

MADRID DECLARATION ON OZONE THERAPY

Approved at the "International Meeting of Ozone Therapy Schools" held at the Royal Academy of Medicine in Madrid on the 3rd and 4th of June, 2010, under the auspices of the Spanish Association of Medical Professionals in Ozone Therapy (AEPROMO)

Taking into account that since the discovery of ozone by the German chemist Christian Friedrich Schönbein in 1840, its medical use has increased in different parts of the world; there is more interest from health professionals to know how it works and what are its benefits; the number of ozone therapists keeps growing all around the world; and an increasing number of patients are benefiting from it. However its consolidation has not been easy, resistance it still found within the medical community and its recognition in the legal field will require more and coordinated efforts.

Recalling that pre-clinical research and clinical trials on the use of ozone therapy have been carried out in Cuba, Germany, Italy, Russia and other countries, with considerable scientific rigor, obtaining results that support its practice using different medical protocols.

Bearing in mind that the preclinical studies, genotoxics, toxicology and clinical studies carried out, endorse the application and the innocuous character of this medical therapy using a fairly wide range of doses.

Emphasizing that research and clinical experience with medical ozone are making progress, despite the various obstacles they face, becoming a permanent challenge for researchers and for ozone therapy associations, mainly due to the lack of access to financial resources which they need in order to be able to continue with the scientific research that is required.

Stating that it is absolutely necessary to work with specific objectives, planning globally those necessary actions, so that ozone therapists working together will be forwarding with great precision and securely the practice of ozone therapy.

Recognizing that there is variance that the medical community wishes to standardize, and that progress already has been made, that it should be taken into account; it is necessary to continue with the development of medical definitions of procedures and protocols determining the best applications where it is necessary, as well as a code of good practice, in order to overcome more efficiently the possibility of malpractice.

Welcoming with great satisfaction that ozone therapy practice was regularized in Russia in 2007 by the Federal Service Public Health Control and Social Development, the first country in the world to do so; in Cuba in 2009, by the Ministry of Public Health; in Spain, by the Balearic Islands, and the Canary Islands (2007), Madrid (2009) and Galicia, Castilla-La Mancha, and Castilla y León (2010) Autonomous Communities; that in Italy significant advances have been done towards ozone therapy by the Regions of Lombardy (2003), Emilia-Romagna (2007) and Marche (2009), and favorable court decisions have been taken by the Administrative Court of Lazio (1996

and 2003).

The speakers at the "International Meeting of Ozone Therapy Schools" as well as the associations of ozone therapy present at the same have adopted the following

CONCLUSIONS

First. To approve the "**Therapeutic Ranges for the Use of Ozone**" detailed within the "Recommendations" section of this Declaration.

Second. To increase the exchange of knowledge, research, and experiences, both positive and negative that occur in the field of ozone therapy, in furtherance of increasing the knowledge of the huge benefits that this therapy has. To stimulate the publications of research results in specialized medicine journals.

Third. To encourage health researchers to increase their creative efforts, so that, ozone therapy continues to demonstrate its therapeutic benefits with safety and effectiveness under the development of controlled clinic trials.

Fourth. To stimulate the creation of Standardized Operative Procedures, according to good clinical practices for each procedure, taking into account new developments, with the view to increase the quality and make homogeneous diverse treatments.

Fifth. To make systematic efforts to ensure that each scientific congress/meeting to be organized adopts conclusions that reflect the progress made and set achievable and realistic targets, sharing the findings and aims to encourage and promote research to deepen the understanding of ozone therapy. To work towards the harmonization and unification of criteria at the international level among different scientific societies.

Sixth. To encourage the different associations to work in their own countries where the ozone therapy has not yet been regularized to get it properly regularized and therefore to enjoy a legal status.

Seventh. To encourage the preparation of text books, the organization of theoretical courses and practical training on ozone therapy, so that those who practice it do so based on sound knowledge; this will necessarily be reflected on a more efficient medical health care which will benefit the patients.

