Good morning

Today I have included 3 articles with a pediatric focus. The first is an elegant discussion on the role of T cell recognition and the possibility of cross reacting immunity from other common coronaviruses known to cause the common cold. The second looks at hospitalizations for children. The third is a nice description of MIS-C with a new classification. The fourth article supports the use of steroids in ventilated patients. The last article looks at the experience of using ECMO for SARS-CoV-2 patients. Their outcomes are in my opinion remarkable.

Have a wonderful Wednesday

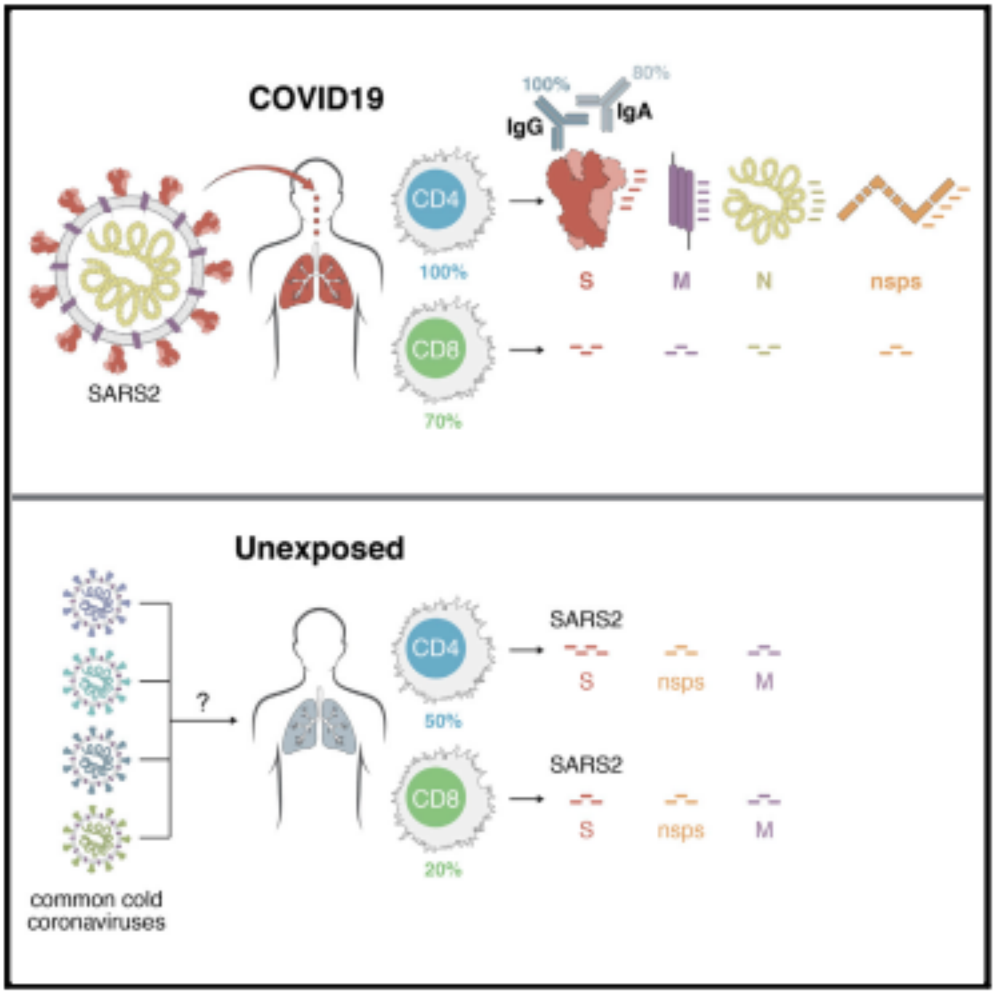
Ed

Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals

2020; 181:1489-1501

Limited information is also available about which SARS-CoV-2 proteins are recognized by human T cell immune responses. In some infections, T cell responses are strongly biased toward certain viral proteins, and the targets can vary substantially between CD4+ and CD8+ T cells. A key issue to consider in the study of SARS-CoV-2 immunity is whether some degree of cross-reactive coronavirus immunity exists in a fraction of the human population, and whether this might influence susceptibility to COVID-19 disease. This issue is also relevant for vaccine development, as cross reactive immunity could influence responsiveness to candidate vaccines. [current vaccine candidates all seem to stimulate a T-cell response. Donors had uncomplicated disease of moderate duration.

