# Rapid recovery of peripheral oxygen saturation in hypoxic COVID-19 patients with ivermectin/doxycycline/zinc multidrug therapy

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**Abstract:** Several combination therapies for the early outpatient treatment of COVID-19 were proposed by independent research groups at the onset of the pandemic during 2020 and 2021. In this observational study, we report on the outcomes of an off-label triple combination therapy, consisting of ivermectin, doxycycline, and zinc, with adjunct vitamin C and D3 supplementation, which was used on high-risk COVID-19 patients. These patients refused an initial recommendation to seek inpatient care, despite a high-risk presentation compounded with one or more comorbidities and/or severe hypoxia. Telemedicine was used to administer personalized treatment to patients at home, who did not have access to supplemental oxygen. Descriptive statistics was used to describe patient characteristics and outcomes. Of 26 consecutive patients, 25 presented with baseline $SpO_2 \leq 90\%$ at room air. All 24 of 26 patients accepting the 10-day treatment survived without hospitalization. Within 24 hours on combination therapy, a rapid response of $SpO_2$ levels at room air was observed with median +6% (IQR 5% to 7%) increase between baseline (day 1) and day 2, with 18 patients stabilized at $SpO_2 > 90\%$ by day 2, and with full recovery of $SpO_2$ levels at room air within 10 days for all 24 patients who completed the 10-day treatment. All other symptoms were resolved within less than 20 days for 23 of 24 patients accepting treatment. All 24 patients fully recovered within 33 days, with no long covid symptoms after recovery. The rapid recovery of $SpO_2$ levels at room air provides temporality evidence in favor of the combination therapy. Furthermore, it has been replicated in two other studies and is further supported with experimental in-vitro studies and mechanistic evidence.

**Keywords:** coronavirus; COVID-19; doxycycline; ivermectin; SARS-CoV-2; zinc

## 1. Introduction

At the onset of Coronavirus Disease 2019 (COVID-19) and throughout years 2020 and 2021 there was minimal guidance from government authorities in the United States about the early outpatient treatment of COVID-19. Given the complexity of the disease, and the need to take decisive action to save lives in response to an emergency crisis (McCullough and Oskoui, 2020), several combination therapy protocols were proposed by independent research groups (Derwand, Scholz, and Zelenko, 2020; McCullough et al., 2020; Procter et al., 2021a, 2021b; Santin, Scheim, McCullough, Yagisawa, and Borody, 2021).

Combination therapies previously demonstrated superior efficacy over monotherapies in treating other viral diseases, such as HIV, tuberculosis, Hepatitis B, C, and Herpes simplex virus (Dolai et al., 2024; Lange, 1995). The combination therapy for COVID-19, reported in this study, was first proposed by Thomas Borody (Santin et al., 2021), who in 1990 published the first clinical trial of a triple-drug combination therapy for peptic ulcers targeting *Helicobacter pylori* (George et al., 1990); that combination therapy became the worldwide standard of care for that condition a decade later, after which the associated discovery of *H. Pylori* was honored with the Nobel Prize (Marshall, 2005; Warren, 2005). Specifically, this study reports on the

application of a 10-day combination therapy of ivermectin, doxycycline, zinc on 26 consecutive patients with severe COVID-19, who were initially referred to inpatient care, but were treated as outpatients via telemedicine at home with off-label treatment because they refused hospitalization. Vitamins D3 and C were also included in this regimen.

The inclusion of ivermectin and zinc in this combination therapy was initially motivated by ivermectin's antiviral action against SARS-CoV-2 (Caly, Druce, Catton, Jans, and Wagstaff, 2020; Heidary and Gharebaghi, 2020; Lehrer and Rheinstein, 2020), its synergistic zinc ionophore antiviral mechanism (Derwand and Scholz, 2020; Rizzo, 2020; te Velthuis et al., 2010), and early clinical evidence (Marik, 2024; Procter et al., 2021a, 2021b; Rajter et al., 2021). However, several anti-inflammatory and/or anticoagulant mechanisms are at play independently for both ivermectin (Babalola and Ajayi, 2023; Zaidi and Dehgani-Mobaraki, 2022) and zinc (Rheingold, Raval, Gordon, and Hardigan, 2023; Skalny et al., 2020; Tabatabaeizadeh, 2022). Favorable characteristics of ivermectin include its excellent safety record, the wide range of well-tolerated dosage (Guzzo et al., 2002; Navarro et al., 2020), and lack of toxicity at higher doses beyond the therapeutic range (Chung, Yang, Wu, Deng, and Tsai, 1999; de Castro Jr., Gregianin, and Burger, 2020), allowing for flexible dose adjustments. Doxycycline was included prophylactically against opportunistic bacterial superinfections, because it acts as another zinc ionophore, and because it may reduce lung damage by calming the cytokine storm in severe COVID-19 (Malek, Granwehr, and Kontoyiannis, 2020; Wong et al., 2017; Yates et al., 2020). Finally, there are both mechanistic (Biancatelli, Berrill, and Marik, 2020; Mercola, Grant, and Wagner, 2020) and epidemiological evidence (Borsche, Glauner, and von Mendel, 2021; Castillo et al., 2020; Kow, Hasan, and Ramachandram, 2023; Qin et al., 2024) supporting the addition of vitamin C and vitamin D3 to the combination therapy protocol.

This study is of unique interest for the following reasons: (1) Almost all patients were hypoxic with $SpO_2 \leq 90\%$ at room air and all had covid susceptible comorbidities. (2) Circumstances necessitated treating the patients at room air, as they did not have access to oxygen concentrators at home. (3) Rapid stabilization of oxygen saturation above 90% was observed in response to the combination therapy for almost all patients accepting treatment within 24 hours, followed with full recovery of oxygen saturation levels within 10 days. Thus, within the framework of the Bradford Hill criteria (Hill, 1965; Howick, Glasziou, and Aronson, 2009), these results provide *temporality* evidence in favor of using the combination therapy to treat COVID-19 patients at home, ideally at the early onset of symptoms.

