The Daily COVID-19 Literature Surveillance Summary

February 02, 2021

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COVID-19 Daily Literature Surveillance

COVID19LST

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LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".

Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

** OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson*

EXECUTIVE SUMMARY

Epidemiology

- The chronic neuropsychiatric sequelae of COVID-19 continue to raise questions. A literature review conducted internationally during 2020 by the CNS SARS-CoV-2 Consortium found that varying autoimmune reactions, anosmia, and delirium in COVID-19 patients suggests potentially long-term implications for central nervous system disorders. While immune profiles, age, and activity levels may explain variations in the effects, long-term evaluation will be performed to properly understand post-infectious biological changes in the CNS.

Management

- WHO recommends corticosteroids for patients with severe or critical COVID-19. An international team of researchers associated with the World Health Organization summarized recommendations regarding the use of corticosteroids in COVID-19 patients based on results from 8 RCTs with an n=7184, which found the use of corticosteroids in severely or critically ill patients resulted in a lower 28-day mortality. However, corticosteroid treatment in non-severe COVID-19 patients showed no change in mortality rate. These recommendations provide updated treatment guidelines for COVID-19 patients based on disease severity.

TABLE OF CONTENTS

CLIMATE

GLOBAL

VACCINATING CHILDREN AGAINST COVID-19 - THE LESSONS OF MEASLES

Klass P, Ratner AJ.. N Engl J Med. 2021 Jan 20. doi: 10.1056/NEJMp2034765. Online ahead of print.
Level of Evidence: 5 - Expert Opinion

BLUF

An opinion article from pediatricians at NYU highlight the similarities between parents' hesitation to vaccinate their children against COVID-19 to their hesitation to vaccinate against measles in the 20th century, and make a call to action to provide parents with transparent and abundant information on vaccine efficacy in children to make every effort to combat distrust that may arise through social media.

EPIDEMIOLOGY

PHYSICIAN DEATHS FROM COVID-19 HAVE BEEN LOWER THAN EXPECTED

Kaplan RM.. Occup Med (Lond). 2021 Jan 5:kqaa210. doi: 10.1093/occmed/kqaa210. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

This observational study conducted at Stanford University utilized obituary records to certify COVID-related physician deaths nationwide and found that, given the national death toll of 210,000 as of October 2020, the death rate among physicians was only 16% of the expected rate adjusted for the population size of physicians (Figure 1). Additionally, about three-quarters of those deaths were physicians over the age of 60, and half of those apparently retired from clinical practice. While strict use of personal protective equipment may explain these rates, the influences of other variables are not yet well understood.

ABSTRACT

BACKGROUND: More than 100 US physicians have died from COVID-19. I considered the number of US physician deaths in comparison to the expected COVID death rate in the general population. AIMS: To estimate the whether US physicians are at increased risk of death from COVID-19 due to occupational exposures. METHODS: COVID-related physician deaths were identified through searches using Medscape In Memoriam, and multiple internet searches using Google and Facebook. An obituary or death notice was obtained in all but one case. Death rates among physicians were compared to the expected rate based on COVID deaths in the US population. RESULTS: Up to 7 October 2020, there were 108 deaths among US physicians. Physicians make up about 0.33% of the US population. By 1 October 2020, there were 210 000 COVID deaths in the US population with 693 expected physician deaths. Observed deaths were 16% of expected. Seventy-five per cent of the deaths occurred among physicians older than age 60 and about half appeared to be among those retired from clinical practice. CONCLUSIONS: Observed physician deaths were significantly below expected based on deaths the general population. Prudent use of personal protective equipment may explain the lower-than-expected death rates.

FIGURES

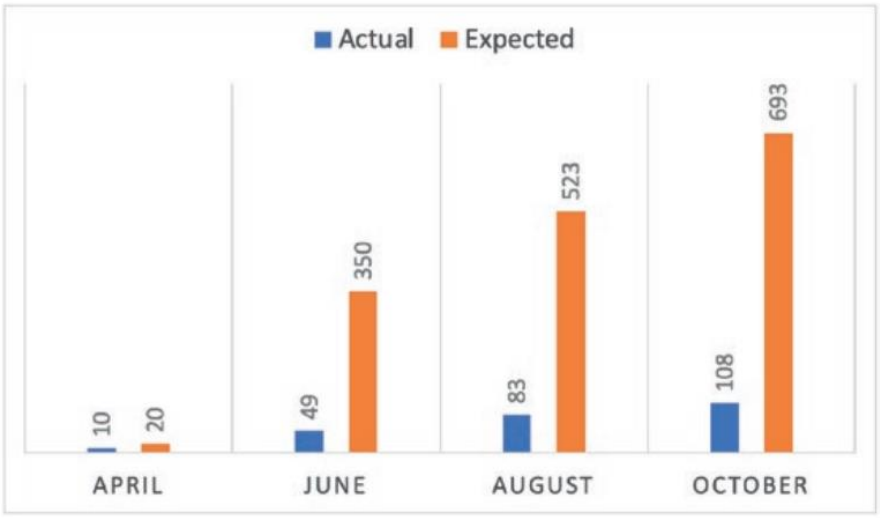


Figure 1. Expected and observed COVID-19 physician deaths in the USA at 2-month intervals in 2020.