Using HLA class I and II predicted peptide megapools, circulating SARS-CoV-2-specific CD8+ and CD4+ T cells were identified in 70% and 100% of COVID-19 convalescent patients, respectively. CD4+ T cell responses to spike, the main target of most vaccine efforts, were robust and correlated with the magnitude of the antiSARS-CoV-2 IgG and IgA titers. The M, spike, and N proteins each accounted for 11%–27% of the total CD4+ response, with additional responses commonly targeting nsp3, nsp4, ORF3a, and ORF8, among others. For CD8+ T cells, spike and M were recognized, with at least eight SARS-CoV-2 ORFs targeted. Importantly, they detected SARS-CoV-2-reactive CD4+ T cells in 40%–60% of <u>unexposed</u> individuals, suggesting cross reactive T cell recognition between circulating ‘‘common cold” coronaviruses and SARS-CoV-2.

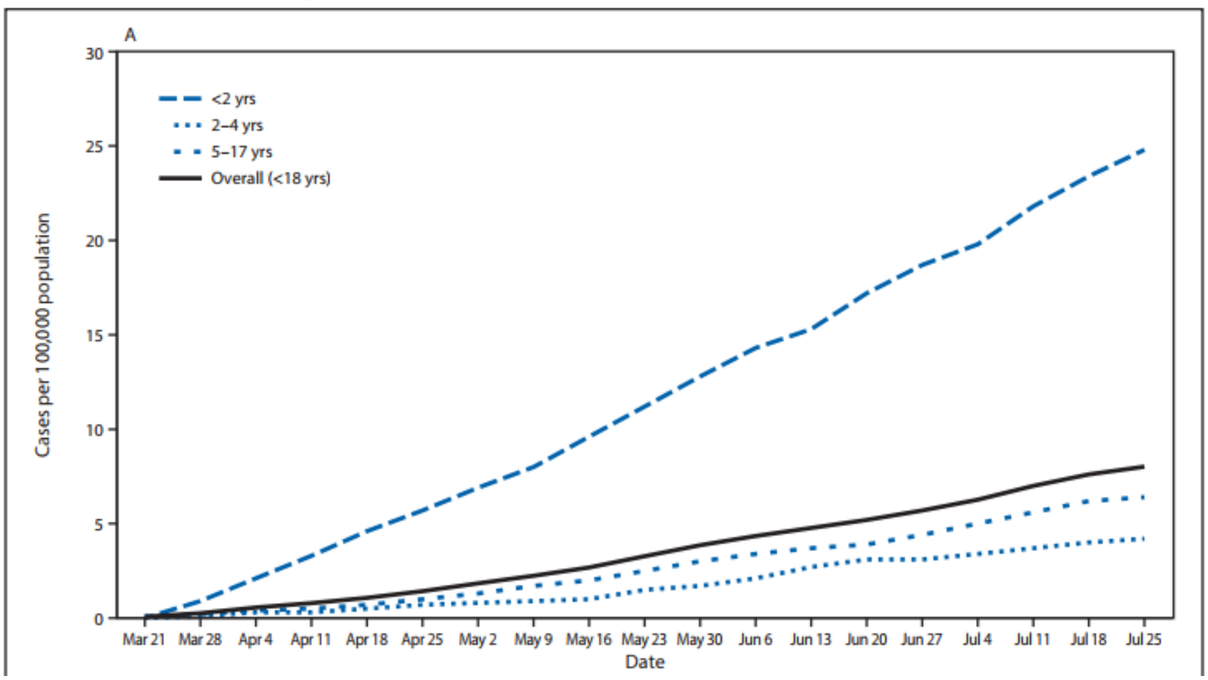


Comment: This publication is an elegant discussion on the role of T cell recognition and the possibility of cross reacting immunity from other common coronaviruses known to cause the common cold. Thinking back to the last pandemic with 2009 H1N1, the value of cross-reactive T cells, influenza immunology in relationship to pandemics may be instructive. The presence of cross-reactive T cells was found to correlate with less severe disease on older adults (born before 1950) compared to younger adults. The frequent availability of cross-reactive memory T cell responses might have been one factor contributing to the lesser severity of the H1N1 flu pandemic. Lack of detailed information on common cold history or matched blood samples preexposure to SARS-CoV-2 limits conclusions regarding the cross-reactive coronavirus T cells before exposure to SARS-CoV-2 and any potential protective efficacy of such cells. Could this partially explain lower infections and transmissions in children ages 2-9 who are commonly exposed to the “common cold” early in life many due to other coronaviruses?

