Journal of IMAB
ISSN: 1312-773X
https://www.journal-imab-bg.org

https://doi.org/10.5272/jimab.2022281.4284
Journal of IMAB - *Annual Proceeding (Scientific Papers)*. 2022 Jan-Mar;28(1)

Review article

MODERN APPLICATIONS OF OZONE FOR COVID-19 DISINFECTION AND TREATMENT

Galina Yaneva[1], Tsonka Dimitrova[1], Dobri Ivanov[1], Diana Ivanova[2], Gergana Ingilizova[3], Sergei Slavov[4,5]
1) Department of Biology, Faculty of Pharmacy, Medical University of Varna, Bulgaria.
2) Department of Biochemistry, Molecular Medicine and Nutrigenomics, Faculty of Pharmacy, Medical University, Varna, Bulgaria.
3) Vita" Multidisciplinary Hospital for Active Treatment – Sofia, Bulgaria.
4) University Hospital of Obstetrics and Gynecology "Maichin Dom", Sofia, Bulgaria.
5) Department of Obstetrics and Gynecology, Medical University, Sofia, Bulgaria.

ABSTRACT:

Coronavirus disease 2019 represents a serious challenge for modern society worldwide because of the considerable and unfavourable consequences of the pandemic in terms of human health, economics and social life. In the present concise survey, some essential peculiarities of ozone as disinfecting and therapeutic means under the conditions of COVID-19 pandemic as reflected in the recent literature are described. Particularttention is paid to modern hospital disinfection means and methods. Ozone exerts antiviral activity through the inhibition of viral replication and direct inactivation of viruses by interfering with the virus replication phase and attacking capsid proteins. Ozone therapy is very inexpensive and may safely exploit the critical vulnerability in COVID-19.

Keywords: COVID-19 pandemic, ozone, ozone disinfection, ozone therapy,

INTRODUCTION

Since March 2019, coronavirus disease 2019 has represented a serious challenge for modern society worldwide because of the considerable and unfavourable consequences of the pandemic in terms of human health, economics and social life. Recent intensive international research uninterruptedly reveals a series of important characteristics of COVID-19 pandemic and identifies the peculiarities of its prevention and patients' management.

Peculiarities of ozone as disinfection means

Ozone is a highly oxidizing gas easily generated from atmospheric oxygen with inexpensive equipment. It is commonly used for the disinfection of municipal water, foods, and surfaces [1]. It has unique biological properties and can be used as a gas at recommended levels with monitoring and if dispersed in water [2]. Ozone can be used in the disinfection of environments contaminated by viruses [3]. Its maximum antiviral efficacy requires a short period of high humidity (>90% relative humidity) after the attainment of peak ozone gas concentration (20-25 ppm, 39-49 mg/m^3) [4]. Gaseous ozone can be an effective disinfectant that successfully inactivates viruses such us influenza A H1N1, MERS-CoV, SARS-CoV-1 or even SARS-CoV-2 in aerosols or fomites [5]. Low ozone exposures around 0.1-0.4 mg/L min achieve about 4 $\log_{10}$ of aerosol inactivation.

Ozone gas can be harmful to personnel when inhaled, and, therefore, its air levels should be monitored according to federal regulations [6].

According to the findings in the scientific literature available, ozone inactivates viruses by attacking capsid proteins [7]. A decontamination method using ozone to inactivate SARS-CoV-2 as well as practical recommendations to implement a simple disinfection box system using inexpensive and readily available components used for respirators are proposed.

Ozone is a disinfectant featured with high bactericidal effect, and since the ozone disinfection has the capacity of decolouring and deodorizing, the wastewater after treatment becomes bright and transparent without odour [8]. As the molecule structure of ozone is unstable, strong oxidative atomic oxygen produced by the decomposition of ozone molecule would quickly decompose microorganisms, such as bacteria and viruses, in wastewater. Although ozone disinfection could improve the water quality in shorter time with higher efficiency, the operation costs of ozone preparation are high [9]. The by-products, which are produced through the chemical reaction with bromide and iodide, are hazardous to human health [10]. Using appropriate generators at appropriate ozone concentrations, ozone helps to decontaminate public transport, hotel room, cruise liner cabins, offices, etc. [4].

