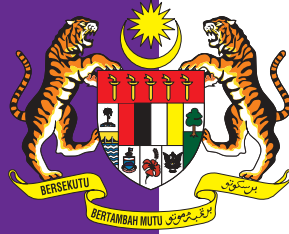


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REPORT

**OZONE  
THERAPY**

**HEALTH TECHNOLOGY ASSESSMENT UNIT  
MEDICAL DEVELOPMENT DIVISION  
MINISTRY OF HEALTH  
MOH/P/PAK/110.06 (TR)**

**Ozone Therapy**  
**Completed December 2005**

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# EXECUTIVE SUMMARY OZONE THERAPY

## INTRODUCTION

Ozone (O<sub>3</sub>) is a controversial gas because, owing to its potent oxidant properties, it exerts damaging effects on the respiratory tract and yet it has been used for decades as a therapy. The disinfectant activity of O<sub>3</sub> is widely used however the use of ozone in medical therapy is still controversial.

Presently there are nine methods of ozone therapy in medical practice namely direct intra-arterial and intravenous application, rectal insufflations, intramuscular injections, major and minor autohemotherapy, ozonated water, intra-articular injection, ozone bagging, ozonated oil and inhalation of ozone.

## OBJECTIVES

To assess the safety and effectiveness of ozone therapy in clinical care.

## RESULTS

### *Safety*

There are some case reports of the use of ozone resulting in air embolism, blood borne infections and bilateral visual field loss after receiving ozone therapy.

### *Effectiveness*

(i) **HIV and other infectious diseases**

There is only anecdotal evidence to support the effectiveness of ozone therapy in the treatment of HIV or other blood borne infectious diseases. The current evidence is insufficient to recommend the use of ozone in the treatment of HIV infected patients.

(ii) **Ischemia**

There is insufficient evidence showing the benefits of ozone in the treatment of limb ischemia, stroke and ischemic heart disease.

(iii) **Ophthalmology**

There was temporary improvement in three studies that patients had retinitis pigmentosa who were treated with ozone therapy.

(iv) **Ortholaryngology**

There is insufficient evidence to recommend ozone therapy in the treatment of ENT conditions.

(v) **Obstetric and Gynaecology**

The evidence showing the effectiveness of ozone therapy treatment in reducing the infection rate in caesarian section are observational studies only.

Similarly, there is insufficient evidence to recommend the use of ozone in the treatment of puerperal diseases.

The evidence is only anecdotal in nature as with regards to the use of ozone in the treatment of primary infertility.

**(vi) Orthopedic Disorders**

There are only three relevant clinical trials on these subjects, thus making it difficult to draw conclusive results.

**(vii) Cancer**

There is insufficient evidence with regards to the effectiveness and safety of ozone therapy in cancer patients.

**(viii) Skin disorders**

The evidence is only anecdotal in nature as with regards to the use of ozone in the treatment of skin conditions.

**CONCLUSIONS**

Current data on the usage of ozone therapy as therapeutic options for various health conditions lacks sufficient safety and therapeutic advantage over available conventional therapeutic modalities.

**RECOMMENDATIONS**

There is insufficient evidence to recommend the use of ozone therapy as a form of alternative treatment in patients with haematological disorders, autoimmune diseases, ischaemia, eye conditions, ENT, obstetric and gynaecology, orthopaedic conditions, cancer and skin disorders.

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# OZONE THERAPY

## 1. INTRODUCTION

Ozone is an elemental form of oxygen occurring naturally in the Earth's atmosphere. It surrounds the earth at an altitude of 50 000 to 100 000 feet. Ozone, in its gaseous state, is toxic to the human tissues. In aqueous form, however, it may have therapeutic effects.

Ozone was first discovered by the German chemist Christian Frederick Schonbein in the year 1840 in the University of Basel in Switzerland. Ozone was used for the first time to disinfect operating rooms in 1856 and subsequently for water treatment in 1860 (Foundation for alternative science & Technology). The German Army used ozone to treat battle wounds and other infections during World War I.

According to the Europe based Medical Society for Ozone and the National Centre for Scientific Research in Cuba, physicians are currently treating the following diseases with different forms of ozone: abscesses, acne, AIDS, allergies, anal fissures, arthritis, asthma, cancerous tumors, cerebral sclerosis, circulatory disturbances, cirrhosis of liver, constipation, corneal ulcers, cystitis, decubitus ulcers (bedsores), diarrhea, fungal diseases, gangrene, gastroduodenal ulcers, glaucoma, hepatitis, herpes simplex and zoster, hypercholesterolemia, osteomyelitis, Parkinson's disease, Raynaud's disease, rheumatoid arthritis, senile dementia, sepsis, sinusitis, spondylitis, thrombophlebitis, wound healing and others. This list is not exhaustive. (Ref: Proceedings of the first Ibero Latin American Congress on Ozone Application 1990)

Ozone therapy is still a controversial form of alternative therapy. Young children and adults with lung problems are told to stay indoors, because ozone can aggravate allergies, bronchitis, asthma and other health problems. On the other hands, many believe that ozone will help heal them of cancer, heart disease, candida, HIV-related problems and a host of other diseases including autoimmune disease, rheumatoid arthritis and low back pain. There are few elements that have been as controversial as ozone, and none that have created such a medical paradox: how can a gas be both dangerous to health as a pollutant, yet can also be used to effectively treat some of humanity's most threatening diseases?

Many physicians and clinics offering this form of therapy in Canada and the United States have been forced out of practice by various government agencies. Yet, in the past decade this therapy has gained more prominence and credibility in other part of the world. For the most part, ozone therapy is only available in Mexico, some Caribbean countries like the Bahamas, Cuba and the Dominican Republic as well as in Europe, especially Germany and eastern Europe.

## 2. BACKGROUND

### Medical Ozone

After the turn of the century, interest began to focus on the uses of ozone in medical therapy. However, it was not until 1932 that ozone was seriously studied by the scientific community, when ozonated water was used as a disinfectant by Dr. E.A. Fisch, a German dentist. One of his patients was the surgeon Erwin Payr, who immediately saw the therapeutic possibilities of ozone in medical therapy. Dr. Payr, along with the French physician P. Aubourg, was the first medical doctor to apply ozone gas through rectal insufflations to treat mucous colitis and Fistulae.

At the present time, there are eight simple methods and one highly complex method of ozone therapy that are used in medical practice.

### 1. Direct intra-arterial and intravenous application

An ozone/oxygen mixture is slowly injected into an artery or vein with a hypodermic syringe. This method is used primarily for arterial circulatory disorders. According to Gerard V. Sunnen, M.D., "Due to accidents produced by too rapid introduction of the gas mixture into the circulation, this technique is now rarely used" (1988).



## **2. Rectal insufflations**

First pioneered by Payr and Aubourg in the 1930's, a mixture of ozone and oxygen is introduced through the rectum and absorbed into the body through the intestine. Used for a wide variety of health problems, this method is considered one of the safest. In a typical treatment for ulcerative colitis, for example, 75 micrograms of ozone per milliliter of oxygen are used (treatment begins with 50ml of oxygen which can be increased slowly to 500 ml per treatment) 16 While administered under medical supervision in Germany, Russia and Cuba, a growing number of private individuals in the United States use this method for self-treatment for cancer, HIV-related problems and other diseases.

## **3. Intramuscular injection**

A small amount of an ozone and oxygen mixture (up to 10 ml) are injected into the patient (usually in the buttocks) like a normal injection would be. This method is commonly used to treat allergies and inflammatory diseases. Intramuscular injections are sometimes utilized as an adjunct to cancer therapies in Europe.

## **4. Major and minor autohaemotherapy**

Used since the 1960's, minor autohaemotherapy involves removing a small amount (usually 10 ml) of the patient's blood from a vein with a hypodermic syringe. The blood is then treated with ozone and oxygen, and given back to the patient with an intramuscular injection. Thus the blood and ozone becomes a type of auto-vaccine given to the patient that is derived from their own cells, thus forming a unique vaccine that can be very specific and effective in treating the patient's health problem. Major autohaemotherapy calls for the removal of between 50-100 ml of the patient's blood. Ozone and oxygen are then bubbled into the blood for several minutes, and then the ozonated blood is re-introduced into a vein. These methods have been used to treat a wide variety of health problems, including herpes, arthritis, cancer, heart disease and HIV-infection. It is probably the most commonly used type of ozone therapy today.

## **5. Ozonated water**

This method calls for ozone gas to be bubbled through water, and the water is used externally to bathe wounds, burns and slow-healing skin infections. It is also used as a disinfectant by dentists who perform dental surgery. In Russia, physicians are using ozonated water to irrigate body cavities during surgery. In both Russia and Cuba, ozonated water is used to treat a wide variety of intestinal and gynecological problems, including ulcerative colitis, duodenal ulcers, gastritis, diarrhea and vulvovaginitis (Proceedings of the First Iberolatinamerican Congress on Ozone Applications, 1990).

## **6. Intra-articular injection**

In this method, ozone gas is bubbled through water and the mixture is injected directly between the joints. It is used primarily by physicians in Germany, Russia and Cuba to treat arthritis, rheumatism and other joint diseases.

## **7. Ozone bagging**

This non-invasive method uses a specially made plastic bag that is placed around the area to be treated. An ozone/oxygen mixture is pumped into the bag and the mixture is absorbed into the body through the skin. Ozone bagging is primarily recommended for treating leg ulcers, gangrene, fungal infections, burns and slow-healing wounds.

## **8. Ozonated oil**

Used primarily to treat skin problems, ozone gas is added to olive oil and applied as a balm or salve for long-term, low-dose exposure.

## **9. Inhalation of ozone**

The lungs are the organs most sensitive to ozone. Physicians who use medical ozone warn that inhaling ozone into the lungs can bring about alterations in the density of the lung tissue, can damage delicate lung membranes, irritate the epithelium [the surface layer of mucus] in the trachea and bronchi, and can lead to

emphysema. They caution users that no ozone should escape into the room in which it is being used. Modern medical ozone generators are specially designed so that the accidental escape of ozone gas cannot take place. Dr. Stephen A. Levine, the co-author of Antioxidant Adaptation, cautions people against using commercial air purifiers which generate small amounts of ozone to clean the air, since ozone should not be inhaled.

The therapeutic concentrations of ozone vary with the mode of administration, the lowest concentration being in major autohaemotherapy.

Various private medical practitioners located mainly in the Klang Valley currently offer ozone therapy for various indications like cancer treatment, rheumatism, chronic viral infections and maintaining youthful looks. In addition, ozonated water is commercially available

### **3. TECHNICAL FEATURES**

Ozone is an inactivated, trivalent ( $O_3$ ) form of oxygen ( $O_2$ ). Ozone breaks down into two atoms of regular oxygen by giving up an atom of singlet oxygen over a period of 20 to 30 minutes. Ozone is considered one of the most potent oxidants in nature, but the mechanism of its therapeutic action is unclear. Some of the possible explanations for this include the generation of peroxides by ozonolysis with unsaturated fatty acids in cell membranes, activation or generation of reactive oxygen species which function as physiological enhancers of various biological processes (including increased production of ATP), and increased expression of intracellular enzymes with antioxidant activity. It has been reported that exposure to ozone results in a change in the level of a variety of biological factors, e.g. cytokines [IFN $\gamma$ , TNF $\alpha$ , TGF $\beta$  and IL-8], acute phase reactants and adhesion molecules from the integrin family such as CD11b. Other reports suggest increased motility and adhesion of peripheral blood polymorphonuclear cells to epithelial cell lines after exposure to ozone. Similarly, major autohaemotherapy-induced leucocytosis and enhanced phagocytic activity of polymorphonuclear cells have been reported.

### **4. POLICY QUESTION**

Should ozone therapy be offered as standard therapy for specific indications?

### **5. OBJECTIVE**

To assess the safety and effectiveness of ozone therapy in treatment of medical conditions. This assessment doesn't look at the effects of ozone in the atmosphere onto the health of the individual or patient.

### **6. METHODOLOGY**

The databases searched were Pubmed, Cochrane Library, E-medicine, International Ozone Association database, Foundation for Alternative Science & Technology, general databases like Google as well as webpages, and many other collections of articles downloaded from internet. The key words used for search included ozone, ozone therapy, medical ozone, oxygen-ozone therapy, ozone therapy and autoimmune diseases, ozone therapy and RA OR rheumatoid arthritis, ozone therapy AND low back pain, ozone AND haematolog\*, ozone AND obstetric, ozone AND gynaecology, ozone AND orthopaedic, ozone AND ischaemia, ozone AND cancer and ozone AND skin.

There were no limits in search; papers of any language were included. Problems encountered in the literature search were related to the paucity of randomised control clinical trials in the area of ozone therapy in all fields of medicine.

A critical appraisal of all relevant literature was carried out and the evidence graded according to the modified Catalonian Agency of Health Technology Assessment (CAHTA) scale.

## **7. RESULTS**

Ozone's use in medicine has been debated for decades, but references to its use were sporadic in the major medical journals. Most of the claims of its efficacy were anecdotal. Ozone had been claimed to be able to kill viruses, bacteria, parasites, fungi and be useful for cancers (Bocci, 1992). The treatment may activate the host's immune system by inducing the production of immunoactive cytokines. It is also suggested that since viruses, bacteria and other organisms need an anaerobic environment, exposure to ozone should kill these harmful organisms.

### **7.1. SAFETY**

There has been a reported case of death due to air embolism during the use of ozone in the treatment of psoriasis (Marchetti & Monaca, 2000).

Hepatitis C and HIV infections have also been reported following ozone autohaemotherapy (Daschner, 1997). A more recent cross sectional study demonstrated that transmission of HCV infection due to cross contamination occurred amongst 6 out of 31 patients who were exposed to autohaemotherapy or intramuscular injection in a outpatient department of a hospital in Italy (Faustini et al 2005).

Apart from this, it has been reported that a 45-year-old woman complained of acute bilateral visual loss after intra-discal and peri-ganglionic injection of ozone-oxygen gas mixture for lumbar disk herniation (Lo Giudice, 2004). Corea (2004) also reported a case of vertebrobasilar stroke after treatment with ozone-oxygen for lumbar disc herniation.

### **7.2. EFFECTIVENESS**

#### **7.2.1. HIV AND INFECTIOUS DISEASES**

An anonymous report (1994) claimed that ozone together with oxygen can inactivate the HIV virus. Carpendale et al (1993) reported the efficacy of ozone in the treatment of AIDS related diarrhoea. In this paper, three of the four patients with diarrhoea of unknown etiology treated with daily insufflations of medical ozone, experienced complete resolution, while the other patient had marked improvement.

A review by Wells et al (1991) reported that ozone inactivates HIV-1 virions in a dose dependant manner.

Two studies reported that ozone being a strong oxidizer, can stimulate the increase of cellular anti-oxidant enzymes, eventually inhibiting the oxidative stress, and these may have implications in the treatment of many diseases including HIV (Rodder et al 1991, Bocci 1996).

A non randomized controlled study in patients suffering from Hepatitis A, B or C demonstrated that all 40 patients who received ozone were totally cured of hepatitis, and the rate of healing was faster in this group, but there was no mention of the breakdown of patients infected with hepatitis in the respective groups (Betancourt et al)

#### **7.2.2. ISCHAEMIA**

##### *Limb ischaemia*

While there have been a number of reports on the effectiveness of ozone in the treatment of limb ischemia (Sroczyński et al, 1992; Turczyński et al, 1991; Maslennikov et al, 1997; Tylicki et al, 2001; Tylicki et al, 2003; Biedunkiewicz et al, 2004), these were small non-randomized clinical trials, from a few centers mainly in Poland and Russia. Tafil-Klawe et al (2002) study involving 62 patients with lower limb ischaemia, of whom 32 patients were treated with ozone whereas the remainder were treated with traditional balneology, found better results with ozone.

### *CNS Ischaemia*

A study of 85 patients with ischaemic insult by Kotov et al treated with ozone demonstrated a decrease in the intra-cerebral blood circulation asymmetry, increased cerebral circulation reactivity and a functional restoration in the circle of Willis.

### *Ischaemic Heart Disease*

Another cross sectional study of ozone therapy in patients with progressive angina pectoris resulted in elimination of non-stable conditions with significant reduction of coronary insufficiency symptoms (Shaarov et al).

### 7.2.3. OPHTHALMOLOGY

A double blind RCT involving 123 subjects suffering from retinitis pigmentosa demonstrated that ozone treatment was effective, although its action is temporary (Moreno et al). A cross sectional study by Mapolon et al reported remission of photophobia and photopsia in all 50 patients with retinitis pigmentosa treated with ozone.

Similarly, another study by Diaz et al comprising of 180 patients with different ophthalmologic diseases like retinitis pigmentosa, myopia, chronic open angle glaucoma, optic atrophy and diabetic retinopathy were treated with daily rectal ozone therapy, demonstrated improvement ranging from 23%- 63% at follow-up over one year.

Satiesteban et al in a cross sectional study of 60 patients suffering from optic nerve dysfunction treated with ozone demonstrated 86% and 83% improvement in Pelli Robson Contrast Sensitivity Test (PRCST) and visual field (VF) by Goldmann Perimetry.

### 7.2.4. ORTHOLARYNGOLOGY

In a small randomized controlled trial by Basabe it was demonstrated that there was improvement in audiometry, electrophysiological threshold and the latency of the wave V to 90 DB for the same ear, in a great percentage of children that received ozone therapy.

A cross sectional study of patients with chronic purulent mesotympanitis treated with ozone in Russia, observed inflammation control of mucous membrane, discharge reduction and restoration of auditory tube function that (Shakov & Edeleva 1996)

### 7.2.5. OBSTETRICS & GYNAECOLOGY

Two unpublished non randomized controlled trials demonstrated that the patients with caesarian sections treated with ozone had less infectious complications compared to controls (Kovalev & Clemente-Apumayta, Kovalev). An unpublished cross sectional study by Kachlina reported that the maximum positive effect of ozone was seen in those patients with intrauterine infections without signs of inflammation compared to those with signs of inflammatory process.

Similarly, another non randomized controlled trial noted benefits in patients with various puerperal diseases in postnatal period treated with ozone compared with the control group (Kachalina et al - unpublished article)

Two cross sectional studies using ozone therapy in the treatment of female infertility and for endometritis showed improvement. However, these studies had small sample sizes (Mello & 'Mello;, Gretchkanev et al - unpublished article)

### 7.2.6. ORTHOPAEDIC DISORDERS

There were only 3 relevant clinical trials available on these subjects, thus making it difficult to draw conclusive results (D'Erme M et al 1998; Andreula CF et al 2003; Alex B)

### 7.2.7. CANCER

A review by Ernst (2001) concluded that knowledge regarding the potential benefit and harm of ozone in cancer patients is insufficient. Therefore such therapy can't be recommended as an alternative form of treatment for cancer patient.

Similarly the American Cancer Society has recommended in two review articles that that there is little or no evidence that ozone is effective for the treatment of cancer (Cancer Journal for Clinicians 1993, Cancer Journal for Clinicians 1994).

### 7.2.8. SKIN CONDITIONS

The evidence is only anecdotal in nature as with regards to the use of ozone in the treatment of skin conditions (Jordan et al 2002; Panminerva et al 1995).

## 8. CONCLUSIONS

Current data on the usage of ozone therapy as therapeutic options for various health conditions lacks sufficient safety and therapeutic advantage over available conventional therapeutic modalities.

## 9. RECOMMENDATIONS

There is insufficient clinical evidence to recommend ozone therapy as a form of alternative treatment in patients with HIV AND infectious diseases, autoimmune diseases, ischaemia, eye conditions, ENT, obstetrics and gynecology, orthopedic disorders, cancer and skin conditions.

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113. Y. Betancourt Y., J.M. Toledo, E. Recio<sup>1</sup>, A. Gómez, M. Rodríguez<sup>1</sup>, C. Harrys<sup>1</sup>, J.P. Pina<sup>2</sup>. Ozone therapy: an useful alternative on virulent hepatitis treatment. (Abstract from 2<sup>nd</sup> International Symposia on Ozone Applications, Cuba)
114. Y. Mapolon, M. Palma<sup>1</sup>, E. Resio, M. Rodríguez, E. Dyce<sup>1</sup>, C. Harrys, J. C. Pina<sup>1</sup> Effects of ozone in patients with retinitis pigmentosa. (Abstract from 2<sup>nd</sup> International Symposia on Ozone Applications, Cuba)

**EVIDENCE TABLE: OZONE THERAPY  
ASPECT: HIV/ HBV**

No	Author, Title, Journal, Year, Volume, Page Number	Study Design, Sample Size Follow-up	Outcomes and Characteristics	Grade & Comment
1.	<p>Garber GE, Cameron DW, Hawley-Foss N, Greenway D, Shannon ME (1991)</p> <p>The use of ozone-treated blood in the therapy of HIV infection and immune disease: a pilot study of safety and efficacy.</p> <p>AIDS. Aug; 5(8): 981-4.</p>	RCT	<p>A phase I study of ozone blood treatments in 10 patients with HIV. No significant toxicity was observed. Three patients with moderate immunodeficiency showed improvement in surrogate markers of HIV-associated immune disease.</p> <p>A phase II controlled and randomized double-blinded study was initiated comparing reinjection of ozone-treated blood, and reinjection of unprocessed blood for 8 weeks, followed by a 4-week observation period. Ozone had no significant effect on hematologic, biochemical or clinical toxicity when compared with placebo. CD4 cell count, interleukin-2, gamma-interferon, beta 2-microglobulin, neopterin and p24 antigen were also unaffected by both treatment arms.</p> <p>In conclusion, ozone therapy does not enhance parameters of immune activation nor does it diminish measurable p24 antigen in HIV-infected individuals.</p>	<p>This study claimed the methodology used was RCT. However, the description given does not reflect this.</p> <p>Small sample size</p>
2.	<p>Wells KH, Latino J, Gavalchin J, Poiesz BJ (1991).</p> <p>Inactivation of human immunodeficiency virus type 1 by ozone in vitro.</p> <p>Blood. Oct 1; 78(7): 1882-90</p>	Review	<p>This study suggest that ozone via a specially designed device administered to body fluids offers promise as a means to inactivate human retroviruses in human body fluids and blood product preparations.</p> <p>Ozone was found to inactivate HIV-1 virions in a dose-dependent manner. The data indicate that the antiviral effects of ozone include viral particle disruption, reverse transcriptase inactivation, and/or a perturbation of the ability of the virus to bind to its receptor on target cells.</p>	
3.	<p>Roder W, Muller WE, Merz H (1991).</p> <p>Is ozone suitable for sterilization of HIV infected bones?</p> <p>Unfallchirurg. Jan; 94(1):50 [Article in German]</p>		<p>This experimental in vitro study showed that ozone treatment cannot inactivate HIV in bone for transplantation</p> <p>HIV infection can be transferred by blood, blood products and organ transplantation. In traumatic surgery allogeneic bone transplantation is commonly used for reconstruction in severe bone injuries. This technique has been abandoned since the appearance of reports of infections with HIV.</p>	

No	Author, Title, Journal, Year, Volume, Page Number	Study Design, Sample Size Follow-up	Outcomes and Characteristics	Grade & Comment
4.	<p>Carpendale MT, Freeberg J, Griffiss JM (1993). Does ozone alleviate AIDS diarrhea? J Clin Gastroenterol. Sep; 17(2): 142-5.</p>	Cross sectional	<p>Five patients with acquired immune deficiency syndrome (AIDS) or AIDS-related complex (ARC) and intractable diarrhea were treated with daily colonic insufflations of medical ozone (oxygen/ozone mixture) for 21-28 days.</p> <p>Three of the four patients whose diarrhea was of unknown etiology experienced complete resolution, and one patient had marked improvement. The fifth patient, whose diarrhea was due to Cryptosporidium, experienced no change. No consistent change in the absolute number of helper (CD4) or suppressor (CD8) lymphocytes was detected, and no obvious changes were seen in the PO2 or the results of routine hematologic and blood chemistry studies.</p> <p>The results of this series suggest that medical ozone administered by rectal insufflation is simple, safe, and effective.</p>	
5.	<p>Bocci V (1999). Biological and clinical effects of ozone. Has ozone therapy a future in medicine? Br J Biomed Sci 56(4):270-9.</p>	Review article	<p>This paper summarises studies aimed at clarifying biological effects, defining any possible damage, the therapeutic window, and suitable doses of ozone that was able to express therapeutic activity. This paper states that ozone therapy, although unfashionable and unpopular needs to be critically assessed by the orthodox medicine</p>	
6.	<p>Bocci V (1992). Ozonization of blood for the therapy of viral diseases and immunodeficiencies. A hypothesis. Med Hypotheses. Sep; 39(1):30-4.</p>	Review	<p>In the last 3 decades major autohemotherapy after exposure to ozone has been used in Europe in uncontrolled trials carried out in patients with many illnesses, particularly chronic viral diseases and neoplasms.</p> <p>It appears that the treatment may activate the host's immune system by inducing the production of immunoreactive cytokines and it may now be possible to rationalize the procedure, improve the regimen and assess the outcome. It is apparent, however, that such a therapeutic approach, in order to be acceptable, requires an investigative effort of biologists and clinicians.</p> <p>Once this is done, owing to the large range of medical applications and the simplicity of the procedure, autohemotherapy could become very valuable particularly in underdeveloped countries.</p>	

No	Author, Title, Journal, Year, Volume, Page Number	Study Design, Sample Size Follow-up	Outcomes and Characteristics	Grade & Comment
7.	<p>Y. Betancourt, J.M. Toledo, E. Recio1, A. Gómez, M. Rodríguez1, C. Harrys1, J.P. Pina2.</p> <p>Ozone therapy: a useful alternative on virulent hepatitis treatment.</p> <p>(Abstract from 2<sup>nd</sup> International Symposia on Ozone Applications, Cuba)</p>	<p>Non-randomised controlled trial</p> <p>80 subjects, Patients, between 17 and 45 years old,</p> <p>A study with 80 patients suffering from A, B, C hepatitis, since August 1996, in Cuba was performed</p>	<p>Conventional treatment (response and diet prescribed) plus ozone therapy was applied to 40 patient, the other 40 patients only received conventional treatment.</p> <p>During the first week of treatment, remission of all the symptoms took place as well as the enlargement of the liver, improving their conditions and their appetite. All patients were totally cured at the end of the treatment. Under the conventional treatment these symptoms remain for more than 10 days and the totally cure was achieved approximately 6 months later.</p> <p>Comparing these results we can say that ozone therapy is a suitable treatment against hepatitis, improving the patient's health and the healing time of the disease.</p>	<p>Fair</p> <p>Small sample size.</p> <p>Not a randomized control study - Element of bias.</p> <p>The paper doesn't inform us on the breakdown of how many patients infected with hepatitis in both groups i.e. ozone or conventional treatment.</p> <p>Therefore there could be more patients with hepatitis A in those receiving ozone</p>
<b>SAFETY</b>				
1.	<p>Marchetti D, La Monaca G. (2000)</p> <p>An unexpected death during oxygen-ozone therapy.</p> <p>Am J Forensic Med Pathol. 2000 Jun;21(2):144-7</p>	<p>Case Report</p>	<p>An unexpected death is described that was caused by gas embolism that occurred during oxygen-ozone (O2/O3) therapy administered by autohemotransfusion for psoriasis. This unusual complication suggests the necessity of investigating benefits and adverse effects of medical ozone application.</p>	

No	Author, Title, Journal, Year, Volume, Page Number	Study Design, Sample Size Follow-up	Outcomes and Characteristics	Grade & Comment
<b>CANCER</b>				
1.	<p>[No authors listed]</p> <p>Questionable methods of cancer management: hydrogen peroxide and other 'hyperoxygenation' therapies.</p> <p>CA Cancer J Clin. 1993 Jan-Feb; 43(1):47-56.</p>	Review	<p>Hyperoxygenation" therapy—also called "oxymedicine," "bio-oxidative therapy," "oxidative therapy," and "oxidology"—is a method of cancer management based on the erroneous concept that cancer is caused by oxygen deficiency and can be cured by exposing cancer cells to more oxygen than they can tolerate. The most highly touted "hyperoxygenating" agents are hydrogen peroxide, germanium sesquioxide, and ozone. Although these compounds have been the subject of legitimate research, there is little or no evidence that they are effective for the treatment of any serious disease, and each has demonstrated potential for harm. Therefore, the American Cancer Society recommends that individuals with cancer not seek treatment from individuals promoting any form of hyperoxygenation therapy as an "alternative" to proven medical modalities.</p>	
<b>ASTHMA</b>				
1.	<p>Bosson J, Stenfors N, Bucht A, Helleday R, Pourazar J, Holgate ST, Kelly FJ, Sandstrom T, Wilson S, Frew AJ, Blomberg A. (2003)</p> <p>Ozone-induced bronchial epithelial cytokine expression differs between healthy and asthmatic subjects.</p> <p>Clin Exp Allergy. Jun; 33(6):777-82. (Abstract only )</p>	<p>Clinical trial without control group</p> <p>Sample size not mentioned</p>	<p>Healthy and mild allergic asthmatic subjects (using only inhaled beta2-agonists pm) were exposed for 2 h in blinded and randomized sequence to 0.2 ppm of O3 and filtered air. Bronchoscopy with bronchial mucosal biopsies was performed 6 h after exposure.</p> <p>When comparing the two groups at baseline, the asthmatic subjects showed a significantly higher expression of IL-4 and IL-5. After O3 exposure the epithelial expression of IL-5, GM-CSF, ENA-78 and IL-8 increased significantly in asthmatics, as compared to healthy subjects.</p> <p>The present study confirms a difference in epithelial cytokine expression between mild atopic asthmatics and healthy controls, as well as a differential epithelial cytokine response to O3. This O3-induced upregulation of T helper type 2 (Th2)-related cytokines and neutrophil chemoattractants shown in the asthmatic group may contribute to a subsequent worsening of the airway inflammation, and help to explain their differential sensitivity to O3 pollution episodes.</p>	

## LIMB ISHAEMIA

No	Author, Title, Journal, Year, Volume, Page Number	Study Design, Sample Size Follow-up	Outcomes and Characteristics	Grade & Comment
1.	<p>Tylicki L, Niew glowski T, Biedunkiewicz B, Burakowski S, Rutkowski B (2001)</p> <p>Beneficial clinical effects of ozonated autohemotherapy in chronically dialysed patients with atherosclerotic ischemia of the lower limbs—pilot study.</p> <p>Int J Artif Organs. Feb; 24(2):79-82.</p>	<p>Cross sectional study</p> <p>12 patients</p> <p>5 hemodialyzed patients and 7 patients treated with peritoneal dialysis were examined immediately before and after 14 sessions of ozonated autohaemotherapy</p>	<p>This is a preliminary study on the influence of blood ozonation on the intensity of symptoms of ischemia of the lower extremities among dialysed patients with chronic renal failure.</p> <p>Eleven patients (91.6%) reported a subjective decrease in perceived intensity of ischemic pains, or observed prolongation of intermittent claudication distance. During march tests performed on a treadmill, there was a significant prolongation of intermittent claudication distance in all examined patients - 65.6% (mean value, <math>p &lt; 0.01</math>). Patients treated with peritoneal dialysis achieved much greater improvement than did hemodialyzed patients (165% vs. 42%).</p> <p>It was concluded that autohemotherapy with ozone, in a concentration of 34.4 mcg/ml of blood, is safe, easily applied and may be useful in the therapy of atherosclerotic ischemia of lower extremities among dialyzed patients.</p>	<p>Poor</p>
2.	<p>Tylicki L, Nieweglowski T, Biedunkiewicz B, Chamienia A, Debska-Slizien A, Aleksandrowicz E, Lysiak-Szydłowska W, Rutkowski B (2003).</p> <p>The influence of ozonated autohemotherapy on oxidative stress in hemodialyzed patients with atherosclerotic ischemia of lower limbs.</p> <p>Int J Artif Organs. Apr; 26(4):297-303. (Abstract only)</p>	<p>Non randomized control trial</p> <p>12 subjects</p>	<p>The aim of the study was to investigate the influence of ozonated autohemotherapy on the oxidative stress extent in hemodialyzed patients, known to be particularly exposed to generation and deleterious effects of free radicals.</p> <p>Twelve continuously hemodialyzed subjects with atherosclerotic ischemia of the lower limbs were examined in a prospective, controlled, single blind study. Autohemotherapy with blood exposure to oxygen served as a control. The protein and lipid peroxidation products, the reduced glutathione level in red blood cells and free hemoglobin plasma concentration was measured.</p> <p>The study showed that ozonated autohemotherapy with ozone concentration 50 microg/ml per gram of blood induced a significant decrease in glutathione level after 9 sessions of this procedure. Therapy did not cause either the enhancement of protein and lipid peroxidation, or erythrocytes damage.</p>	<p>Fair</p>



No	Author, Title, Journal, Year, Volume, Page Number	Study Design, Sample Size Follow-up	Outcomes and Characteristics	Grade & Comment
3.	<p>Tylicki L, Biedunkiewicz B, Niewegłowski T, Chamienia A, Slizien AD, Luty J, Lysiak-Szydłowska W, Rutkowski B (2004). Ozonated autohemotherapy in patients on maintenance hemodialysis: influence on lipid profile and endothelium. <a href="mailto:leszek.tylicki@wp.pl">leszek.tylicki@wp.pl</a> Artif Organs Feb; 28(2):234-7. (Abstract only)</p>	<p>Controlled trial Twelve hemodialyzed subjects with atherosclerotic ischemia of lower limbs (AILL) received autohemotherapy with oxygen as a control followed by O3-AHT with ozone concentration of 50 micro g/ml.</p>	<p>Serum lipids and plasma activity of von Willebrand factor (vWF) were measured. After O3-AHT, total cholesterol significantly decreased compared to the baseline (-8.34%) [P &lt; 0.01]. LDL cholesterol was also significantly lower than the initial value (-17.71%) [P &lt; 0.001]. No significant changes in the activity of vWF were found after the first session of O3-AHT and after all nine sessions of O3-AHT. The study showed that O3-AHT did not affect deleteriously the endothelium in patients with chronic renal failure on maintenance hemodialysis. It may stimulate beneficial changes in serum lipid profile manifesting as a decrease in the total- and LDL-cholesterol levels.</p>	<p>Fair The same subjects served as controls. Hence comparison more valid.</p>
4.	<p>Biedunkiewicz B, Tylicki L, Niewegłowski T, Burakowski S, Rutkowski B (2004). Clinical efficacy of ozonated autohemotherapy in hemodialyzed patients with intermittent claudication: an oxygen-controlled study. Int J Artif Organs. Jan; 27(1):29-34. (Abstract only)</p>	<p>Cross over single blinded 10 subjects</p>	<p>Ten subjects with intermittent claudication (Fontain II stage) received the cycle of ozonated autohemotherapy with ozone concentration of 50 microg/ml and the cycle of oxygen autohemotherapy as a control in a crossover, single-blind manner. Pain-free distance and maximal walking distance were measured. Patients assessed the efficacy of therapy subjectively. The results showed significant prolongation of maximal walking distance after ozonated autohemotherapy compared to. There was also significant increase in pain-free distance after ozonated autohemotherapy, compared to baseline (by 71.7%) and to the oxygen control (by 62.8%) 90% of patients reported clinical improvement relative to baseline after ozonated autohemotherapy, compared to only 40% after the oxygen-control treatment.</p>	<p>Poor Subjective evaluation Time frame not mentioned. No mention of washout period between the cross over</p>
5.	<p>Sroczyński J, Antoszewski Z, Matyszczyk B, Krupa G, Rudzki H, Zbronska H, Skowron J (1992). Clinical assessment of treatment results for atherosclerotic ischemia of the lower extremities with intraarterial ozone injections [Article in Polish] Pol Tyg Lek. Oct 19-26; 47(42-43):964-6.</p>	<p>Clinical trial Ten injections of O3 into femoral arteries were administered 50 patients with atherosclerotic ischemia of the lower extremities and to 49 diabetic patients</p>	<p>All patients were assessed clinically with the ankle-arm index, measurement of intermittent claudication distance prior to and after the treatment. The treatment showed a significant improvement in both groups manifested by an increase in ankle-arm index, and prolongation of the intermittent claudication distance by more than twice. The treatment of atherosclerotic ischemia of the lower extremities with O3 is both valuable and safe.</p>	

No	Author, Title, Journal, Year, Volume, Page Number	Study Design, Sample Size Follow-up	Outcomes and Characteristics	Grade & Comment
6.	<p>Maslennikov OV, Sharov IG, Potekhina IP, Dushkina NG, Kryzhanovskaia NA, Maslennikova NO, Bolgov VF, Pavlovskaja EE, Zheglava LV, Chalkina SN (1997). Effect of ozone therapy on hemostatic changes in patients with vascular atherosclerosis Klin Med (Mosk). 75(10):35-7. (Abstract only )</p>	<p>Clinical trial without control group 81 subjects [Article in Russian]</p>	<p>It was found that use of ozone-oxygen mixtures leads to hypocoagulatory changes (diminution of platelet aggregation, lowering of fibrinogen concentration, prolongation of activated partial thromboplastin time, enhanced fibrinolytic activity) which contribute to clinical response</p>	<p>Poor</p>
7.	<p>Turczynski B, Sroczyński J, Antoszewski Z, Matyszczyk B, Krupa G, Mlynarski J, Strugala M (1991). Ozone therapy and viscosity of blood and plasma distance of intermittent claudication and certain biochemical components in patients with diabetes type II and ischemia of the lower extremities Pol Tyg Lek. Sep 9-30; 46(37-39):708-10 [Article in Polish]</p>		<p>A significant improvement in intermittent claudication and reduction in blood and plasma viscosity occurred after ozone therapy.</p>	
8.	<p>Peralta C, Leon OS, Xaus C, Prats N, Jallil EC, Planell ES, Puig-Parellada P, Gelpi E, Rosello-Catafau J. Protective effect of ozone treatment on the injury associated with hepatic ischemia-reperfusion: antioxidant-prooxidant balance. Department of Medical Bioanalysis, Instituto de Investigaciones Biomédicas de Barcelona, CSIC-IDIBAPS, Spain</p>		<p>The effect of ozone treatment on the injury associated to hepatic ischemia-reperfusion (I/R) was evaluated. Ozone treatment (1 mg/kg daily during 10 days by rectal insufflation) is shown to be protective as it attenuated the increases in transaminases (AST, ALT) and lactate levels observed after I/R. I/R lead to a decrease in endogenous antioxidant (SOD and glutathione) and an increase in reactive oxygen species (H2O2) with respect to the control group. The present study reports a protective effect of ozone treatment on the injury associated to hepatic I/R. The effectiveness of ozone could be related to its action on endogenous antioxidants and prooxidants balance in favour of antioxidants, thus attenuating oxidative stress</p>	

No	Author, Title, Journal, Year, Volume, Page Number	Study Design, Sample Size Follow-up	Outcomes and Characteristics	Grade & Comment
9.	<p>S. Kotov; A. Gustov and A.Mochalov.Nizhni Novgorod</p> <p>Ozone therapy influence on hemodynamics in patients with ischemic insult.</p> <p>(Abstract from 3<sup>rd</sup> International Symposia on Ozone Applications, Cuba)</p>	<p>Clinical trial without control group</p> <p>85 subjects treated with intravenous ozonized normal saline solution (ONS) with an ozone concentration of 300ug/l.</p>	<p>In 85 patients with ischemic insult are shown that positive ultrasonic dopplerography dynamics was marked in 79 % of cases, in the acute period, and in 63 % of cases in the restoration period of ischemic insult.</p> <p>It was shown a decrease in the intercerebral blood circulation asymmetry and in the circulatory resistance, as well as an increase of the cerebral circulation reactivity and a functional restoration of forward and backward connecting arteries in the Willis circle. In this case linear blood velocity did not vary.</p> <p>The ONS infusions also promoted maintenance of the effective heart work. The stroke volume by the end of the treatment course has grown on 29 %, and the minute volume on 24 %. The general peripheral circulatory resistance has decreased on 31 %. As a whole, eukinetic type of circulation is 1, 5 times more often after ozonotherapy.</p>	Poor
10.	<p>Y. Shaarov, N. Maslennikova, N. Dushkina, O. Maslennikov.</p> <p>Ozone therapy in ischemic heart disease (ihd).</p> <p>(Abstract from 2<sup>nd</sup> International Symposia on Ozone Applications, Cuba)</p>	<p>Clinical trial without control group</p> <p>85 subjects, 80 having stable II-III stenocardia, 5 patients had progressive angina pectoris.</p> <p>The treatment course was done in 3-4 weeks. Ozone/oxygen mixtures were administered in intraveous drops infusions and rectal insufflations. The patients condition was checked by clinical signs (number of stenocardial attacks and nitroglycerine use), tolerance to physical loads data, EKG readings, echocardiography.</p>	<p>Positive results were received in 76 patients (of 80 patients with stable stenocardia -95%) that were on ozone therapy. Attacks of stenocardial pains were completely controlled in 46 out of 80 patients (58%) with stable stenocardia. The amount of pain attacks was diminished in 50% in 30 patients (37.5%). This enabled the patients to low the dose of nitrates and in a number of cases to discontinue their use. 4 patients (5%) did not have any improvement in their condition.</p> <p>Ozone therapy proved to be highly effective in patients with progressive angina pectoris and resulted in elimination of non-stable condition with significant reduction of coronary insufficiency symptoms.</p> <p>All the patients showed the increase to domestic and dosed physical loads. Instrumental readings had positive dynamics. Hence, ozone therapy can be regarded as a highly efficient method of IHD treatment. Positive results are provided by ozone influence on antioxidant, coagulation and oxygen-transport</p>	Poor

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<b>EYE</b>				
1.	<p>N. Moreno, O. Peláez, T. Alemán, C. Barceló.</p> <p>Controlled clinical trial on the use of ozonated blood as a treatment for retinitis pigmentosa.</p> <p>(Abstract from 2<sup>nd</sup> International Symposia on Ozone Applications, Cuba)</p>	<p>A double blind RCT, 123 subjects, 15 to 65 years, and suffering from typical forms of retinitis pigmentosa participated</p> <p>62 patients assigned to the treatment and 61 to control group (placebo)</p>	<p>A complete general and ophthalmologic examination was performed after signing an informed consent. Snellen visual acuity was measured (less than 2.5 lines considered non significant changes) and Goldmann kinetic visual field with 31.5 asb. Background and V-4e target. Visual field areas were digitized and measured with a computer program (VISUAL). Ozonated blood was administered to patients in the treatment group, in a daily fashion for 15 days, while patients in the control group received only blood. Participants were blind with regards to this, throughout the duration of the study. Visual acuity remained the same, 6 months after the treatment, in 74.2% of the patients, improve in 21% and worsen in 4.8%. Visual field area remained the same, 6 months after the treatment, in 41.9% of the patients, improve in 46.7% and worsen in 11.35%. Significant differences were observed between groups with lower frequencies of improvements in controls are larger proportions of worsening. Improvements were not observed in 91.9% of patients one year after the treatment. This tendency was first noted after 6 months from the treatment. Ozone treatment is proved of benefit in patients with RP, although its action is temporary.</p>	Good
2.	<p>E. C. Díaz, L. Borrego I, S. Menéndez2, L. R. Borrego3, R. A. Borrego3. I.</p> <p>Ozone therapy in different ophthalmologic diseases.</p> <p>(Abstract from 2<sup>nd</sup> International Symposia on Ozone Applications, Cuba)</p>	<p>Clinical trial without group</p> <p>180 subjects 1-year follow-up</p> <p>Patients were treated with daily rectal ozone therapy, during 20 days, representing 80 with Retinitis Pigmentosa (no systemic, stage I and II), 45 with progressive myopia, 25 with chronic glaucoma of open angle (tonometrically compensated), 20 with optic atrophy (less than one year of evolution and not hereditary), 10 with diabetic retinopathy (no proliferative).</p>	<p>Clinical evaluation was made each 3 months, up to 1 year. In patients with Retinitis Pigmentosa, 75 % improved their visual acuity (post-treatment and 6 months later).</p> <p>After 1 year, 23% of improvement still remained. According to visual field, 76% of patients improved it after treatment and up to 9 months, but after 1 year, 16% lost their improvement. Respect to progressive myopia, the visual acuity increased in 78% (post-treatment and 9 months later) and remained 58% after 1 year. In glaucoma, 65% increased the visual acuity (post-treatment and 9 months later), maintaining 53% of improvement after 1 year. Visual field increased in 76% of patients, post-treatment and after 1 year. In diabetic retinopathy, 60% improved their visual acuity (post-treatment), diminishing to 40%, 6 months later and 20%, after 1 year. Respect to optic atrophy, 45% of improvement in visual field was achieved (post-treatment) maintaining its figure after 1 year.</p>	<p>Poor</p> <p>Small subset sample size. Those who participated in this study with the ophthalmologic diseases were with mild or no complications. This study has a short follow-up. There is a need for a randomized clinical trial looking at various severities of each ophthalmological condition.</p>

No	Author, Title, Journal, Year, Volume, Page Number	Study Design, Sample Size Follow-up	Outcomes and Characteristics	Grade & Comment
3.	<p>Y. Mapolon, M. Palma1, E. Resio, M. Rodríguez, E. Dycel1, C. Harrys, J. C. Pina1.</p> <p>Effects of ozone in patients with retinitis pigmentosa.</p> <p>(Abstract from 2<sup>nd</sup> International Symposia on Ozone Applications, Cuba)</p>	<p>Descriptive report</p> <p>50 subjects</p> <p>The effect of ozone in 50 patients with retinitis pigmentosa was evaluated in the Retinitis Pigmentosa Center, Camagüey, Cuba.</p>	<p>The patients suffer of photophobia, photopsia and reduce vision on dark places.</p> <p>Considering that the patients with remission of two symptoms of the disease after the ozone treatment is considered as signs improvement, in this case all of them after the 7th and 8th ozone application didn't present photophobia and photopsia, increasing also the quality of their vision (by means of improvement in the visual acuity and visual field). In spite of, after 6 month the appearance of signs and symptoms in all the patients took place.</p>	<p>Poor</p> <p>A long term follow-up or a cohort study is required to determine whether these findings are on short term or long term basis.</p>
4.	<p>R. Santiesteban, S. Menéndez1, M. Francisco, S. Luis.</p> <p>Ozone therapy in patients suffering from optic nerve dysfunction.</p> <p>(Abstract from 2<sup>nd</sup> International Symposia on Ozone Applications, Cuba)</p>	<p>Clinical trial without control group</p> <p>60 patients suffering from OND of different etiologies and time of evolution were given mixture of ozone/oxygen endovenously by autohemotherapy, during 15 sessions.</p>	<p>The main object of this study was to evaluate the feasibility of improving the visual function of a group of patients, with different degrees of OND with reduced possibilities of vision improvement, by means of ozone therapy.</p> <p>Ozone concentration and doses are used according to the biochemical status of each patient. An ophthalmological examination and a set of tests conformed by visual acuity (VA), visual field by Goldmann Perimetry (VF), visual evoked potentials (VEP), Pelli Robson Contrast Sensitivity Test (PRCST) was applied to patients before and after ozone therapy treatment.</p> <p>PRCST and VF were the parameters mostly improved in patients with 86% and 83% respectively, followed by VA (55%) and VEP (37%). Good results were achieved in all etiologies studied, except Leber optic atrophy, where no improvement was observed, neither objective nor subjective.</p>	<p>Poor</p>

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<b>ENT</b>				
1.	E. Basabe. Analysis of the electrophysiological threshold, audiometry and latency of the wave V in children with hearing loss submitted to ozone therapy. (Abstract from 2 <sup>nd</sup> International Symposia on Ozone Applications, Cuba)	RCT, double blind study 34 children were selected with the same educational profile and divided at random in 2 groups: 17 received rectal oxygen and the others 17 received rectal ozone	Comparing the results, audiometry, electrophysiological threshold and the latency of the wave V to 90 DB, for the same ear, improved in a great percentage of children that received ozone therapy.  Different behavior among subjects treated with ozone compared to children that received oxygen, was observed.	Good
2.	V. Shakhov, A. Edeleva. The Use Of Ozone Therapy In Chronic Purulent Mesotympanitis (Abstract from 2 <sup>nd</sup> International Symposia on Ozone Applications, Cuba)	Non randomized controlled trial 50 subjects. 40 patients underwent a course of treatment that consisted of 7-10 daily procedures. Control group of 10 patients was on a conventional therapy.	The results demonstrated that ozone therapy have no negative effect on internal ear or labyrinth function, even in prolonged applications of high ozone concentrations effecting mucous membrane of medial wall.  Clinical effect was observed in inflammation control of mucous membrane, discharge reduction and restoration of auditory tube function.	Fair
<b>OBSTRETIC &amp; GYNAECOLOGY</b>				
1.	V. M. Zuev; N. M. Pobedynsky; D. G. Krasnicov; T. A. Djibladze; L. S. Alexandrov y M. I. Kovalev. Ozone effectiveness in the treatment of chronic fetal hypoxia. (Abstract from 3 <sup>rd</sup> International Symposia on Ozone Applications, Cuba)	Non randomized controlled trial 166 subjects Treatment group 132 and control- 34	Monitoring by ultrasound, Doppler, steroid, cardiotochography, morfological investigation of placenta.  Ozone therapy was applied by intravenous administration of ozonized solution of sodium chloride.  In the ozone group, normal state of fetus was obtained much earlier and was supported with high intensification of adaptive mechanism, showed in placenta blood circulation.	Fair

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<b>OBSTRETIC &amp; GYNAECOLOGY</b>				
2.	Clemente-Apumayta .J. M, Zuev V. M, Ljashko E. S. Voloschuk I. N, Kovganko P. A. Sechenov M.  Ozone therapy in chronic placental insufficiency  Source: Abstracts from 3 <sup>rd</sup> International Symposium on Ozone Application, Cuba	Non randomized controlled trial  48 pregnant women with at the beginning and at the end of the gestation ages from 26 to 37 weeks were examined. Control group was represented by 20 pregnant women that were treated by means of common therapeutic methods	Doppler examination (S/D ratio, PI and RI) was carried out one, two and three weeks post treatment in the uterine, spiral and umbilical (including the end-branches) arteries.  Morphological examination of placenta from the women underwent ozone application revealed activation of the compensatory processes, i.e., the increased number of vessels, their remarked plethora; in some cases the development of the villi angeomatosis foci was detected.  The improvement of the PLO indices and disappearance of hyper coagulation were also shown.	Fair
3.	M.I.Kovalev y I.M.Clemente-Apumayta.  Immune status during ozone therapy for the prophylaxis of infections after ceasarean.  (Unpublished full article)	Non randomized controlled trial  80 subjects in the treatment group  Number of subjects in the control group not mentioned. The control group did not received ozone therapy, only traditional methods.	80 women, who had delivery by cesarean, were treated on the 1st, 2nd, 3rd and 4th postoperative day by intravenous ozone solution.  All the patients have got before and after the treatment a complete blood count and T and B cell differentiation. Immunoglobulins levels, phagocyte activity were also studied.  The ozone treated group had significantly less infectious complications after the cesarean compared to the control group. An immune modulating action of the ozone therapy could be shown in the treated group, the mean quantity CD4+cell and phagocyte activity was higher in comparison with the control group.	Poor
4.	I.Kovalev.  Ozone treated women after caesarean and interferon profile.  (Unpublished full article)	Non randomized controlled trial  78 subjects  Number of subjects in the control group not mentioned.	78 consecutive women, who had delivery by cesarean, were treated on the 1st, 2nd, 3rd and 4th postoperative day by I.V. ozone. Interferon was measured in all patients before and after the ozone treatment. Control group had got no ozone therapy.  The levels of alfa- and gamma-interferon in the ozone treated group were higher than in the control group. The ozone treated group had significantly less infectious complications after the cesarean compared with the traditionally treated group.	Poor

No	Author, Title, Journal, Year, Volume, Page Number	Study Design, Sample Size Follow-up	Outcomes and Characteristics	Grade & Comment
5.	Grechkanov GO, Katchalina TS, Katchalina OV The new method of treatment of inflammatory diseases of lower female genital organs. (Unpublished full article)	Non randomized controlled trial 60 patients with non-specific colpitis were divided into 2 groups. 40 in test group and 20 controls	The test group received vaginal circulatory insufflations of an ozone-oxygen mixture, while controls received antiseptics solutions. This was repeated daily within 7-10 days. All underwent bacterioscopic and bacteriological investigation pre and post-treatment. After treatment, 76% in the treated group didn't show any opportunistic infection, while in the control group, 50% returned to normal and 25% got worse.	Poor No statistical test available
6.	Kachalina T. S, Peretyagina N. S, Antonova N. S. Possibility for parenteral application of ozone in early postnatal period in case of infectious complications. (Unpublished full article)	Non randomized controlled trial The sample consisted of 34 patients in early postnatal period (7 - 10 days) with various puerperal diseases. (N=19) received traditional treatment in combination with daily intravenous ozonated saline infusions. Control group (n=15) was performed antibacterial, detoxification and desensibilization therapy, as well as the use of physical factors.	Results - efficiency of the ozone therapy, in combination with traditional treatment in patients with infectious postpartum complications. In this group, the values of endogenic intoxication were decreased much faster, as well as erythrocyte sedimentation rate, leukocytosis, index of leukocyte intoxication and level of middle molecule peptides. Also the pH-value had a tendency to balance. The lipid peroxidation values confirmed the important action of ozone, increasing the antioxidant defence system. The efficiency of ozone therapy used in combination with traditional treatment was demonstrated by reducing hospital care time by 5 days.	Fair Details of the study are not given
7.	Kachalina T. S, Katkova N. Yu, Grechkanov G. O. The use of ozone therapy in the treatment and prophylaxis of intrauterine fetus infection. (Unpublished full article )	Clinical trial without control group 102 pregnant women with a risk group of intrauterine infection of fetus and newborn child were examined. The patients were divided into 2 groups, the 1st group comprising 60 patients with intrauterine infection carriers without inflammation signs, and the 2nd one including 45 patients showing the signs of an inflammatory process.	Each group was treated with the traditional methods (including antibiotics and immunomodulators). All the women received an ozonated physiological saline solution, intravenously, daily for 3 - 5 days. This study revealed the maximum positive therapeutic effect in patients of the 1st group. The normalization of the lipid peroxidation and the antioxidative system index were observed in 72 % of women of this group. The normalization of the immune system index was obtained in 42 %. Patients with uteroplacental blood flow disturbances showed a tendency to improve the doppler index (78 %). Besides, no one case of infectious agent transmitted to fetus was revealed in the 1st group. The described effects were not revealed in the 2nd group. Thus, application of ozone has maximum effect when a mother shows the presence of TORCH-infection agents without the signs of inflammatory process activation.	Poor



No	Author, Title, Journal, Year, Volume, Page Number	Study Design, Sample Size Follow-up	Outcomes and Characteristics	Grade & Comment
8.	R Chandra-D'Mello, R 'Mello Ozone therapy in female infertility (Unpublished full article )	Clinical trial without control group 56 subjects	56 patients with infertility of inflammatory etiology were given complete ozonotherapy course for 12 days. Then after 44 patients were prescribed rectal insufflations and vaginal applications daily for 3 days with an interval of 15 days.  12 patients were given a gap of 25 to 30 days. Lab investigations were done pre and post treatment. Ozonotherapy has a good positive effect in.	Poor
9.	Gretchkanov GO, Katchalina TS, Katchalina OV The treatment of endometritis in combination with ozonotherapy (Unpublished full article)	Clinical trial without control group 15 subjects	15 patients with acute form of postabortive and postnatal endometritis received intrauterine irrigation with ozonised-distilled water. The treatment was carried out once a day within 1-3 days without intervals, with combination of gentamicin. Patients showed improvements in general state, decreased symptoms of intoxication, better sleep and appetite and faster pain relief.	Poor
<b>ORTHOPAEDICS</b>				
1.	A. Mochalov and S. Kotov. Ozone Therapy And The Neurologic Behaviour Of A Backbone Osteochondrosis.  (Abstract from 3 <sup>rd</sup> International Symposia on Ozone Applications, Cuba)	Non randomized controlled trial  107 patients with musculotonic, neurodystrophic and radicular syndromes of backbone osteochondrosis (cervical and lumbar localization) were investigated.	The average age of patients was 43.8 years; mean duration of the disease was about 6.5 years. In the treatment of the basic group (81 patients, all men) was used ozone therapy by introduction of ozone-oxygen mixture (OOM) in paravertebral zones and in biologically active points, and also local autohemotherapy (LAHT).  Control group included 26 a patient (all men) at which introduction of oxygen (as a placebo) was combined with LAHT with not ozonized blood. At the end of the treatment, the patients marked essential improvement of health state expressed in decrease of pain, disappearance of hyperpathic component, time intervals without pain, narrowing of irradiation zone. Simultaneously, the backbones mobility was enlarged, the night a dream was improved.	Fair
2.	D'Erme M et al (1998) Ozone therapy in lumbar sciatic pain Radiol Med (Torina) Jan-Feb; 95(1-2): 21-4	Non-randomised controlled prospective trial N= 50  Follow-up for 6 months	At 3 months post treatment, 68% had positive results and 32% negative results	Fair

No	Author, Title, Journal, Year, Volume, Page Number	Study Design, Sample Size Follow-up	Outcomes and Characteristics	Grade & Comment
3.	<p>Andreula CF et al (2003) Minimally invasive oxygen-ozone therapy for lumbar disk herniation AJNR Am J Neuroradiol May; 24(5): 996-1000</p>	<p>Double blind prospective trial N=600 Follow-up 6 months</p>	<p>Group A (patient whom received single session of oxygen- ozone intradiscal and perianglionic). Group B (patient whom received treatment as group A in addition a perianglionic injection of corticosteroid and anesthetic. Group A-success in 70.3%, poor outcome in 29.7% Group B-Success in 78.3% and failure in 21.7%. The different in outcome was Statistically significant (P&lt;. 05)</p>	Good
4.	<p>Alex B Ozonotherapy in complex surgical treatment of patients with infected tibial fractures and soft tissue defects (Abstract from 3<sup>rd</sup> International Symposia on Ozone Applications, Cuba)</p>	<p>Non randomized controlled trial 25 subjects Institute of Traumatology and Orthopedics, N.Novgorod, Russia.</p>	<p>Between 1997 and 1999, 18 patients with infected tibial fractures (14 patients with soft tissue defects) received complex surgical treatment combined with ozone therapy. Infectious complications were not found in the sample. In the control group made up of 11 patients, ozone therapy was not carried out, only the conventional treatment was used. In two of them deep wound infection was developed with an osteomyelitis outcome.</p>	Fair
5.	<p>Alex B. Osseous residual treatment in patients with chronic osteomyelitis of long tubular bones using ozone (Abstract from 3<sup>rd</sup> International Symposia on Ozone Applications, Cuba)</p>	<p>Clinical trial without control group 63 patients with chronic osteomyelitis of long tubular bones were studied.</p>	<p>The surgical intervention consists of sequestra and implants removal, osteonecrosis resection, irrigation and external fixation by Ilizarov device or plaster bandage. Immediately after the patient awakened, suction drainage of residual osseous and soft tissues cavity by saline solution with ozone concentration was started. On the 2nd–3rd day the perfusate was cleared of blood, on the 7th day fibrin was not seen. By the end of the second week the solution and the perfusate did not differ visually. Average terms of drainage tube removal in control group (39 patients), were 24 days, in the sample - 17 days. This procedure, in patients with purulent complications of lower limbs can reduce the time of postoperative wound lavage and complete debridement by putting a suture. Local inflammatory reaction to drainage tube long-term stay in soft tissues was never found.</p>	Poor

No	Author, Title, Journal, Year, Volume, Page Number	Study Design, Sample Size Follow-up	Outcomes and Characteristics	Grade & Comment
6.	<p>Escarpanter J.C. Ozone therapy in the treatment of bone infections. (Abstract from 2<sup>nd</sup> International Symposia on Ozone Applications, Cuba)</p>	<p>Clinical trial without control group Sample size not mentioned.</p>	<p>General treatment was performed using ozone rectal application and local ozone treatment and ozonized oil (OLEOZON). Ozone therapy directly into the septic bone was applied as a unique treatment or combined with antibiotic therapy, surgery of lesions, etc.  Good results were obtained in a great percent of patients, but an outstanding improvement was seen in patients treated with ozone as the only therapeutic method.  It was well accepted by patients and no side effects were observed. It was concluded recommending its application in the treatment of chronic infections of the osteoarticular system.</p>	Poor
7.	<p>Conde B, Casas M, Delgado M., Ramos F. Ozone therapy in the treatment of osteoarthritis. (Abstract from 2<sup>nd</sup> International Symposia on Ozone Applications, Cuba)</p>	<p>Descriptive study 200 subjects</p>	<p>We have been using ozone therapy, during 5 years, in 200 patients with different types of arthritis, for example: lumbar arthritis, generalized arthrosis, hiposteoarthritis and knee arthrosis. In our group of patients, 60% female and 40% of male were present (80% with more than 40 years old). Three groups of treatment were considered: group I, using ozone therapy alone; group II, ozone therapy plus medication (antinflamatory and/or analgesics drugs) and group III, ozone therapy plus medication and physiotherapy. In general. 85% of improvement was obtained.</p>	Poor

No	Author, Title, Journal, Year, Volume, Page Number	Study Design, Sample Size Follow-up	Outcomes and Characteristics	Grade & Comment
8.	<p>Gorbunov S, Gorbunova L., Romashov Ph, V. Dmitriev V.</p> <p>Total ozone therapy of trophic ulcers of lower extremities in elderly patients.</p> <p>(Abstract from 2<sup>nd</sup> International Symposia on Ozone Applications, Cuba)</p>	<p>Case series</p> <p>42 subjects</p> <p>Ozone has been used in the complex treatment of 42 patients with long-term trophic ulcers of foot and crus (age range 61-84 years).</p>	<p>Complex ozone therapy included local effect of gaseous ozone in plastic sac. Besides, for the first 8-10 days the ulcer was covered with ozone saturated antiseptic dressing. With the signs of marked epithelization, antiseptic dressings were substituted by the ones with ozonated olive oil.</p> <p>Ulcers with pyo-necrotic deposit were covered with ozonated enterosorbents for the first 3-5 days. Along with external treatment in plastic sacs, the surrounding surface of ulcer was subcutaneously injected with ozone/oxygen mixture. With the aim of detoxication, as well as normalization of oxygen-dependent processes and improvement of microcirculation, all the patients received intravenous injections of ozonated rheopolyglukine, daily. The most efficient was found to be a complex treatment of vulnerosorbition with press-vacuum external ozone therapy in hard-frame chamber.</p> <p>By the 10 - 12 day of treatment the ulcer surface became sterile, epithelization rate being not more than 4-5 % a day, starting from the third week it reached 11-12 % a day. Only one patient, out of 42, did not have a complete cover of ulcerative defect in skin surface.</p>	<p>Poor</p> <p>Subject to bias</p>
9.	<p>Conde B., Casas M, Martínez, C. Ramos F.</p> <p>Ozone therapy in reactive arthritis.</p> <p>(Abstract from 2<sup>nd</sup> International Symposia on Ozone Applications, Cuba)</p>	<p>Descriptive report</p> <p>30 subjects</p> <p>We have used ozone therapy, like part of the treatment, of 30 patients suffering from reactive arthritis, in the last three years.</p>	<p>No significant differences in sex distribution were present, with predominance in ages less than 45 years.</p> <p>Patients with reactive polyarthritis and Reiter Syndrome were included in our study. In 55 % of patients, reactive arthritis was consequence of upper respiratory sepsis. The clinical evaluation was satisfactory, with a fast improvement and without side-effects.</p>	<p>Poor</p>

