2020 Year in Review: Pharmacologic Treatments for COVID-19

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Conflicts of Interest/Funding Disclosure: MDD is funded by NHLBI 1 PO1 HL128192 and the Indiana CTSI UL 1 TR002529. He also is a patent holder of Optate and a co-founder of Airbase Breathing Company. JLS is funded by the Cystic Fibrosis Foundation 1st and 2nd Year Clinical Fellowship Grant.

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Abstract

COVID-19, caused by SARS-CoV-2 infection, has led to a pandemic of acute respiratory illness. Pharmacologic treatments for COVID-19 have included treatments targeting infection prevention, prevention of viral replication, reducing inflammation and managing symptoms of respiratory failure caused by the disease. This is a review of key pharmacologic treatments for COVID-19 based on peer-reviewed articles from 2020.

Key Words: COVID-19, SARS-CoV-2, Remdesivir, REGN-CoV-2, Optate, Airway pH, Dexamethasone

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Introduction

The novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in Wuhan, China at the end of 2019[1]. Since that time, it has affected over 100 million people around the world leading to over 2 million deaths[2]. The virus causes an acute respiratory illness that the World Health Organization has termed Coronavirus Disease 2019 (COVID-19). Due to the severity and effects of this illness, great efforts have been undertaken to identify effective pharmacologic therapies to prevent infection, prevent viral replication, prevent damaging inflammation or to manage the symptoms of respiratory failure caused by the virus.

This reviews six pharmacologic treatments potentially useful for patients with COVID-19. Remdesivir, REGN-CoV-2, and Optate directly target viral infection and replication. Dexamethasone is a corticosteroid that reduces inflammation post-infection. Finally, oxygen and inhaled pulmonary vasodilators are used to treat and manage respiratory symptoms in patients with COVID-19.

The purpose of this article is to review the literature available in the past year regarding these pharmacologic therapies for COVID-19. Recent pharmacologic treatment strategies for COVID-19 will also be summarized.

Methods

Pharmacologic agents included in the National Institute of Health (NIH) COVID-19 Treatment Guidelines with the most supporting evidence at the time of this publication were included in this review[3]. A PubMed search was conducted to identify articles published in 2020 that related to these COVID-19 pharmacologic treatments.

Searches were conducted using the key words “remdesivir”, “REGN-CoV-2”, “Optate”, “dexamethasone”, “oxygen” and “inhaled pulmonary vasodilators” in conjunction with “COVID-19”. A summary for each of the reviewed pharmacologic agents, based upon the findings of this literature search, is included below.

Discussion

Remdesivir

Remdesivir is an intravenous prodrug of an adenosine analog which incorporates into viral RNA and results in premature termination. It has a broad-spectrum antiviral activity against several viruses such as respiratory syncytial virus, Nipah virus, Ebola virus, Middle East respiratory syndrome, and severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1)[4-6]. Remdesivir was authorized for emergency use by the FDA in May of 2020 for hospitalized adults with severe COVID-19. This emergency use authorization led to a double blind, randomized, placebo-controlled trial sponsored by the National Institutes of Health[7].

This initial trial enrolled hospitalized adults with confirmed cases of COVID-19 and evidence of lower respiratory tract infections, treated them with either 10 days of remdesivir or placebo, and monitored their time to recovery. In this study, subjects who received remdesivir had a significantly decreased median recovery time compared to subjects who received the placebo (Figure 1, 95% CI, 9-11 vs 13-18). Subjects who received remdesivir were also more likely to have clinical improvement at day 15 (odds ratio, 1.5; 95% CI, 1.2-1.9, after adjustment for disease severity) when compared to those treated with placebo. Although there was no statistically significant difference in

mortality noted between the two groups, the authors concluded that remdesivir shortened the time to recovery and hastened clinical improvement when compared to the placebo group and may have prevented progression to more serious illness in some cases[7].

A subsequent trial evaluated different courses of remdesivir (5 days vs 10 days) compared each other and the standard of care[8]. Subjects who received 5 days of remdesivir had significantly higher odds of having a better clinical status than those receiving standard care alone (odds ratio, 1.65; 95% CI, 1.09-2.48; P = 0.02). Of note, those who received 10 days of remdesivir therapy did not show a statistically significant difference when compared to the standard of care group (P = 0.18) and there was no significant difference in mortality between the three groups after 28 days. Although repeated studies suggest that remdesivir is a promising therapy for COVID-19, ongoing studies are needed to determine whether it reduces mortality[8].

