REVIEW

Ozone and oxidation therapies as a solution to the emerging crisis in infectious disease management: a review of current knowledge and experience

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Abstract

Medicine faces crisis with emerging "super bugs," lethal viruses (Ebola), and stealth pathogens such as tick-borne infections. Thousands are dying worldwide of once easily treatable diseases. Ozone therapy, extensively studied, may be a valuable adjunctive or stand-alone therapy. Ebola again ravages Africa with over 2000 already dead, carrying a 65% mortality rate. The world desperately needs safe, inexpensive and effective anti-infective therapy to which microbes will not develop resistance. Oxidation therapies have shown an extremely high safety profile, lacking credible reports of significant injury beyond vein irritation. Ozone therapy, the most studied and least expensive to perform, is in itself a germicide, not an antibiotic, and improves several physiological parameters essential for infection defense. Recent reports indicate very favorable responses to both bacterial and viral disease, inclusive of Ebola. Despite lack of commercial profitability (not patentable), medicine would do well to revisit its pre-antibiotic era oxidation therapy roots, especially ozone in the current crisis.

Key words: ozone therapy; Ebola; infection therapy; antiviral; antimicrobial; antibiotic; germicide; immune modulation; biofilm; Lyme disease

doi: 10.4103/2045-9912.273962
How to cite this article: Rowen RJ. 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. 2019;9(4):232-237.

Introduction

The world faces a crisis with failures of the very drugs that ushered in the modern medical era. Common bacteria have responded to man's use/abuse of antibiotics with stunning resistance and emergence of "superbugs." We face growing morbidity from traditionally difficult to treat infections such as Lyme and Mycobacterium avium. We have no reliably effective treatment for aggressive viral diseases, such as Ebola or viral pneumonia. Research is showing that use of antibiotics in any sector (agriculture, medicine, *etc*.) will cross contaminate the sensitivity of bacteria in all sectors. Antibiotic resistant genes are shared and transmitted across species.[1] Differing microorganisms are further responding by aggregating in mutually supportive bunker-like collectives called biofilms, where they assist and support each other.[2] These are extremely difficult to treat. A new study has shown a simple but key mechanism of how bacteria armor themselves against antibiotics by membrane charge.[3,4]

Alarms have sounded for development of new pharmaceutical antimicrobials, but every time one is released, resistance slowly or rapidly appears. "Superbugs" have emerged; thousands worldwide are dying from "untreatable" infections, and/or suffering the aftereffects of drug treatment such as Clostridium difficile or actual drug toxicity (such as fluoroquinolone). Politically, hospitals have escalated the crisis further by permitting only (U.S. Food and Drug Administration (FDA)) approved therapies out of policy. State "right to try" laws are trumped by FDA approval restrictions.[5] Yet we are ignoring utilizing the very germicides and immune enhancers provided by Nature, both external and internally generated by the body. Physicians have used germicides for generations, but in a very limited venue, generally externally or on wounds or surgeries, not systemically.

Oxidation therapies are not new, they long antedate the modern antibiotic era, but are largely ignored or forgotten. The therapies include ozone therapy (OT), ultraviolet blood irradiation therapy (UBI), IV hydrogen peroxide therapy, and high dose intravenous ascorbate. These therapies are not patentable. It is unlikely that we will ever see industry funded studies for therapies relatively inexpensive to do, and which will not generate commercial profit. Corporate Medicine and Pharma are naturally profit driven. And, oxidation suffers further (tomato effect), because many of its achievements are regarded as impossible to believe.[6]

Bacteria have had billions of years to develop resistance to oxidants/germicides in nature, such as ultraviolet light and ozone, but have not succeeded. Otherwise, we would not be here. Our immune system acutely responds to infection with immune cells generating strong oxidants, crippling invaders. Neutrophils undergo a "respiratory burst" consuming 50 or more times the amount of oxygen than at rest. Products of this burst include germicides: hydrogen peroxide, sodium hypochlorite (bleach), other oxidative species, and even ozone, a remarkable discovery.[7]

