



## Case Report

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# Complementary use of ozone therapy in Covid-19 with ulcerative lesions. Case report

## Uso complementario de la ozonoterapia en Covid-19 con lesiones ulcerosas. Reporte de un caso

**R. Farfaglia**

Manerbio Hospital Manerbio BS, Italy

**B. Antonini**

Manerbio Hospital Manerbio BS, Italy

**A. Bussi**

Manerbio Hospital Manerbio BS, Italy

**R. Pelizzari**

Manerbio Hospital Manerbio BS, Italy

**G. Martínez-Sánchez**

Consultor científico independiente, Ph.D., Pharm. D., Ancona, Italy

**A. Izzo**

Intermed onlus, Brescia BS, Italy

**A. Bertolotti**

Intermed onlus, Brescia BS, Italy

**Filles St. Camille**

Social Health Center Bienheureuse Luigi Tezza Sanguera, Togo

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### Keywords

ozone therapy;  
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### Abstract

*SARS-CoV-2 is responsible for the outbreak of severe respiratory illness (COVID-19). Patients affected by COVID-19 during hospitalization may develop bedsores, in addition patients with previous ulcerative lesion have less chance of a successful evolution. These case report shown the evolution of two patients affected simultaneously by SARS-CoV-2 and lesions of various aetiology. One patient develop bedsore of about 14 cm in diameter in the sacral region during the hospitalization and other was affected by the Buruli ulcer. Both patients were treated locally using ozone bagging technique and local ozonized oil. The clinical evolution of the lesions was favourable after the first three applications, granulation tissue was evident during the first week and a total recovered was reached after 4-6 months. Ozone therapy may serve as complementary therapy in those conditions. The potential role of ozone therapy in this syndrome merits further research...*

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## Palabras clave

ozonoterapia;  
COVID-19; Úlcera de  
Buruli; aceites  
ozonizados.

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## Resumen

El SARS-CoV-2 es responsable del brote de la enfermedad respiratoria grave (COVID-19). Los pa-cientes afectados por COVID-19 durante la hospitalización pueden desarrollar úlceras por presión, además los pacientes con lesiones ulcerativa previas tienen menos posibilidades de una evolución exi-tosa. Este reporte de este caso muestra la evolución de dos pacientes afectados simultáneamente por SARS-CoV-2 y lesiones de diversa etiología. Un paciente desarrolló una úlcera por decúbito de unos 14 cm de diámetro en la región sacra durante la hospitalización y otro se vio afectado por la úlcera de Buruli. Ambos pacientes fueron tratados localmente utilizando la técnica de ensacado de ozono y un-güento a base de aceites ozonizados. La evolución clínica de las lesiones fue favorable después de las primeras tres aplicaciones, se evidenció tejido de granulación durante la primera semana y se alcanzó una recuperación total a los 4-6 meses. La ozonoterapia puede servir como terapia complementaria en esas condiciones. El papel potencial de la ozonoterapia en este síndrome merece más investigación.

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## 1. Introduction

The infection caused by the novel coronavirus, named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) that cause the Coronavirus disease 2019 (COVID-19), has become a pandemic condition. According to the current data of World Health Organization (WHO), the number of infected and dead cases has increased to 80 million and 1,7 million, respectively (Dec 2020).<sup>1</sup> The high virulence and unpredictability of the evolution of the infection caused by this pathogen put the Italian health system in crisis, with particular difficulties in the Lombardy region where from March to June 2020, there were the highest number of deaths. There is now grave concern regarding the Italian national health system's capacity to effectively respond to the needs of patients who are infected and require intensive care for SARS-CoV-2 pneumonia. The percentage of patients in intensive care reported daily in Italy between March 1 and March 11, 2020, has consistently been between 9% and 11% of patients who are actively infected. The number of patients infected since Feb 21 in Italy closely follows an exponential trend.<sup>2</sup>

