PureLine™ Report: Advantages of Chlorine Dioxide for Medical Device Sterilization

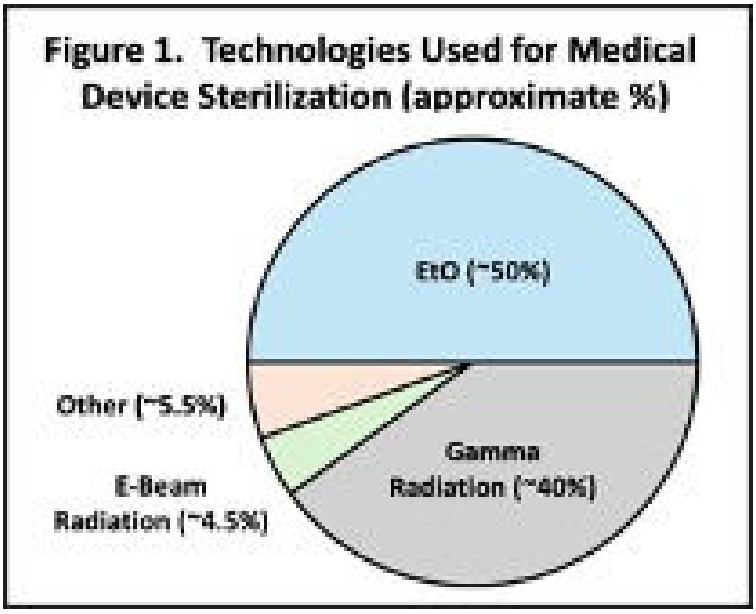
BACKGROUND

Today, in the US, approximately 100 million surgical procedures are performed annually. These procedures involve contact of a medical device or surgical instrument with patient tissue or mucous membrane. This contact creates the potential for infection.[1] There are currently 1.7 million healthcare associated infections (HAIs) in the US annually,[2] at a cost of $28 to $45 billion.[3]

In 1968, an approach to disinfection and sterilization of various items used in patient ward was published.[4] This approach has been widely accepted and is still used today in modified form. This approach dealt specifically with the type of patient contact. Since that time, the role of biofilm in infection has become widely known.[5] Thus, any technology used to sterilize medical instruments or other material used in patient contact must not only be capable of sterilizing specific pathogenic microbial organisms, but also able to penetrate biofilm that harbor such organisms and inactivate those organisms.

Sterilization of single-use medical devices are split into two categories; those done on-site and the other off-site. The International Irradiation Association has determined that the relative percentages of various technologies used to sterilize medical devices are those shown in Figure 1. EtO comprises approximately 50%, Gamma radiation approximately 40%, electron-beam radiation approximately 4.5%. The remaining 5.5% comprises technologies such as steam, x-ray and other technologies.

Figure 1. Technologies Used for Medical Device Sterilization (approximate %)



CLASSES OF MICROBIAL INACTIVATION

There are three classes of microbial inactivation recognized by the EPA. These include Sanitation, Disinfection, and Sterilization.[6]

SANITATION

Sanitation provides the lowest margin of safety and is the reduction of the number of microbial contaminants to a relatively safe level. This type of treatment is reserved for surfaces which at not critical or for surfaces which might be corroded by antimicrobial agents. There is no standard or test methodology for this type of treatment.

DISINFECTION

Disinfection provides an environment in which pathogenic microorganisms can be inactivated but is not sufficient to inactivate bacterial spores. Application of chemical agents are normally considered as disinfectants.

STERILIZATION

Sterilization provides the highest level of safety and involves complete inactivation of all microbial life. In general, this process is monitored by use of bacterial indicator (BI) spore strips, which contain 10^6 bacterial spores, the incubation of which, after treatment by an appropriate method, shows that no bacterial spores remain. (The choice of the appropriate bacterial spore inoculated onto a BI strip is determined by the choice of the sterilant used.) The type of bacterial spore which is the most resistant to the particular sterilant is generally selected, because if 1,000,000 of these are inactivated (as shown by the BI), the chances of any pathogen surviving treatment is near zero.