THE CHRONIC NEUROPSYCHIATRIC SEQUELAE OF COVID-19: THE NEED FOR A PROSPECTIVE STUDY OF VIRAL IMPACT ON BRAIN FUNCTIONING

de Erausquin GA, Snyder H, Carrillo M, Hosseini AA, Brugha TS, Seshadri S; CNS SARS-CoV-2 Consortium.. Alzheimers Dement. 2021 Jan 5. doi: 10.1002/alz.12255. Online ahead of print.
Level of Evidence: 5 - Review / Literature Review

BLUF

A literature review conducted internationally during 2020 by the CNS SARS-CoV-2 Consortium found that varying autoimmune reactions, anosmia, and delirium in COVID-19 patients suggests potentially long-term implications for central nervous system disorders. While immune profiles, age, and activity levels may explain variations in the effects, long-term evaluation will be performed to properly understand post-infectious biological changes in the CNS.

SUMMARY

Introduction

In spite of being considered an acute infection, understanding the direct effects of COVID-19 infection on the Central Nervous System will provide insight into the wider societal impact of the pandemic on global health.

Viral Impact on Brain Functioning

Neurotropic respiratory viruses is characteristic of multiple viral illnesses, including the 1918 influenza pandemic, and HSV 1, and experiments demonstrate how the latter stimulates cognitive decline, and the same processes behind Alzheimer's.

Neurotropism

The ACE2 pathway, widely understood as the entry point of COVID-19, stimulates brain inflammation via release of VEGF, with effects on the brain correlated positively with the degree of ACE2 deficiency. For instance, Delirium, which may be the sole symptom of an infection with COVID-19, points to intracerebral viral invasion of the virus, which could further effect sensorimotor and motor functions.

Brain Imaging

MRI findings of patients with COVID-19 has been abnormal, with patterns similar to seizures, hypoglycemia, or hypoxia, even in patients with solely sensory dysfunction, such as anosmia.

Possible Determinants

The variation in disease severity can be explained by lifestyle factors, sex, and even disparities in hospitalizations according to ethnicity, adjusted for confounding variables.

Implications for Neuropsychiatric Disorders

Due to meta-analyses pointing to incident risk for dementia and stroke in patients, there is a pressing need to test recently recovered patients for changes in brain physiology to establish mechanisms by which abnormalities develop.

Psychiatric Disorders

Patients have displayed traumatic stress symptoms, exacerbated by pre-existing psychiatric disorders, at significant rates, though the reasons for this remain unclear.

Cognitive Decline and Motor Impairment

The high levels of proinflammatory cytokines likely stimulates cognitive decline in patients, which is in line with the current

understanding of the influenza epidemics role in neurodegenerative disease. At the moment, it is only possible to speculate how COVID-19 may play a role in neurodegenerative disorders months to years after an acute episode of viral infection.

Conclusion

Given the insights provided by the literature review, study teams across the world with study patients from hospitals every 6 months for 18 months to obtain additional data regarding underlying biology.

ABSTRACT

INTRODUCTION: The increasing evidence of SARS-CoV-2 impact on the central nervous system (CNS) raises key questions on its impact for risk of later life cognitive decline, Alzheimer's disease (AD), and other dementia. METHODS: The Alzheimer's Association and representatives from more than 30 countries-with technical guidance from the World Health Organization-have formed an international consortium to study the short-and long-term consequences of SARS-CoV-2 on the CNS-including the underlying biology that may contribute to AD and other dementias. This consortium will link teams from around the world covering more than 22 million COVID-19 cases to enroll two groups of individuals including people with disease, to be evaluated for follow-up evaluations at 6, 9, and 18 months, and people who are already enrolled in existing international research studies to add additional measures and markers of their underlying biology. CONCLUSIONS: The increasing evidence and understanding of SARS-CoV-2's impact on the CNS raises key questions on the impact for risk of later life cognitive decline, AD, and other dementia. This program of studies aims to better understand the long-term consequences that may impact the brain, cognition, and functioning-including the underlying biology that may contribute to AD and other dementias.