Hospitalization Rates and Characteristics of Children Aged <18 Years Hospitalized with Laboratory-Confirmed COVID-19 — COVID-NET, 14 States, March 1–July 25, 2020
MMWR published online August 7, 2020
The findings are based on an analysis of data from the COVID-19-Associated Hospitalization Surveillance Network, a surveillance system that monitors laboratory-confirmed cases and hospitalizations in 14 states. The analysis covered the period between March 1 and July 25

Roughly one in three children hospitalized with COVID-19 in the United States has required treatment in the intensive care unit, however, adults are about 20 times more likely to need hospital care after getting infected than children the cumulative COVID-19-associated hospitalization rate among children is low compared with that among adults. Children can develop severe COVID-19 illness, eight children for every 100,000 in the general population was hospitalized for COVID-19. For adults, that figure was 164 per 100,000 in the general population, Although ICU admission rates were about the same for children and adults, invasive mechanical ventilation was required in less than 6% of children, compared to nearly 19% of adults, The COVID-19 hospitalization rate for children, however, increased four-fold over the nearly five-month period, and were highest for children age 2 and younger, at roughly 25 per 100,000 in the population. Nearly 30% of children hospitalized for COVID-19 between March and July were Black and 46% were Hispanic. More than 40% of the hospitalized children also had an underlying chronic health condition, with obesity being the most common. Fewer than 1% of children infected with COVID-19 died as a result. Most reported cases of COVID-19 in children appear to be asymptomatic or mild.

FIGURE 1. Cumulative (A) and weekly (B) COVID-19–associated hospitalization rates*,† among children aged <18 years, by age group — COVID-NET, 14 states§, March 1–July 25, 2020¶



Comment: This report confirms that children can be infected, but most are either asymptomatic or have mild symptoms. Young children (2-9) may be less likely to transmit infection-see above publication. Of interest hospitalization rate was highest for children age 2 and younger. (? before adequate exposure to other coronaviruses and development of adequate T-cell response)

COVID-19–Associated Multisystem Inflammatory Syndrome in Children — United States, March–July 2020

MMWR published August 7, 2020

Local and state health departments reported suspected MIS-C patients to CDC using CDC's MIS-C case report form, which included information on patient demographics, clinical findings, and laboratory test results. Patients who met the MIS-C case definition and were reported to CDC as of July 29, 2020, were included in this analysis.

As of July 29, 2020, a total of 570 MIS-C patients with onset dates from March 2 to July 18, 2020, had been reported from 40 state health departments, the District of Columbia, and New York City. The median patient age was 8 years (range = 2 weeks–20 years); 55.4% were male, 40.5% were Hispanic or Latino (Hispanic), 33.1% were non-Hispanic black (black), and 13.2% non-Hispanic white (white). Obesity was the most commonly reported underlying medical condition, occurring in 30.5% of Hispanic, 27.5% of black, and 6.6% of white MIS-C patients. 490 (86.0%) patients involved four or more organ systems. Approximately two thirds did not have preexisting underlying medical conditions before MIS-C onset. The most common signs and symptoms reported during illness course were abdominal pain (61.9%), vomiting (61.8%), skin rash (55.3%), diarrhea (53.2%), hypotension (49.5%), and conjunctival injection (48.4%). Most patients had gastrointestinal (90.9%), cardiovascular (86.5%), or dermatologic or mucocutaneous (70.9%) involvement. A significant percentage of MIS-C patients had severe complications, including cardiac dysfunction (40.6%), shock (35.4%), myocarditis (22.8%), coronary artery dilatation or aneurysm (18.6%), and AKI (18.4%). The majority of patients (63.9%) were admitted to an ICU. The median length of ICU stay was 5 days. Almost all patients underwent SARS-CoV-2 testing. All had a positive test result by RT-PCR or serology; 46.1% had only serologic evidence of infection and 25.8% had only positive RT-PCR test results. 527 (92.5%) were treated, including 424 (80.5%) who received intravenous immunoglobulin (IVIG), 331 (62.8%) who received steroids, 309 (58.6%) who received antiplatelet medication, 233 (44.2%) who received anticoagulation medication, and 221 (41.9%) who were treated with pressors. Ten (1.8%) patients died.

