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Review

Ozone therapy in COVID-19: A narrative review

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ABSTRACT

The main objective of this narrative review is to describe the available evidence on the possible antiviral activity of ozone in patients with COVID-19 and its therapeutic applicability through hospital protocols. Amongst different possible therapies for SARS-CoV-2 pneumonia, ozone therapy seems to have an immunological role because of the modulation of cytokines and interferons, including the induction of gamma interferon. Some data suggest the possible role of ozone therapy in SARS, either as a monotherapy or, more realistically, as an adjunct to standard treatment regimens; therefore, there is increasing interest in the role of ozone therapy in COVID-19 treatment

The PubMed and Scopus databases and the Italian Scientific Society of Oxygen Ozone Therapy website were used to identify articles focused on ozone therapy. The search was limited to articles published from January 2011 to July 2020. Of 280 articles found on ozone therapy, 13 were selected and narratively reviewed. Ozone exerts antiviral activity through the inhibition of viral replication and direct inactivation of viruses. Ozone is an antiviral drug enhancer and is not an alternative to antiviral drugs. Combined treatment with involving ozone and antivirals demonstrated a reduction in inflammation and lung damage. The routes of ozone administration are direct intravenous, major autohaemotherapy and extravascular blood oxygenation-ozonation.

Systemic ozone therapy seems useful in controlling inflammation, stimulating immunity and as antiviral activity and providing protection from acute coronary syndromes and ischaemia reperfusion damage, thus suggesting a new methodology of immune therapy. Systemic ozone therapy in combination with antivirals in COVID-19-positive patients may be justified, helpful and synergic.

1. Introduction

In December 2019, a novel *Betacoronavirus* causing coronavirus disease 2019 (COVID-19), provisionally named 2019 novel coronavirus (2019-nCoV) and subsequently officially renamed as SARS-CoV-2 by the International Committee on Taxonomy of Viruses, was associated with a cluster of respiratory tract infections in Wuhan, Hubei Province, China and has rapidly spread across continents (Yang et al., 2020; Lupia et al., 2019).

COVID-19 causes clusters of severe respiratory illness (with serious infection of the lower respiratory tract followed by bronchitis, pneumonia and fibrosis (Conti et al., 2020)) similar to SARS-CoV and is associated with intensive care unit admission and high mortality (Huang et al., 2020).

The CoV virion contains at least four structural proteins: the spike (S), the envelope (E), the membrane (M) and the nucleocapsid (N) (Tortorici and Veesler, 2019); coronavirus entry into host cells is mediated by the transmembrane spike (S) glycoprotein that forms homotrimers protruding from the viral surface. S comprises two functional subunits responsible for binding to the host cell receptor (S_1 subunit) and fusion of the viral and cellular membranes (S_2 subunit) (Walls et al., 2020): S1 contains the receptor-binding domain, which directly binds to the peptidase domain of angiotensin-converting enzyme 2 (ACE2), whereas S2 is responsible for membrane fusion. When S1 binds to the host receptor ACE2, another cleavage site on S2 is exposed and cleaved by host proteases, a process that is critical for viral infection. The first step in viral entry is the binding of the viral trimeric spike protein to the human receptor ACE2, which is a type I membrane

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protein expressed in the lungs (Walls et al., 2020; Yan et al., 2020).

The complete clinical manifestation of COVID-19 is not clear yet, as the reported symptoms range from mild to severe, with some cases even resulting in death. The most commonly reported symptoms are fever, cough, myalgia or fatigue, pneumonia and complicated dyspnea, whereas the less common reported symptoms include headache, diarrhoea, haemoptysis, runny nose and cough.

As SARS-CoV-2 is a newly emerged virus, there is no established therapy for it; several therapeutic options have been considered, either as supportive therapies (i.e. steroids, heparin) or as antiviral or immunomodulatory treatment (i.e. remdesivir, hydroxychloroquine, tocilizumab, hyperimmune plasma). There has been an expanding number of studies published online and in academic journals on this topic, but some of these articles may be of limited quality and are pre-published without sufficient peer review. A critical appraisal of existing studies is needed to determine whether existing evidence is sufficient to support currently proposed management strategies (Bhimraj et al., 2020).

