I hope everyone had a great weekend

Today I start with an editorial on current status of vaccines especially in light of the pause in J&J vaccine – comments always welcomed.

Under Journal Review a nice article on vaccine response in chronic HD patients, followed by an NH study which suggests even in older NH population a single dose may be sufficient in patients with prior infection. The last article is an excellent editorial on 3 articles on vaccine-induced ITT just published in the NEJM.

Have a good week

Ed

VII editorial

Many of us have been worried on the impact of the FDA decision to pause the rollout of Johnson & Johnson's Covid vaccine while it investigates reports of rare blood clots on vaccine hesitancy. Instead, I think we should celebrate that our vaccine surveillance system works! All drugs and vaccines have rare side effects, not all of which can be detected in phase III clinical trials. The FDA collects safety information after approval and is charged with making decisions about how to balance the risks and benefits of medical products. This is an essential part of our drug-safety system.

Covid-19 vaccines are under especially intense study. Let me be clear, the Covid-19 vaccines are medical marvels. No vaccine is foolproof, and even though the Covid-19 vaccines are highly protective, sometimes vaccinated people still get infected. But breakthrough cases of vaccinated people are very rare, even as variants are fueling a surge in case counts in the US. And the vaccines clearly prevent severe illness and hospitalization in the few vaccinated patients who do get infected. Last week the Daily Briefing reported on a CDC study which identified about 5,800 breakthrough cases of Covid-19 infection among more than 66 million Americans who have been fully vaccinated against Covid-19. This calculates to breakthrough cases of infection in 0.008%! Two recent studies reviewed in the Daily Briefing (from NEJM) several weeks ago reported on vaccinated health care workers, who have a much higher risk of virus exposure than the general population, offer important insights. One study found that just four out of 8,121 fully vaccinated employees at the University of Texas Southwestern Medical Center in Dallas became infected. The other found that only seven out of 14,990 workers at UC San Diego Health and UCLA, tested positive two or more weeks after receiving a second dose of either the Pfizer or Moderna vaccines. Both reports are a sign that even as cases were surging in the United States, breakthrough cases were uncommon, even among individuals who were often exposed repeatedly to symptomatic patients. Putting it another way, vaccines have nearly eliminated death, hospitalization and other serious Covid-19 illness among people who are fully vaccinated. But there is no such thing as zero risk. To be honest they will not be zero anytime in the foreseeable future. Victory over Covid-19 will not mean its elimination. Victory will instead mean turning it into the sort too small to be worth altering our lives. To put into perspective, automobiles kill many more than 1,000 young Americans each year; the total U.S. death toll hovers at about 40,000 annually. We accept this toll because vehicle crashes have become part of our lives. Seat belts lower our risk of dying but they do not eliminate it. We often underestimate large, chronic dangers such as car crashes and even seasonal influenza.

The news about coronavirus variants can sound scary. B.1.1.7 is now the predominant variant in the US. The main concern about B.1.1.7 is that it is more transmissible and can spread rapidly among the

