Since tomorrow is a religious observance, I am sending tomorrow's Daily Briefing tonight

I thought it would be a nice change to link a recent case with one of the articles reviewed. So, I start with a recent case followed by a meta-analysis on susceptibility of SARS-CoV-2 infections in children and adolescence compared to adults. Conclusion, it does appear that children overall are relatively less susceptible to becoming infected as well having less severe infection itself. The next article may provide a clue – children have a more active innate immune response compared to adults. The next article reports that some patients with life threatening SARS-CoV-2 pneumonia have neutralizing autoAbs against type I IFNs which highlights the crucial role of type I IFNs in protective immunity against SARS-CoV-2. The last article reviews the GI complications of SARS-CoV-2 infection which related to the case at the start of tomorrow's Daily Briefing.

Ed

Case

This is a 40-year-old male admitted for sudden onset of generalized abdominal pain with bloody stools. He had diffuse abdominal pain. Patient was known HIV on antiretroviral therapy. Lab: WBC 8500 90 P, 10 L, D-dimer 4.6, CRP 189. He was seen by GI who did a limited coloscopy which disclosed inflammation and early necrosis. Later that day a CXR was done which revealed free air. Patient was taken to surgery which revealed a perforate and gangrenous distal colon. On day of surgery his flow panel returned which suggested the diagnosis. -What was the clue? (see the last article for answer)-

FLOW PANEL	
AB TOT LYMPH	363
CD3 T-CELL AG:	72
AB CD3 T CELL	261 L
CD4 T-HELPER:	16 L
AB CD4 T-CELL	59 L
CD8 T-SUPPRESS:	56 H
AB CD8 T-CELL	202
H/S RATIO:	0.29 L
CD16+56 NK	14
CD 16 56 NK #	51 L
CD19 EARLY B-CELL	13
AB CD19 ERLY	46 L
CD4-CD8 INTERPRETATION	CD4-CD8 Interp

Susceptibility to SARS-CoV-2 Infection Among Children and Adolescents Compared with Adults: A Systematic Review and Meta-Analysis

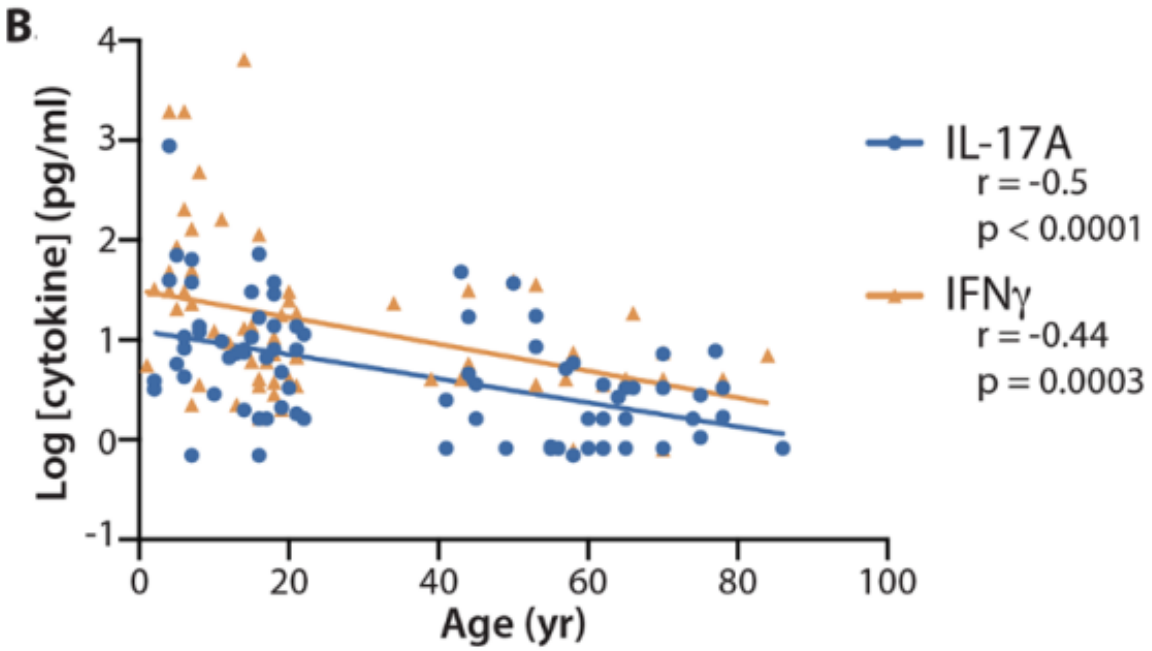
JAMA Pediatr published online September 25, 2020