Amongst different possible therapies, ozone therapy seems to have an immunological role because of the modulation of cytokines and interferons, including the induction of gamma interferon. Some data suggest the possible role of ozone therapy in SARS, either as a monotherapy or, more realistically, as an adjunct to standard treatment regimens; therefore, there is increasing interest in the role of ozone therapy in COVID-19 treatment (Elvis and Ekta, 2011). The aim of this narrative review is to summarise current evidence on the antiviral activity of ozone in patients with COVID-19 and its possible therapeutic applicability in clinical practice.

2. Material and methods

A literature search was performed using the PubMed and Scopus database and the Italian Scientific Society of Oxygen Ozone Therapy (SIOOT) website (ZZZZZ, 2020). The search was limited to articles focused on ozone therapy published from January 2011 to July 2020. Search terms included “ozone” and “coronavirus”. The MeSH terms were “ozone” [All Fields] AND “coronavirus” [All Fields]. Articles were selected and narratively reviewed. All authors reviewed the title of the articles found by the initial search. Titles suggestive of ozone therapy in viral diseases were selected for abstract review. Articles not focused on the medical application of ozone (i.e. ambient and air pollution, sanitisation, disinfection and sterilisation of surfaces and water) and articles focused on ozone therapy uses other than pulmonary diseases or viral diseases were excluded.

3. Results

A total of 280 articles met the search criteria applied (Fig. 1). Of these, 33 titles appeared to be relevant to ozone therapy use in viral diseases; 220 titles were excluded because they were not focused on the medical application of ozone, and 27 were removed because they were focused on uses of ozone therapy other than pulmonary diseases or viral diseases. Nineteen articles were then excluded after the abstract review. Of the remaining 14 articles, one was a specific case report, and it was not included in the qualitative analysis.

3.1. Ozone therapy

3.1.1. Pharmacological properties

Ozone is triatomic oxygen (O_3). It is the most powerful oxidant found in nature and is produced by lightning and solar ultraviolet radiation. The pharmacological properties of ozone are attributed to its molecular structure (Fig. 2). It reacts with organic compounds containing double bonds (i.e. polyunsaturated fatty acids), and it adds the three oxygen atoms to the unsaturated bond, forming ozonides. In blood, ozonides are immediately transformed into stable hydroperoxides, which have the ability to release oxygen when the pH increases as it occurs in

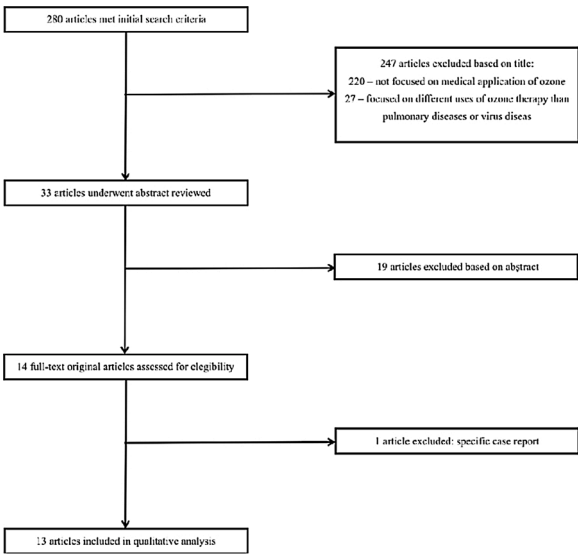

Fig. 1. Narrative literature review flow chart.

