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SARS-Cov-2 and the Case for Empirical Treatment

By Richard P. Bartlett, MD & Alexandria Watkins, DNP

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The goal is to call attention to the success of proactive, early empirical treatment, combining a classic corticosteroid (budesonide) administered via a nebulizer and an oral macrolide antibiotic known as clarithromycin (Biaxin).

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SARS-Cov-2 and the Case for Empirical Treatment

Richard P. Bartlett, MD ^α & Alexandria Watkins, DNP ^ο

Summary- As of June 17, 2020, Google Trends reports that the topics "steroids and coronavirus" have increased +4,750%.¹² This is an outpatient case study that examines two patients in the United States with unique cases that involve oncology and Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), also known as COVID-19. This case study aims to reveal the identification process, diagnosis, clinical course, and management of such a distinctive case - including the patient's prodromal phase and subsequent progression of the disease in an outpatient setting utilizing telemedicine.

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I. INTRODUCTION

A classic drug and a novel case, it is a story out of a Disney playbook - *Beauty and The Beast*.⁴¹ A beauty named budesonide and a beast named SARS-CoV-2. Budesonide, a drug initially patented in 1973 and on the World Health Organization's (WHO) List of Essential Medicines, and SARS-CoV-2 first presenting itself in the United States on January 20, 2020.⁸ & 46 This is a case study that demonstrates the effectiveness of treating a respiratory disease with a pinpoint focused nebulized therapy versus systemic therapy. One can go as far back as ~1554 BC and find that even the ancient Egyptians had an appreciation for the therapeutic effects of sequestered aerosol inhalation.³⁸ The aim of pinpoint focused treatment is to find specific targets and treat effectively with minimal side effects. 'Work smarter, not harder' is an underlying theme with early, pinpoint focused empirical treatment.

Like asthma, SARS-CoV-2 is a form of a respiratory inflammatory disease that is more severe and acts on the angiotensin-converting enzyme (ACE) receptors of the lungs. SARS-CoV-2 presents as a local vascular problem due to the activation of B1 receptors on endothelial cells within the lungs - B1 receptors increase the response to proinflammatory cytokines. This activation takes place when the angiotensin-converting enzyme 2 (ACE2) acts as a receptor, permitting the spike protein of SARS-CoV-2 to bind to host cells. When ACE2 is interrupted, and the ligands of B1 are active, the lung environment is predisposed to

vascular leakage and angioedema - rapid swelling in the mucosa. The primed spike protein is also allowed viral entry and spread by the transmembrane protease, serine 2 (TMPRSS2).^{24, 34 & 43} Multiple studies agree with our discovery that inhaled corticosteroids (ICS) via nebulizer permit for localized down- regulation of proinflammatory cytokine synthesis and decreased expression of ACE2 (receptor of SARS-CoV-2) and TMPRSS2, thus reducing mortality.^{15, 23, 24, 28, 34 & 49}

For this reason, this case study postulates that focused treatment with nebulized budesonide has clinical significance over systemic corticosteroids and does not increase the risk of infection with SARS-CoV-2.2, 24 & 30 This case study supports early empirical treatment in symptomatic patients.

II. METHODS

a) Study Population, Setting, and Data Collection

This case study involves two patients in the outpatient setting - treated via telemedicine, with laboratory-confirmed SARS-CoV-2 infection in the West Texas region between March 29th, 2020, and May 14th, 2020. The cases presented are confirmed SARS-CoV-2 positive cases as defined by a positive result on a reverse-transcriptase-polymerase- chain-reaction (RT-PCR) assay of a specimen collected on a nasopharyngeal swab.

The two identified adults were identified and managed through telemedicine by a primary care provider in an outpatient family medicine practice.

Informed consent for medical records release was obtained through password-protected emails, and patients were interviewed by phone.