The speakers at the "International Meeting of Ozone Therapy Schools" as well as the participants associations at the same have adopted the following

RECOMMENDATION

That the "**Therapeutic Ranges for the Use of Ozone**" as detailed in the annex to this "Madrid Declaration" and an integral part thereof, serve as a reference to ozone therapists in order for them to implement them carefully and systematically.

These "**Therapeutic Ranges for the Use of Ozone**" are the summary of scientific research in different countries and are the result of many years of experiential and

clinical practice.

The speakers at the "International Meeting of Ozone Therapy Schools" as well as the participants associations at the same

We express our most sincere recognition to **Dr. Velio Bocci**, Emeritus Professor of Physiology at the University of Siena, for the significant and important contributions he has made in favor of ozone therapy in the fields of research, teaching, information and patient care, to the point that within the ozone therapy history he must be considered as one of its most important pioneers.

Finally we express our gratitude to the **Spanish Association of Medical Professionals in Ozone Therapy (AEPRIMO)** for its initiative and implementation of this "International Meeting of Ozone Therapy Schools" warmly housed in the centenarian walls of the Royal National Academy of Medicine in Madrid.

Madrid, June 4, 2010

ANNEX TO THE MADRID DECLARATION ON OZONE THERAPY WHICH IS INTEGRAL PART THEREOF

Recommendation approved at the "International Meeting of Ozone Therapy Schools" held at the Royal Academy of Medicine in Madrid on the 3rd and 4th of June, 2010, under the auspices of the Spanish Association of Medical Professionals in Ozone Therapy (AEPRIMO)

THERAPEUTIC RANGES FOR THE USE OF OZONE

1. THERAPEUTIC BASIS

Ozone therapeutic indications are based on the knowledge that low physiological concentrations of ozone may play important roles within the cell. At molecular level, different mechanisms of action have been shown that support the clinical evidence for this therapy.

There are therapeutic, non effective, and toxic concentrations, of ozone. It has been proved that concentrations of 10 or 5 µg/ml and even smaller, have therapeutic effects with a wide security margin, so it is now accepted that the therapeutic concentrations range from 5 to 60 µg/ml. This range applies to local and systemic application techniques.

It should be emphasized that each route of application has a minimum and a maximum dosage as well as concentration and volume to manage.

All the therapeutic dosages are divided into three types, according to their mechanism of action:

a) Low doses: These doses have an immunomodulatory effect and are used in those diseases where there is suspicion that the immune system is compromised.

b) Medium doses: They are immunomodulators and stimulate the antioxidant enzyme Defence System. They are most useful in chronic degenerative diseases such as diabetes, atherosclerosis, COPD, Parkinson syndrome, Alzheimer, and senile dementia.

c) High doses: They are employed especially in ulcers or infected injuries. Also they are used to ozonize oil and water. The ozonization of oils never can be produced with a medical generator because it cannot be avoided that oil steam diffuse in the high-voltage pipes. The result is the production of several very toxic substances! Except in the generators with valve that cuts the exit of ozone.

2. OZONE THERAPY BASIC PRINCIPLES

The three basic principles that must be taken into account before any ozone treatment process is implemented are the following:

a) Primum non nocere: Before anything else, not to do any harm.

b) Stagger the dose: Start always with low doses, and increase them gradually. The exception will be in infected ulcers or injuries, where the reverse will be applied (start with a high concentration, and diminish it according to the improvement in the patient's condition).

c) Apply the necessary concentration: Higher ozone concentrations are not necessarily better, in the same way that it occurs with all the medicines.

Should the redox balance not be known (antioxidants/pro-oxidants) and the patient is in an oxidative stress, an initial medium or high dose, may damage cellular antioxidant mechanisms and aggravate the clinical picture. It is therefore preferable to start with low doses and to phase in the increase according to patient response.

