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# Evaluation of Immune Bolstering Therapies to support Prevention and Treatment of COVID-19 Disease

*Executive Summary*

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## Situation

This review will focus on Immune Bolstering Therapies and the evolving state of practice for immune bolstering therapies and modalities to support prevention and treatment of COVID-19 disease for health care workers during the COVID-19 pandemic.

**Problem Statement:**
With health care workers at the front lines of the COVID-19 pandemic, does evidence exist to support immune bolstering therapies to protect health care workers, in addition to the general public? What is the current and evolving state of practice for immune bolstering therapies to support optimal health status for health care workers under the conditions of the COVID-19 pandemic?

**Goal(s) of Assessment:**

1. Review the literature and evidence to support immune bolstering therapies to support health care workers' optimal health during the COVID-19 pandemic.
2. Identify the evidence for use of immune bolstering therapies and other related modalities during the COVID-19 pandemic.
3. Report information on the state of practice for immune bolstering therapies and other related modalities.

## Background

Understanding immune bolstering therapies that can help mitigate the impact of COVID-19 is key to enhancing outcomes for COVID-19 disease. Given that health care workers are on the front line with exposure to COVID-19, a better understanding of immune bolstering therapies and other related modalities presents a critical piece of information to support health care workers optimal health during the COVID-19 pandemic.

Preliminary findings for COVID-19 patients have shown that those with co-morbidities such as diabetes and hypertension which are treated with Angiotensin Converting Enzyme [ACE] Inhibitor drugs are at higher risk for developing severe disease due to COVID 19. Patients on ACE inhibitors have greater expression of ACE 2 receptors which have been shown to be the entry point into human cells for COVID-19 virus (Athikarisamy and Jacob, 2020). This leads to the corollary that any drug or vaccine which has the potential to increase the level of ACE may help down regulate the expression of ACE2 receptors, thereby having some beneficial effect on the host immune system against COVID-19.

One example of a potential immune bolster therapy for use with COVID-19 patients that has been suggested is Bacillus Calmette–Guérin (BCG). Earlier animal studies have shown that ACE like activity increased with inflammation induced by Bacillus Calmette–Guérin (BCG) and captopril, a competitive inhibitor of ACE activity, has been helpful in reducing the induction of the inflammatory response in both lungs and spleen (Athikarisamy and Jacob, 2020).

Alternatively, researchers are evaluating different mechanisms of passive immunity to help either prevent or treat COVID-19 disease. The rush to develop a COVID-19 vaccine is one example to help prevent COVID-19 disease. Another example of passive immunity therapy is Convalescent Plasma therapy, which would be used to provide antibodies from recovered COVID-19 patient blood plasma to a sickened COVID-19 patient, in an effort to support the COVID-19 patient's immune system response.

Immune bolstering therapies that stop the novel coronavirus from replicating entirely with antiviral medications, such as remdesivir, are beginning to show promise for COVID-19 patients. Another antiviral under development, EIDD-2801, introduces genetic mutations into the virus's RNA. As the RNA makes its copies, so many damaging mutations accumulate, that the virus is no longer able to infect cells.

Ongoing evaluation of potential immune bolstering therapies for the prevention and treatment of COVID-19 is necessary, given the limited amount of studies that have been conducted to date. We have summarized our findings discovered to date in the following sections.

## Assessment

A review of the published literature to determine the evidence for immune bolstering therapies and other related modalities is presented in the following sections. The results have identified the following guidelines and position statements addressing immune boosting therapies as evidence to support achieving optimal health status for health care workers during the COVID-19 pandemic.

**Position Statements and Guidelines:**
**Table 1. Clinical Guidelines/Practice Statement**

| Name of Organization | Date Searched | Guidance Identified |
|---|---|---|
| Department of Defense DoD COVID-19 Practice Management Guide Version 2 | April 15, 2020 | N/A |
| **Centers for Disease Control and Prevention (CDC)** | | |
| Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19) | April 15, 2020 | Link provided. |
| **World Health Organization (WHO)** | | |
| WHO INTERIM GUIDANCE DOCUMENT: Clinical Management of Acute Respiratory Distress Syndrome in Patients with suspected Novel Coronavirus Disease | April 15, 2020 | N/A |
| **National Institute Centers for Excellence** | | |
| NICE Guidance | April 15, 2020 | N/A |
| **Society of Critical Care Medicine** | | |
| SCCM Guidance: Surviving Sepsis Campaign | April 15, 2020 | N/A |