Aqueous solutions of ozone are in use as disinfectants in many commercial situations such as waste water treatment [11]. Ozone is considered a highly effective disinfectant for virus control [12].

It is a natural compound, is easily generated *in situ* from oxygen or air, and breaks down to oxygen with a half-life of about 20±10 min depending on the environment [13]. As a gas ozone penetrates all areas within a room, much more efficiently than manually applied liquid sprays and aerosols [14]. Its ability to corrode certain materials, e.g. natural rubber, on prolonged exposure and its potential toxicity to humans are its only significant disadvantages.

Wastewater surveillance is an ideal, non-invasive, cost-effective, and an early warning epidemiological approach to detect the genetic material of COVID-19 identified by means of reverse transcriptase amplification, nucleic acid sequence-based amplification, helicase dependent amplification, loop-mediated isothermal amplification, recombinase polymerase amplification, high throughput screening, and biosensor assays [15]. Modern disinfectants include ozone, ultraviolet radiations, chlorine dioxide, hypochlorites, and hydrogen peroxide.

Hospital disinfection means and methods during COVID-19 pandemic

Hospitals are important sources of pollutants resulted from diagnostic, laboratory and research activities as well as medicine excretion by patients, which include active component of drugs and metabolite, chemicals, residues of pharmaceuticals, radioactive markers, iodinated contrast media, etc. [8]. The discharge of hospital wastes and wastewater, especially those without appropriate treatment, exposes the public in danger of infection. Under COVID-19 pandemic context, it is of great significance to reduce the health risks to the public and environment. In China, liquid chlorine, sodium hypochlorite, chlorine dioxide, ozone, and ultraviolet irradiation disinfection are commonly used for hospital wastewater disinfection. Hydrogen peroxide vapour, chlorine dioxide, ozone and ultraviolet radiation could be applied to reduce viral load present in aerosols with appropriate precautions to avoid inadvertent exposure to personnel to these antimicrobials [6]. The most promising methods for disinfection of disposable masks during the COVID-19 pandemic are those that use hydrogen peroxide vapour, ultraviolet radiation, moist heat, dry heat and ozone gas [16].

The effects of various biocides such as ozone, alcohols, povidone iodine, quaternary ammonium compounds, hydrogen peroxide, sodium hypochlorite, peroxyacetic acid, chlorine dioxide, ultraviolet light, metals, and plant-based antimicrobials when used for elimination or reduction of coronaviruses such as COVID-19 from fomites, skin, oral/nasal mucosa, air, and food contact surfaces are studied [17].

Simple barrier hand hygiene measures and respiratory measures through the use of anti-projection or surgical masks are effective measures for preventing the transmission of SARS-CoV-2 [18]. Strict infection prevention and control measures, including patient isolation, hand hygiene, personal protective equipment that is doffed on exiting the patient room, and environmental cleaning, should be implemented to prevent COVID-19 spread [19]. Environmental testing demonstrates that COVID-19 patients contaminate the patient area (11 of 26 tests; 42.31%), but contamination of general ward areas is minimal (1 of 30 tests; 3.33%), and the virus is detected after cleaning on one item only (1 of 25 items; 4.00% of the cases) [19].

The results from recently published studies indicate that in small chambers, 10-20 mg ozone/m^3 applied for 10 to 50 min are sufficient to significantly reduce the COVID-19 load of personal protection equipment, while in large rooms, 30 to 50 mg ozone/m^3 are needed for treatments of 20-30 min [20]. Maximum antiviral ozone activity is achieved at high humidity.