This review concentrates on OT as a unique and novel treatment for infection. Databases used include PubMed, Google Scholar, the referenced books by Veilo Bocci and Silvia Menendez (see references), and a bound volume of original

published references from the now defunct Foundation for Blood Irradiation). Finally, my extensive personal experience and knowledge of the field assisted in locating references which might not appear on any database due to dated material. Keywords for search: 1) Regarding ozone therapy: ozone therapy, Ebola, virus inactivation, antimicrobial, ozone physiology. 2) Regarding vitamin C, intravenous ascorbate. 3) Regarding ultraviolet blood irradiation, most of the world literature is older and not readily available. The author personally did a hand medical search in a university medical library to retrieve hard copies of several dozen original articles. 4) Regarding intravenous hydrogen peroxide: intravenous hydrogen peroxide, influenza pneumonia.

Ozone History

Ozone was discovered first by electrolysis of oxygen, by its peculiar odor. As triatomic oxygen, it is the strongest naturally occurring oxidant, produced in nature by lightning and solar ultraviolet radiation. Ozone was found to rapidly destroy bacteria, and employed in water purification in the late 1800s (to the present). Nikola Tesla[8] patented the first American ozone generator. Charles Kenworthy, MD, president of the Florida State Medical Association, published "Ozone" in 1885.[9] Pediatrician Robert Mayer brought the therapy to his Florida practice having learned of it from German prisoners of war on Ellis Island during World War II. He successfully treated thousands of children for various conditions, including intrathecal use for meningitis.[10] Germans further evolved OT. The development of ozone resistant materials propelled reliable generator production. The use of ozone has exploded worldwide though still relatively unknown in conventional drug-based medicine. It is produced by passing medical grade oxygen over a corona arc discharge, creating medical "ozone" from 1–5% O_3 and 95–99% O_2, or 5–70 μg/mL ozone concentration.

Ozone Chemical and Physical Characteristics

As a triatomic oxygen molecule, ozone is a most powerful oxidant. Once created medically, it is metastable, with a half-life of about 30 minutes at room temperature (72°F (~22.2°C)) and sea level before dismuting back to O_2. Two research teams have independently found major biochemical modulation induced by ozone in well published research, summarized in their two books.[11,12] Amongst these effects are 1) increased red blood cell 2,3 diglycerophosphate (greater hemoglobin oxygen release), 2) improved rheological properties of red blood cells and endothelial nitric oxide production, 3) greater arterial/venous partial pressure difference, indicating greater mitochondrial consumption of oxygen (energy production), 4) immune system modulation and reduction of inflammation, 5) improvement of antioxidant status, antioxidant enzymes (including superoxide dismutase), and glutathione in cells. The effects may be accomplished through OT generating downstream cell signaling redox molecules called ozonides and other shorter-lived reactive oxygen species (peroxides, aldehydes, *etc*.), which will affect redox status. (Bocci summarizes ozone's natural induction of cytokines, mediated by hydrogen peroxide, as safer and more effective than exogenous administration of a single cytokine, and considers ozone treated erythrocytes as "supergifted").[11]

Menendez's group also found significant "antibiotic" activity for ozone. Ozone preconditioning (absent any other treatment) of rats improved their survival to subsequent lethal injection of fecal material into the peritoneum up to 62.5%.[13] In another report, they found intraperitoneal preconditioning in combination with antibiotic synergistically improved survival up to 93%.[14] Such preconditioning also rivaled steroids in reducing tumor necrosis factor alpha release in endotoxic shock.[15]

OT has been reported to prevent human drug resistance by Mycobacterium tuberculinum.[16,17] OT may be ideal therapy for viruses. In order to successfully penetrate cells, many viruses require membrane glycoproteins in the reduced R-S-H form rather than oxidized (R-S-S-R). Reduced sulfhydryl appears required for Ebola virus to avoid neutralizing antibodies.[18] Ozone inactivates many viruses directly.[19-23]

