

Photocatalytic techniques to prevent and combat healthcare associated infections

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Abstract. An ever-increasing rate of morbidity and mortality caused by healthcare associated infections is reported annually. Air circulation mediates contact with microbial contaminated aerosols and represents a major risk of transmitting healthcare associated infections. We propose a revolutionary technique for the protection of interior surfaces based on a photocatalytic composition with doped TiO₂ or ZnO type semiconductor metal oxides which exert antimicrobial effect. In principle, there is an activation of the photocatalytic coating with light from the normal lighting apparatus, which may incorporate one or more sources of photocatalytic excitation light. By studying the air circulation in the hospital, it is possible to design light fixtures with specific design of light distribution, in order to perform the disinfection of the air and surfaces and to amplify the antimicrobial effect. The disinfection process does not affect patients or healthcare professionals, it can be done in their presence and has a continuous, controllable effect. Photocatalytic paint in combination with a prototype luminaire with a precise spectrum light sources, light output and a light intensity distribution curve relative to the shape and dimensions of the rooms, shows that the proposed method may represent a successful alternative to classical methods of disinfection in hospitals. This technique can also be used in other areas of interest.

1. Introduction

1.1 Infections associated with medical care that are due to nosocomial microbial species

Preventing and controlling the spread of healthcare associated infections is the greatest challenge of a health system. Control authorities have reported over the past few years increasing morbidity and mortality rates of these infections, which is causing a growing pressure on public health systems due to the high cost of treating them. In a study in 2016 [1], *Cassini and collaborators* showed that more than 2.5 million cases of healthcare associated infections occur in the European Union and the European Economic Area (EU / EEA) each year. The total weight of the most important healthcare associated infections was higher than that of all other communicable diseases under ECDC supervision [2]. According to reports from the *Canadian Agency for Drugs and Technologies in Health* [3], the cost of hospital-acquired infection treatment ranges from Canadian \$ 2,265 to \$ 22,400 Canadians, and the total annual spending associated with hospital-acquired infections estimated at over 1 billion Canadian dollars. Approximately 8,000 Canadians die from hospital-acquired infections and over 200,000 people get infected each year. Therefore, it is necessary to implement immiscible measures to improve the effectiveness of

methods of decontamination and prevention of infections associated with medical care arising from nosocomial microbial species.

1.2 Contamination of medical facilities

The emergence and spread of nosocomial infections require a chain of 3 elements:

- a) a susceptible recipient organism
- b) a source of pathogen
- c) pathogen transmission vectors

Pathogens come from exogenous and endogenous sources. Exogenous sources are the contaminated areas that generate and transmit through pathogens transport vectors. Most of these areas are sites that have developed mono or polyspecific microbial biofilms: different areas such as the surface of the walls of medical institutions, care facilities patients, medical devices or pathogens. Endogenous sources of pathogens are the colonizing microorganisms of different sites in the body of the immunocompromised patient. These opportunistic microorganisms cause host disease or, through transport vectors, spread from the infected patient to the entire in-hospital environment

Transport vectors ensure the dissemination of microorganisms in the environment, favoring the colonization of medical surfaces, as well as the contamination of patients susceptible to infection. A first category of transport vectors consists of medical care

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staff, hospital visitors, and medical equipment used in various medical procedures and which have not been properly disinfected. Another category of transport vectors is the air circulation generated by the ventilation systems of the medical rooms.