Clinical applications of ozone and oxygen-ozone therapy in patients with COVID-19 disease

The first step in COVID-19 viral entry is the binding of the viral trimeric spike protein to the human receptor angiotensin-converting enzyme 2, which is a type I membrane protein expressed in the lungs [21]. COVID-19 causes clusters of severe respiratory illness with a serious infection of the lower respiratory tract followed by bronchitis, pneumonia and fibrosis [22].

Ozone therapy has been used in medicine since World War I. It exerts several effects, including modulating the immune system, enhancing circulation, destroying microorganisms including bacteria and viruses, and enhancing oxygen delivery and consumption by the body [23].

The results from the analysis of 13 out of 280 papers focused on ozone therapy in COVID-19 pandemic that have been published from January 2011 to July 2020 and retrieved from *PubMed* and *Scopus* databases demonstrate that ozone exerts antiviral activity through the inhibition of viral replication and direct inactivation of viruses by interfering with the virus replication phase [24]. This feature is linked to its ability to oxidize cysteine residues through the formation of disulphide bridges present in the structures of the virus itself in high quantities. Combined treatment with ozone and antivirals shows reduced inflammation and lung damage and seems useful in stimulating immunity and providing protection from acute coronary syndromes and ischaemia reperfusion damage, thus suggesting a new methodology of immune therapy.

The oxygen-ozone therapy can restore the right immune response by stimulating signal transduction molecules via nuclear factor erythroid 2-related factor and thus enhancing the nuclear transduction via specific microribonucleic acids restoring the normal antioxidant and immunostimulating reaction [25].

The ozone therapy could be easily deployed worldwide, even in very poor countries. With few conventional treatments for viral pneumonia, this epidemic could provide impetus to study ozone therapy very ethically under the auspices of an institution's review board in treating, with ozone therapy, seriously ill patients, who might otherwise expire [23].

Ozonated autohemotherapy induces a significant change of the serum concentrations of the cytokines interleukin-8, interleukin-12 and monocyte chemoattractant protein in gouty patients suggesting that modulating the inflammatory process is one of the underlying therapeutic mechanisms of this treatment [26].

Ozone therapy stabilizes hepatic metabolism, and fibrinogen and prothrombin plasma levels tend to normalize in infected patients, suggesting an improvement of the hepatic protein synthesis [23]. Numerous investigations demonstrate that ozone prevents oxidative damage to some organs such as the heart [27].

Ozone exerts its antiviral actions, and ozone therapy demonstrates usefulness in influenza and novel viruses [28]. Following ozone exposure, the alveolar parenchyma responds with the activation of genes involved in immunoactivation [29]. Processes such as cell chemotaxis, leukocyte chemotaxis, and granulocyte chemotaxis, responses to cytokines such as cytokine receptor binding, and inflammation are significantly triggered.

Biochemical and pharmacological ozone characteristics provide reasons for considering this molecule useful in the treatment of several viral infections, e.g. of COVID-19 [30].

Hyperbaric oxygen therapy, packed red blood cell transfusions and erythropoiesis-stimulating agent therapy are currently available, routinely utilized in the treatment of other conditions and thus could be tried among COVID-19 patients with severe respiratory pathology [31].

Ozone may exert its antiviral actions, and ozone therapy demonstrates its usefulness in influenza and novel viruses [28]. In two severe cases with COVID 19, this therapy promotes recovery of clinical condition and improvement of chest computed tomography images, as well as shortens the duration of viral shedding and length of hospital stay.

The beneficial effects of the systemic oxygen-ozone therapy in patients with early-phase SARS COV-2 disease before worsening, up to the need of tracheal intubation, are evaluated within an Italian multicentre study [32]. This type of treatment is effective, positively influencing the disease evolution, and/or mitigates the onset of the cytokine storm syndrome, at least partially.

