Good morning. I hope everyone had a good weekend.

Today I selected 4 articles for your review. The first 2, as promised, review the impact of zinc, vitamin C, and D in different settings. The next article reviews a study which showed significant early reductions in SARS-CoV-2 infection and symptomatic COVID-19 rates following first dose administration of Pfizer COVID-19 vaccine. The last article is a nice review and meta-analysis on convalescent plasma therapy.

I hope this week is much better than last week for many of us impacted by this winter storm.

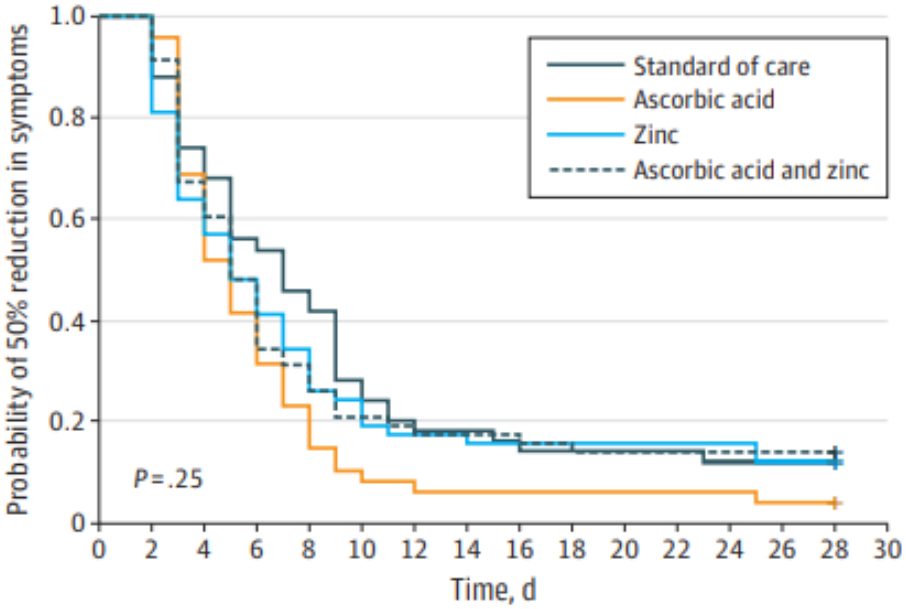
Ed

Effect of High-Dose Zinc and Ascorbic Acid Supplementation vs Usual Care on Symptom Length and Reduction Among Ambulatory Patients With SARS-CoV-2 Infection: The COVID A to Z Randomized Clinical Trial

JAMA Netw Open published online February 12, 2021
doi:10.1001/jamanetworkopen.2021.0369

This is a multicenter, single health system randomized clinical factorial open-label trial which enrolled 214 adult patients with a diagnosis of SARS-CoV-2 infection confirmed with a PCR who received outpatient care in sites in Ohio and Florida. The objective of the trial was to examine whether high-dose zinc and/or high-dose ascorbic acid reduce the severity or duration of symptoms compared with usual care among ambulatory patients with SARS-CoV-2 infection. Patients were randomized in a 1:1:1:1 allocation ratio to receive either 10 days of zinc gluconate (50 mg), ascorbic acid (8000 mg), both agents, or standard of care.