Circulation of air inside medical rooms is one of the most important routes for transmitting long-distance pathogens. But the most important role is the thermal air currents generated by the thermal gradient from the patient-to-air interface. The emergence of these thermal currents mediates the contact and contamination of surfaces of medical facilities with different aerosols loaded with pathogenic microorganisms. Generally, within medical units, the ambient temperature does not exceed 24°C. The body temperature of the patient above 37°C generates an ascending thermal current with a starting point at the patient's level. By moving them, the masses of ascending currents trains aerosols and pathogenic microorganisms existing in the patients. Thermal currents have a natural tendency to go to cold areas, areas of wall surfaces and medical supplies. Surfaces, at ambient temperature, cool down the thermal currents that they come into contact with and colonize with the aerosols and microorganisms discharged from these currents. Bacteria have the ability to be viable in the air, to adhere to and contaminate all the surfaces they come into contact with and form biofilms on these surfaces. Microorganisms thus form a microbial community defined as a biofilm that carries out metabolic activity in the toughest conditions [12]. Through this form of specialized organization, pathogens survive and become resistant to biocides, antibiotics and physical stressors [17, 18]. Colonization with microbial biofilms of interior walls, furniture surfaces or medical equipment explains the long-term survival of microorganisms in the hospital environment [14, 16, 17, 18]. It has been found that many aspects of human pathogen are strictly related to the emergence and development of biofilms [7, 30, 31]. Biofilms have been shown to reduce the susceptibility of microorganisms to many physical processes, such as exposure to ultraviolet (UV) radiation, most likely due to poor UV penetration into biofilm [12]. Since some anti-infectious agents have a low infectious dose, these biofilms formed on different medical surfaces represent a high risk of transmitting pathogens even at low concentrations. Biofilms raise great problems for medical units being adherent to surfaces, are very difficult to remove and represent the most important sources of pathogens [7].

1.3 Methods of prevention of nosocomial infections

The implementation of effective measures to combat and control healthcare associated infections in medical institutions is an essential component of the work of any public health service. Cleaning and disinfection practices are adapted to the clinical risk, taking into account the built-up areas, the design of the rooms, the medical equipment as well as the air circulation in the buildings. It is necessary to adopt measures to prevent and limit the

formation of microbial biofilms on different surfaces. Their fight is done by applying to the medical units protocols containing active practical measures and passive protection measures. Active measures are implemented by screening patients and monitoring areas susceptible to contamination or infection transmission. Concurrently, cleansing and disinfection protocols are applied in sensitive areas. Active measures are complemented by passive antibacterial protection measures for all surfaces [30]. Passive measures are achieved by covering critical areas with a series of antimicrobial and antiadhesion compositions. In these compositions - washable paints, protective resins, fabrics and linen - antimicrobial agents such as 1,2-Benzisothiazol-3-one, triclosan, various polymers, copper or silver are incorporated in various forms of presentation. The adoption of these passive protection measures is justified by two observations:

- resistant biofilms are formed in hospital surfaces and where pathogens can survive for a long time;
- active disinfection and cleaning methods are often ineffective in mechanically and chemically removing these biofilms.

The imposition of passive surface protection methods is also based on the following theory: the permanent action of passive antimicrobial protection measures reduces the possibility of biofilm formation and is followed by a decrease in microbial load on the contact surfaces. It has been found that, by promoting and applying passive antimicrobial protection measures to the various critical areas, the transmission capacity of bacterial strains has decreased [10]. This is to limit the formation of biofilms on the surfaces of the medical premises, but also to prevent the transmission of pathogens through the air currents.

There are currently numerous discussions about the effectiveness of the infection control measure and the contamination rate of patients with pathogens following the application of medical procedures. Although they have proven effective, they do not fully cover the risk of infecting patients, especially when they report an increase in antibiotic resistance to microbes. In the application of protocols for the disinfection and decontamination of medical facilities there were a number of deficiencies [4, 7, 30, 32, 33] which have often led to infections.

Traditional surface cleaning methods are ineffective for decontamination and new approaches have been proposed including steam disinfection, automated dispersion systems and the creation of antimicrobial surfaces [4]. There is a growing confusion as to the responsibility for the application of cleaning and disinfection protocols, especially in many medical institutions that much of the cleaning service has been outsourced [9]. There is a risk of wrong choice of the disinfectant formula used in active methods, and cumulative with insufficient training of medical and auxiliary staff and incomplete maneuvers may generate in-hospital infections. New research is being undertaken to develop formulations of detergents and disinfectants capable of destroying bacterial biofilms. Regarding the

new hospital decontamination strategies, the persistence of pathogens in biofilms and the prevention of their attachment to different surfaces should be considered in the future study [30]. The use of disinfectants under certain conditions can become dangerous for healthcare staff and patients, a recognized risk by the regulatory authorities, excessive use of disinfectants causing respiratory allergies or exacerbation of asthma [10].