MANAGEMENT

TREATMENT OF SEVERE COVID-19 WITH CONVALESCENT PLASMA IN BRONX, NYC

Yoon HA, Bartash R, Gendlina I, Rivera J, Nakouzi A, Bortz Iii RH, Wirchnianski AS, Paroder M, Fehn K, Serrano-Rahman L, Babb R, Sarwar UN, Haslwanter D, Laudermilch E, Florez C, Dieterle ME, Jangra RK, Fels JM, Tong K, Mariano MC, Vergnolle O, Georgiev GI, Herrera NG, Malonis RJ, Quiroz JA, Morano NC, Krause GJ, Sweeney JM, Cowman K, Allen SA, Annam J, Applebaum A, Barboto D, Khokhar A, Lally BJ, Lee A, Lee M, Malaviya A, Sample R, Yang XA, Li Y, Ruiz RE, Thota R, Barnhill J, Goldstein DY, Uehlinger J, Garforth SJ, Almo SC, Lai JR, Reyes Gil M, Fox AS, Chandran K, Wang T, Daily JP, Pirofski LA.. JCI Insight. 2021 Jan 21:142270. doi: 10.1172/jci.insight.142270. Online ahead of print.
Level of Evidence: 4 - Case-series, case-control studies, or historically controlled studies

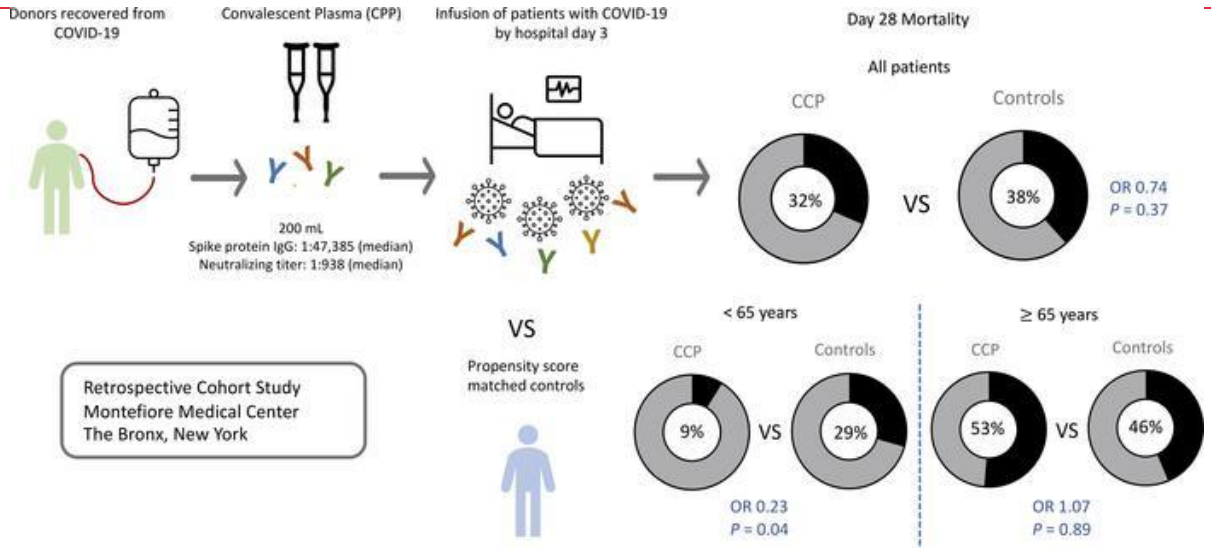
BLUF

A multidisciplinary team of physicians and laboratory scientists evaluated clinical outcomes after administration of convalescent plasma (CPP) containing SARS-CoV-2 antibodies to 73 COVID-19 patients with spike protein titer ≥1:2,430 in the Bronx, New York between April 13 and May 4, 2020 (Figure 1). While there there was no difference in overall mortality at day 28 compared to propensity score matched controls (32% vs 38%, p=0.37), a stratified group of patients under 65 years of age did have significantly reduced mortality with CCP treatment (9% vs 29%, OR: 0.23; p=0.04)(Graphical Abstract, Figure 2). Authors suggest CPP may benefit patients under 65 with high spike protein titers, and recommend further research to corroborate their findings.

ABSTRACT

Convalescent plasma with severe acute respiratory disease coronavirus 2 (SARS-CoV-2) antibodies (CCP) may hold promise as treatment for Coronavirus Disease 2019 (COVID-19). We compared the mortality and clinical outcome of patients with COVID-19 who received 200mL of CCP with a Spike protein IgG titer >=1:2,430 (median 1:47,385) within 72 hours of admission to propensity score-matched controls cared for at a medical center in the Bronx, between April 13 to May 4, 2020. Matching criteria for controls were age, sex, body mass index, race, ethnicity, comorbidities, week of admission, oxygen requirement, D-dimer, lymphocyte counts, corticosteroids, and anticoagulation use. There was no difference in mortality or oxygenation between CCP recipients and controls at day 28. When stratified by age, compared to matched controls, CCP recipients <65 years had 4-fold lower mortality and 4-fold lower deterioration in oxygenation or mortality at day 28. For CCP recipients, pre-transfusion Spike protein IgG, IgM and IgA titers were associated with mortality at day 28 in univariate analyses. No adverse effects of CCP were observed. Our results suggest CCP may be beneficial for hospitalized patients <65 years, but data from controlled trials is needed to validate this finding and establish the effect of ageing on CCP efficacy.