STERILIZATION TECHNOLOGIES

Historically, a number of technologies have been used to sterilize medical instruments. These include both physical and chemical agents. There are several types of sterilization technologies. The most common are shown in Table 1.

Table 1. Sterilization Technologies*

Sterilization Type	Description
Physical Methods	
Steam/Autoclave	Enclosed steam
Dry Heat	Enclosed dry heat
Radiation	Use of gamma, electron beam, UV or other radiation source
Sporicidal Chemicals	
Ethylene oxide gas	Enclosed gas and humidity
Hydrogen peroxide vapor	Enclosed liquid and gas (vapor)
Peracetic acid vapor	Enclosed liquid and gas (vapor)
Chlorine dioxide gas	Enclosed gas and humidity
Liquid	Liquid submersion

*https://www.fda.gov/medical-devices/general-hospital-devices-and-supplies/sterilization-medical-devices. **Accessed 5/30/2024.**

PHYSICAL STERILIZATION TECHNOLOGIES

There are three primary physical sterilization technologies: Steam, dry heat, and radiation. Each are summarized below.

Moist Heat (Steam): Steam sterilization technology is the least expensive and most understood of the sterilization of methods. When water reaches 100 °C (212 °F), steam forms. Thermally tolerant organisms, called thermophiles, can resist temperatures up to about 80 °C. Hyperthermophiles can survive in temperatures above 100 °C. To reach sufficiently high-temperatures in steam sterilization, water must be heated under pressure to temperatures that exceed about 250 °F.

Moisture, or the water content of the steam, is controlled. Steam quality must be > 97%. Steam quality is defined as follows:

Steam quality = mass of steam/(mass of steam + mass of liquid)

Many types of medical devices are stored in sterile packaging. 'Sterile packs' refers to non-reusable plastic shells, wrappings, and other packing materials that have been terminally sterilized. Manufacturers use this packaging to wrap medical devices, instruments, and other healthcare products, to ensure they stay germ-free. Although steam quality does not affect sterilization, too low a steam quality will result in wet packaging.

The definition of a wet pack, according to the Association for the Advancement of Medical Instrumentation (AAMI), is the presence of any moisture (internal or external) left in or on a package after sterilization.

Three factors must be controlled to ensure adequate steam sterilization. These include time, temperature, and moisture content.

Advantages and disadvantages of steam sterilization are shown in Table 2.

Table 2. Advantages and Disadvantages of Steam Sterilization

Advantages	Disadvantages
Nontoxic	Destructive to heat-sensitive materials
Sterilization cycle easy to control and monitor	Long-Term damage to instruments
Rapidly microbicidal•	May rust instruments
Least affected by organic/inorganic soils	Potential for burns
Rapid cycle time	No electronics
Penetrates medical packing and device	
Used for surgical instruments, implantable medical devices, flexible containers, syringes, vials	

•106 Bacillus stearothermophilus spores require 12 minutes for inactivation at 250° F. At 270° F, 1 minute is required, and at 285 °F, 8 seconds is required for inactivation.[7]

Dry Heat: This approach uses an enclosed space where devices can be batch treated, or the space may have a conveyor which allows the devices to move through an enclosed heated space to allow the devices to reach the appropriate temperature for the appropriate amount of time to inactivate pathogenic organisms.

This technology has the same advantages and disadvantages of steam, with the exception that dry heat is non corrosive and will not rust instruments.

Radiation: Radiation sterilization is a method that destroys microorganisms with gamma radiation, electron beam, or ultraviolet light. The radiation attacks the DNA of any organism present. Radiation sterilization doesn't require elevated temperature to sterilize.

Approximately 40% of all medical devices are sterilized by gamma radiation (normally ^{60}Co). Another 4.5% are sterilized by electron beam radiation, and another 5% by other technologies.

Table 3. Advantages and Disadvantages of Radiation Sterilization

Advantages	Disadvantages
Fast turnaround	Capital cost
No residuals	Requires requalification of operator
Can be treated in original packaging	
Good penetration	

CHEMICAL STERILIZATION TECHNOLOGIES

A number of chemical sterilant technologies have been approved by the FDA. These include those listed in Table 1, but also some combination of them. Some are rapid actors, while others may require up to 12 hours of contact time. Of those listed, the order of performance appears to be:

Gas sterilants > vapor phase sterilants > liquid phase sterilants

The reason for this lies in the penetrating ability of each. Also, some of the devices are wrapped in a protective packaging and this packaging must be breathable (i.e., the sterilant must be able to penetrate it). For liquid phase sterilants, a rinse may be required (requiring the rinse water to be sterile) and medical devices cannot be wrapped during processing.