Being new immunotherapy and an inexpensive and safe modality, ozone therapy has its rationality in the treatment of COVID-19 patients [33]. Since SARS-CoV-19 is rich in cysteine, which residues must be intact for viral activity and sulfhydryl groups are vulnerable to oxidation, this therapy may exploit the critical vulnerability of SARS-CoV-19 [33].

The analysis of 74 peer-reviewed original articles dealing with systemic ozone therapy in COVID-19 focuses mainly on ozone as a modulator of the nuclear factor kappa B/nuclear factor erythroid 2-related factor pathways and interleukin-6 and interleukin-1â expression [34]. This therapy ensures the homeostasis of the free radical and antioxidant balance. These molecular mechanisms support the cytoprotective effects of ozone therapy against tissue and organ damage in many inflammatory diseases, including viral infections and, especially, COVID-19 [35]. The potential cytoprotective role of ozone therapy in the management of organ damage induced by COVID-19 merits further research.

Two simple, low-cost adjuvant therapies to administer without side effects which are useful for the treatment of acute severe COVID-19 infection, are extensively reviewed [36]. The first is ozone whose effectiveness has been demonstrated in multiple studies, and the second is intravenously administered vitamin C which plays a key role in lung injury due to COVID-19 infection by reducing the pulmonary inflammation.

Another important characteristic of ozone therapy against COVID-19 infection is shown by the contrast ability toward severe hypoxemia, typical of this virus [30].

As there are no ‘vaccines or specific pharmaceutical treatments available’ in the management of COVID-19, the International Scientific Committee of Ozone Therapy offers a contribution to fight the coronavirus proposing the potential use of ozone therapy as a complementary therapy, exclusively based on scientific data available [4].

Systemic ozone therapy can be ‘potentially’ useful in SARS-CoV-2 [4]. The rationale of action is proven clinically in other viral infections and is highly effective. The mechanism of action is by: i) the induction of adaptation to oxidative stress, hence a re-equilibration of the cellular redox state; ii) the induction of interferon-gamma and proinflammatory cytokines; iii) the increase of blood flow and tissue oxygenation to vital organs and iv) it has the potential to act as an auto-vaccine when administered in the form of minor autohemotherapy.

The recommended routes of administration are the following: major autohemotherapy, ozonized saline solution, extracorporeal blood oxygenation-ozonation, and a variant of the minor autohemotherapy [4]. The clinical protocol should adhere to the standard doses and procedures as defined in the Madrid Declaration of Ozone Therapy. It is a complementary therapy because while the infected patient continues to be treated with allopathic medicine, at the same time, the patient receives the treatment proposed herewith.

Ozone therapy could be used in the treatment of COVID-19 in two therapeutic categories:

1) Disinfection: i) contaminated environments (hospitals, transport, vehicles, all surfaces where the virus may have been deposited etc.) and ii) in aqueous solutions such as disinfection of drinking water, waste water treatment, laundry facilities, and food processing [13].

2) Potential systemic application as complementary medicine in order to i) improve the health status of the patients and reduce the viral load [36] and ii) in the form of ozonated water mouthwash to reduce the incidence of ventilator-associated pneumonia in patients connected to mechanical ventilation [37].

Rectal ozone decreases oxygen supply, improves oxygen saturation and decreases inflammation biomarkers in patients with severe bilateral COVID-19 pneumonia [38]. It represents a safe, effective, cheap, and simple adjunctive therapeutic option capable of acting on the SARS-CoV-2 virus. Rectal ozone insufflation inactivates the virus by direct or indirect oxidation and stimulates the cellular and humoral immune systems, being useful in the early COVID-19 infection phase [39]. Ozone improves gas exchange and modulates the antioxidant system, so it is useful in the hyper inflammation or 'cytokine storm' as well as in the hypoxemia and/or multiorgan failure phase.