Three classes of patients, each of which had significantly different illness manifestations related to some of the key indicator variables.

1. Class 1 represented 203 (35.6%) patients who had the highest number of involved organ systems. Within this group, 99 (48.8%) had involvement of six or more organ systems; those most commonly affected were cardiovascular (100.0%) and gastrointestinal (97.5%). Compared with the other classes, patients in class 1 had significantly higher prevalences of abdominal pain, shock, myocarditis, lymphopenia, markedly elevated C-reactive protein (produced in the liver in response to inflammation), ferritin, troponin, (BNP), or proBNP ($p<0.01$).
2. Class 2 included 169 (29.6%) patients; among those in this group, 129 (76.3%) had respiratory system involvement. These patients were significantly more likely to have cough, shortness of breath, pneumonia, and acute respiratory distress syndrome (ARDS), indicating that their illnesses might have been primarily acute COVID-19 or a combination of acute COVID-19 and MIS-C. The rate of SARS-CoV-2 RT-PCR positivity (without seropositivity) in this group (84.0%) was significantly higher than that for class 1 (0.5%) or class 3 (2.0%) patients ($p<0.01$). The case fatality rate among class 2 patients was the highest (5.3%) among all three classes ($p<0.01$).
3. Class 3 included 198 (34.7%) patients; the median age of children in this group (6 years) was younger than that of the class 1 patients (9 years) or class 2 patients (10 years) ($p<0.01$) (Table 1). Class 3 patients also had the highest prevalence of rash (62.6%), and mucocutaneous lesions (44.9%). Although not statistically significant ($p = 0.49$), the prevalence of coronary artery aneurysm and dilatations (18.2%) was higher than that in class 2 patients (15.8%), but lower than that in class 1 patients (21.1%). Class 3 patients more commonly met criteria for complete Kawasaki disease (6.6%) compared with class 1 (4.9%) and class 2 (3.0%) patients ($p = 0.30$), and had the lowest prevalence of underlying medical conditions, organ system

involvement, complications (e.g., shock, myocarditis), and markers of inflammation and cardiac damage. Among class 3 patients, 63.1% had positive SARS-CoV-2 serology only and 33.8% had both serologic confirmation and positive RT-PCR result.

Comment: Most cases of MIS-C have features of shock, with cardiac involvement, gastrointestinal symptoms, and significantly elevated inflammatory markers, with positive laboratory test results for SARS-CoV-2. Of the 565 patients who underwent SARS-CoV-2 testing, all had a positive test result by RT-PCR or serology. Distinguishing MIS-C from other severe infectious or inflammatory conditions poses a challenge to clinicians caring for children and adolescents.

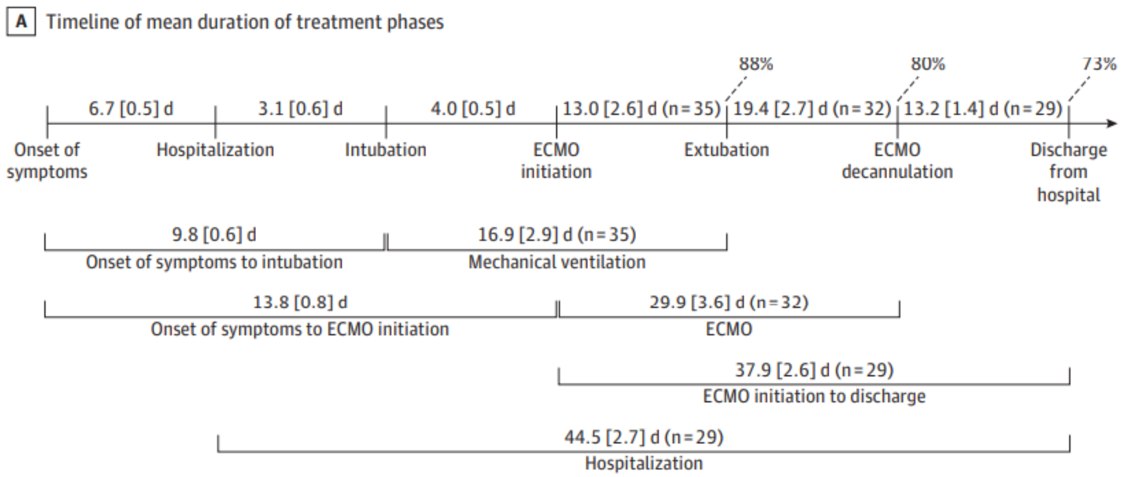
Clinical Outcomes Associated with Methylprednisolone in Mechanically Ventilated Patients with COVID-19
Clin Infect Dis published online August 9, 2020
Clinical outcomes associated with the use of methylprednisolone were assessed in an unmatched, case-control study; a subset of patients also underwent propensity-score matching. The primary outcome was ventilator-free days by 28 days after admission. Secondary outcomes included extubation, mortality, discharge, positive cultures, and hyperglycemia. Dosing protocol for methylprednisolone was 1 mg/kg/day with a max dose of 80 mg/day, with a recommended duration of 5 days, although the course could be extended at the discretion of the treating physician.

