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The Utilization of Ozone for External Medical Applications

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INTRODUCTION

There are many medical conditions which, in spite of the wondrous advances in antibiotic science, present clinical conundrums relative to their resistance to healing. The conditions surveyed in this text include infected wounds, poorly healing wounds, diabetic and decubitus ulcers, fungal lesions, and burns, among others.

In most of the above conditions, multiple factors play into healing resistance. Among them are circulatory difficulties, tissue injury, and immunological compromise. The central factor, however, has to do with the fact that these conditions involve the proliferation of microorganisms, which by their sheer abundance, the variety of their families, their toxin-producing capacities, and their resistance to antibiotics, offer daunting obstacles to standard treatment regimens.

Needed for optimal wound healing are agents capable of overcoming these treatment hurdles. The following discussion centers on therapeutic considerations relative to utilizing ozone/oxygen gaseous mixtures in the management of external pathological conditions.

Ozone, a natural molecule

Ozone is a molecule composed of three oxygen atoms. Created in the upper stratosphere as a result of solar ray interactions with oxygen and thus forming the outermost layer of our biosphere, ozone possesses unique properties that are being defined and applied to clinical practice. As a molecule containing high energetic potential, ozone, through still incompletely understood mechanisms, manifests bactericidal, virucidal, and fungicidal actions that may make it a treatment of choice in certain conditions and an adjunct to treatment in others.

The oxygen atom exists in nature in several forms: (1) As a free atomic particle, singlet oxygen (0), it is highly reactive and unstable. (2) Oxygen (02), its most common and stable form, is colorless as a gas and pale blue as a liquid. (3) Ozone (03), has a molecular weight of 48, a density one and a half times that of oxygen, and contains a large excess of energy (03 > 3/2 02 + 143 KJ/mole). It has a bond angle of 127° ± 3°, resonates among several hybrid forms, is distinctly blue as a gas, and dark blue as a solid. (4) 04 is a very unstable, rare, nonmagnetic pale blue gas that readily breaks down into two molecules of oxygen.

Ozone is a powerful oxidant, surpassed in this regard only by fluorine. Exposing ozone to organic molecules containing double or triple chemical bonds yields many complex and as yet incompletely configured transitional compounds (e.g., zwitterions, molozonides, cyclic ozonides), which may be hydrolysed, oxidized, reduced, or thermally decomposed to a variety of substances, chiefly aldehydes, ketones, acids and alcohols. Ozone also reacts with saturated hydrocarbons, amines, sulfhydryl groups, and aromatic compounds.

In view of the above, it is evident that external ozone application for medicinal ends is a specialized discipline requiring knowledge of ozone's physical, physiological, and antimicrobial dynamics.

OZONE AS A DRUG

Ozone's capacity to offer its oxidation potential to the task of inactivating microorganisms has been fully appreciated since the turn of the last century. In the past few decades, ozone's action against bacteria, viruses, fungi, and many protozoan species has sparked keen interest for its use as a therapeutic agent.

Ozone is a gas which, properly interfaced with pathologically afflicted tissues, exerts significant antimicrobial activity. As with many medications, however, ozone has a range of therapeutic action that, in the terminology of pharmacokinetics, is referred to as a therapeutic window. Indeed, ozone applied in concentrations that are too low, has little therapeutic effect. Applied in too high concentrations, it becomes toxic.

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Due to ozone's demarcated therapeutic range, ozone concentrations administered to the patient need to be carefully calibrated and controlled. Optimally therapeutic ozone/oxygen mixtures require state of the art quantitative (dosage, concentration), as well as qualitative (purity) controls, currently available in contemporary ozone generation technologies.

OZONE GENERATION AND ADMINISTRATION

As a gas with a half-life of approximately one hour at room temperature, medical ozone generation and delivery systems require that ozone be created at the moment it is to be administered. Ozone, in this sense is not a drug that has a shelf life enabling it to be kept for long periods of time.

Importantly, the oxygen source must be of medical grade quality and thus devoid of nitrogen or other impurities. The presence of nitrogen favors the production of tissue-toxic nitrogen oxides. With these considerations in mind, ozone needs to be conceptualized as a medication with complex therapeutic dynamics, deserving to be carefully adapted to the particular medical conditions under treatment.

