TGIF

Today I have chosen a diverse group of articles I hope are of interest. The first article reviews the impact of bacterial infections in patients infected with SARS-CoV-2 and the importance of antimicrobial stewardship. The next two articles provide insight into the pathogenesis of endothelial injury and the importance in severe SARS-CoV-2 infection. The fourth article although a small study suggests breast milk is unlikely to be a source of infection for the infant. The last article adds to our knowledge of infection in children. The findings also show that although a low expression of ACE2 in younger children (< 10) likely does corresponds to reduced infection rates, once infected, they may carry high SARS-CoV-2 viral loads.

Have a great weekend. Monday I will review the updated CDC guidance on antigen testing and the updated IDSA guidance on serologies.

Ed

Bacterial Infections and Patterns of Antibiotic Use in Patients with COVID-19
J Med Virology published August 18, 2020
This is a retrospective study of 242 patients admitted to the hospital for COVID-19. The study included patients aged older than 18 years who were admitted to the intensive care unit (ICU) and non-ICU settings between March 1 and April 24, 2020 with a confirmed diagnosis of COVID-19 via PCR performed on nasopharyngeal swab specimens. Almost half of the patients were female (119), and 70% were African American. Chronic comorbidities included hypertension (74%), diabetes (49%), and chronic obstructive pulmonary disease or asthma (19%).

The study showed a significantly higher mortality rate among the 46 patients with concomitant bacterial infections (50% vs 15%; $P < .0001$), as well as the need for mechanical ventilation (44% vs 17%; $P < .0001$).

Even after adjusting for demographic factors and comorbidities, concomitant bacterial infections were still independently significantly associated with increased inpatient mortality (odds ratio = 5.838; 95% confidence interval [CI], 2.647-12.876).

Urinary tract infection (UTI) was the most frequent source of bacterial co-infection (57%), and the most common organism was *Escherichia coli* (26%). [fairly low] Other infection sources included gastrointestinal infections (8%), skin infections (10%), and respiratory infections (8%).

When looking at only patients with UTIs, there was still a significantly higher rate of inpatient mortality (50% vs 18%; $P < .0001$). Even after adjustment for demographic factors and comorbidities by multivariable regression, UTIs were still independently associated with inpatient death (OR = 4.224; 95% CI, 1.692-10.540; $P < .002$).

Higher rates of coinfection in our study population may be explained by a relatively sicker patient population with higher rates of hypertension and diabetes, as well as higher body mass index, compared with [other] COVID-19 studies. There are proposed theories that patients with cardiometabolic comorbidities tend to have higher rates of bacterial coinfection in viral infection due to an underlying dysregulated immune response. The presence of coinfection may not be causative of worse clinical

outcomes but rather signify clinical deterioration. Cytokine storm is known to promotes dysregulated innate immune responses, and in vulnerable patients predispose to bacterial coinfection. The study also showed that patients who had bacterial coinfection were significantly older [median age, 71.35 ± 11.20 years vs 64.78 ± 15.23 years].

Overall, 67% of the patients in the study received antibiotic therapy, yet 72% did not have an obvious source of bacterial infection. There was a significantly higher rate of inpatient mortality among patients who received antibiotics compared with those who did not (30% vs 5%; *P*< .0001), but this finding should be interpreted with caution as there may be selection bias since many were older and sicker.

Comment: This article and others have a highlighted increase antibiotic use and at times suspension of antimicrobial stewardship programs due to the pandemic. Simultaneous co-infection with bacteria on admission appears less common than influenza. In ICU especially if patient receive IL-6 inhibitors, there is an increased risk of secondary bacterial infections.

