Introduction

Ozone (O₃) is a: “a bluish explosive gas or blue liquid, which is an allotropic and more active form of oxygen… it is an antiseptic and disinfectant. It is formed when oxygen is exposed to the silent discharge of electricity, and is both irritating and toxic in the pulmonary system.”¹ According to the Canadian Centre for Occupational Health and Safety, ozone is used in many processes, including the purification and disinfection of drinking water, disinfection of wastewater and swimming pools, as a food preservative, and in hospital air ducts and air conditioning systems. Ozone is found naturally in the earth’s stratosphere. It can also be produced from equipment and manufacturing processes, such as, electric arc welding, high voltage electrical equipment, X-ray generators, photocopiers and ultraviolet light sources.²

Ozone therapy has been advocated for numerous medical conditions and is administered in various ways (e.g. topically, by injection, in baths, as an oral solution or through rectal insufflation). In wound care, ozone is promoted as an anti-bacterial, anti-fungal and anti-viral agent. During the treatment an ozone generator produces ozone into a bag that surrounds the patient’s leg ulcer. The treatment is administered three times per week for several weeks.

Research Questions

A hospital administrator contacted CCOHTA for information on topical ozone therapy for the treatment of diabetic leg ulcers. This therapy was being used in an alternative medicine centre at the hospital.

The two main questions surrounding the use of topical ozone therapy are:

1. Is this an effective therapy for diabetic leg ulcers?
2. Are there any safety concerns for patients and hospital staff exposed to ozone?

Assessment Process

Preliminary literature searches were performed using PubMed, The Cochrane Library and the UK Centre for Reviews and Dissemination databases (NHS EED, DARE, and the HTA Database). A search of Internet resources was also run and the web sites of other HTA agencies were checked. We also contacted Dr. Nicky Cullum, from the Cochrane Wounds Group. The Group searched their Wounds Trials register but no controlled studies of topical ozone therapy were identified.
As much of the information on ozone therapy appears to originate from Germany we also contacted Dr. Bernhard Gibis, at the National Association of Statutory Health Insurance Physicians (NASHIP), in Berlin, to determine if they have conducted assessments of this technology.

The Canadian Centre for Occupational Health and Safety (http://www.ccohs.ca) was contacted for general information on the toxicity of ozone. Similar information was sought on the US Food and Drug Administration and Health Canada web sites.

**Summary of Findings**

There is little information in the peer-reviewed medical literature on ozone therapy, and in particular, its use in treating diabetic leg ulcers. The information that is available is mainly in languages other than English and seems to discuss small case series studies. A 1985 Australian paper reported favourably on the use of ozone therapy in an uncontrolled study of 73 patients with leg ulcers. This was one of the most recent English language papers identified. According to one web site, ozone therapy is used in Germany, Austria, Switzerland, Italy, Russia and Cuba. There is a plethora of Internet web sites which promote ozone therapy.

Dr. Bernhard Gibis, of NASHIP, provided the following information: “…all sorts of ozone therapy are fashionable in Germany and so far we have not found evidence that it works. Similar to hyperbaric oxygen therapy the treatment effects were rarely evaluated in comparative studies. We’ve done a report on ionized oxygen, in 2001, which found inconclusive evidence for the use of ozone, regardless of the way it was applied (inhalation, topical, etc… We denied on the basis of the report the reimbursement of this technology…” Dr. Gibis suggests that the technology is an ideal subject for a randomized controlled trial and that, in the absence of such evidence there is no basis for introduction of this therapy, or, where the technology is already in use, a registry should be established to determine more about the effectiveness of this treatment (Bernhard Gibis, NASHIP, Berlin: personal communication, 2002 June 25).

A 1995 US article briefly discussed the promotion of ozone as a treatment for AIDS:

> Ozone generators, which produce a toxic form of oxygen gas, have been touted as being able to cure AIDS. To date this is still unproven, and FDA considers ozone to be an unapproved drug and these generators to be unapproved medical devices. At least three deaths have been connected to the use of these generators…
The US Food and Drug Administration Code of Federal Regulations Title 21 – Food and Drugs states the following:

Subpart H--Special Requirements for Specific Devices

Sec. 801.415 Maximum acceptable level of ozone.