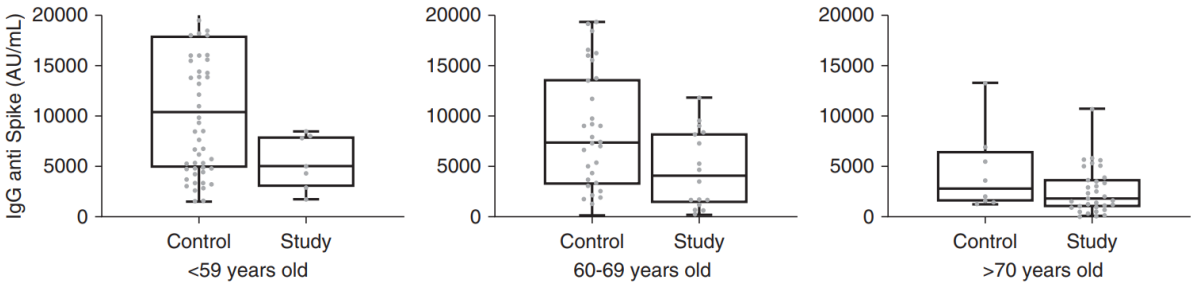
unvaccinated, potentially overwhelming hospitals in areas where cases are surging like Michigan. All of the major vaccines in use — Pfizer, Moderna, Johnson & Johnson, AstraZeneca, Sputnik and Novavax — have been shown to be effective against B.1.1.7. There is clinical trial data, particularly from Johnson & Johnson and AstraZeneca (which is the most widely used vaccine around the world), that shows they are highly effective against both preventing infection and serious illness in areas where B.1.1.7 is circulating. And in Israel (90% of strains circulating is B.1.1.7), for instance, where 80 percent of the eligible population is vaccinated, case counts are plummeting, even as schools, restaurants, movies, and workplaces open up, suggesting that vaccines are reducing new infections, including those caused by variants. We do not yet have precise estimates of vaccine effectiveness against B.1.351 (South African variant), but studies show that the various vaccines still lower overall risk for infection and help prevent severe disease. A large study of Johnson & Johnson's vaccine in South Africa found it was about 85 percent effective at preventing severe disease, and lowered risk for mild to moderate disease by 64 percent.

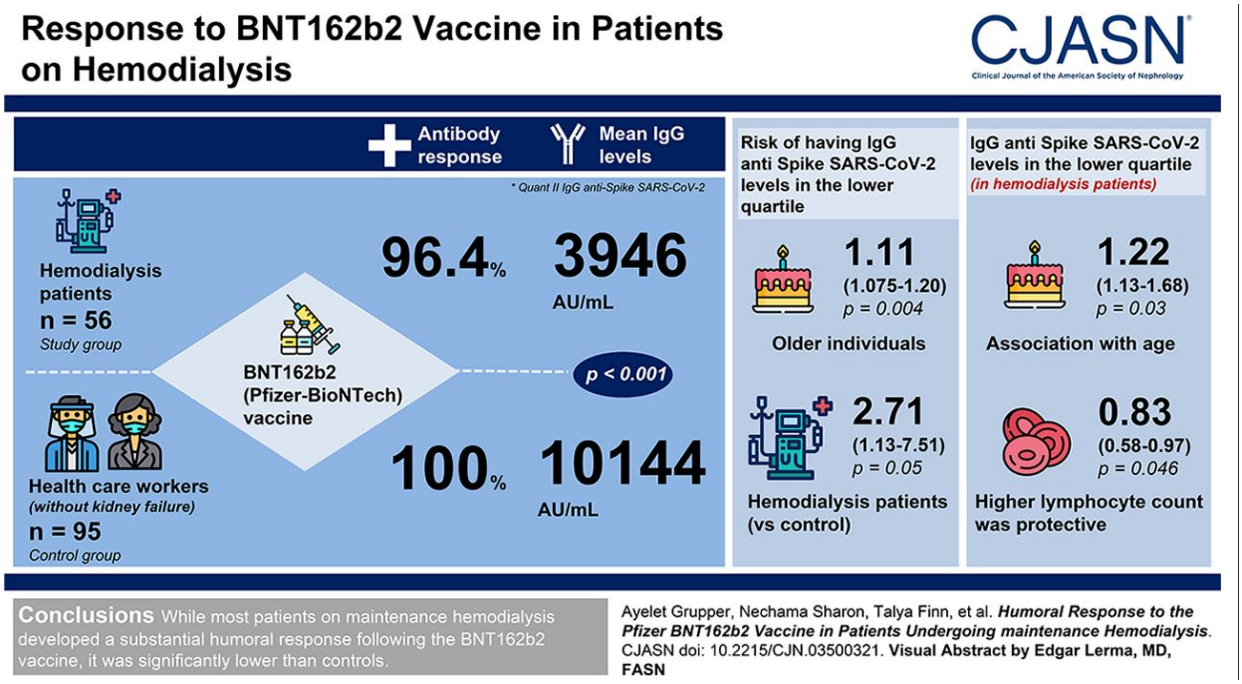
Finally large, rigorous trials across many countries (not just South Africa), populations, and viral variants have shown the Johnson & Johnson vaccine's overall benefit. The vaccine is administered in a single dose and easier to store than Pfizer's and Moderna's, making it an important part of the Covid-19 arsenal, especially in low- and middle-income countries. Barring significant new findings, Johnson & Johnson's vaccine should return to use soon. (see last review) Bottom line: **The vaccines protect you and work, so go get vaccinated.**