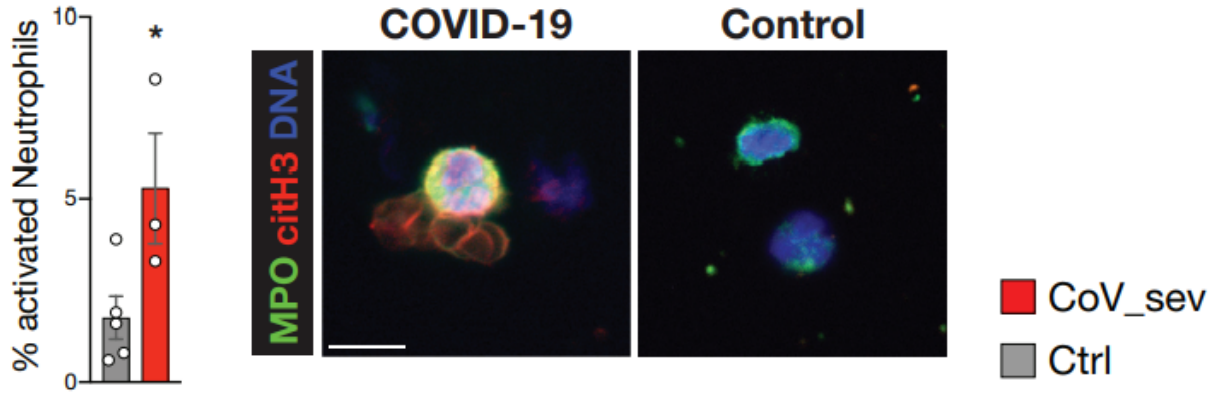
Immunothrombotic Dysregulation in COVID-19 Pneumonia is Associated with Respiratory Failure and Coagulopathy

Circulation published online July 28, 2020

Investigators describe the lung histopathology from a fatal case of severe COVID-19. They found microvascular thrombosis in the presence of antemortem respiratory and renal failure, myocardial injury, and dysregulated coagulation, as evidenced by elevated D-dimer. The microvascular thrombi contained platelets, fibrin, and large numbers of neutrophils. Neutrophils were also evident in microthrombi from an additional four fatal cases — also in lung, cardiac, and renal tissue.

The investigators then compared the neutrophil activation state from severe COVID-19 cases (requiring mechanical ventilation) and from patients with less severe disease (requiring only supplemental oxygen). They determined that neutrophil activation marker CD177 was highly upregulated in severe cases compared with less severe infections.

The authors next examined platelet dynamics and found a small but highly activated platelet subpopulation in severe cases. Hemostatic measurements under high shear conditions showed increased plug formation in response to collagen-epinephrine, suggestive of platelet hyperactivity in severe cases. Severe cases also showed shorter clot formation times, increased maximal clot firmness, and reduced maximal clot lysis, which correlated with neutrophil counts and illness severity. Finally, neutrophils from healthy donors were combined with platelet-rich plasma from severe cases or controls. The platelets from severe cases showed enhanced neutrophil adhesion and enhanced neutrophil extracellular trap (NET) formation. NET-like structures were subsequently identified in pulmonary, kidney, and heart specimens.



Comment: This study helps in our understanding of severe SARS-CoV-2 disease. The study links the interaction of activation of neutrophils and platelets and the dysregulation immunothrombosis that results in multiorgan dysfunction. Microvascular thrombi containing neutrophils, platelets, and NETs are a hallmark of severe SARS-CoV-2 infection, linking multi-organ failure and systemic hypercoagulability in COVID-19. Further work is necessary to determine the role of immunothrombosis in COVID-19.

Circulating Endothelial Cells as a Marker of Endothelial Injury in Severe COVID
J Infect Dis published online August 2020
All patients in this study presented with viral pneumonia and tested positive for SARS-CoV-2 on PCR assay of nasopharyngeal swab, sputum or bronchoalveolar lavage. Of the hospitalized patients, 19 required admission to the ICU.