FIGURES



Graphical Abstract

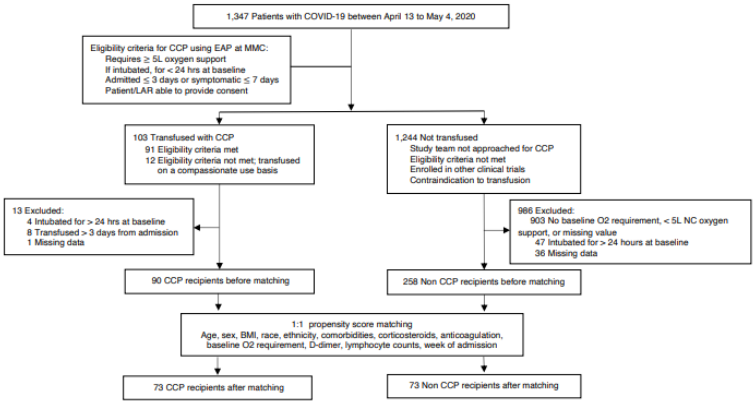


Figure 1. Enrollment of Study Patients and Distribution of Study Cohorts. Study baseline was defined as time of CCP transfusion for CCP recipients and admission day 2 for non CCP recipients. COVID-19, coronavirus disease 2019; CCP, COVID-19 convalescent plasma; EAP, expanded access protocol; LAR, legally authorized representative; MMC, Montefiore Medical Center; NC, nasal cannula.

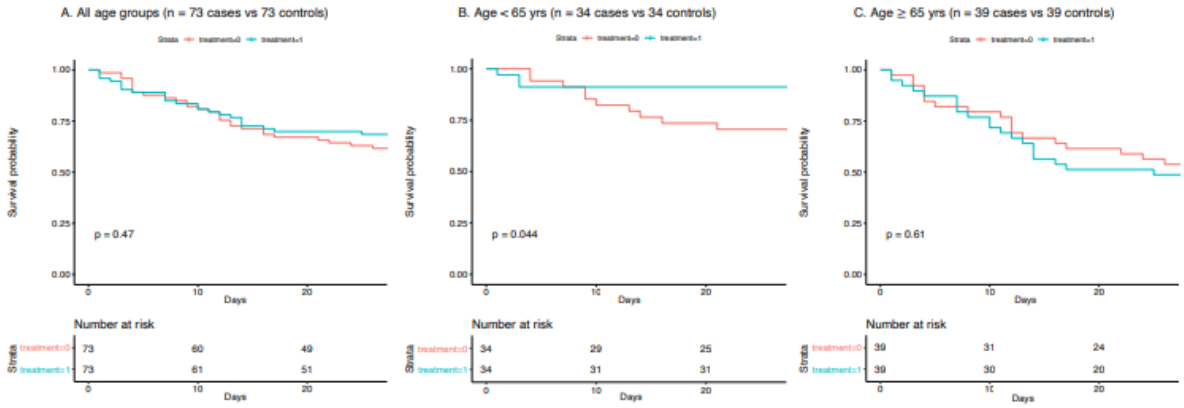


Figure 2. Kaplan–Meier Plot of the Probability of Survival from time of transfusion to day 28 in CCP recipients (n = 73) vs matched controls (n = 73). A. All age groups. B. Age < 65 years. C. Age ≥ 65 years. The *P* value of a log-rank test is shown for each plot.

ACUTE CARE

CRITICAL CARE

MANAGEMENT OF PATIENTS WITH SEVERE ACUTE RESPIRATORY FAILURE DUE TO SARSCOV-2 PNEUMONIA WITH NON-INVASIVE VENTILATORY SUPPORT OUTSIDE INTENSIVE CARE UNIT

Diaz de Teran T, Gonzales Martinez M, Banfi P, Garuti G, Ferraioli G, Russo G, Casu F, Vivarelli M, Bonfiglio M, Perazzo A, Barlascini C, Bauleo A, Nicolini A, Solidoro P.. Minerva Med. 2021 Jan 19. doi: 10.23736/S0026-4806.21.07134-2. Online ahead of print.

Level of Evidence: 4 - Case-series, case-control studies, or historically controlled studies

BLUF

This multi-center retrospective study conducted by interdisciplinary researchers from Spain and Italy analyzed the efficacy of using non-invasive ventilatory support (NIVS) in patients with COVID-19 as a replacement for positive expiratory pressure therapy. The study included 138 patients who were confirmed to be COVID-19 positive via nasopharyngeal swab and were experiencing acute respiratory distress as characterized by a pa02/Fi02 less than 250. Groups were divided based on severity

of illness, and three modes of NIVS were used to treat these patients: pressure support ventilation, Bi-level positive airway pressure, and pressure control ventilation. Results showed successful use of NIVS in terms of improving mortality rate (23.18% vs. 30.55%) compared to control ICU patients receiving positive expiratory pressure therapy (figure 1). Authors argue that the results of this study support the possibility of replacing positive expiratory pressure therapy with NIVS treatment in resource-limited settings.