Typical devices that are reused include heat-sensitive devices, scissors, stethoscopes and thermometers.

Each chemical sterilant is discussed in more detail below.

Ethylene Oxide (EtO): EtO has been used almost exclusively since the 1950's in US hospitals to sterilize those instruments which are not tolerant to heat. Today it is used in > 50% of medical devices in the US. EtO is a gas at room temperature, with a boiling point of 10.4 °C (about 51° F).

It is about 2 times heavier than air with a molecular weight of 44.05. It is both flammable and explosive in the gaseous state at a concentration of > 3 mole% in air. The explosive reaction of some metal compounds including rust.

It has a detectable sweet odor at ~ 430 ppm, with an odor that is similar to ether or almond. It is generally considered noncorrosive.

The first EtO gas sterilizers used a mixture of EtO plus an inert gas such as CO2 or a chlorofluorocarbon, the most combination was 12% EtO and 88% freon. Freon was phased out due to environmental considerations, and the newest EtO gas mixtures consist of EtO plus a hydrochlorofluorocarbon.

Four factors must be controlled to ensure sterilization by EtO. These include time, temperature, gas concentration and % relative humidity. (Bacterial spores exist in two states, ensporulated and vegetative. One can think of a bacterial spore as a clam, which can ensporulated, i.e., close a hard shell to protect it from toxic agents. With increased humidity and temperature, the spore can open up, return to its vegetative state, and in that state becomes susceptible to attack by chemical agents.)

Expensive medical devices may need quick turnaround. The time required to sterilize with EtO (12-16 hours), coupled with several other factors have increased the need for a more rapid sterilization process. In the late 1970s, several additional factors began to put pressure on the use of EtO as a sterilant. These included the toxicity of EtO, an increase in the use of expensive heat-sensitive equipment and the increase in sterilization requirements as new health issues began to appear, such as HIV.

EtO is the most commonly used sterilization method for medical devices in the U.S., with more than 20 billion devices sold in the U.S. every year sterilized with EtO, accounting for approximately 50% of devices that require sterilization. Since 2019, the FDA has promoted the development of alternatives to EtO and has implemented a number of programs and initiatives to support innovation in medical device sterilization.

No ideal vapor-phase sterilant capable of sterilizing rapidly without affect packaging, equipment or sterilization techniques has been identified.

Table 4. Advantages and Disadvantages of EtO Sterilization

Advantages	Disadvantages
90-Year proven track record	Extended time required (up to 16 hours)
Compatible with materials that cannot tolerate heat or are degraded by radiation	Devices must be packed in gas permeable packaging
Penetrates packaging materials	Toxic, carcinogen, flammable
Simple to operate and monitor	Organic matter reduces microbicidal effect
Compatible with most medical materials	Can leave residuals on products

Hydrogen Peroxide Gas Plasma (HPP) or Vaporized Hydrogen Peroxide (VHP): This technology involves the vaporization of H_2O_2 in an enclosed chamber to which an electric field is applied, producing a cloud of highly energized, sporicidal species. The medical device is exposed to the HPP for a period of time, typically ~½ to ~1 hour. Then, the byproducts of HPP decomposition, which includes water vapor or oxygen, are removed prior to handling the medical devices. BIs are commonly used to ensure that the sterilization procedure has been successful.

This technology works for devices that are harmed by high temperatures or humidities, such as laser probes, thermometers, or defibrillator paddles.

Table 5. Advantages and Disadvantages of H_2O_2 Sterilization

Advantages	Disadvantages
Low temperature requirements	Low oxidizing ability of H_2O_2 at dosage used
Low concentration of H_2O_2 vapor	Rapid decomposition of H_2O_2
Minimal pressure differences	Presence of oxygen radicals
Penetrates most materials	Corrosive to tissue
	Human exposure issues

On 1/8/2024, the U.S. Food and Drug Administration announced that it had approved vaporized hydrogen peroxide (VHP) to be an established method of sterilization for medical devices, recognizing VHP's long history of safety and effectiveness.[8]

Peracetic Acid (PAA) Vapor: PAA, also known as peroxyacetic acid, is a clear, colorless pungent non-foaming liquid that has a pH < 2. It is miscible with water and is soluble in polar organic solvents. It is stronger than either Cl_2 or ClO_2. It is marketed in concentrations from about 5% to about 35%. Commercial formulations contain H_2O_2.

PAA is made by reacting H_2O_2 and acetic acid or acetic anhydride, with sulfuric acid as a catalyst.[9] Sulfuric acid increases the rate of reaction. The concentration of PAA is proportional to the concentration of H_2O_2 and the acetic acid / H_2O_2 molar ratio. The concentration of the H_2SO_4 varies from 1 to 9%.[10]

Equation 1

$$CH_3COOH + H_2O_2 \underset{k2}{\overset{H_2SO_4,\ k1}{<\ -\ >}} CH_3COOOH + H_2O$$

This reaction is reversible and proceeds to an equilibrium. Both forward and reverse reactions are fairly slow at room temperature, and a long time is necessary for equilibrium to establish. The reactants may be allowed to react for up to 10 days to maximize production of PAA.

PAA is used as both a liquid and vapor phase sterilant.

Table 6. Advantages and Disadvantages of PAA Sterilization

Advantages	Disadvantages
Broad spectrum sporicide	Can be corrosive
Leaves no residue	Causes discoloration of endoscopes over time
Non-reactive with organic soils	Cost
Rapid cycle time	Human contact issues

OTHER LIQUID PRODUCTS

A number of liquid products have been used for sterilization, but these have the distinct disadvantage that, unlike gaseous sterilants, their performance cannot be measured by using BI spore strips, as the spores would tend to wash off the strip and render the monitoring program useless. Liquid products include glutaraldehyde, H_2O_2, H_2O_2 with ozone, PAA, H_2O_2 with PAA, Otho-phthalaldehyde (OPA), or various mixtures of these.

ABOUT CHLORINE DIOXIDE

ClO_2 has some very unusual properties, some of which make it an ideal choice as a potentially exceptional low temperature sterilant. The chemical properties, the disinfection properties, the ability to penetrate biofilm and inactivate bacteria within, and other factors will be discussed in the following. Also discussed will be some case histories where ClO_2 has been used to sterilize medical instruments.

CHEMICAL PROPERTIES OF CHLORINE DIOXIDE[11]

ClO_2 is a very unusual chemical; a free radical, e.g, as a molecule it has an unpaired electron, which would normally make it very unstable and highly reactive. But it is unusual because of its stability and relative non-reactivity with a large number of organics. A gas in its natural state at room temperature, it is very soluble in water; it is in that form that it has been used until the last few decades.

The ability of aqueous chlorine dioxide (ClO_2) to inactivate bacterial spores has been known since the late 1940s.[12]

Its use in the gaseous form as a chemosterilizing agent has been known since the 1980s.[13] More recently (since the 1990s) it has been studied as a gaseous disinfectant in the food industry.t[14]

DISINFECTING PROPERTIES OF CHLORINE DIOXIDE

ClO_2 has been used to disinfectant potable water, food, and industrial cooling water, along with other uses, historically. It's first use in potable water was in the 1940s to control tastes and odors caused by algae.[15]

ClO_2 is generally recognized as second only to ozone in terms of water disinfection of a clean (uncontaminated) system. In a system contaminated with ammonia nitrogen or organics, ClO_2 is unmatched as a disinfectant.

In general, each type of microbe is thought to be or more resistant to inactivation to chemical disinfectants. Bacterial spores are thought to be among the most, if not the most, difficult to kill of all microorganisms.[16] As an example of the performance of ClO_2 when compared to other potable water disinfectants, Table 7 is provided. It shows the relative performance for inactivation of cryptosporidium, an Oocyst.