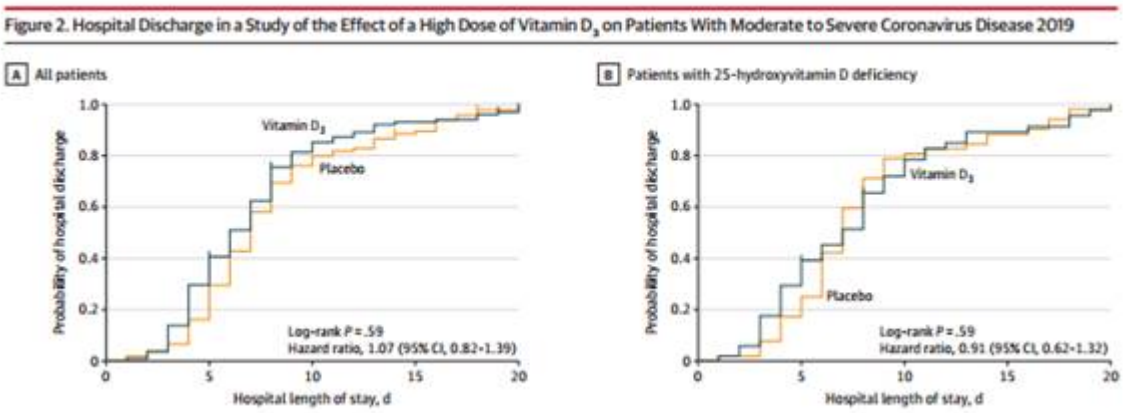
A total of 214 patients were randomized, with a mean (SD) age of 45.2 (14.6) years and 132 (61.7%) women. The study was stopped for a low conditional power for benefit with no significant difference among the 4 groups for the primary end point. Patients who received usual care without supplementation achieved a 50% reduction in symptoms at a mean (SD) of 6.7 (4.4) days compared with 5.5 (3.7) days for the ascorbic acid group, 5.9 (4.9) days for the zinc gluconate group, and 5.5 (3.4) days for the group receiving both (overall $P = .45$). There was no significant difference in secondary outcomes among the treatment groups.



Comment: These findings suggest that treatment with zinc, ascorbic acid, or both does not affect SARS-CoV-2 symptoms. A major limitation was that there was no placebo control group; the current study was open label, and patients were not masked to which therapy they received. Stratification of symptoms by age, sex, race, or duration of symptoms prior to testing were not taken into consideration in the current analysis.

Effect of a Single High Dose of Vitamin D3 on Hospital Length of Stay in Patients with Moderate to Severe COVID-19: A Randomized Clinical Trial
JAMA published online February 17, 2021
doi:10.1001/JAMA2020.26848
This was a multicenter, double-blind, randomized, placebo-controlled trial. The study included 240 hospitalized patients with COVID-19 who were moderately to severely ill at the time of enrollment. Patients were randomly assigned to receive a single oral dose of 200,000 IU of vitamin D3 (n = 120) or placebo (n = 120). The primary outcome was length of stay, defined as the time from the date of randomization to hospital discharge. Secondary outcomes included mortality during hospitalization; the number of patients admitted to the ICU; the number of patients who required mechanical ventilation and the duration of mechanical ventilation; and serum levels of 25-hydroxyvitamin D, total calcium, creatinine, and C-reactive protein.

Then results demonstrated that the median (interquartile range) length of stay was not significantly different between the vitamin D3 (7.0 [4.0-10.0] days) and placebo groups (7.0 [5.0-13.0] days) (log-rank *P* = .59; unadjusted hazard ratio for hospital discharge, 1.07 [95% CI, 0.82-1.39]; *P* = .62). The difference between the vitamin D3 group and the placebo group was not significant for in-hospital mortality (7.6% vs 5.1%; difference, 2.5% [95% CI, –4.1% to 9.2%]; *P* = .43), admission to the intensive care unit (16.0% vs 21.2%; difference, –5.2% [95% CI, –15.1% to 4.7%]; *P* = .30), or need for mechanical ventilation (7.6% vs 14.4%; difference, –6.8% [95% CI, –15.1% to 1.2%]; *P* = .09). Mean serum levels of 25-hydroxyvitamin D significantly increased after a single dose of vitamin D3 vs placebo (44.4 ng/mL vs 19.8 ng/mL; difference, 24.1 ng/mL [95% CI, 19.5-28.7]; *P* < .001).



Comments: This study reported that among hospitalized patients with COVID-19, a single high dose of vitamin D3 did not significantly reduce hospital length of stay. Given the small sample size in this trial the study was underpowered. Second, patients who required mechanical ventilation or admitted to the ICU were excluded so population in the study would actually be considered to have moderate disease. Third, because the patients had several coexisting diseases and were subjected to a diverse medication regimen, the results could have been affected by the heterogeneity of the sample and its treatment. Next, the patients were given a dose of vitamin D3 after a relatively long time from symptom onset to randomization (i.e., mean of 10.3 days). Lastly only about 50% study participants had vitamin D deficiency and only 25% had severe vitamin D deficiency. Further studies should be performed to determine whether preventive or earlier use of vitamin D3 would impact outcomes. Nonetheless, these findings and other existing RCTs currently do not support the use of a high dose of vitamin D3 for treatment of moderate to severe COVID-19.