The application of oxygen-ozone mixture as an oxygen-ozone-immunoceutical therapy in 50 elderly hospitalized COVID-19 patients with acute respiratory disease syndrome leads to fast recovery due to reduction of inflammatory and thromboembolic markers such as C-reactive protein, interleukin-6 and D-dimer and improvement of major respiratory indexes and blood gas parameters after relatively short dispensed forced ventilation [40].

Ozone therapy is very inexpensive and safe, without resistance and thus may safely exploit the critical vulnerability in many viruses, including SARS-CoV-2 (COVID-19) [33]. It should be administered after careful patient's examinations as a measure of precaution to avoid eventual adverse effects of ozone.

CONCLUSION

This systematic review allows us to draw the conclusion that further interdisciplinary research could provide additional evidence of the benefits of ozone as an effective and inexpensive disinfecting and therapeutic means in the continuous fight against COVID-19 in our united world.

REFERENCES:

1. Blanchard EL, Lawrence JD, Noble JA, Xu M, Joo T, Ng NL, et al. Enveloped virus inactivation on personal protective equipment by exposure to ozone. Version 2. *medRxiv.* 2020 May 26:2020.05.23.20111435.

2. Kumar GD, Williams RC, Sumner SS, Eifert JD. Effect of ozone and ultraviolet light on Listeria monocytogenes populations in fresh and spent chill brines. *Food Control*. 2016; 59: 172-177.

3. Pachejieff A, Kostov I. [Contamination in cord blood samples]. [in Bulgarian] *Akush Ginekol*. 2017; 56(10):30-34.

4. ISCO3. Potential use of ozone in SARS-CoV-2/COVID-19. Madrid: International Scientific Committee of Ozone Therapy. 2020 March 14. [Internet]

5. Bayarri B, Cruz-Alcalde A, López-Vinent N, Micó MM, Sans C. Can ozone inactivate SARS-CoV-2? A review of mechanisms and performance on viruses. *J Hazard Mater.* 2021 Aug 5;415:125658. [PubMed]

6. The National Institute for Occupational Safety and Health (NIOSH). Ozone. CDC. June 22, 2019. [Internet]

7. Dennis R, Cashion A, Emanuel S, Hubbard D. Ozone gas: scientific justification and practical guidelines for improvised disinfection using consumer-grade ozone generators and plastic storage boxes. *J Sci Med*. 2020 Apr; 2(1). [Crossref]

8. Wang J, Shen J, Ye D, Yan X, Zhang Y, Yang W, et al. Disinfection technology of hospital wastes and wastewater: Suggestions for disinfection strategy during coronavirus disease 2019 (COVID-19) pandemic in China. *Environ Pollut*. 2020 Jul;262: 114665. [PubMed]

9. Arslan A, Topkaya E, Özbay B, Özbay I, Veli S. Application of O3/UV/H2O2 oxidation and process optimization for treatment of potato chips manufacturing wastewater. *Water Environ J*. 2017 Feb;31(1):64-71.

10. Kleinbohl A, Willacy K, Friedson AJ, Chen P, Swain MR. Buildup of abiotic oxygen and ozone in moist atmospheres of temperate terrestrial exoplanets and its impact on the spectral fingerprint in transit observations. *Astrophys J*. 2018 Aug 1;862(2)1-12. [Crossref]

11. Gottschalk C, Libra JA, Saupe A. Ozonation of water and waste water: a practical guide to understanding ozone and its application. Hoboken NJ: John Wiley & Sons; 2008.

12. Wolf C, von Gunten U, Kohn T. Kinetics of inactivation of waterborne enteric viruses by ozone. *Environ Sci Technol*. 2018 Feb;52(4): 2170-2177.

13. Hudson JB, Sharma M, Petric M. Inactivation of Norovirus by ozone gas in conditions relevant to healthcare. *J Hosp Infect*. 2007 May;66(1): 40-45.

14. Hudson JB, Sharma M, Vimalanathan S. Development of a practical method for using ozone gas as a virus decontaminating agent. *Ozone Sci Engin*. 2009 May;31(3): 216-223.

