PHARMACEUTICAL INTERVENTIONS

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

Thomas et al. conducted a prospective randomized open-label clinical trial to determine the effects of high doses of zinc gluconate and ascorbic acid (Vitamin C) supplements on the severity and duration of symptoms after infection with SARS-CoV-2. This study was conducted in multiple hospitals in Ohio and Florida and included 214 patients with a positive COVID-19 PCR test. There were four treatment strategies: 800 mg of ascorbic acid taken 2-3 times per day, 50 mg of zinc gluconate at bedtime, combined therapy, and usual care with none of the therapies. Participants were randomized to the different therapies with 22.4% receiving ascorbic acid, 27.1% receiving zinc gluconate, 27.1% receiving both, and 23.4% receiving no treatment. Participants were asked to complete a daily questionnaire of different symptoms and give each symptom a score of 0-3, with 0 having no symptoms and 3 having severe symptoms. The primary endpoint for the study was to determine the number of days it took for the symptom score to reach 50% of the peak score. However, the study was stopped early because no statistical differences were found between the four groups; mean number of days was 5.5, 5.9, 5.5, and 6.7 for ascorbic acid, zinc gluconate, both, and none respectively. This study did not show that ascorbic acid and zinc gluconate provide a faster resolution of COVID-19 symptoms, though providers may currently prescribe medications with less side effects to help reduce symptoms of COVID-19.

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

This double-blinded, parallel-group, randomized placebo-controlled trial aimed to see whether administration of vitamin D had an effect on the length of hospital stay and other clinical outcomes for patients with moderate to severe COVID-19. Two hundred and forty SARS-CoV-2-positive (PCR or ELISA) participants were recruited from two hospitals in Sao Paulo, Brazil. Half of these participants received a single oral dose of 200,000 IU of vitamin D dissolved in 10 mL of peanut oil solution, and half received only 10 mL of the peanut oil solution. The median length of hospital stay was 7 days in both groups and no significant differences were found in clinical outcomes including in-hospital mortality, admission to intensive care unit, and need for medical ventilation. There were also no significant differences between the two groups for levels of calcium, creatinine, C-reactive protein, and serum D-dimer. These results do not support the use of vitamin D to reduce hospital stay or for other significant therapeutic benefit in moderate to severe COVID patients.
Association between clinical frailty scale score and hospital mortality in adult patients with COVID-19 (COMET): an international, multicentre, retrospective, observational cohort study

The COVID Medication (COMET) study aimed to assess possible associations between clinical frailty score (CFS) score of COVID-19 positive adults across 63 hospitals in Europe and hospital mortality and/or ICU admission. Of the patients hospitalized for COVID-19 from March 30 to July 15, 2020, 2434 were included in the analysis with a median age of 68. CFS score for each patient was categorized as fit, mildly frail, or frail. Findings showed mildly frail and frail patients had higher mortality risk compared to their fit counterparts (OR 1.54 and OR 2.71, respectively). Frail patients under the age of 65 had a higher mortality risk compared to fit patients in that age group (OR 2.22). For ICU admission, frail patients were more likely to be admitted compared to fit patients (OR 1.54), but patients who were mildly frail were less likely to be admitted to the ICU compared to fit (OR 0.71). Mildly frail patients over the age of 65 were less likely to be admitted to the ICU than fit patients in the same age group (OR 0.66). For frail patients under 65, they were more likely to be admitted than fit patients (OR 2.96). This study indicated that CFS scores can be used to assess patient risk for mortality and ICU admission for patients with COVID-19.