3. MAIN ROUTES OF APPLICATION

Medical ozone can be applied locally or parenterally. The various routes of application of ozone can be used alone or combined, in order to attain a synergistic effect.

3.1 RECOMMENDED ROUTES OF APPLICATION

The routes of application described below are safe and proven because they are the result of many years of experience and research.

We welcome the therapeutic range indicated by the guidelines of the Russian Ozone Therapy Association, published in its "Handbook of Ozone Therapy" (2008); the "Guidelines for the Use of Medical Ozone" published by the German Medical Society for the Use of Ozone in Prevention (2009); the guidelines published by the Ozone Research Centre, scientific unit of the Cuban National Centre for Scientific Research, in its book "Ozone Basics Aspects and Clinical Applications" (2008); and the significant contribution from Dr. Velio Bocci in "Has Oxygen-Ozone Therapy a Future in Medicine? (Rev. 2010) and sent by the author to this "International Meeting."

Routes of application	LOW	LOW	LOW
	Conc. µg/ml	Vol. ml.	Doses µg
RI*	10 20	100	1000 2000
MAHT**	10 20	50 100	500 2000
MiAHT***	5 10	5	25 50

Application Routes	MEDIUM	MEDIUM	MEDIUM
	Conc. µg/ml	Vol. ml.	Doses µg
RI*	20 30	100 150	2000 4500
MAHT**	20 30	50 100	1000 3000
MiAHT***	10 20	5	50 100

Application Routes	HIGH	HIGH	HIGH
	Conc. µg/ml	Vol. ml.	Doses µg
RI*	30 60* ^a	150 30-50	4500 18000-3000
MAHT**	35 60** ^b	50 100	1500 6000
MiAHT***	10 20	5	50 100

*** RI: Rectal insufflation.**

Bear in mind that major concentrations of 40 µg/ml can hurt the enterocyte.

*^a Exceptionally, in case of acute bleeding, begin with a high concentration (60 µg/ml / ml and 50 ml Vol.) Once the bleeding diminishes, reduce concentration.

** **MAHY:** Major Autohemotherapy

*** **MiAHT:** Minor Autohemotherapy

**^b Although in general is preferred to employ concentrations around 40 µg/ml, in some cases it could be assessed the employment of until 60 µg/ml which has proved to be safe and with greater capacity of induction of citoquines.

3.1.1 Major Autohemotherapy (MAHT)

The rank of volumes to use varies between 50 ml and 100 ml. Blood volumes greater than 200 ml must be avoided to prevent any risk of hemodynamic disturbances, especially in elderly or unbalanced patients. The perfusion set to be used must be certified and never should be made of PVC or other materials that react to ozone.

Ozone concentrations of 80 µg/ml and above, should also be avoided because of the increased risk of haemolysis, reduction of 2, 3 DPG and a consequent inability of activating immunocompetent cells.

The number of treatment sessions and the ozone dosage administered will depend on the patient's general condition, age and main disease. As a general rule, every five sessions the dose of ozone is increased and it is given in cycles that vary between 15 and 20 sessions. From the clinical point of view the patient's improvement occurs between the fifth and tenth session, and it is considered that after the twelfth session the antioxidant defense mechanisms are already activated. The treatment is given in a cycle that is administered daily, from Monday to Friday and also could be administered two to three times a week.

3.1.2 Intramuscular, paravertebral and intrarticular injection

3.1.2.1 Paravertebral

The infiltration is made 2 cm lateral from the spine/column. The distribution of the needles is always bilateral, lateral or 2 cm. above and 2 cm below the hernia.

A depth from 2 to 4 cm should be considered when taking into account the patient's constitution and/or the area to be treated (smaller in thin patients and in dorsal region and greater in obese patients and lumbar region).