degenerative processes and/or ischemic conditions (Di Mauro et al., 2019; Smith et al., 2017). Ozone is a molecule that could perform antiviral action by interfering with the virus replication phase; this feature is linked to the ability of ozone to oxidise cysteine residues through the formation of disulphide bridges present in the structures of the virus itself in high quantities. Coronaviruses, including SARS-CoV-2, are rich in cysteine, and these residues must be intact for viral activity (Rowen, 2019; Rowen and Robins, 2020). Ozone’s action consists of oxidation and inactivation of the specific viral receptors used for the creation of the bond structure of the cell membrane, therefore inhibiting the level of its first phase: cellular penetration. ACE2 receptors’ activity can be regulated and blocked through the control of Nrf2, an important nuclear message transductor. Ozone acts directly on Nrf2, and it could be an important physiological mechanism to block endogenous COVID-19 replication by preventing contact with SARS-CoV-2 receptors. Moreover, the activation of Nrf2 leads to a reduction of iron overload and the subsequent oxidative stress induced by elevated ferritine; thus, this ozone activity protects from apoptosis induced by oxidative stress (Smith et al., 2017; Sagai and Bocci, 2011). NLRP3 inflammasome, a cytosolic complex responsible for the production of IL-1β and IL-18, plays a crucial role at the beginning of and during inflammation in various diseases, including viral infections such as COVID-19. Ozone shows its anti-inflammatory activity through the modulation of the NLRP3 inflammasome. Therefore, it could protect from acute coronary syndromes and ischaemia reperfusion damage that occurs in the lungs of patients affected by COVID-19, attenuating NLRP3-mediated inflammation, enhancing the antioxidant activity of Nrf2 and inhibiting apoptosis (Wang et al., 2018).

Ozone stimulates both the humoural and cellular immune systems through the activation of pathways linked to the transcriptional factors nuclear factor of activated T-cells and activated protein 1, which, in turn, induce the transcription of genes linked to cytokines. Therefore, there is an increase in the production of gamma-interferon, interleukin-2 and alpha-tumour necrosis factor (Di Mauro et al., 2019).

Ozone also reduces inflammation processes through the molecular pathways involving an important network of transcription factors as well as having antioxidant activity; it acts on proteasome and inflammation cascade by inhibiting nuclear factor NFkB (Smith et al., 2017; Galiè et al., 2018).

3.1.2. Studies that support the antiviral activity of ozone

Three articles were found to support the antiviral activity of ozone: one is an in vitro study which showed that ozone can inactivate herpes

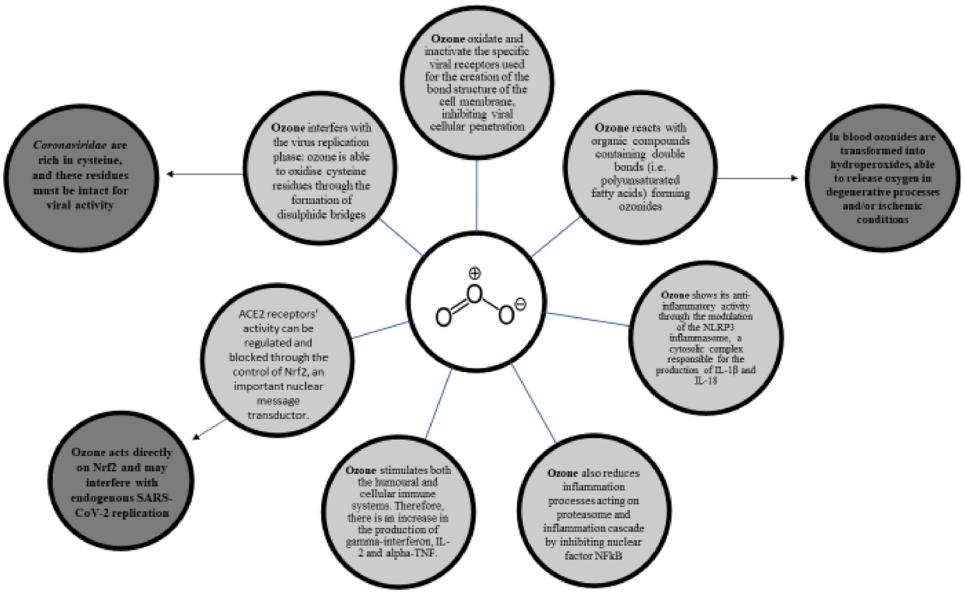

Fig. 2. Pharmacological, biochemical and antiviral properties of Ozone therapy.
Abbreviations: ACE- angiotensin converting enzyme; TNF- tumor necrosis factor; IL-interleukin,

simplex virus type 1 (HSV-1) (Petry et al., 2014) and two articles describing clinical studies with the aim of evaluating antiviral activity against hepatitis C virus (HCV) (Zaky et al., 2011; mn and tt, 2012).