ABSTRACT

BACKGROUND: COVID-19 has high mortality rate mainly stemming from acute respiratory distress leading to respiratory failure (ARF). Aim of the study is evaluating the management of severe ARF due to COVID-19 pneumonia using non-invasive ventilatory support (NIVS), studing safety and effectiveness of non-invasive ventilatory support (NIVS). METHODS: This is a retrospective, multicenter study. Primary outcomes were NIVS failure with intubation rate and hospital mortality . Secondary outcomes were: hospital stay and factors related to NIVS failure and mortality. These outcomes were compared with patients intubated and admitted to ICU. RESULTS: 162 patients were hospitalized because of severe respiratory failure (PaO2/FiO2 ratio < 250). 138 patients were admitted to Respiratory Intermediate Care Unit (RICU) for a NIVS trial. One hundred patients were treated successfully with NIVS (74.5%); 38 failed NIVS trial (27.5%). In-hospital mortality was 23.18% in RICU group and 30.55% in ICU group. Patients with NIVS failure were older, had a lower number of lymphocytes, a higher IL-6 , lower PaO2, PaCO2, PaO2/FiO2 ratio, higher respiratory rate (RR) and heart rate at admission and lower PaO2 and PaO2/FiO2 ratio and higher RR after 1-6 hours . Multivariate analysis identified higher age, C-reactive protein as well as RR after 1-6 hours and PaO2/FiO2 ratio after 1-6 hours as an independent predictor mortality. CONCLUSIONS: NIVS is a safe and effective strategy in the treatment of severe ARF due to COVID 19 related pneumonia, that reduces mortality and length of hospital stay in the carefully selected patient.

FIGURES

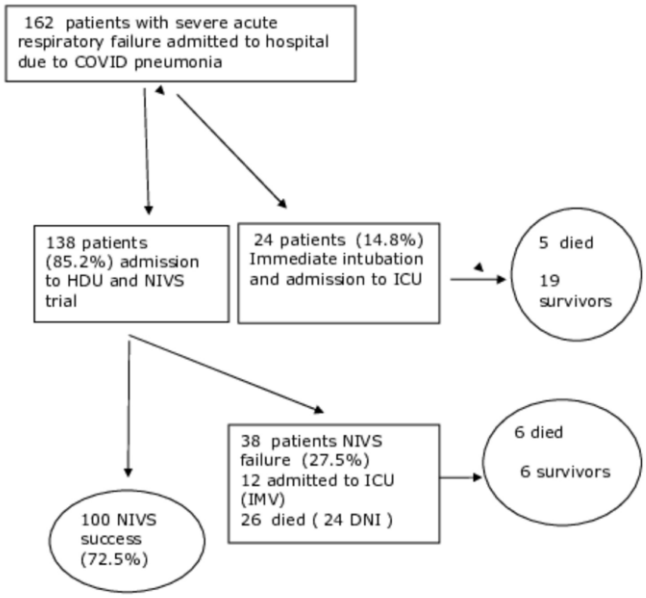


Figure 1. Patient Selection Flowchart

WHO RECOMMENDS CORTICOSTEROIDS FOR PATIENTS WITH SEVERE OR CRITICAL COVID-19

Keyt H.. Ann Intern Med. 2021 Jan 5. doi: 10.7326/ACPJ202101190-002. Online ahead of print.

Level of Evidence: 5 - Guidelines and Recommendations

BLUF

An international team of researchers associated with the World Health Organization summarized recommendations regarding the use of corticosteroids in COVID-19 patients based on results from 8 RCTs (n=7184), which found the use of corticosteroids in severely or critically ill patients resulted in a lower 28-day mortality. However, corticosteroid treatment in non-severe COVID-19 patients showed no change in mortality rate. These recommendations provide updated treatment guidelines for COVID-19 patients based on disease severity.

ABSTRACT

SOURCE CITATION: Lamontagne F, Agoritsas T, Macdonald H, et al. A living WHO guideline on drugs for covid-19. BMJ. 2020;370:m3379. 32887691.

MEDICAL SUBSPECIALTIES

ENDOCRINOLOGY

HOW TO BEST PROTECT PEOPLE WITH DIABETES FROM THE IMPACT OF SARS-COV-2: REPORT OF THE INTERNATIONAL COVID-19 AND DIABETES SUMMIT

Zhang JY, Shang T, Ahn D, Chen K, Coté G, Espinoza J, Mendez CE, Spanakis EK, Thompson B, Wallia A, Wisk LE, Kerr D, Klonoff DC.. J Diabetes Sci Technol. 2021 Jan 21:1932296820978399. doi: 10.1177/1932296820978399. Online ahead of print.
Level of Evidence: 5 - Review / Literature Review

BLUF

Organizers of the International COVID-19 and Diabetes Virtual Summit summarize the topics covered during their virtual meeting from August 26-27, 2020. They include the key points from 24 sessions (see summary) examining how to protect patients with diabetes from COVID-19 and optimal management for those who become infected given that people with diabetes are at increased risk of complications from COVID-19. The authors argue this well-attended meeting provided an important venue for education and collaboration on new approaches to better care for patients with diabetes duri ng the pandemic.