15. Singh S, Kumar V, Kapoor D, Dhanjal DS, Bhatia D, Jan S, et al. Detection and disinfection of COVID-19 virus in wastewater. *Environ Chem* Lett. 2021 Feb 22:1-17. [PubMed]

16. Rubio-Romero JC, Pardo-Ferreira MDC, Torrecilla-García JA, Calero-Castro S. Disposable masks: Disinfection and sterilization for reuse, and non-certified manufacturing, in the face of shortages during the COVID-19 pandemic. *Saf Sci*. 2020 Sep;129:104830. [PubMed]

17. Dev Kumar G, Mishra A, Dunn L, Townsend A, Oguadinma IC, Bright KR, et al. Biocides and novel antimicrobial agents for the mitigation of coronaviruses. *Front Microbiol*. 2020 Jun 23;11:1351. [PubMed]

18. Lepelletier D, Grandbastien B, Romano-Bertrand S, Aho S, Chidiac C, Géhanno JF, et al. What face mask for what use in the context of COVID-19 pandemic? The French guidelines. *J Hosp Infect.* 2020 Apr 26;105(3):414-8. [PubMed]

19. Jerry J, O'Regan E, O'Sullivan L, Lynch M, Brady D. Do established infection prevention and control measures prevent spread of SARS-CoV-2 to the hospital environment beyond the patient room? *J Hosp Infect*. 2020 Aug;105(4):589-592. [PubMed]

20. Blanco A, Ojembarrena FB, Clavo B, Negro C. Ozone potential to fight against SAR-COV-2 pandemic: facts and research needs. *Environ Sci Pollut Res Int*. 2021 Apr;28(13):16517-16531.

21. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. *Science*. 2020 Mar;367(6485):1444-1448.

22. Conti P, Gallenga CE, Tetè G, Caraffa A, Ronconi G, Younes A, et al. How to reduce the likelihood of coronavirus-19 (CoV-19 or SARS-CoV-2) infection and lung inflamma-

tion mediated by IL-1. *J Biol Regul Homeost Agents*. 2020 Mar-Apr;34(2): 333-338.

23. Rowen RJ. Ozone therapy as a primary and sole treatment for acute bacterial infection: case report. *Med Gas Res*. 2018 Sep;8(3):121-124.

24. Cattel F, Giordano S, Bertiond C, Lupia T, Corcione S, Scaldaferri M, et al. Ozone therapy in COVID-19: A narrative review. *Virus Res*. 2021 Jan 2;291:198207. [PubMed]

25. Bocci V, Zanardia I, Valacchi G, Borrelli E, Travagli V. Validity of oxygen-ozone therapy as integrated medication form in chronic inflammatory diseases. *Cardiovasc Hematol Disord Drug Targets*. 2015;15(2):127-138.

26. Li LY, Ma RL, Du L, Wu AS. Ozonated autohemotherapy modulates the serum levels of inflammatory cytokines in gouty patients. *Open Access Rheumatol*. 2017 Aug;9:159-165.

27. Simonetti V, Quagliariello V, Franzini M, Iaffaioli RV, Maurea N, Valdenassi L. Ozone exerts cytoprotective and anti-inflammatory effects in cardiomyocytes and skin fibroblasts after incubation with doxorubicin. *Evid Based Complement Alternat Med*. 2019 Nov18;2019:2169103. [PubMed]

28. Zheng Z, Dong M, Hu K. A preliminary evaluation on the efficacy of ozone therapy in the treatment of COVID-19. *J Med Virol*. 2020 Nov; 92(11):2348-2350.