The aim of the in vitro study (Petry et al., 2014) was to evaluate the antiviral activity of ozone against the herpes virus and its possible cytotoxic effect on cultured Madin-Darby bovine kidney (MDBK) cells. Experiments were performed in a laminar flow chamber, and ozone was generated by a commercial air purifier. Antiviral activity was measured by tittering aliquots of HSV-1 and bovine herpes virus type 1 (BoHV-1) exposed for 1, 2 and 3 h to ozone. Viral samples incubated in the absence of ozone were also tittered as a control. A progressive and significant reduction in HSV-1 titter was observed after 1, 2 and 3 h (68.4 %, 82.2 % and 90.0 %, respectively). For BoHV-1, although no viral inhibition could be detected after a 1 h exposure, a 3 h exposure inhibited viral viability more than 99 %.

The possible cytotoxic effect was evaluated by exposing the MDBK cells to ozone for 3 h and testing cell viability immediately after and after culturing for 24 h. Control cells were kept for the same period in the absence of ozone. In this assay, the viability of control cells was considered 100 %, and the concentration of ozone that reduced cell viability by more than 80 % was considered cytotoxic. The viability of MDBK cells exposed to ozone for 3 h and further cultured for 24 h was 94.8 % and 122.8 %, respectively, in comparison to the control value. Therefore, cell viability was higher than 80 %, and there was no significant difference between the control and ozonated cells in both conditions.

The aim of the first in vivo study (Zaky et al., 2011) was to evaluate the role of ozone therapy in decreasing HCV ribonucleic acid (RNA) load and its effect on liver enzymes amongst patients with chronic hepatitis C. For this study, a prospective case-control design was used. Fifty-two patients were recruited and divided into two groups: the ozone group with 40 patients who received major autohaemotherapy, minor autohaemotherapy and rectal ozone insufflation and the control group with 12 patients who received silymarin and/or multivitamins. All 40 patients of the ozone group were treated with ozone for 30 sessions, and 18 of them had 30 additional sessions. The patients in the control group were treated with conventional treatment for 5 months. All patients were subjected to complete blood count and liver function tests monthly, quantitative polymerase chain reaction (qPCR) for HCV RNA before starting and after 10 and 20 weeks of treatment. Following 30 sessions of ozone therapy, there were significant improvements in most of the presenting symptoms of the patients in the ozone group compared with the conventional group. Liver enzyme (ALT and AST) levels normalised in 57.5 % and 60 %, respectively, of the patients in the ozone group, compared with 16.7 % and 8% in the control group. PCR for HCV RNA was negative amongst 25 % and 44.4 % of the patients after 30 and 60 sessions of ozone therapy compared with 8% in the conventional group.

In the third article (mn and tt, 2012), two similar studies were described. Both studies were performed to evaluate the effectiveness and safety of ozone therapy in hepatitis C genotype 4 infections. Investigations including liver function tests and qPCR for HCV were carried out before and at 8 and 24 weeks after starting ozone therapy. General health and daily activities were also recorded. The first study included 60 patients (45 males and 15 females aged between 34 and 65 years) who received ozone treatment with MAH three times a week for 8 weeks, followed by twice a week for 16 weeks. It was found that following 8 weeks of ozone therapy, the viral load decreased in 91.67 % of the cases, and enzyme levels were back to normal in 20 % of the cases. Following 24 weeks, there was a further decrease in viral load, reaching 95 % of the cases. The negative PCR cases increased from 20 % after 8 weeks of treatment to 36.67 % after 24 weeks.

The second study included 50 patients (44 males and 6 females aged between 23 and 58 years) who received ozone treatment with MAH three times a week for 12 weeks, followed by twice a week for 12 weeks. General conditions improved in 94 % of the cases, and there was a viral load decrease in 63.85 % of the cases after 8 weeks and in 71.84 % after 24 weeks. The negative PCR cases for the HCV virus increased from 24 % after 8 weeks of treatment to 36 % after 24 weeks. After 8 weeks, enzyme levels were back to normal in 28 % of the cases.