## 2. Material and Methods

### 2.1. Setting

This study is a retrospective observational case series reviewing and analyzing the medical records of consecutive COVID-19 patients who received individualized outpatient off-label medical care via telemedicine through an outpatient clinic (ProgenaBiome) in Ventura, CA. Most patients in this study were drawn from a cohort initially considered for outpatient clinical trials, administered by ProgenaBiome, during the time period between August 2020 and February 2021, who were excluded from those due to either presenting with baseline room air $SpO_2 \leq 90\%$ or due to not satisfying the trial's inclusion criteria. Other patients in this study were initially enrolled in outpatient clinical trials, but their participation was discontinued by the trial investigator when they were deemed treatment failures, due to $SpO_2$ at room air deteriorating below $SpO_2 \leq 90\%$ or due to being deemed too sick to qualify for continuing participation in a placebo-controlled outpatient clinical trial. Patients from both cohorts were advised to seek inpatient care. The case series in this study is comprised of all consecutive patients from both cohorts who refused hospitalization for various personal reasons, including a preference to remain at home with family during a critical illness. Consequently, these patients received individualized outpatient medical care from their home by ProgenaBiome physicians via telemedicine using off label medications outside the scope of any clinical trial. All patients were informed about the potential risks of treatment, that they would be administered off-label treatment, and provided written informed consent.

Table 1: Case series subjects, COVID-associated symptoms on presentation and other characteristics

| ID | Age | Race | Sex | Symptoms | Temp | $SpO_2$ | | Rx start | | Resolved | | PCR | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | base | +24 h | days | date | days | date | positive | negative |
| 1 | 66 | Caucasian | M | Runny nose, sore throat, dizzy, low energy | 99.3 | 90 | 94 | 38 | 12/14/2020 | 7 | 12/21/2020 | 11/6/2020 | 1/17/2021 |
| 2 | 62 | Caucasian | M | SOB, chest congestion, productive cough, nausea, vomiting | 105 | 77 | 87 | 8 | 12/8/2020 | 10 | 12/18/2020 | 11/30/2020 | 12/18/2020 |
| 3 | 75 | Caucasian | M | Low energy | 101 | 88 | 96 | 11 | 10/26/2020 | 6 | 11/1/2020 | 10/15/2020 | 10/30/2020 |
| 4 | 66 | Caucasian | F | Loss of appetite, cough, chills, SOB | 101 | 97 | 96 | 11 | 10/26/2020 | 3 | 10/29/2020 | 10/15/2020 | 10/30/2020 |
| 5 | 66 | Caucasian | F | Vomiting, weak, body aches, anosmia | 101 | 89 | 95 | 0 | 12/18/2020 | 4 | 12/22/2020 | 12/18/2020 | NA |
| 6 | 43 | Caucasian | F | PE, headache, body ache, cough | 101 | 88 | 94 | 0 | 1/26/2021 | 17 | 2/12/2021 | 1/26/2021 | 2/9/2021 |
| 7 | 62 | Caucasian | M | Productive cough, headache | 102 | 86.5 | 91 | 11 | 11/24/2020 | 14 | 12/8/2020 | 11/13/2020 | 12/8/2020 |
| 8 | 57 | Caucasian | M | Cough, nasal congestion, SOB, body aches | 102 | 88 | 96 | 1 | 10/27/2020 | 14 | 11/10/2020 | 10/26/2020 | 11/15/2020 |
| 9 | 94 | Hispanic | F | Low energy, SOB, confusion, loss of appetite, shaking | 102 | 88 | 94 | 19 | 1/10/2021 | 10 | 1/20/2021 | 12/22/2020 | NA |
| 10 | 66 | Hispanic | M | Cough, SOB, respiratory failure | 100.6 | 72 | 87 | NA | Declined | NA | Death | 12/22/2020 | NA |
| 11 | 63 | Hispanic | F | Cough, SOB | 102 | 90 | 96 | 19 | 1/10/2021 | 10 | 1/20/2021 | 12/22/2020 | NA |
| 12 | 47 | Hispanic | M | SOB | 104 | 84 | 91 | 3 | 12/19/2020 | 6 | 12/25/2020 | 12/16/2020 | NA |
| 13 | 69 | Caucasian | F | Cough, congestion, rash | 102 | 88 | 91 | 4 | 11/17/2020 | 16 | 12/3/2020 | 11/13/2020 | NA |
| 14 | 69 | Caucasian | M | Post-nasal drip, cough, sinus pain | 98 | 88 | 91 | 4 | 11/17/2020 | 16 | 12/3/2020 | 11/13/2020 | NA |
| 15 | 71 | Hispanic | M | Low energy, productive cough, anosmia | 101 | 88 | NA | 4 | 12/17/2020 | 19 | 1/5/2021 | 12/13/2020 | NA |
| 16 | 67 | Hispanic | F | Dry cough, body aches, low energy, anosmia | 100 | 88 | NA | 4 | 12/17/2020 | 19 | 1/5/2021 | 12/13/2020 | NA |
| 17 | 46 | Caucasian | F | Diarrhea, rash, renal pain | 102 | 87 | 94 | 37 | 8/8/2020 | 11 | 8/19/2020 | 7/2/2020 | NA |
| 18 | 86 | Caucasian | M | Cough, fever, low energy | 102 | 88 | 95 | 1 | 1/9/2021 | 10 | 1/19/2021 | 1/8/2021 | 1/19/2021 |
| 19 | 59 | Caucasian | F | Stomach pain, diarrhea, cough, rash | 102 | 90 | 95 | 28 | 9/16/2020 | 9 | 9/25/2020 | 8/19/2020 | NA |
| 20 | 54 | Other | M | Cough, fever, loss of appetite, chills | 101.2 | 88 | NA | 1 | 10/16/2020 | 12 | 10/28/2020 | 10/15/2020 | 10/28/2020 |
| 21 | 92 | Caucasian | M | Low energy | 102 | 85 | 91 | 3 | 2/5/2021 | 6 | 2/11/2021 | 2/2/2021 | 2/15/2021 |
| 22 | 63 | Hispanic | M | Cough, low energy, loss of appetite | 101.3 | 90 | 96 | 0 | 2/2/2021 | 10 | 2/12/2021 | 2/2/2021 | NA |
| 23 | 57 | Hispanic | M | Cough, SOB | 98 | 73 | 90 | 7 | 1/6/2021 | 33 | 2/8/2021 | 12/30/2020 | 1/24/2021 |
| 24 | 46 | Hispanic | F | Chest pain, SOB | 98.6 | 90 | NA | 1 | 2/18/2021 | 6 | 2/24/2021 | 2/17/2021 | NA |
| 25 | 87 | Hispanic | M | Severe SOB, low energy, trouble walking | 101.6 | 90 | 95 | 10 | 2/27/2021 | 6 | 3/5/2021 | 2/17/2021 | NA |
| 26 | 86 | Caucasian | M | SOB | 102 | 88 | NA | NA | Declined | NA | Death | 10/6/2020 | NA |