All over the world the pandemic has caused a very high number of deaths. Sub-Saharan Africa has apparently been hit less hard than Europe. However, the cases in some of the poorest states in West Africa, have put a strain on the district health services that are without ventilators, consumables, personal protective equipment and drugs. As of December 26, 2020, there were about 2 623 086 confirmed cases on the African continent, compared with the 2,028,354 number of cases in Italy and more than 18 768 116 in the United States.<sup>3,4</sup> But rather than inviting relief or complacency, the numbers from Africa are like the early drops of rain before the clouds open up. Despite the slow arrival of Covid-19, a storm is building, and the 1.2 billion people living in Africa are at tremendous risk.<sup>5</sup> In this emergency context, in Togo (3 546 cases of Covid-19 by December 26, 2020),<sup>3</sup> West Africa, considering of the absence of hospitals equipped with an intensive care unit, is one of the states in risk.

Currently, there is no approved therapy for COVID-19. The WHO therefore endorses supportive care only. The antiviral therapies remdesivir, lopinavir/ritonavir and umifenovir, if considered, should be initiated before the peak of viral replication for an optimal outcome. Ribavirin may be beneficial as an add-on therapy but is ineffective as monotherapy. Corticosteroid use should be limited to specific co-morbidities. Intravenous immunoglobulin (IVIg) is not recommended owing to lack of data in COVID-19. The efficacy of interferon is unclear owing to conflicting outcomes in coronavirus studies. Chloroquine and hydroxychloroquine have shown *in vitro* inhibition of SARS-CoV-2, but studies on their clinical efficacy and whether the benefits outweigh the risk of dysrhythmias remain inconclusive. For patients who develop cytokine release syndrome, interleukin-6 inhibitors may be beneficial.<sup>6</sup>

Ozone, a low-cost medical device with rare side effects<sup>7</sup> can be used as a complementary therapy in the treatment of AIDS, Ebola and SARS1.<sup>8</sup> There are solid arguments and molecular and preclinical data to support the use of ozone therapy in Covid-19. The main proposal mechanisms are: Nrf2/NF-κB modulation, cytokines release modulation, improve hypoxia, improvement in blood flow, release NO, modulating the oxidative stress, cytoprotective and regulator of the intestinal microbiota.<sup>9-11</sup> There are, different clinical trials in course and a group already published, who demonstrated the efficacy of ozone therapy in Covid-19 patients.<sup>12-15</sup>

The study highlights the efficacy of ozone therapy in two patients affected simultaneously by SARS-CoV-2 and lesions of various aetiology. This research was carried out by the medical staff of Intermed onlus in Italy in collaboration with the intensive care, surgery and medicine units of the hospital of Manerbio, ASST of Garda, Lombardy, Italy and in Togo at the health center of the Sisters of San Camillo in Sanguera. The therapeutic approach with drugs recommended by WHO, combined as complementary therapy with systemic and local use of ozone has proved very useful in the treatment of bedsores due to prolonged bed rest during illness, or for the treatment of pre-existing lesions before the Covid-19, aggravated during the course of the disease itself. The second objective was to establish the effectiveness of ozone through local applications to the lesion area and its effectiveness in normalize the systemic effect originated by the virus, for that purpose ozone was administered by rectal insufflation.

## 2. Materials and Methods

The use of ozone as a complementary therapy was carried out following the guidelines and good practices of the Italian Federation of oxygen-ozone therapy (a scientific society recognized by the Ministry of Health pursuant to Law 8 March 2017, No. 24),<sup>16</sup> the Declaration of Helsinki,<sup>17</sup> the Good Practices of the International Conference of Harmonization.<sup>18</sup>

### 2.1 Site

The complementary use of ozone was carried out from April 2020 until November 2020, with the aim of treating patients suffering from Covid 19 and, at the same time, suffering from lesions. One patient was enrolled at the hospital of Manerbio, ASST of Garda, Lombardy, Italy and other patient was treated in Togo at the health centre of the Sisters of San Camillo in Sanguera.