Mirazmi et al.[24] found if the thiol groups were oxidized, cytomegalovirus lost infectivity. When thiols were chemically re-reduced (by dithiothreitol), the virus regained 65% infectivity. Sampling of viruses inactivated by ozone includes cyromegalovirus, human immunodeficiency virus, Norwalk, bacteriophage MS2, hepatitis A and poliovirus.[20-25] Reflecting on the reduction of "critical" disulfide bonds for vaccinia virus cellular entry, Ryser found that protein disulfide isomerase inhibitors limited human immunodeficiency virus-1 entry into T cells.[26] Ozone directly inactivates viruses.[19-22] Ozone gas is directly microbicidal, killing bacteria virtually on contact.[27] This will be very valuable for biofilm infections.

Routes of Administration

OT has several routes of administration. It has been used intravenously, intramuscular, into body cavities (rectum, bladder, vagina), joints, subcutaneous and soft tissue, intraperitoneal, and even intrathecally. It is highly irritating to lungs and cannot be inhaled. The most common administration method worldwide is by direct intravenous gas (direct intravenous administration (DIV)). DIV provides ease of administration, minimal medical waste, and very inexpensive (requiring only 27-gauge butterfly and a syringe once ozone generator is procured). Howard Robins has improved DIV ozone, generally starting with 20 mL gas 30–55 μg/mL and increasing volume as tolerated to 80 mL or more. However, it can irritate veins, depending on ozone concentration used. However, one benefit is that it can be used on patients with small veins.

Schmidt[28] considered intravenous oxygen to be superior to hyperbaric oxygen (HBO) in improving circulatory status of blood. (OT has been reported to be superior to HBO in reducing blood viscosity.[29]) HBO is well accepted as a treatment for osteomyelitis, and its utility demonstrates the crucial role of enhanced oxygen availability. Thousands of direct intravenous oxygen gas administrations have been accomplished in Europe for decades with no record of injury and reports of improvement in circulation, rheologic properties of blood, prostacyclin/thromboxane ratio improvement, and enhancement of eosinophil generated 15-lipo-oxygenase-1, which is an immune modulator.[28,30,31]

A commonly accepted delivery method is major autohemo-

therapy (MAH). An aliquot of blood, 50–200 mL is withdrawn in glass (preferable) or plastic container. An equal volume of ozone gas is added with mixing the two phases, and reinfused under gravity.

An apparently superior method is using a glass bottle, and adding the gas to blood under pressure (up to 2 atmospheres absolute), mixing and reinfusing the blood (not gas). It is termed hyperbaric ozone therapy (HBO_3). The method creates better admixing of the phases, and, also solubilizes oxygen gas into the blood by Henry's law, and is a much faster treatment then MAH. Depending upon concentration used, it provides up to 14.4 mg of ozone in a single 200 mL blood treatment. HBO_3 appears to provide more rapid and greater observed clinical benefits, supporting Regelsberger's intravenous oxygen concepts. HBO_3 requires a more sophisticated and expensive ozone generator. Austrian physician Johann Lahodny, MD, has pioneered "high-dose" OT by repeating the 200 mL of treated blood volume 10 times for total delivery of 144 mg ozone. He presented extraordinarily fast resolutions of wounds and clinical resolution of illness.[32] The drawback of MAH and HBO_3, especially in poorer areas, is cost and medical waste and also requires larger veins. Ten passes at 2 atmospheres absolute can also deliver up to 80 mL of plasma dissolved oxygen gas by Henry's Law, likely adding to efficacy.

Ozone is very commonly injected into body cavities, soft tissues and joints (prolozone or proloozone therapy). Local injections may have additional benefits. Ozone gas is directly germicidal and can cut through biofilm.[33,34] Ozone can be administered by rectal gas insufflation, and ingesting ozonated water.