In the practice of external ozone application, a specially designed ozone-resistant envelope is used to enclose the area being treated. A precise fitting of the envelope is needed in order to ensure a constant ozone/oxygen concentration within the envelope milieu and a proper containment of the gas. Ozone will thus be prevented from escaping into the ambient environment, reducing respiratory exposure to treating personnel.

The ozone concentrations prescribed during the course of treatment, the duration and frequency of individual sessions, and the lengths of the overall course of therapy are all predicated upon the evolution of the specific medical condition under treatment. In extensive wet burns, for example, initial topical ozone concentrations will need to be low in order to prevent excessive systemic ozone absorption. On the other hand, in severely infected burns, ozone concentrations may require greater initial concentrations to repel bacterial growth. With progressive epitheliazation of the burn wound, reduced ozone concentrations respect healing's delicate process.

THE EFFECTS OF OZONE ON WOUND PATHOGENS

Bacteria fare poorly when exposed to ozone, a fact appreciated since the 19th century. Ozone is a strong germicide needing only micrograms per liter for measurable action. At a concentration of 1 mg per liter of water at 1?C, ozone rapidly inactivates coliform bacteria, staphylococcus aureus, and *Aeromonas hydrophilia* [Lohr 1984]. The inactivation rate of enteroviruses is more rapid than for *E coli*, takes place in relatively small concentrations of ozone, and is influenced by pH, temperature, and the presence of ambient organic compounds (Ivanova 1983).

At dosage concentrations used in external therapy, ozone essentially inactivates all bacterial species. This holds true for oxygen-dependent aerobic organisms, for oxygen-independent anaerobic bacteria well known for causing gangrene, and for facultative species that can go either way. Ozone's universal antibacterial action makes it an agent of choice in the management of wound infections colonized by bacterial species belonging to diverse groups.

An incomplete list of bacterial families susceptible to ozone inactivation includes: The *Enterobacteriaceae*, a large group of microorganism families whose natural habitat is the intestinal tract of humans. These Gram-negative organisms include *Escherichia coli, Salmonella, Enterobacter, Shigella, Klebsiella, Serratia, and Proteus.* Other ozone-sensitive bacterial species include *Streptococci, Staphylococci, Legionella, Pseudomonas, Yersinia, Campylobacteri,* and *Mycobacteria*.

The cell envelopes of bacteria are composed of intricate multilayers. Covering the bacterial cytoplasm to form the innermost layer of the envelope is the cytoplasmic membrane, made of phospholipids and proteins. Next, a polymeric layer built with giant peptidoglycan molecules provides bacteria with a stable architecture. In Gram-positive organisms, the pepticoglycan shell is thick and rigid. By contrast, Gram-negative bacteria possess a thin pepticoglycan lamella on which is superimposed an outer membrane made of lipoproteins and lipopolysaccharides. In acid-fast bacteria, such as *Mycobacterium*, up to one half of the capsule is formed of complex lipids and glycolipids. The high lipid content of the cell membranes of these ubiquitous bacteria may explain their sensitivity, and eventual demise, subsequent to ozone exposure

The outermost bacterial layer is the polysaccharide capsule. In many bacterial species, the capsule, by way of its stickiness, enables adherence to host tissues. The capacity of Streptococcus mutans to accrete to tooth enamel, for example, is due to its capsular properties.

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The most cited explanation for ozone's bactericidal effects centers on disruption of cell membrane integrity through oxidation of its phospholipids and lipoproteins. There is evidence for interaction with proteins as well (Mudd 1969). In one study exploring the effect of ozone on E. coli, evidence was also found for ozone's penetration through the cell membrane, reacting with cytoplasmic contents, and converting the closed circular plasmid DNA to open circular DNA, which would presumably diminish the efficiency of bacterial procreation (Ishizaki 1987). Capsular polysaccharides may be possible sites for ozone action.

Fungi are frequent inhabitants of infected wounds. One study of fungal infections of burn wounds (Moussa 1999) found colonization mainly by Candida and Aspergillus. Fungal organisms neutralized by exposure to ozone include *Candida, Aspergillus, Histoplasma, Actinomycoses*, and *Cryptococcus*. The cell walls of fungi are multilayered and are composed of approximately 80% carbohydrates and 20% of proteins and glycoproteins. The presence of many disulfide bonds has been noted, making this a possible site for oxidative inactivation by ozone. Ozone has the capacity to diffuse through the fungal wall into the organismic cytoplasm, thus disrupting vital cellular function.