REGN-CoV-2

REGN-CoV-2 is an antibody cocktail that prevents viral entry into human cells via the angiotensin converting enzyme 2 receptor. It is made up of two noncompeting, neutralizing human IgG1 antibodies, REGN10933 and REGN10987, that target the SARS-CoV-2 spike protein[9]. Viruses mutate frequently which may result in new mutant viruses that are not affected by a specific antibody – a process known as “viral escape”. By combining two (or more) antibodies, a therapy is less vulnerable to viral escape because the virus would have to mutate in multiple specific ways[10].

Initial trials evaluated the effects of 8.0 g or 2.4 g of REGN-CoV-2 compared to placebo on non-hospitalized subjects with COVID-19. Subjects that received either dose of REGN-CoV-2 had a significantly decreased SARS-CoV-2 viral load than those that received the placebo (Figure 2, 95% CI, −1.02 to −0.11). Additionally, medical visits for COVID-19 were significantly decreased in subjects that received REGN-CoV-2 than those that received the placebo (95% CI, −29 to 11)[11]. As with remdesivir, further studies are needed to determine the effects of REGN-CoV-2 on mortality in patients with COVID-19.

Optate

Optate is an inhaled isotonic, isosmotic, alkaline medication designed to safely raise airway pH without irritating the airway epithelium. Raising intracellular pH partially prevents activation of SARS-CoV-2 in normal primary human airway epithelial (NHAE) cells, decreasing viral replication by altering endosomal trafficking and preventing viral entry and replication[12]. Optate has been previously shown to be safe to inhale in healthy human subjects and those with stable airways disease[13]. These studies also demonstrated that Optate raised airway lining fluid pH, with is airway epithelial extracellular pH.

In 2020, in vitro studies demonstrated that Optate also safely increases intracellular pH of NHAE cells. Optate also ablated SARS-CoV-2 viral infection and replication in NHAE cells after 48 hours compared to placebo (Figure 3, $P < 0.001$). Due to its demonstrated safety profile in man and anti-viral effects in vitro, Optate inhalation may be well suited for a clinical trial in patients with COVID-19 infection[14].

Dexamethasone

Dexamethasone is a potent corticosteroid with anti-inflammatory properties that has often been used as a supplemental treatment for viral pneumonia[15]. Inflammation is a known component of COVID-19, leading to rationale of dexamethasone as a potential therapy[16]. The RECOVERY Trial Collaborative Group performed a randomized, controlled, open label trial comparing subjects treated with oral or intravenous dexamethasone (6 mg daily for up to 10 days) to those who received the standard of care alone and assessed mortality at 28 days. They found that those who received dexamethasone had significantly decreased mortality within 28 days compared to those who received the standard of care (Figure 4, 22.9% vs 25.7%, age-adjusted rate ratio, 0.83; 95% CI, 0.75 to 0.93; P<0.001). Subjects requiring mechanical ventilation at the time of randomization also had lower mortality rates when receiving dexamethasone therapy compared to the standard of care (Figure 4, 29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81). Similarly, those receiving non-invasive oxygen therapy at the time of randomization had lower mortality rates when they were randomized to the dexamethasone group (Figure 4, 23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94). Of note, this decrease in mortality was not noted in subjects who did not require oxygen therapy at time of randomization (Figure 4, 17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.92 to 1.55)[17].

Oxygen

Hypoxic respiratory failure is a severe complication of SARS-CoV-2 and affects approximately 19% of patients with COVID-19[18]. The Surviving Sepsis Campaign COVID-19 panel issued several recommendations regarding oxygen use in adults with COVID-19, including:

• Start supplemental oxygen if the peripheral oxygen saturation (SpO2) is < 92% (weak recommendation);

• Start supplemental oxygen if SpO2 is < 90% (strong recommendation);

• Maintain SpO2 no higher than 96% in patients with acute hypoxemic respiratory failure requiring oxygen (strong recommendation)[19].