3.1.3. *Ozone in lung diseases*

DIV ozone has been used on patients with lung malignancies, as supportive therapy both during cancer therapy and in a palliative setting with no significant side effects (Tirelli et al., 2018). Furthermore ozone therapy may be a valuable resource in chronic inflammatory diseases such as chronic obstructive pulmonary disease, asthma, bronchiectasis and pulmonary fibrosis with theoretically good efficacy and contained costs (Bocci et al., 2015Hernández Rosales et al., 2005).

3.1.4. *Ozone preparation and administration*

Ozone has a short half-life and cannot be stored, and it must be

produced at the time of use. Special equipment that transforms medical oxygen into ozone and makes it available for immediate administration is needed.

The Italian Multiossigen company produces medical devices for ozone therapy that meet the requirements of Medical Device Directive 93/42/EEC and S.M.I. in class IIA and are compliant with SIOOT guidelines. Specifically, three different types of equipment are available: two for hospital/outpatient use and one for home use (ZZZZZ, 2020).

Ozone can be administered with great flexibility. One of the most important routes of administration is direct intravenous (DIV). It is based on intravenous administration, generally starting with 20 mL gas 30–55 μg/mL and increasing the volume, as tolerated, to 80 mL or more. The treatment time is variable, from a few to several minutes (Rowen, 2019; Rowen and Robins, 2020). Another commonly accepted delivery method is MAH, in which a predetermined volume of blood is withdrawn, sodium citrate or eparin (20 UI/mL of blood) is added and then the blood can be exposed to an equal volume of ozone gas and mixed; the ozonated blood is reinfused under gravity (Rowen, 2019; Rowen and Robins, 2020; Tirelli et al., 2018). The SIOOT protocol provides the ozonation of 180 mL of blood and then the reinfusion. This practice could be repeated for up to five times. Udine Hospital protocol allows withdrawal of 200 mL of blood, ozonation for 10 min and then reinfusion; this practice could be repeated for up to three or four times. Another possible procedure is the extravascular blood oxygenation-ozonation (EBOO), which is used especially in emergency because of complexity and invasiveness. It consists of blood collection and infusion from two contralateral veins through an ozone-resistant gas exchanger. Blood is then reinfused using a peristaltic pump. About 5 L of blood can be oxygenated-ozonated within 1 h. However, this procedure is expensive and must be performed by technicians specialising in extravascular blood circulation (Hernández Rosales et al., 2005).

3.1.5. Adverse reactions, special warnings and contraindications

There are no reports of ozone allergic reactions. Ozone is irritating and toxic during inhalation because in humans, the great expanse of the alveolar surface is protected only by a scanty volume of lining fluid, which has small antioxidant content and cannot quench the strong oxidant activity of ozone. Plasma and blood cells have a remarkable quantity of mutually cooperating antioxidants, so if therapeutic doses are used, ozone will be safe through this route of administration (Tirelli et al., 2018). DIV administration carries a risk of chest tightness and cough, and it can cause vein sclerosis (Rowen, 2019). To avoid coughing, administration of low-flow oxygen by nasal canula avoids lung reactions virtually entirely (Bocci et al., 2011). Ozone dissolves instantly in the blood after administration, with almost no risk of fatal embolisms from ozone entering the venous system, despite that air embolous after venipuncture were reported in literature (Flanagan et al., 1969Toung et al., 2001).

Ozone therapy is contraindicated in pregnant women and in patients with uncontrolled hypothyroidism, whereas MAH is not recommended in patients with glucose 6-phosphate dehydrogenase deficiency (Bocci et al., 2009).

4. Discussion

Ozone seems to have low antiviral activity by inhibiting viral replication and inactivating viruses; it is also an antiviral drug enhancer. Ozone is not an alternative to antiviral drugs, but antiviral activity is decreased with the combination of ozone therapy and antiviral drug treatment.

Combined ozone therapy and antiviral drugs demonstrated a reduction in inflammation and lung damage, helping to increase host immunity against infection. It can activate the cellular and humoural immune systems, and it can reduce inflammatory/apoptotic processes (Smith et al., 2017; Sagai and Bocci, 2011; Wang et al., 2018; Galiè et al., 2018). Several data describe the role of ozone in treating hypoxia by improving oxygen saturation and increasing oxygen supply (Elvis and Ekta, 2011; Rowen, 2019; Rowen and Robins, 2020).