The treatment is done twice a week for the first two weeks and once clinical improvement is achieved, the treatments are spaced to once a week for four to six weeks and then one session every 15 days until one cycle of 20 sessions is completed, these can be shortened once the symptoms have disappeared. The recommended needle sizes for this procedure is 25 to 30 G x 1½". In some cases and with expert hands, longer needles may be used.

It is important that the physician examines adequately the muscles within the lumbo sacra region and the sacro iliac articulations to detect inflammation at this level or "trigger points" in that zone, above all in patients with discartrosis that do not respond adequately to the paravertebral infiltrations. If these points are detected they must be infiltrated.

Concentration [µg/ml] 10-20

Volume / ml 5-10

Dose / µg 50-400

3.1.2.2 Hernias

Cervical hernias

Concentration of 10 and 20 µg/ml, a volume of 5 ml is given.

Dorsal Hernias

Concentration of 10-20 µg/ml, a volume of 5 ml is given.

Lumbar Hernias

Concentration of 10-20 µg/ml, a volume of 5-10 ml is given.

3.1.2.3 Intraarticular treatment

Concentration: 5-10-20 µg/ml

Volume in function of the articulation size:

Fingers: 1-2 ml
Rest: 5 - 20 ml

3.1.2.4 Intradiscal Treatment

In general only one intradiscal infiltration should be performed, although it could be repeated within 2 - 4 weeks, under mobile radiologic arch or fluoroscopic control or CT. The patient has to be under sedation (no general anaesthesia) and with an antibiotic prophylactic therapy the same day of the procedure.

For lumbar discosis a 5-10 ug/ml mixture of oxygen - ozone at a concentration of 25-30 ug/ml is used. For cervical discosis 5 ml with the same concentration. The discosis with ozone, although is effective after only one treatment, it requires specific infrastructure (for radiological control), anaesthetist and experienced personnel in the execution of the technique. Despite the fact that the paravertebral technique requires more sessions, it is equally effective and has a minimum level of risk.

3.1.2.5 Peridural treatment (translaminar)

An infiltration is performed in the peridural space, twice weekly previous identification of the peridural space. It uses a mixture of oxygen-ozone in a volume of 5 ml at a concentration of 20 ug/ml.

The translaminar peridural method or through the sacral hiatus route is an alternative to consider in the treatment of hernial disc with ozone therapy, despite being an indirect method in relation to the intradiscal method because:

- With this method, neither the operator is exposed to the risk of undergoing radiation nor the patient.
- Upon deposit of the gas in the peridural space at the level of the conflict zone disco-radicular, the same acts over both the disk and the damaged root.
- It is easy to perform, causing no neurological damage and incorporating the patient to his/her normal life soon.
- It requires few material resources and equipment which makes it a less expensive and effective method.
- It requires fewer sessions compared to the paravertebral method as an indirect method.
- It is very useful in the presence of multiple disc hernias.
- The success rate frequency is above 70%.
- It requires a minimum time to recover.
- It can be performed in patients with major associated diseases.

In any case, the three commented techniques require of strict asepsis and sterility measures and of an informed written consent.

3.1.3 Ozone Bag

Concentrations of 60 - 40 - 30 - 20 µg/ml, are used for periods of 20 to 30 minutes, depending on the stage and evolution of the lesion. It can use 60-70 µg/ml only in purulent infections. Once the infection is controlled and the healthy granulation tissue appears, the procedure is to reduce the concentration and to space the sessions in order to support the healing.

3.1.4 Subcutaneous application

The concentration of ozone used is 5 to 10 µg/ml in very small volumes of gas (1-2 ml) with a 30 G needle.

It is also efficient in the treatment of neuropathic pain. Can also be used for cosmetic purposes in cellulite, never using a volume larger than 100 ml per session.

3.1.5 Ozone Bell or Ventosa

Using concentrations ranging from 15 to 60 µg/ml, with a variation in the duration of the treatment between 15 to 20 minutes.