Patients requiring ICU care were younger than patients hospitalized in non-ICU departments (median age, 55.3 vs 68.2 years), and had a higher percentage of patients that were obese (47% vs 19%). None of the patients in ICU had chronic kidney disease (CKD) [I was surprised] compared with 28 (35%) patients in the non-ICU group. The non-ICU group also had more patients with hypertension (54% vs 21%) and cardiovascular disease (30% vs 0%). All patients in the ICU group required mechanical ventilation.

Overall, 55% of hospitalized patients had circulating endothelial cell counts (CEC) >20 cells/mL; however, levels were significantly higher in ICU patients than in non-ICU patients (49 [24-103] vs 18 [6-70] cells/mL; *P* = .03). CECs were negatively correlated with platelet (r = -0.334; *P* = .0008) and lymphocyte counts (r = -0.336; *P* = .0007). There was also a positive correlation between the circulating endothelial cell counts and the length of hospital stay (r =0 .261; *P* = .02).

The plasma concentrations of IL-6, IP-10, E-Selectin, and sVCAM-1 were also significantly higher in ICU patients than non-ICU patients, but only sVCAM-1 (r = 0.374; *P* = .0002) and IP-10 concentrations (r = 0.487; *P* < .0001) correlated with CECs.

Multivariate analysis integrating age, obesity, hypertension, CKD, cardiovascular disease, and ICU hospitalization showed that only CKD could be identified as independently associated with CEC counts (P = .011). Admission in ICU was also associated with high CEC levels independently of all comorbidities that differ between ICU and non-ICU patients (P = .046). Consequently, after the exclusion of patients with CKD, the difference between CEC levels in ICU patients compared to non-ICU patients was even more pronounced (*P* = .002).

Comment: The impact of endothelial damage is now appreciated as a key step in the pathogenesis of severe SARS-CoV-2 infection. Any endothelial injury, including infections, impairs regulatory functions of the endothelium with subsequent vasoconstriction, ischemia, inflammation and activation of the coagulation cascade, ultimately leading to vessels denudation and exposure of the thrombogenic subendothelium. This study provides direct proof of endothelial damage during the course of COVID-19 and a clinically informative biomarker of disease severity. The data may also bring rationale for therapies that stabilize the endothelium in addition to limiting inflammation in vulnerable patients. The prior article links the interaction of activation of neutrophils and platelets and the dysregulation immunothrombosis.

Evaluation for SARS-CoV-2 in Breast Milk From 18 Infected Women

JAMA published online August 19, 2020

Eighteen U.S. women with COVID-19 who were breast-feeding provided 64 breast milk samples for analysis (nearly all women were symptomatic). PCR detected SARS-CoV-2 RNA in one sample, which was collected on the day of symptom onset. However, culture to detect replication-competent virus was negative for all samples, including the one with positive PCR results. The researchers write, "