SUMMARY

Authors provide summaries of the key points from the 24 sessions presented at the conference:
(1) Historic Pandemics and Impact on Society
(2) Pathophysiology/Risk Factors for COVID-19
(3) Social Determinants of COVID-19
(4) Preparing for the Future
(5) Medications and Vaccines
(6) Psychology of Patients and Caregivers
(7) Outpatient Treatment of Diabetes Mellitus and Non-Pharmacologic Intervention
(8) Technology and Telehealth for Diabetes Outpatients
(9) Technology for Inpatients
(10) Management of Diabetes Inpatients with COVID-19
(11) Ethics
(12) Accuracy of Diagnostic Tests
(13) Children
(14) Pregnancy
(15) Economics of Care for COVID-19
(16) Role of Industry
(17) Protection of Healthcare Workers
(18) People with Diabetes
(19) International Responses to COVID-19
(20) Government Policy
(21) Regulation of Tests and Treatments
(22) Digital Health Technology
(23) Big Data Statistics
(24) Patient Surveillance and Privacy

ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has rapidly involved the entire world and exposed the pressing need for collaboration between public health and other stakeholders from the clinical, scientific, regulatory, pharmaceutical, and medical device and technology communities. To discuss how to best protect people with diabetes from serious outcomes from COVID-19, Diabetes Technology Society, in

collaboration with Sansum Diabetes Research Institute, hosted the "International COVID-19 and Diabetes Virtual Summit" on August 26-27, 2020. This unique, unprecedented real-time conference brought together physicians, scientists, government officials, regulatory experts, industry representatives, and people with diabetes from six continents to review and analyze relationships between COVID-19 and diabetes. Over 800 attendees logged in. The summit consisted of five sessions: (I) Keynotes, (II) Preparedness, (III) Response, (IV) Recovery, and (V) Surveillance; eight parts: (A) Background, (B) Resilience, (C) Outpatient Care, (D) Inpatient Care, (E) Resources, (F) High-Risk Groups, (G) Regulation, and (H) The Future; and 24 sections: (1) Historic Pandemics and Impact on Society, (2) Pathophysiology/Risk Factors for COVID-19, (3) Social Determinants of COVID-19, (4) Preparing for the Future, (5) Medications and Vaccines, (6) Psychology of Patients and Caregivers, (7) Outpatient Treatment of Diabetes Mellitus and Non-Pharmacologic Intervention, (8) Technology and Telehealth for Diabetes Outpatients, (9) Technology for Inpatients, (10) Management of Diabetes Inpatients with COVID-19, (11) Ethics, (12) Accuracy of Diagnostic Tests, (13) Children, (14) Pregnancy, (15) Economics of Care for COVID-19, (16) Role of Industry, (17) Protection of Healthcare Workers, (18) People with Diabetes, (19) International Responses to COVID-19, (20) Government Policy, (21) Regulation of Tests and Treatments, (22) Digital Health Technology, (23) Big Data Statistics, and 24) Patient Surveillance and Privacy. The two keynote speeches were entitled (1) COVID-19 and Diabetes-Meeting the Challenge and (2) Knowledge Gaps and Research Opportunities for Diabetes and COVID-19. While there was an emphasis on diabetes and its interactions with COVID-19, the panelists also discussed the COVID-19 pandemic in general. The meeting generated many novel ideas for collaboration between experts in medicine, science, government, and industry to develop new technologies and disease treatment paradigms to fight this global pandemic.

UMBILICAL CORD MESENCHYMAL STEM CELLS FOR COVID-19 ACUTE RESPIRATORY DISTRESS SYNDROME: A DOUBLE-BLIND, PHASE 1/2A, RANDOMIZED CONTROLLED TRIAL

Lanzoni G, Linetsky E, Correa D, Messinger Cayetano S, Alvarez RA, Kouroupis D, Alvarez Gil A, Poggioli R, Ruiz P, Marttos AC, Hirani K, Bell CA, Kusack H, Rafkin L, Baidal D, Pastewski A, Gawri K, Leñero C, Mantero AMA, Metalonis SW, Wang X, Roque L, Masters B, Kenyon NS, Ginzburg E, Xu X, Tan J, Caplan AI, Glassberg MK, Alejandro R, Ricordi C.. Stem Cells Transl Med. 2021 Jan 5. doi: 10.1002/sctm.20-0472. Online ahead of print.
Level of Evidence: 2 - Randomized trial or observational study with dramatic effect

BLUF

A double-blind, phase 1/2a, randomized, controlled trial conducted at the University of Miami Miller School of Medicine in Miami, Florida randomized 24 patients hospitalized for COVID-19 to either umbilical cord mesenchymal stem cell (UC-MSC) treatment (n=12) or control (n=12), and found that UC-MSC infusions for COVID-19 positive patients in acute respiratory distress lead to significantly decreased pro-inflammatory cytokines (Figure 3) and increased patient survival (91% vs. 42%, p=0.015) with fewer adverse effects (2/12 vs 8/12, p=0.04), suggesting this method could be incorporated into the treatment plan of COVID-19 ARDS (Figure 2).