A total of 117 patients met inclusion criteria. Propensity matching yielded a cohort of 42 well-matched pairs. Case patients and control patients were well-matched, but patients who received steroids were less likely to have received hydroxychloroquine (91% vs 100%; $P = 0.040$) or azithromycin (45% vs 88%; $P < 0.001$). There was also a trend toward higher median lactate dehydrogenase levels in the steroid group (637 U/L vs 521 U/L; $P = 0.089$), as well as in use of tocilizumab (29% vs 12%; $P = 0.057$). Mean ventilator-free days were significantly higher in patients treated with methylprednisolone (6.21±7.45 versus 3.14±6.22; P = 0.044). The probability of extubation was also increased in patients receiving methylprednisolone (45% versus 21%; P = 0.021), and there were no significant differences in mortality (19% versus 36%; P = 0.087). In a multivariable linear regression analysis, only methylprednisolone use was associated with higher number of ventilator-free days (P = 0.045). The incidence of positive cultures and hyperglycemia were similar between groups.

Comment: The study only included patients with COVID-19 requiring mechanical ventilation, which limits the generalizability to less critically ill patients. They observed a trend towards improved mortality both at day 28 and day 60 in patients treated with methylprednisolone, but the study may not have been powered to detect a significant difference in mortality between the two groups. They end by saying: “Given the limitations of our study design, a randomized-controlled trial is needed to better able to evaluate survival benefits associated with methylprednisolone”. Fortunately, we now have the RECOVERY study. [N Eng J Med July 17, 2020] The dexamethasone RECOVERY study showed benefit for patients on mechanical ventilation and patients on supplemental oxygen only, but no benefit if no oxygen was required. IDSA and NIH now recommend dexamethasone for SARS-CoV-2 patients who require supplemental oxygen or mechanical ventilation.

Extracorporeal Membrane Oxygenation for Patients With COVID-19 in Severe Respiratory Failure
JAMA Surg August 11, 2020
This report describes the experience of using single-access, dual-stage venovenous ECMO, with an emphasis on early extubation of patients even while they received ECMO support. Data were collected retrospectively from 40 consecutive patients with COVID-19 who were in severe respiratory failure and

supported with ECMO. The ages were between 22 and 64 years (mean [SE] age, 48.4 [1.5] years); 30 (75%) were men, 16 (40%) were African American individuals, and 14 (35%) were Hispanic individuals. The primary outcome was survival following safe discontinuation of ventilatory and ECMO supports. Obesity was the primary preexisting condition (28 patients [70%]). All patients reached maximum ventilator support, with 90% placed in a prone position (29 patients [73%]), paralyzed (31 patients [78%]), or both, pre-ECMO; 24 patients (60%) required vasopressors. The mean time from intubation to ECMO was 4.0 days. As of July 17, ventilator support had been successfully discontinued in all patients, resulting in a mean (SE) time of 13.0 (2.6) days from ECMO initiation to extubation, while 32 (80%) were no longer receiving ECMO care. Twenty-nine (73%) have been discharged from the hospital while no longer receiving oxygen. Complications have been minimal, with no ischemic strokes, inotropic support, or tracheostomies! They observed thrombosis within the ECMO circuits and oxygenators. For these reasons, all patients received systemic anticoagulation.



Comment: This study demonstrates surprisingly promising outcomes, with most patients alive and no longer receiving ventilator care and ECMO support and 73% discharged and no longer receiving oxygen. Mortality was only 15%. Tremendous credit to their ECMO team. More studies are required to see if other centers can duplicate these results and to further define the long-term outcomes of this approach.