Early Rate Reductions of SARS-CoV-2 Infection and COVID-19 in BNT162b2 Vaccine Recipients
Lancet published online February 18, 2021
doi.org/10.1016/ S0140-6736(21)00448-7
To assess vaccine-associated rate reductions, researchers analyzed a retrospective cohort of 9,109 vaccine-eligible health-care workers (HCWs). Of the eligible staff, 7,214 (79%) had received a first dose of BNT162b2 and 6,037 (66%) had received the second dose of the vaccine by January 24, 2021. Among the fully vaccinated HCWs, 5,505 (91%) received the second dose on days 21 or 22 after the first dose. Overall, there were 170 SARS-CoV-2 infections among HCWs in the period between December 19, 2020, and January 24, 2021, of which 99 (58%) HCWs were symptomatic COVID-19 cases. Of the 170 HCWs who became infected, 89 (52%) were unvaccinated, 78 (46%) tested positive after the first dose, and only three (2%) tested positive after the second dose. Meanwhile, most (61%) of the 99 symptomatic COVID-19 cases were reported among unvaccinated HCWs.

Compared with a SARS-CoV-2 infection rate of 7.4 per 10,000 person-days in unvaccinated HCWs, infection rates were 5.5 per 10,000 person-days and 3.0 per 10,000 person-days on days 1-14 and 15-28 after the first dose of the vaccine, respectively. Adjusted rate reductions of SARS-CoV-2 infections were 30% (95% confidence interval [CI] 2–50) and 75% (95% CI 72–84) for days 1–14 and days 15–28 after the first dose, respectively. On the other hand, symptomatic COVID-19 rates were 2.8 and 1.2 per 10,000 person-days on days 1-14 and days 15-28 after the first dose of the vaccine, respectively, compared with a rate of 5·0 per 10,000 person-days in unvaccinated HCWs. Adjusted rate reductions of COVID-19 disease were 47% (95% CI 17–66) and 85% (71–92) for days 1–14 and days 15–28 after the first dose, respectively.

Comment: Findings from this study showed significant early reductions in SARS-CoV-2 infection and symptomatic COVID-19 rates following first dose administration of COVID-19 vaccine BNT162b2 (Pfizer). Israel just reported that a single dose of the Pfizer vaccine is 85% effective in preventing symptomatic disease 15-28 days after vaccination. Moderna probably has a similar profile. Early reductions of COVID-19 rates following the first dose of vaccine provide support of delaying the second dose in countries facing vaccine shortages to allow higher population coverage with a single dose. Longer follow-up to assess long-term effectiveness of a single dose is needed to inform a second dose delay policy.

