Egyptian Journal of Occupational Medicine, 2014; 38 (1) : 111-123

OXYGEN THERAPY

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Abstract

Oxygen is the life-giving, life-sustaining element. All body activities require oxygen. Long-term oxygen therapy is the only intervention known to increase life expectancy in such patients. The goal of therapy is to provide oxygen continuously (for at least 19 hours a day) at a level that alleviates hypoxemia, thereby avoiding cellular hypoxia, a condition in which the tissue oxygen level is so low that cellular metabolism is disrupted. Hyperbaric medicine is an emerging medical specialty which utilizes oxygen at greater-than-atmospheric pressure to treat a variety of disorders. Hyperbaric oxygen therapy saturates the patient's plasma with oxygen resulting in increased oxygen delivery to tissues. Medical ozone therapy is a natural alternative used to detoxify, kill infectious disease causing by bacteria, mycoplasmas and virus organisms.

Ozone disrupts the integrity of the bacterial cell envelope through oxidation of the phospholipids and lipoproteins. In fungi, ozone inhibits cell growth at certain stages. Ozone treatment is safe because healthy cells are surrounded by an enzyme coating, which ozone does not penetrate. Bacteria and viruses have no such coatings and are oxidized on contact by ozone. Hydrogen peroxide (H_2O_2) is a natural by-product of most ozone oxidizing processes. Hydrogen peroxide is another great natural alternative for health.

Key Words: O_3 –H_2O_2-Hyperbaric oxygen therapy-Healing crisis

Introduction

Oxygen is the most vital element required for human life and it is the key to good health.

The more oxygen we have in our system, the more energy we produce, and the more efficiently we can eliminate wastes. Oxygen purifies the blood, keeping it free of cellular waste buildup. Sufficient oxygen allows the body to rebuild itself and maintain the immune system. Healthy cells require sugar, amino acids, minerals, hormones, enzymes and oxygen (Wedzicha and Calverley, 2006).

Oxygen in Medical Practice

I-Long-term oxygen therapy for COPD:-

Oxygen is an effective prescription drug for hypoxemic patients with chronic obstructive pulmonary disease (COPD) (Thomas and William, 2006). Long-term oxygen therapy is the only intervention known to increase life expectancy in such patients.

The goal of therapy is to provide oxygen continuously (for at least 19 hours a day) at a level that alleviates hypoxemia, thereby avoiding cellular hypoxia, a condition in which the tissue oxygen level is so low that cellular metabolism is disrupted.

Main causes of hypoxic hypoxia or arterial hypoxia (Hemangi, 2011):

1. **Hypoventilation:** Obstruction of air passages, paralysis of respiratory muscles, skeletal deformity as kyphoscoliosis, depression of respiratory muscles as in morphine poisoning, decreased elasticity of the lung as in emphysema and lung collapse.
2. **Diffusion impairment:** Decrease in surface area of the lung as in lobectomy or pneumonectomy, pneumonia, pulmonary edema, pulmonary fibrosis.
3. **Ventilation perfusion imbalance:-**

Defect in the perfusion of unventilated alveoli as in emphysema or collapse.

4. **Shunting of venous blood:-**

This occurs into arterial blood bypassing the lungs as in the presence of congenital abnormal opening between right and left auricles.

Indications (Clemens et al., 2009):

1. Absolute PaO_2 <55 mm Hg or SaO_2 <88%.

Treatment goal: PaO_2 >60 mm Hg or SaO_2 >90% appropriately adjusted oxygen dose during sleep and exercise

2. In patients with cor pulmonale PaO_2 55 to 59 mm Hg or SaO_2 >89%.

Electrocardiographic evidence of P pulmonale, hematocrit >55%, and congestive heart failure

Treatment goal: Same as above

3. Specific indications: Nocturnal hypoxemia

Treatment goal: Appropriately adjusted oxygen dose during sleep

4. Sleep apnea with nocturnal desaturation not corrected by constant positive airway pressure

Treatment goal: Appropriately adjusted oxygen dose during sleep

5. No hypoxemia at rest, but desaturation during exercise or sleep (PaO_2 <55 mm Hg)

Treatment goal: Appropriately adjusted oxygen dose during exercise

Oxygen therapy should be initially prescribed on the basis of the PaO2.

Short-term oxygen therapy

Short-term oxygen therapy is appropriate for patients with acute exacerbations of COPD (usually requiring hospitalization) who meet the requirements for long-term therapy and are undergoing optimal pharmacologic therapy (eg, bronchodilators, cardiovascular drugs) and control of infection. This requires that such patients undergo reevaluation 1 to 3 months after initiation of oxygen therapy, because 30% to 45% of them do not need long-term therapy (Gallagher et al., 2012).

Oxygen supply:

Supplemental oxygen for use at home is supplied by three types of stationary sources: 1-oxygen concentrators, 2-compressed gas cylinders, and 3-liquid oxygen reservoirs.

Portable oxygen systems are available for ambulatory patients. As mentioned, the amount of oxygen required should be determined with the equipment which the patient will use, because both the supply and the delivery system affect the delivery of oxygen.

1-Oxygen concentrators

They are electrically powered. The most common concentrator uses molecular beds to filter and concentrate oxygen molecules from the ambient air, generating oxygen concentrations of 90% to 98%.

Maximum flows of 3 to 5 L/min can be attained, although delivered fraction

of inspired oxygen (FIO2) decreases as flow increases. Concentrators are the most cost-effective type of stationary oxygen delivery system. A backup oxygen supply with a cylinder is necessary. http://www.aerocareusa.com/products/concentrators/what_is_an_oxygen_concentrator.html:

2-Compressed gas cylinders:

They are especially useful when a reliable electrical source is a problem. The H-sized cylinder is used for stationary delivery; it is large and heavy. It provides oxygen for about 57 hours at a flow of 2 L/min, and flows up to 15 L/min can be attained. The E-sized cylinder is a readily available and inexpensive oxygen supply for patients who require 2 L/min or less and only occasionally leave home (Wedzicha and Calverley, 2006).

3-Liquid oxygen reservoirs:

Last 5 to 7 days (at 2 L/min) and can be used to refill portable units.

Disadvantages include a relatively high cost for equipment and delivery, occasional "freezing" of the valve at flows of about 8 L/min, and some evaporation of the liquid oxygen when not in use.

Oxygen delivery devices:

Most of the more than 800,000 patients receiving long-term oxygen therapy in the United States use the standard nasal cannula. Although simple and inexpensive, the nasal cannula is an inefficient delivery method. The maximum delivered FIO2 is about 0.45 at 6 L/min.

Three other systems have been developed to conserve oxygen and improve delivery: demand-flow devices, reservoir cannulas, and transtracheal oxygen catheters (Wedzicha and Calverley, 2006).

Prescribing long-term oxygen therapy in patients with COPD:

1-Measure PaO_2 at rest to determine oxygen dose at rest and during exercise. The correct dose should result in a PaO_2 of 60 mm Hg or higher or an oxygen saturation of 90% or higher, or both.

2- Prescribe the specific oxygen dose (L/min) for the required number of hours per day and the appropriate doses with activity and during sleep.

3-Prescribe the specific oxygen supply and delivery devices for stationary and ambulatory use (Tiep et al., 2013).

II-Hyperbaric oxygen therapy

What is Hyperbaric Oxygen Therapy?

Hyperbaric medicine is an emerging medical specialty which utilizes oxygen at greater-than-atmospheric pressure to treat a variety of disorders. In hyperbaric oxygen therapy, patients breathe 100% oxygen at elevated atmospheric pressure. The increased pressure (up to 3 atmospheres) causes a 10 to 15 fold increase in plasma oxygen concentration and tissue oxygenation. This effect is delivered to the developing capillary bed promoting capillary growth, white blood cell activity, fibroblast proliferation, and new tissue development (Mechem, 2011).

How does Hyperbaric Oxygen Therapy Work?

Hyperbaric oxygen therapy saturates the patient's plasma with oxygen resulting in increased oxygen delivery to tissues. Specifically, hyperbaric oxygen therapy: Dissolves oxygen in the plasma, increases oxygen tension in hypoxic areas, enhances white blood cell activity at the wound site, reduces edema by vasoconstriction, blocks cytotoxic effects of carbon monoxide and hypoxia associated with cyanide poisoning.

What difference does extra pressure create?

Hemoglobin (in red blood cells) holds 97% of its maximum amount of oxygen from normal air or holds 100% when breathing pure oxygen. One gram of hemoglobin can only combine with 1.34 ml of oxygen.

The O_2 in physical solution is 0.3 ml/100 ml arterial blood and 0.13 ml/100 ml of venous blood, an average of 0.17 ml of O_2 is transported to tissues in dissolved state. The O_2 in physical solution determines the O_2 tension in the blood.

Some disease conditions impair oxygen utilization. Also, injuries or conditions with swelling can cause pressure that cuts off circulation flow. This problem drops the pO_2 gravely low, destroys tissue, and slows healing. Research has shown optimal tissue healing occurs if pO_2 rises to between 50 and 80 mmHg.

Oxygen given in a normal room is not sufficient to raise tissue oxygen levels to that level because red blood cells cannot carry the extra oxygen. The answer is to deliver the oxygen in a pressurized chamber to raise oxygen tension beyond red blood cell saturation (Mechem, 2011).

Common uses of hyperbaric oxygen therapy:-

Air or Gas Embolism:

Air or gas embolism occurs when gas bubbles enter arteries, veins and/or capillaries.

This results in reduced blood flow and poor oxygen delivery to the areas supplied by the affected circulation. If not fatal, gas embolism can result in severe, long-standing and irreversible physical and emotional disabilities.

Hyperbaric oxygen has been shown to reduce the size of bubbles obstructing circulation. The increased pressure in the hyperbaric chamber reduces bubble size and drives the remaining gas into physical solution, while the high oxygen pressure washes out inert gas from the bubble. When bubbles are smaller or resolved, blood flow resumes (Christiani , 2011).

Carbon Monoxide:

Approximately 5-6% of patients evaluated in emergency departments for CO poisoning are treated with hyperbaric oxygen (HBO_2). CO binds to hemoglobin in red blood cells at the sites usually utilized to carry oxygen to tissues. Oxygen, and especially hyperbaric oxygen, accelerates the clearance of CO from the body, thereby restoring oxygen delivery to sensitive tissues such as brain and heart (Christiani, 2011).

Clostridial Myositis & Myonecrosis (Gas Gangrene):

Clostridial myositis and myonecrosis is an acute, rapidly progressive infection of the soft tissues commonly known as "gas gangrene. "The infection typically spreads from a discrete focus of clostridium within the body. The original source can actually be within the body, as clostridium normally live in the gastrointestinal tract.

Clostridium bacteria are "anaerobic". If clostridium is exposed to high amounts of oxygen, their replication, migration, and exotoxin production can be inhibited. This is the rationale for the use of hyperbaric oxygen in the treatment of gas gangrene (Rabinowitz and Caplan, 2009).

Crush Injury:

Crush injuries occur when body tissues are severely traumatized such as accidents, falls, and gunshot wounds. HBO_2 increases oxygen delivery to the injured tissues, reduces swelling and provides an improved

environment for healing and fighting infection. Hyperbaric oxygen treatments should be started as early as possible (Rabinowitz and Caplan, 2009).

Decompression Sickness or Illness and Arterial Gas Embolism:

On scuba diving, additional oxygen and nitrogen dissolve in body tissues. The oxygen is consumed by the tissues, but the excess nitrogen must be washed out by the blood during decompression. During or after ascent this excess nitrogen gas form bubbles in the tissues. These bubbles may then cause symptoms that are referred to as decompression sickness (Diana et al., 2002).

Intracranial Abscess:

Abscess formation in the brain can be a complication of sinus or bone infections (osteomyelitis) of the skull. Brain abscesses are frequently multiple. It is well known that white blood cells require a minimum level of oxygen to kill bacteria. Most intracranial abscesses are caused by anaerobic bacteria. Hyperbaric oxygen raises the environmental oxygen level in the region of the abscess, exposing the bacteria to levels which may inhibit or kill them, as well as providing sufficient oxygen for white blood cells to exercise their killing power (Rabinowitz and Caplan, 2009).

Refractory Osteomyelitis:

Refractory osteomyelitis is a bone infection which has not responded to appropriate treatment.

Hyperbaric oxygen increases the oxygen concentration in infected tissues, including bone.

Hyperbaric oxygen directly kills or inhibits the growth of organisms .These effects occur through the oxygen-induced production of toxic radicals or through an indirect effect medicated through the white blood cells (Rabinowitz and Caplan, 2009).

Complications of Radiation Therapy:

Side effects of radiation therapy can be very toxic, especially when combined with chemotherapy. Some people are more sensitive to radiation damage than others.

The high dose oxygen provided in the hyperbaric chamber is carried in the patient's circulation to the site of injury to be available for repair of the damage done by the narrowing and scarring of the blood vessels. Each treatment typically

takes one to two hours, and usually 30-40 daily treatments are needed for healing radiation damage. (http://membership.uhms.org/?page=Indications. Accessed , 2011).

Skin Grafts and Flaps:

A "flap" consists of one or more tissue components including skin, deeper tissues, muscle and bone. Flaps are transferred with either their own, original blood supply (pedicle flap) or with detached blood vessels which are attached at the site of the wound (free flap). Flaps also require oxygen and nutrients to survive. The outer, visible portion (usually skin) is furthest from the source of blood supply for the flap. This is the area most likely to be compromised by inadequate oxygen. Factors such as age, nutritional status, smoking, and previous radiation result in an unpredictable pattern of blood flow to the skin. If a flap is found to have less than adequate oxygen after it has been transferred, HBO2 can help to minimize the amount of tissue which does not survive and also reduce the need for repeated flap procedures. (http://membership.uhms.org/?page=Indications. Accessed, 2011).

Thermal Burns:

Adjunctive hyperbaric oxygen (HBO_2) therapy has been shown to limit the progression of the burn injury, reduce swelling, reduce the need for surgery, diminish lung damage, shorten hospitalization, and result in significant overall cost savings. These benefits are more apparent if therapy is initiated within 6-24 hours of the burn injury. (http://membership.uhms.org/?page=Indications. Accessed , 2011).

Contraindications (http://www.cancer.org/Treatment/TreatmentsandSideEffects, 2011). :-

Untreated pneumothorax, congenital spherocytosis, Disulfiram (Antabuse), Doxorubicin (Adriamycine), Cis-Platinum, and Mafenide Acetate (Sulfamylone).

Side effects:-

The most common side effect is barotrauma to the ears and sinuses caused by pressure changes. To minimize this risk, patients learn techniques to promote adequate clearing of the ears during compression. Other side effects are rare, but may include oxygen toxicity, claustrophobia, temporary changes in sight, and accelerated maturation of cataracts.

It is well known that exposure to pure oxygen for a prolonged period, that is, in excess of 24 hours at 1 atm p causes reversible damage to the endothelium of pulmonary capillaries.

Short term exposure to very high oxygen pressures, for example, over 3 atm p for 2 hours may cause convulsions resembling grand mal epilepsy.

(http://www.cancer.org/Treatment/TreatmentsandSideEffects, 2011).

How are treatments given and how often?

The chamber is compressed with 100% O_2.

Compression usually takes 10 minutes and decompression may take up to 10 minutes.

Treatment duration, chamber pressure and number of treatments are based upon established protocols for each diagnosis.

Conditions such as decompression illness and carbon monoxide poisoning may only require one or two treatments, while wound healing may require 20-30 treatments and radiation tissue damage and osteomyelitis more than 30.

The patient will be asked not to wear the following materials while in the chamber: hair oils, hair spray, perfumes, make-up, nylons (panty hose), ointments, petroleum or Vaseline products, wigs or hair pieces, aftershave, synthetics (i.e. rayon, nylon, etc.), or salves. Watches should not be worn in the chamber because they may break under the increased pressure.

Because the therapy involves 100 percent oxygen, any form of smoking material, lighters or matches are STRICTLY prohibited in the chamber. (http://www.cancer.org/Treatment/TreatmentsandSideEffects,2011).

III-Ozone Therapy O_3:

Medical ozone therapy is a natural alternative used to detoxify, kill infectious disease causing by bacteria, mycoplasmas and virus organisms. Oxygen therapies have many therapeutic uses with effective and beneficial effects on every part of the body.

Ozone (also known as activated oxygen, O3, or ozein) is recognized as the most powerful and versatile therapy known in alternative health because it plays a vital role in maintaining the well-being of the body (Elvis and Ekta, 2011). What Does Ozone Do?