There is some rationale for heightened caution of the overuse of supplemental oxygen therapy in patients with COVID-19 due to concern for upregulation of SARS-CoV-2 receptor expression in airway epithelium. Increased receptor expression could lead to increased susceptibility to SARS-CoV-2 infection. Myti et al compared levels of mRNA for genes encoding SARS-CoV-2 receptors in lung cells of mouse pups and preterm human infants exposed to chronically elevated FiO2 (>0.5)[20]. Levels of two different SARS-CoV-2 receptors, TMPRSS2 and TMPRSS11D, were both increased in the groups treated with high FiO2 (Figure 5, $P < 0.001$). Increased levels of SARS-CoV-2 receptors could increase susceptibility to infection, however, further studies determining the effects of oxygen on SARS-CoV-2 infection in vivo are warranted[20].

Inhaled Pulmonary Vasodilators

Inhaled pulmonary vasodilators have been shown to improve oxygenation and VQ mismatch in patients with ARDS, which could lead to benefits in patients suffering from COVID-19. Inhaled pulmonary vasodilators include inhaled nitric oxide, prostacyclins and prostacyclin analogs. At the time of this publication, the Surviving Sepsis Campaign for COVID-19 panel does not recommends the routine use of inhaled pulmonary vasodilators for patients with COVID-19. They do recommend a trial of inhaled pulmonary vasodilators for mechanically ventilated adults with severe ARDS and hypoxemia secondary to COVID-19 and refractory to optimized ventilation and other rescue strategies. However, this is a weak recommendation with low quality evidence[19].

Franco et al. explored the mechanism of action of several inhaled pulmonary vasodilators and current ongoing clinical trials. They discussed the potential benefits of nitric oxide for benefit patients with COVID-19 by directly treating endothelial dysfunction/VQ mismatch, improving cardiac reserve, and by direct anti-viral effects[21]. Currently, a clinical trial is underway to assess these benefits as well as the safety of pulsed inhaled nitric oxide in patients with COVID-19 requiring supplemental oxygen[22]. Studies are also ongoing evaluating that effects of inhaled prostacyclin therapy on outcomes for mechanically ventilated adults with COVID-19[23].

Summary

In 2020, several pharmacologic agents have been identified and trialed for use in patients suffering from COVID-19. Several of these treatments target viral replication, inflammation, and symptom management. Due to the ongoing nature of this novel

pandemic, recommendations for treatment of patients with COVID-19 are ever evolving. The most up-to-date guidelines from the NIH can be found at https://www.covid19treatmentguidelines.nih.gov/. Knowledge of therapeutic options and best practice of their use is crucial for battling this pandemic. Of note, at the time of this publication, vaccination against SARS-CoV-2 is recommended as an effective prevention of COVID-19[24].

References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497-506.
2. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis 2020;20(5):533-534.
3. National Institutes of Health. NIH COVID-19 Treatment Guidelines. https://www.covid19treatmentguidelines.nih.gov/. March 30, 2021.
4. Agostini ML, Andres EL, Sims AC, Graham RL, Sheahan TP, Lu X, et al. Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease. mBio 2018;9(2).
5. Lo MK, Jordan R, Arvey A, Sudhamsu J, Shrivastava-Ranjan P, Hotard AL, et al. GS-5734 and its parent nucleoside analog inhibit Filo-, Pneumo-, and Paramyxoviruses. Sci Rep 2017;7:43395.

6. Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med 2017;9(396).

7. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med 2020;383(19):1813-1826.

8. Spinner CD, Gottlieb RL, Criner GJ, Arribas Lopez JR, Cattelan AM, Soriano Viladomiu A, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. JAMA 2020;324(11):1048-1057.

9. Baum A, Fulton BO, Wloga E, Copin R, Pascal KE, Russo V, et al. Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies. Science 2020;369(6506):1014-1018.

10. Hansen J, Baum A, Pascal KE, Russo V, Giordano S, Wloga E, et al. Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail. Science 2020;369(6506):1010-1014.

11. Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19. N Engl J Med 2021;384(3):238-251.

12. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020;181(2):271-280 e278.

13. Davis MD, Walsh BK, Dwyer ST, Combs C, Vehse N, Paget-Brown A, et al. Safety of an alkalinizing buffer designed for inhaled medications in humans. Respir Care 2013;58(7):1226-1232.

14. Davis MD, Clemente TM, Giddings OK, Ross K, Cunningham RS, Smith L, et al. A Treatment to Eliminate SARS-CoV-2 Replication in Human Airway Epithelial Cells Is Safe for Inhalation as an Aerosol in Healthy Human Subjects. Respir Care 2021;66(1):113-119.