**NA:** not available; **SOB:** shortness of breath; **PE:** pulmonary embolism; **ID:** identification number; **Age:** patient age in years; **Symptoms:** Patient symptoms upon presentation other than hypoxia; **Temp:** Patient temperature in Fahrenheit upon first presentation; **$SpO_2$:** Room air peripheral oxygen saturation at baseline (base) and after 24 hours (+24 h); **Rx start:** Onset of IDZCT treatment since positive PCR test (days) and date of beginning of IDZCT treatment administration (date); **Resolved:** Days to symptom resolution since initiating treatment (days) and date of symptom resolution (date); **PCR:** Date of first positive PCR test (positive) and date of first negative PCR test (negative).

### 2.2. Patients

Of the 26 patients comprising this case series (shown on Table 1), 21 were excluded from concurrent clinical trials. The remaining 5 patients were previously enrolled in an outpatient placebo-controlled clinical trial; however, they were deemed treatment failures and their participation in that clinical trial was discontinued by the trial investigator (patients #4, #7, #8, #17, and #19).

Inclusion criteria for this patient case series were: (1) informed consent; (2) positive RT-PCR COVID-19 test; (3) age $\geq$ 18 years; (4) agreement to practice two highly effective methods of birth control, if of childbearing potential. All screened patients were consecutive and met the inclusion criteria. Exclusion criteria were: (1) allergies or drug interactions with the combination therapy components; (2) contraindications to ivermectin and/or doxycycline, including seizure risk and pregnancy.

### 2.3. Treatment

At home treatment was initiated as soon as was practical, within 72 hours of patients presenting to ProgenaBiome. Treatment, defined as *"ivermectin/doxycycline/zinc combination therapy"* (IDZCT) consisted of a protocol of 10 days of oral doxycycline (100 mg twice daily), ivermectin (12mg minimal dose on day 1, day 4, and day 8), zinc (25 mg twice daily), with adjunct use of vitamin D3 (1500 IU twice daily) and vitamin C (1500 mg twice daily). IDZCT was administered daily for 10 days only. Because the rate of $SpO_2$ increase at room air was responsive to increased ivermectin dosage, ivermectin dosage was increased in 12 mg increments for some patients on day 1 and day 4, as needed, with the goal of stabilizing patients on room air with $SpO_2 > 90\%$ by the end of day 2 and sustaining an upward trend throughout treatment. Patients were given customized and lab-tested vitamins C, D3, and zinc to ensure quality and consistency. Patients did not have access to oxygen concentrators at home and were treated on room air throughout the 10-day treatment period.

### 2.4. Monitoring

Patients were required to self-record their symptoms for the first 10 days in their daily logs. Vital signs, including electrocardiograms (EKGs), blood pressure, and temperature (in Fahrenheit), were measured at home using provided medical equipment. Additionally, patients self-collected SARS-CoV-2 testing swabs on days 1, 5, 10, and 30, which were then sent to a pathology lab for analysis. Pregnancy tests were conducted as necessary.

FDA-approved oximeters were provided to patients to ensure the accuracy of room air $SpO_2$ measurements. Baseline $SpO_2$ at room air was measured before commencing treatment. Afterwards, room air $SpO_2$ was continuously monitored and reported to the treating physician during at least day 1 and day 2 to guide ivermectin dose adjustments, as needed. Continuous monitoring of $SpO_2$ beyond day 5 was generally unnecessary unless clinically indicated. All patients accepting treatment reported oxygen levels throughout their 10-day treatment period, except for 4 patients that missed data collection of room air $SpO_2$ on day 2.

### 2.5. Outcomes

This study reports on the following outcomes: recovery of room air $SpO_2$ within 24 hours, patient survival, progression to hospitalization, time from presentation to resolution of all symptoms.

### 2.6. Data analysis

Descriptive statistics were used to summarize the case series characteristics and outcomes. All statistical calculations were performed using R version 4.1.3 (R Core Team, 2022).