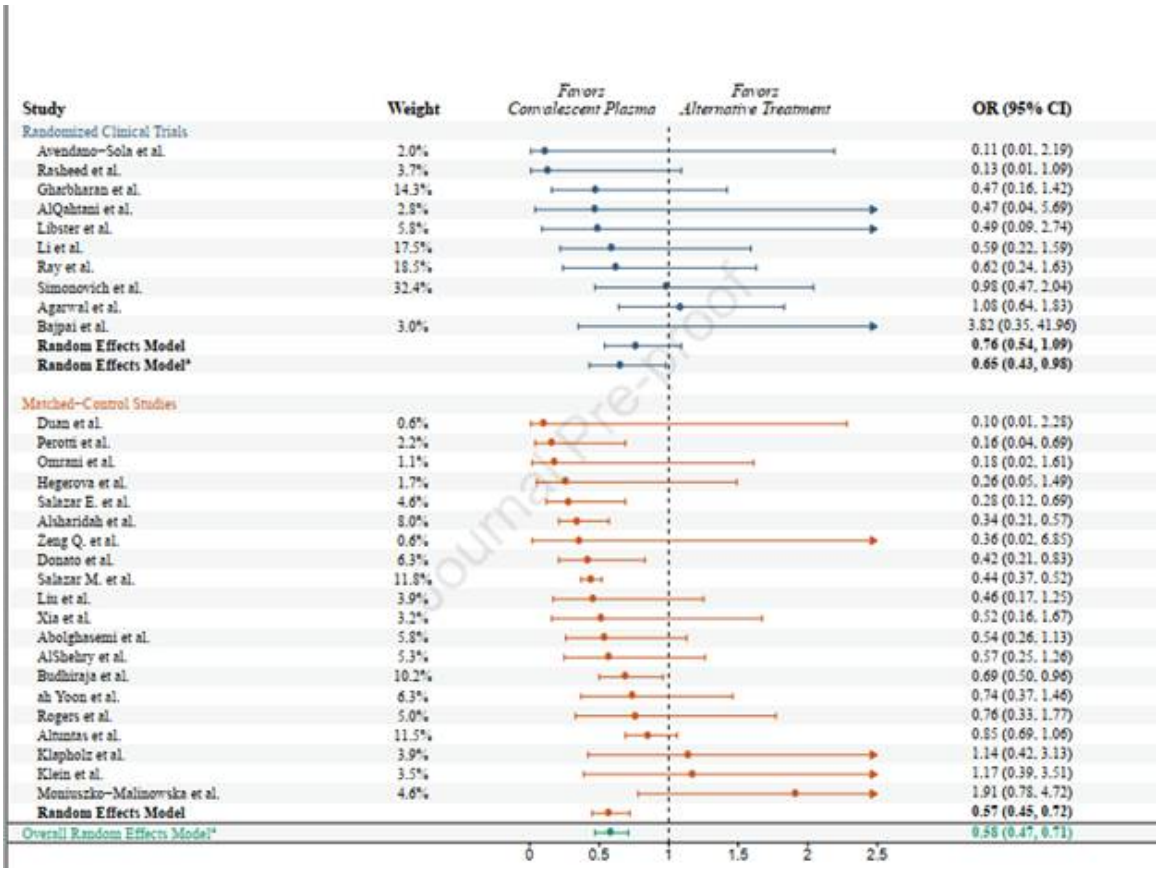
The Effect of Convalescent Plasma Therapy on COVID-19 Patient Mortality: Systematic Review and Meta-Analysis

Mayo Cl Proc published online February 17, 2021

doi.org/10.1016/j.mayocp.2021.02.008

The authors combined patient outcome data from 10 randomized clinical trials (RCT), 20 matched-control studies, two dose response studies, and 96 case-reports or case-series. Studies published between January 1, 2020 - January 16, 2021 were identified through a systematic search of online PubMed and MEDLINE databases.

Random-effects analyses of RCT and matched-control data demonstrated that COVID-19 patients transfused with convalescent plasma exhibited a lower mortality rate compared to patients receiving standard treatments. Additional analyses showed that early transfusion (within 3 days of hospital admission) of higher-titer plasma is associated with lower patient mortality.



Comment: High titer early convalescent plasma administration can increase SARS-CoV-2 clearance in COVID-19 patients including immunocompromised individuals suggesting it has an antiviral effect. Viral neutralization can then reduce the inflammatory response if given early. In addition, convalescent plasma transfusion is associated with reductions in inflammatory markers, such as chemokines, cytokines, and CRP. Concomitant reductions in inflammation and improved gas exchange may reduce oxygen requirements and improve outcomes. With the availability with monoclonals, a head-to-head trial may provide additional information. However, it is unlikely that giving convalescent plasma in patients who come in late and already in the inflammatory phase will impact outcomes as several studies have shown. The use of remdesivir follows a similar story – given early in patients on ≤15 liters does improve outcomes, but if patient has already progressed to vapotherm or mechanical ventilation remdesivir does not improve outcomes. Lastly, with the variants emerging how convalescent plasma or monoclonals will perform is unclear.