Passive procedures for applying the antimicrobial coatings to surfaces, have proven useful by lowering the ability to form biofilms on the surfaces. These coatings effectively reduce the risk of transmitting pathogens. But **triclosan**, one of the most used antimicrobial agents, is toxic to aquatic bacteria [11] and has negative effects on the endocrine system and the nervous system [4, 10]. After exposure to UV radiation, **triclosan** decomposes with the production of toxic dioxins [6]. **1,2-Benzisothiazol-3-ona** is a product mainly used in biocide paints, as well as in some medical materials such as surgical gloves. Numerous cases of dermatologic allergy caused by long exposure to this product have been reported [13, 29]. There is a concern of the European control authorities to limit the use of **1,2-Benzisothiazol-3-ona** in various products in order to eliminate the risk of dermatological allergies in antimicrobial compositions. Silver has been used since antiquity as an antibacterial product. The new types of silver-polymer composites are based on the incorporation of silver nanoparticles into different substrates. It is known that there is a microbial resistance to silver, especially bacteria Gram Negative, not Gram Positive. It is possible that this silver resistance is genetically encoded on chromosomes or plasmids transferable to other bacteria [10]. Some authors [4] have argued that although UV radiation has a microbicidal effect, they should not be used as a first-line decontamination measure. It has to be applied as an additional strategy, for example under conditions of high infections or escalation rates. Factors to consider before implementing the routine UV-C technology include hospital design, room and equipment finishing, installation of furniture and medical devices, integration into cleaning, UV management. UV light is less effective for places in the corner of walls or areas protected by solid objects. UV-C light damages plastics and polymers used in the medical environment for repeated and long-term exposure. There are a number of studies that have shown that UV-C radiation very little penetrates the matrix of mucopolysaccharides of bacterial biofilms [12]. Because of this, it appears that under certain conditions, UV-C radiation is less effective to remove biofilms.

The development of antimicrobial coatings strategies that assure an efficient protection of critical surfaces is an important goal for finding new systems for surfaces decontamination in medical premises. The implementation of these strategies would also influence the costs of disinfection and decontamination [19]. New technologies are being developed based on the addition of different antimicrobial agents not only on the medical devices surface, but also in medical rooms (walls, ceiling, flooring) that can be contaminated with

pathogens. Surfaces of materials in patient care areas are of particular interest as they are a reservoir of pathogens related with the contamination from one person to another.

2. Antimicrobial photocatalytic surfaces

Workload, lack of staff, high bed occupancy, inadequate ventilation, transfer between different clinical sections of microbial contaminated patients, or agglomeration of medical facilities may compromise disinfection and control efforts, favoring the nosocomial infections. Decreasing the microbial load of medical facilities and optimizing conventional disinfection methods is done by antimicrobial and anti-adherent coatings of interior surfaces.

The first studies on antimicrobial and anti-adherent strategies have been made since 1964 by KINGSTON and NOBLE [20].

Researchers have developed new antimicrobial and antibiofilm methods using **light-activated antimicrobial agents (LAAAs)**. They are photosensitizing compounds (**FS**) which, through photocatalytic processes, generate a series of non-selective microbial toxic active radicals [6]. Microorganisms do not have specific defense mechanisms or enzyme equipment to neutralized this radicals. The photocatalytic method is the key benefit to avoid the problems that would arise from the antibiotic resistance phenomena. The semiconductor metallic oxides Photosensitizers (**FS**), such as TiO_2 or ZnO , are successfully used as light-activated antimicrobial agents. Numerous articles have investigated the mode of action of these metal oxide semiconductors and the mechanisms of photocatalysis and how these mechanisms inhibits pathogens [2, 21, 22, 26]. On the other hand, personal researches (consisting in unpublished results) regarding the antimicrobial efficiency of photosensitizing compounds based on TiO_2 and ZnO showed that, after exposure to natural light and 470 nm light they inhibited the growth of some Gram positive and Gram negative bacterial strains.

2.1 Mechanism of the photocatalytic process

By definition, photocatalytic processes are chemical reactions triggered by the interaction of a photosensitive substance, called photosensitizer (**FS**), with incident radiation of certain **hν** energy.

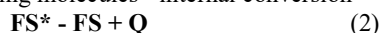
The mechanism of these processes takes place in several stages. The initial step is the activation reaction to the action of incident radiation whereby the energy of the photosensitizer molecule increases to a maximum. This peak is called E_A activation energy specific to the state of electronic excitation and allows the molecule to initiate and participate in various chemical reactions. The activation process is conventionally described by the equation:



where **FS** is the fundamental molecule, and **FS*** is the activated (excited) molecule. Activation is done by

absorbing the photon from the solid-liquid or solid-gas interface only if its energy satisfies the equation $h\nu > E_A$. The electronic transition generated by photon absorption generates changes in the vibrational and rotational quantum levels of the molecule. According to the Franck-Condon principle, the electrons on valency molecular orbitals in the quantum fundamental state take up the energy of the absorbed photon and pass on the higher molecular energy orbital (excited state). The life time of the excited FS^* molecule is very short. It extinguishes in the second stage, taking part in a series of chemical reactions in which the energy surplus is released and returns to the fundamental state of rest. This stage is called a state-of-the-art extinction process and is done in several ways:

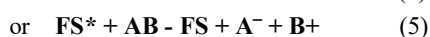
- energy release in the form of heat absorbed by neighbouring molecules - internal conversion



- emission of electromagnetic radiation through fluorescence or phosphorescent phenomena



- Dissociation or ionisation processes



The efficiency of the photocatalytic process is controlled by the light absorption characteristics at the interface with the substrate. The reaction speed is determined by radiation intensity absorbed and complies with photochemical laws:

1. Bunsen-Rosco Law – The photochemical effect produced by the radiation is proportional to irradiation and irradiation time (irradiation is defined as the energy of the photons that fall into the unit of time on the surface unit).

2. Stark-Einstein Law – An absorbed photon causes the transformation of only one molecule. The quantum efficiency for the primary act is equal to the unit, since for each absorbed photon a primary process is triggered.

The biocidal activity of a light activated antibacterial surface implies the initial absorption of photons by the substrate to produce highly reactive states of excitation. The result of these processes is the formation of *reactive oxygen species (ROS)*, with a microbicidal character located in the area of light irradiation. The phenomenon is conditioned by the concurrent existence of three key elements:

1. a photosensitizer – FS , capable of interacting with light radiation;
2. a stream of photons of a certain $h\nu$ energy;
3. the presence of oxygen at the interface of the stimulator with the environment.

2.2 Semiconductor metal oxides with light-activated antimicrobial agents (LAAAs)

The new generation of biocides and disinfectants are **light-activated antimicrobial agents (LAAAs)** capable of absorbing the kinetic energy of the incident photons.

They are semiconductor metallic oxide crystals as FS photosensitizers in photocatalytic reactions. The most commonly used are zinc oxide ZnO or titanium dioxide TiO_2 currently being used in antiseptic creams, in cosmetics, as UV filters, as pigments in the lacquer and paint industry, but also as catalysts in industrial applications. TiO_2 absorbs light in the UV range ($\lambda = 370$ nm) and photostimulates the redox reactions on its surface, producing reactive oxygen species (**ROS**) [24]. Zinc oxide - ZnO - is a material with unique optical, chemical, semiconductor, and piezoelectric properties. It has a strong ionic bond in the crystal structure [25].

The photocatalytic effect of any substrate is determined by two factors: the banned strip energy and the redox potential of the adsorbent. Semiconductor metal oxides are crystalline ionic structures characterized by a forbidden energy band. This energy band represents the energy difference between the last valence band and the electronic conduction band of the metallic structure. Its value depends on the nature and density of defects in the crystalline network and determines the concentration of free electrons and mobile holes in the crystalline solid. Structural defects or impurity doping of the crystalline structure alter the concentration of the load carriers. Most oxides of ion type crystals are non-stoichiometric. This deviation involves an excess of anions or cations in the crystalline structure. Compensation of excess loads is through the emergence of free electrons or mobile holes. Zinc oxide ZnO and titanium dioxide TiO_2 are part of the class of semiconductor oxides of type n - type, where there is an excess of positive loads due to anionic holidays (TiO_2 case) or an excess of cations (ZnO case). The excess positive charge is offset by the presence of free electrons that ensure solid neutrality and the value of the forbidden band of **3.2 eV - 3.3 eV** for both types of crystals. This energy level corresponds to the near-ultraviolet spectral range with wavelength between 370 nm and 380 nm. By irradiating a semiconductor metallic oxide with light energy equal to or above the energy of the forbidden band, the incident photon expels an electron from the valent band and promotes it on a conduction band where a mobile negative charge occurs. The oxide molecule switches to excited state with a nanosecond lifetime. The semiconductor particle becomes very reactive and transfers the free electron from the surface of the activation site to an adsorbed molecule. The adsorbed species on the surface take up the energy of the promoted electron on the conduction band, and the semiconductor oxide molecule relaxes. If the oxide molecule does not undergo chemical transformation during the process, and the transfer of charge to the adsorbed species is continuous and exothermic, the reaction mechanism is called heterogeneous photocatalysis [22].

The electron transfer process is more efficient if the species are preadsorbed to the surface of the semiconductor metal oxide crystal. The oxygen molecule, preadsorbed to the surface of the crystal, is an electron acceptor, taking up the free electron arising from the process of activating the metal oxide crystal (electron reduction process). Thus, superoxide radicals of reactive oxygen species of the **ROS** type are formed

(of type $O_2^1\Delta_g$ or $O_2^1\Sigma_g^+$) [27]. These reactive oxygen species act on the membrane of the bacterial cell that they destroy due to the oxidative nature of these chemical species.

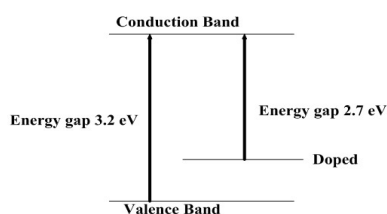


Figure 1.

Photoactivation of the UV-ray semiconductor oxide particle has a major drawback because this radiation is dangerous for humans. By the chemical doping method of the semiconductor crystal using doped metallic impurities, it is possible to reduce the energy of the forbidden band so that the semiconductor oxide is activated by light radiation from the visible spectrum. Transitional metal cations such **Ag** or **Cu**, **Au**, **Ni**, **Fe**, **Cr**, **Co**, **Mn** are commonly used. Semiconductor metallic oxides chemically modified by this process are photocatalytically activated by light irradiation **with a wavelength of 470 nm** (see Fig.1).

They can be incorporated as photocatalytic pigments in paints, varnishes or resins, products which thus acquire antimicrobial photocatalytic properties when activated in visible light. Compositions containing doped metal oxide pigments are applied to the surfaces of the hospital premises by providing hygienic, antimicrobial and disinfectant protection. The activation of the photocatalytic process of these compositions is made in the visible field using the light radiation emitted by the light sources of the luminaires in the respective rooms. The light emitted by these lamps initiates the photocatalytic chemical process from the semiconductor metallic oxides dispersed in the composition. A chemical photocatalysis process is generated in visible light, resulting in the appearance of chemical reactive species with a biocidal role at the surface of the composition.

2.3 Formation of species of bio toxic singlet oxygen reactive radicals

Molecular oxygen is a homonuclear diatomic molecule. In the fundamental state S_0 , molecular oxygen has a structure consisting of 16 electrons distributed according to the theory of molecular orbits OM as follows: $(\sigma_g 1S)^2$, $(\sigma_u^* 1S)^2$; $(\sigma_g 2S)^2$, $(\sigma_u^* 2S)^2$; $(\sigma_g 2p_z)^2$, $(\pi_g 2p_{xy})^4$, $(\pi_g^* 2p_{xy})^2$. Compared to other homonuclear molecules, in the fundamental state S_0 the molecular oxygen has the highest level of double degeneration, corresponding to 2 anti-lethal orbits. According to Hund's II rule, the last two unbounded electrons are each disposed on a single orbital counterclockwise, with the parallel orientation of the electron spins, so that the

multiplicity of the link is maximal. In spectral terms, free molecular oxygen has the fundamental fundamental term triplet with notation $O_2^3\Sigma_g^-$ (see Fig.2).