3.1.6 Insufflation in fistulas

Always the practitioner must be sure first that not communication with the respiratory tract exists. It is important to keep in mind the possible gas build-up in a closed cavity, blocked or cystic to avoid dangerous or painful increases in pressure, for example in cutaneous, perianales and surgical fistulas.

3.1.7 Ophthalmologic

In ophthalmological cases (queratitis, corneal ulcers, conjunctivitis and ocular burns), a special glass attachment adapted to the contour of the eye is used. Anesthetic eye drops are applied previously and a concentration of ozone between 20 and 30 µg/ml during 5 mn. Two to three applications per week can be made combined with subconjunctival application of ozone, at a concentration of 35 µg/ml with a volume of 1-2 ml.

3.1.8 Vaginal Insufflation

Ozone concentrations of 20-40 µg/ml and a volume between 1000-2000 ml at a continuous flow rate of 0,1 to 0,2 l/min for 10 min. are used. A vaginal wash with ozonized water must be carried out previously. For this application an ozone destructor device is required.

3.1.9 Insufflation vesicourethral

Insufflate between 50 and 100 ml of ozone into the bladder or urethra, according to the case to be treated. The recommended concentrations are from 10-15-20 and 25 µg/ml (increasing them progressively). The treatment could be combined with a pre-irrigation procedure with ozonized water.

3.1.10 Otic route

The external ear is moistened and then it is insufflated using a syringe or a special headset with an ozone destructor device. Check that the eardrum is intact. Concentrations between 20-30 µg/ml during 5 mn are used.

3.1.11 Intratonsillar route

It is a secure route in patients older than 12 years old, with the condition that they can actively cooperate when they are asked to hold their breath (apnea) meanwhile the medical ozone injection is applied. Concentrations of 15-20 µg/ml with a volume of 2.5 ml per point to infiltrate at the anterior and rear pillar of both tonsils are used. Four to five sessions are required.

3.1.12 Ozone micro doses in trigger points and acupuncture

As a general rule the trigger points are located in the muscles and often deeply, so the

application has to be intramuscular and the volume can be between 5-10 ml depending on the anatomical place, and, the concentration between 10 and 20 mcg/ml.

For acupuncture points or reflexology areas the application is intradermal and fluctuates between 0.1 to 0.3 ml and up to 1 ml (maximum) of the gas mixture of O₂.O₃ with concentrations below 30 µg/ml.

3.1.13 Topical application of water, oil and ozonized creams

It is applied on wounds, ulcers and several infected lesions at different concentrations: high, medium, and low, depending on what it is intended to achieve (to disinfect, to regenerate) and of the type of tissue where it will be applied.

3.1.14 Ozonized Saline Solution

The rank of concentrations of ozone used in the phase of gas (from the ozone equipment) is of 500 mcg/l to 5000 mcg/l.

The ozonization is carried out with very low ozone concentrations which are calculated according to the weight of the patient. The formula used is 25 mcg by 1 kg of patient's weight. For example: if the patient weighs 80 kg, it is multiplied as follows: $80 \times 25 = 2000$ mcg (2 mcg/ml or 2 mg/l).

This figure corresponds to the concentration generated by the equipment, which is very low and it does not reach the 2,0 mcg/ml. Under this method concentrations generated by the ozone equipment above 3,000 mcg/l are never used.

The procedure consists of:

- To bubble 200 ml of saline solution at 0,9% during 10 mn, time necessary to obtain an adequate saturation of the solution that goes from 20 µg/ml until 200 µg/ml of concentration.
- To initiate then the transfusion of the solution by drip to the patient during 25-30 mn, keeping a constant bubbling of ozone in the bottle, to maintain its concentration in the solution.
- To cut the bubbling and the transfusion at the 150 ml, leaving in the bottle 50 ml of solution as safety margin.
- Nowadays, an ozone equipment that maintains the ozone concentration in the solution without needing to maintain the bubbling during the transfusion is available.

3.1.15 Pediatrics dosages through rectal insufflation

Systemic application via, only by via rectal.