Table 2: Demographic and clinical characteristics of patients upon presentation

| **Characteristic** | **Intention-to-treat** | | **Per-protocol** | |
|---|---|---|---|---|
| | N | % | N | % |
| **Sex** | | | | |
| Male | 16 | 61.5 | 14 | 58.3 |
| Female | 10 | 38.5 | 10 | 41.7 |
| **Age** | | | | |
| 41 to 50 years | 4 | 15.4 | 4 | 16.7 |
| 51 to 60 years | 4 | 15.4 | 4 | 16.7 |
| 61 to 70 years | 11 | 42.3 | 10 | 41.7 |
| 71 to 80 years | 2 | 7.7 | 2 | 8.3 |
| 81 to 90 years | 3 | 11.5 | 2 | 8.3 |
| 91 years or older | 2 | 7.7 | 2 | 8.3 |
| **Race** | | | | |
| Caucasian | 15 | 57.7 | 14 | 58.3 |
| Hispanic | 10 | 38.5 | 9 | 37.5 |
| Other | 1 | 3.8 | 1 | 4.2 |
| **Baseline temperature** | | | | |
| No fever | 2 | 7.7 | 2 | 8.3 |
| Low-grade fever | 3 | 11.5 | 3 | 12.5 |
| Moderate-grade fever | 19 | 73.1 | 17 | 70.8 |
| High-grade fever | 2 | 7.7 | 2 | 8.3 |
| **Baseline $SpO_2$ on room air** | | | | |
| $90\% < SpO_2 \leq 95\%$ | 0 | 0.0 | 0 | 0.0 |
| $85\% < SpO_2 \leq 90\%$ | 20 | 76.9 | 19 | 79.2 |
| $80\% < SpO_2 \leq 85\%$ | 2 | 7.7 | 2 | 8.3 |
| $75\% < SpO_2 \leq 80\%$ | 1 | 3.8 | 1 | 4.2 |
| $70\% < SpO_2 \leq 75\%$ | 2 | 7.7 | 1 | 4.2 |

*Intention-to-treat:* Reports on all 26 patients; *Per-protocol:* Reports on 24 patients that adhered to 10-day treatment; *Low-grade fever:* 37.0 °C $\leq T <$ 38.0 °C (98.6 °F $\leq T <$ 100.4 °F); *Moderate-grade fever:* 38.0 °C $\leq T <$ 39.0 °C (100.4 °F $\leq T <$ 102.2 °F); *High-grade fever:* 39.0 °C $\leq T <$ 41.0 °C (102.2 °F $\leq T <$ 105.8 °F)

## 3. Results

### 3.1. Patients

Table 1 shows the details of the 26 patients who consented to treatment in the setting stated in the Methods section and comprise this case series. Included are patient demographic details (age, sex, and race), initial presentation (temperature, baseline $SpO_2$ at room air, symptoms other than hypoxia), date of positive PCR test, date of onset of treatment, and outcomes (day 2 $SpO_2$ at room air and date of symptom resolution). Because continuous monitoring of patients' $SpO_2$ levels at room air revealed a sustained upward trend throughout day 1 and day 2, Table 1 shows the baseline room air $SpO_2$ prior to IDZCT treatment on day 1 and the peak value of room air $SpO_2$ by the end of day 2. An attempt was made to gather data on the date of the first negative PCR test. Table 1 also shows the calculated number of days between positive PCR test and beginning of treatment and the number of days between the beginning of treatment and the resolution of symptoms. For 25 out of 26 patients, the initial presentation was severe with baseline room air $SpO_2 \leq 90\%$, all below the 93%

Table 3: Prevalence of comorbidities in patients

| Comorbidity | Intention-to-treat | | Per-protocol | |
|---|---|---|---|---|
| | N | % | N | % |
| **COVID-19 susceptible comorbidities** | | | | |
| Type 1 or type 2 diabetes | 6 | 23.1 | 4 | 16.7 |
| Heart or cardiovascular disease | 7 | 26.9 | 6 | 25 |
| Chronic obstructive pulmonary disease | 3 | 11.5 | 3 | 12.5 |
| Pulmonary embolism | 1 | 3.8 | 1 | 4.2 |
| Kidney disease | 3 | 11.5 | 2 | 8.3 |
| Liver disease (primary biliary cirrhosis) | 1 | 3.8 | 1 | 4.2 |
| Immunocompromised state (HIV/AIDS) | 1 | 3.8 | 1 | 4.2 |
| Overweight (BMI: 25.0–29.9 $kg/m^2$) | 4 | 15.4 | 4 | 16.7 |
| Obese (BMI: 30.0–39.9$kg/m^2$) | 2 | 7.7 | 2 | 8.3 |
| Morbidly obese (BMI: 40 $kg/m^2$ or more) | 4 | 15.4 | 4 | 16.7 |
| Hypertension | 12 | 46.2 | 11 | 45.8 |
| Sleep apnea | 10 | 38.5 | 10 | 41.7 |
| Asthma | 2 | 7.7 | 2 | 8.3 |
| Neurocognitive disorders (dementia or Alzheimer's) | 3 | 11.5 | 3 | 12.5 |
| Psychological disorders (anxiety or depression) | 2 | 7.7 | 2 | 8.3 |
| **Other comorbidities** | | | | |
| Prediabetic | 5 | 19.2 | 5 | 20.8 |
| Hyperlipidemia | 9 | 34.6 | 7 | 29.2 |
| Thyroid | 2 | 7.7 | 2 | 8.3 |
| Rheumatic diseases (gout or Sjorgren's) | 2 | 7.7 | 1 | 4.2 |
| Gastrointestinal disorders (GERD/gastritis) | 3 | 11.5 | 2 | 8.3 |
| Musculoskeletal disorders (osteoarthritis or osteopathy or osteoporosis) | 3 | 11.5 | 3 | 12.5 |
| Other | 2 | 7.7 | 2 | 8.3 |
| **Concurrent COVID-19 susceptible comorbidities in patients** | | | | |
| No concurrent comorbidities | 0 | 0.0 | 0 | 0.0 |
| One comorbidity | 7 | 26.9 | 6 | 25 |
| 2 concurrent comorbidities | 8 | 30.8 | 8 | 33.3 |
| 3 concurrent comorbidities | 6 | 23.1 | 6 | 25 |
| 4 concurrent comorbidities | 5 | 19.2 | 4 | 16.7 |
| **All concurrent comorbidities in patients** | | | | |
| No concurrent comorbidities | 0 | 0.0 | 0 | 0.0 |
| One comorbidity | 4 | 15.4 | 4 | 16.7 |
| 2 concurrent comorbidities | 5 | 19.2 | 5 | 20.8 |
| 3 concurrent comorbidities | 3 | 11.5 | 2 | 8.3 |
| 4 concurrent comorbidities | 8 | 30.8 | 8 | 33.3 |
| 5 concurrent comorbidities | 4 | 15.4 | 4 | 16.7 |
| 6 concurrent comorbidities | 2 | 7.7 | 1 | 4.2 |