NON-CLINICAL TRENDS

Simpler and faster Covid-19 testing: strategies to streamline SARS-CoV-2 molecular assays

While RT-qPCR is the current gold standard for SARS-CoV-2 diagnostic testing, it is time-intensive, expensive, and difficult to conduct at the point-of-care and in resource-poor settings. Panpradist and colleagues addressed these limitations by modifying several steps in the assay. RT-PCR reagents were lyophilized to remove the need for creating a master mix and aliquoting liquid to individual reaction tubes. RNA extraction steps were bypassed by adding eluate from the swabbing test tube directly to the RT-PCR reagents. Finally, expensive fluorescence readers for endpoint analysis were replaced with smart phone imaging software. An assay containing lyophilized reagents and eluate directly from the swab reported an analytical sensitivity of 20 copies/reaction, which is within CDC guidelines. Fluorescence imaging from cell phones commonly used across the globe were also found to accurately distinguish between 20 copies/reaction and the negative control. The authors suggest that these strategies can be used to facilitate the workflow of RT-qPCR diagnostics and make this technology more widely accessible.

SCREENING AND TESTING

Managing intensive care admissions when there are not enough beds during the COVID-19 pandemic: a systematic review
Tyrrell et al. conducted a systematic review of different intensive care unit (ICU) triage protocols used in hospitals during the pandemic to develop informed recommendations for a new, standardized ICU triage system. Nine unique guidelines were identified from 1902 records; one international, six national/transnational, one state-level, and one military-specific. For each guideline, nine themes were identified and evaluated. Scores for each theme were created using the Appraisal of Guidelines for Research and Evaluation Instrument II (AGREE II) and the Appraisal of Guidelines for Research and Evaluation Instrument Recommendation EXcellence (AGREE REX). Guidelines scored poorly for applicability (median score 8, IQR 4-10) and developmental rigor (9, 4-14). Only one guideline scored greater than 50% for clinical applicability. In general, guidelines held higher scores for clarity of presentation (58, 47-64) and description of scope and purpose (78, 67-83). Guidelines also stressed the importance of using ethical frameworks when designing triage protocols. The authors added that the expert panels used to develop these guidelines must be transparent about the data they use to inform their decisions, as well as their own qualifications.

CLINICAL PRESENTATION AND MANAGEMENT

COVID-19 vaccination intent, perceptions, and reasons for not vaccinating among groups prioritized for early vaccination- United States, September and December 2020

The CDC surveyed U.S. adults (≥18 years) assessing vaccination intent (very likely to receive vaccination), vaccination nonintent (not likely to receive vaccination), and vaccine perceptions in September (n=3,541) and December (n=2,033) of 2020. Nonintent in September 2020 was highest among non-Hispanic Black adults (56%), followed by adults without health insurance (49%), adults with a high school education or less (47%), adults with an income of less than 35,000 (44%), adults aged 18 to 49 (40%) and 50 to 64 (42%), women (42%), and adults in the southern region of the U.S. (41%). When comparing responses from December to September, vaccination intent increased from 39% to 49% and vaccination nonintent decreased from 38% to 32%. During this same period, vaccination intent among elderly (≥65 years) increased from 49% to 66%, that among essential workers increased from 37% to 46%, and that among adults with underlying medical conditions under the age of 65 increased from 37% to 42%. Common reasons for vaccination nonintent included concern for vaccine side effects and safety, the speed at which the vaccine was developed, and intentions to wait and observe longer term effects of vaccine and its safety. Based on these findings, the authors suggest the need to address vaccination nonintent to ensure vaccination coverage for all populations.

MENTAL HEALTH

Post-traumatic stress disorder symptoms in COVID-19 survivors: online population survey
In May 2020, Cambridge University surveyed post-traumatic stress disorder (PTSD) in 13,049 suspected or confirmed COVID-19 survivors in the United Kingdom to analyze unit deviation in disease severity and treatments. In comparison to COVID-19 patients who did not experience breathing problems, mean PTSD symptom scores was greater in COVID-19 patients who had severe respiratory symptoms which required assistance at home (effect size 0.178 s.d.), were admitted into a hospital without a ventilator (effect size 0.234 s.d.), or were admitted into a hospital and required a ventilator (effect size 0.454 s.d.). In these groups, intrusive imagery was found to be the most common PTSD symptom reported. These findings demonstrate the importance of adequate mental health support and follow up for recovered COVID-19 patients.