ABSTRACT

Acute respiratory distress syndrome (ARDS) in COVID-19 is associated with high mortality. Mesenchymal stem cells are known to exert immunomodulatory and anti-inflammatory effects and could yield beneficial effects in COVID-19 ARDS. The objective of this study was to determine safety and explore efficacy of umbilical cord mesenchymal stem cell (UC-MSC) infusions in subjects with COVID-19 ARDS. A double-blind, phase 1/2a, randomized, controlled trial was performed. Randomization and stratification by ARDS severity was used to foster balance among groups. All subjects were analyzed under intention to treat design. Twenty-four subjects were randomized 1:1 to either UC-MSC treatment (n = 12) or the control group (n = 12). Subjects in the UC-MSC treatment group received two intravenous infusions (at day 0 and 3) of 100 +- 20 x 106 UC-MSCs; controls received two infusions of vehicle solution. Both groups received best standard of care. Primary endpoint was safety (adverse events [AEs]) within 6 hours; cardiac arrest or death within 24 hours postinfusion). Secondary endpoints included patient survival at 31 days after the first infusion and time to recovery. No difference was observed between groups in infusion-associated AEs. No serious adverse events (SAEs) were observed related to UC-MSC infusions. UC-MSC infusions in COVID-19 ARDS were found to be safe. Inflammatory cytokines were significantly decreased in UC-MSC-treated subjects at day 6. Treatment was associated with significantly improved patient survival (91% vs 42%, P = .015), SAE-free survival (P = .008), and time to recovery (P = .03). UC-MSC infusions are safe and could be beneficial in treating subjects with COVID-19 ARDS.