The efficacy of ozone therapy is shown in the early stage of viral diseases before invasive ventilation is necessary; it is unsuccessful when used in cases of serious or critical conditions.

DIV is the easier route of administration, and its use has been hypothesized in the treatment of several pulmonary diseases (Bocci et al., 2015Hernández Rosales et al., 2005). This route of administration requires minimal medical waste and very inexpensive (it only requires a butterfly syringe once an ozone generator is procured). EBOO results in rapid improvement, but it is expensive and must be performed by technicians who specialise in extravascular blood circulation. For the treatment of pulmonary diseases, MAH is preferred because it does not produce adverse lung reactions. A specific device is necessary to create ozone by medical oxygen when MAH is applied.

Ozone therapy is very inexpensive and safe, and resistance is not developed, so it may safely exploit the critical vulnerability in many viruses, including SARS-CoV-2 (Rowen, 2019; Rowen and Robins, 2020).

5. Conclusion

Systemic ozone therapy has several positive effects, such as control of inflammation, stimulation of immunity, low antiviral activity and protection from acute coronary syndromes and ischaemia reperfusion damage. This therapy could be a new method of immune therapy, so its use in combination with other antiviral drugs in COVID-19-positive patients may be justified, helpful and synergic. Ozone therapy carries no known adverse or toxic effects when performed properly. DIV is the easier route of administration, and its use has been hypothesized in the treatment of several pulmonary diseases, including theoretically SARS-CoV-2 infections.

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Authors' contribution

The search on databases and the selection of articles were performed by Susanna Giordano and Cecilia Bertiond. The first draft of the manuscript was written by Susanna Giordano and Cecilia Bertiond. Silvia Corcione, Tommaso Lupia and Matilde Scaldaferri revised the manuscript and all authors commented on subsequent versions of the manuscript. All authors read and approved the final manuscript.

Author statement

The submitting author affirms that all individuals listed as authors agree that they have met the criteria of authorship and agree to the conclusions of the study. In order to meet the requirements of authorship, each author must have contributed to at least one aspect of each of the four criteria, as listed below. Please note that for Criteria 1 and 2, authors only to meet one of the two items listed. These criteria are not to be used as a means to disqualify colleagues from authorship who otherwise meet authorship criteria by denying them the opportunity to meet criteria 2 or 3. Therefore, all individuals who meet the first criterion should have the opportunity to participate in the drafting, review, and final approval of the manuscript. Any individuals not meeting the criteria may be mentioned in the Acknowledgements section of the manuscript.

Per the criteria defined by the International Committee for Medical Journal Editors (ICJME), please note the contribution made by each author listed in the manuscript. Please check all boxes that apply.

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Bertiond C.: contributed to conception and design drafted manuscript gave final approval agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Corcione S.: contributed to design critically revised manuscript gave final approval agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Lupia T. contributed to design critically revised manuscript gave final approval agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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Declaration of Competing Interest

The authors report no declarations of interest.

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References

Bhimraj et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19; Clinical Infectious Diseases, ciaa478, https://doi.org/10.1093/cid/ciaa478 Published: 27 April 2020.

Bocci, V., Zanardia, I., Valacchi, G., Borrelli, E., Travagli, V., 2015. Validity of oxygen-ozone therapy as integrated medication form in chronic inflammatory diseases. Cardiovasc. Hematol. Disord. Drug Targets 15 (2), 127–138. https://doi.org/10.2174/1871529x150215120911464 2. PMID: 26126818.

Bocci, V., Zanardi, I., Travagli, V., 2011. Oxygen/ozone as a medical gas mixture. A critical evaluation of the various methods clarifies positive and negative aspects. Med. Gas Res. 1 (April 28 (1)), 6. https://doi.org/10.1186/2045-9912-1-6. PubMed PMID: 22146387; PubMed Central PMCID: PMC3231820.

Bocci, V., Borrelli, E., Travagli, V., Zanardi, I., 2009. The ozone paradox: ozone is a strong oxidant as well as a medical drug. Med. Res. Rev. 29 (July (4)), 646–682. https://doi.org/10.1002/med.20150. PMID: 19260079.