NON-PHARMACEUTICAL/ PUBLIC HEALTH INTERVENTIONS

Maximizing Fit for Cloth and Medical Procedure Masks to Improve Performance and Reduce SARS-CoV-2 Transmission and Exposure, 2021

In January 2020, the CDC conducted experimental simulations to examine the degree to which double masking and knotted and tucked medical masking could decrease exposure to simulated respiratory droplets. The authors first simulated cough emission while wearing a 3-ply cotton cloth mask, an untucked 3-ply medical mask, a knotted and tucked medical mask, and double masking (specifically, fitting a cloth mask over an untucked medical mask). They found that double masking blocked the highest portion of the aerosol emitted (~85%), followed by the knotted and tucked medical mask alone (77%), the medical mask alone (~56%), then the cloth mask alone (~51%). Next, the authors simulated cough exposure with various combinations of masking techniques on both the source of the cough and the recipient. The highest proportion of aerosols blocked was with double masking for both source and recipient (96.4%), followed closely by both knotting and tucking medical masks (95.9%). When the recipient was unmasked, double masking of the cough source blocked ~82% of the aerosol and knotting and tucking the medical mask blocked ~63%. When the cough source was unmasked, the recipient double masking blocked 83% and knotting and tucking the medical mask blocked ~65%. These results emphasize the role of properly fitted masks in reducing the spread of COVID-19.

TRANSMISSION PATTERNS

Bioaerosol Sampling for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in a Referral Center with Critically Ill Coronavirus Disease 2019 (COVID-19) Patients March-May 2020

Lane et al. aimed to assess the presence of SARS-CoV-2 in aerosols outside of critically ill COVID-19 patient rooms to understand better the safety concerns posed to healthcare personnel. Data was collected via National Institute for Occupational Safety and Health (NIOSH) BC 251 2-stage cyclone samplers placed at 102 cm and 152 cm above the floor throughout the nursing stations, patient room hallways, and visitor corridors of 6 intensive
care units (ICUs) in a tertiary referral hospital in Atlanta, GA, USA. Samples were taken for 22 days, and the sampling period lasted 6 hours at the same time of day, which spanned the morning shift change to the next shift change. Results revealed that none of the 528 aerosol samples taken tested positive for SARS-CoV-2 RNA via reverse transcriptase polymerase chain reaction (rRT-PCR) testing. As the ICUs contained both positive and negative pressure rooms, the authors suggest that, given the lack of SARS-CoV-2 aerosols detected in the hallway, negative pressure may not be necessary to prevent viral aerosols from dispersing outside patient rooms. The authors assert that this study’s results highlight that environmental controls and personal protective equipment are important and effective at controlling the presence of SARS-CoV-2 aerosols. Tentatively, such findings provide reassurance for alternatives to the use of tight-fitting respirators outside of patient rooms.

**BIOENGINEERING**

**Plitidepsin has potent preclinical efficacy against SARS-CoV-2 by targeting the host protein eEF1A**

White et al. identified the limitations of the current care standards for COVID-19 (remdesivir and dexamethasone). Alternatively, they suggest plitidepsin as a potential treatment for SARS-CoV-2 exhibiting antiviral activity. Plitidepsin targets the host protein eEF1A, known to interact with the proteins of SARS-CoV-2, proven by a previous experiment with a drug-resistant mutant (A399V) of eEF1A verifying that the antiviral activity is due to the eEF1A inhibition pathway. The antiviral efficacy of plitidepsin inhibiting the SARS-CoV-2 replication in a human cell line (hACE2-293T) was represented by the 90% inhibitory concentration (IC90) of 0.88nM, having 27.5-fold more than remdesivir, which is currently used for antiviral treatment during COVID-19 emergency. Phase I/II clinical studies of plitidepsin used to treat various myeloma confirmed the safety profile of plitidepsin, not having a significant adverse effect. The current study includes tests of two different established animal models for in vivo efficacy. For both models, BALB/c mice expressing human ACE2 and K18-hACE2, results showed the reduction of SARS-CoV-2 from the lung viral titer by two orders of magnitude and reduced lung inflammation (histopathology score of 1/16). The findings of this study establish plitidepsin as a host-targeted anti-SARS-CoV-2 agent with in vivo efficacy. Strong consideration is suggested for expanded clinical trials of COVID-19 treatment with plitidepsin.