III. CASE REPORT

The first patient is a 63-year-old female, non-smoker, who is diagnosed with Waldenstrom's Macroglobulinemia (2012) and Primary Cutaneous Marginal Zone Lymphoma (2020) and currently being treated with ibrutinib (Imbruvica). The patient also has a history of hypertension and hypothyroidism; treatment for these comorbidities includes losartan potassium 50mg tab once-daily, and levothyroxine 50mcg tab once- daily respectively. The patient reports complete isolation until May 7th, 2020, when her family visited, this

Author ^α: MD. e-mail: richardbartlett@sbcglobal.net

Author ^ο: DNP, APRN. e-mail: alexandriawatkins.aw@gmail.com

is the initial exposure date. On May 10th, 2020, the patient became symptomatic with sinus cavity pressure, fever, aches, and chills. In the early morning hours of May 11th, the patient had multiple episodes of nausea and vomiting and, by that evening, had fever greater than 100.4°F, constant chills, unproductive cough, decreased appetite related to change in taste and smell. The patient remained symptomatic and continued to self-isolate until May 15th, she received news that she had been exposed to a family member on May 7th, that tested positive for SARS-CoV-2. Upon hearing the report, the patient reached out via telemedicine to an outpatient family medicine doctor. The patient was tested for SARS-CoV-2 via nasopharyngeal swab using a reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay. At this time (May 15th, 2020), the patient was empirically started on budesonide 0.5mg nebulizer twice daily, clarithromycin (Biaxin) 500mg tab twice daily for ten days, Zinc 50mg tab twice daily, and aspirin 81mg tab daily. The patient reported for the next two-days, symptoms improved once nebulized budesonide had been administered. By May 19th, the patient developed a productive cough, pleuritic pain, and

diarrhea. On May 20th, the patient's RT-PCR assay for SARS-CoV-2 was confirmed positive, ten days after initial symptoms. A telemedicine consult was performed the same day (May 20th), and budesonide administration was increased from twice daily to three times daily. The patient reports that on May 24th, symptoms started to improve, and on May 25th, the patient completed the clarithromycin (Biaxin) prescription and notes that this was the first day of no fevers. As the patient continued to remain symptom-free, a second RT-PCR assay was ordered via telemedicine on May 29th, and on June 2nd, the patient was still positive for SARS-CoV-2; this is 24-days from initial symptoms. On June 8th, the patient had been symptom-free for 14-days, a third RT-PCR assay was ordered via telemedicine, and on June 10th, the patient received their first negative result for SARS-CoV-2. A fourth RT-PCR assay was ordered on June 11th, via telemedicine, and on June 17th, the patient received a second negative result. The patient has remained symptom-free, and as of June 11th, has no longer needed nebulized budesonide therapy.

Assumed Initial Exposure Date: May 7, 2020	
Empirical Treatment Start Date: May 15, 2020	
Test Date:	Result and Date Received:
May 15, 2020	Positive – May 20, 2020
May 29, 2020	Positive – June 2, 2020
June 8, 2020	Negative – June 10, 2020
June 11, 2020	Negative – June 17, 2020

The second patient is a 38-year-old male, non-smoker, who has the following comorbidities: Type II Diabetes Mellitus (DM), hypertension, and gout. The patient takes Metformin 1,000mg tab, twice daily and Pioglitazone 15mg tab, daily for Type II DM, Lisinopril 2.5mg tab, daily for hypertension, and Probenecid 500mg tab, daily for gout.

The patient believes initial exposure was in Frisco, TX, on March 7th, 2020, while shopping at a shopping center. On March 29th, 2020, the patient became symptomatic with cough, sore throat, loss of smell and taste, fever (>100.4°F), aches, and chills.

March 29th, the patient was tested for Influenza using the rapid influenza diagnostic test (RIDT), the test was negative, and the patient was discharged home. At this time, the patient accessed his primary care doctor via telemedicine, he was treated empirically and started on budesonide 0.5mg nebulizer twice daily, clarithromycin (Biaxin) 500mg tab twice daily for 10 days, Zinc 50mg tab twice daily, and aspirin 81mg tab

daily. April 1st, 2020 (three days after onset of symptoms), the patient was able to undergo SARS-CoV-2 testing, he was tested by nasopharyngeal swab using an RT-PCR assay. On April 3rd, the patient was informed that he had tested positive for SARS-CoV-2, six days after initial symptoms had ensued. The patient reports that he was symptom-free April 4th, and completed his full round of clarithromycin (Biaxin) on April 7th. The patient continued budesonide 0.5mg nebulizer twice daily, Zinc 50mg tab twice daily, and aspirin 81mg tab daily. As the patient continued to remain symptom-free, a second RT-PCR assay via nasopharyngeal swab was ordered via telemedicine on April 15th ending with a positive result for SARS-CoV-2. At this time azithromycin 500mg tab on day one, then 250mg tab, daily for four-days was started. On April 27th, the patient was re-tested via RT-PCR assay and again tested positive. It was not until May 1st that the patient tested negative per the nasopharyngeal swab