No credible reports exist of injury by any of these methods, performed properly, other than vein irritation from DIV. (The author has surveyed his trainees on the hyperbaric technique and found no reports of problems in over 29,000 treatments). Jacobs reported OT to be exceptionally safe, with a complication rate of only 0.7 per 100,000 treatments, virtually all due to improper application.[35]

Sister Oxidation Therapies

The value of oxidation therapies in infection has been known for decades. UBI, intravenous hydrogen peroxide, and high dose intravenous vitamin C appear to work through similar mechanisms as OT.[36] UBI was widely reported as stand-alone treatment for even serious infections.[37]

Intravenous hydrogen peroxide therapy likewise antedated the antibiotic era, and was utilized to halve the death rate from influenzal pneumonia in 1918.[38] Ozone is believed to act through peroxide intermediary mechanisms. High dose ascorbate has been found to act as a prodrug for hydrogen peroxide and has been long used to treat infection.[39,40]

Published Ozone Therapy Accomplishments

The *in vivo* biochemistry and recognized virus redox dependencies spurred Dr. Robins and me to bring OT to the West African Ebola epidemic, upon invitation of Sierra Leone's president.

OT was applied by the method of DIV. Twenty cc of gas at 55 μg/mL was administered intravenously over 2–4 minutes at a volume between 20–40 mL. Patients were also provided "rectal ozone." Ozone gas was administered rectally at a concentration of 36 μg/mL and volume between 150–350 mL. "Ozone water" was made by bubbling ozone gas at approximately 70 μg/mL into water for 15 minutes, and administered by mouth, volume 300–500 mL. Additionally, the cases were provided nutritional supplements provided by donation. Thiodox® and Buffered Vitamin C® were donated by Allergy Research Group. Thiodox dose: one tablet twice daily. Vitamin C (ascorbate): 4–8 g daily during the days of ozone treatment. Due to political complications (quarantines, accessibility, disarray) during the Ebola crisis, and access to these patients, each received slightly different treatments. The exact protocol for each is available.[41]

All five patients responded immediately. Upon administration of ozone in any form, deterioration ceased. All patients made a full recovery within four days or less. The fifth case was originally reported as being asymptomatic. She was loath to disclose clinical symptoms at the time as she would have been quarantined making treatment impossible. The author discovered more than a year later, in a personal hand written letter, photoimage sent by text, that she had onset of Ebola symptoms (only a day after her physician consort died of the disease), and thanked God for availability of ozone. This patient received daily rectal and ozone water with just one DIV treatment. None of the patients suffered long-term Ebola aftereffects.

Additional Ebola cases

The author received information from the first Ebola case, a front-line physician, that the death rate at his facility "mysteriously" dropped from 60% to 20% after his return to duty. He was spiriting ozone in plastic bags for rectal administration, and ozone water, having been barred from administering it parenterally.

The small sample size, as well as the ethics of doing a "study" on a placebo for a lethal infection makes a statistical analysis moot. However, the epidemic carried a 60% mortality in the best of treatment centers. (Similar to the 65% mortality carried by the current epidemic in Congo.) The statistical "chance" result of 5 of 5 recoveries would be 0.4^5 or 0.064. However, that number only applies to "recoveries." It does not reflect the nearly instantaneous turnaround and absence of complications in our group, compared to the usual explosive deterioration once symptoms appear. Subsequent studies have shown from 77–90% "post Ebola" complication rate including, but not limited to, eye disease, arthralgias, and pain.[42,43] None of our cases had complications. The author believe that is because of OT's large scope of beneficial effects on physiology. Menendez's Cuban group demonstrated very significant protection of animals by preconditioning them with OT prior to otherwise lethal insults (lethal infection and chemical poisoning). If we add the complication rate of 77% to the above mathematics, our results by random chance would be 0.064×0.023 or 0.014.