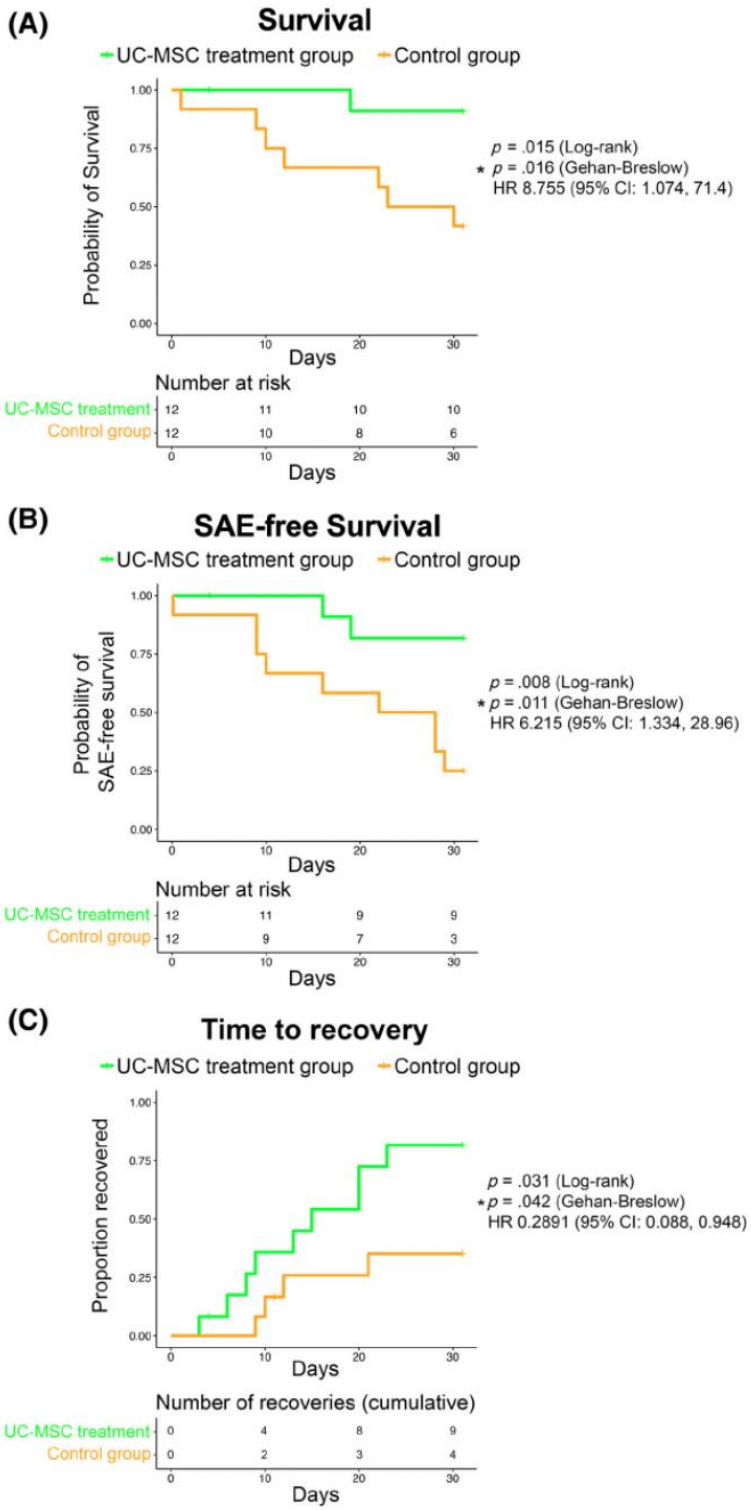


Figure 2. Kaplan-Meier curves. A, Survival. At 31 days after the first infusion (corresponding to 28 days after the last infusion), patient survival was 91% vs 42% in the UC-MSC and control group, respectively (P=0.015). The difference between the groups was statistically significant. B, SAE-free survival. SAE-free survival was significantly improved in the UC-MSC treatment group compared with the control group (P=0.008). SAEs affected two vs eight patients in the UC-MSC and control group, respectively. C, Time to recovery. Time to recovery was significantly shorter in the UC-MSC treatment group compared with the control group (P=0.031).

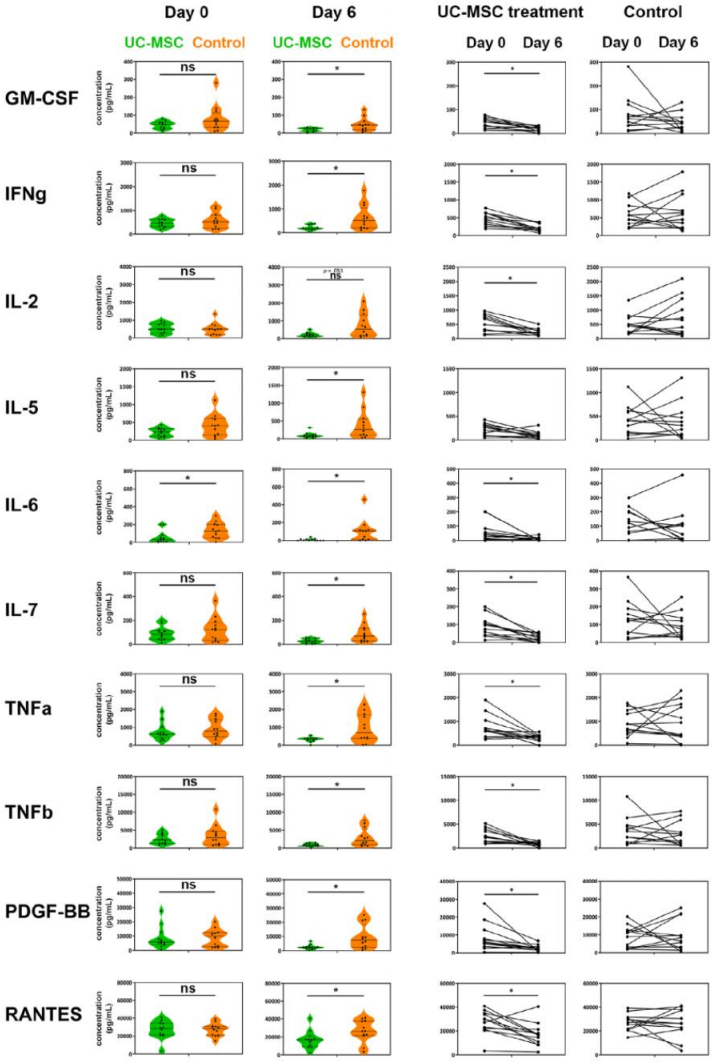


FIGURE 3. Analysis of inflammatory cytokines, chemokines, and growth factors in plasma of randomized subjects. In the comparison between groups at day 6 and in the longitudinal analysis from day 0 to day 6, inflammatory cytokine concentrations showed marked and statistically significant decreases from day 0 to day 6 only in the UC-MSC treatment group. The overall "signature" of the response in the UC-MSC treatment group is characterized by a reduction of the levels of key inflammatory molecules involved in the COVID-19 "cytokine storm," including IFNg,IL-6, and TNFa cytokines and RANTES chemokine. GM-CSF and PDGF-BB also decreased significantly only in the UC-MSC treatment group. ns, not significant; UC-MSC, umbilical cord mesenchymal stem cell

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