Journal Review

Humoral Response to the Pfizer BNT162b2 Vaccine in Patients Undergoing Maintenance Hemodialysis
CJASN published online April 6, 2021
doi: 10.2215/CJN.03500321
This study included 56 patients on maintenance hemodialysis and a control group composed of 95 health care workers. All participants had received two doses of the Pfizer vaccine. The serology testing was done using Quant II IgG anti-Spike severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) assay by Abbott a median of 30 days after receipt of the second dose of the vaccine.

All subjects in the control group developed an antibody response compared with 96% (54 of 56) positive responders in the dialysis group. The IgG levels in the dialysis group (median, 2900; interquartile range, 1128–5651) were significantly lower than in the control group (median, 7401; interquartile range, 3687–15,471). There was a significant inverse correlation of age and IgG levels in both groups.





Comment: The size of this trial was small, however, most patients on maintenance HD developed a substantial humoral response following the Pfizer vaccine, which was significantly lower than controls. There was a considerable age difference between the dialysis group and the control group that stems from the nature of both populations. They tried to overcome this limitation by adjusting the statistical analysis for age and by dividing into similar age groups in both cohorts. However, age was an important factor in the humoral response, regardless of chronic medical conditions. They did not perform baseline antibody titers, and thus, they could not exclude the possibility that the seroresponse results may reflect infection versus vaccination in some patients. The clinical implications of the serology test and the presence of antibodies and their levels remain to be fully clarified. However, patients on maintenance HD did develop a humoral immune response following the Pfizer vaccine. This finding is reassuring and should encourage patients on maintenance HD to be vaccinated.

Spike Antibody Levels of Nursing Home Residents With or Without Prior COVID-19 3 Weeks After a Single BNT162b2 Vaccine Dose