15. Zoorob RJ, Cender D. A different look at corticosteroids. Am Fam Physician 1998;58(2):443-450.

16. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395(10229):1033-1034.

17. Group RC, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med 2021;384(8):693-704.

18. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 2020;323(13):1239-1242.

19. Alhazzani W, Evans L, Alshamsi F, Moller MH, Ostermann M, Prescott HC, et al. Surviving Sepsis Campaign Guidelines on the Management of Adults With Coronavirus Disease 2019 (COVID-19) in the ICU: First Update. Crit Care Med 2021;49(3):e219-e234.

20. Myti D, Gunjak M, Casado F, Khaghani Raziabad S, Nardiello C, Vadasz I, et al. Elevated FiO2 increases SARS-CoV-2 co-receptor expression in respiratory tract epithelium. Am J Physiol Lung Cell Mol Physiol 2020;319(4):L670-L674.

21. Franco V, Bradley EA, Badagliacca R, Sabanayagam A, Rajpal S, Lastinger LT, et al. Pulmonary vasodilators: beyond the bounds of pulmonary arterial hypertension therapy in COVID-19. Pulm Circ 2020;10(4):2045894020970369.

22. A Study to Assess Pulsed Inhaled Nitric Oxide vs Placebo in Subjects with Mild or Moderate COVID-19. https://www.clinicaltrials.gov/ct2/show/NCT04421508. March 30, 2021.

23. VentaProst in Subjects with COVID-19 Requiring Mechanical Ventilation. https://clinicaltrials.gov/ct2/show/NCT04452669. March 30, 2021.

24. Centers for Disease Control. Ensuring COVID-19 Vaccines Work. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/effectiveness.html. March 8, 2021.

Figure Legends

Figure 1: Remdesivir shortens time to recovery in patients with COVID-19. Subjects who received remdesivir had a median recovery time of 10 d (95% CI 9–11 d) compared to subjects who received the placebo whose median recovery time was 15 d (95% CI 13–18 d). Data from Reference 7.

Figure 2: REGN-CoV-2 significantly decreases viral load compared to placebo. Time-weighted average change in viral load from day 1 to day 7. Subjects that received REGN-CoV-2 SARS-CoV-2 had a significantly decreased SARS-CoV-2 viral load than those that received the placebo (95% CI −1.02 to −0.11). Data from Reference 11.

Figure 3: Optate decreases SARS-CoV-2 viral replication in Vero E6 and NHAE cells. A: PFUs were measured in culture media from control and Optate-treated Vero E6 cells infected with SARS-CoV-2. Optate ablated viral infection in the Vero E6 cells (P <.001). B: Control and Optate-treated primary NHAE cell cultures were infected with SARS-CoV-2, PFUs in culture media were analyzed under similar conditions for 120 h, starting from 24 h after infection. After infection was established (24 h), viral infection was ablated in the Optate-treated cells (P <.001). From Reference 14.

Figure 4: Dexamethasone decreases mortality in hospitalized patients with COVID-19. Shown is the effect of dexamethasone on 28-d mortality according to respiratory support at time of randomization. Subgroups include all subjects, those undergoing mechanical ventilation, those receiving supplemental oxygen, and those who were receiving no oxygen at the time of randomization. Data from Reference 17.

Figure 5: Steady-state levels of lung mRNA transcripts encoding SARS-CoV-2 entry receptors and co-receptors in experimental animals and clinical subjects chronically exposed to elevated FiO_2. A: mRNA levels of *Ace2*, *Tmprss1*, *Tmprss2*, and *Tmprss11d* in mouse pup lungs (5 animals per group) at post-natal day (P)2, 3, 5,

10, and 14, and then exposed to room air (FiO_2 0.21; white bars) or hyperoxia (FiO_2 0.85; black bars) for the first 14 d of post-natal life. B: mRNA levels were similarly determined for *ACE2*, *TMPRSS1*, *TMPRSS2*, and *TMPRSS11D* in the lungs of infants without (control, n = 8 subjects; white bars) or with bronchopulmonary dysplasia (BPD; n = 10 subjects; black bars). Data reflect mean ΔCt ± SD. Pairwise comparisons were made between the 21% O_2 and 85% O_2 groups by unpaired Student's t test (A), and between the Ctrl and BPD groups by Mann-Whitney U test (B). *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001. From Reference 20, with permission.