No	Author, Title, Journal, Year, Volume, Page Number	Study Design, Sample Size Follow-up	Outcomes and Characteristics	Grade & Comment
10.	<p>Cursio L.,Menaldo G.  Oxygen ozone and colocynthis-cimifuga treatment in slipped disc.  (Abstract from 2<sup>nd</sup> International Symposia on Ozone Applications, Cuba)</p>	<p>Clinical trial without control group  73 subjects</p>	<p>This study looked at hernia of the spinal column located in L4-L5, L5-S1, as these sites represent 90 % of all back bone hernias.  In 73 patients, mixture of oxygen-ozone and colocyntis-cimicifuga were injected intramuscularly around the vertebra. The mixture of 20 mL of oxygen-ozone was injected into four sites with 4 mL (total) of colocyntis-cimicifuga near vertebra l4-l5 and l5-s1, bilaterally.  The pain felt after the injection, lasted only a few minutes, no side effect or complication was referred. In 57 patients pain totally disappeared and all symptoms and muscles tone returned to normal. In 16 patients the pain improved and symptoms were reduced, but none completely suppressed.</p>	<p>Poor  76</p>
<b>Cancer</b>				
1.	<p>Ernst E (2001).  A primer of complementary and alternative medicine commonly used by cancer patients.  Med J Aust. Jan 15;174(2):88-92</p>	<p>Review</p>	<p>Complementary and alternative medicine including ozone therapy is frequently used by cancer patients. Several techniques of administering ozone are being promoted as treatment for cancer. However, few vigorous clinical trials of the treatment exist. Those published have demonstrated no evidence of effect. Numerous reports of serious complications, including hepatitis, and at least five fatalities have been reported. Until more positive evidence emerges, ozone therapy should be avoided.</p>	
2.	<p>No authors listed (1994)  Questionable methods of cancer management; electronic devices.  This information is current as of November 10, 2005  CA Cancer J Clin; 44: 115-127</p>	<p>Review</p>	<p>American Cancer society has stated that there is no evidence that the ozone generators are safe and effective for the treatment of cancer. Lacking such evidence, the American Cancer Society strongly urges individuals with cancer not to seek treatment with such devices.</p>	

No	Author, Title, Journal, Year, Volume, Page Number	Study Design, Sample Size Follow-up	Outcomes and Characteristics	Grade & Comment
3.	<p>No authors listed (1993)</p> <p>Questionable methods of cancer management: hydrogen peroxide and other "hyperoxygenation" therapies.</p> <p>CA Cancer J Clin. Jan- Feb; 43 (1): 47-56</p>	Review	<p>'hyperoxygenation" therapy also called; 'oxymedicine", "biooxidative therapy", "oxidative therapy" and 'oxidology" is a method of cancer management based on the erroneous concept that cancer is caused by oxygen deficiency and can be cured by exposing cancer cells to more oxygen that they can tolerate. Although ozone has been subject to legitimate research, there is little or no evidence that they are effective for the treatment of serious disease, and each has demonstrated potentials for harm.</p> <p>Therefore the American Cancer society recommends that individuals with cancer not seek treatment from individuals promoting any form of hyperoxygenation therapy as an alternative to proven medical therapies.</p>	
<b>SKIN DISORDERS</b>				
1.	<p>Jordan Liz, Beaver K, Foy S (2002)</p> <p>Ozone treatment for radiotherapy skin reactions; is there an evidence base for practice?</p> <p>European Journal of Oncology Nursing. 6(4); December, 220-227</p>	Review	<p>This paper reports the practice of treating severe radiotherapy skin reactions with ozone therapy. A multidisciplinary team of clinical staff and researchers questioned the evidence base for this practice and a literature search revealed little support for the effectiveness of this treatment for the particular context.</p> <p>While patients perceived the ozone treatment to be beneficial in terms of pain relief, it was impossible to isolate the impact of ozone alone as other treatments were given.</p> <p>A more formal evaluation of this treatment is being planned with regards tot his issue.</p>	

No	Author, Title, Journal, Year, Volume, Page Number	Study Design, Sample Size Follow-up	Outcomes and Characteristics	Grade & Comment
<b>SAFETY</b>				
1.	<p>Lo Giudice G, Valdi F, Gismondi M, Prodocimo G, de Belvis V (2004).            Acute bilateral vitreo-retinal hemorrhages following oxygen-ozone therapy for lumbar disk herniation.            Am J Ophthalmol. Jul; 138(1): 175-7. (Abstract only)</p>	A Case Report	<p>This is a case-report of a 45-year-old woman who complained of acute bilateral visual loss after intradiscal and perianglionic injection of ozone-oxygen gas mixture for lumbar disk herniation.</p> <p>Ophthalmoscopy revealed a premacular hemorrhage involving the left macula.</p> <p>In the right eye, multiple, flat, retinal hemorrhages around the optic disk and the posterior pole were observed. However, the MRI scan for intracranial hemorrhage was unremarkable.</p>	Poor
2.	<p>Corea F, Amici S, Murgia N, Tambasco N (2004)            A case of vertebrobasilar stroke during oxygen –ozone therapy            Journal of Stroke and Cerebrovascular Disease; 13(6), November- December 2004, pages 259-261</p>	Case Report	<p>A patient with lumbar disc herniation failed to respond to conservative management and was given combined therapy intradiscal and perianglionic injection of medical ozone and perianglionic injection of steroids. However the patient developed a vertebrobasilar stroke as a result of the procedure.</p>	

## OZONE THERAPY STUDY PROTOCOL

### Research question

1. Should ozone therapy be used for treatment of specific condition?

### Requested by

Medical Department, Hospital Sultanah Aminah, Johor Bharu.

### Background

Ozone therapy is a term that describes a number of different practices in which oxygen, ozone, or hydrogen peroxide are administered via gas or water to kill disease microorganisms, improve cellular function and promote the healing of damaged tissues. The rationale behind bio-oxidative therapies (as ozone is a powerful oxidizing agent), is that as long as the body's needs for antioxidants are met, the use of certain oxidative substance will stimulate the movement of oxygen atoms from the bloodstream to the cells. With higher levels of oxygen in the tissues, bacteria and viruses are killed along with defective tissue cells. The healthy cells will survive and multiply more rapidly. The result is a stronger immune system.

#### I. Objectives

To assess the safety, effectiveness and cost implications of ozone therapy.

#### II. Scope

##### 1. The technology

Ozone is an activated, trivalent (three atoms) form of oxygen. Oxygen is O<sub>2</sub> whereas ozone is O<sub>3</sub>. Over a period of 20 to 30 minutes, ozone breaks down into two atoms of regular oxygen by giving up one atom of singlet oxygen. Medical ozone is made of electrically activated medical grade Oxygen (using ozone generator), made from air or oxygen by ozone discharge or by ionizing radiation. Ozone is germicidal, bactericidal and fungicidal.

#### Inclusion criteria:

#### Exclusion criteria:

Oxygen therapy –use of hydrogen peroxide, hyperbaric oxygen, stabilized oxygen, ionization.

##### 1. Scope

- ◆ IV/Intramuscular/intraarticular injections
- ◆ Rectal insufflation (1.5 litres)
- ◆ Vagina insufflation (5 minutes)
- ◆ Autohemotherapy (withdrawing blood and reinfusing after putting ozone in)
- ◆ Air purification – low levels of O<sub>3</sub> in room air
- ◆ Ozonated drinking water
- ◆ Ozonated oil
- ◆ Sauna/Ozone bagging –body excluding head in bag full of O<sub>3</sub> for up to 2 hours
- ◆ Ear insufflation (5 minutes)



## 2. Medical problems

- i) Arteriosclerosis obliterans
- ii) Skin disease - Indurative hypodermatitis and localised lipodystrophies, skin cancer, psoriasis,
- iii) Cancer – cervical, prostate,
- iv) Ischaemic, stroke
- v) Pulmonary diseases
- vi) Immune system disorders
- vii) Degenerative diseases
- viii) Peripheral nervous system diseases
- ix) Aging process
- x) Arthritis
- xi) Bruises, burns, fistula, decubitus, gangrene, infections, muscle pains, radiation damage, and used to promote the healing of wounds.
- xii) Parkinson's and Alzheimer's diseases
- xiii) Ophthalmology

## III. Aspects to be considered

### 1. Safety

- patient side effects- death due to gas embolism
- Operator - poisoning/others (FDA- ozone is toxic gas with no medical uses)
- US Environmental Protection Agency- ozone level in air 'unhealthy' if  $>0.015$ ppm, lung and eye irritant

### 2. Cost

- Direct cost such as the cost of the technology, and the equipment, disposables

### 3. Effectiveness

### 4. Training

## **STRATEGY**

### 1. New Health Technology Assessment.

## METHODOLOGY

1. Systematic review
  - a) Gathering of all available evidence
    - Health Technology Assessment reports
    - Literature (Published/unpublished)
  - b) Analysis of evidence drawing up Evidence Table(Under various aspects identified)
  - c) Synthesis of evidence
2. Collection of information on local situation
  - survey on different tests planning to be carried out/ has been carried out, equipment models, costs implications involved, safety, improve quality of service
3. Report writing
  - Report writing for individual section
  - Suggested headings of the report
  - Background
  - Introduction
  - Objective
  - Methodology
  - Results-synthesis of evidence (evidence tables)
  - Conclusions
  - Recommendations
4. Merging of individual reports and preparation of draft reports
5. Feedback on Draft report and preparation of final report
6. Presentation of report to Technical Advisory Committee
7. Presentation of report to HTA Council
8. Approved policy sent to implementing agency
9. Translation into CPG and clinical pathway
10. Monitoring of feedback

### Websites searched

1. MSN
2. Alta Vista
3. Ovid- Cancerlit
4. MEDline
5. Cochrane database
6. [www.geocities.com/ojoronen/oz.HTM](http://www.geocities.com/ojoronen/oz.HTM)