## Guidelines

1. CDC Interim Clinical Guidance for the Management of Confirmed Coronavirus Disease (COVID-19)

**Clinical Management:**

**Mild to Moderate Disease**

Patients with a mild clinical presentation (absence of viral pneumonia and hypoxia) may not initially require hospitalization, and many patients will be able to manage their illness at home. The decision to monitor a patient in the inpatient or outpatient setting should be made on a case-by-case basis. This decision will depend on the clinical presentation, requirement for supportive care, potential risk factors for severe disease, and the ability of the patient to self-isolate at home. Patients with risk factors for severe illness (see People Who Are at Higher Risk for Severe Illness) should be monitored closely given the possible risk of progression to severe illness in the second week after symptom onset.

For information regarding infection prevention and control recommendations, please see Interim Infection Prevention and Control Recommendations for Patients with Confirmed Coronavirus Disease 2019 (COVID-19) or Persons Under Investigation for COVID-19 in Healthcare Settings.

**Severe Disease**

Some patients with COVID-19 will have severe disease requiring hospitalization for management. No specific treatment for COVID-19 is currently FDA approved. Corticosteroids have been widely used in hospitalized patients with severe illness in China; however, the benefit of corticosteroid use cannot be determined based upon uncontrolled observational data. By contrast, patients with MERS-CoV or influenza who were given corticosteroids were more likely to have prolonged viral replication, receive mechanical ventilation, and have higher mortality. Therefore, corticosteroids should be avoided unless indicated for other reasons, such as management of chronic obstructive pulmonary disease exacerbation or septic shock. More information can be found at Healthcare Professionals: Frequently Asked Questions and Answers.

Inpatient management revolves around the supportive management of the most common complications of severe COVID-19: pneumonia, hypoxemic respiratory failure/ARDS, sepsis and septic shock, cardiomyopathy and arrhythmia, acute kidney injury, and complications from prolonged hospitalization including secondary bacterial infections, thromboembolism, gastrointestinal bleeding, and critical illness polyneuropathy/myopathy.

The Infectious Diseases Society of America has released guidelines on the treatment and management of patients with COVID-19. For more information, please visit: Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19 Infection.

The World Health Organization and the Surviving Sepsis Campaign have both released comprehensive guidelines for the inpatient management of patients with COVID-19, including those who are critically ill. For more information visit: Interim Guidance on Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected (WHO) and Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19).

For more information on the management of children, see Information for Pediatric Healthcare Providers and the Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children.

**Investigational Therapeutics**

No FDA-approved drugs have demonstrated safety and efficacy in randomized controlled trials for patients with COVID-19. Use of investigational therapies for treatment of COVID-19 should ideally be done in the context of enrollment in randomized controlled trials. Several clinical trials

are underway testing multiple drugs with in-vitro antiviral activity against SARS-CoV-2 and/or immunomodulatory effects that may have clinical benefit. For the latest information, see Information for Clinicians on Therapeutic Options for COVID-19 Patients. For the information on registered trials in the U.S., see ClinicalTrials.gov

**Clinical Studies:**

A review of existing clinical studies of immune bolstering therapies to support prevention and treatment of COVID-19 is provided in Table 2. This information is a summary of the literature reviewed to date.

**Table 2. Summary of Study Methods and Findings**

Keywords: CSS, cytokine storm syndrome; CoV, coronavirus; Remdesivir; SARS-COV-2, COVID-19, IVIG, clinical efficacy, mortality.

| Authors/Study Design | Study Population | Treatment | Results | Key Findings/ Strengths/Limitations |
|---|---|---|---|---|
| Shen C et al, 2020.<br><br>Uncontrolled, case series<br><br>Dates: January 20, 2020, to March 25, 2020; final follow-up date March 25, 2020<br><br>Funding Source: NR | n=5 critically ill patients with COVID-19 and acute respiratory distress syndrome (ARDS), meeting following criteria:<br><br>1. Severe pneumonia with rapid progression<br><br>2. Continuously high viral load, despite antiviral treatment<br><br>3. Pao2/Fio2 <300<br><br>4. Mechanically ventilated | All 5 patient cases were transfused with convalescent plasma, containing the following:<br><br>1. SARS-CoV-2–specific antibody (IgG) binding titer greater than 1:1000 (end point dilution titer, by enzyme-linked immunosorbent assay [ELISA])<br><br>2. Neutralization titer greater than 40 (end point dilution titer) from 5 recovered COVID_19 patients.<br><br>All transfusions were administered from day 10 to 22 after admission. | Following plasma transfusion, the following was observed:<br><br>1. Body temperature normalized within 3 days in 4 of 5 patients<br><br>2. SOFA score decreased<br><br>3. Pao2/ Fio2 increased within 12 days (range, 172-276 before and 284-366 after)<br><br>4. Viral loads decreased and became negative within 12 days after the transfusion<br><br>5. SARS-CoV-2–specific ELISA and neutralizing antibody titers increased following the transfusion (range, | Preliminary findings suggest treatment with convalescent plasma containing neutralizing antibody will improve clinical status for critically ill patients with COVID-19 and ARDS.<br><br>*Strengths:*<br><br>• N/A<br><br>*Limitations*:<br><br>• Limited sample size<br>• Study design<br>• Requires further study in randomized, clinical trial.<br>*Conflicts of Interest*: None stated |

| Authors/Study Design | Study Population | Treatment | Results | Key Findings/ Strengths/Limitations |
|---|---|---|---|---|
| | | | 40-60 before and 80-320 on day 7)<br><br>6. ARDS resolved in 4 patients at 12 days after transfusion<br><br>7. 3 patients weaned from mechanical ventilation within 2 weeks of treatment<br><br>8. 3 of 5 patients discharged from the hospital (length of stay: 53, 51, and 55 days); and<br><br>9. 2 of 5 patients in stable condition at 37 days after transfusion | |
| Shao et al, 2020<br><br>Multicenter, retrospective cohort study<br><br>Funding Source: Grants from 1) PLA Logistics Research Project of China: 2) Sanming Project of Medicine in Shenzhen; and 3) Clinical Research Project of Health and Family Planning Commission of | 325 adult critical COVID-19 patients | Study to determine the clinical efficacy of intravenous immunoglobulin (IVIG) therapy on COVID-19.<br><br>Demographic, clinical, treatment, and laboratory data.<br><br>Prognoses was extracted from electronic medical records, and IVIG was exposure factor.<br><br>*Outcomes:* Improved outcomes for critical COVID-19 patients treated with IVIG; negative outcomes for noncritical COVID-19 patients. | Comparison of two groups, Group #1: 174 cases used IVIG; Group #2) 151 cases did not use IVIG.<br><br>Patients in IVIG group showed:<br><br>1. Higher Acute Physiology and Chronic Health Evaluation (APACHII) score<br><br>2. Higher Sequential Organ Failure Assessment (SOFA) score<br><br>3. Higher IL-6 and lactate level | Early and high dose of IVIG therapy may improve the prognosis of COVID-19 patients only in critical type.<br><br>*Strengths:* N/A<br><br>*Limitations*:<br><br>Small, single site study<br><br>*Conflicts of Interest*: None stated |

| Authors/Study Design | Study Population | Treatment | Results | Key Findings/ Strengths/Limitations |
|---|---|---|---|---|
| Shenzhen Municipality. | | | 4. Lower lymphocyte count and oxygenation index (all P<0.05).<br><br>Subgroup analysis of critical type patients treated with IVIG:<br><br>1. 28-day mortality significantly reduced<br><br>2. inflammatory response decreased<br><br>3. Improve some organ functions (all p<0.05)<br><br>4. 60-day mortality reduced significantly by using IVIG in the early state (admission≤7 days) and with high dose (>15 g/d) | |

**State of Practice:**

Based on the literature reviewed, the state of practice for several of the immune bolstering therapies to both prevent and treat COVID-19 are discussed below. Ongoing monitoring of the literature is recommended, given the increasing number of immune bolstering therapies to support COVID-19 prevention and treatment.

**Table 3. State of Practice Observations related to Immune Bolstering and Boosting Therapies in Response to COVID-19**

| Phase | Therapy | Observation | SOP Implication | Source/Organization |
|---|---|---|---|---|
| Prevention | Bacillus Calmette–Guérin (BCG) vaccine | BCG vaccine's heterologous beneficial effect against non-tuberculosis infections is well known.<br><br>BCG vaccine works on the innate immune system and produces a memory like | Analysis suggests that mandated BCG vaccination may be effective in the fight against COVID-19.<br><br>Countries that have required BCG vaccination to prevent tuberculosis have been | Berg, 2020 |

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| | | response termed “trained immunity”.<br><br>Triggers a quicken inflammatory response through faster recognition. | observed to have a “flatter” curve for COVID-19 infections case rates. | |
| | Antibody-based, plasma derived therapies | Utilizes one or more antibodies most effective in neutralizing SARS-CoV-2, delivered through injection to prevent COVID-19 disease.<br><br>Developing companies are currently working with antibodies taken from human blood.<br><br>Researchers have identified two different antibodies to neutralize the virus. | Healthcare workers and other high-risk individuals could get the shots as a preventative measure, and they could be given to sick patients to prevent their symptoms from escalating.<br><br>Injections could be monoclonal, with just a single form of antibody, or a “polyclonal” cocktail with multiple antibodies. | McDonnell T, 2020 |
| | Vitamin D | Vitamin D can support the immune system through a number of immune pathways involved in fighting SARS2COV.<br><br>Vitamin D is important in regulation and suppression of the inflammatory cytokine response, which causes the severe consequences of COVID-19 and 'acute respiratory distress syndrome' associated with ventilation and death. | Many recent studies confirm the pivotal role of vitamin D in viral infections.<br><br>Circumstantial and experimental data suggests that Vitamin D may reduce serious COVID-19 complications. | Laird E, 2020 |
| **Treatment** | Heat stress | Heat stress has multiple actions when dealing with infections that include direct inhibition of pathogens.<br><br>Heat stress activates immune cells by making their cell membranes more fluid, which increases cell differentiation and activation by viral antigens, | Hyperthermia induces hyperventilation and subsequent respiratory alkalosist, an alkaline condition that may be more favorable to host defenses against virus, like SARS-CoV-2.<br><br>Heat applied to the upper airways in the initial phase of infection can support the immune system’s | Cohen M, 2020<br><br>Crinnion W, 2011 |

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| | | enabling a faster and more effective response to viral threats.<br><br>Heat stress increases cardiac output, plasma volume and peripheral blood flow, and induces detoxification through the liver and kidneys, as well as through the skin via sweating through which some toxic elements are preferentially excreted.<br><br>Heat-stress may offer a further advantage against respiratory viral infections by altering blood pH. | first line of defense by supporting muco-ciliary clearance and inhibiting or deactivating the virus in the place lodged.<br><br>Deactivating fvirus in the upper airway can be further enhanced by the inhalation of steam containing essential oils with anti-viral, mucolytic and anxiolytic properties.<br><br>Heat applied to the whole body can further support the immune system's second line of defense by mimicking fever and activating innate and acquired immune defenses and building physiological resilience. | |
| | EIDD-2801 | An experimental antiviral medication that interferes with a key mechanism that allows the SARS-CoV-2 virus to reproduce in high numbers and cause infections. | Two potential uses:<br><br>#1: Prophylaxis health care workers can take to prevent an infection.<br><br>#2: Uninfected nursing home residents and workers if an outbreak occurs inside a facility. | Waldorf A, 2020 |
| | Remdesivir | An investigational, broad-spectrum, small-molecule antiviral drug.<br><br>Has demonstrated destructive activity against RNA viruses in several families, including Coronaviridae. | Compassionate care studies are showing preliminary impact on COVID-19 patients severely ill.<br><br>Cautious consideration of the preliminary results.<br><br>Available in IV administration only; used for critically ill COVID-19 patients only. | Amirian, 2020 |
| | Convalescent plasma therapy | Convalescent plasma, (or passive antibody therapy), is a passive immunity, provides antibodies from donated COVID-19 survivors immediately.<br><br>Donated plasma is used to determine whether it contains | Continue monitoring of NIH sponsored clinical trial, National COVID-19 Convalescent Plasma Project, for FDA approval. | Cunningham A, 2020 |

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| | | neutralizing antibodies, a type of antibody that prevents virus from entering a host cell.<br><br>Spike protein, a particular SARS-CoV-2 protein that the virus uses to bind to human protein cells, is targeted by the neutralizing antibody. | Project will test plasma in 3 groups:<br><br>Trial #1: Randomized clinical trial designed to investigate whether plasma can prevent infection in people exposed to COVID-19 by a close contact, such as a family member. The trial will test plasma from recovered COVID-19 patients against a placebo — plasma taken from patients prior to the December 2019 start of the epidemic.<br><br>Trial #2: Plans to test whether plasma can keep people with moderate disease who are in the hospital from needing intensive care.<br><br>Trial #3: Trial aims to study whether the therapy helps the most critically ill patients. | |
| | Monoclonal Antibodies | The proposed use of previously unknown antibodies that specifically block SARS-CoV-2 from attaching to human cells by locking onto two slightly different places on SARS-CoV-2.<br><br>Specifically, antibodies B38 and H4 block the binding between virus S-protein RBD and cellular receptor ACE2, effectively neutralizing SARS-CoV-2.<br><br>A competition assay indicates their different epitopes on the RBD, making them a potential virus-targeting pair to avoid immune escape in future clinical applications. | Goal is to use these antibodies in combination to block the virus from entering cells, limiting COVID-19's destructive spread throughout the lungs and other parts of the body. | Collin F, 2020<br><br>Wu Y, 2020 |
| | Intravenous Immunoglobulin therapy (IVIG) | Historically used for patients with antibody deficiencies.<br><br>Therapy by administration of blood product from patients, containing polyclonal | Proven, potent and safe immune modulator. | Li T, 2020 |

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| | | immunoglobulin G isolated and pooled from healthy donors.<br><br>Experimental use for COVID-19 patients by administration of 25 gm/day for 5 days, at the point where each patient's condition deteriorated. | | |

## Recommendations/ Summary

In this review, we identified the current literature for immune bolstering therapies to support mitigation of COVID-19 disease, particularly for health care workers. As identified in the Assessment section, the clinical studies reviewed identified therapies that are currently being evaluated, some with greater success than others. Although several of the reviewed therapies are promising, to date there are no FDA approved prevention or treatment therapies for COVID-19. Further monitoring is necessary to inform decision making and update the state of practice for immune bolstering therapies to support prevention and treatment of COVID-19 disease.

## Abstracts

**Turning up the heat on COVID-19: heat as a therapeutic intervention.**

Cohen M. F1000Research. 9:292 https://doi.org/10.12688/f1000research.23299.1 Last updated: May 21, 2020.

Enveloped viruses such as SAR-CoV-2 are sensitive to temperature and are destroyed by temperatures tolerable to humans. All mammals use fever to deal with infections and heat has been used throughout human history in the form of hot springs, saunas, hammams, steam-rooms, sweat-lodges, steam inhalations, hot mud and poultices to prevent and treat respiratory infections and enhance health and wellbeing. This paper reviews the evidence for using heat to treat and prevent viral infections and discusses potential cellular, physiological and psychological mechanisms of action. In the initial phase of infection, heat applied to the upper airways can support the immune system’s first line of defense by supporting muco-ciliary clearance and inhibiting or deactivating virions in the place where they first lodge. This may be further enhanced by the inhalation of steam containing essential oils with anti-viral, mucolytic and anxiolytic properties. Heat applied to the whole body can further support the immune system’s second line of defense by mimicking fever and activating innate and acquired immune defenses and building physiological resilience. Heat-based treatments also offer psychological benefits by directing focus on positive action, enhancing relaxation and sleep, inducing 'forced-mindfulness', and invoking the power of positive thinking and remembered wellness. Heat is a

cheap, convenient and widely accessible therapeutic modality and while no clinical protocols exist for using heat to treat COVID-19, protocols that draw from traditional practices and consider contraindications, adverse effects and infection control measures could be developed and implemented rapidly and inexpensively on a wide scale. While there are significant challenges in implementing heat-based therapies during the current pandemic, these therapies present an opportunity to integrate natural medicine, conventional medicine and traditional wellness practices, and support the wellbeing of both patients and medical staff, while building community resilience and reducing the likelihood and impact of future pandemics.

**Clinical Features of Patients Infected with 2019 Novel Coronavirus in Wuhan, China**

Huang C et al. www.thelancet.com Published online January 24, 2020.