**Structure-guided multivalent nanobodies block SARS-CoV-2 infection and suppress mutational escape**

Koenig et al. identified and engineered variable domains of heavy-chain-only antibodies (nanobodies) associated with the spike protein receptor-binding domain (RBD) of SARS-CoV-2. Engineered nanobodies solve issues with conventional antibodies, such as high production costs, low thermostability, and difficult modifiability. Researchers identified the nanobodies by screening alpaca and llama nanobody libraries using phage display. Their work produced 23 potential nanobodies, which were assessed for their neutralizing activity. Four nanobodies – E, U, H, and V – neutralized SARS-CoV-2-pseudotyped virus infection in a dose-dependent manner. A competitive binding assay found that the nanobodies bind to two distinct interfaces of the RBD; U, H, V competed for the same epitope and were able to
bind concurrently with the E nanobody. X-ray crystallography and cryo-electron microscopy revealed that E stabilized the spike protein complex in an “up” conformation. As a result, the spike fusion process was triggered, which caused a premature change in the spike protein, irreversibly preventing infection. Flow cytometry data shows that U, H, and V bound outcompeted ACE2 for the RBD, keeping the spike protein in the “down” conformation. Significantly, the “down” conformation is thought to be less accessible to neutralizing antibodies for binding. Koenig et al. manipulated the nanobodies to create multivalent nanobodies with over 100 fold neutralizing monovalent nanobody activity. Since E nanobodies do not compete directly with U, H, and V, combinations of such nanobodies yield strong synergistic neutralizing ability.

S-variant SARS-CoV-2 lineage B1.1.7 is associated with significantly higher viral loads in samples tested by ThermoFisher TaqPath RT-qPCR12

Kidd et al. utilized ThermoFisher ‘TaqPath’ reverse transcriptase qualitative polymerase chain reaction (RT-qPCR), which co-amplifies the SARS-CoV-2 viral gene targets ORF1ab, N, and S, on the SARS-CoV-2 variant B1.1.7. This variant is thought to result in S-gene target failure (SGTF) due to its Δ69/70 deletion. 641 SARS-CoV-2 positive results were analyzed from a one-month period in which the variant incidence was rising in the United Kingdom and found a significantly higher number of SGTF samples compared to undetectable ORF1ab or N-gene samples (p<.00001). Furthermore, SGTF samples had significantly lower thresholding crossing values of ORF1ab and N (p<.0001), indicating increased viral load. Compared to the median non-SGTF viral load, variants could have up to a 10,000-fold higher viral load, with conservative extrapolations estimating 1x10⁷ to 1x10⁸ copies per mL. The significantly higher number of subjects with extreme viral load is concerning. Further studies should account for the duration of this high viral load and its significance in virus transmission. Despite the present findings, it is expected that additional mutations in B.1.1.7 are directly related to increased viral load and that SGTF serves as an indirect marker for the presence of B.1.1.7 mutation. Whole-genome sequencing of individual samples is necessary to elucidate the mutational association.

ADDITIONAL RESOURCES
UCSF Library COVID-19 Research and Information Resources
UCSF Institute for Global Health Sciences COVID-19 Resources
UC Davis One Health Institute COVID-19 FAQs
Harvard Viswanath Lab Myths vs Facts
Accesocovid.com

Note on this Document: This document was assembled by undergraduate and doctoral students attending the University of California, Los Angeles and the University of California, San Francisco with the intent of facilitating the rapid dissemination of information to the global community. Alyssa Bercasio, Caihla Petiprin, Mariam Carson, Diana Etwaru, Bryan Maghen, Hannah Han, Griffith Hughes, Jooeun Yoon, and Jiho Kim contributed to these summaries. This work is volunteer based.
References:


