8TH WORLD OZONE THERAPY FEDERATION MEETING

WFOT's Good Clinical Practices in Medical Ozone Treatment Guidelines in Medicine

WFOT official document on the occasion of the Sao Paulo World Congress, August 2024

WORLD FEDERATION OF OZONE THERAPY

This work was developed by the Scientific Advisory Committee of the WFOT (World Federation of Ozone Therapy), which played an essential role in curating and validating the content presented. We especially relied on the invaluable contributions of Dr. Lamberto Re, whose expertise was crucial in the analysis and preparation of this document, along with the significant contributions of the authors whose articles are referenced in the bibliography.

PREFACE

WFOT (https://wfoot.org/wfot-members-list) currently represents the majority of world associations active in scientific research and applicative methods of medical ozone treatment (MOT).

In accordance with the statute of our association aimed at **surveying, organizing** and **supporting** all ozone professionals around the world, WFOT proposes this official document which must be understood as an ***"International Consultative Reference"*** with the most recent indications on the best practices of the MOT.

The text was drawn up following the directives of the WFOT Scientific Advisory Committee and listening to the most recognized colleagues who have practiced ozone since its first uses in medicine as an integrative tool in mainstream healthcare, in the prevention of the damage of aging and in the improvement of the quality of life.

However, we had to clarify that in certain medical conditions that involve inflammation at its maximum expression, like disc herniation, MOT is more than a tool for prevention or improvement of quality of life, but rather it is an etiological treatment.

Since the beginning of its constitution, WFOT has been active in giving support to facilitate the recognition of the clinical uses of ozone in medicine in agreement with the Best Clinical Practice in most of the Countries whose Ozone Associations are included in its organization without any political or economic preclusion towards all the other countries in the world interested in promoting acts and initiatives to support the best use of Medical Ozone **(MO)** for the sole purpose of providing a further therapeutic option of care and support to people who cannot find relief with the common medical treatments.

Being the oldest International Federation, WFOT is aware of the difficulties encountered over the years in making MOT recognized as a medical approach with strong scientific evidences and thus obtaining a clear and complete acceptance as a novel medical resource by the medical authorities themselves.

Today, however, we can rejoice at the attention we are starting to receive from some supranational and political institutions which finally opens a glimmer of concrete hopes towards new horizons.

At the beginning of its first uses, starting from the early years of the last century, MOT was introduced mostly as a medical act according to the empirical approaches *"let's try to do"*

or *"right-to-try"* without any regulation by the competent authorities and for this reason mostly considered as *"quake"* therapy.

Furthermore, the lack of scientifically based guidelines has relegated this technique to the margins of official medicine with considerable damage to the image of a treatment that deserves other judgments and in any case a more serious and critical evaluation in relation to its increasingly evident clinical actions.

However, the time is now ripe to re-evaluate the MOT also in light of a new methodological approach according to different pharmacotherapy schemes where the use of protocols such as that of one *"tablet-per-day"* is no longer acceptable and appropriate when compared to a personalized administration of the various drugs taking into account the nature of the active ingredients as well as the characteristics of the various patients as proposed for psychiatric patients[1].

In fact, the body weight and mass, the life style, the rate of metabolism and the diet are elements that must be always considered for any modern therapeutic approach. Furthermore, the characteristics of the active molecule, its hydrophilicity or lipid solubility, its rate of first hepatic passage, its acidity or alkalinity, and so on, have pushed clinicians towards new guidelines which cannot be constructed with rigid schemes but must be designed with a certain variability taking into account the above, especially in the case of the MOT.

With this document it is our intention to fill the gap giving to physicians, dentists, veterinarians and all health professionals working in the field of MOT the best basis on its uses, indicating the suggested ranges of dosage and modality of administration but avoiding to suppress the individual experience of the physician which only listening and seeing his patient could decide for the best therapeutic procedure to be used following science and conscience.

It is strongly recommended to approach each person who could benefit from this treatment with an interview based first on a clear explanation of the MO characteristics and subsequently aimed at collecting information relating to the anamnestic parameters and to the description of the symptoms as they are perceived.

Any instrumental tests that can help to refine the best protocol to use must be finally evaluated only after these first steps.

We must never forget that MOT requires much more personal involvement than that which may be required for a conventional pharmacological treatment!

Despite the above, we reinforce the concept that for any medical treatment it becomes essential to listen to those who turn to the doctor for help, and this is even more important and necessary for those innovative holistic treatments such as those based on MO.

WFOT is also active in defending MOT from the too many attacks and accusations too often based on not scientific reasons and simply due to the lack of the minimum knowledge on the ozone molecule and on its properties when used at appropriate doses[2].

However, most of the side effects happened during MOT are mainly due to malpractice or lack of a basic knowledge of the application technique. We will focus on them in separate chapter 2.

Furthermore, the best recommendations on the medical ozone generator (MOG) that could better satisfy the delivery of the appropriate doses in the different protocols have been already produced by WFOT[3].

We have found MOG that produce 50% or less of the ozone amount they should, producing remarkable pitfalls in the treatments.

This is the reason of the partnership program that WFOT has set up in order to guarantee the quality of the MOG's.

Following the international references[4, 5, 6,] ***guideline*** is a document with the aim of guiding decisions and criteria regarding diagnosis, management, and treatment in specific areas of healthcare.

In contrast to previous approaches, which were often based on tradition or authority, modern medical guidelines are based on an examination of current evidence within the paradigm of **evidence-based medicine.**

They usually include summarized consensus statements on best practice in healthcare.

A healthcare provider is obliged to know the medical guidelines of his/her profession and must decide whether to follow the recommendations of a guideline for an individual treatment.

Modern clinical guidelines identify, summarize and evaluate the highest quality evidence and most current data about prevention, diagnosis, prognosis, therapy including dosage of medications, risk/benefit and cost-effectiveness.

Guidelines may lose their clinical relevance as they age[7, 46] and newer research emerges. As such, the quality of guidelines may vary substantially, especially for guidelines that are published on-line.

In response to many of these problems with traditional guidelines, the BMJ created a new series of trustworthy guidelines focused on the most pressing medical issues called BMJ Rapid Recommendations[8].

It is an idea to develop by WFOT as soon as these guidelines are published.

Last but not least, the recent event organized at the European Parliament under the auspices of MEP Dolors Montserrat by the title ***"New horizons for healthcare in Europe: the medical ozone therapy and its multiple benefits"*** with the participations of members of WFOT as expert of the sectors and chaired by our vice president Prof. Jose Baeza Noci, will open new perspectives for a possible introduction of its regulation in order to obtain the final recognition at the highest Institutional level ***(European Parliament, Bruxelles, Feb 14th 2024).***

"I strongly hope that this first step will encourage the development of other initiative at governmental level in the aim to start up official directives and rules to regulate the field of MOT and its full recognition by the health authority worldwide",

Lamberto Re M.D., Chairman of the WFOT Scientific Committee.

ACKNOWLEDGMENTS

The creation of this document on Ozone Treatment Guidelines, launched worldwide during the 8th WORLD OZONE THERAPY FEDERATION MEETING – held from August 29 to 31, 2024, in São Paulo, Brazil – is the result of a collective and tireless effort by many professionals and collaborators committed to advancing science and clinical practice. We would like to express our deepest gratitude to all those who, throughout this journey, have dedicated their time, knowledge, and passion to make this work a reality.

To those who have always supported the World Federation of Ozone Therapy (WFOT), and who, with vision and determination, have driven initiatives, debates, and research that have significantly contributed to the development of this work, we extend our sincere thanks. This document, which now materializes, reflects the commitment of a community that understands the importance of a practice grounded in ethical, human, and scientific principles.

We recognize, with special appreciation, all those who have sacrificed precious moments with their families, leisure time, and even their professional activities to dedicate themselves to this project. The construction of this work required not only technical and scientific knowledge but also immense personal dedication. This publication is undoubtedly a testament to the joint effort of many who shared the belief that Ozone Treatment plays a fundamental role in the health and well-being of society.

To the healthcare professionals, researchers, and educators who, directly or indirectly, contribute to making Ozone Treatment increasingly recognized, ethical, and effective, we extend our gratitude. You are the pillars that support and promote the growth and credibility of this practice on the global stage.

We also cannot fail to express our gratitude to the patients, who are ultimately the reason for all our work. Your trust drives us to continuously seek the best for health and well-being, and it is for you that we dedicate ourselves tirelessly to the pursuit of innovations and improvements in Ozone Treatment. Each advance achieved is a step further toward a safer, more effective, and more accessible practice.

Finally, to all those who, directly or indirectly, have contributed to the creation of this work

of excellence, our deepest and most sincere gratitude. This WFOT official document, “Good Clinical Practices in Medical Ozone Treatment Guidelines in Medicine,” is a milestone, not only in the history of Ozone Treatment but also in the history of those who, with passion and dedication, work for its recognition and appreciation worldwide.

Antonio Teixeira

President of the World Federation of Ozone Therapy (WFOT)

President of the 8th WFOT MEETING

President of the ABOZ (Brazilian Association of Ozone Therapy)

CHAPTER 1

INTRODUCTION TO OXIDATIVE MEDICINE

Oxidative Medicine (OM) deals with all those activities or treatments that from a purely neuro-physiological and metabolic point of view involve the cellular mechanisms responsible for maintaining the oxidative homeostasis of our organism and the metabolism of oxygen at the mitochondrial level.

Moderate physical activity, although not included among conventional medical therapies, represents an example of OM that can help the human organism to reduce metabolic imbalances linked to obesity or metabolic diseases such as diabetes, as reported by many prestigious scientific journals[9, 10, 11].

Recently, more and more scientific works are indicative of therapeutic actions associated with a good nutritional lifestyle, *"nutraceuticals"*, or resulting from a brief and adequate oxidative stimulus, very similar to the "physiological oxidative stress" defined as *"eustress"*, which could successfully integrate conventional therapies, moreover at low costs and without side effects[12, 13, 14].

MO falls into this last category which, in common with the other techniques mentioned above, involves the key metabolic pathway for the control of oxidative stress and therefore aging, the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway.

GENERAL REMARKS ON MO AND OM

MO is an oxygen (O_2)/ozone (O_3) mixture (OO) consisting of purest oxygen and purest ozone, produced from medical graded pure oxygen (in accordance with pharmaceutical legislation) using a MO generator (MOG: REGULATION (EU) 2017/745 or equivalent directives in non-European countries) in a concentration range between 1 and 100 µg/ml (mg/L)[15].

Contrary to technical and smog ozone, the MO is produced from pure medical oxygen via silent electrical discharge; it is not recommended to use oxygen concentrators or oxygen/air mixtures due to their nitrogen component and the consequent possibility of nitrogen oxides being formed in the discharge tube.

MO is a molecule with a well-defined spectrum of action and a half-life of about 30-40 minutes at 20°C and must be prepared on site to be available for any type of application required.

As the concentration and decomposition rate of ozone is extremely dependent on different parameters such as temperature, pressure, volume flow rate, etc., MOG should be designed to ensure continuous concentration control.

Ozone produced in excess, either as part of the generator gas or after local application, must always be completely reduced back to oxygen to avoid odor and inconvenience to the respiratory tract; correspondingly, the system must be equipped with high-power catalysts as destructor.

Quality assurance has been widely described in the WFOT document on MOG to which we refer the readers[3].

The maximum workplace concentration according WHO[16] is 100 µg/m3 (for 8 hours time); although specially sensible people are only safe at a concentration of 70 µg/m3.

The more recent discoveries on ozone mechanisms indicate an model of action similar to that of the *hormetic response*[17, 18]. Indeed, being a *strong oxidant,* when used at higher doses could be useful for cleansing infected wound and to produce ozonated water, while

a paradoxical antioxidant response is promoted at *adequate lower doses.*

The latest scientific evidence indicates that the Nrf2 biochemical pathway represents the master regulator activated following MOT[19, 20]. Interestingly, the same mechanism seems to be involved also in other field of ***evidence based medicine*** like nutrition, physical activity, supplementation with agents like curcumin and other.

A dietary support based on nutraceutical rules could induce surprising modulation of many vital functions like MOT does. Our body burns oxygen to produce energy and the Nrf2 pathway is the key to maintain it efficient, reducing the unavoidable damaging of age secondary to redox imbalance[21].

This hormetic behaviour related to ozone modulation is also observed in several molecules or even particles called *"stressors"*[22, 23, 24]. Venoms, ultraviolet, X-ray, laser beam and almost any radiation induces in the body a similar *hormetic response*[25, 26, 27].

This is the reason why we propose to define MOT better as a ***health resource*** in which the gas ozone is the tool used to induce a controlled stimulus (*acute oxidative stress*) that consequently induce the same cells to modulate their redox balance and, secondary, reducing inflammation status throughout the Nrf2 and the nuclear factor-kB (NF-kB) pathways.

The concentration and dose ranges for therapeutic application proposed by WFOT are listed below and will be discussed, justified and defined properly in the chapter 3.

Application	Ozone Concentration Range (µg/mL)	Ozone Volume Range (mL)*	Total Dosage Range (mg)
Systemic Treatment (Blood)			
Major Blood Ozonation (MBO)	15-50	70-200	1.05-12.0
Minor Blood Ozonation (mBO)	15-40	10	0.15-0.4
Systemic Treatment (Insufflations)			
Rectal Insufflations (RI)	15-40	50-300	0.75-12.0
Parenteral Treatment (Injections)			
Pain Syndrome	8-25	5-30	0.04-0.75
Aesthetic	2-15	20-200	0.04-3.0
Disk Herniation	12-30	5-40	0.06-1.2

Topical Treatment (Bagging)			
Wound cleansing	60-100	not defined yet	
Wound healing	10-30	not defined yet	
Others			
Vaginal	15-40	100-200	1.5-8.0
Auricular	5-40	50-200	1.5-8.0

*** Regarding the MBO, former Auto Hemo Therapy, the WFOT Advisory Committee, in the aim to maintain constant the dose per Kg of ozone administered, suggested to withdraw an amount of blood equal to the Body Weight multiplied by 1.5. An equal volume of OO at ozone doses varying from 15 to 50 µg in relation of the patient illness, will be then mixed to the taken blood.**

However, application techniques and doses still vary to a certain extent and more comparative studies are needed to base the final decision on solid evidences; in the present document we propose dosage based on evidences when possible (EB guideline) or on consensus when we lack of good evidence (RGP).

PROPOSED DEFINITION OF MO

Treatments based on MO, former Ozone Therapy, include those techniques which are based on the administration of the ozone molecule in its unique chemical formulation deriving from an electrical or UV excitation of the oxygen molecule through various routes.

All other techniques that involve the manipulation or modification of the ozone molecule after its production and before its administration cannot, for obvious reasons, fall into this context, regardless of their presumed clinical activity.

The reasons are not only linked to the lack of adequate scientific literature that can support a certain clinical efficacy deriving from the administration of chemical species other than the ozone mother molecule, but to the possibility of promoting serious and unpredictable side effects that would inevitably harm the entire healthcare sector of the OM.

In fact, the most important exception for not including among the MOT the techniques based on the administration of the ozone molecule not in its primitive form, is mainly linked to the lack of studies on the potential toxicity, acute or chronic, resulting from the administration of products derived from the possible chemical interaction after its production.

PREPARING THE MO

From the premises it can be understood that one of the fundamental factors for good therapeutic success, and to guarantee maximum safety in terms of patient protection, is represented by the generator of the OO mixture to be administered during a MOT.

It is worth remembering here that the oxygen molecule simply represents the transporter of the main ingredient ***"ozone molecule".***

Furthermore, a gentle mixing of the mixtures is suggested just for a few seconds, being the kinetics of ozone decomposition very rapid in presence of organic material.

To date there are no regulations or laws that govern the sector indicating the essential characteristics for a MOG for human or animal use.

All scientific societies in the sector, in the absence of obvious conflicts of interest such as WFOT, should promote the marketing of any equipment that meets the minimum good manufacturing requirements such as component quality, concentration accuracy, use of medical oxygen and any other characteristic aimed at protecting good clinical practices (Good Clinical Practice) for the sole purpose of directing the operator towards the most accurate choice.

Unfortunately, in the absence of regulations imposed by the health authorities, this is not sufficient and sometimes we witness the use of generators marketed without the necessary controls which can represent not only a risk for the patient, but above all the production of mixtures that are not adequate to activate those surprising actions which, according to the most accredited scientific literature, are consequent to the use of this resource.

THE OZONE MOLECULE IS ONE AND ONLY ONE WITHOUT ANY TRADEMARK!

PHARMACOLOGY OF MO

As is known, MOT is not comparable to any pharmacological treatment and therefore other definitions and protocols are needed to describe its clinical activity, in order to design adequate clinical studies.

We also agree on the need for a more in-depth evaluation to better characterize the possible mechanisms of action, both from a biochemical, physiological and also pharmacological point of view.

These data will be fundamental for the implementation of adequate clinical studies that could finally confirm, or not, the positive effects that this treatment produces in many apparently heterogeneous pathologies.

In this context, epigenetics may represent the best solution to understand this apparent paradox, especially in aging: *the modulation of gene expression*[28].

In fact, we know that in some conditions, such as *cytosine methylation*[29], a silencing of a gene can be observed and therefore a lack of expression of the same gene *(epigenetic antagonism).*

In contrast, *histone acetylation*[30] makes DNA more accessible for transcription because chromatin takes on a more relaxed shape due to increased steric hindrance. Therefore, gene expression will increase *(epigenetic agonism).*

Epigenetic describes what happens in organisms or cells identical in genotype but with different phenotypic expression, therefore without any change in the DNA sequence[31, 32].

Every day we introduce food into our body or carry out moderate physical activity which can modify the expression of our genome.

A classic example is homozygote twins, individuals who have the same genotype and who have no differences at birth, not even at an epigenetic level, but who, due to different environmental stimuli, may or may not develop different pathologies, such as diabetes.

For the above considerations, but not only, MOT could represent a fundamental complement to pharmacotherapy and surgery in supporting conventional medicine protocols.

In fact, it can represent a powerful aid both in promoting the action of the drug and in reducing the inevitable side effects.

In particular, some recently discovered biochemical mechanisms and pathways represent a formidable help in making more understandable and scientifically incontrovertible the possible positive effects induced by oxidative treatments and ozone in particular.

The evolution of mammals on our planet strictly depends on oxygen and its mitochondrial metabolism capable of allowing life in a hostile environment such as the one that temporarily hosts us.

It seems at least probable that the cells of organisms so dependent on this molecule have been equipped with control mechanisms capable of verifying, and possibly correcting, any anomalies in both the supply and metabolism of oxygen.

Two fundamental molecules deputed to the regulation of cellular oxidative processes, and therefore concerning the OM, are represented by HIF-1α[33] (*hypoxia-inducible factor 1-alpha,* Fig. 1) and by the transcription factor Nrf2[34] *(nuclear factor erythroid 2-related factor 2,* Fig. 2).

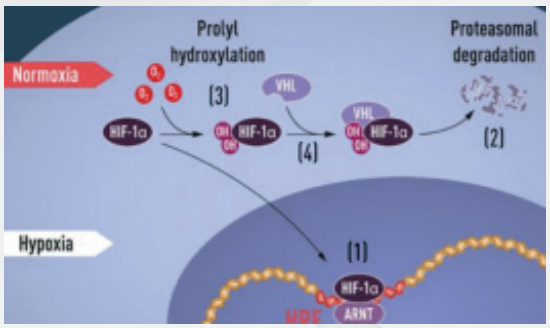


Fig. 1

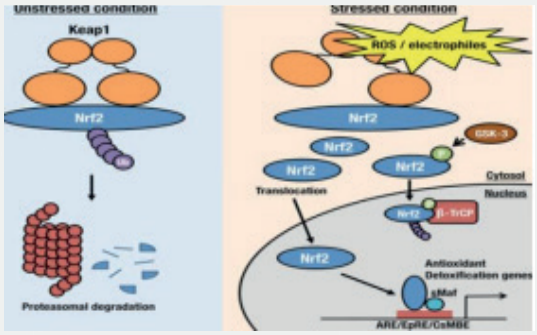


Fig. 2

In 1997, Itoh et al[35] published the first work proposing Nrf2 as a transcription factor capable of modulating hundreds and perhaps more genes involved in the cytoprotective response helpful in restoring the oxidative homeostasis and more.

Under physiological conditions, i.e. when the oxidative homeostasis of the cell is normal, Nrf2 is maintained at a low level and, like HIF-1α, is degraded by the ubiquitin-proteasome system.

Alternatively, in case of *mild oxidative stress, environmental stimuli or pharmacological* interactions, the Nrf2 protein migrates towards the DNA segments of the ARE (Antioxidant Response Elements) area.

This activation in turn favours the synthesis of proteins that regulate the redox state and many other functions, with the aim of keeping our cells healthy and protected from excess oxidative stress.

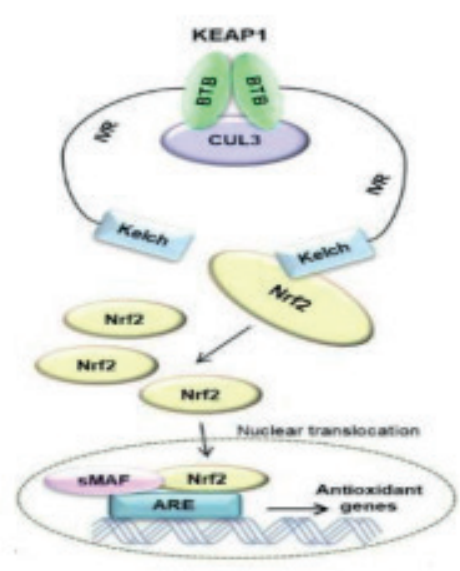
The first hypotheses on the mechanisms of action of ozone in mammals, when used in adequate doses, were based on the fact that a short and controlled oxidative stimulus leads to the formation of reactive oxygen species and lipid peroxides, which in turn act as second messengers[36].

The seemingly paradoxical concept that ozone can induce an antioxidant response able to reverse transient oxidative stress is common in the animal and plant kingdom and is supported by the

evidence of an increase in the level of antioxidant enzymes after a brief and adequate oxidative stimulus.

Today we know that cellular adaptation to oxidative stress is successfully modulated by a surprising intracellular mechanism: *"The Nrf2 pathway"*.

In fact, we now have proof that, in addition to other pharmacological agents or adequate stimuli, ozone is also able to activate Nrf2 (Fig. 3), thus explaining the multi-organ effects promoted by adequate doses of this gas.



The first two articles that demonstrated a direct effect of ozone on the Nrf2 metabolic pathway in humans were by Sagai and Bocci in 2011[37] and confirmed in vivo by Re et al in 2014[14].

All other effects induced at a systemic level can be interpreted as the result of an adaptive response mediated at a genetic level and activated by moderate oxidative stress or other agents as described in the work of Cuadrado et al[38] in the prestigious scientific journal Pharmacol Res.

Indeed, MOT should be better defined as a *"resource"* to maintain a healthy body by preventing apparently heterogeneous pathological conditions, such as immune, inflammatory, cardiovascular, neurological, dermatological, as well as oncological conditions that share the same pathogenetic and biochemical: *"oxidative stress"* and *"Nrf2"*.

The concepts illustrated above, far from being considered obsolete or out of date, are described as follows in the work of Cuadrado mentioned above:

"Life expectancy has almost doubled in the last century and diseases specific to aging are becoming increasingly frequent. However, the pathological mechanisms underlying most of them are not well understood and are treated more with symptomatic therapies than with prevention and correction of risk factors."

In the case of MOT, as in all the medical treatments and in particular when oxidative stress is involved[39], it is important to personalize the therapy which must be adapted to the patient's own characteristics, taking into account his or her aptitudes such as nutrition, lifestyle and need for supplementation.

For example, the lack of some cofactors essential for the antioxidant activity at mitochondrial level (manganese, Mn) and cytosolic (copper, Cu and zinc, Zn) enzymes such as superoxide dismutases (SOD 1, 2 and 3) can modify their antioxidant activity and cause variability in the patient's overall response.

This fact, together with other individual characteristics, makes us understand how treatments based on indirect techniques such as oxidative ones require more accurate personalization both in the treatment and in the protocol, which can never be identical in all patients treated. Reading Cuadrado's 2018 work the concept of *"Systems Medicine"* (SM), already proposed by Zeng BJ in 1992[40], seemed the most appropriate to understand effects similar to those obtained with MOT.

Therefore, we suggest to use this concept as a likely explanation for the striking effects of ozone on seemingly heterogeneous human diseases, including the physiological process of aging, in which a common epigenetic mechanism controlled by Nrf2 is shared.

In the same article cited above, the authors described the complexity of a series of diseases included in a group called "*the NRF2 diseasome*" that share the same mechanism linked to the nuclear transcription factor *(erythroid-derived 2)-like* 2 (Nrf2): "*Interestingly, this network includes heterogeneous phenotypes such as autoimmune, respiratory, digestive, cardiovascular, metabolic and neurodegenerative diseases, along with cancer and many other conditions.*"

Colleagues with some experience in the field of ozone will note the similarity between the clinical results obtained with this gas with the same apparently heterogeneous diseases included in the group cited by Cuadrado, in which the modulation of Nrf2 represents the common etiopathogenetic mechanism for all diseases included in the same group.

In a work proposed by Hybertson et al[15], Nrf2 is described as a regulatory factor and is defined as follows: *"Nrf2 is known as the 'master regulator' of the antioxidant response, modulating the expression of hundreds of genes, including not only the well-known antioxidant enzymes, but a host of seemingly disparate genes that control processes such as immune and inflammatory responses, of tissue and fibrosis, carcinogenesis and metastasis, and including cognitive and neurological dysfunctions in general".*

One of the major problems in the interpretation and clinical evaluation of treatments that act with an indirect mechanism compared to the drug, which acts mostly via receptor action, is the poor *"reproducibility"* and the low *"reliability"* in relation to the doses to be used and the underlying result in terms of the patient's clinical response as occurs precisely in a receptor-type steric bond. Deepest study following SM paradigm will be, to our opinion, one of the primary task for the better evaluation of clinical action induced by MOT.

CHAPTER 2

CONTRAINDICATIONS, SIDE EFFECTS AND SUPPLEMENTATION

We summarize below the main conditions that must be evaluated before administering MO and mostly related to the treatment to be executed.

Obviously, as for any kind of medical approach, a careful clinical evaluation of the patients with a full anamnesis is mandatory to exclude any attitude or risk to develop a side effect.

In chapter 7 section 2 of the document entitled ***"WFOT's review on Evidence Based OT"***[41], we proposed a short list of contraindications and justify them with the appropriate literature.

Infiltrative Treatments:

- Pre-existing infection of the skin, muscles or at the injection site.

  To be noted by the current literatures, most of the complications are simply due to bad asepsis;

- Any condition that could hinder the injections, as convulsive syndrome, that is, sudden frequent involuntary contractions of the muscles caused by pathological impulses of the central nervous system (CNS).

Systemic Treatments:

- a decrease in the blood's ability to clot (e.g. thrombocytopenia; major G6PD deficiency); (excluding rectal applications);

- hyperthyroidism and cardiac anomalies;
- any acute disease that could lead to death without a clear recommendation for MOT.

Relative contraindications:

- pregnancy.
- any uncontrolled and severe disease that could worsen without a clear recommendation for MOT.

SIDE EFFECTS

Regarding the side effects, we must always remember that most of the literature is related to pollution and to the severe negative effects of ozone when breathed due to the complete lack of antioxidants in the alveoli.

We can therefore consider this the only real side effect of ozone which, however, in our opinion, does not justify the complete closure by the majority of health authorities, including the FDA, who continue to consider this molecule devoid of any potential activity in the medical field and should always be considered as a toxic agent!

In the context of the injection methods we suggest paying particular attention to the following conditions:

- Erisipela or phlebitis. Any condition of vascular complications.
- Pain and vagotonic reaction after puncture.

The Table below include all the complications associated with MO found on PubMed in the period 2000-2024 using the following Keywords:

Ozone Treatment complications and side effects.

Procedure	Side Effect	Probable Cause	Explanation	Year	Reference
AHT (MBO)	Death	Air embolism	Was it really an MBO? The patient had POF	2000	Marchetti D, La Monaca G. An unexpected death during oxygen-ozone therapy. Am J Forensic Med Pathol. 2000 Jun;21(2):144-7
AHT (MBO)	Acute Myocardial Infarction	This side effect was not associated with procedure There was an author's bias	The authors seems to have poor knowledge regarding MOT. They attribute AMI to ozone, 12 hours after the procedure. They do not justify their conclusion with adequate bibliography. Our comment included	2017	Üreyen ÇM, Baş CY, Arslan Ş. Myocardial Infarction after Ozone Therapy: Is Ozone Therapy Dr. Jekyll or Mr. Hyde? Cardiology. 2015; 132:101-104. Lamberto Re, Robert Rowen and Valter Travagli, Ozone Therapy and Its Use in Medicine, Cardiology 2016; 134:99–100

AHT (MBO)	Sinus arrest	There isn`t enough data in this paper. 9 continius AHT in an hipertensive patient.	Hemolysis produced by continuous transfusions Release of potassium in a patient with alterations in creatinine clearance	2017	Tang WJ, Jiang L, Wang Y, Kuang ZM. Ozone therapy induced sinus arrest in a hypertensive patient with chronic kidney disease: A case report. Medicine (Baltimore). 2017 Dec;96(50):e9265.
AHT (MBO)	Non ST myocardial Infarction	There isn`t enough data. There isn´t clear syncope causes. Patient had POF	Authors don`t substantiate their conclusion and association is not clear The bibliography is not correlated with the conclusions. It could be an error in the implementation of the technique. See our comment	2020	Bingham A, Platt M. A Non-ST Elevation Myocardial Infarction Associated with Alternative Medicine Ozone Infusion. J Emerg Med. 2020 Jan;58(1):106-109. Lamberto Re, Dane Keller Rutledge, Angeles Erario, Jose Baeza Noci, Valter Travagli, Silvia Menendez, and Philip J. Mollica. Correcting Misinformation about the Science and Practice of Evidence-Based, Safe and Effective Ozone Therapy, 2021, ISSN 0736-4679, https://doi.org/10.1016/j.jemermed.2021.08.001.
Intradiscal	Acute bilateral vitreo-retinal hemorrhages	Increase in intracranial pressure	Accidentally Intradural infiltration	2004	Lo Giudice G, Valdi F, Gismondi M, Prosdocimo G, de Belvis V. Acute bilateral vitreo-retinal hemorrhages following oxygen-ozone therapy for lumbar disk herniation. Am J Ophthalmol. 2004 Jul;138(1):175-7.
Intradiscal	Anton´s syndrome	Vertebrobasilar stroke Hypoperfusion of the basilar trunk.	Vasogenic edema	2004	Corea F, Amici S, Murgia N, Tambasco N. A case of vertebrobasilar stroke during oxygen-ozone therapy. J Stroke Cerebrovasc Dis. 2004 Nov-Dec;13(6):259-61.
Intradiscal	Ventral and dorsal root injury	Abrupt and transient increase of the CFP	Mechanism underlining this injury is not clear. Accidental intradural infiltration	2006	Ginanneschi F, Cervelli C, Milani P, Rossi A. Ventral and dorsal root injury after oxygen-ozone therapy for lumbar disk herniation. Surg Neurol. 2006 Dec;66(6):619-20; discussion 620-1
Intradiscal	Thunderclap headache	Pneumocephalus	Accidental intradural infiltration	2007	Devetag Chalaupka F, Caneve G, Mauri M, Zaiotti G. Thunderclap headache caused by minimally invasive medical procedures: description of 2 cases. Headache. 2007 Feb;47(2):293-5.
Intradiscal	Pyogenic discitis	Infection	Lack of sterility during infiltration	2009	Bo W, Longyi C, Jian T, Guangfu H, Hailong F, Weidong L, Haibin T. A pyogenic discitis at c3-c4 with associated ventral epidural abscess involving c1-c4 after intradiscal oxygen-ozone chemonucleolysis: a case report. Spine (Phila Pa 1976). 2009 Apr 15;34(8):E298-304

Intradiscal	Discitis	Infection	Complication of the percutaneous treatment	2014	Fort NM, Aichmair A, Miller AO, Girardi FP. L5-S1 Achromobacter xylosoxidans infection secondary to oxygen-ozone therapy for the treatment of lumbosacral disc herniation: a case report and review of the literature. Spine (Phila Pa 1976). 2014 Mar 15;39(6): E413-6. doi: 10.1097/BRS.0000000000000195. PMID: 24384664.
Intradiscal	Anton´s syndrome	inhalation oxygen-O3 therapy for 1 week	Error in the implementation	2015	Avcı S, Büyükcam F, Demir ÖF, Özkan S. Anton syndrome during oxygen-ozone therapy. Am J Emerg Med. 2015 Jun;33(6): 856.e1-2. doi: 10.1016/j.ajem.2014.11.041. Epub 2014 Dec 2. PMID: 25511367.
Intradiscal	Persistent low back pain	hard adhesions between the soft tissues and bony structures	Authors don´t explain mechanism	2015	Vanni D, Galzio R, Kazakova A, Pantalone A, Sparvieri A, Salini V, Magliani V. Intraforaminal ozone therapy and particular side effects: preliminary results and early warning. Acta Neurochir (Wien). 2016 May;158(5):991-3. doi: 10.1007/s00701-016-2755-y. Epub 2016 Mar 15. PMID: 26976001.
Intradiscal	Discitis	Infection	Accidental transesophageal infiltration	2016	Andrés-Cano P, Vela T, Cano C, García G, Vera JC, Andrés-García JA. Cervical Spondylodiscitis After Oxygen-Ozone Therapy for Treatment of a Cervical Disc Herniation: a Case Report and Review of the Literature. HSS J. 2016 Oct;12(3):278-283. doi: 10.1007/s11420-016-9500-1. Epub 2016 Apr 18. PMID: 27703423; PMCID: PMC5026656.
Intradiscal	Anton´s syndrome	Gas embolism	Accidental vascular infiltration in a patient with POF	2016	Vaiano AS, Valente C, De Benedetti G, Caramello G. Transient cortical blindness after intradiscal oxygen-ozone therapy. Indian J Ophthalmol. 2016 Dec;64(12):944-946. doi: 10.4103/0301-4738.198858. PMID: 28112142; PMCID: PMC5322716.
Intradiscal	Thunderclap headache	Pneumocephalus	Accidental intradural infiltration	2017	Toman H, Özdemir U, Kiraz HA, Lüleci N. Severe headache following ozone therapy: Pneumocephalus. Agri. 2017 Jul;29(3):132-136. doi: 10.5505/agri.2016.36024. PMID: 29039154.

Intradiscal	Abscess	Infection	Accidental trans-esophageal infiltration	2018	Yang CS, Zhang LJ, Sun ZH, Yang L, Shi FD. Acute prevertebral abscess secondary to intradiscal oxygen-ozone chemonucleolysis for treatment of a cervical disc herniation. J Int Med Res. 2018 Jun;46(6):2461-2465. doi: 10.1177/0300060518764186. Epub 2018 Mar 27. PMID: 29584512; PMCID: PMC6023037.
Intradiscal	Paradoxical embolism Acute Myocardial Infarction	Gas embolism	Patient with POF	2019	He R, Huang Q, Yan X, Liu Y, Yang J, Chen X. A Case of Paradoxical Embolism Causing Anterior Spinal Cord Syndrome and Acute Myocardial Infarction Following the Intradiscal Oxygen-Ozone Therapy. Front Neurol. 2019 Feb 22;10:137. doi: 10.3389/fneur.2019.00137. PMID: 30853936; PMCID: PMC6395432.
Intradiscal	Severe Headache	Pneumocephalus	Accidental intradural infiltration	2020	Andreini I, Arrigucci U, Monti L, Bellini M, Battisti C, Federico A. A case of pneumocephalus as complication of ozone therapy: diagnosis and treatment. Neurol Sci. 2020 Feb;41(2):481-483. doi: 10.1007/s10072-019-04062-4. Epub 2019 Sep 2. PMID: 31478149
Intradiscal	Sudden dyspnea, followed by coma and death	Suspected Pulmonary Embolism	The authors don´t have enough data and assume gas embolism due to the symptoms and because it is a gas.	2019	Chirchiglia D, Chirchiglia P, Stroscio C, Volpentesta G, Lavano A. Suspected Pulmonary Embolism after Oxygen-Ozone Therapy for Low Back Pain. J Neurol Surg A Cent Eur Neurosurg. 2019 Nov;80(6):503-506. doi: 10.1055/s-0039-1685197. Epub 2019 Aug 20. PMID: 31430795.
Intradiscal	Discitis	Infection	Lack of sterility during infiltration	2020	Shahi PB, Panigrahi V, Adsul N, Kumar M, Acharya S, Kalra KL, Chahal RS. Mycobacterium abscessus mimicking tubercular spondylodiscitis following ozone therapy: A case report and review of literature. Surg Neurol Int. 2020 Apr 4;11:63. doi: 10.25259/SNI_50_2019. PMID: 32363058; PMCID: PMC7193194.
Intradiscal	Discitis	Infection	Lack of sterility during infiltration	2021	Salaria AK, Dhatt SS, Kumar V, Neradi D, Sodavarapu P, Kumar N. Mycobacterium tuberculosis Infection of the Spine Secondary to Oxygen - Ozone Therapy for Prolapse Intervertebral Disc: A Scoping Review. J Orthop Case Rep. 2021 Jun;11(6):23-26. doi: 10.13107/jocr.2021.v11.i06.2242. PMID: 35437492; PMCID: PMC9009488.

Intradiscal	Spondylodiscitis, septic arthritis and gluteal abscess	Infection	No isolating the etiological agent Lack of sterility during infiltration	2023	Erroi F, Rotondo C, Sciacca S, Trotta A, Cantatore FP, Corrado A. Serious spondylodiscitis, septic sacroiliitis and multiple abscesses after ozone therapy for low back pain: A case report on good response to combined treatment with empiric antibiotic and neridronate. Int J Rheum Dis. 2023 Aug;26(8):1590-1593. doi: 10.1111/1756-185X.14632. Epub 2023 Feb 22. PMID: 36814395.
Para-vertebral	Septicemia; death	Local infection with systemic dissemination	Lack of sterility during infiltration Insufficient data	2007	Gazzeri R, Galarza M, Neroni M, Esposito S, Alfieri A. Fulminating septicemia secondary to oxygen-ozone therapy for lumbar disc herniation: case report. Spine (Phila Pa 1976). 2007 Feb 1;32(3):E121-3. doi: 10.1097/01.brs.0000254125.85406.6e. PMID: 17268255.
Para-vertebral	Neurological symptoms	bilateral cerebral hypoperfusion	Vasogenic edema	2012	Rolán DV, Lopez MM, Cuberas-Borrós G, Cuñat JL, Hervás JV, Vilamajó AM, Escudero D. Neurological symptoms following exposure to ozone. J Neurol. 2012 Dec;259(12):2740-2. doi: 10.1007/s00415-012-6667-3. Epub 2012 Sep 27. PMID: 23014692.
Para-vertebral	Abscess	Infection	Lack of sterility during infiltration	2014	Menéndez P, García A, Peláez R. Absceso paravertebral e intraabdominal secundario a ozonoterapia por lumbalgia [Paravertebral and intra-abdominal abscess due to oxygen-ozone therapy for lower back pain]. Rev Esp Cir Ortop Traumatol. 2014 Mar-Apr;58(2):125-7. Spanish. doi: 10.1016/j.recot.2013.06.003. Epub 2013 Aug 4. PMID: 24071048.
Para-vertebral	Multifocal stroke	Gas embolism	Accidental arterial infiltration	2019	Freund PR, Alshafai L, Margolin EA. Multifocal Stroke From Ozone Gas Emboli. J Neuroophthalmol. 2019 Dec;39(4):518-519. doi: 10.1097/WNO.0000000000000754. PMID: 30741783.
Para-vertebral	Posterior Reversible Encephalopathy Syndrome	Hypoperfusion	Vasogenic edema	2020	Nociti V, Picarelli C, Losavio FA, Reale G, Giuliano G, Della Marca G, Tumbarello M. Posterior Reversible Encephalopathy Syndrome After Intramuscular Oxygen-Ozone Therapy. Can J Neurol Sci. 2020 May;47(3):416-418. doi: 10.1017/cjn.2020.35. PMID: 32077386.

Para-vertebral	Massive emphysema and pneumomediastinum	Air in the mediastinum	Accidental and inappropriate infiltration	2021	İlhan B, Doğan H. Novel complication of ozone therapy: Massive emphysema and pneumomediastinum. Am J Emerg Med. 2021 Mar;41:190-192. doi: 10.1016/j.ajem.2020.03.045. Epub 2020 Mar 25. PMID: 32245704.
Para-vertebral	Neurological symptoms	Hypoperfusion	Vasogenic edema	2021	Haggiag S, Prosperini L, Stasolla A, Gerace C, Tortorella C, Gasperini C. Ozone-induced encephalopathy: A novel iatrogenic entity. Eur J Neurol. 2021 Aug;28(8):2471-2478. doi: 10.1111/ene.14793. Epub 2021 Mar 19. PMID: 33657263.
Intra-articular	Septic arthritis	Infection	Lack of sterility during infiltration	2012	Seyman D, Ozen NS, Inan D, Ongut G, Ogunc D. Pseudomonas aeruginosa septic arthritis of knee after intra-articular ozone injection. New Microbiol. 2012 Jul;35(3):345-8. Epub 2012 Jun 30. PMID: 22842605.
Experimental Model	DNA-damage in human leukocytes	Insufficient data	The paper has methodological biases.	2002	Díaz-Llera S, González-Hernández Y, Prieto-González EA, Azoy A. Genotoxic effect of ozone in human peripheral blood leukocytes. Mutat Res. 2002 May 27;517(1-2):13-20. doi: 10.1016/s1383-5718(02)00022-0. PMID: 12034304.
Experimental Model	Inflammation	Insufficient data	The paper has methodological biases.	2004	Torossian A, Ruehlmann S, Eberhart L, Middeke M, Wulf H, Bauhofer A. Pre-treatment with ozonized oxygen (O3) aggravates inflammation in septic rats. Inflamm Res. 2004 Aug;53 Suppl 2:S122-5. doi: 10.1007/s00011-004-0352-7. Epub 2004 Aug 10. PMID: 15338062.
Experimental Model	Worst clinic status	Insufficient data	The paper has methodological biases.	2015	Martín-Barrasa JL, Méndez Cordovez C, Espinosa de los Monteros y Zayas A, Juste de Santa Ana MC, Clavo Varas B, Herráez Thomas P, Bordes Benitez A, Montoya-Alonso JA, García-Bello M, Artiles Campelo F, Tejedor-Junco MT. Rectal pre-treatment with ozonized oxygen (O3) aggravates clinic status in septic rats treated with amoxicillin/clavulanate. Enferm Infecc Microbiol Clin. 2015 Aug-Sep;33(7):469-75. doi: 10.1016/j.eimc.2014.09.006. Epub 2014 Nov 4. PMID: 25459192.

We can conclude that all MOT techniques SHOULD be done or controlled by physicians well trained in their execution, as most of the side effects arise when there is malpractice[2], usually due to a bad training or to ignoring what has been learned.

This is also the conclusion of the classic work of M.T. Jacobs, published in 1981[42] *"We have the feeling that doctors don't learn from our past mistakes!"*

In Annex I, we propose a form for reporting adverse reactions (ADR-OT) to WFOT.

NOTES REGARDING SUPPLEMENTATION DURING MOT

MOT integration/supplementation includes the following:

- Cofactors of the oxidative stress (Se , Mn, Cu, Zn, Iron, other[43])

- Amino acids and derivatives (arginine, acetylcysteine, etc.[44])

- Antioxidant (glutathione, Vit C, Vit E, etc.[45]);

- Other (NSAID's, Corticoids, Homotoxicological Products, Iron, other)

Integration before, during or after the MOT is not prohibited but rather recommended as long as some precautions are taken into account in order to avoid unwanted interactions in relation to the mechanism of action of the MO.

Furthermore, being the activity of ozone mostly bound to the modulation and the over expression of detoxifying enzymes like superoxide dismutase (SOD), catalase (CAT) and other, it is essential the presence of cofactors indispensable for their enzymatic activity.

Indeed, the mitochondrial and cytosolic SOD are dependent from Selenium-Manganese and Copper-Zinc respectively. The lack of these trace elements could delay or reduce the clinical efficacy of an ozone treatment.

Regarding aminoacids like arginine we know that most of the vascular activities induced by MOT are driven by nitric oxide (NO). Thus, the lack of the precursor of the synthesis of NO could similarly reduce or delay any clinical action induced at this level.

Finally, it is strongly recommended to avoid the administration of antioxidants, both orally and parenterally, at least in the days preceding each MOT treatment in order to minimize any interference with the characteristic mechanism of action of MO with effects that could delay or reduce the adaptive response of the organism.

On the other hand, the supplementation with antioxidant agents after the treatment with

ozone of agents acting with different mechanisms of action, could help to reach the best response from our patients in relation to the total antioxidant status taking into account that the concept of the "*total antioxidant capacity (TAC)*" has many limitations that preclude its significant application in vivo conditions, being a measure applicable mainly in vitro.

The concomitant use of NSAIDs or steroids could be a powerful remedy during the first sessions in subjects with severe pain or inflammation. In fact, in addition to counteracting drug-induced side effects, ozone is also able to increase the clinical efficacy of painkillers such as diclofenac or similar when administered simultaneously. Many clinical observations (unpublished data) are indicative of an increased anti-inflammatory action when used in combination with ozone. Injections of diclofenac 50 mg and betamethasone 2-4 mg together with MO could help increase patient compliance during the first sessions in case of severe pain. Patients report that the use of the same drugs before starting ozone treatment did not produce any positive action on the symptoms while their administration together with ozone drastically reduced the symptoms with the onset of a surprising well-being of the patients.

Obviously, the use of *betamethasone* is absolutely forbidden in diabetic patients and that of *diclofenac* in patients with atopic predisposition to allergy.

CHAPTER 3

USES IN MEDICINE

Let's start by saying that looking at the latest discoveries which are indicative of an indirect action of ozone through second messengers activated by different metabolic pathways such as Nrf2, NF-κB and others, the dose of ozone in the OO mixtures to be administered cannot be considered as a key factor, at least as regards the desired clinical action.

Indeed, while in the past the effects induced by ozone where defined following the dose administered to patients, looking at the fact that its activity is completely different to that of drugs for the lack of any interactions with specific receptors, this concept must be revised.

Nevertheless, the dose is always very important and must be personalized following individual susceptibility to the induced oxidative stress. This is the only reason why it is important to adapt the amount of ozone to the response of the patients, also in terms of clinical and individual characteristic like oxidative status in the moment of the treatment, the thyroid function, the body weight and other.

Once again we want to emphasize that the issue of the patient's oxidative status must be definitively clarified, since, being a dynamic variable that changes at every moment of daily life, it is strictly linked to the current metabolic activity and therefore very difficult to measure in real time. However, it is certainly a factor of fundamental importance in relation to the overall response of the patient treated with medical ozone.

The dosages indicated below for the different clinical conditions and treatment modalities must be considered as indicative ranges deriving from the experience gained on thousands and thousands of treatments performed throughout the world by health professionals expert in MOT and suggested in the various consensus conferences that have taken place over the years.

It will be a task of the single clinician to modify and to adapt the doses looking at the best response of every single patients but always taking care of the indications of this docu-

ment that, as said above, is derived from the experience and clinical practice of the most authoritative experts in the sector.

Finally, we can state that MO could be useful in all pathologies, acute, sub-acute or chronic, resulting from trauma or aging of the musculoskeletal system thanks to its action in increasing the availability of oxygen to the tissues, in reducing inflammation and in the ability to induce a marked positive action on the microcirculation.

All of the above must always be taken into account in the preparation of protocols for each individual patient as ozone is a very useful multi-target option to promote the innate healing of all tissues of the body by reducing the damage resulting from age or any postural or functional anomaly.

Approach to patients – General Rules

Patient clinical evaluation:

Medical examination:

Concomitant Drugs Regimen:

Customized Informed Consent Form for the therapy:

Reading and signing of the Informed Consent by the Patient:

Blood Tests

Prescriptions on the utilized materials:

- Disposable vinyl gloves;
- Mandatory use of recognized Medical Devices;
- MOG Devices Following WFOT directives;
- Accurate sterility during the performance.

I Session – Human Medicine

A – Injections - General Rules

Method description:

1. Position the patient in relation to the treated part of the body.

2. Ozone-resistant antibacterial filter on the valve of the machine or on the collection syringe.

3. Perform an extensive and deep cutaneous disinfection with sterile gauze.

4. See the respective protocols for technique.

5. Remove the antibacterial filter and connect the needle directly to the syringe.

6. Then proceed and aspirate with the syringe piston in order to avoid the wrong positioning of the tip of the needle in a vein/artery. In case of presence of venous/arterial material, change area and repeat the preventive aspiration procedure.

7. Refill the syringe by collecting from the ozone machine, through the ozone-resistant antibacterial filter, the OO with the defined ozone concentration.

8. Remove the antibacterial filter and connect the needle directly to the syringe.

9. Proceed with the OO administration, by following these rules:

   a. Slowly, by avoiding relevant pain manifestations.

   b. Pull out slowly the tip of the 1÷3 mm needle in the presence of high administration pressure, by performing the aspiration again as explained in point 6.

   c. By limiting the OO quantity to be injected in the recommended dosages and volume.

10. The infiltration is to be repeated bilaterally.

11. Leave the patient in a prone position for a few minutes.

12. Invite the patient to take a supine position until a full subjective wellbeing condition is achieved.

13. Invite the patient to take a sitting position, while checking the absence of dizziness or vagal symptoms.

14. During the whole procedure keep a constant verbal contact with the patient.

First Aid plan to recover potential patient situations when needed:

Symptom	Treatment
Heaviness or local tension: sometimes during or right after infiltration, caused by the mechanical action of the OO in the muscular tissue.	Generally spontaneous regression doesn't need treatment.
Muscular hematoma.	Local ice wrapping
Pain Burn and intense pain that might persist for an hour.	Generally there is a spontaneous regression
Vagal hypertonus crisis with sweating, face paleness.	Supine patient in Trendelemburg
Vagal hypertonus crisis with bradycardia, hypotension.	Supine patient in Trendelemburg
Loss of consciousness or cardiorespiratory arrest	Phlebological therapy (250 cc. saline solution)
	Alert the emergency service (JB35)

In case of no results symptomatic pharmacological therapy:

- Oxygen mask at 12 l/min.
- Atropine e.v. 0,5 mg.
- hydrochloride etilephrine, 2 mg.

(ex : dilution of 10 mg in 10 ml of saline solution, administrate 2ml refractory boles).

In case of extreme bradycardia or cardio respiratory arrest start cardiopulmonary resuscitation:

Basic Life Support (BLS)

A open air ways

B forced ventilation

C cardiac massage

Advanced Life Support (ALS)

Adrenaline and Defibrillator if present.

Brilliant scotoma, headache, sensation of thorax constriction, tingling limbs (also mono lateral), loss of visus (also mono ocular) Lateral Left Decubitus.

Call anesthetist resuscitating doctor, if present in the building.

Alert the emergency service following directives of the actual country.

Medicine and necessary medical devices list for MOT emergencies

- Epinephrine (ex. Effortil) EV phials or drops
- Atropine EV phials
- saline solution ml. 500 with infusion kit
- cannula needle a/o Butterfly
- NSAID's EV phials , tablets o drops (ex. Diclofenac, Ketorolac)
- AMBU with dedicated facial masks
- Oro tracheal cannulas
- Oxygen tank
- Oxygen mask with connection tube for the oxygen tank
- Adrenaline
- Metilprednisolone (ex. Solumedrol)
-

Attention!

Prearrange medicine and medical devices list;

Check at least once a month the presence or due date of the medicines and medical;

Miscellanea;

OO microdoses generally reduce the side effects of possible associated therapies (NSAIDs or some steroids), leading to better compliance and greater therapeutic efficacy.

A1 - Paravertebral

Conditions suggested for treatment: Back Pain, Disk Protrusion and Hernia, Spinal Arthrosis, Post disk hernia surgery residual pain (FBSS), Spinal Canal Stenosis

A1_1 Lumbar Area

Anatomic part: L1÷S1 spine

Number of infiltrations for each cycle : 12 ÷ 15

Minimum time interval between one infiltration and the next one: 2-3 days

Maximum time interval between one infiltration and the next one: 15-30 days

Time interval between a treatment cycle and the next one: 6 months (Follow UP)

OO Volumes to be injected: 5 ml for each infiltration.

Maximum total volume to be injected for session: 40 ml.

OO concentration: from 10 to 20 µg/ml.

References: 47-59

Disposable materials:

- Needle:

    Diameter/Gauge: from 21 to 27 G

    Length: from 16 to 50 mm in relation to the thickness of the adipose tissue

- Antibacterial filter : 0.22 µm x 25 mm

    - Single use syringe for MOT: from 20 to 30 ml in Polypropylene

- Pre-treatment medication : Sterile Gauze Taps, Disinfectant

- Post-treatment medication : Medicated patch, Gauze

Technique:

Once the disk spaces are identified through the cutaneous anatomical landmarks represented by the spinous processes or through instrumental guide, insert the needle in the paravertebral muscle bundles perpendicularly to the skin 2-3 cm from the inter spinous area to be treated. The needle is introduced so that it goes beyond the adipose tissue, punctures the muscle bundle and reaches the paravertebral muscle.

A1_2 - Cervical Area

Anatomic part: C3÷T1 spine and trapezoidal/supraspinatus muscles

Number of infiltrations for each cycle : 10 ÷ 12

Minimum time interval between one infiltration and the next one: 3 days

Maximum time interval between one infiltration and the next one: 7-15 days

Time interval between a treatment cycle and the next one: 6 months (Infiltrations recalls if needed)

OO Volumes to be injected: 2-4 ml for each infiltration.

Maximum total volume to be injected for session: 25 ml.

OO concentration: from 10 to 20 µg/ml

References: 60-61

Disposable materials:

- Needle:

Diameter/Gauge: from 25 to 30 G

Length: from 13 to 35 mm in relation to the thickness of the adipose tissue

- Antibacterial filter : 0.22 µm x 25 mm

- Single use syringe for MOT: from 20 to 30 ml in Polypropylene

- Pre-treatment medication : Sterile Gauze Taps, Disinfectant

- Post-treatment medication : Medicated Patch, Gauze

Technique:

Once the disk spaces are identified through the cutaneous anatomical landmarks represented by the spinous processes or through instrumental guide, insert the needle in the paravertebral muscle bundles perpendicularly to the skin 2-3 cm from the inter spinous area to be treated. The needle is introduced so that it goes beyond the adipose tissue, punctures the muscle bundle and reaches the paravertebral muscle.

A1_3 - Dorsal Area

Anatomic part: T1÷T12 spine

Number of infiltrations for each cycle : 10 ÷ 12

Minimum time interval between one infiltration and the next one: 3 days

Maximum time interval between one infiltration and the next one: 7-15 days

Time interval between a treatment cycle and the next one: 6 months (Infiltrations recalls if needed)

OO Volumes to be injected: 3-5 ml for each infiltration.

Maximum total volume to be injected for session: 30 ml.

OO concentration: from 12 to 25 µg/ml

References: 62-65

Disposable materials:

- Needle:

Diameter/Gauge: from 21 to 27 G

Length: from 20 to 50 mm in relation to the thickness of the adipose tissue

- Antibacterial filter : 0.22 µm x 25 mm

- Single use syringe for MOT: from 20 to 30 ml in Polypropylene

- Pre-treatment medication : Sterile Gauze Taps, Disinfectant

- Post-treatment medication : Medicated Patch, Gauze

Technique:

Once the disk spaces are identified through the cutaneous anatomical landmarks represented by the spinous processes or through instrumental guide, insert the needle in the paravertebral muscle bundles perpendicularly to the skin 2-3 cm from the inter spinous area to be treated. The needle is introduced so that it goes beyond the adipose tissue, punctures the muscle bundle and reaches the paravertebral muscle.

A2 – Perinervous percutaneous in nervous entrapment syndrome

Conditions suggested for treatment: Median Nerve (Carpal Tunnel Syndrome), Ulnar Nerve (Guyon Syndrome), Posterior Tibial Nerve (Tarsal Medial Tunnel Syndrome), Deep Peroneal Nerve (Anterior Tarsal Tunnel Syndrome), External Popliteus Sciatic Nerve, Lateral femoral cutaneous nerve (Meralgia Paraesthetica)

Anatomic part: Wrist, Foot, anterior higher iliac spine .

Number of infiltrations for each cycle : 5 ÷ 12

Minimum time interval between one infiltration and the next one: 2-3 days

Maximum time interval between one infiltration and the next one: 7-15 days

Time interval between a treatment cycle and the next one: 6 months (Infiltrations recalls if needed)

OO Volumes to be injected: 1.5-4 ml for each infiltration.

Maximum total volume to be injected for session: 15 ml.

OO concentration: from 8 to 12 µg/ml

References: 66-69

Disposable materials:

- Needle:

    Diameter/Gauge: from 23 to 27 G

    Length: from 13 to 25 mm in relation to the thickness of the adipose tissue

- Antibacterial filter : 0,22 µm x 25 mm

    - Single use syringe for MOT: from 10 to 20 ml in Polypropylene

    - Pre-treatment medication : Sterile Gauze Taps, Disinfectant

    - Post-treatment medication : Medicated Patch, Gauze

Technique:

Once the space through the anatomical osteo-muscular-cutaneous landmarks is identified, insert the needle in the perinervous site. The needle is introduced so that it passes the skin and get to the nerve; it's possible to evoke a paraesthesia followed by a 1-2 mm retraction of the needle, in order to avoid an intra neural administration..

A3 – Trapezoid-metacarpal periarticular percutaneous

Conditions suggested for treatment: Rhizarthrosis

Anatomic part: Trapezoid-Metacarpal joint.

Number of infiltrations for each cycle : 10 ÷ 12

Minimum time interval between one infiltration and the next one: 3 days

Maximum time interval between one infiltration and the next one: 7-15 days

Time interval between a treatment cycle and the next one: 6 months (Infiltrations recalls if needed)

OO Volumes to be injected: 1.5-3 ml for each infiltration.

Maximum total volume to be injected for session: 10 ml.

OO concentration: from 10 to 20 µg/ml.

References: 70, 71

Disposable materials:

- Needle:

    Diameter/Gauge: from 27 to 30 G

    Length: from 13 to 25 mm in relation to the thickness of the adipose tissue

- Antibacterial filter : 0,22 µm x 25 mm

    - Single use syringe for MOT: from 5 to 10 ml in Polypropylene

    - Pre-treatment medication : Sterile Gauze Taps, Disinfectant

    - Post-treatment medication : Medicated Patch, Gauze

Technique:

Once the spaces are identified through the cutaneous anatomical landmarks of the Trapezoid-Metacarpal joint, insert the needle subcutaneously and in the premises of the articulation, by introducing 2-3 ml in 3-4 points. The needle is introduced with a 45° inclination so that it passes the skin and gets to the subcutaneous tissue, deepens and surrounds the articulation.

A4 – Plantar interdigital nerve perinervous percutaneous

Conditions suggested for treatment: Morton Neuroma

Anatomic part: Foot.

Number of infiltrations for each cycle : 10 ÷ 12

Minimum time interval between one infiltration and the next one: 3 days

Maximum time interval between one infiltration and the next one: 7-15 days

Time interval between a treatment cycle and the next one: 6 months (Infiltrations recalls if needed)

OO Volumes to be injected: 1.5-3 ml for each infiltration.

Maximum total volume to be injected for session: 10 ml.

OO concentration: from 8 to 12 µg/ml

References: 72

Disposable materials:

- Needle:

    Diameter/Gauge: from 23 to 27 G

    Length: from 13 to 25 mm in relation to the thickness of the adipose tissue

- Antibacterial filter : 0,22 µm x 25 mm

    - Single use syringe for MOT: from 5 to 10 ml in Polypropylene

    - Pre-treatment medication : Sterile Gauze Taps, Disinfectant

    - Post-treatment medication : Medicated Patch, Gauze

Technique:

Once the space through the anatomical osteo-muscular-cutaneous landmarks is identified, insert the needle in the peri nervous site. The needle is introduced so that it passes the skin and get to the nerve; it's possible to evoke a paresthesia followed by a 1-2 mm retraction of the needle, in order to avoid an intra neural administration.

A5 – Ozone Blistering – peritendinous percutaneous

A5-1- Conditions suggested for treatment: Tendonitis, Tendinosis

Anatomic part: Achilles Tendon, Rotula Tendon, Long Abductor Tendon , Short extensor thumb Tendon, Sopra spinous Tendon, Underspinous Tendon, Tendon with insertion on the Humeral Epicondyle, Tendon with insertion on the Humeral epicondyle, other tendons

Number of infiltrations for each cycle : 10 ÷ 12

Minimum time interval between one infiltration and the next one: 3 days

Maximum time interval between one infiltration and the next one: 7-15 days

Time interval between a treatment cycle and the next one: 3 ÷ 6 months (Infiltrations recalls if needed)

OO Volumes to be injected: 1-3 ml for each infiltration.

Maximum total volume to be injected for session: 15 ml.

OO concentration: from 10 to 20 µg/ml.

References: 73

Disposable materials:

- Needle:

Diameter/Gauge: from 23 to 27 G

Length: from 13 to 25 mm in relation to the thickness of the adipose tissue

- Antibacterial filter : 0,22 µm x 25 mm

- Single use syringe for MOT: from 10 to 20 ml in Polypropylene

- Pre-treatment medication : Sterile Gauze Taps, Disinfectant

- Post-treatment medication : Medicated Patch, Gauze

Technique:

Once the space through the anatomical osteo-muscular-cutaneous landmarks is identified, insert the needle in the peritendinous site. The needle is introduced so that it passes the skin and gets to the to the tendon, in order to avoid to puncture it.

A5-2- *Conditions suggested for treatment:* Stenosing Tenosynovitis (Trigger finger)

Anatomic part: Interested Pulley flexor muscles.

Number of infiltrations for each cycle : 10 ÷ 12

Minimum time interval between one infiltration and the next one: 3 days

Maximum time interval between one infiltration and the next one: 7-15 days

Time interval between a treatment cycle and the next one: 6 months (Infiltrations recalls if needed)

OO Volumes to be injected: 1-4 ml for each infiltration.

Maximum total volume to be injected for session: 15 ml.

OO concentration: from 8 to 15 µg/ml.

<u>References:</u> 74-76

Disposable materials:

- Needle:

    Diameter/Gauge: from 27 to 30 G

    Length: from 13 to 25 mm in relation to the thickness of the adipose tissue

- Antibacterial filter : 0,22 µm x 25 mm

    - Single use syringe for MOT: from 5 to 10 ml in Polypropylene

    - Pre-treatment medication : Sterile Gauze Taps, Disinfectant

    - Post-treatment medication : Medicated Patch, Gauze

Technique:

Once the space through the anatomical osteo-muscular-cutaneous landmarks is identified, insert the needle in the paratendinous site. The needle is introduced so that it passes the skin and gets to the to the tendon, in order to avoid to puncture it.

A6 –Extra/Intra Articular knee administration

Pathologies to be treated: Gonarthrosis

A6_1 - Extra Treatment

Anatomic part: Knee Joint

Number of infiltrations for each cycle : 10 ÷ 12

Minimum time interval between one infiltration and the next one: 4-6 days

Time interval between a treatment cycle and the next one: 3 ÷ 6 months

OO Volumes to be injected: 5-10 ml for each infiltration.

Maximum total volume to be injected for session: 20 ml.

OO concentration: from 8 to 15 µg/ml.

References: 77

Disposable materials:

- Needle:

  Diameter/Gauge: from 25 to 27 G

  Length: from 12 to 16 mm in relation to the thickness of the subcutaneous tissue

- Antibacterial filter : 0,22 µm x 25 mm

  - Single use syringe for MOT: from 10 to 20 ml in Polypropylene

  - Pre-treatment medication : Sterile Gauze Taps, Disinfectant

  - Post-treatment medication : Medicated Patch, Gauze

Technique:

Once the space through the anatomical osteo-muscular-cutaneous landmarks is identified , insert the needle in intrarticular site:

- Lateral approach: after positioning the rotula laterally insert the needle with a 45% inclination in the cutaneous pocket between the rotula and the femur (used often)

- Medial approach: Insert the needle horizontally, in the middle part of the joint, in correspondence to the inferior half of the rotula (used less frequently)

- Anterior approach : with the knee flexes in a 60°-90° angle the needle is inserted medially or laterally to the rotula tendon in a parallel position to the tibia plateau (used frequently especially in clinical conditions of advanced arthrosis)

A6_2 - Intra Treatment

Anatomic part: Knee Joint

Number of infiltrations for each cycle : 8 ÷ 10

Minimum time interval between one infiltration and the next one: 6 days

Time interval between a treatment cycle and the next one: 6 months

OO Volumes to be injected: 2-8 ml for each infiltration intra or extra articular respectively.

Maximum total volume to be injected for session: 8 ml.

OO concentration: from 10 to 20 µg/ml.

References: 78-81

Disposable materials:

- Needle:

    Diameter/Gauge: from 23 to 25 G

    Length: from 25 to 40 mm in relation to the thickness of the subcutaneous tissue

- Antibacterial filter : 0,22 µm x 25 mm

    - Single use syringe for MOT: from 10 to 20 ml in Polypropylene

    - Pre-treatment medication : Sterile Gauze Taps, Disinfectant

    - Post-treatment medication : Medicated Patch, Gauze

Technique:

Once the space through the anatomical osteo-muscular-cutaneous landmarks is identified , insert the needle in intrarticular site:

- Lateral approach: after positioning the rotula laterally insert the needle with a 45% inclination in the cutaneous pocket between the rotula and the femur (used often)

- Medial approach: Insert the needle horizontally, in the middle part of the joint, in correspondence to the inferior half of the rotula (used less frequently)

- Anterior approach : with the knee flexes in a 60°-90° angle the needle is inserted medially or laterally to the rotula tendon in a parallel position to the tibia plateau (used frequently especially in clinical conditions of advanced arthrosis)

A7 –Extra/Intra Articular hip administration

Pathologies to be treated: Hip Arthrosis

A7_1 – Extra normal treatment

Anatomic part: Hip Joint

Number of infiltrations for each cycle : 2 ÷ 4

Minimum time interval between one infiltration and the next one: 7 days

Time interval between a treatment cycle and the next one: 3-6 months (Infiltrations recalls if needed)

OO Volumes to be injected: 2-8 ml for each infiltration.

Maximum total volume to be injected for session: 8 ml.

OO concentration: from 10 to 25 µg/ml.

References: 82

Disposable materials:

- Needle:

    Diameter/Gauge: from 20 to 22 G

    Length: from 90 to 130 mm in relation to the thickness of the subcutaneous tissue

- Antibacterial filter : 0,22 µm x 25 mm

    - Single use syringe for MOT: from 5 to 10 ml in Polypropylene

    - Pre-treatment medication : Sterile Gauze Taps, Disinfectant

- Post-treatment medication : Medicated Patch, Gauze

Technique:

Identify through the ultrasound machine positioned in the groin area the femoral vein and artery, move the ultrasound medially to the vein and identity the coxo-femural joint

Insert the needle down to the joint. The use of the specific introductory-guide applied to the ultrasound makes the maneuver simpler.

In case of articular spilling, proceed with arthrocentesis before administrating OO

A7_2 – INTRA with ultrasound guide

Anatomic part: Hip Joint

Number of infiltrations for each cycle : 2 ÷ 4

Minimum time interval between one infiltration and the next one: 7 days

Time interval between a treatment cycle and the next one: 3-6 months (Infiltrations re-calls if needed)

OO Volumes to be injected: 2-8 ml for each infiltration.

Maximum total volume to be injected for session: 8 ml.

OO concentration: from 10 to 25 µg/ml.

References: 83 -85

Disposable materials:

- Needle:

  Diameter/Gauge: from 20 to 22 G

  Length: from 90 to 130 mm in relation to the thickness of the subcutaneous tissue

- Antibacterial filter : 0,22 µm x 25 mm

- Single use syringe for MOT: from 5 to 10 ml in Polypropylene

- Pre-treatment medication : Sterile Gauze Taps, Disinfectant

- Post-treatment medication : Medicated Patch, Gauze

Technique:

Identify through the ultrasound machine positioned in the groin area the femoral vein and artery, move the ultrasound medially to the vein and identity the coxo-femural joint

Insert the needle down to the joint. The use of the specific introductory-guide applied to the ultrasound makes the maneuver simpler.

In case of articular spilling, proceed with arthrocentesis before administrating OO

A8 – Lumbar intraforaminal percutaneous

Pathologies to be treated: Protrusion and Disk Hernia, Spinal Arthrosis, Post disk hernia surgery residual pain (FBSS), Spinal Canal Stenosis

References: 86-102

A8_1 - with CT Guide

Anatomic part: From L1 to S1

Number of infiltrations for each cycle : 2 ÷ 5

Minimum time interval between one infiltration and the next one: 7 days

Time interval between a treatment cycle and the next one: 2-3 months (Infiltrations re-calls if needed)

OO Volumes to be injected: 5-8 ml for each infiltration.

Maximum total volume to be injected for session: 30 ml.

OO concentration: from 10 to 25 µg/ml.

References: 103-107

Disposable materials:

- Needle:

    Diameter/Gauge: from 20 to 22 G

    Length: from 90 to 130 mm in relation to the thickness of the subcutaneous tissue

- Antibacterial filter : 0,22 µm x 25 mm

    - Single use syringe for MOT: from 20 to 30 ml in Polypropylene

    - Pre-treatment medication : Sterile Gauze Taps, Disinfectant

    - Post-treatment medication : Medicated Patch, Gauze

Technique:

Proceed to cutaneous anesthesia with Ethyl Chloride Spray.

Identify the disk spaces through CT scans , insert needle in the paravertebral muscle bundles with a 45° inclination in comparison to the Sagittal plane and in a side-medial direction towards the site

to be treated. The entering point of neeedle will be at 6-8 cm from the inter spinal line. The needle is introduced so that it passes the muscle bundle and gets to the foraminal region.

Perform CT scans to verify the right positioning of the needle , with the tip at l 4÷5 mm from the foraminal region.

Proceed with 3ml administration in the foraminal region, take out the needle for 4÷10 mm by injecting 3÷5 ml of gas solution at massive articular level , after aspirating and following these rules:

Slowly, by avoiding relevant pain manifestations.

Slowly take out the tip of the needle for 1÷3 mm in the presence of high administration pressure, by performing the aspiration.

The infiltration is to be repeated bilaterally.

In case of disk a/o arthritic pathologies on multiple levels it is possible to infiltrate up to 2 inter vertebral spaces bilaterally.

CT control scan to check the correct distribution of the solution.

NOTE:

spaces it might be easier to direct, frontally, the needle in cauda-cranial direction.

L1-L2, L2-L3, L3-L4 spaces it might be easier to direct, frontally, the needle in cauda-cranial direction.

For the treatment of L4-L5 spaces it might be easier to direct, frontally, the needle in cauda-cranial direction.

For the treatment of L5-S1 spaces is necessary to direct, frontally, the needle in cauda-cranial direction with a 30° inclination in order to avoid the iliac crest.

TECHNICAL NOTE :

The obstacles for the injection are usually bone:

- Superficial: Iliac crest

- Profound: transversal apophyses, Isthms, Articular posterior articulation

ATTENTION!

The foraminal approach might result impossible with:

- hypertrophic degenerative arthropathy of the massive articular

- Particularly high Iliac Crests

- Transversal hypertrophic apophysis

- Isthmic Hypertrophies

- Hypertrophies of the posterior massive articular

A8_2- with Image Intensifier

Anatomic part: From L1 to S1

Number of infiltrations for each cycle : 2 ÷ 5

Minimum time interval between one infiltration and the next one: 7 days

Time interval between a treatment cycle and the next one: 2-3 months (Infiltrations re-calls if needed)

OO Volumes to be injected: 5-8 ml for each infiltration.

Maximum total volume to be injected for session: 30 ml.

OO concentration: from 10 to 25 µg/ml.

References: 108-109

Disposable materials:

- Needle:

  Diameter/Gauge: from 20 to 22 G

  Length: from 90 to 130 mm in relation to the thickness of the subcutaneous tissue

- Antibacterial filter : 0,22 µm x 25 mm

  - Single use syringe for MOT: from 20 to 30 ml in Polypropylene

  - Pre-treatment medication : Sterile Gauze Taps, Disinfectant

  - Post-treatment medication : Medicated Patch, Gauze

Technique:

Proceed to cutaneous anesthesia with Ethyl Chloride Spray.

Identify the disk spaces through CT scans , insert needle in the paravertebral muscle bundles with a 45° inclination in comparison to the Sagittal plane and in a side-medial direction towards the site to be treated. The entering point of neeedle will be at 6-8 cm from the inter spinal line. The needle is introduced so that it passes the muscle bundle and gets to the foraminal region.

Perform CT scans to verify the right positioning of the needle , with the tip at l 4÷5 mm from the foraminal region.

Proceed with 3ml administration in the foraminal region, take out the needle for 4÷10 mm by injecting 3÷5 ml of gas solution at massive articular level , after aspirating and following these rules:

Slowly, by avoiding relevant pain manifestations

Slowly take out the tip of the needle for 1÷3 mm in the presence of high administration pressure, by performing the aspiration again as explained in point 7

The infiltration is to be repeated bilaterally.

In case of disk a/o arthritic pathologies on multiple levels it is possible to infiltrate up to 2 inter vertebral spaces bilaterally.

CT control scan to check the correct distribution of the solution.

NOTE:

spaces it might be easier to direct, frontally, the needle in cauda-cranial direction.

L1-L2, L2-L3, L3-L4 spaces it might be easier to direct, frontally, the needle in cauda-cranial direction.

For the treatment of L4-L5 spaces it might be easier to direct, frontally, the needle in cauda-cranial direction.

For the treatment of L5-S1 spaces is necessary to direct, frontally, the needle in cauda-cranial direction with a 30° inclination in order to avoid the iliac crest.

TECHNICAL NOTE :

The obstacles for the injection are usually bone:

- Superficial: Iliac crest

- Profound: transversal apophyses, Isthms, Articular posterior articulation

ATTENTION!

The foraminal approach might result impossible with:

- hypertrophic degenerative arthropathy of the massive articular

- Particularly high Iliac Crests

- Transversal hypertrophic apophysis

- Isthmic Hypertrophies

- Hypertrophies of the posterior massive articular

A9 – Extra/Intra articular shoulder administration

Pathologies to be treated: Shoulder Arthrosis

A9_1 - Extra

Anatomic part: Shoulder Joint

Number of infiltrations for each cycle : 3 ÷ 4

Minimum time interval between one infiltration and the next one: 7 days

Time interval between a treatment cycle and the next one: 6 months (Infiltrations recalls if needed)

OO Volumes to be injected: 4-6 ml for each infiltration.

Maximum total volume to be injected for session: 12 ml.

OO concentration: from 12 to 25 µg/ml.

References: 110, 82

Disposable materials:

- Needle:

    Diameter/Gauge: from 22 to 25 G

    Length: from 40 to 90 mm in relation to the thickness of the subcutaneous tissue

- Antibacterial filter : 0,22 µm x 25 mm

    - Single use syringe for MOT: from 5 to 10 ml in Polypropylene

    - Pre-treatment medication : Sterile Gauze Taps, Disinfectant

    - Post-treatment medication : Medicated Patch, Gauze

Technique:

Center in radioscopy, in anterior or posterior oblique projection the intermedium portion of the gleno-humerus articular interline, by putting the glena parallel to the radiant beam; while pointing this target insert the needle through the cutaneous surface directing it straight on and slowly (medially in case of posterior access) along the direction of the incident beam until it passes the articular capsule and reaches the joint.

A9_2 – Intra with Image Intensifier

Anatomic part: Shoulder Joint

Number of infiltrations for each cycle : 3 ÷ 4

Minimum time interval between one infiltration and the next one: 7 days

Time interval between a treatment cycle and the next one: 6 months (Infiltrations recalls if needed)

OO Volumes to be injected: 4-6 ml for each infiltration.

Maximum total volume to be injected for session: 12 ml.

OO concentration: from 12 to 25 µg/ml.

References: 110-112

Disposable materials:

- Needle:

    Diameter/Gauge: from 22 to 25 G

    Length: from 40 to 90 mm in relation to the thickness of the subcutaneous tissue

- Antibacterial filter : 0,22 µm x 25 mm

    - Single use syringe for MOT: from 5 to 10 ml in Polypropylene

    - Pre-treatment medication : Sterile Gauze Taps, Disinfectant

    - Post-treatment medication : Medicated Patch, Gauze

Technique:

Center in radioscopy, in anterior or posterior oblique projection the intermedium portion of the gleno-humerus articular interline, by putting the glena parallel to the radiant beam; while pointing this target insert the needle through the cutaneous surface directing it straight on and slowly (medially in case of posterior access) along the direction of the incident beam until it passes the articular capsule and reaches the joint.

A10 – Oedematous Panniculosis and localized adipose tissues

Pathologies to be treated: Oedematous panniculopathy

- Anatomic part: Inferior limbs, Peri umbilical region

Number of infiltrations for each cycle : 15 ÷ 20

Minimum time interval between one infiltration and the next one: 2-4 days

Time interval between a treatment cycle and the next one: 3-6 months (Infiltrations recalls if needed)

OO Volumes to be injected: 3-5 ml for each infiltration.

Maximum total volume to be injected for session: 150 ml.

OO concentration: from 4 to 8 µg/ml.

References: 113, 114

Disposable materials:

- Needle:

    Diameter/Gauge: from 27 to 30 G

    Length: from 6 to 12 mm in relation to the thickness of the subcutaneous tissue

- Antibacterial filter : 0,22 µm x 25 mm

    - Single use syringe for MOT: from 30 to 50 ml in Polypropylene

    - Pre-treatment medication : Sterile Gauze Taps, Disinfectant

    - Post-treatment medication : Medicated Patch, Gauze

B - Systemic Blood Treatment - General Rules

In the aim to avoid any kind of interference both with other techniques in which blood of patients is used for medical procedure or there is a direct access to the blood stream to inject drugs or ozone, WFOT recommend the use of a more suitable term like Major Blood Ozonation (MBO) when referred to the former Major Auto Hemotherapy (To be revised in Consensus Conference LR).

In this text, for more convenience of the reader, we will indicate the acronyms MBO for Major Blood Ozonation and mBO for Minor Blood Ozonation.

For more detailed informations regarding these procedures please refer to:

https://www.wfoot.org/wp-content/uploads/2016/01/WFOT-OZONE-2015-ENG.pdf.

These terms indicate the classical procedure by which a specific volume of blood is withdrawn from a peripheral vein, then exposed to oxygen-ozone for a few seconds/minutes (according to the used device) and retransfused by the same route either intra venous (MBO) or intramuscularly (mBO) in the donor. Both procedures only differ according to the blood volume and modality of administration: 80-200 ml IV for the MBO and 5-10 ml IM for the mBO.

The original idea for exposing blood ex vivo to a gas mixture was proposed by Wehrli and Steinbart115, who published the method of blood irradiated with UV light in presence of pure oxygen. This procedure termed HOT (Hematogenous Oxidation Therapy) is no longer used due to uncertainty related to actual ozone concentration during UV irradiation of oxygen.

In addition, the procedure is a little be complicated and risky because the quartz ampoule had to be cleaned and sterilized after each treatment. In fact, some cases by cross infection with HCV, due to improper sterilization, were widely diffused and denigrated modern ozone treatment[116].

This type of serious cross infections has taken place in the past due to doctors and nurses' negligence compromising ozone therapy's progress. In the 60's, reliable medical generators were already available and HANS WOLFF PROPOSED DIRECT EXPOSURE OF

BLOOD TO OXYGEN-OZONE, with the advantage of being cognizant of its exact concentration. In 1974, reports referred that he used this method in many patients without any difficulty nor serious reactions.

To introduce ozone into a patient's blood, several methods have been used throughout history, some of which involve certain risks and/or excessive manipulation. For example, there are systems that use soft bags such as those for storing blood in blood banks and which could have the great disadvantage of containing large quantities of plasticizers, mainly around 43% phthalates[117, 118, 119, 120, 121, 122, 123].

It has been demonstrated that ozone interaction with plastic from these bags provokes particles from them to come off and speed up partial dissolution of phthalates in blood, that later on will reinfuse into the patient and which consequences in both cases may be worrying. In fact, in Italy, where the use of these bags spread to a certain extent in the 1990s, a erroneously named *"ozone allergy"* was even reported (difficult to occur given the simplicity and instability of the molecule), while, probably, the causes of some mild feverish reactions and malaise were precisely due to the aforementioned factors. Furthermore, the use of soft bags significantly lengthens the blood collection process, since, in practice, the butterflies used for this purpose must not have a maximum thickness of G21 or G19 (1.1 mm).

Fortunately, by 2000, new plastic containers had been developed without plasticizers, inert to ozone and more solid and safer, counting on the European Commission certificate for their exclusive use in MBO with ozone. With them, the *"allergy reaction"* has disappeared due to absence of phthalates and release of plastic micro-particles.

At present 3 systems mainly coexist. They are closed, single use and disposable circuits:

1- A sterile and disposable system consisting of a plastic bag free of phthalates, which comes with a conventional transfusion system for collection–infusion of blood previously anticoagulated (anti-clotting) with sodium citrate and required needles to carry on with the procedure. There are several models, all of them homologated for their use in MBO by different notified entities.

2- Rigid plastic container in sterile package especially designed to that, with 2 different tubings, one for blood, with its corresponding anti-clotting filter, and the other to apply the vacuum and ozone, alternatively, directly from the ozone therapy equipment. The vacuum can be applied in a controlled manner as well as measured with the modern machines thus extremely facilitating blood withdrawal and allowing completing the whole treatment

in less than 15 minutes. Likewise, ozone which is subsequently introduced is measured in real time. The devise is also specifically homologated for MBO.

3- Traditional glass bottle with vacuum pre-applied in factory where conventional transfusion equipment are connected for blood collection-infusion and syringes with needles for introducing ozone (Fig. 6.3). As anticoagulant in this system, i.v. sterile dissolution of sodium citrate 3.13% is generally used in mono-dose ampoules of 10 ml with an effective anticoagulant effect only in vitro, disappearing once it infuses and dilutes in blood circulation. It is safe for almost every patient, even those undergoing treatment with anticoagulants (Warfarin, heparin, hirudin), antiaggregant pharmaceuticals (aspirin, dipyridamole, ticlopidin, clopidogrel) and thrombolytic agents (streptokinase, tissue plasminogen activator) or patients with hepatic conditions and low level of prothrombin. Heparin can be also used as anticoagulant, but its repeated use can worsen dis-coagulation and cause severe hemorrhages. Notwithstanding, considering the abovementioned restrictions, only by means of a thorough analysis of the patient, the physician will be able to choose the suitable anticoagulant.

Several modifications to the techniques for administering ozone into the blood have been attempted, which should be mentioned briefly:

- The first modification (patented in the USA) uses hollow capillary fibers (like hemodialysis filters) but is an expensive and unnecessary complex for the which failed.

- The second system breaks down the gas into small bubbles through the blood, claiming that this increases the rate at which ozone is absorbed into the blood. However, the rate of infusion of ozone into the bottle indicated by the manufacturer must be strictly followed since excessive bubbling produces a certain degree of hemolysis and a lot of foam.

Blood volume withdrawn for ozonation must be flexible and keep a relationship with patient's body mass as well as the kind and phase of his/her disease. Trying to get a safe margin for avoiding hypovolemic side effects, no more than 225 ml of blood (for an individual of 75 kg - it is a 30% of the theoretical safe amount for donation) should be withdrawn to a sterile container, inert to ozone, with, at least, double capacity of blood draw volume, or homologated kit for MBO.

In Europe, many consider that a maximum of 100 ml of blood is optimal, although recently prevailing view of considering the body mass of the individual feeling 100-150 ml the minimum and maximum range for a person of 75 kg. This means that for a patient weighing

100 kg, the recommended amount of blood will be taken between 130 and 200 ml while in the case of a subject of 50 kg between 70 and 120 ml, depending on the disease to be treated and the patient's general condition. It is evident that ozone administered with any of these blood volumes generate crucial messengers such as ROS, LOPs, intermediate metabolites and autacoids which dilute, degrade, and excrete but which after interacting with cells, express key pharmacologic effects as long as we surpass the 4 mg of ozone, as mentioned in chapter 4.

Standard accuracy consists in undertaking 2 or 3 weekly treatments during 10-15 sessions. This program is a practical, very effective as proven in the great majority of patients.

However, it can be modified to meet individual needs. More recently and taken into account the great diffusion of this method as antiaging and in prevention, most of the customers ask to carry out the treatment on a monthly or personalized basis, considering this technique as a resource for maintaining a good lifestyle and preventing the damage of aging, like constant physical activity or a regular diet.

Adequate reinfusion of 80 - 200 ml of the previously withdrawn blood plus the 10% in ml of citrate solution can usually last between 5 and 15 minutes without any problem or complication for the patient. Nevertheless, we must check hemostasis carefully and avoid hematic extravasation that could compromise the course of therapy.

An important issue to highlight is that over the past 15 years, during dozens of thousand treatments carried out and reported in studies presented in multiple congresses of the sector and published internationally in Spain as well as in many European countries, such as Germany, Italy, Austria, Switzerland, Portugal, etc., no significant side effects have ever been reported. Sort of transitory slight dizziness similar to a sudden hyperventilation could rarely be produced. This could be related with transitory increase in the amount of oxygen transported to tissues, produced by MBO.

Initially the treatment was mainly intended as support therapy in many ailments. Recently, as said above, the huge clinical data obtained in many people treated with systemic ozone suggested that it could represent a formidable resource in reducing the damage of age and thus suggested and proposed for any kind of conditions and mainly in reducing the fatigue syndrome and in prevention.

However the first uses, following indexed clinical studies, were proposed for the following pathologies: Peripheral Vasculopathies, Microcirculation Pathology, Degeneration Retinal Maculopathy, Adjuvant in Chronic Degenerative Diseases, Lower limb ulcers in Diabetic

patient.

Pathologies could be treated following Case Reports, and the evidence medicine:

Herpes Simplex, Herpes Zoster, HBV, HCV, HIV, ALS, MS, SD, Parkinson's, Alzheimer's, Vascular Headaches, Fibromyalgia, CGS, Acne, Rheumatoid Arthritis, Chronic Respiratory Pathways in COPD, Decubitus Ulcers, Chronic Bacterial Infections that mycotic, Psoriasis, Adjuvant in Oncology and helpful during radiation or chemotherapy, Immunomodulation, Ulcerative Colitis, Asthma, Allergies, Depressions, Hepatopathies

Prescriptions on the utilized materials:

- Strict Latex Free single-use
- Disposable vinyl gloves
- Sole use of marked Medical Devices
- Customized MOT Medical Devices
- Accurate sterility during the performance

Absolute drawbacks for the specific pathology

- Favism
- Pregnancy
- Severe decompensated cardiac pathology
- Uncontrolled Hypertension
- Uncontrolled hyperthyroidism
- Not compensated Systemic pathologies
- Pre-existent skin, muscular or in the injection point infection
- Oral Anticoagulant

Related drawbacks:

- Patency of the oval foramen
- Underage
- Systemic anticoagulant or double platelet anti-aggregation therapies

Methods Description:

1) Place the patient sitting or lying down, with the trunk slightly raised.

2) Define the concentration to be produced with the device (see Table 1 at the end of this document with all the concentrations for any kind of condition).

3) Insert the anticoagulant into the vial. Use 3.8% Sodium Citrate with a volume ratio of 1:10 with respect to the blood volume programmed for collection. In some bottles available on the market, the anticoagulant is already positioned inside: in this case the blood volume must necessarily be 10 times the volume of the anticoagulant declared by the manufacturer on the label of the glass bottle.

4) Measure the patient's blood pressure.

5) Locate a good peripheral vein and place the "flat band extendable" tourniquet on the arm to definitively highlight the vein.

6) Perform extensive and accurate cutaneous disinfection with sterile gauze in the venipuncture area.

7) Insert the butterfly needle into the closed clamp vein and secure it with the patch.

8) Assemble the transfusion kit together with the IV stand.

9) Connect the needle to the two-line set (or a line) to drain the blood inside the bottle. Open the clamp.

10) Close the clamp as soon as the volume of blood to be taken is reached (in the kit it is generally 80 ÷ 200 ml).

11) Produce the desired concentration with the ozone generator.

12) Filling the syringes with the gaseous mixture of OO at the defined concentration, according to the pathology to be treated. More syringes are needed to arrive at the required OO volume, so it is important to prepare the OO in the syringes and immediately use it, in order not to have time decay of the concentration of the gaseous mixture.

13) Place an ozone-resistant antibacterial filter on the syringe before injecting ozone into the bottle, or on the gas injection catheter into the glass bottle. In almost all kits the antibacterial filter is already placed in the ozone insertion tube.

14) Connect the syringe filled with OO to the glass bottle through the tube with roller clamp and needle provided in the kit. The needle must pierce the silicone cap to access the inside of the bottle, following the kit manufacturer's instructions. The vacuum will draw the OO into the glass bottle. The roller clamp allows you to adjust the negative pressure that tends to drag the OO into the bottle. The operation must be carried out with care to prevent the gas from coming into contact with the blood too abruptly.

15) The volume of gas inserted in the bottle must be in a ratio 1: 1, with the volume of the blood taken.

16) Gently shake the bottle for the time recommended by the Kit Manufacturer to obtain a homogeneous blood-gas mixing.

17) Slowly reinfuse the blood through the re-infusion line of the two-piece set (or a line) with a drip chamber that has the macro-aggregate filter.

18) At the end of the administration, close the set of two (or a line) and remove the needle from the patient's vein.

19) Hold the needle insertion point to avoid the formation of hematomas and to medicate it.

20) Place a patch on the needle puncture area.

21) Allow the patient to sit or lie down for 5-10 minutes, evaluating his condition before dismissing him, keeping constant verbal contact.

References: 124-135

B1- Systemic Blood Treatment (MBO) with Glass Bottle

Materials:

- Tourniquet
- Needle: 19 to 21 G Butterfly (Pay attention to possible blood clot with thin Butterfly)
- 50-100 ml Silicon Syringe
- Glass vacuum Bottle
- Transfusion Set
- Germ Trap with antibacterial filter
- Stand.

B2 – Systemic Blood Treatment (MBO) with Plastic Puche

Materials:

- Tourniquet
- Needle: 19 to 21 G Butterfly (Pay attention to possible blood clot with thin Butterfly)
- 50-100 ml Silicone Siringe
- Ozone Resistant Plastic Bags
- Transfusion Set
- Antibacterial filter
- Stand.

B3 – Intramuscular Blood Treatment (mBO)

In the 50´s intramuscular injections were used, from recently withdrawn autologous blood, sterile milk as well as unspecific immunomodulators. This is an old practice and still used without ozone[135]. Wolff was able to have the idea of ozonating blood with the expectation of activating its components.

The technical procedure is empirical and simple: first, peripheral blood is withdrawn (5 ml) in a syringe of 10 ml and immediately after, by means of two-way stopcock, equal filtered oxygen-ozone volume is added with an ozone concentration between 30 and 70 µg/ml depending on the scope of treatment and the disease. One can also first collect 5 ml of gas from the ozone generator and, then, withdraw 5 ml of blood from the patient with same syringe. In both cases, the blood, mixed with the gas, absorbs and reacts with ozone immediately. After disinfecting skin on buttock and checking that no blood vessel has been penetrated, the ozonated blood is injected in glutei, slowly without pain. We can carry out multiple injections and/or repeat them 2-3 times per week. We also suggest to change the needle before injection with a new one avoiding the risk of possible clot in the needle used to collect blood.

Logic of this unspecific kind of *protein therapy enhanced by ozone* is hypothetical and adequate scientific research would be needed. At the moment, we can speculate that blood, without anticoagulants, can infiltrate into muscle tissue or subcutaneous cell tissue and be able to coagulate due to platelet and prothrombin activation. If we take too long to inject, the blood will probably coagulate in the syringe.

Different processes such as fibrinolysis, reabsorption via lymphatic vessels and an inflammatory reaction are likely to occur occasionally, due to slight swelling on the site of injection, reported by several patients over the following days. Chemotactic compounds released on the site of injection may stimulate local infiltration of monocytes and neutrophils absorbing hemolysed erythrocytes and denatured proteins. Activated monocytes and lymphocytes can release interferons and interleukins, regulating physiologic response to cytokine[136, 137]. Therefore, it is most interesting to assess immunologic parameters and determine if there is simultaneous induction of heme-oxygenase-1(HO-1) and other heat shock proteins[138], which can enhance immunologic reactivity and explain the beneficial effects.

mBO is easy to perform; it is atoxic, economic, and if we could conduct a controlled clinical trial, it would become a useful tool for some condition. So far, we only count on anecdotal data (Konrad, 2001) from patients with herpes I and II, acute herpes zoster and neuralgia post-herpetic neuralgia[139].

The problem of new vaccines is becoming urgent and the use of ozone has been proposed as agent able to eliminate infectivity, while improving immunogenicity of a pathogen[140].

No side effects have been reported with mBO, despite a great deal of experience.

- Anatomic part: Gluteus Muscle

Number of infiltrations for each cycle : 15 ÷ 20

Minimum time interval between one infiltration and the next one: 2-4 days

Time interval between a treatment cycle and the next one: 3-6 months (Infiltrations re-calls if needed)

OO Volumes to be injected: 5 ml for each infiltration.

Maximum total volume to be injected for session: 10 ml.

OO concentration: from 20 to 50 µg/ml.

References: 141

Disposable materials:

- Needle:

    Diameter/Gauge: from 22 G

    Length: from 30 mm in relation to the thickness of the subcutaneous tissue

- Antibacterial filter : 0,22 µm x 25 mm

    - Single use syringe for MOT: from 10 ml in Polypropylene

    - Pre-treatment medication : Sterile Gauze Taps, Disinfectant

    - Post-treatment medication : Medicated Patch, Gauze

C - Systemic Rectal Treatment - General Rules

Pathologies recognized curable by dedicated Indexed Scientific studies: Peripheral Vasculopathies, Microangiopathies, Adjuvant in Chronic Degenerative pathologies, Ulcerative colitis, Crohn Disease, Anal and Rectal Fissures, Fistula Abscesses and other.

Pathologies recognized improvable with MBO according to Case Reports, in which the use is delegated to a “science and conscience” evaluation:

Vascular cephalea, Fibromyalgia, CGS, Acne, Chronic infections of the airways in COPD, Decubitus ulcers, Bacterial and fungus chronic infections, Psoriasis, Adjuvant in Tumor

therapy, Immunomodulation, Allergies, Depressions, Hepatopathy, Hemorrhoids, Coli-bacillosis, constipation, Proctitis.

Patient clinical evaluation

Medical examination

Anatomic part: Rectal Ampulla

References: 142 - 152

Number of infiltrations for each cycle: 10 ÷ 15 every two weeks in relation to the pathology and its phase of activity.

Minimum Time interval between an infiltration and the next one: 1 day.

Time interval between an infiltration and the next one: 1÷6 months, depending on the phase (first or maintenance therapy).

Necessary materials:

Bladder catheter:

Diameter from 14 Ch to fr (Charriére scale o French 1Ch= 1/3 di mmm)

Length: from 25 to 40 cm

Single use MOT syringe : 50 or 100 ml in Polypropylene

Auxiliary materials:

Anesthetic cream or Vaseline or Ozonised oil

Prescriptions on the utilized materials:

- Strict Latex Free single-use
- Disposable vinyl gloves
- Sole use of marked Medical Devices

-Maximum chemical resistance to the ozone oxidation

Method description:

- Position the patient in lateral decubitus.

- Define the ozone concentration to be produced with the ozone generator.

- Produce the concentration desired with the ozone machine (see point 11).

- Refill the syringe by collecting from the ozone generator, through the ozone-resistant antibacterial filter, the OO with the defined concentration.

- Lubricate the tip of the catheter with anaesthetic cream, Vaseline or ozonised oil.

- Insert gently the catheter for 8÷10 cm through the anus in order to get to the rectal ampoule. Don't force in presence of resistance, but take out and reintroduce.

- Proceed with the OO administration, by following these rules:

Slowly, by avoiding sudden distensions of the ampoule that would cause evacuation.

Once the administration is over clamp with the specific clamp the catheter, take off the syringe.

- When bigger volumes are necessary, repeat the procedure in point 7

- OO Volumes to be injected : 100÷150 ml for each single session progressively

- Maximum volume to be injected per session: 250 ml.

- OO concentration in µg/ml: see chart 1.

- Invite the patient to stay in a lateral decubitus position for 5÷10 minutes until a feeling of full well-being is reached.

- Invite the patient to take a sitting position, while checking the absence of dizziness or vagal symptoms.

- Invite the patient to take an erect position, while checking the absence of dizziness or vagal symptoms.

- during the whole procedure keep a constant verbal contact with the patient.

WARNING:

In order to ensure maximum therapeutic effectiveness it is necessary for the rectal ampulla to be completely free of feces. It might be necessary to precede the insufflation with an evacuation enema. Because of the gastro-cholic reflex fasting is recommended for the 2 hours before the treatment.

Absolute drawbacks for the specific pathology:

Uncontrolled Hypertension

Not compensated Systemic pathologies

Pre-existent skin, muscular or in the injection point infection

Oral uptake antibiotic treatment

Related drawbacks:

Patency of the oval foramen

Systemic anticoagulant therapies

Severe decompensated cardiac pathology

Uncontrolled Hypertension

Diverticulitis

Pregnancy

CHART 1

	Condition	OO [µg/ml]	OO volume [ml]	
1	Peripheric Vasculopathy	20,25,30,35	100÷150	
2	Microcircle Pathology	20,25,30,35	100÷150	
4	Adjuvant in Chronic Degenera-tive	20,25,30,35,40	100÷150	
6	Ulcerative Colitis	20,25,30,35,40,60*	50*÷150	See note
9	Fibromyalgia	25,30,35,40	100÷150	
10	Acne	20,25,30,35	100÷150	
14	Decubitus Ulcers	20,25,30,35	100÷150	
15	Bacterial and fungus chronic infections	25,30,35,40	100÷150	
16	Psoriasis	20,25,30,35	100÷150	
17	Adjuvant in Oncology	20,25,30,35,40	100÷150	
18	Immunomodulation	20,25,30,35,40	100÷150	
19	Allergies	20,25,30,35	100÷150	
23	Hepatopathy	25,30,35,40,45	100÷150	
24	Vascular Headache	20,25,30,35	100÷150	
25	Depressions	25,30,35,40	100÷150	
27	BPCO	20,25,30,35	100÷150	
33	Colibacillosis	20,25,30,35	100÷150	
34	Hemorrhoids	20,25,30	100÷150	
35	Proctitis	25,30,35,40	100÷150	
36	Stipsis	25,30,35,40	100÷150	

Note on dosages:

During the first session with the patient start from the lowest dosage indicated above and goes increasing by 5 [µg/ml] every session, until the maximum value.

Use the same prudent logic with the OO Volume.

Important notes

- It's good practice to avoid performing rectal insufflations in the acute phase of the pathologies indicated in chart 1.

-* In Ulcerative Colitis in bleeding phase USE ONLY FOR THE FIRST SESSION: 60 µg/ml with 50 ml OO volume, with haemostatic functions .

- Concentrations higher than 40 µg/ml might damage the enterocytes.

The ozone concentration must be controlled through a photometer or an alternative system of indirect measurement, because if the concentrations produced by the machine are higher than declared, they might cause damage to the patient.

D - Topical Application

D1 - Bagging - General Rules

Conditions to be treaded: Vascular ulcers, Decubitus ulcers, Diabetic foot, Onychomycosis, Osteomyelitis, Cutaneous and subcutaneous lesions with or without infection, Chronic infections both bacterial and fungus.

Patient clinical evaluation.

Medical examination.

Anatomic part: Part of the body interested by the lesion.

References: 153 - 159

Number of treatment for each cycle: Variable

Minimum Time interval between an application and the next one: variable

Time interval between an application and the next one: no limit

Necessary materials:

- PP, LDPE, HDPE, PET or PVC NO DOP (phthalates free) transparent pouch, of the right measure to contain the part to be treated.
- Adjustable lace with closing Velcro
- Physiological solution
- Sterile gauze
- Ozone-resistant plastic sprayer to spray the Physiological solution

Auxiliary materials: Post-treatment medication: medicated patch, gauze, possible advanced medication(depending on necessity)

Prescriptions on the utilized materials:

- Strict Latex Free single-use

- Disposable vinyl gloves

- Sole use of marked Medical Devices

- Maximum chemical resistance to the ozone oxidation

Method description:

- Position the patient sitting or reclining

- Remove possible medication on the area to be treated.

- Moisture or spray abundant physiological solution on the lesion. Ozone needs to be activated.

- Blot the lesion with sterile gauze , without grinding, with the purpose of eliminating possible residue of medication prior to the therapy to be performed.

- Put the anatomic part to be treated in the pouch, with adequate measures for the complete containment of the part.

- Fix the near extremity in the pouch with a lace , so that loss of gas can be avoided during the therapy, but being careful not to tighten too much.

- Connect the connection tube of the vacuum pump to the pouch access tube (it's a small tube attached to the pouch that has a closing clamp or a roller)

- Open the tube clamp

- Turn on the Vacuum Pump, aspirate the air in the pouch, until you almost completely empty the air in it, by avoiding the pouch to get too attached ad the possible wound.

- Close the tube clamp.

- Disconnect the vacuum pump tube from the pouch tube.

- Connect the tube that takes the ozone machine ozone to the pouch tube.

- Open the tube clamp.

- Turn on the ozone production.

- Define the ozone concentration to be produced by the machine (see chart 2 at the end of this document)

- Produce the desired concentration with the ozone machine

- Fill the pouch with OO from the ozone machine , at the definite concentration in relation to the pathology to be treated (see **chart 2**). It is not necessary for the pouch to be too swollen, to avoid that too high pressures might cause OO

- leakage from the pouch.

- Let the swollen pouch for the necessary time, depending on the pathology to be treated (see chart 2)

- After the necessary time, turn off the ozone production, close immediately the tube clamp , connect the vacuum pump tube to the pouch tube.

- Open the tube clamp

- Aspire the residual gas mix by turning on the vacuum pump until the pouch is empty.

- Take off the pouch from the patient. In case of residual ozone in the room use the active carbon vacuum or open a window.

- Perform the necessary medication depending on the lesion.

- Position the patient in a sitting or reclining position for 5-10 minutes, by evaluation his conditions before letting him go.

CHART 2

Nr.	Condition	OO concentration Time	
		[µg/ml]	Exposing time [min]
1	Diabetic foot without infection	15,20	15÷30
2	Decubitus ulcers	15, 20	15÷30
3	Bacterial and fungus chronic infections	15, 50	15÷30
4	Vascular ulcers	15, 20	15÷30
5	Onycomicosis	15, 50	15÷30
6	Osteomyelitis	15, 20, 25	15÷30
7	Cutaneous and subcutaneous lesions with infection	15, 20, 25, 40	15÷30
8	Cutaneous and subcutaneous lesions with NO infection	15, 20	15÷30

In case of massive ulcers or infections start with high OO concentrations in a short time and decrease gradually in time depending on the clinical improvement, by considering possible pain of the patient.

D2 - Ozonated Oils

Recently, attention has been focused on the use for medical and cosmetological uses of some derivative of the ozone molecule: *the ozonated biological oils.*

About 25 years ago prof. Bocci prophetically predicted: *"I would like to predict that the application of ozonated oil, a simple and inexpensive remedy, will become far more useful than expensive pharmaceutical creams and will herald a medical evolution for the topical treatment of topic ulcers and wounds. Under these terms, it is not exaggerated to proclaim ozone as the wonder drug of the XXI century"*[160].

Interestingly, in spite of its instability, the O3 molecule can be stabilized as an ozonide between the double bonds of a monounsaturated fatty acid such as oleic acid[161]. Ozonation of edible oil is performed by bubbling the gas mixture OO for either five min or up to two days, respectively. One gram of oil can bind up to 160 mg of ozone. As a consequence, ozonated olive oil remains stable for 2 years at 4 ºC. This preparation is proving to be ideal for the topical use of O3 in the treatment of chronically infected cutaneous and mucosal areas of the body[162]. O3 is widely recognized as one of the best bactericidal, antiviral and antifungal agents and therefore it is profitably and practically employed as ozonated olive oil with well defined peroxide contents.

The ozonated oil is now used topically for the treatment of war wounds, anaerobic infections, herpetic infections (HHV I and II), trophic ulcers and burns, cellulitis, abscesses, anal fissures, decubitus ulcers (bedsores), fistulae, fungal diseases, furunculosis, gingivitis and vulvovaginitis[160]. Even radiodermatitis lesions in patients with cancer have been found to be beneficially influenced by exposure to a simple application of ozonated oil[163].

D2-1 How ozonated oil acts?

This still remains an open question. Probably, when the stable triozonide comes into contact with the warm exudates of the wound, it slowly decomposes to reactive ozone, which readily dissolves in water, generating hydrogen peroxide and lipoperoxides that can explain the prolonged disinfectant and stimulatory activity. If it is correct, this reasoning im-

plies that we should have titrated preparations with high, medium or low triozonide concentrations to be used during the inflammatory septic phase I, regenerating phase II or remodeling phase III, respectively. These phases have been related to the rapidly changing cell types and to the release of cytokines and growth factors that modulate the complex healing process[160].

On the other hand, it has recently been observed that olive oil, which during ozonation traps O3 in the form of a stable ozonide, when applied to all sorts of acute and chronic cutaneous infections, slowly release O3 which, in comparison with conventional creams, displays effective disinfectant and stimulatory activities that lead to rapid healing[162].

It has been demonstrated that antimicrobial effect is not only attributable to the ozonides present in the ozonazed oil, but to the all complex mixture of compound derived from the ozonization process[164]. After the contact ozonized oil - microorganism it was observed severe alteration of the cytoplasm[165]. In addition, application of ozonized oil leads to a significant reduction in amylase, lipase, keratinase and urease enzyme activities in the microorganism in line with a reduction in nucleic acid content[166].