Background: A recent cluster of pneumonia cases in Wuhan, China, was caused by a novel betacoronavirus, the 2019 novel coronavirus (2019-nCoV). We report the epidemiological, clinical, laboratory, and radiological characteristics and treatment and clinical outcomes of these patients.

Methods: All patients with suspected 2019-nCoV were admitted to a designated hospital in Wuhan. We prospectively collected and analyzed data on patients with laboratory-confirmed 2019-nCoV infection by real-time RT-PCR and next-generation sequencing. Data were obtained with standardized data collection forms shared by the International Severe Acute Respiratory and Emerging Infection Consortium from electronic medical records. Researchers also directly communicated with patients or their families to ascertain epidemiological and symptom data.

Outcomes were also compared between patients who had been admitted to the intensive care unit (ICU) and those who had not.

Findings: By Jan 2, 2020, 41 admitted hospital patients had been identified as having laboratory-confirmed 2019-nCoV infection. Most of the infected patients were men (30 [73%] of 41); less than half had underlying diseases (13 [32%]), including diabetes (eight [20%]), hypertension (six [15%]), and cardiovascular disease (six [15%]). Median age was 49·0 years (IQR 41·0–58·0). 27 (66%) of 41 patients had been exposed to Huanan seafood market. One family cluster was found. Common symptoms at onset of illness were fever (40 [98%] of 41 patients), cough (31 [76%]), and myalgia or fatigue (18 [44%]); less common symptoms were sputum production (11[28%] of 39), headache (three [8%] of 38), haemoptysis (two [5%] of 39), and diarrhea (one [3%] of 38). Dyspnea developed in 22 (55%) of 40 patients (median time from illness onset to dyspnea 8·0 days [IQR 5·0–13·0]). 26 (63%) of 41 patients had lymphopenia. All 41 patients had pneumonia with abnormal findings on chest CT. Complications included acute respiratory distress syndrome (12 [29%]), RNAaemia (six [15%]), acute cardiac injury (five [12%]) and secondary infection (four [10%]). 13 (32%) patients were admitted to an ICU and six (15%) died. Compared with non-ICU patients, ICU patients had higher plasma levels of IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1A, and TNFα.

Interpretation: The 2019-nCoV infection caused clusters of severe respiratory illness similar to severe acute respiratory syndrome coronavirus and was associated with ICU admission and

high mortality. Major gaps in our knowledge of the origin, epidemiology, duration of human transmission, and clinical spectrum of disease need fulfilment by future studies.

**Compassionate Use of Remdesivir for Patients with Severe COVID-19.**

Grein J et al. www.nejm.org. N Engl J Med. Accessed April 15, 2020. April 10, 2020. DOI: 10.1056/NEJMoa2007016

Background: Remdesivir, a nucleotide analogue prodrug that inhibits viral RNA polymerases, has shown in vitro activity against SARS-CoV-2.

Methods: We provided remdesivir on a compassionate-use basis to patients hospitalized with Covid-19, the illness caused by infection with SARS-CoV-2. Patients were those with confirmed SARS-CoV-2 infection who had an oxygen saturation of 94% or less while they were breathing ambient air or who were receiving oxygen support. Patients received a 10-day course of remdesivir, consisting of 200 mg administered intravenously on day 1, followed by 100 mg daily for the remaining 9 days of treatment. This report is based on data from patients who received remdesivir during the period from January 25, 2020, through March 7, 2020, and have clinical data for at least 1 subsequent day.

Results: Of the 61 patients who received at least one dose of remdesivir, data from 8 could not be analyzed (including 7 patients with no post-treatment data and 1 with a dosing error). Of the 53 patients whose data were analyzed, 22 were in the United States, 22 in Europe or Canada, and 9 in Japan. At baseline, 30 patients (57%) were receiving mechanical ventilation and 4 (8%) were receiving extracorporeal membrane oxygenation. During a median follow-up of 18 days, 36 patients (68%) had an improvement in oxygen-support class, including 17 of 30 patients (57%) receiving mechanical ventilation who were extubated. A total of 25 patients (47%) were discharged, and 7 patients (13%) died; mortality was 18% (6 of 34) among patients receiving invasive ventilation and 5% (1 of 19) among those not receiving invasive ventilation.

Conclusion: In this cohort of patients hospitalized for severe Covid-19 who were treated with compassionate-use remdesivir, clinical improvement was observed in 36 of 53 patients (68%). Measurement of efficacy will require ongoing randomized, placebo-controlled trials of remdesivir therapy. (Funded by Gilead Sciences.)