- The concentrations to be used depend on the grade of the oxidative stress of the patient and the pathology to be treated.
- The volume to be administered depends on the age of the patient.
- To perform the rectal insufflation a catheter is introduced 1-2 cm inside the anal sphincter.

3.1.15.1 Dosages for patients with an initial value of oxidative stress graded “0” or “1” (Light one)

Weeks of treatment	Concentration O₃ (µg/ml)
First	20
Second	25
Third	30
Fourth	35

3.1.15.2 Dosages for patients with an initial value of oxidative stress graded “2” or “3” (Moderated)

Weeks of treatment	Concentration O₃ (µg/ml)
First	15
Second	20
Third	25
Fourth	30

3.1.15.3 Dosages for patients with an initial value of oxidative stress graded “4” (Severe)

Weeks of treatment	Concentration O₃ (µg/ml)
First	10
Second	15
Third	20
Fourth	25

3.1.15.4 Volumes to be administered according to patient’s age

Age of the patient	Volumes to be administered
28 days-11 months	15-20 cc
1 -3 years	20-35 cc
3-10 years	40-75 cc
11-15 years	75-120 cc

The dosage changes every five sessions. Cycles of 15-20 sessions are indicated every three months during the first year. Later the patient will be evaluated to determine frequency of the cycles for the second year.

3.1.16 Ranges of diseases for rectal insufflation and major autohemotherapy applications

3.1.16.1 LOW RANGE

- Biological regeneration
- Gout
- Fibromyalgia

3.1.16.2 LOW-MIDDLE RANGE

- Chronic kidney failure
- Cancer
- Nephropathies

3.1.16.3 MIDDLE RANGE

- Neurovegetatives illnesses: Alzheimer, parkinson, dementia syndromes.
- Pulmonary illnesses: Emphysema, COPED, acute respiratory distress syndrome.
- Ophthalmological illnesses: Retinosis pigmentarias, cataract, glaucoma, macular degeneration related to age.
- Hematology illnesses: Thalassaemia B, sickle cell anemia. • Vascular Illnesses: HTN, venous insufficiency, peripheral arterial illness, CVA, cardiac ischemia, venous stasis.

3.1.16.4 MIDDLE-HIGH RANGE

- Viral Illnesses: Herpes simple, herpes zoster, AIDS, hepatitis A, B, C, papilloma human virus.
- Diabetes
- Cerebral palsy
- Dermatological illnesses
- Orthopedic illnesses
- Giardiasis
- Candidiasis and cryptosporidiosis.
- Allergic illnesses
- Chronic fatigue syndrome
- Lupus Erythematosus Systemic
- Rheumatoid arthritis
- Crohn's illness
- Intestine inflammatory illnesses
- HIV/AIDS
- Multiple sclerosis

3.2 APPLICATION ROUTES NOT RECOMMENDED FOR NOT BEING SAFE

3.2.1 Direct intravenous injection of ozone

Its application is strongly discouraged due to the risk of air embolism which can occur

even in the case of using an slow infusion pump and volumes of 20 ml. The complications of stroke range from a simple axillary bubbling sensation, then cough, a feeling of retrosternal weight, dizziness, to changes in vision (ambliopia), hypotensive crisis, with signs of cerebral ischemia (paresis of the members) and death.

Furthermore, there is no justification to put the patient and the therapy at risk when there are methods that are safe, have been tested and are effective such as the major autohemotherapy, minor autohemotherapy and rectal insufflation.

3.2.2 Vitamins and ozone

During the treatment with ozone is necessary to suspend all the antioxidant supplements that contain vitamin C and vitamin E. The presence of these compounds in high concentrations in the blood, interferes with the ozone's action as an oxidant agent and therefore the good course of the therapy. It is important to communicate to the patient that s/he must not consume excessive quantities of foods very rich in these vitamins. In consequence, the vitamins or antioxidants should be given before or after the ozone therapy but never during the treatment.