(a) Ozone is a toxic gas with no known useful medical application in specific, adjunctive, or preventive therapy. In order for ozone to be effective as a germicide, it must be present in a concentration far greater than that which can be safely tolerated by man and animals.

(b) Although undesirable physiological effects on the central nervous system, heart and vision have been reported, the predominant physiological effect of ozone is primary irritation of the mucous membranes. Inhalation of ozone can cause sufficient irritation to the lungs to result in pulmonary edema. The onset of pulmonary edema is usually delayed for some hours after exposure; thus, symptomatic response is not a reliable warning of exposure to toxic concentrations of ozone. Since olfactory fatigue develops readily, the odour of ozone is not a reliable index of atmospheric ozone concentration.

(c) A number of devices currently on the market generate ozone by design or as a byproduct. Since exposure to ozone above a certain concentration can be injurious to health, any such device will be considered adulterated and/or misbranded within the meaning of sections 501 and 502 of the act if it is used or intended for use under the following conditions:

(1) In such a manner that it generates ozone at a level in excess of 0.05 part per million by volume of air circulating through the device or causes an accumulation of ozone in excess of 0.05 part per million by volume of air (when measured under standard conditions at 25 [deg]C (77 [deg]F) and 760 millimeters of mercury) in the atmosphere of enclosed space intended to be occupied by people for extended periods of time, e.g., houses, apartments, hospitals and offices. This applies to any such device, whether portable or permanent or part of any system, which generates ozone by design or as an inadvertent or incidental product.

(2) To generate ozone and release it into the atmosphere in hospitals or other establishments occupied by the ill or infirm.
Topical Ozone Therapy for the Treatment of Diabetic Leg Ulcers

(3) To generate ozone and release it into the atmosphere and does not indicate in its labelling the maximum acceptable concentration of ozone which may be generated (not to exceed 0.05 part per million by volume of air circulating through the device) as established herein and the smallest area in which such device can be used so as not to produce an ozone accumulation in excess of 0.05 part per million.

(4) In any medical condition for which there is no proof of safety and effectiveness.

(5) To generate ozone at a level less than 0.05 part per million by volume of air circulating through the device and it is labelled for use as a germicide or deodorizer.

(d) This section does not affect the present threshold limit value of 0.10 part per million (0.2 milligram per cubic meter) of ozone exposure for an 8-hour-day exposure of industrial workers as recommended by the American Conference of Governmental Industrial Hygienists.

(e) The method and apparatus specified in 40 CFR part 50, or any other equally sensitive and accurate method, may be employed in measuring ozone pursuant to this section.

A Health Canada document on ozone generators includes the following description of how these devices are regulated under the Canadian Food and Drugs Act:

Prior to July 1, 1998, The Medical Devices Regulations of the Food and Drugs Act prohibited medical devices which were designed to generate airborne ozone to which humans may be exposed. A limit of 0.05 ppm (vol/vol) was set for other medical devices which generated ozone incidental to their normal operation. However, when the new Medical Devices Regulations came into effect on July 1, 1998, the old regulations and schedules ceased to exist and presently there are no regulations on medical devices that produce ozone. To replace the old Schedule VIII, the Therapeutic Products Programme has drafted a policy on ozone generators. Meanwhile, the new Medical Devices Regulations establish general safety and effectiveness requirements for medical devices. The policy describes the performance and quality standards in which to measure the safety and effectiveness of subject devices. Health Canada does not recognize any health benefits from human exposure to ozone and therefore precludes approval of such devices under the Medical Devices Regulations.
Dr. Philip Neufeld, of the Medical Devices Bureau at Health Canada confirmed that Health Canada does not recognize any health benefits of human exposure to ozone. He explained that “This policy is consistent with those of the US and Australia. Health Canada has not licensed any ozone generators for this purpose. Ozone therapy has been identified by the Canada-US-Mexico Health Fraud Group as both a direct and indirect health hazard. A direct hazard is one in which the device itself can cause injury. An indirect hazard is one in which reliance on the product encourages the user to delay or discontinue appropriate medical treatment where delay can worsen the condition…” (Philip Neufeld, Health Canada, Ottawa: personal communication, 2002 Sep 10).