29. Di Mauro R, Cantarella G, Bernardini R, Di Rosa M, Barbagallo I, Distefano A, et al. The biochemical and pharmacological properties of ozone: the smell of protection in acute and chronic diseases. *Int J Mol Sci*. 2019 Feb;20(3):634. [PubMed]

30. Valdenassi L, Franzini M, Ricevuti G, Rinaldi L, Galoforo AC, Tirelli U. Potential mechanisms by which the oxygen-ozone (O2-O3) therapy could contribute to the treatment against the coronavirus COVID-19. *Eur Rev Med Pharmacol Sci*. 2020 Apr; 24(8):4059-4061.

31. Geier MR, Geier DA. Respiratory conditions in coronavirus disease 2019 (COVID-19): Important considerations regarding novel treatment strategies to reduce mortality. *Med Hypotheses*. 2020 Jul;140:109760. [PubMed]

32. Marini S, Maggiorotti M, Dardes N, Bonetti M, Martinelli M, Re L, et al.; Italian Oxygen-Ozone Federation. Oxygen-ozone therapy as adjuvant in the current emergency in SARS-COV-2 infection: a clinical study. *J Biol Regul Homeost Agents*. 2020 May-Jun; 34(3):757-766.

33. Rowen RJ, Robins H. A plausible "penny" costing effective treatment for corona virus-ozone therapy. *J Infect Dis Epidemiol*. 2020;6(2):113. [Crossref]

34. Martinez-Sanchez G, Schwartz A, Donna VD. Potential cytoprotective activity of ozone therapy in SARS-CoV-2/COVID-19. *Antioxidants* (*Basel*). 2020 May 6;9(5):389. [PubMed]

35. Hernández A, Papadakos PJ, Torres A, González DA, Vives M, Ferrando C, et al. Two known therapies could be useful as adjuvant therapy in critical patients infected by COVID-19. *Rev Esp Anestesiol Reanim*. 2020 May;67(5):245-252.

36. Huiling H, Tong X. [A multicenter randomized controlled trial for ozone autohemotherapy in the treatment of novel coronavirus pneumonia (COVID-19).] [in Chinese] *ChiCTR*. 2020 Oct;(10). [Internet]

37. Soodmand M. A survey of the effect of ozonated water mouthwash on oral health and incidence of ventilator-associated pneumonia in patients connected to mechanical ventilation in intensive care units - a randomized clinical trial. *IRCT*. 20180213038720 N2, 20.05.2020. [Internet]

38. Fernández-Cuadros ME, Albaladejo-Florín MJ, Álava-Rabasa S, Usandizaga-Elio I, Martinez-Quintanilla Jimenez D, Peña-Lora D, et al. Effect of rectal ozone (O3) in severe COVID-19 pneumonia: preliminary results. *SN Compr Clin Med*. 2020 Aug 3;1-9. [PubMed]

39. Fernández-Cuadros ME, Albaladejo-Florín MJ, Peña-Lora D, Álava-Rabasa S, Pérez-Moro OS. Ozone (O3) and SARS-CoV-2: physiological bases and their therapeutic possibilities according to COVID-19 evolutionary stage. *SN Compr Clin Med*. 2020 Jul 7;1-9. [PubMed]

40. Franzini M, Valdenassi L, Ricevuti G, Chirumbolo S, Depfenhart M, Bertossi D, et al. Oxygen-ozone (O2-O3) immunoceutical therapy for patients with COVID-19. Preliminary evidence reported. *Int Immunopharmacol*. 2020 Nov;88:106879. [PubMed]

Please cite this article as: Yaneva G, Dimitrova T, Ivanov D, Ivanova D, Ingilizova G, Slavov S. Modern applications of ozone for COVID-19 disinfection and treatment. *J of IMAB.* 2022 Jan-Mar;28(1):4284-4288.
DOI: https://doi.org/10.5272/jimab.2022281.4284

Received: 21/06/2021; Published online: 18/03/2022

Address for correspondence:
Galina Yaneva, BS, PhD
Department of Biology, Faculty of Pharmacy, Medical University of Varna
84, Tsar Osvoboditel Blvd., Varna-9002, Bulgaria
E-mail: galina.yanevaa@gmail.com