Studies were selected that provided data on the prevalence of SARS-CoV-2 in children and adolescents (younger than 20 years) compared with adults (20 years and older) derived from contact tracing or population screening were included. Main outcome was secondary infection rate (contact-tracing studies) or prevalence or seroprevalence (population screening studies) among children and adolescents compared with adults.

A total of 32 studies comprising 41 640 children and adolescents and 268 945 adults met inclusion criteria, including 18 contact-tracing studies and 14 population screening studies. This meta-analysis of contact tracing data revealed a significantly lower proportion of children acquiring the infection than adults from infected index cases within the household (odds ratio, 0.41; 95% CI, 0.22-0.76). Looking specifically at studies of household contacts, perhaps the most reliable indicator of relative infection susceptibility, these data suggest young children in particular (age <12-14 years) are less than half as likely to acquire infection with SARS-CoV-2 than adults, given an equivalent, or at least very similar, exposure. This is consistent with other studies which showed that this difference is less for older children and adolescents (age <9 years).

Comments: In spite of everything we had understood about other respiratory viral infections to date, it does now appear that children overall are relatively less susceptible to becoming infected as well having less severe infection itself. Explanations discussed in the Daily Briefing have included immunity to other common cold human coronaviruses which may provide cross-protection with other coronaviruses (age 2-9) and children have fewer ACE2 receptors. The article below is another attempt to explain differences between hospitalized pediatric and adult patients. We are still early in the COVID-19 pandemic, and science continues to evolve. It is possible that unknown factors related to age, e.g., transience of infection or waning of immunity, may change our initial findings in ways we do not yet understand.

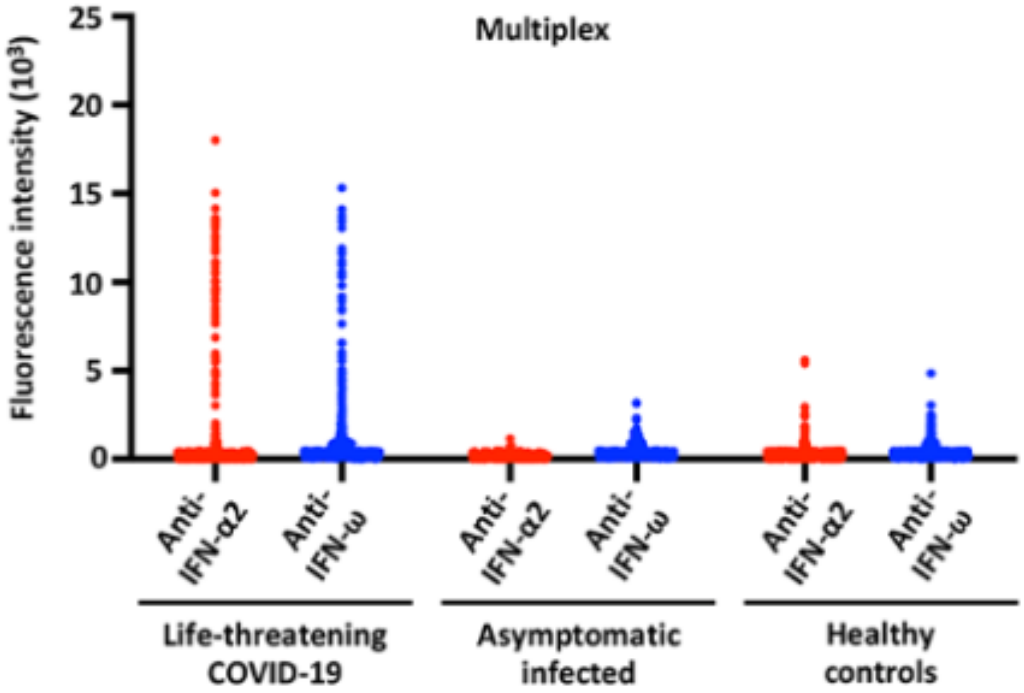
Immune Responses to SARS-CoV-2 Infection in Hospitalized Pediatric and Adult Patients
Science Trans Med published online September 21, 2020
The investigators compared cytokine, humoral, and cellular immune responses in pediatric (children and youth, age < 24 years) [older than other studies] (n=65) and adult (n=60) patients with COVID-19 at a metropolitan hospital system in New York City. The pediatric patients had a shorter length of stay, decreased requirement for mechanical ventilation and lower mortality compared to adults. The serum concentrations of IL-17A and IFN-**γ**, but not TNF-**α** or IL-6, were inversely related to age. Pediatric patients had higher serum concentrations of IL-17A and IFNγ shortly after presentation. (see below) This age-associated difference was most striking for IL-17A, which persisted even after excluding the MIS-C patients who were delayed in their hospitalization from the initial SARS-CoV-2 exposure compared to patients in the other groups. This observation suggests that IL-17A or the cells that produce it may contribute to immune protection. These molecules were most abundant in the youngest patients and decreased progressively with age. When a patient encounters an unfamiliar pathogen, it can respond within hours, called an innate immune response. Children more often encounter pathogens that are new to their immune system. Adults mounted a more robust T cell response to the viral spike protein compared to pediatric patients as evidenced by increased expression of CD25+ on CD4+ T cells and the frequency of IFN-**γ**+CD4+ T cells. Moreover, serum neutralizing antibody titers and antibody-dependent cellular phagocytosis were higher in adults compared to pediatric COVID-19 patients. The neutralizing antibody titer correlated positively with age and negatively with IL-17A and IFN-**γ** serum concentrations. There were no differences in anti-spike protein antibody titers to other human coronaviruses.



Comment: The innate immune system makes sense biologically because adults infrequently encounter a virus for the first time. But SARS-CoV-2 is new to everyone, and since the innate system declines as adults grow older, this may leave adults more vulnerable to new pathogens. Bottom line is, yes, children do respond differently immunologically to this virus. I think of the innate immune response as emergency responders first on the scene to protect the host. As this article suggests children have a more active innate immune response which may partially explain the differences in outcomes between children and adults.

Auto-Antibodies Against Type I IFNs in Patients with Life Threatening COVID-19
Science published online September 24, 2020 article provided by Cesar Arias
The authors enrolled 987 patients with proven life-threatening SARS-CoV-2 infection, 663 asymptomatic or pauci-symptomatic individuals with proven SARS-CoV-2 infection, and 1127 healthy controls in this study. Serum/plasma samples were screened for autoantibodies against 18 targets in a multiplex particle-based assay, in which magnetic beads with differential fluorescence were covalently coupled to recombinant human proteins. Patients with a fluorescence intensity (FI) of > 1500 for IFN-α2, IFNβ, or > 1000 IFNω were tested for blocking activity as were patients positive for another cytokine. The blocking activity of anti-IFNα and anti-IFNω autoantibodies was determined by assessing STAT1 phosphorylation in healthy control cells following stimulation with the appropriate cytokines in the presence of 10% healthy control or patient serum/plasma.

They report that at least 101 of 987 patients with life-threatening SARS-CoV-2 pneumonia had neutralizing IgG auto-Abs against IFN-**ω** (13 patients), the 13 types of IFN-**α** (36), or both (52), at the onset of critical disease; a few also had autoAbs against the other three type I IFNs. The auto-Abs neutralize the ability of the corresponding type I IFNs to block SARS-CoV-2 infection in vitro. These auto-Abs were not found in 663 individuals with asymptomatic or mild SARS-CoV-2 infection and were present in only 4 of 1,227 healthy individuals. Patients with auto-Abs were aged 25 to 87 years and 95 were men. A B cell auto-immune phenocopy of inborn errors of type I IFN immunity underlies life-threatening SARS-CoV-2 pneumonia in at least 2.6% of women and 12.5% of men.



Comment: This **report** showed that at least 10% of patients with life threatening SARS-CoV-2 pneumonia have neutralizing autoAbs against type I IFNs. This study highlights the crucial role of type I IFNs in protective immunity against SARS-CoV-2. Can we screen SARS CoV-2-infected patients to identify individuals with auto-Abs at risk of developing life-threatening pneumonia? This finding paves the way for a potentially therapeutic intervention, including plasmapheresis, monoclonal Abs depleting plasmablasts, and the specific inhibition of type I IFN-reactive B cells. Finally, in this patient group, early treatment with IFN-α is unlikely to be beneficial. However, treatment with injected or nebulized IFN-β may have beneficial effects, as auto-Abs against IFN-β appear to be rare in patients with auto-Abs against type I IFNs.

Gastrointestinal Complications in Critically Ill Patients with and Without COVID-19
JAMA published online September 25, 2020
Critically ill patients with COVID-19 may develop gastrointestinal complications during their hospital stay, including bowel ischemia, transaminitis, gastrointestinal bleeding, pancreatitis, Ogilvie syndrome, and severe ileus. The question is whether the high incidence of gastrointestinal complications is a manifestation of critical illness in general or is specific to SARS-CoV-2 remains unclear. Therefore, the investigators compared the incidence of gastrointestinal complications of critically ill patients with COVID-19-induced acute respiratory distress syndrome (ARDS) vs comparably ill patients with non-COVID-19 ARDS using propensity score analysis. Propensity score matching was performed adjusting for demographics (e.g., age, sex, body mass index, smoking status), comorbidities (e.g., chronic lung/kidney disease, congestive heart failure, coronary artery disease, hypertension, diabetes), and severity of illness on ICU admission (Sequential Organ Failure Assessment score). They examined in both groups the following gastrointestinal complications: transaminitis, ileus, Ogilvie syndrome, and mesenteric ischemia.

A total of 486 patients with ARDS met eligibility criteria, of which 244 had non–COVID-19 ARDS and 242 had COVID-19 ARDS. Ninety-two patients with COVID-19 and ARDS were propensity score matched to 92 patients with non–COVID-19 ARDS. Patients with COVID-19 were more likely to develop gastrointestinal complications compared with those without COVID-19 (74% vs 37%; *P* < .001; incidence rate ratio, 2.33 [95% CI, 1.52-3.63]). The difference in incidence was more evident after the third day of critical illness. Specifically, patients with COVID-19 developed more transaminitis (55% vs 27%; *P* < .001), severe ileus (48% vs 22%; *P* < .001), and bowel ischemia (4% vs 0%; *P* = .04). Three of the 4 patients with COVID-19 and bowel ischemia were taken to the operating room and had intraoperative findings consistent with COVID-19 bowel as previously described. Pathology findings demonstrated fibrin thrombi in the microvasculature underlying areas of necrosis.

Comment: This study found a higher rate of gastrointestinal complications, including mesenteric ischemia, in critically ill patients with COVID-19 compared with propensity score-matched patients without COVID-19. The case at the top of today's Daily Briefing fits this report. The clue was the very low absolute lymphocyte count and what initially appeared to be an unexplained finding of bowel necrosis in a 40-year-old. A COVID-19 PCR was ordered based on very low lymphocyte count which was positive. Pathology is consistent with thrombi and necrosis. He had a high D-dimer as well. High expression of angiotensin-converting enzyme 2 receptors along the epithelial lining of the gut can act as host-cell receptors for SARS-CoV-2 has been used to explain involvement of abdominal organs. COVID-19-induced coagulopathy may also explain the disproportionately high rate of ileus and ischemic bowel disease.