3.3 APPLICATION ROUTE ON ANIMAL EXPERIMENTATION PHASE

Intraperitoneal

This route is still in the scientific experimental phase in animals, to which various tumor cell lines have been implanted, having found that ozone is more cytotoxic to tumor cells than many of the cytostatics used, without causing the adverse effects of the chemotherapy. The research into this matter is being undertaken by the Veterinary Services and Laboratory Animal Medicine of the Philipps-University of Marburg (Germany) by Medical Veterinarian Professor Siegfried Schulz.

It is exhorted that investigations in animals continue to be carried out.

Experimental studies for the treatment of cancer in human beings have not yielded convincing data so far.

In human beings has been used for peritonitis' treatment applying a peritoneal wash with ozonized water using 200 to 300 ml in volume with a concentration between 10 and 20 µg/ml, through a silicone catheter fixed into the cavity.

3.4 APPLICATION ROUTE PROHIBITED

Inhalation route

The inhalatory route is absolutely prohibited because of being highly toxic. The anatomical and biochemical characteristics of the lung make it extremely sensitive to oxidative damage by ozone.

3.5 APPLICATION ROUTE THAT HAS NOT RECEIVED TOTAL CONSENSUS

Ozonized Saline Solution

The Ukrainian and Russian schools utilize it as another form of systemic application of the ozone and its practice is well extended in those two countries. Its efficiency is

testified by the results of the scientific research submitted at the eight Practical Scientific Conferences that have taken place in Russia from 1992 to 2009.

Nevertheless this methodology still has not found the consensus between some schools and it is left to the criteria of the doctors whether or not to use this method.

3.6 ESSENTIAL REQUIREMENTS

The described routes of application require of technically qualified personnel to carry out any procedure, as well as a written informed consent, followed by strict measures of asepsis and sterility.

As with any another medical practice, all the material used in ozone therapy that be in contact with patient's tissue or fluids must be either disposable after only one use, or be sterilized (ex. surgical equipment), and before the administration of the ozone must pass an antimicrobial sterile filter <of 20 µm.

4. PATHOLOGIES MORE APPROPRIATE TO BE TREATED WITH OZONE THERAPY

The diseases sensible to the ozone treatment may be classified into three categories, based on the therapeutic success grade proved and obtained.

4.1 Diseases in the first category

These include among others:

- a) Osteomyelitis, pleural emphysema, abscesses with fistula, infected wounds, bed sores, chronic ulcers, diabetic foot and burns.
- b) Advanced ischemic diseases.
- c) Related to age, macular degeneration (atrophic form) because the orthodox ophthalmology gives no significant treatment.
- d) Orthopedic diseases and localized osteoarthritis.
- e) Chronic fatigue syndrome and fibromyalgia.
- f) Dental injury-related to primary cariogenic lesions, particularly in children.
- g) Estomatology for chronic and recurrent infections in the oral cavity.
- h) Acute and chronic infectious diseases, particularly those caused by bacteria resistant to antibiotics or to chemical treatments, viruses, fungi (hepatitis, HIV-AIDS, herpes and herpes zoster infection, papillomavirus infections, onichomycosis and candidiasis, giardiasis and cryptosporidiosis). Bartolinitis and vaginal candidiasis.

Although the ozone therapy represents a useful support for the treatment of these diseases, it is worth to underline that neither the ozone nor its metabolites, among them the H₂O₂, reach a germicide tisular concentration, because the free pathogens are protected by plasma antioxidants and intracellular viruses are unattainable.

For these pathologies the ozone therapy either used only as exclusive form or as a support for a specific treatment, according to the cases, becomes a medicine/treatment with a high therapeutic success.

4.2 Diseases in the second category

These include:

- a) Cancer-related fatigue. The ozone therapy associated with orthodox treatments, may

accelerate and improve results. However, ozone therapy has so far not been able to show a therapeutic effect on cancer. For all these pathologies ozone treatment should be integrated with the conventional treatment, there is evidence of its utility, but more precise studies are required

b) Asthma.