Conti, P., Gallenga, C.E., Tetè, G., Caraffa, A., Ronconi, G., Younes, A., Toniato, E., Ross, R., Kritas, S.K., 2020. How to reduce the likelihood of coronavirus-19 (CoV-19 or SARS-CoV-2) infection and lung inflammation mediated by IL-1. J. Biol. Regul. Homeost. Agents 34 (March 31 (2)). https://doi.org/10.23812/Editorial-Conti-2 [Epub ahead of print] PubMed PMID: 32228825.

Di Mauro, R., Cantarella, G., Bernardini, R., Di Rosa, M., Barbagallo, I., Distefano, A., Longhitano, L., Vicario, N., Nicolosi, D., Lazzarino, G., Tibullo, D., Gulino, M.E., Spampinato, M., Avola, R., Li Volti, G., 2019. The biochemical and pharmacological properties of ozone: the smell of protection in acute and chronic diseases. Int. J. Mol. Sci. 20 (February 1 (3)) https://doi.org/10.3390/ijms20030634 pii: E634.Review. PubMed PMID:30717203; PubMed Central PMCID: PMC6387239.

Elvis, A.M., Ekta, J.S., 2011. Ozone therapy: a clinical review. J. Nat. Sci. Biol. Med. 2 (January (1)), 66–70. https://doi.org/10.4103/0976-9668.82319. PubMed PMID: 22470237; PubMed Central PMCID: PMC3312702.

Flanagan, J.P., Gradisar, I.A., Gross, R.J., TR, Kelly, 1969. Air Embolus–a lethal complication of subclavian venipuncture. New England J. Med. Aug 28.

Galiè, M., Costanzo, M., Nodari, A., Boschi, F., Calderan, L., Mannucci, S., Covi, V., Tabaracci, G., Malatesta, M., 2018. Mild ozonisation activates antioxidant cell response by the Keap1/Nrf2 dependent pathway. Free Radic. Biol. Med. 20 (124), 114–121. https://doi.org/10.1016/j.freeradbiomed.2018.05.093. Aug Epub 2018 Jun 2. PubMed PMID: 29864481.

Hernández Rosales, F.A., Calunga Fernández, J.L., Turrent Figueras, J., Menéndez Cepero, S., Montenegro Perdomo, A., 2005. Ozone therapy effects on biomarkers and lung function in asthma. Arch. Med. Res. 36 (September-October(5)), 549–554. https://doi.org/10.1016/j.arcmed.2005.04.021. PMID: 16099337.

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., Xiao, Y., Gao, H., Guo, L., Xie, J., Wang, G., Jiang, R., Gao, Z., Jin, Q., Wang, J., Cao, B., 2020. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395 (February 15 (10223)), 497–506. https://doi.org/10.1016/S0140-6736(20)30183-5. Epub 2020 Jan 24. Erratum in: Lancet. 2020 Jan 30;:. PubMed PMID: 31986264; PubMed Central PMCID: PMC7159299.

Lupia, T., Scabini, S., Mornese Pinna, S., Di Perri, G., De Rosa, F.G., Corcione, S., 2019. Novel coronavirus (2019-nCoV) outbreak: a new challenge. J. Glob. Antimicrob. Resist. 2020 (21), 22–27. https://doi.org/10.1016/j.jgar.2020.02.0.

mn, Mawsouf, tt, Tanbouli, 2012. Vielbahn-hänsler ozone therapy in patients with viral hepatitis C: ten year's experience. Ozone Sci Eng 34 (6), 451–458. https://doi.org/10.1080/01919512.2012.720161.

Petry, G., Rossato, L.G., Nespolo, J., Kreutz, L.C., 2014. Dallazem Bertol C in vitro inactivation of herpes virus by ozone. Ozone Sci Eng 36 (3), 249–252. https://doi.org/10.1080/01919512.2013.862165.

Rowen, R.J., 2019. Ozone and oxidation therapies as a solution to the emerging crisis in infectious disease management: a review of current knowledge and experience. Med. Gas Res. 9 (October-December (4)), 232–237. https://doi.org/10.4103/2045-9912.273962. Review. PubMed PMID: 31898609.