### 2.2 Participants

In this study we considered two coronavirus patients. Both patients had respiratory symptoms with dyspnoea, cough and fever. One patient, who will be define as "patient A", 65 years old, from Lombardy (Italy), had severe respiratory symptoms, cough, dyspnoea, moderate fever and oxygen saturation of 70% at baseline. The patient was treated with antibiotics, antiviral, heparin, steroidal anti-inflammatory, antipyretic and oxygen therapy. The severity of the respiratory situation meant that the patient was intubated in the intensive care unit for a month and then was transferred to the medical ward where he remained hospitalized for another month. During the hospitalization phase the patient developed a bedsore of about 14 cm in diameter in the sacral region.

The second patient, "patient B", was a 35-year-old Togolese, presented respiratory symptoms of medium severity, poor dyspnoea and cough, moderate fever, oxygen saturation of 88 % at baseline. The patient presented a supramalleolar ulceration on the left leg of 8 cm in diameter. This lesion, present for over 6 months, had previously been treated with rifampicin 10 mg/kg orally and streptomycin 15 mg/kg i.m. for 8 weeks, according to the WHO guidelines for the treatment of Buruli ulcers.<sup>19</sup>

### 2.3 Investigations

Both patients A and B had a nasopharyngeal swab which tested positive for coronavirus. Both patients underwent chest x-rays which revealed the presence of bilateral pneumonia with "ground glass" effect.

Patient B: was submitted histological analysis, following the guidelines of the WHO,<sup>19</sup> of tissue taken from the lesion in the supramalleolar region. Ziehl Neelsen staining was carried out and tested positive for *Mycobacterium*. The molecular PCR analysis performed subsequently (polymerase chain reaction for *Mycobacterium*)<sup>20,21</sup> confirmed the presence of *Mycobacterium ulcerans*, the causative agent of Buruli's disease, a tropical ulcer due to the inoculation by an insect (vector) that lives in lagoon and marshy areas of some parts of Togo, from where the patient came.

### 2.4 Procedures

Treatment of respiratory syndrome of patient A: According to the WHO protocol both patients A and B received the standard care: Hydroxychloroquine 2 x 200 mg per day for 10 days plus azithromycin 500 for 6 days and Sodium Heparin 2 x 4000 U per day and paracetamol 1000 mg in case of fever. Due to the worsening of the symptoms, patient A was intubated and subjected to oxygen therapy.

Treatment of respiratory syndrome of patient B: Due to the worsening of the respiratory symptoms from Covid 19 and the inability to access an intensive care unit in a particularly poor area with no health care facilities, patient B, in the health center of the Daughters of St. Camillus in Togo, was subjected to the following protocol proposed by ISCO3.<sup>7</sup>

- 1) Disinfection of the upper respiratory tract with ozonated water (500 mL of bi-distilled water was bubble with ozone 25 µg/mL for 15 min immediately after the application).
- 2) 1g vitamin C i.m. three times a week
- 3) Endorectal insufflation of oxygen-ozone mixture according to Tab. 1.

**Table 1.** Schedule of treatment following endorectal ozone insufflation.

Day of treatment	Concentration (µg/mL)	Volume (mL)	Dose (mg)
1-2	20	100	2
3-4	25	150	3.75
5-6	30	150	4.5
7-8	35	200	7
8-14	40	200	8

The endorectal insufflation was performed using a siliconized catheter inserted in the rectal ampulla, after emptying the intestine, with slow insufflation to favour the absorption of the oxygen-ozone mixture.<sup>7,8,22</sup>

Treatment of lesions: The bedsore, due to prolonged bed rest, in the sacral region of patient A and the Buruli ulcer of patient B in the supra-malleolar region, were both treated with applications of local oxygen-ozone mixture and an ozonized oil-based cream as follow: Local applications of oxygen-ozone mixture with the pouch technique, placing a plastic bag around the wound and blowing in an oxygen-ozone mixture at a concentration of 30 µg/mL. The bag, was closed to prevent gas escaping. The bagging was applied three times a week for 15 min, for a month. Then a weekly ozone session and daily wound dressings with ozonated water and ozonized cream. At the end of each ozone therapy session, both patient A and patient B were medicated with 15% ozone cream (Ozonia 15, Innovares, Italy).