Protozoan organisms are sometimes found in infected wounds. Protozoan species disrupted by ozone include *Giardia, Cryptosporidium*, and free-living amoebas, namely *Acanthamoeba, Hartmonella*, and *Negleria*. Spores of *Bacillus cereus and Bacillus megaterium* were susceptible to ozone exposure at 5 minutes (Broadwater 1973). Several authors have demonstrated ozone's capacity to penetrate through the walls of *Giardia* cysts causing structural damage, and their demise (Widmer 2002, Wickramanayake 1984, Finch 1993).

CUTANEOUS PHYSIOLOGICAL EFFECTS OF OZONE

The beneficial effects of oxygenation of many dermatological conditions has long been established and forms the basis for the use of hyperbaric oxygen treatment for conditions such as carbon monoxide poisoning, decompression sickness, and gas gangrene, among others. Oxygen under pressure diffuses into tissues preferentially inhibiting the growth of anaerobic bacteria.

Ozone, however, as an added ingredient, has properties that clearly transcend oxygen administration alone. The two properties invoked are (I) A very broad range of antipathogenic action, and (2) The vasodilation of arterioles, stimulating blood and oxygen flow to lesions. This, in itself, promotes organ oxygenation, the delivery of nutrients and immunological factors to compromised tissues, and an increased venous outflow accelerating the removal of toxins.

EXTERNAL MEDICAL CONDITIONS BENEFITED BY OZONE THERAPY

In view of the above-mentioned principles of external ozone/oxygen applications, the following are conditions beneficially influenced by this unique drug therapy, utilized as a monotherapy or in conjunction with other treatment modalities:

INFECTED WOUNDS

This category of wound has, by definition, not yet reached the status of chronicity. In fact, this category of wound may simply be post-surgical and only potentially prone to infection.

The use of topical ozone therapy in these cases may be solely preventive, aimed at improving circulation on one hand and inhibiting the proliferation of potentially infective organisms on the other.

POORLY HEALING WOUNDS

Wounds healing in an indolent manner are frustratingly difficult to master. Some of these wounds are apt to regress if treatment continuity is interrupted. Generally speaking, poorly healing wounds owe their appellation to their chronicity and to the varieties of microorganisms they harbor.

Organisms are constantly in contact with pathogens, which in health, are kept at bay. Under conditions of tissue injury and stress, however, these same pathogens can blossom. Many different types of microorganisms may become involved in poorly healing wounds showing an extensive spectrum of infective diversity:

In poorly healing wounds, anaerobic bacteria - bacteria that do not need oxygen for their growth (e.g., *Bacteroides, Clostridium*) - may be active at deeper levels of the dermis, insulated from the healing influence of oxygen. Anaerobic bacteria are responsible for many devastating infections including gas gangrene. Aerobic bacteria such as *Staphylococcus epidermis, Corynebacteria*, and *Propionobacteria*, normally free-living on epidermal layers, are remarkably capable of aggressive infectivity.

DIABETIC FOOT ULCERS AND DECUBITUS ULCERS

Approximately 15 to 20% of the estimated 16 to 20 million Americans afflicted with diabetes mellitus will require hospitaliza-

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tion during the course of their illness for associated foot ulcerations, infections, or gangrene. Many of these patients, often even after prolonged intensive management, will require toe or above ankle amputations.

Diabetic ulceration is promoted by poor circulation and neuropathy. One study (Anandi 2004) reported bacterial culture results for 107 patients with diabetic foot lesions. Bacterial families cultures included: *E. coli, Klebsiella, Pseudomonas, Proteus, Enterobacter, Clostridium perfringens, Bacteroides, Prevotella*, and *Peptostreptococcus*.

Decubitus ulcers arise when a patient stays in bed, or in a wheelchair, in one position for prolonged periods of time. The pressure exerted upon the skin contact points compresses the dermal arterioles, preventing the proper perfusion of tissues. This leads to impaired skin resilience and tissue breakdown. Ulceration develops. Devoid of natural defenses normally supplied by adequate circulation, the ulcer becomes fertile ground for pathogenic microorganisms. At times, the tissue collapse is so severe and the denudation of dermal tissues so complete, that the crater of the ulcer reaches the bone and osteomyelitis begins.