*Intention-to-treat:* Reports on all 26 patients; *Per-protocol:* Reports on 24 patients that adhered to 10-day treatment; *Other:* includes glaucoma, prostate disease, and essential tremors; *BMI:* Body mass index; *GERD:* Gastroesophageal reflux disease; *HIV/AIDS:* Human immunodeficiency virus, acquired immunodeficiency syndrome.

threshold for severe COVID-19, proposed by NIH guidelines (National Institutes of Health, 2024). Of the 26 patients, 24 patients adhered to the prescribed 10-day treatment (all except patient #10 and patient #26). Patients #10 and #26 both consented to treatment; however, patient #10 discontinued IDZCT treatment on day 2 and his condition deteriorated leading to his death. Patient #26 died before starting IDZCT treatment. Thus,

for intention-to-treat calculations, data from all 26 patients was utilized, whereas for per-protocol analysis the subgroup of 24 patients that adhered to the 10-day treatment protocol was utilized.

Two patients (patient #10 and patient #23) received on day 1 an initial stat dose of 36 mg ivermectin (instead of 12 mg) due to critically low baseline room air $SpO_2$ or expected clinical need. Three patients were prescribed hydroxychloroquine concurrently with IDZCT treatment (patients #18, #20 for 10 days and patient #10 who discontinued IDZCT after day 1). One patient was on an ongoing hydroxychloroquine prescription for an autoimmune condition prior and during IDZCT treatment (patient #6). Two patients were given remdesivir during hospitalization prior to consultation for IDZCT treatment (patient #17 and #26). One patient was given monoclonal antibodies prior to initiating IDZCT treatment (patient #21). Five patients received zinc, vitamin C, vitamin D, and they may have received either hydroxychloroquine and azithromycin or placebo in a clinical trial; the participation of these patients in that clinical trial was discontinued by the trial investigator prior to commencing IDZCT treatment, as explained in the Methods section (patients #4, #7, #8, #17, #19).

### 3.2. Patient baseline characteristics

Table 2 shows the demographic characteristics of the patients and their baseline temperature and room air $SpO_2$ upon presentation prior to treatment. Males are 61.5% of the entire cohort, thus more prevalent than females. The age distribution peaks at the 61 to 70 years interval with the majority of the patients being older than 50 years (22 patients for intention-to-treat and 20 patients for per-protocol). Some patients were older than 80 years (5 patients for intention-to-treat and 4 patients per-protocol). All patients but one (patient #4) had baseline room air $SpO_2 \leq 90\%$ with a majority at $85\% < SpO_2 \leq 90\%$. Of 26 intention-to-treat patients, 5 patients were at the 70% to 85% range with baseline $SpO_2$ as low as 72% (patient #10), 73% (patient #23), and 77% (patient #2). Fever temperature prior to treatment is also reported on Table 2 and categorized according to the thresholds of 37 °C, 38 °C, and 39 °C for low-grade, moderate-grade, and high-grade fever correspondingly. Most patients presented with moderate-grade fever. Two patients, who presented with no fever (patient #14 and patient #23), were both hypoxic with baseline $SpO_2$ at room air of 88% and 73% correspondingly. All patients were unvaccinated against SARS-CoV-2.

Table 3 shows all known comorbidities of the patients and organizes them into two groups. One group consists of comorbidities associated with COVID-19 vulnerability, according to current CDC guidelines (Center for Disease Control and Prevention, 2025). The other group includes all other reported comorbidities. Table 3 also shows the count of patients with a specific number of concurrent COVID-19 susceptible comorbidities and the count of patients with a specific number of any concurrent comorbidities. All patients had COVID-19 susceptible comorbidities. In the per-protocol subgroup, 18 of 24 patients had 2 to 4 concurrent COVID-19 susceptible comorbidities, and 20 of 24 patients had 2 to 6 concurrent comorbidities of any type.

### 3.3. Rapid recovery of oxygen saturation at room air

The most important result of this study is the rapid response of room air $SpO_2$ levels to treatment, without the use of oxygen concentrators. Table 4 highlights this rapid normalization of room air $SpO_2$ levels within 24 hours, for the 21 patients where day 2 data were available. Specifically, Table 4 displays the change $\Delta$ of room air $SpO_2$ between baseline (day 1), prior to commencing treatment for all patients, and its peak value at the end of day 2, the difference $\Delta_{90}$ between its day 2 peak value and the patient stabilization threshold of 90% $SpO_2$ at room air, and the difference $\Delta_{95}$ between its day 2 peak value and the curative threshold of 95% $SpO_2$ at room air. The median $\Delta$ between day 1 and day 2 was +6% (IQR +5% to +7%), which provides temporality evidence in favor of this combination therapy (further addressed in the Discussion section). Notably, the two outliers with the largest $\Delta$ were patient #10 (with $\Delta = +15\%$) and patient #23 (with $\Delta = +17\%$), both of whom received the increased 36 mg ivermectin stat dose at the start of IDZCT treatment, which is consistent with a biological gradient effect.