### 3. Results and discussion

Patient A, during the first month in the intensive care, was treated with daily session of local ozone therapy. After one month in intensive care the patient was transferred to the medical ward.

The daily treatment with ozone continued even in the medical ward for a month until discharge of the patient. After discharge from the hospital, our medical staff performed three treatments per week for five months at home. Bedsore improved progressively after the applications of the



oxygen-ozone blend with the bagging technique. Patient A showed improvement of the bedsore with appearance of granulation tissue just after three applications (Fig. 1).



**Figure 1.** Evolution of the patient A. A, Patient bedsore at baseline; B, lesion after three applications (on week); C, illustrative photo of the way of application of ozone; D, granulation tissue after 2 months of treatment; E, lesion appearance after 6 months of treatment.



Patient B's respiratory symptoms had already improved after the first week of endorectal insufflation. After three applications of ozone therapy with the bagging technique, was observed a complete cleansing of the sore on the leg and, on histological examination followed by PCR, was negative for *Mycobacterium ulcerans*. The Buruli ulcer was treated for four months with three applications per week. After each application of ozone, the patient was medicated with ozonized oil cream, until recovery of the wound.



**Figure 2.** Evolution of the patient B. A, evolution of the Buruli ulcer after 3 application of ozone; B, illustrative photo of the bagging technique; C, Buruli lesion after 4 months of treatment.

Wound-associated infections during COVID-19 are a significant and rising health concern throughout the world owing to aging population, prevalence of diabetes, and obesity. The most important risk factors include immobility and reduced perfusion which are also the features of critical ill COVID-19 patients.<sup>23</sup> In addition, the rapid increase of life-threatening antibiotic resistant infections has resulted in challenging wound complications with limited choices of effective therapeutics. Recently, topical ozone therapy has shown to be a promising alternative approach for treatment of non-healing and infected wounds by providing strong antibacterial properties while stimulating the local tissue repair and regeneration.<sup>24-26</sup>

Medical ozone has potential anti-bacterial and proliferative activities. Increasing local blood supply, can increase the availability of oxygen and nutrients and assists repairing chronic wounds. Anti-bacterial properties of medical ozone along with its ability to activate the immune system can further aid wound healing.<sup>24,26-31</sup>

## Conclusion

The purpose of the collaboration between Intermed onlus, Hospital of Manerbio-Brescia, Italy and the Health Center of the Sisters of San Camillo di Sanguera, Togo, is to optimize, through the support of oxygen-ozone therapy, the treatments for patients affected by Covid-19 and from various kinds of lesions (bedsores, Buruli, infections etc.). The synergy between drug therapy and ozone therapy was decisive for the success of the treatment in the two case reports analysed by our staff.<sup>32-34</sup>

The bactericidal and static virus power of ozone, administered both systemically and locally, also led to the reduction of symptoms from Covid-19 and the negativization of both lesions in culture tests for patient A, while for patient B suffering from Buruli ulcer, histological and molecular control tests with PCR<sup>21</sup> were carried out. There was also progressive scarring without problems of over infections.

Another aim of the collaboration between Manerbio Hospital, Intermed onlus and the St Camille Health Center, Sanguera Togo, is to improve the use of Oxygen-Ozone therapy and provide assistance to patients affected by Covid-19 and Buruli ulcer, using an affordable (and cheap) treatment.

The holistic approach, including health education, could improve both the physical and psychological condition of patients who, in addition to Covid-19 infection, are often victims of terrible complications such as skin ulcers of various etiologist. Ozone therapy, including the treatment with gas or ozonized oil, serve as complementary therapy in these conditions. Clinical trials are need in this direction.

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