The treatment of diabetic and decubitus ulcers requires a multidisciplinary approach, including surgical, topical, and systemic interventions. Topical antibiotics often fail to penetrate far enough into the wound and not infrequently cause secondary dermatitis in their own right. Furthermore, topical as well as systemic antibiotics can only address a portion of the spectrum of infective microorganisms cultured from such wounds, and are often found to have been surpassed by bacterial resistance (e.g., b-lactam antibiotic resistance, as in methicillin-resistant staphylococcus).

External ozone therapy in diabetic and decubitus ulcers provides the essential dual functions of broad-spectrum microorganism destruction and circulatory stimulation. In addition, ozone, with multiple serial applications, is able to penetrate deeper tissue layers where anaerobic bacteria are apt to reside.

GAS GANGRENE

Gas gangrene, also known as necrotizing fascitis, myositis, and myonecrosis is feared because of its rapid evolution and the galloping and irreversible demise of affected tissues. Gas gangrene may be a rapidly fatal complication of traumatic injuries such as automobile accidents, war injuries, surgical wounds, burns, and diabetic and decubitus ulcers, among many other conditions.

Predisposing factors include diabetes, arteriosclerosis, lesions associated with colon cancer, surgeries involving the intestinal tract, and septic abortions.

Gas gangrene is a fulminant infection of soft tissues. Several bacterial species are implicated in this process, the most common being *Clostridium* and toxin-producing Group A Streptococcus families. Other bacterial species are implicated in gas gangrene include *Enterobacteria, E. coli, Proteus, Staphylococcus, Vibrio, Bacteriodes, and Fusiforms*.

These anaerobic and facultative bacteria feed on glycogen and sugars, produce lactic acid, and gases such as methane, carbon dioxide, and hydrogen. Their life threatening toxins cause severe local tissue breakdown, hemolysis, renal failure, and shock.

The dynamics of tissue destruction inhibit proper antibiotic perfusion. Furthermore, many of the bacterial families implicated are apt to show antibiotic resistance.

Emergency ozone application to necrotizing lesions is an important adjunct to the multidisciplinary intensive interventions these impressively destructive wounds demand. The effectiveness of ozone is tempered, however, by the extent of tissue injury at depths that may be inaccessible to ozone action.

CIRCULATORY DISORDERS: ARTERIOSCLEROSIS and DIABETIS MELLITUS

This class of disorders has one common denominator, namely the impaired circulation to tissues via compromise of vascular integrity. A prototypic disease showing this phenomenon is diabetes. Diabetes is a complex disease marked by disturbances of carbohydrate metabolism and by vascular restriction to organ systems (e.g., retina, kidney, peripheral nerves). In situations where diabetes affects circulation to the extremities, normally minor injuries may be slow in healing.

Diabetic ulcers frequently develop following simple abrasions, contusions, and lacerations. These ulcers, not unlike decubitus ulcers, are notoriously difficult to treat and are apt to be chronically treated with topical creams and ointments. Cultures of chronic diabetic wounds, as can be expected, show the presence of numerous and different bacterial species, many of which are toxin-producing.

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Ozone topical therapy, applied serially, offers the opportunity to inactivate most - if not all - offending pathogens, thus subduing, and eventually terminating, the inexorable progression of infection. Systematically eliminating microorganisms by way of serial ozone administrations is a catalyst to accelerated healing and cicatrisation.

LYMPHEDEMA

The lymphatic system is essential for proper fluid equilibration within the body, and most importantly for adequate defense against infections. Lymphedema is a condition caused by blockage to lymphatic drainage. It may be secondary to trauma, surgical procedures, and infections.

Increasingly common is lymphedema resulting from surgical removal of lymph nodes following surgery for breast cancer. The affected arm in these patients is likely to be chronically swollen and exercises are often prescribed to develop collateral circulation. Most importantly, however, in the absence of lymphatic drainage, is the proneness to infection following even minor injuries to the affected hand and arm.