Additional ozone cases

Case reports of OT have shown infection treatment utility both as stand-alone treatment (tick bite cellulitis), and in combina-

tion with oral antibiotic (the first reported non-surgical/non-parenteral intravenous cure of a septic prosthetic joint).[44,45] The latter utilized local joint injection which may cut through septic biofilm, along with the high-dose HBO_3 mode of blood treatment.

The tick bite cellulitis case was a male previously treated years before with OT only for Lyme with apparent full remission. He consequently refused antibiotics for his new tick bite condition. His cellulitis fully resolved within 72 hours of a single high-dose HBO_3 treatment

A male with a highly aggressive and totally uncontrolled (4 drugs including 120 mg prednisone) dermatomyositis with CK exceeding 9000 U/L arising from occult dental infection resolved totally with removal of infected jaw pathology and DIV/HBO_3 ozone therapy.[46]

Private office unreported cases of interest: A current case of Mycobacterium avium with pulmonary cavitation and debility has had an essentially full clinical recovery over 18 months with no antibiotics, using only HBO_3 and UBI. She had been given only a 30% chance of improvement by her specialists who offered antibiotics. Symptoms of measles in a person returning to the USA from abroad remitted in a few days with DIV OT.

Discussion

Oxygen is indisputably he most important factor in all healing and tissue repair. Oxidation therapies have been shown to improve oxygen metabolism and/or the intermediates involved with oxygenation. Ozone, in particular, has been the most researched, with proven modulation of cytokines, interferons, including the induction of gamma interferon.[47] It modulates inflammation, especially crucial in infection where the inflammatory process itself may take down the organism, as with Ebola. The redox properties of ozone may provide enough oxidant power to inactivate viruses, *via* membrane oxidation of sulfhydryl groups. Ozone is known to kill bacteria on contact. The germicides ozone, ultraviolet, bleach, hydrogen peroxide, *etc*. have been in medical use for well over 100 years and there has been no development of resistance. Our leukocytes make oxidant germicides to counter pathogens.

Since ozone reacts with blood components in microseconds, it is not likely that ozone itself is acting as a direct germicide (unless administered in gas form to local infection). However, its favorable effects on oxygen delivery, immune modulation, redox balance, induction of superoxide dismutase and, glutathione, and ozonide pro-oxidant byproducts, such as peroxides, all might contribute synergistically to anti-infective effects. Regarding Ebola, we surmised that as lethal as the virus is, that its redox status is its Achilles heel, which can easily and safely be exploited with OT.

Ozone is extensively used in dentistry for a wide variety of pathologies, including infection, biofilm treatment, accelerated healing, and more.[48] Ozone appears to be safe in latter pregnancy, actually improving placental function.[49]

CDC reports at least 300,000 new yearly cases of difficult-to-diagnose-and-treat Lyme disease. Antibiotic treatment failure is very high,[50-52] and there is high long-term morbidity.[53] My office has seen less than 20% failure of treatment (HBO_3 and/or UBI) to significantly (and long term) restore clinical normalcy to patients suffering tick born disease symptoms over many years of use, and without any use of chemical antibiotics. "Brain fog" often clears in the office on the first treatment, which the author believe represents rapid modulation of neurological inflammation.

Issues in the use of ozone

1. Ozone is currently regarded by the FDA as a toxic gas with no medical uses despite the presence of a plethora of publications to the contrary, which apparently, the agency has ignored. It is toxic to lungs, but its reported toxicity ends there. (Liquid water is also toxic to lungs). The worldwide medical paradigm revolves around patented profitable synthetic pharmaceuticals, which ushered in the antibiotic and modern medical era. Ozone cannot be patented for profit. Hence, financing for full study to obtain "approval" is highly unlikely. There is no financial gain. Any study funding would have to come from fully altruistic sources.

Ozone suffers from the "tomato effect".[5] Though published as safe and effective, it is ignored by conventional medicine, for the reasons listed herein and medicine's reluctance to consider anything outside FDA "approval."