Ozone inactivates viruses, bacteria, yeast, fungus and protozoa. stimulates

the immune system, cleans arteries and veins, improves circulation, purifies the blood and lymph , normalizes hormone and enzyme production, reduces inflammation, reduces pain, calms the nerves, stops bleeding, prevents shock, prevents stroke damage, reduces cardiac arrhythmia ,improves brain function and memory, oxidizes toxins, allowing their excretion and chelates heavy metals.

It works well in conjunction with EDTA, prevents and reverses degenerative processes, prevents and treats communicable diseases, prevents and eliminates auto-immune diseases (Elvis and Ekta, 2011).

How Does Ozone Work? (Masaru and Velio, 2011)

1. Inactivation of bacteria, viruses, fungi, yeast and protozoa:

Ozone disrupts the integrity of the bacterial cell envelope through oxidation of the phospholipids and lipoproteins. In fungi, ozone inhibits cell growth at certain stages.

2. Enhancement of circulation:

Ozone reduces or eliminates clumping and red cell flexibility is restored, along with oxygen carrying ability. Oxygenation of the tissues increases as the arterial partial pressure increases and viscosity decreases. Ozone also oxidizes the plaque in arteries, allowing the removal of the breakdown products, unclogging the blood vessels.

3. Stimulation of oxygen metabolism:

Ozone causes an increase in the red blood cell glycolysis rate. This leads to the stimulation of 2, 3-diphosphoglycerate (2, 3-DPG) which leads to an increase in the amount of oxygen released to the tissues. There is a stimulation of the production of the enzymes which act as free radical scavengers and cell wall protectors: glutathione peroxidase, catalase, and superoxide dismutase. Ozone activates the Krebs cycle by enhancing oxidative carboxylation of pyruvate, stimulating production of ATP.

Ozone also causes a significant reduction in NADH and helps to oxidize cytochrome C. Prostacyclin, a vasodilator, is also induced by ozone.

4. Formation of peroxides:

Ozone reacts with the unsaturated fatty acids of the lipid layer in cellular membranes, forming hydro peroxides. There is a synergistic effect with cellular- formed H_2O_2.

5. Dissolution of malignant tumors:

Ozone inhibits tumor metabolism. In addition, ozone oxidizes the outer lipid layer of malignant cells and destroys them through cell lyses.

Safety of Ozone therapy (http://falconblanco.com/health/ozone/safe.htm):-

Ozone treatment is safe because healthy cells are surrounded by an enzyme coating, which ozone does not penetrate. Bacteria and viruses have no such coatings and are oxidized on contact by ozone.

Ozone also promotes the production of glutathione peroxidase, catalase, reductase and super-oxide dismutases which are the enzymes forming the cell wall coating and therefore cellular immunity is enhanced.

When ozone is introduced into the area, it immediately attacks the unhealthy cells because they lack a proper enzyme coating. If sufficient ozone is administered over time, the tumor will be dissolved.

Diseases treated by ozone therapy:

AIDS , arthritis ,athletic injuries of all types, fractures, chronic fatigue syndrome , Candidiasis and all fungal infections, cancer, Herpes and other venereal diseases, hepatitis, Mononucleosis

circulatory diseases ,cardiovascular disease ,diabetes ,sickle cell anemia, skin ulcers, infected wounds, gangrene , burns , colitis , psoriasis and almost all skin disorders (Bocci et al., 2010).

Protocols of Ozone Administration and Ozone Equipment:-

There are twenty-two methods of administering medical ozone. They are:

In the clinic:

1. Autohemotherapy 2. Intravenous injection 3. Intra- arterial injection 4. Direct injection into a tumor 5. Intracutaneous (blistering) 6. Intramuscular 7. Subcutaneous 8. Uterine insufflation

9. Bladder insufflation 10. Sub-atmospheric bagging 11. Dental use of ozonate water.

At home or the clinic:

12. Rectal insufflation 13. Vaginal insufflation 14. Drinking water 15. in the ear 16. ozonated water enema 17. Breathing through olive oil 18. Deep lymphatic massage with ozonated olive oil 19. ozonate bath with sea salt 20. Body suit 21. Steam cabinet 22.

External limb bagging (Elvis and Ekta, 2011).

The Healing Crisis:-

A healing crisis occurred when the body is in the process of eliminating toxins.

Reactions may be mild or they may be severe. One should expect this and work toward it.