RT-PCR assay. On May 7th, the patient was tested with another RT-PCR assay by nasopharyngeal swab to confirm the negative test result but tested positive for SARS-CoV-2. The patient had no new exposure and been self-quarantined since April 1st. The patient was re-screened again by nasopharyngeal swab using RT-PCR May 11th and tested negative for SARS-CoV-2. The patient completed a total of four rounds of Azithromycin

500mg tab on day one, then 250mg tab, daily for four-days, and stopped budesonide 0.5mg nebulizer twice daily, May 13th. He continued Zinc 50mg tab twice daily, and the aspirin 81mg tab daily, until a second consecutive negative was obtained. On May 14th, the last test that was performed on the patient was the nasopharyngeal swab using an RT-PCR assay and again confirmed a negative result.

March 29, 2020	
Test Date:	Result and Date Received:
April 1, 2020	Positive – April 3, 2020
April 15, 2020	Positive – April 19, 2020
April 27, 2020	Positive – April 27, 2020
May 1, 2020	Negative – May 3, 2020
May 7, 2020	Positive – May 10, 2020
May 11, 2020	Negative – May 13, 2020
May 14, 2020	Negative – May 15, 2020

IV. DISCUSSION

a) *Budesonide*

Since the outbreak of the novel SARS-CoV-2 infection, there have been inconsistencies in the information that has been disseminated regarding the potentially deleterious effect of treating patients with corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and non-NSAIDs. Nonsteroidal anti-inflammatory drugs induce their intrinsic inhibitory functions on the cyclooxygenase enzymes (COX-1/COX-2). These enzymes are involved in the synthesis of crucial biological mediators - mediators that regulate inflammation. Corticosteroids, such as budesonide, participate in several basic physiological processes such as aiding in immune system response and inflammatory regulation. Budesonide destabilizes the messenger RNA (mRNA) of the inflammatory gene, COX-2, by blocking the protein synthesis, thus suppressing the transfer of genetic information that allows for inflammation to take place.⁵

Corticosteroid pretreatment abates cytokine stimulation significantly by reducing both inflammatory mediators' cytosolic phospholipase A2 (cPLA2) and COX-2 mRNA status as well as prostaglandin (PGE) release. The physiological effect of budesonide in reducing PGE production occurs primarily at the mRNA level by preventing the launch of cPLA2 and particularly COX-2.²⁹ Using nebulized budesonide early on in the treatment plan of symptomatic SARS-CoV-2 patients is valuable when trying to avoid an overreaction of the immune system causing a 'cytokine storm' – a response that wreaks havoc on healthy cells rather than incapacitating the virus.

Budesonide represents the first example of a drug able to inhibit the production of proinflammatory cytokines/chemokines like IL-6, IL-8, and TNF- α from human lung macrophages activated by secretory phospholipids A2 (sPLA2).⁴⁰ Corticosteroids like budesonide were universally used during the SARS-CoV outbreak because of their recognized ability to regulate a variety of involved cytokines (including IL-1, IL-3, IL-4, IL-5, IL-6, IL-8, IL-11 IL-12, IL-17A GM-CSF, and TNF- α).^{11, 23, 33, 36 & 50} Research shows that early intervention with ICS like budesonide decreases the need for systemic corticosteroid use. Inhaled corticosteroids modestly improve airflow function.^{32 & 51} According to Russell et al., there is no "definitive evidence" that establishes a stance on the use of NSAIDs for the treatment of SARS-CoV-2. Still, there is evidence that corticosteroids can produce favorable results in the treatment of SARS-CoV.³⁶ Oncology patients who are immunocompromised benefit from prescribed low-dose corticosteroids.^{9 & 36} There is also a decreased risk of pneumonia in COPD patients who use nebulized budesonide.¹⁶ In contrast, when systemic corticosteroids were used in SARS-CoV-2 hospital patients there was no evidence of shortened pneumonia duration, decrease in days stayed in the hospital, or reduced risk of mortality.⁴⁸ This case study has affirmed that an empirical treatment protocol with nebulized budesonide and the efficacy of treating symptomatic patients earlier rather than later has significant implications. Halpin et al. is in agreeance with early management and encourages increased dosing with ICS for SARS-CoV-2 patients.¹⁷ The treatment plan

has evolved and become more effective by increasing the dosage and frequency of nebulized budesonide.