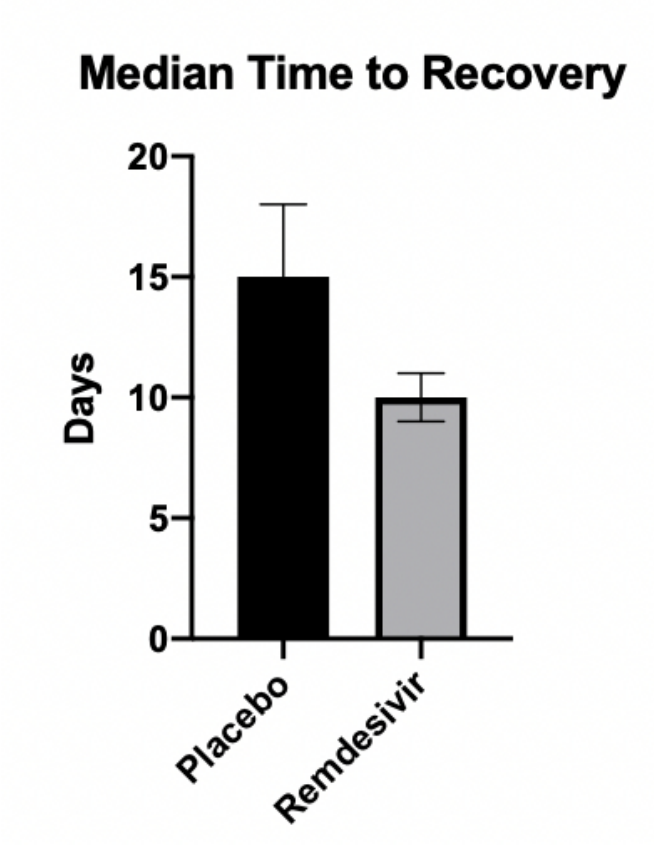

Figure 1

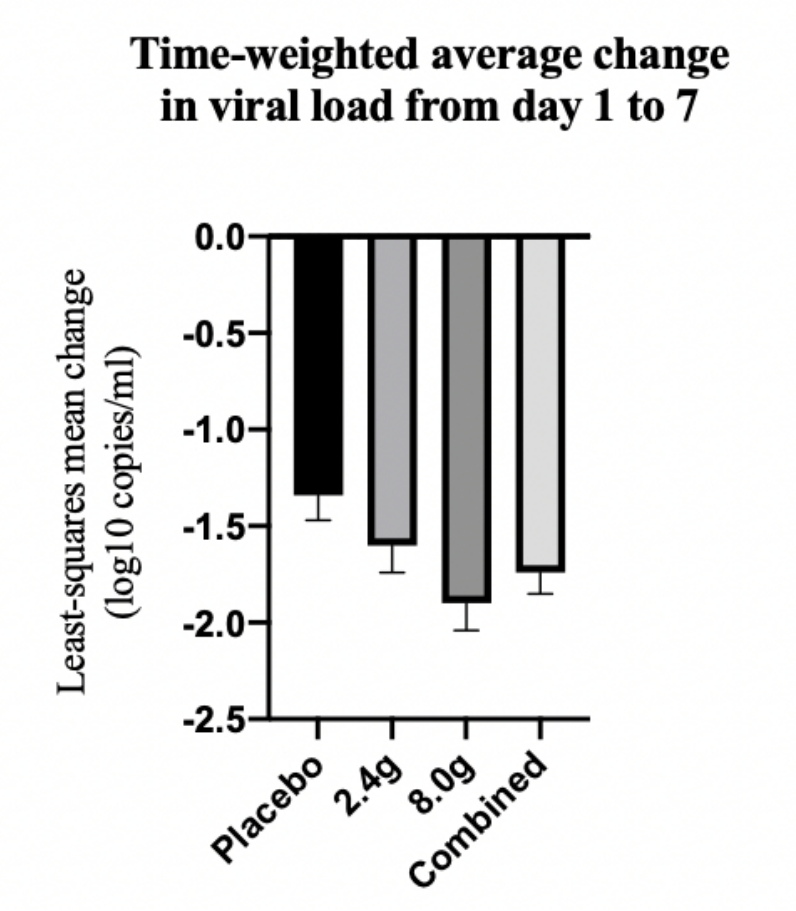

Figure 2

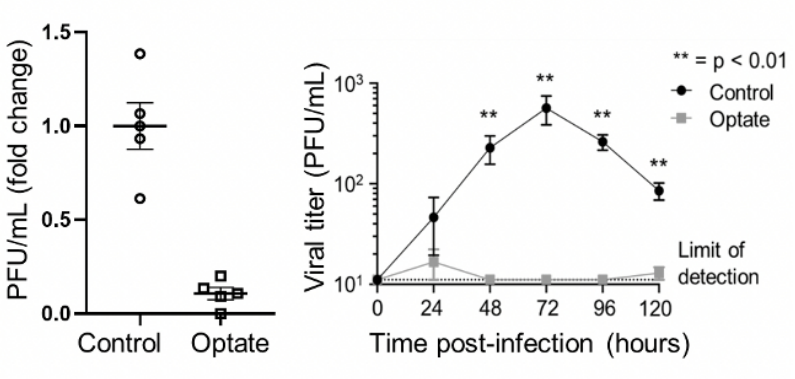