For all 20 of 21 patients, where data were available, $SpO_2$ at room air showed substantial increase by the

Table 4: Baseline $SpO_2$ vs $SpO_2$ on day 2 at room air for all intention-to-treat patients

| ID | $SpO_2$ | | | | | ID | $SpO_2$ | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **day 1** | **day 2** | **Δ** | **$\Delta_{90}$** | **$\Delta_{95}$** | | **day 1** | **day 2** | **Δ** | **$\Delta_{90}$** | **$\Delta_{95}$** |
| 1 | 90 | 94 | +4 | +4 | -1 | 14 | 88 | 91 | +3 | +1 | -4 |
| 2 | 77 | 87 | +10 | -3 | -8 | 15 | 88 | NA | NA | NA | NA |
| 3 | 88 | 96 | +8 | +6 | +1 | 16 | 88 | NA | NA | NA | NA |
| 4 | 97 | 96 | -1 | +6 | +1 | 17 | 87 | 94 | +7 | +4 | -1 |
| 5 | 89 | 95 | +6 | +5 | 0 | 18 | 88 | 95 | +7 | +5 | 0 |
| 6 | 88 | 94 | +6 | +4 | -1 | 19 | 90 | 95 | +5 | +5 | 0 |
| 7 | 86.5 | 91 | +4.5 | +1 | -4 | 20 | 88 | NA | NA | NA | NA |
| 8 | 88 | 96 | +8 | +6 | +1 | 21 | 85 | 91 | +6 | +1 | -4 |
| 9 | 88 | 94 | +6 | +4 | -1 | 22 | 90 | 96 | +6 | +6 | +1 |
| 10 | 72 | 87 | +15 | -3 | -8 | 23 | 73 | 90 | +17 | 0 | -5 |
| 11 | 90 | 96 | +6 | +6 | +1 | 24 | 90 | NA | NA | NA | NA |
| 12 | 84 | 91 | +7 | +1 | -4 | 25 | 90 | 95 | +5 | +5 | 0 |
| 13 | 88 | 91 | +3 | +1 | -4 | 26 | 88 | NA | NA | NA | NA |

**day 1:** Baseline $SpO_2$ on room air prior to commencing IDZCT treatment.
**day 2:** Peak $SpO_2$ on room air by the end of day 2.
**Δ** = Change of $SpO_2$ on room air from day 1 to day 2.
**$\Delta_{90}$** = Difference between peak $SpO_2$ on day 2 and the 90% $SpO_2$ stabilization threshold.
**$\Delta_{95}$** = Difference between peak $SpO_2$ on day 2 and the 95% $SpO_2$ curative threshold.
**NA:** Not available; **ID:** identification number.

end of day 2, without the use of oxygen concentrators, and 18 of these 21 patients were successfully stabilized with $SpO_2 > 90\%$ at room air (except for patients #2, #10, and #23, for whom $\Delta \geq +10\%$). For patient #4, who was deemed high-risk because of shortness of breath upon presentation, room air $SpO_2$ decreased from 97% to 96% over the initial 24-hour period, however both values were within the curative range and full resolution of all symptoms occurred within 72 hours from commencement of IDZCT treatment. For all other patients, the absolute minimum $\Delta$ is $\Delta \geq +3\%$, with $\Delta = +3\%$ observed for patients #13 and #14, both successfully stabilized at $SpO_2 > 90\%$ by the end of day 2. Peak $SpO_2$ data for day 2 is missing for 4 per-protocol patients, each of whom had baseline room air $SpO_2 \geq 88\%$, close to the stabilization threshold.

An ivermectin dosing schedule spread across day 1, day 4, and day 8 was sufficient for sustaining a trend of improvement in room air $SpO_2$ levels throughout treatment. By day 10, $SpO_2$ levels at room air were successfully restored above 95% for all 24 patients in the per-protocol subgroup and were maintained without further treatment.

### 3.4. Mortality and hospitalization outcomes

The per-protocol outcome was 24 patients adhering to treatment for the full 10-day protocol with 0 deaths and 0 hospitalizations. The intention-to-treat outcome was 2 deaths (patients #10 and #26) out of 26 patients.

### 3.5. Full symptom resolution

Table 5 shows the distribution of the number of days between positive PCR test diagnosis and the onset of treatment and the number of days between the onset of treatment and resolution of all symptoms for the per-protocol subgroup of patients that completed the 10-day treatment. Approximately half of the patients initiated treatment within 5 days (13 of 24 patients), although there was an additional unknown delay between symptomatic infection and diagnosis with a PCR test that may have varied from patient to patient. Of 24

Table 5: Number of days for onset of treatment and symptom resolution for per-protocol subgroup

| **Duration** | **Treatment onset** | | **Symptom resolution** | |
|---|---|---|---|---|
| | N | % | N | % |
| 0 days | 3 | 12.5 | 0 | 0.0 |
| 1 to 5 days | 10 | 41.7 | 2 | 8.3 |
| 6 to 10 days | 3 | 12.5 | 12 | 50 |
| 11 to 20 days | 5 | 20.8 | 9 | 37.5 |
| 21 to 30 days | 1 | 4.2 | 0 | 0.0 |
| 31 to 40 days | 2 | 8.3 | 1 | 4.2 |

*Treatment onset:* Number of days from date of positive PCR test to date of start of IDZCT protocol
*Symptom resolution:* Number of days from date of start of IDZCT protocol to date of symptom resolution

patients, 22 patients delayed treatment by no more than 20 days. However, 2 patients waited as long as 38 days (patient #1) and 37 days (patient #17).

$SpO_2$ levels at room air were fully resolved and sustained for all 24 per-protocol patients within 10 days. Table 5 shows that for 14 of these 24 patients all other symptoms were also fully resolved within 10 days, and for 23 of these 24 patients all other symptoms were fully resolved within 20 days. For patient #23, who presented with baseline $SpO_2$ of 73% at room air and no fever, symptoms resolved within 33 days. No patients presented with long covid symptoms after recovery.

### 3.6. Safety

An adverse drug event (dizziness) was reported by patient #1, who nonetheless successfully completed the IDZCT 10-day treatment. No adverse drug events were observed for the other patients during the course of their treatment.