A recent study[167] was undertaken to evaluate the therapeutic effects of topical ozonated olive oil on acute cutaneous wound healing in a guinea pig model and also to elucidate its therapeutic mechanism. After creating full-thickness skin wounds on the backs of guinea pigs by using a 6 mm punch biopsy, authors examined the wound healing effect of topically applied ozonated olive oil (ozone group), as compared to the pure olive oil (oil group) and non-treatment (control group). The ozone group of guinea pig had a significantly smaller wound size and a residual wound area than the oil group, on days 5 ($p<0.05$) and 7 ($p<0.01$ and $p<0.05$) after wound surgery, respectively. Both hematoxylin-eosin staining and Masson-trichrome staining revealed an increased intensity of collagen fibers and a greater number of fibroblasts in the ozone group than that in the oil group on day 7. Immunohistochemical staining demonstrated upregulation of platelet derived growth factor (PDGF), transforming growth factor-β(TGF-β) and vascular endothelial growth factor (VEGF) expressions, but not fibroblast growth factor expression in the ozone group on day 7, as compared with the oil group. In conclusion, these results demonstrate that topical application of ozonated olive oil can accelerate acute cutaneous wound repair in a guinea pig in association with the increased expression of PDGF, TGF-β, and VEGF.

Even when the exact action mechanism of the ozonized oil was not describe there are many pre-clinical and clinical evidence of its antimicrobial and wound healing beneficial efficacy. Papers reported that the most sensible bacteria was Staphylococus aureus while the main resistant was Pseudomona aeruginosa[168].

In general, a lethal effect of ozonized oil is evident when it was applied to multi-resistant strain of Staphylococcus epidermis, Stafilococcus aureus, also when was applied to fungi from the genus Trichophyton, Epidermophyton and Microsporum, yeast as Candida albicans and protozoan as Giardia lamblia [166, 169, 170].

The wound healing action mechanism of ozonized oil may be connected in part to its antimicrobial effect, but also with its ability to promote the liberation of gown factors[171], activate local antioxidant mechanism[172, 174] and promote tissue reparation[173].

In summary, the most probable mechanism of action of ozonized oil should be due to:

1) Direct oxidation: slowly release of O3, trioxolane and lipoperoxides can destroy by oxidation the infective germs[162, 165].

2) Cytotoxicity: Trioxolane, lipoperoxides and aldehydes are cytotoxic to microorganism, they can inactivates enzymatic pathways by mechanism involved disruption of nuclear mediators[166].

3) Grow factors Release: O3 and other oxidized oil components can release grow factor from platelets160 or from the local tissues (increased expression of PDGF, TGF-β, and VEGF) that act as tissue remodeling factors[167].

4) Oxidative pre-conditioning, local oxidation of tissue by oxidized oil components can stimulate the expression of endogenous antioxidant mechanism[172, 173] and promote tissue reparation[174].

D2-2 Quality of ozonated Oils

A quality ozonized oil to be used with medical purpose should be prepared follow the good manufacture practice. That means a strictly quality control during its production in a high quality reactor by fixing the quality of the raw materials and important reaction variables as: time of reaction, ozone concentration, ozone sources, burbling size, reaction temperature and others.

A quality control of the active component (ozonized oil) should involve chemical-physical analysis, microbiological analysis and biological analysis. Biological analysis should be demonstrated the pharmacological effect attributed to the oil and the absence of toxicity. Microbiology should demonstrate the microbiological quality of the preparation. Finally, chemical/physical analysis will be done to guaranty the homogeneous chemical content of active component and the stability.

Chemical analysis will involve the measurement of the content of lipoperoxides and alde-

hydes, iodine and saponification indices. Physical analysis will take into consideration the acid values, density and viscosity of the active component. Test will be do according to the pharmacopeia methods and should be also used to demonstrate the stability of the preparation[175].

The diverse tests performed with ozonized sunflower oil showed the safety of this kind of products: toxicological tests, histological tests, mutagenic tests, genotoxic tests and teratogenic tests168. In clinical assays using ozonized oil in the treatment of infective lesion, side-effect was not reported[162, 163].

D2-3 Uses of ozonated Oils

A- Dermatology

"As soon as the medical community will appreciate their efficacy, ozonated oil will become indispensable tools in chronic wound healing units"[160].

The germicidal properties of the ozonized vegetable oil It has been already established. The ozonized vegetable oils have been used in the treatment of microbial infections of the skin (infected wounds, fistulas, acne, infected burns and ulcers), in the treatment of nasal, ear and vaginal infections and in post-operatory disorders. They have been also used in the treatment of the Giardia lamblia, Tynea Pedis, recidivating genital Herpes simplex, Helicobacter pylori, infection and in external hemorrhoids and bedsores[169].

The ozonized vegetable oils and fats have been also used in cosmetics. Since the 1950s, in France, the ozonized solutions have been used as cosmetics, directly on the skin or in baths, as stimulants, purifiers, as decongestant, tranquilizers and regenerating substances of the epidermal tissue. The properties for stimulating the tissue regeneration, the oxygenation of the cells and tissues and the moderated whitening properties are added to the acknowledged germicidal activity of the products from the ozonation of unsaturated compounds, such as terpenes, fatty acids, triglycerides and vegetable oils in the cosmetic applications. The highly oxygenated compounds, such as the ozonized vegetable oils, favor the flexibility and the softening of the skin and is used also to prepare creams for repairing the epithelial tissue.

How and when ozonated oils are used? Chronic wounds range from diabetic foot to putrid and deep ulcers due to limb atherosclerosis, or trauma and burns. Moreover, both im-

munosuppressive chemotherapy and/or malnutrition cause abscesses, anal fissures and fistulae, bed sores, furunculosis, and osteomyelitis which are difficult to treat and often fail after prolonged treatments. About 7 million patients in the United States are affected with a cost over US$ 25 billion annually. Various types of disinfectants, antibiotics, antifungal, antiprotozoal, and growth factors are scarcely effective because the deranged metabolism and local hypoxia are not modified. Several other approaches such as vacuum therapy, maggot therapy and devices for providing topical oxygen therapy in a clinical setting have been proposed and variably used. This last approach has a rationale in the sense that enhanced oxygenation is useful for activating the metabolism and cell proliferation of ischemic tissues. However, it has also considerable limitations because it is a cumbersome therapy, with minimal disinfectant activity and modifications of the fundamental pathogenetic mechanisms[176].

Ozonized oil preparation is proving to be ideal for the topical use in the treatment of chronically infected cutaneus and mucosal areas of the body and studies are in progress in support of the following conditions:

B- Bacterial infections

Evidence of its positive effects on Gingivostomatitis, Acute Tonsilitis.

In addition it was recently demonstrated, in animal models, that topically-applied ozonated oil, may has a positive influence in bone density and in the quality of osteointegration around dental implants[177].

Among the microorganisms in the first exudate we found Streptococcus pyogenes, Haemophylus influenzae, Bordetella pertussis, and others. At the end of the treatment, all patients were cured, taking into account the microbiological and clinical tests performed[164].

C- Viral infections

Application of the Ozonized Sunflower Oil in the Treatment of the Acute Herpetic Gingivostomatitis showed excellent results after seven days and usually the symptoms disappeared on the tenth day.

Ozonized Sunflower Oil in the Treatment of the Infection Caused by the Human Papilloma Virus has been studied on sixteen women with the human papilloma virus (HPV) in the vagina or in the cervix were studied and treated with embrocations of ozonized sunflower

oil on the affected areas, using the speculum for the curing. The treatment was daily performed for 15 days. The results, by colposcopy and cytology, showed an effectiveness of 94%. Application of Ozonized Sunflower Oil in the Treatment of Lower Limb Ulcers Caused by Chronic Venous Insufficiency[178, 164.]

D- Fungal infections

Application of Ozonized theobroma Oil in the Treatment of Tynea Pedis was already discussed[168].

Sun Flower Oil and Olive ozonized oil are fungicide, active against fungi, produces of superficial mycosis in human, such as Candida albicans, Trichophyton mentagraphytes, Microsporum canis, Thichophyton rubrum178, 164. Topical Sun Flower ozonized oil was evaluated in a controlled randomized phase III assay, using ketoconazole (Nizoral®) as the comparing group. The results demonstrated no significant differences between the two medications, nor side-effect or bacterial superinfection were observed in the study164.

E- Mix infections

Application of Ozonized Sunflower Oil in the Treatment of Lower Limb Ulcers Caused by Chronic Venous Insufficiency was widely studied by the Menendez group[164].

F- Bedsores and wounds

Twenty patients suffering from bedsores in the sacral region were studied and showed a time of healing shorter when treated with ozonated sunflower oils[164].

Furthermore, the application of the ozonized oil in the treatment of fistulae and chronic surgical wounds was performed with excellent clinical outcome[163].

Ozonated oil has also proved to be very effective in burns[160]. In addition Ozonized oils are used for the long-term treatment of injuries, burns and local infections such as skin and nail mycosis, as well as in the follow-up treatment of ulcus cruris and decubitus ulcers[179].

G- Sport, Physical Activity and Minor Traumatism

It has been demonstrated that dermal application of ozonized oil could increase the threshold of resistance to physical stress by accelerating the elimination of lactic acid (In-

stitute of Physiology and Sports Science, University of Padua, Italy). A double-blind vs. placebo experiment conducted on 30 subjects (recreational cyclists) shown a reduction in blood lactic acid 10 min after exercise and the reduction of fatigue in subject treated topically with a cream based in ozonized oil compared to a placebo cream.

Lactic acid levels were measured before and after the race in the two groups. The average elevation of lactic acid level in the control group (108%) was higher than the treated group (15%), compared to their basal levels. No pilots, in the treated group, overcome their aerobic limit, whereas, in the control group, two pilots overcome their aerobic limit. Cardiac frequency presented no significant changes between the two studied groups[180].

Following the first observation on ozone in Sport Traumatism[181] a trial was assessed following the criteria indicated in the attached article.

Indeed several papers are indicative of many positive effects induced by ozonated oil in a variety of ailments[182, 168] (; Silvia Méndez,Leopoldina Falcón, Mayulin B. Argote, Ivonne Menéndez, Dignora Fernández, Bárbara-Elías Calle, Magdalena Valero, Lamberto Re. Safety of Topical Oleozon® in the Treatment of Tinea Pedis: Phase IV Clinical Trial, Int Journal of Ozone Therapy, 7, 1, 55-59, 2008).

CHAPTER 4

ADVERSE REACTION TO MOT - SURVEILLANCE

WFOT proposes the following Form for the purpose of collecting and reporting valid ADR-MOTs for the purpose of cataloging clear and evident side effects deriving from the use of MO in medicine. WFOT strongly recommends that all physicians using MO contribute to the goal of providing all our patients with the best treatment and maximum safety when treated with this procedure.

ADR-MOT Form

1 Patients Data

a. Initials _____

b. Date of Birth ___/_____/_____

c. Weight (Kg) _____

d. Sex Male Female

e. Ethnic origin _____

f. Nationality _____

g. date first became aware of the event ___/_____/_____

2 Relevant Medical History

_____
_____
_____
_____
_____

3 Type of ADR-MOT (see Appendix)

a. Serious

b. Unexpected A

c. Unexpected B

4 Description of the Reaction

5 Protocol Used

a.	MBO	Vol. (ml)	Conc. (µg/ml)
b.	mBO	Vol. (ml)	Conc. (µg/ml)
c.	Rectal Insufflations	Vol. (ml)	Conc. (µg/ml)
e.	Injections	SC IM IA IF ID PV	
		Vol. (ml)	Conc. (µg/ml)

6 Severity of the Reaction

a. Mild Moderate Severe Life Threatening

7 Previous Treatment with MO (leave unchecked if not)

a. 1-2 Year 3-5 Years More than 5 year

8 Causality

a. Definite Probable Possible Unlikely Unrelated

9 Concomitant Medications

_____

_____

10 Years of Expertise in MOT of the Operator

a. 1-2 Year 3-5 Years More than 5 year

11 Medical Ozone Generator (MOG)

a. WFOT Compliant YES NO

b. Years of Work 1-2 years 2-5 years more than 5 years

12 Other Relevant Data

13 Reporting Doctor or Nurse

a. Signature _____

b. Institution _____

c. Date _____

APPENDIX

ADVERSE REACTION TO MEDICAL OZONE TREATMENT (ADR-MOT) DEFINITION

A response to a ozone treatment which is noxious and unintended and which occurs at doses normally used in man or animals for the therapy of diseases or for the restoration, correction or modification of physiological function following a certain protocol of administration and taking into account all the procedures used for its preparation and administration.

Serious ADR-MOT

An adverse reaction which results in death, patient hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

Unexpected ADR-MOT

An adverse reaction, the nature, severity or outcome of which is not consistent with the summary of MO characteristics.

A adverse reactions are those that are the result of an exaggerated but otherwise predictable pharmacological effect of the MOT (Hyperthyroidism, Favism, Severe Cardiomyopathy).

B adverse reactions are those that are aberrant effects of the MO (Not Predictable).

CONCLUSIONS

The time has come for all healthcare professionals working in the MO sector to become aware of the clinical and integrative importance of this medical resource which, to out opinion, is currently not adequately valorised, especially in light of the most recent discoveries despite its first use dating back to at the beginning of the last century as reported in prestigious international Journals[183, 184].

Much bibliography not cited above has been included as miscellany (185-300) and contains important scientific and clinical data demonstrating that it is no longer possible to ignore this treatment which on the contrary should be regulated, allowing all operators to have indications regarding its application and the currently most popular used methods.

In this document, which we hope will represent a guide for healthcare professionals all over the world, presented and discussed for the first time in a country at the forefront in proposing not only ethical but also political solutions, the WFOT wants to represent a fundamental guide which will only be the beginning of a path towards that clinical improvement which will have to continue over time as new acquisitions and knowledge in the sector will be proposed and scientifically validated.

The recent discovery that some metabolic pathways, including the Nrf2-dependent one, may represent a key factor for our health has opened up new interpretative perspectives.

Aging itself is a process resulting from the deterioration or imbalance of several factors that lead to an increase in reactive oxygen species (ROS) and multiorgan damage, especially in the elderly.

The relatively low cost of medical ozone-based treatments could represent an important strategic element in view of the increase in health spending which is worrying the governments of many countries around the world.

Research coordinated by the Institute for Health Metrics and Evaluation published recently by The Lancet[279] reported that global life expectancy has increased by a total of 6.2 years over the last thirty years, thus reinforcing the need for new strategies aimed at maintaining one state of well-being and health for this segment of the population with a notable saving of healthcare resources.

The help and supervision of supranational societies such as WFOT (www.wfoot.org), scrupulously non-profit and without conflicts of interest, will be fundamental for the better development and organization of Ozone Societies at both a national and international level.

WORLD FEDERATION OF OZONE THERAPY

We also hope that in the near future we will be able to count on both public health bodies and those of universities and other international institutions to promote professional training courses of high scientific and clinical standards and we strongly hope a bright future for this document which must represent a beacon and concrete help to support all healthcare workers active in the sector:

The Sao Paulo Document

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ABBREVIATIONS AND ACRONYMS

WFOT	World Federation Ozone Therapy
WHO	World Health Organization
MO	Medical Ozone
OM	Oxidative Medicine
SM	Systems Medicine
SOD	Superoxide Dismutases
CAT	Catalases
NO	Nitric Oxide
MOT	Medical Ozone Treatment
MOG	Medical Ozone Generator
COPD	Chronic Obstructive Pulmonary Disease
MBO	Major Blood Ozonation
mBO	Minor Blood Ozonation
RI	Rectal Insufflations
OO	Oxygen Ozone Mixtures
IM	IntraMuscular
SC	SubCutaneous
IA	IntraArticular
IF	IntraForaminal
ID	IntraDiscal
PV	ParaVertebral
BLS	Basic Life Support
ALS	Advanced Life Support

II Session – Dentistry

III Session – Veterinary