4.3 Diseases in the third category

Among others include:

a) Autoimmune diseases (multiple sclerosis, rheumatoid arthritis, Cohn's disease)

b) Senile dementia

c) Lungs diseases: emphysema, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis and acute respiratory distress syndrome.

d) Skin diseases: Psoriasis and atopic dermatitis.

e) Cancer metastasis

f) Severe sepsis and multiple organ dysfunction.

In these cases the combination of orthodox treatments and ozone therapy, at least on theoretical grounds, show that it may be useful but there is no real clinical evidence. The anecdotal evidence suggests the existence of therapeutic effectiveness but, in many cases the efficacy has been achieved by using various types of therapy, therefore the results are not reliable. In some studies the combination of ozone therapy with another treatment has been evaluated, concluding that ozone therapy acts as complement.

5. GENERAL BASIS FOR TREATMENT

Not all patients respond equally to the small, controlled oxidative stress that is produced by the ozone therapy. Therefore, the ozone treatment should always be applied in a gradual and progressive manner, starting with low doses and increasing it gradually to avoid unnecessary risks, until a clinic diagnostic method for the oxidative stress is available, which allows to adjust the dose.

It is advisable to measure and classify the state of oxidative stress on the patient, using markers such as malon-aldehyde, catalase, superoxide dismutase, glutathione peroxidase and indicators of the total antioxidant activity in the medical cabinet.

If it is not possible to measure the oxidative stress degree of the patient by either of the established methods, it is very important that the physician value according to the clinical state of the same, if he is eligible or not to receive the treatment with ozone at that moment, or if it is necessary to improve his/her nutritious state first.

As with any medical treatment, patients may be divided into three types: Normo-responders, hyper-responders and hypo-responders.

There are factors which can not be controlled, that depend of the patient's idiosyncrasy and the characteristics how the disease manifests itself.

Ozone therapy is a "medical act" and should be practiced by medical personnel and implemented with a scientific rigor, it can produce with a low frequency a minimum of adverse cases. Is for this reason that we consider that the regularization of the ozone therapy carried out by the authorities should include the following requirements, and in those cases where this has not been done the ozone therapists should apply them,

The medical centers where the ozone therapy is practiced should have the mandatory sanitary authorization for its functioning and should abide by the following requirements:

- 5.1** To have a qualified doctor with training and recognized experience in ozone therapy, this will be the persona responsible for the management of the treatment.
- 5.2** To use the appropriate equipment to generate and apply the ozone therapy, these should have also the required authorizations from the appropriate sanitary authorities. In the case of the European Community, should be marked with the CE. The equipment to generate ozone must be calibrated or revised periodically, according to the recommendation of the manufacturer, to avoid incorrect applications or concentrations.
- 5.3** To use medical oxygen provided by an authorized company.
- 5.4** To implement the various and appropriate protocols, according to the administration route chosen, in order to guarantee the quality in the treatment. The protocols should be appropriately validated and recognized by the scientific ozone therapy associations.
- 5.5** To establish an informed written consent, this should be signed by the patient and the medical doctor responsible for the implementation of the ozone therapy, leaving a copy in the clinical history of the patient.
- 5.6** To have an appropriate airing and ventilation system.
- 5.7** To have life saving drugs, ventilation support equipment or an Ambu balloon.
- 5.8** To take into account that the inter disk application of ozone should be done in a surgical room within a hospital centre or in an ambulatory unit for major surgery.
- 5.9** The key to the therapeutic success depends on diverse controllable factors that include the scientific preparation and technique of the ozonoterapist, the method that is employed, the quality of the ozone, the general application of the good clinical practices. The non controllable factors depend on the patient idiosyncrasy and in what is current state of the illness.

Madrid, June 4, 2010

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