**Treatment of 5 Critically Ill Patients with COVID-19 with Convalescent Plasma**

Shen C et al. *JAMA.* Published online March 27, 2020. doi:10.1001/jama.2020.4783

IMPORTANCE: Coronavirus disease 2019 (COVID-19) is a pandemic with no specific therapeutic agents and substantial mortality. It is critical to find new treatments.

OBJECTIVE: To determine whether convalescent plasma transfusion may be beneficial in the treatment of critically ill patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

DESIGN, SETTING, AND PARTICIPANTS: Case series of 5 critically ill patients with laboratory-confirmed COVID-19 and acute respiratory distress syndrome (ARDS) who met the following criteria: severe pneumonia with rapid progression and continuously high viral load despite antiviral treatment; PAO2/FIO2 <300; and mechanical ventilation. All 5 were treated with convalescent plasma transfusion. The study was conducted at the infectious disease department, Shenzhen Third People's Hospital in Shenzhen, China, from January 20, 2020, to March 25, 2020; final date of follow-up was March 25, 2020. Clinical outcomes were compared before and after convalescent plasma transfusion.

EXPOSURES: Patients received transfusion with convalescent plasma with a SARS-CoV-2–specific antibody (IgG) binding titer greater than 1:1000 (end point dilution titer, by enzyme-linked immunosorbent assay [ELISA]) and a neutralization titer greater than 40 (end point dilution titer) that had been obtained from 5 patients who recovered from COVID-19. Convalescent plasma was administered between 10 and 22 days after admission.

MAIN OUTCOMES AND MEASURES: Changes of body temperature, Sequential Organ Failure Assessment (SOFA) score (range 0-24, with higher scores indicating more severe illness), PAO2/FIO2, viral load, serum antibody titer, routine blood biochemical index, ARDS, and ventilatory and extracorporeal membrane oxygenation (ECMO) supports before and after convalescent plasma transfusion.

RESULTS: All 5 patients (age range, 36-65 years; 2 women) were receiving mechanical ventilation at the time of treatment and all had received antiviral agents and methylprednisolone. Following plasma transfusion, body temperature normalized within 3 days in 4 of 5 patients, the SOFA score decreased, and PAO2/FIO2 increased within 12 days (range, 172-276 before and 284-366 after). Viral loads also decreased and became negative within 12 days after the transfusion, and SARS-CoV-2–specific ELISA and neutralizing antibody titers increased following the transfusion (range, 40-60 before and 80-320 on day 7). ARDS resolved in 4 patients at 12 days after transfusion, and 3 patients were weaned from mechanical ventilation within 2 weeks of treatment. Of the 5 patients, 3 have been discharged from the hospital (length of stay: 53, 51, and 55 days), and 2 are in stable condition at 37 days after transfusion.

CONCLUSIONS AND RELEVANCE: In this preliminary uncontrolled case series of 5 critically ill patients with COVID-19 and ARDS, administration of convalescent plasma containing neutralizing antibody was followed by improvement in their clinical status. The limited sample size and study design preclude a definitive statement about the potential effectiveness of this treatment, and these observations require evaluation in clinical trials.

**Sauna as a Valuable Clinical Tool for Cardiovascular, Autoimmune, Toxicant-induced and other Chronic Health Problems**

Crinnion W. Alternative medicine review: a journal of clinical therapeutic 16(3):215-25 · September 2011.

Sauna therapy has been used for hundreds of years in the Scandinavian region as a standard health activity. Studies document the effectiveness of sauna therapy for persons with hypertension, congestive heart failure, and for post-myocardial infarction care. Some individuals with chronic obstructive pulmonary disease (COPD), chronic fatigue, chronic pain, or addictions also find benefit. Existing evidence supports the use of saunas as a component of depuration (purification or cleansing) protocols for environmentally-induced illness. While far-infrared saunas have been used in many cardiovascular studies, all studies applying sauna for depuration have utilized saunas with radiant heating units. Overall, regular sauna therapy (either radiant heat or far-infrared units) appears to be safe and offers multiple health benefits to regular users. One potential area of concern is sauna use in early pregnancy because of evidence suggesting that hyperthermia might be teratogenic.

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