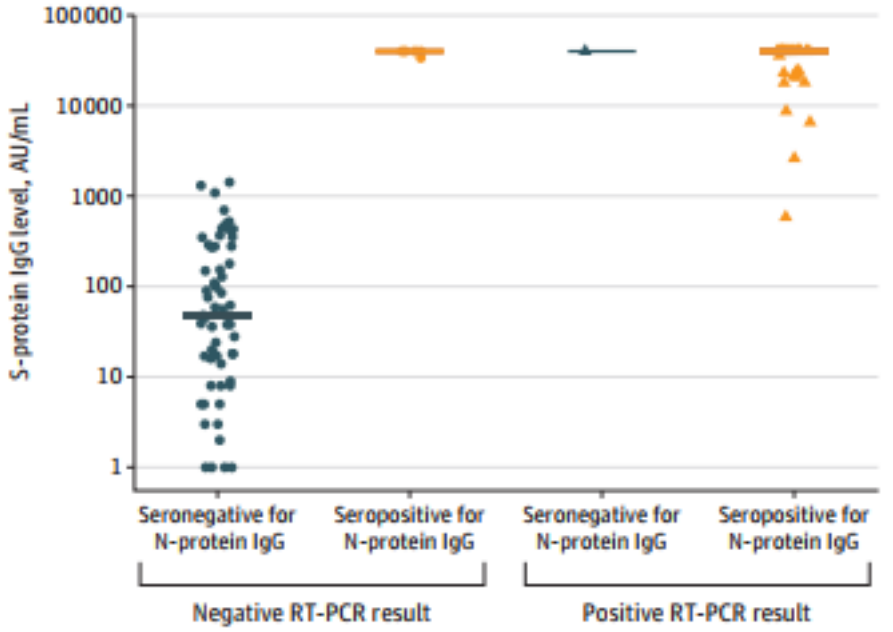
JAMA published online April 15, 2021

Between March and June 2020, the investigators studied residents from nursing homes after a COVID-19 outbreak. Six weeks after the end of the outbreak, all residents underwent blood testing for levels of IgG antibody against the SARS-CoV-2 nucleocapsid (N) protein. All residents from 6 nursing homes were offered a first vaccine dose (Pfizer) in January 2021. Three weeks later, all residents underwent blood testing to quantitatively assess IgG antibody levels against the SARS-CoV-2 spike (S) protein and N protein. Levels of IgG antibody against the SARS-CoV-2 receptor-binding domain was quantified using the SARS-CoV-2 IgG II Quant assay (Abbott Diagnostics). In residents with or without a prior history of COVID-19, they compared IgG antibody levels against SARS-CoV-2 proteins S and N.

Of the 102 residents, 60 had no prior SARS-CoV-2 infection, 36 had a positive RT-PCR result and were seropositive for SARS-CoV-2 N-protein IgG in June 2020, and 6 had a positive RT-PCR result or were seropositive for SARS-CoV-2 N-protein IgG. Of the 36 residents who had a positive RT-PCR result and were seropositive for SARS-CoV-2 N-protein IgG in June 2020, 26 remained seropositive in January-

February 2021 (72.2%). All 36 residents with prior COVID-19 were seropositive for S-protein IgG after 1 vaccine dose vs 29 of 60 residents (49.2%) without prior COVID-19. Among residents with prior COVID-19, the median level of S-protein IgG was 40 000 AU/mL or greater (interquartile range [IQR], 22 801-≥40 000 AU/mL) vs 48.0 AU/mL (IQR, 14.0-278.0 AU/mL) in those without prior COVID-19 ($P < .001$).

Figure. Levels of IgG Antibody Against the SARS-CoV-2 Spike (S) Protein After a Single Dose of Vaccine in Nursing Home Residents



Comment: This study suggests that a single dose of BNT162b2 (Pfizer) vaccine may be sufficient to obtain a high level of S-protein IgG antibody in nursing home residents previously diagnosed with COVID-19 based on RT-PCR results. This is in line with results based on IgG to spike trimer and neutralization antibody titers reported among health care workers with prior COVID-19 (diagnosed using SARS-CoV-2 IgG) [JAMA. Published online March 1, 2021]. There is growing evidence that persons with a history of prior infection probably only need 1 dose of mRNA vaccine. Limitations of the study include the small sample size.

SARS-CoV-2 Vaccine-Induced Immune Thrombotic Thrombocytopenia

Editorial N Engl J Med published online April 16, 2021

The N Engl J Med has now published three independent descriptions of 39 persons with a newly described syndrome characterized by thrombosis and thrombocytopenia that developed 5 to 24 days after initial vaccination with ChAdOx1 nCoV-19 (AstraZeneca), a recombinant chimpanzee adenoviral vector encoding the spike protein of SARS-CoV-2. [N Engl J Med. DOI: 10.1056/NEJM oa2104840.; N Engl J Med. DOI: 10.1056/NEJMoa2104882; N Engl J Med. DOI: 10.1056/NEJMoa2105385] Below are key points from this editorial.