The Canadian Centre for Occupational Health and Safety provided the following information on the potential health effects of ozone from their CHEMINFO database:

**EFFECTS OF SHORT-TERM (ACUTE) EXPOSURE:**

**INHALATION:**

Even very low concentrations of ozone can be harmful to the upper respiratory tract and the lungs. The severity of injury depends on both the concentration of ozone and the duration of exposure. Severe and permanent lung injury or death could result from even a very short-term exposure to relatively low concentrations. Exposure to extremely low concentrations of ozone initially increases the reactivity of the airways to other inhaled substances (bronchial hyperresponsiveness) and causes an inflammatory response in the respiratory tissue. Exposure to ozone during exercise or work increases susceptibility to this effect. Increased bronchial responsiveness has been observed following 7-hour exposures to 0.08, 0.1 or 0.12 ppm (with moderate exercise), or a 1-hour exposure to 0.35 ppm. This response occurs almost immediately following exposure to ozone and persists for at least 18 hours. Other symptoms observed following acute exposures to 0.25-0.75 ppm include cough, shortness of breath, tightness of the chest, a feeling of an inability to breathe (dyspnea), dry throat, wheezing, headache and nausea. More severe symptoms have been seen following exposure to higher concentrations (greater than 1 ppm) and have included reduced lung function, extreme fatigue, dizziness, inability to sleep and to concentrate and a bluish discolouration of the skin (cyanosis). Intermittent exposure to 9 ppm for 3-14 days has produced inflammation of the bronchi and lungs. An acute occupational exposure to approximately 11 ppm for 15 minutes caused severe respiratory irritation and almost caused unconsciousness. A 30-minute exposure to 50 ppm is considered
potentially lethal. Animal studies indicate that ozone can also cause a potentially fatal accumulation of fluid in the lungs (pulmonary edema). Symptoms of pulmonary edema, such as shortness of breath, may not appear for 24 hours after exposure and are aggravated by physical exertion.

The severity respiratory responses to ozone becomes reduced following repeated daily exposures. This "functional adaptation" to the effects of ozone may persist for several days after exposure stops. Decreases in respiratory function do not appear to be more pronounced in cigarette smokers or people with pre-existing lung disorders.

SKIN CONTACT:
There is no information available. Ozone gas can probably cause skin irritation due to its oxidizing ability, but only at concentrations capable of causing severe respiratory injury.

EYE CONTACT:
Ozone concentrations greater than 2 ppm can be irritating to the eyes within minutes. No definite effects on vision were noted in volunteers exposed for 3 or 6 hours to 0.2-0.5 ppm, although some increase in side vision (peripheral) and a slight reduction in visual sharpness (acuity) was noted during dark adaptation tests.

INGESTION:
Ingestion is not an applicable route of exposure for gases.

EFFECTS OF LONG-TERM (CHRONIC) EXPOSURE:
A small number of studies examining the potential effects of long-term occupational exposures to ozone have reported headache, irritation of the nose and throat, chest constriction and lung congestion in exposed workers. Human population studies indicate that people living in communities with high background ozone levels have experienced a greater decrease in lung function over five years than people living in communities with lower background levels. These studies suggest that long-term exposures to ozone may result in impaired lung function. These reports are consistent with animal studies which also indicate that long-term exposure to ozone can impair lung function and cause structural changes to the lungs.

Based on animal evidence, exposure to ozone may increase susceptibility to bacterial infections of the respiratory system.

CARCINOGENICITY:
There is no human information available. Animal studies are inconclusive.


TERATOGENICITY AND EMBRYOTOXICITY:
There is no human information available. No conclusions can be drawn from the available animal studies because effects were either seen in the presence of maternal toxicity or maternal toxicity was not evaluated.