Intensive topical wound care is often recurrently instituted following serial injuries. When local measures fail, systemic antibiotics are prescribed. Preventive ozone treatment, on the other hand, applied as soon as an injury is noted, aborts infectious developments and ultimately averts the repeated use of topical and systemic antibiotics.

FUNGAL SKIN INFECTIONS

Fungi are present on human skin in a quasi-symbiotic relationship. *Candida*, *Aspergillus,* and *Histoplasma* are often found on intact skin, without causing clinical problems.

Under certain conditions, however, the normal balance of the dermis is disturbed, allowing superficial fungi to proliferate. Tinea capitis is manifested by pustular eruptions of the scalp, with scaling and bald patches. Tinea cruris is a fungal pruritic dermatitis in the inguinal region.

Fungi families are frequent invaders of wounds. *Candida, Aspergilus, Histoplasma, Actinomycoses* and *Cryptococcus*. The cell walls of fungi are multilayered composites of approximately 80% carbohydrates and 20% proteins and glycoproteins. Numerous disulfide bonds are probable sites for oxidative inactivation by ozone. In all likelihood ozone has the capacity to diffuse through the fungal wall into the organismic cytoplasm, thus disrupting cellular organelles.

Serial topical ozone applications have shown success in eradicating the most chronic and stubborn fungal skin conditions.

BURNS

Thermal burns are divided into first, second, and third degrees, depending upon the depth of tissue damage. First degree burns are superficial, and include erythema, swelling, and pain. In second degree burns, the epidermis and some portion of the underlying dermis are damaged, leading to blister and ulcer formation. Healing occurs in one to three weeks, usually leading to minimal or no scar formation. In third degree burns, muscle tissue and bone may be involved, and secondary infection is common.

In burn marked by significant tissue injury, and especially in clinical situations involving infection, topical ozone therapy finds significant usefulness. Colonizing pathogenic organisms in infected burns may show an extremely broad spectrum of colonizing families (see the section on poorly healing wounds), and thus may be ideally suited for ozone therapy.

VIRAL CUTANEOUS AFFLICTIONS

Ozone is actively neutralizing to numerous viral families. Most clearly documented are ozone's neutralizing effects on lipid-enveloped virions. These include diverse viral groups, among them the *Herpesviridae*, responsible for herpetic skin lesions.

Herpes viruses are widespread in the human population. Two distinct types of viruses are known, namely Herpes simplex type I and II. Type I is transmitted via contact through mucosa or broken skin (often through saliva), while type II is more specifically sexually propagated.

In herpetic lesions, fluid accumulates between the dermis and epidermis, producing vesicles that rupture, releasing virions. Broken vesicles are then open to bacterial suprainfections.

Herpes lesions have been extensively studied with reference to topical ozone administration. Ozone in these cases (I)

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Functions as an antiviral agent, neutralizing the herpes viruses by direct action (2) Functions as a bactericidal agent in cases involving secondary infections, and (3) Promotes the healing of tissues through circulatory enhancement. It is postulated as well that ozone may have beneficial effects on the peripheral neurons harboring these viruses.

NAIL AFFLICTIONS
Nail afflictions therapeutically assisted by topical ozone treatment include the following:

1. *Candida albicans*. Nails in this condition are painful, with swelling of the nail fold and thickening and transverse grooving of the nail architecture. Loss of the nail itself is not infrequent. Hypertrophic and dystrophic toenails mark Tinea unguium. There are currently no antifungal agents showing satisfactory efficacy for this condition.
2. *Tinea Pedis* (Athlete's Foot). This common disorder is caused by species of *Trichophyton* and *Epidermophyton floccosum*. Chronic infection involving the webbing of the toes can invite bacterial involvement. Lymphadenitis may be present, as well as infection of the nails themselves (*Tinea unguium, Onychomycosis*). Nails can become thickened, yellow, and brittle. The development of allergic hypersensitivity to these fungal organisms may be expressed systemically.

Topical ozone therapy, often prescribed for more extended periods of time, offers unique treatment opportunities for these obstinate infections. Ozone penetrates the affected areas, including the nails proper. With repeated administration, ozone is capable of inactivating all species of fungi mentioned above. Healing occurs slowly yet consistently, and skin integrity and nail anatomy gradually regain normal configurations.