- Cases of immune thrombocytopenia and bleeding without thrombosis that were induced or revealed after exposure to the messenger RNA (mRNA)-based vaccines produced by Moderna

(mRNA-1273) and Pfizer–BioNTech (BNT162b2) have been reported. [Am J Hematol 2021;96:534-7]

- Most of the patients included in these reports were women younger than 50 years of age, some of whom were receiving estrogen-replacement therapy or oral contraceptives.
- A high percentage of the patients had thromboses at unusual sites — specifically, cerebral venous sinus thrombosis or thrombosis in the portal, splanchnic, or hepatic veins.
- The median platelet counts at diagnosis were approximately 20,000 to 30,000 per cubic millimeter (range, approximately 10,000 to 110,000).
- High levels of d-dimers and low levels of fibrinogen were common and suggest systemic activation of coagulation.
- This constellation of thrombosis and thrombocytopenia prompted consideration of heparin induced thrombocytopenia as the diagnosis. However, none of the patients had known exposure to heparin before the onset of illness.
- The pathogenesis of this syndrome of vaccine-induced immune thrombotic thrombocytopenia (VITT) is not yet clear, certain findings were consistent across the three studies. In almost every patient, high levels of antibodies to platelet factor 4 (PF4)-polyanion complexes were identified, as well by assays based on platelet activation, which, when tested, was enhanced by addition of PF4.
- On the basis of these reports, the diagnosis of VITT should be confirmed with an approved PF4 ELISA.
- Limited information available relating to management suggests that intravenous immune globulin and high-dose glucocorticoids can improve the platelet count within days, which may limit the risk of hemorrhaging. Immune globulin impedes antibody-mediated platelet clearance and may down-regulate platelet activation by immune complexes by blocking platelet FcRγIIA receptors, as in heparin-induced thrombocytopenia.
- The incidence of VITT, as initially estimated, is perhaps 1 case per 100,000 exposures. This should be considered in the context of the incidence of cerebral venous sinus thrombosis in the general population (estimated at 0.22 to 1.57 cases per 100,000 per year).
- Additional cases have now been reported to the European Medicines Agency, including at least 169 possible cases of cerebral venous sinus thrombosis and 53 possible cases of splanchnic vein thrombosis among 34 million recipients of the ChAdOx1 nCoV-19 vaccine, 35 possible cases of central nervous system thrombosis among 54 million recipients of the Ad26.COV2.S adenoviral vector vaccine (J&J), and 5 possible (but unvetted) cases of cerebral venous sinus thrombosis among 4 million recipients of the Moderna mRNA vaccine; no cases have been reported thus far with the Pfizer mRNA vaccine.

Comment: This rare complication of vaccination, however severe, must be weighed against the relative benefits of preventing Covid-19 (a condition with up to 1 to 2% mortality and potential long-term sequelae) must be emphasized. 125 out of every 1 million Americans between 18 and 48 have died of COVID-19 since early last year. In the US 6 cases [up to 8 cases] have occurred in women 18-48 years old after receiving the J&J vaccine. Symptom onset occurred 6-13 days after administration of the single-dose vaccine. In addition to CVST, three of the women had extracranial thromboses. Four women developed intraparenchymal brain hemorrhage, and one unfortunately died. Comorbid conditions included obesity (n=3), hypertension (n=1), hypothyroidism (n=1), and asthma (n=1); one woman was taking estrogen/progesterone. With both adenovirus-based vaccines [J&J and Astra Zeneca], incidence of CVST with thrombocytopenia has been associated with high serum levels of antibodies against platelet factor 4 (PF4)-polyanion complexes similar to those that occur in heparin-induced thrombocytopenia (HIT). The CDC recommends that persons who experience a thrombotic event and

thrombocytopenia after administration of the J&J vaccine be screened with a PF4 HIT enzyme-linked immunosorbent assay (ELISA). If the assay is positive or cannot be completed, heparin should not be used for thrombosis management; other anticoagulants, steroids, and intravenous immune globulin should be considered instead.

We should applaud our surveillance system in the US that was able to detect this rare safety signal. It shows our system is working. ACIP will meet again Friday. Although I cannot predict the final action, my guess is the vaccine will be released with either a warning or a recommendation not to administer the J&J vaccine in premenopausal women.