Table 7. CT Requirements: Disinfectants vs. Cryptosporidium

For *Crytpsporidium parvum*[#]		
Disinfectant	Conc	Min, 99% kill
Ozone	1	5
ClO_2	1.3	60
Cl_2	80	90
Chloramine	80	90

ABILITY TO PENETRATE BIOFILM AND INACTIVATE BIOFILM BACTERIA

It is well known that bacteria within a biofilm are much more difficult to inactivate than those that are free floating.[17]

There is a correlation between the strength of an oxidant with biofilm penetration.[18] Stronger oxidants such as chlorine and ozone are known to penetrate biofilm poorly, as they typically react with biofilm constituents as they penetrate biofilm.

For example, ClO_2 has been shown to penetrate biofilm very rapidly,[19] e.g., 170 times faster than free chlorine,[20] and inactivates bacteria within, including Pseudomonas[21] and Legionella.[22]

USE OF AQUEOUS CHORINE DIOXIDE FOR DISINFECTION OF MEDICAL DEVICES

A report of the British Society of Gastroenterology Endoscopy working group in 1998 indicated that a 2% glutaraldehyde solution was the most commonly used disinfectant in endoscopy units within the UK, despite the common adverse reactions of personnel. Freshly prepared aqueous ClO_2 was cited as a highly effective sporicide, rapidly inactivating B. subtilis spores, along with other, non-sporulating bacteria, including M. Tuberculosis, M. avium intracellulare, and P. aeruginosa. The report also claimed that the ClO_2 formulations used were quite corrosive and damaging to some materials, but they failed to note the impact of the other components of the commercial two-part ClO_2-producing products.[23]

There have been a number of studies that have been done subsequently on the use of aqueous ClO_2 for high level disinfection of various medical instruments.[24]

USE OF GASEOUS CHLORINE DIOXIDE IN MEDICAL DEVICE DISINFECTION

In 2016, a pilot study was done on the use of gaseous ClO_2 for disinfection of endoscopes.[25]

The use of ClO_2 gas as a sterilant was patented in 1985.[26] Spore strips inoculated with 10^6 colonies of ATCC 9372 of Bacillus subtilis var. niger in one experiment and B. subtilis and B. stearothermophilus (NCTC 1003) in another experiment were used to indicate sterility.

Then in 1986 a paper on the gaseous ClO_2 as a sterilant was published.[27] Again B. subtilis was used to measure sterility.

In 1987 a second patent was issued which incorporated the importance of humidity control for inactivation of B. subtilis spores.[28]

In 1990, further experiments were done to investigate the sterilization properties of ClO_2 gas towards B subtilus var. Niger (ATCC 9327).[29] Important factors were ClO_2 concentration, temperature, and humidity. ClO_2 gas was estimated to be 1,075 times more potent that EtO at 30 °C, on a molar basis.

In 1997, ClO_2 was mentioned as a potential gaseous sterilant replacement for EtO.[30] ClO_2, at 27 – 30 C, 10 mg/L, and 80% humidity inactivated spores at 33 – 50% of the time required for EtO. Based on the known properties, it was expected to be a better penetrant than other oxidants, although it penetrates cardboard poorly, degrades aluminum foil, is not compatible with silk, and does not penetrate unbleached paper.

Finally, in late 2020, early 2021, the FDA approved ClO_2 for contract sterilization.[31]

CONCLUSIONS

The unusual properties of gaseous ClO_2 make it a potentially ideal candidate as a gaseous replacement for EtO. These properties, along with other factors, include the following.

- There is a significant body of work which shows that ClO_2 is a very potent biocide.
- The unusual reaction chemistry of ClO_2 means it is less likely to react with various soils that may reside on a medical device.
- Work in other industries shows that ClO_2 has exceptional penetrating power, rapidly penetrating biofilm to inactivate biofilm within.
- Work has been done which shows that ClO_2 is able to activate bacterial spores at lower concentration and lower time than alternatives.
- A ClO_2 residual is measurable and thus controllable.
- ClO_2 has been estimated to be over 1000 times more potent than EtO, thus considerably shorter cycle times.
- Performance can be monitored by using bacterial spore strips, unlike some other technologies.

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