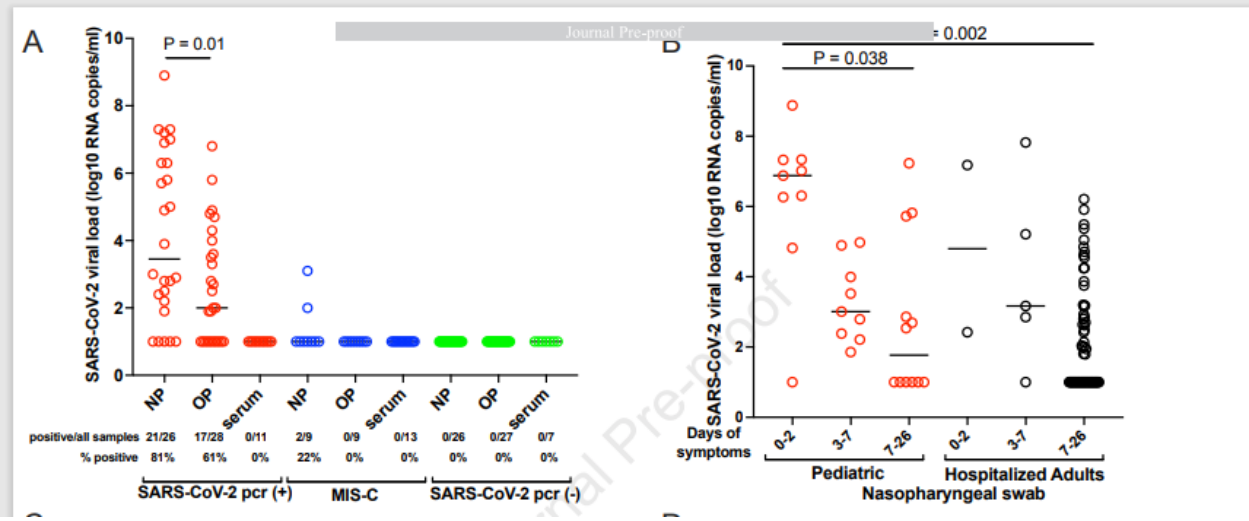
Comment: These data suggest that SARS-CoV-2 RNA does not represent replication-competent virus and that breast milk is unlikely to be a source of infection for the infant. However, this was a small sample with self-collection of milk samples, some before the standard protocol was instituted. This small study, however, supports allowing COVID-19 mothers to breast feed their infants with appropriate infection prevention.

Pediatric SARS-CoV-2: Clinical Presentation, Infectivity, and Immune Responses

J Pediatr published online August 19, 2020

Children ages 0-22 years with suspected SARS-CoV-2 infection presenting to urgent care clinics or being hospitalized for confirmed/suspected SARS-CoV-2 infection or multisystem inflammatory syndrome in children (MIS-C) at Massachusetts General Hospital (MGH) were offered enrollment in the MGH Pediatric COVID-19 Biorepository. Enrolled children provided nasopharyngeal, oropharyngeal, and/or blood specimens. SARS-CoV-2 viral load, ACE2 RNA levels, and serology for SARS-CoV-2 were quantified.

A total of 192 children (mean age 10.2 +/- 7 years) were enrolled. Forty-nine children (26%) were diagnosed with acute SARS-CoV-2 infection; an additional 18 children (9%) met criteria for MIS-C. Only 25 (51%) of children with acute SARS-CoV-2 infection presented with fever; symptoms of SARS-CoV-2 infection, if present, were non-specific. Nasopharyngeal viral load was highest in children in the first 2 days of symptoms, significantly higher than hospitalized adults with severe disease (P = .002). Higher levels of viral load were detected in nasopharyngeal swabs compared with oropharyngeal swabs (unpaired t-test, P=0.01). Age did not impact viral load, but younger children had lower ACE2 expression (P=0.004). IgM and IgG to the receptor binding domain (RBD) of the SARS-CoV-2 spike protein were increased in severe MIS-C (P<0.001), with dysregulated humoral responses observed.



Comment: The investigators found that children can carry high levels of virus (by PCR) in their upper airways, particularly early in an acute SARS-CoV-2 infection, yet they display relatively mild or no symptoms. However, there was no age correlation with viral load, indicating that infants through young adults can carry equally high levels of virus. However, SARS-CoV-2 infected children have higher levels of ACE2 expression, which may pre-dispose certain children to infection. Younger children had lower levels ACE2 expression suggested by some why some studies show lower infection and transmission in this age group. The findings also show that although a low expression of ACE2 in younger children (< 10) likely does corresponds to reduced infection rates, once infected, they may carry high SARS-CoV-2 viral loads. Limiting the spread of SARS-CoV-2 infections in children is of concern as schools plan for re-opening. The findings here suggest that it would be ineffective to rely solely on symptoms or fever. Instead infection prevention measures should be strictly enforced at all times to minimize the possibility of transmission, with focus on strategies including social distancing, mask use, hand hygiene, utilizing open spaces, preventing crowding, disinfection, and improved ventilation.