## 4. Discussion

This study has contributed the following findings: (a) At the onset of IDZCT treatment, rapid increase of $SpO_2$ at room air was observed in the 21 hypoxic patients with available $SpO_2$ data on room air for day 2, of which 18 out of 21 were successfully stabilized at $SpO_2 > 90\%$ within 24 hours; (b) hospitalization was successfully prevented for all 24 patients accepting IDZCT treatment for a period of 10 days with complete and sustained recovery of oxygen levels at room air by day 10; (c) Of these 24 patients, complete resolution of all other symptoms was achieved within 20 days from the onset of treatment for 23 out of 24 patients; (d) All 24 patients accepting treatment survived. These results are noteworthy because the successful treatment of these patients was achieved via telemedicine and the patients were treated at home at room air without access to oxygen concentrators. They are also noteworthy because all but one of the treated patients were hypoxic, with baseline $SpO_2 \leq 90\%$, for whom usual care would involve admission to the hospital; nevertheless, the patients accepting treatment were successfully treated as outpatients. Because all patients were unvaccinated, these findings were not confounded by prior vaccination. Likewise, because all patients were treated before the emergence of the omicron variant, natural immunity used to confer substantial protection against reinfections at that time (Murchu et al., 2022), therefore it is improbable that these patients had any prior natural immunity against SARS-CoV-2 that could have contributed to their recovery.

Noting that the presence of red blood cell microclots in the lungs and throughout the vascular system is the best explanation for oxygen desaturation in severe COVID-19 patients (McGonagle, Bridgewood, and

Meaney, 2021), the rapid recovery of oxygen saturation levels within 24 hours, observed in this study, is consistent with direct evidence from an *in-vitro* experiment showing that the addition of spike protein from SARS-CoV-2 to human blood causes red blood cell clumping, which is rapidly reversed with the addition of ivermectin (Boschi et al., 2022). Further mechanistic and parallel evidence has elucidated this observed rapid reversal of red blood cell clumping in response to ivermectin exposure and explains why other coronaviruses, like the common cold, do not cause a similar clumping effect (Aminpour et al., 2022; Scheim, 2022; Scheim et al., 2024; Scheim, Vottero, Santin, and Hirsh, 2023). In addition, rapid recovery of oxygen saturation levels was also observed in another study of 34 hypoxic patients, treated in Zimbabwe by Stone and colleagues at room air with a similar 10-day protocol from August 2020 through May 2021 (Stone et al., 2022). The 10-day protocol by Stone et al. (2022) used a multidrug combination that included ivermectin, doxycycline zinc, vitamin C, and vitamin D3 in which ivermectin dosage was adapted to patient severity (Gkioulekas, McCullough, and Aldous, 2025a, Table 1). Babalola and colleagues replicated these findings in a Nigerian cohort of 61 patients (April-June 2021) (Babalola et al., 2021), observing a sustained recovery of oxygen saturation levels, although the rate of recovery was slower compared to this study and the findings of Stone et al. (2022), requiring more than 5 days for a similar $SpO_2$ normalization effect (Stone et al., 2022, Figure 6). The protocol by Babalola et al. (2021) was limited to 5 days, used a fixed weight-adjusted dosage for ivermectin, included zinc and vitamin C, but did not include doxycycline or vitamin D3. For cases of hypoxic COVID-19 patients treated under usual care hospital protocols that did not use ivermectin, there was a consistent trend of either decreasing or steady oxygen saturation levels, depending on the extent of pulmonary damage, which did not fully resolve within a 10-day period (Annunziata et al., 2021; Aoki et al., 2021; Ding, Xu, Zhou, and Long, 2020; Metwally et al., 2021; Osman, Farouk, Osman, and Abdrabou, 2020; Quispe-Cholan et al., 2020; Thairu et al., 2022; Wang et al., 2020). This contrast between usual hospital care and case series of patients treated with ivermectin, doxycycline, zinc combination therapies has already been discussed at length in previous work (Scheim et al., 2024) and provides strong temporality evidence in favor of IDZCT combination therapy, both because of the short time interval and because of the strong magnitude of the effect compared with hospital care. Furthermore, an extensive epidemiological analysis based on the Bradford Hill criteria, combining the available direct evidence from all three case series, within the context of all other available mechanistic and parallel evidence, has been presented in Gkioulekas et al. (2025a) and Gkioulekas, McCullough, and Aldous (2025b) .

Despite the available evidence, some regulatory authorities have opposed the use of ivermectin by practicing doctors for treating COVID-19 patients (Aldous, Gkioulekas, and Oldfield, 2024), which is reminiscent of similar reluctance to adopt the combination therapy for the treatment peptic ulcers, which was proposed and proven in a 1990 clinical trial by Thomas Borody (George et al., 1990) – also the senior author of this paper – but not widely adopted as a standard of care until 10 years later, after the expiration of the patents for the palliative medications Tagamet and Zantac (Berndt, Kyle, and Ling, 2003). For example, the World Health Organization (WHO) has discouraged the use of ivermectin in the treatment of COVID-19 (World Health Organization, 2023), even though WHO's own meta-analysis of 5 randomized controlled trials (RCTs) found statistically significant positive mortality rate reduction (RR 0.36; 95% CI 0.17–0.75) associated with the use of ivermectin in the treatment of COVID-19 patients (World Health Organization, 2023, version 14, page 146), which the WHO sidelined by conveniently excluding 2 of the 5 RCTs on the grounds of some perceived risk of bias attributed to inadequate blinding. A careful reading of the excluded studies shows no statistically significant imbalances in the patient baseline characteristics in the first study (Ravikirti et al., 2021, Table 1). In the second study, which exhibited the strongest mortality rate reduction signal in favor of ivermectin, patients with severe initial presentation were more prevalent, by a factor of 1.7, in the combined ivermectin arms of the trial than the non-ivermectin arms of the trial (Niaee et al., 2021, Table 1); however, this only biases the study towards underestimating the observed mortality rate reduction effect size attributed to ivermectin.