Budesonide has proven to be useful in the prevention of asthma (an inflammatory disease in the lungs), and when regularly used, budesonide has shown to decrease the severity and number of asthma attacks. SARS-CoV-2 is a much more severe form of inflammatory disease in the lungs with the primary source of infection at the ACE receptors in the lungs. It is important to note that for asthmatics who are having an acute inflammatory response and people with late symptoms of SARS-CoV-2, budesonide is ineffective. Hence, routine daily treatment of budesonide ICS for asthmatics and early empirical nebulized treatment is critical for SARS-CoV-2 patients. The use of inhaled budesonide has also been shown to be beneficial in the airway epithelial cells by inhibiting the virus-induced cytokines, thymic stromal lymphopoietin (TSLP), and chemokine ligand 26 (CCL26).¹⁸ The inhibition of these cytokines indicates that inhalation of budesonide via nebulizer after SARS-CoV-2 contagion has favorable effects.

Another advantage to nebulized budesonide is that the systemic half-life (the time it takes a drug to decrease to half its initial dose) is much shorter than that of fluticasone propionate. It is understood that budesonide has low lipophilicity relative to other corticosteroids and has a more preferential reversible esterification process, thus extending the exposure in the lungs.¹⁰ It is because of this knowledge and the lung's preference for inhaled budesonide; SARS-CoV-2 patients have been empirically treated with nebulized budesonide.

b) Nebulizer and Concerns of SARS-CoV-2 Transmission

Nebulizers are very effective at treating breathing disorders like SARS-CoV-2, but concerns of spreading particles in size up to 5 μm via aerosol cause concern for providers when considering what route to order for respiratory medications. This case study is focused on treatment in the outpatient setting, and therefore, there are different considerations when examining the efficacy of nebulized therapy. Small-Volume Nebulizers (SVNs) offer several advantages for drug delivery: nebulization delivers higher targeted drug concentrations in the airways achieving rapid onset of action, nebulized corticosteroids can be dosed at considerably lower doses than oral or intravenous alternatives, and there is minimal systemic absorption with nebulized corticosteroids hence, fewer adverse effects.^{7 & 14} In 2004, a study evaluated the distribution of airborne SARS-CoV in hospital patients who were being treated with a combination of humidified oxygen therapy and nebulizers. The study observed that zero percent of the offending pathogen in the air and

environmental samples after a PCR amplification was performed in isolated rooms.⁴³ This study does not coincide with the consensus that using a nebulizer might be a transmitting source for SARS. Deslée et al. and the French Language Respiratory Society note that there is no evidence to support avoiding using ICS (nebulized budesonide) during the SARS-CoV-2 pandemic.¹³ The American College of Allergy, Asthma, and Immunology and Dr. Xi of Keck Medicine of USC suggests that nebulized medications should be administered in a room of the patient's house that is isolated from other household members to minimize exposure.^{1 & 46} The goal is to use a nebulizer in a part of the house where there is no recirculated air or in areas with low foot traffic. It is suggested that patients use nebulizers in an area where it is easy to clean the surfaces, such as a private bathroom or an area that needs no cleaning at all—for instance, the garage or outside on the patio if practical. When cleaning a surface after a nebulization treatment, one can use a disinfectant wipe or a water-absorbent paper towel. It has been shown that more than 95% of the residue left on a surface after a nebulization treatment can be removed with regular water-absorbent tissue paper.²² For the remaining percentage left on the surface, it is not guaranteed that infection will follow if the residue reaches another susceptible individual.³⁹ Collaboration between the healthcare provider and patient, along with continued patient education is vital when prescribing nebulized medication in cases with high contagion risk.

There has to be a big push for educating the patient and all parties involved in the patient's care on appropriate device cleaning and aerosol therapy infection control. According to O'Malley³¹, the recommended steps for nebulizer cleaning and disinfecting in the home include:

- 1) Nebulizer parts cleaned with dish detergent and water
- 2) Disinfect (per manufacturer approval and patient approval)
 - a) Cold techniques:
 - i) Soak for five minutes in 70% isopropyl alcohol
 - ii) Soak for 30 minutes in 3% hydrogen peroxide
 - b) Heat techniques:
 - i) Microwave or Boil for five minutes
 - ii) If patient has a dishwasher that can achieve a temperature of $> 158^{\circ}\text{F}$ or 70°C , it is okay to wash in a dishwasher for 3x0 minutes
 - iii) Electric steam sterilizer
- 3) The patient will need to rinse with sterile water if using the cold disinfectant technique
- 4) Air-dry before storing equipment