Figure 3

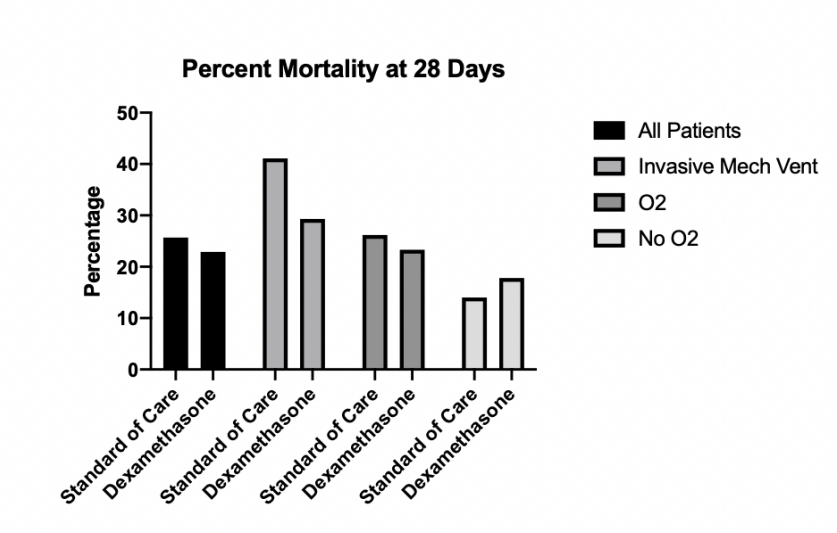

Figure 4

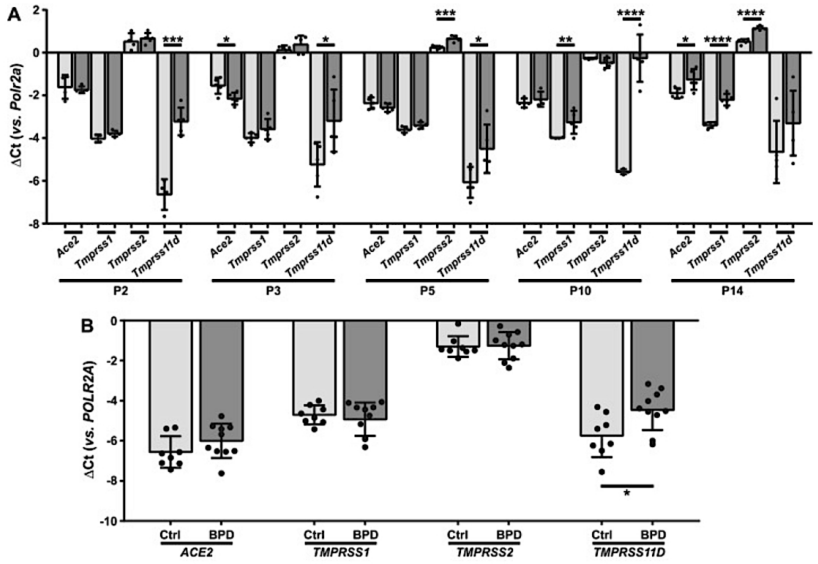

Figure 5