Rowen, R.J., Robins, H., 2020. A plausible "penny" costing effective treatment for corona virus- ozone therapy. J Infect Dis Epidemiol 6, 113. https://doi.org/10.23937/2474-3658-1510113.

Sagai, M., Bocci, V., 2011. Mechanisms of action involved in ozone therapy: is healing induced via a mild oxidative stress? Med. Gas Res. 20 (1), 29. https://doi.org/10.1186/2045-9912-1-29. Dec PubMed PMID: 22185664; PubMed Central PMCID: PMC3298518.

Smith, N.L., Wilson, A.L., Gandhi, J., Vatsia, S., Khan, S.A., 2017. Ozone therapy: an overview of pharmacodynamics, current research, and clinical utility. Med. Gas Res. 7 (October 17 (3)), 212–219. https://doi.org/10.4103/2045-9912.215752 eCollection 2017 Jul-Sep. Review. PubMed PMID: 29152215; PubMed Central PMCID: PMC5674660.

Tirelli, U., Cirrito, C., Pavanello, M., Del Pup, L., Lleshi, A., Berretta, M., 2018. Oxygen-ozone therapy as support and palliative therapy in 50 cancer patients with fatigue - A short report. Eur. Rev. Med. Pharmacol. Sci. 22 (November (22)), 8030–8033. https://doi.org/10.26355/eurrev_201811_16432. PMID: 30536352.

Tortorici, M.A., Veesler, D., 2019. Structural insights into coronavirus entry. Adv. Virus Res. 105, 93–116. https://doi.org/10.1016/bs.aivir.2019.08.002. Epub 2019 Aug 22. PubMed PMID: 31522710; PubMed Central PMCID: PMC7112261.

Toung, T.J., Rossberg, M.I., Hutchins, G.M., 2001. Volume of air in a lethal venous air embolism". Anesthesiology 94 (2). Feb.

Walls, A.C., Park, Y.J., Tortorici, M.A., Wall, A., McGuire, A.T., Veesler, D., 2020. Structure, function, and antigenicity of the SARS-CoV-2 Spike Glycoprotein. Cell. 181 (April 16 (2)), 281–292. https://doi.org/10.1016/j.cell.2020.02.058 e6Epub 2020 Mar 9. PubMed PMID: 32155444; PubMed Central PMCID: PMC7102599.

Wang, Z., Zhang, A., Meng, W., Wang, T., Li, D., Liu, Z., Liu, H., 2018. Ozone protects the rat lung from ischemia-reperfusion injury by attenuating NLRP3-mediated inflammation, enhancing Nrf2 antioxidant activity and inhibiting apoptosis. Eur. J. Pharmacol. 15 (835), 82–93. https://doi.org/10.1016/j.ejphar.2018.07.059. Sep Epub 2018 Jul 31. PubMed PMID: 30075224.

Yan, R., Zhang, Y., Li, Y., Xia, L., Guo, Y., Zhou, Q., 2020. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science 367 (Mar 27 (6485)), 1444–1448. https://doi.org/10.1126/science.abb2762. Epub 2020 Mar 4. PubMed PMID: 32132184; PubMed Central PMCID: PMC7164635.

Yang, Y., Peng, F., Wang, R., Guan, K., Jiang, T., Xu, G., Sun, J., Chang, C., 2020. The deadly coronaviruses: the 2003 SARS pandemic and the 2020 novel coronavirus epidemic in China. J. Autoimmun. 109 (102434) https://doi.org/10.1016/j.jaut.2020.102434. May Epub 2020 Mar 3. Review. PubMed PMID: 32143990; PubMed Central PMCID: PMC7126544.

Zaky, S., Kamel, S.E., Hassan, M.S., Sallam, N.A., Shahata, M.A., Helal, S.R., Mahmoud, H., 2011. Preliminary results of ozone therapy as a possible treatment for patients with chronic hepatitis C. J. Altern. Complement. Med. 17 (March (3)), 259–263. https://doi.org/10.1089/acm.2010.0016. PubMed PMID: 21417811.

SIOOT - Italian Society of Oxygen-Ozone Therapy; http://www.ossigenoozono.it.