Several other meta-analyses of RCTs have confirmed the association of ivermectin with statistically significant mortality rate reduction, especially prior to the emergence of the less virulent omicron variants (Bryant et al., 2021; Kory et al., 2021; Santin et al., 2021). Nevertheless, because of the heterogeneity of

treatment protocols (monotherapy vs combination therapy, variability in dosage and duration of treatment), baseline characteristics of patients (low-risk vs high-risk patients), setting (outpatients vs inpatients), and viral variants in the underlying RCTs, the available ivermectin meta-analyses should be assessed with caution and recent calls highlighting the importance of accounting for the totality of the available evidence (Aldous, Dancis, Dancis, and Oldfield, 2024) deserve further consideration. For ivermectin-based treatments of COVID-19, the totality of the available evidence, showing both ivermectin effectiveness or lack thereof for the treatment of COVID-19, was initially reviewed by Santin et al. (2021) and further reviewed more extensively by Yagisawa, Foster, Hanaki, and Omura (2021, 2024). Further critical reviews of the wide range of evidence, including the most recent RCTs and concerns about their external validity, were presented by Aldous, Gkioulekas, and Oldfield (2024) and Gkioulekas et al. (2025b). These critical reviews reconciled the ongoing controversies, by presenting the coherent picture that emerges when combining what was learned from the details of the available studies, both positive and negative, and by highlighting the importance of: (a) adjusting ivermectin dosage and duration of treatment to severity of patient presentationt; (b) using ivermectin combination therapy protocols instead of ivermectin monotherapies; (c) focusing on high-risk instead of low-risk patient cohorts.

It is our interpretation that the aforementioned body of work in conjunction with the findings of this study provide some support for the following important inferences: (a) severe acute COVID-19 illness is amenable to early ambulatory therapeutics in lieu of hospitalization; (b) early ivermectin-based multidrug protocols were safe and effective; (c) the permissive hypoxemia strategy was safe provided the work of breathing and mentation remained acceptable under close supervision; (d) the majority of COVID-19 hospitalizations could have been avoided with early ambulatory treatment protocols supplemented with home oxygen therapy. Finally, since the late use of this combination 10-day therapy is able to reverse low oxygen saturation in hypoxic COVID-19 patients, early use within the first few days of symptomatic infection, may be able to prevent oxygen desaturation from developing in high-risk patients, resulting in overall clinical benefit.

Limitations of this study include the small sample size of the patient case series, missing data for $SpO_2$ on day 2 for 4 patients, and the lack of systematic recording of $SpO_2$ levels over the full 10-day period. Furthermore, due to the limited sample size, analysis in this study was limited only to descriptive statistics. While this study demonstrated the rapid recovery of $SpO_2$ levels at room air in response to treatment, our analysis did not evaluate the impact on mortality rates or assess the statistical significance of any potential reduction. The ivermectin dosing schedule was specific to COVID-19 variants during the treatment period, and should be empirically adjusted depending on patient response, to successfully treat more lethal variants, should they reemerge again, or more severe cases of high-risk COVID-19 reinfections.

## 5. Conclusion

This study demonstrated rapid recovery of hypoxic COVID-19 patients in response to ivermectin, doxycycline, zinc combination therapy, with adjunct vitamin C and D3 supplementation, within 24 hours and without reliance on oxygen concentrators. A treatment period of 10 days was sufficient for the complete and sustained recovery in all patients accepting the 10-day treatment, who avoided hospitalization and survived. With room air $SpO_2$ being an important indicator of the overall status of COVID-19 patients and closely correlated with mortality risk, these findings provided evidence in favor of the IDZCT combination therapy. They also demonstrated that the benefits of this combination therapy include the alleviation of suffering for hypoxic COVID-19 patients by restoring oxygen saturation levels. Consequently, we believe our findings support the ethical use of this combination therapy in accordance with article 37 of the 2013 Helsinki declaration, which allows the use of an unproven intervention with informed consent *"if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering"* (World Medical Association, 2013). Specifically, the continued use of IDZCT combination therapy, in conjunction with supplemental oxygen in the hospital setting, is a straightforward choice for those hospitalized COVID-19 patients with oxygen requirements. Future research studies of ambulatory combination therapy should be targeted to acute patients at continued high risk for hospitalization and death.

**Acknowledgement**

The authors sincerely appreciate extensive discussions with David Scheim during the writing of this paper.

**Funding Information**

This study was funded by ProgenaBiome, LLC.

**Author's contributions**

**Sabine Hazan:** Conceptualization, Investigation, Resources, Data Curation, Writing Review & Editing, Supervision, Project Administration, Funding Acquisition. **Adriana Vidal:** Data Curation, Writing Review & Editing, Project Administration. **Eleftherios Gkioulekas:** Methodology, Software, Formal Analysis, Data Curation, Writing–Original Draft, Writing Review & Editing, Visualization. **Anoja W. Gunaratne:** Conceptualization, Writing Review & Editing. **Sibasish Dolai:** Conceptualization, Writing Review & Editing. **Robert L. Clancy:** Conceptualization, Supervision, Writing Review & Editing. **Peter A. McCullough:** Conceptualization, Writing–Original Draft, Writing Review & Editing. **Thomas J. Borody:** Conceptualization, Supervision, Writing Review & Editing.

**Ethics**

This study was approved by the Institutional Review Board of Ethical & Independent Review Services (https://www.eandireview.com/) with IRB #21006. This study complied with the 2013 Declaration of Helsinki (World Medical Association, 2013) and applicable regulatory standards.

**Competing interests**

Peter McCullough is the Founder and President of the McCullough Foundation. He is also the Chief Scientific Officer of the Wellness Company, who had no role in conducting this study. Sabine Hazan is the Chief Executive Officer of ProgenaBiome, LLC and Ventura Clinical Trials and she is the Founder of the Microbiome Research Foundation. She owns patents for the treatment and prophylaxis of COVID-19 and patents in the microbiome. She has a pecuniary interest in Topelia Aust Ltd in Australia and Topelia Therapeutics, Inc. in the USA where the development of treatment and prophylaxis options for COVID-19 are being pursued, including the combination therapy reported in this study. Thomas Borody has pecuniary interest in Topelia Aust Ltd in Australia and Topelia Therapeutics, Inc. in the USA. He has filed patents in the field of COVID-19 research and donated them to Topelia Aust Ltd in Australia for no compensation.

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