As always, reinforcing good hand hygiene before and after nebulized therapy is crucial when being proactive in stopping the spread of SARS-CoV-2.

c) *Supportive Therapy*

i. *Clarithromycin*

Biaxin, also known as clarithromycin, is a macrolide that is metabolized in the liver and primarily excreted in the urine. Biaxin inhibits the growth of atypical pathogens and is commonly prescribed to treat bacterial infections and community-acquired pneumonia (affects the lower respiratory tract). The protocol calls for Biaxin to treat atypical pneumonia prophylactically – pneumonia is a known complication of SARS-CoV-2.

When patients with SARS-CoV-2 exchange oxygen (take a breath), they allow the insulting agent to crossover into the bloodstream, thus introducing the alveoli (small air sacs in the lungs) and surrounding tissue to SARS-CoV-2. This exchange, along with inflammation, causes an accumulation of dead cells and fluid, thus leading to pneumonia.

ii. *Aspirin*

Early aspirin use curtails the incidence of cardiovascular complications, mitigates prothrombotic states, reduces the extent of SARS-CoV-2 in severe and critical patients, and will conceivably shorten days in the hospital.^{26 & 35} Prophylactic use of aspirin in SARS-CoV-2 patients has the potential to inhibit viral replication, anti-inflammatory, and anti-lung injuries, as well as anti-platelet aggregation.

iii. *Zinc*

Zinc administration prophylactically restores depleted immune cell function and has the potential to enhance antiviral immunity. Zinc diminishes the RNA-synthesizing activity of SARS-CoV-2.^{21 & 37} Zinc protects the cell membrane, which in return, assists in blocking viral entry into the cell and is an essential component; zinc is a naturally occurring mineral.

d) *False-Negative Covid-19 Test and Empirical Treatment*

In healthcare, tests are used to guide our decision making not be our only decision-making tool. It is imperative to note that the “art of medicine” requires us to ‘treat the patient, not the test.’ New studies show that if SARS-CoV-2 PCR testing takes place within the first five days post-exposure, the patient has a greater than 65 percent chance of receiving a false-negative result, and the average patient that was symptomatic within the first five days of exposure had a false-negative rate of almost 40 percent.^{19, 20 & 42} The consequences of not treating someone who truly has SARS-CoV-2 because they test negative instead of positive can be detrimental to the patient and society as a whole.

Real-Time Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR) test had the best performance eight days after contagion (on average, the patient was symptomatic on day three), but our best still had a false-negative rate of 20 percent – this equates into one in five people with false-negative test results.^{19, 20 & 42} High-risk exposure patients and patients who are immune compromised should be cared for as if they have SARS-CoV-2 until proven otherwise when symptoms are consistent with SARS-CoV-2. In case one and case two had early empirical treatment not been started, the patient would have lost five days and six days of therapy, respectively; thus, diminishing chances of survival. In case two had the patient stopped his treatment on May 3rd instead of May 15th because of a “potential false-negative,” he would have missed 12 days of treatment, potentially exposing him to disease proliferation.

V. CONCLUSIONS

It should be mentioned that telemedicine has been put to the test during these trying times. The success of these two cases and the safety permitted by monitoring remotely and providing real-time consultations by phone could not have been achieved without the integration of telemedicine. This experience has enabled us to witness the advancement of technology in medicine personally.

Inhaled corticosteroids are a powerful tool. The evidence is currently under review in regards to the precision and power that inhaled corticosteroids possess; these studies are being performed by France⁴, Spain⁴⁴, Sweden⁶ the University of Oxford³, and the National Institutes of Health (NIH)²⁷. It is our understanding that there is more than one way to treat SARS-CoV-2, but it is with great respect to the studies that have come before and will come after ours that these case studies and the treatments provided be considered in the arsenal of powerful therapies to be used when treating SARS-CoV-2. A call to arms was sounded on January 20, 2020, when the first case of SARS-CoV-2 was first identified in the United States and in March 2020 a successful empirical treatment plan was put into place (budesonide 0.5mg nebulizer, twice daily, clarithromycin (Biaxin) 500mg tab, twice daily for ten days, Zinc 50mg tab, twice daily, and aspirin 81mg tab, daily).

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