A healing crisis results when all body systems work in concert to eliminate waste products and set the stage for regeneration. The crisis will usually bring about past conditions in reverse order to the original problem. People often forget the diseases or injuries they have had in the past, but are usually reminded during a healing crisis.

Reactions may include skin eruptions, nausea, headache, sleepiness, fatigue, diarrhea, a cold, ear infections, boils, or any other way the body uses to eliminate toxins. It usually lasts three days, but if the energy of the patient is low, it may last for a week or more (Saul , 2001) .

Hydrogen Peroxide H2O2 (Oxidative Therapy):-

Hydrogen peroxide (H_2O_2) is a natural by-product of most ozone oxidizing processes.

There are three methods used for administering hydrogen peroxide for detoxification; orally, intravenous and colonics. These applications are called Oxidative Therapy.

Diseases that have benefited from this oxidative therapy are cardiovascular, pulmonary, infectious and immune diseases; in addition, Cancer, Parkinson's and Alzheimer's.

Some prefer a 25-day program of oral treatments using 35% food grade hydrogen peroxide for cleansing the body. They usually start with 3 drops mixed in an 8-oz. glass of unchlorinated pure water, juice or milk and taken 3 times a day. Dosage is increased by 1 drop per day as they work up to 25 drops 3 times a day. After this program, most people will continue on a daily or weekly program for maintenance, which may last for 1 to 6 months (Bocci et al., 2012).

References

1. Bocci V, Zanardi I, Borrelli E and Travagli V (2012): Reliable and effective oxygen-ozone therapy at a crossroads with ozonated saline infusion and ozone rectal insufflation. J Pharm Pharmacol ;64(4):482-489.

2. Bocci V, Zanardi I and Travagli V (2010): Potentiality of oxygen-ozone therapy to improve the health of aging people. Curr Aging Sci; 3:177-187.
3. Christiani DC (2011): Physical and chemical injuries of the lung. In: Goldman L, Schafer AI, eds. Cecil Medicine. 24th ed. Philadelphia, Pa: Saunders Elsevier: chap 94.
4. Clemens KE, Quednau I and Klaschik E (2009): Use of oxygen and opioids in the palliation of dyspnea in hypoxic and non-hypoxic palliative care patients: a prospective study. Support Care Cancer; 17(4):367-77.
5. Diana M B, Paul C and Keith V M (2002): Decompression illness in divers: A review of the literature. In: The Neurologist 8:186-202. http://www.hbot.com/blog/infinitee/hyperbaric-oxygen-therapy-decompression-illness-divers
6. Elvis AM and Ekta JS (2011): Ozone therapy: A clinical review. Journal of Natural Science Biology & Medicine; 2(1):66-70.
7. Gallagher JL, McKernan G, Slater L and DeRamon A (2012): How Long is short term Oxygen Therapy? Home Oxygen Prescriptions Post Hospitalization. Thorax; 67(82):44.
8. Hemangi H (2011): What Causes Hypoxia. In: http://www.buzzle.com/articles/what-causes-hypoxia.html
9. Masaru S and Velio B (2011): Mechanisms of Action Involved in Ozone Therapy: Is healing induced via a mild oxidative stress? In: Higashi Hiratuka 586-2.
10. Mechem CC (2011): Hyperbaric oxygen therapy. http://www.uptodate.com/home/index.html.
11. Rabinowitz RP and Caplan ES (2009): Hyperbaric oxygen. In: Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases. 7th ed., chap 43.
12. Saul P (2001): What is "the healing crisis" and how to deal with it. In: http://health.groups.yahoo.com/group/ozonetherapy/.
13. Thomas L C and William CB (2006): Long-term Oxygen Treatment in COPD. In: American Journal of Respiratory and Critical Care Medicine; 174:373-378. In: www.atsjournals.org.
14. Tiep B, Carter R and Zachariah F (2013): Oxygen for end-of-life lung cancer care: managing dyspnea and hypoxemia. Expert Rev Respir Med; 7:479.
15. Wedzicha JA and Calverley PM (2006): All change for home oxygen services in England and Wales. Thorax; 61(1):7-9.
http://www.aerocareusa.com/products/concentrators/what_is_an_oxygen_concentrator.html
http://falconblanco.com/health/ozone/safe.htm
http://membership.uhms.org/?page=Indications. Accessed , 2011.
http://www.cancer.org/Treatment/TreatmentsandSideEffects, 2011.