RADIODERMATITIS
This condition occurs when the body is exposed to ionizing radiation. This may take place during nuclear accidents or within the course of radiation therapy. Radiation energy, imparted to tissue cells, produces widespread damage to cellular organelles and genomic matter.

Clinical findings are commensurate with the type, amount, and duration of radiation exposure. Several clinical syndromes have been delineated, including Radiation Erythema, Acute Radiodermatitis, and Chronic Radiodermatitis.

Tissues damaged by radiation are vulnerable to infection. Preventive ozone therapy in radiodermal injuries decreases the probability of developing bacterial lesions.

FROSTBITE
Factors contributing to skin injuries due to cold exposure derive from chronic vasoconstriction and the formation of ice crystals within tissues. As frostbite progresses, loss of sensation occurs and tissues become increasingly hard to the touch. Extended duration of exposure and processes related to the rewarming of tissues contribute to the development of dry gangrene. Dry gangrene may turn to wet gangrene if infection occurs.

Topical ozone/oxygen therapy has proven to be effective in decelerating or halting the evolution of frostbite through (1) The immediate oxygenation of tissues, (2) Increasing blood flow through ozone's vasodilatory effect on dermal arterioles, and (3) The prevention of secondary infection.

ADVANTAGES OF TOPICAL OZONE THERAPY
Topical ozone/oxygen therapy for the disorders mentioned above requires a precise diagnosis of the underlying conditions at hand and an appropriately tailored treatment strategy. Ozone, in some clinical situations, may be used as a sole therapeutic agent. In most situations, however, it is perfectly suited for use as an adjunctive treatment, easily combined with surgical and conventional antimicrobial therapies.

Viruses have no enzymatic protection against the oxidative challenge of ozone. And most bacterial families have only rudimentary defenses. Normal mammalian cells, on the other hand are armed with ozone-protective enzymes (e.g., superoxide dismutase, catalase, peroxidase). It is thus possible to safely treat tissue infections with ozone. Normal tissue cells are spared via their self-protection from oxidative challenge, while pathogenic microbes are felled.

The salient advantages of topical ozone therapy include:

1. The ease of administration of this therapy. Once the principles of ozone dynamics and the art of adapting ozone dosages and treatment protocols are mastered by the clinician, topical oxygen/ozone therapy can safely be applied to several common

and often therapy-recalcitrant conditions.
2. Ozone is an effective antagonist to an enormous range of pathogenic organisms. In this regard, ozone cannot be equaled. It is effective in inactivating aerobic, facultative, and anaerobic bacterial organisms, a wide spectrum of viruses, and a comprehensive range of fungal and protozoan pathogens.

To replicate this therapeutic action, complex infectious conditions would have to be treated with an assortment of various antibiotic agents, prescribed systemically and topically. In the context of contemporary medical practice, this is not feasible.

3. External ozone therapy, applied in a timely fashion, may obviate the need for systemic anti-pathogen therapy, thus saving the patient from all the side effects and organ stresses this option entails. External ozone is both a preventive, acute care, and chronic care therapeutic agent.

4. External ozone application to superficial tissues whose blood supply is abridged enhances tissue blood and oxygen perfusion.

5. There is evidence that ozone, via its oxidizing properties, inactivates bacterial toxins. Toxins are designed to inhibit tissue healing thus providing bacteria with greater colonizing advantage.

6. Ozone exerts its anti pan-pathogenic actions through entirely different mechanisms than conventional antibiotic agents. The latter must be constantly upgraded to surmount pathogen resistance and mutational strategies. Ozone, on the other hand, presents direct oxidative challenges that contemporary pathogens are incapable of circumventing.

CONCLUSIONS
Topical ozone/oxygen therapy has shown effectiveness and safety in an impressive array of medical conditions. In this article, the following are cited with emphasis: Infected wounds, poorly healing wounds, diabetic foot ulcers, decubitus ulcers, gangrene, lymphedema, fungal skin infections, and burns.

Ozone possesses unique physico-chemical attributes enabling it to exert efficient patient-safe pan-bactericidal, pan-virucidal, antifungal and antiprotozoan actions. Ozone, as it is applied in modern treatment protocols, promises to broaden its integration within contemporary medical practice.

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