REPRODUCTIVE TOXICITY:
There is no human information available. No effects were observed in one animal study.

MUTAGENICITY:
A number of studies have examined the potential mutagenicity of ozone in humans. Several of these studies have shown negative results and the two positive studies have had weaknesses in their study designs (no statistical analysis of the data was conducted in one study and the other study did not rule out other possible causes, such as smoking). Therefore, it is not possible to draw any conclusions from these studies. Ozone is mutagenic in isolated human cells, animal cells and bacteria. Positive results have also been observed in animal cells (somatic) following inhalation exposure.

TOXICOLOGICALLY SYNERGISTIC MATERIALS:
Ozone exposures may influence clearance of other hazardous substances from the lung. Individuals with asthma were reported to be sensitized to the effects of other irritants when pre-exposed to 0.12 ppm ozone for 1 hour. Animal studies have shown that rats exposed to ozone prior to an exposure to asbestos had significantly more asbestos in their lungs one month later than animals not exposed to ozone. No synergism has been observed between ozone and either nitrogen dioxide or sulphuric acid in terms of impaired respiratory function.

POTENTIAL FOR ACCUMULATION:
Ozone is absorbed in both the upper and lower respiratory tract. It is a potent oxidant that reacts with protein and lipids, particularly within biological membranes. A small amount of inhaled ozone is absorbed into the blood. The extreme reactivity of ozone limits its ability to accumulate.

The full text of the CCOHS record on ozone can be contacted from the Centre at 1-800-263-8466 (in Canada) or by e-mail: clientservices@ccohs.ca. This document contains further information on the proper handling of ozone, and exposure controls for the protection of personnel in worksites exposed to ozone. The CCOHS also provides plain language summaries of this information, including the American Conference of Governmental Industrial Hygienist recommended exposure limits for ozone, under the OSH Answers section of their web site: http://www.ccohs.ca/oshanswers/ (under the subsection for Chemicals & Materials.)
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All of these reports are available at: http://www.hta.nhsweb.nhs.uk/ProjectData/3_publication_listings_ALL.asp | Please note—these volumes do not cover ozone therapy, but may be of interest for good evidence on other treatments for diabetic leg ulcers. |
|                           | **HTA**                                                            | **Behandlung mit ionisiertem Sauerstoff** [in German]  
Köln (DE): Geschäftsführung des Arbeitsausschusses „Arztliche Behandlung“ des Bundesausschusses der Ärzte und Krankenkassen; 2001. Available: http://www.ikk.de/ikk/generator/IKK/Leistungserbringer/_C4rzte/_DCbersicht,templateId=articlePage.jsp.html | -no appropriate studies were found concerning the effectiveness of the treatment with ionized oxygen for any of the designated indications. -the scientific evidence is lacking and does not justify coverage of this treatment under the health insurance system. |
A 1999 issue of the *FDA Consumer* discusses the prosecution of a US couple who marketed ozone generators – unapproved medical devices in the US. The article states that:

[The] FDA has never approved ozone generators or ozone gas for treating any medical conditions… Proponents of medical ozone generators believe ozone can kill viruses and bacteria in the body. While ozone is used as a germicide in the cleaning of manufacturing equipment, FDA is not aware of any scientific data that supports the safety or effectiveness of ozone generators for treating medical conditions. In fact, the agency believes that at the levels needed to work effectively as a germicide, ozone could be detrimental to human health. “These devices keep popping up,” says Bob Gatling, a biomedical engineer and director of the program operations staff in FDA’s Center for Devices and Radiological Health. “We always tell their makers”: ‘Show us some data,’ but no one ever pursues it.\(^5\)

**Conclusion**

There is insufficient evidence in the published literature to adequately assess ozone therapy in the treatment of diabetic leg ulcers. Evidence from controlled trials of this therapy may be warranted.

Exposure to ozone has known adverse effects, particularly on respiratory function. The safety of hospital staff and patients exposed to ozone during the administration of this procedure is a concern, however, the assessment of occupational health and safety is not within CCOHTA’s mandate or area of expertise.

**References**