2. OT suffers from regulatory board challenges. Not being pharmaceutical "standard of care" physicians have been investigated over their use of OT. The current medical paradigm of only using "approved" therapies handcuffs ozone's integration into medicine.

3. "Condemned to Die with No Right to Try."[5] Hospitals (and most conventional physicians) will not even consider non-approved (FDA) therapies. In 2018, despite providing several original published reports contained in this review's references, the author was refused permission to use ozone to treat a terminally ill infected (superbug) airline pilot, already given up to die, by a Texas hospital after the distraught family so requested, and providing liability waiver to protect the hospital. The hospitalist cited "policy" to me. The man died shortly afterwards.

4. DIV has clear advantages in cost, ease of administration, and medical waste, but can sclerose veins, and cause temporary chest tightness. It may be most suitable in third world countries and for patients who do not have the larger veins required for MAH or HBO_3.

With the critical/emergency need for answers to "superbugs," and "stealth" pathogens like Borrelia, and after effects of antibiotic therapy, medicine might do well to return to the therapies utilized before we became addicted to antibiotics for infection. This is particularly true in poverty-stricken countries, and especially with the frightening new Africa Ebola epidemic. DIV ozone cost is that of a butterfly needle and syringe beyond the ozone generator and compressed oxygen. It can be employed remotely, powered off a car battery. This makes ozone a two-edged sword. It appears to be the therapy the world urgently needs, but will be obstructed by powerful interests vested in patented pharmaceuticals.

Hospitals seeking to reduce their infectious disease mortality rate could lead the way, and quite ethically, since untreatable infections will otherwise lead to death. The "placebo" would be conventional antibiotic therapy alone, with the "experimental" group receiving concurrent OT. A hospital observational

study would be inexpensive and could be overseen by the hospital's IRB, a research luxury those in clinical practice do not have. Lack of IRB greatly hampers the type of study demanded to make the industry take notice (A "Catch-22").

Conclusion

Medicine desperately needs alternatives to antibiotics, which are failing and carry significant adverse effects. OT has the necessary biochemical requisites to offer a powerful stand alone or adjunctive therapy to assist an infected patient. Ebola is again ravaging Africa and a treatment for symptomatic cases is critically needed. Published case reports strongly support ozone utility for infectious disease management.

Ozone (and other oxidation) therapy carries virtually no known adverse or toxic effects when performed properly (other than sporadic vein issues, as can other intravenous therapies). OT can easily be carried out in medical offices, from general practice to infectious diseases.

Progress in this field is hampered by unwillingness of physicians to look/consider "outside the box" of conventional drug-based medicine, along with possible unjustifiable medicolegal concerns. Far from being a "tomato," ozone is widely used around the world with well researched and defined benefits. Office physicians, hospitals and field clinics may do well to consider revisiting oxidation therapy on behalf of infected patients. This will require a shift in the current paradigm of use of "approved" therapies only, to include a "Right to Try."

Acknowledgements

Dr. Howard Robins, private medical practice, New York, NY, USA, for his pioneering work on DIV ozone administration, and providing information on the measles case. Teresa Su, MD, private medical practice, Santa Rosa, CA, USA, my wife, for her steadfast support of the work in oxidation therapy. To Silvia Menendez, PhD, former director Havana Ozone Research Center, and Velio Bocci, MD, University of Sienna for their original basic science research. And, dedicated to the tireless efforts of ozone practitioners worldwide who have labored to overcome the "tomato effect" (an efficacious but neglected therapy because no one will believe it). Thanks to Longevity Resources of Canada for its generous donation of ozone generators for use in the 2014 Ebola epidemic.

Author contributions

Manuscript has been drafted and approved by the single author.

Conflicts of interest

None.

Financial support

None.

Copyright transfer agreement

The Copyright License Agreement has been signed by the author before publication.

Plagiarism check

Checked twice by iThenticate.

Peer review

Externally peer reviewed.

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Received: June 26, 2019
Reviewed: June 28, 2019
Accepted: July 23, 2019