modeling. Rates of major bleeding were low. Results of RCTs evaluating different AC regimens for treatment for hospitalized patients with COVID-19 are needed.

Ocular Manifestations and Clinical Characteristics of Children with Laboratory-Confirmed COVID-19 in Wuhan, China JAMA Ophthalmology published online August 26, 2020

Of 216 children hospitalized with COVID-19 in China, nearly one fourth had ocular symptoms, according to this study. Conjunctival discharge was the most common symptom, followed by eye rubbing and conjunctival congestion. Symptoms resolved without treatment in nearly half the cases; in some cases, antibacterial, antiviral, and antiallergic eye drops were used. Eight children had persistent eye rubbing, while the rest recovered completely.

Figure 1. Ocular Symptoms in Different Age Groups
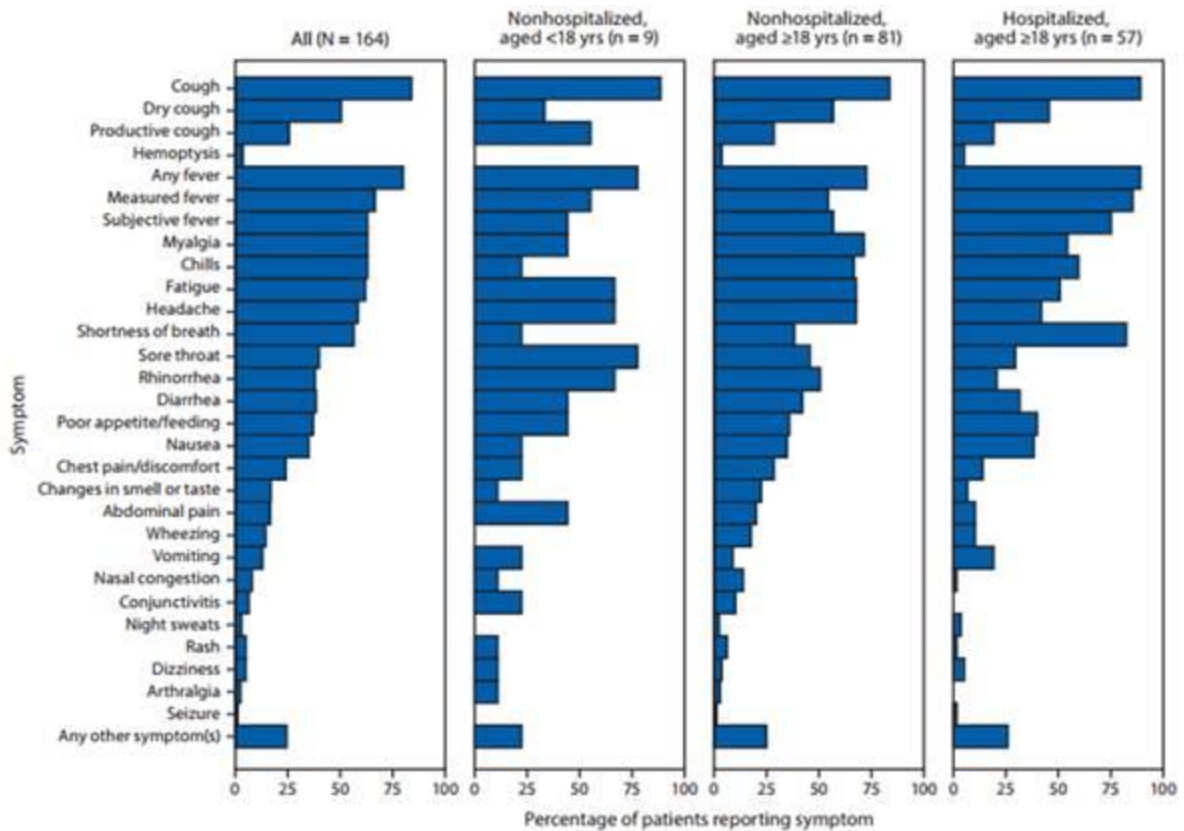
Comment: In this study, children hospitalized with COVID-19 in China, presented with a series of symptoms including fever, cough, and ocular manifestations, such as conjunctival discharge, eye rubbing, and conjunctival congestion. I must admit I had not focused on this finding, but according to the CDC report shown above [MMWR 2020; 69:904-90] children appear to have more conjunctivitis compared to adults. Ocular symptoms recovered or improved eventually.