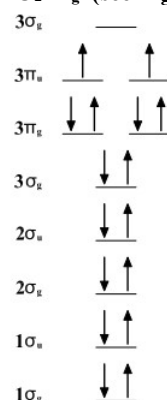


Figure 2.

The positioning of the two free electrons uncoupled on one orbital anti-lever, with the same energy level, ($\pi_g^* 2p_y$ și $\pi_g^* 2p_x$) and with the same parallel orientation of electron spins, explains the characteristic properties of molecular oxygen in terms of spectroscopic, magnetic behavior, chemical reactivity and energy transfer:

- the electrons being uncoupled, can generate a magnetic moment and explain the paramagnetism of the oxygen molecule in the fundamental state S_0 ;
- in the basic triplet state $O_2^3\Sigma_g^-$ the reactivity of the oxygen molecule at room temperature is low;
- can accept two electrons of a species containing pair electrons, only if a spin conversion occurs;
- unlike most compounds, which in the fundamental state S_0 have the singlet's spectral term, the oxygen molecule is an exception, since the fundamental term S_0 is triplet, with the notation $O_2^3\Sigma_g^-$.

Thanks to the parallel-orientated spinners on the two degenerate molecular-type orbital $\pi_g^* 2p_y$ and $\pi_g^* 2p_x$, molecular oxygen easily accepts energy in the two free electrons with parallel spins and forms excitations of singlet type $O_2^1\Sigma_g^+$ (unstable) or $O_2^1\Delta_g$ (metastable). Specifically, single electron oxygen status, free electrons change their spin orientation to the last double degenerate level $\pi_g^* 2p$, and become antiparallel orientation, a change that reflects the energy surplus taken at the excitement of the oxygen molecule.

However, in these two states, the occupation of molecular anti-leakage orbits differs $\pi_g^* 2p$. For the singlet type spectral term $O_2^1\Sigma_g^+$, the configuration of molecular orbits is identical to that of the fundamental state de triplet $O_2^3\Sigma_g^-$, the free electrons are uncoupled, they each occupy a molecular orbit $\pi_g^* 2p_y$ and $\pi_g^* 2p_x$, but the orientation of the spin is antiparallel. In the singlet type spectral term $O_2^1\Delta_g$ the electrons couples with antiparallel thorns and occupy a single orbital molecular counterclock either $\pi_g^* 2p_y$ or $\pi_g^* 2p_x$. Due to

the antiparallel orientation of the electrons in the excited state, the reactivity of the singlet molecule is much increased and has a strong oxidative character, relative to the oxygen molecule in the fundamental state.

Permitted oxygen transitions are from the triplet fundamental state $O_2^3\Sigma_g^-$ first to the excited state of singlet type $O_2^1\Sigma_g^+$ (unstable) (see Fig.3).

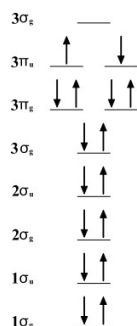


Figure 3.

In this energetic state, the spines of the free electrons uncoupled $\pi_g^*2p_y$ and $\pi_g^*2p_x$ are antiparallel and have an energy level of 154.9 KJ / mol. This state is unstable, has a very short life of 10-9 seconds, and internal conversion relaxes to the excited state of the singlet type $O_2^1\Delta_g$ (metastable) (see Fig.4).

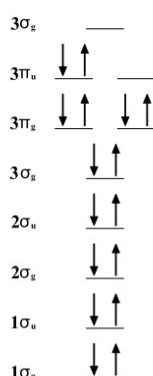


Figure 4.

The singlet oxygen molecule with the spectral term $O_2^1\Delta_g$ has an energy of less than 92.1 kJ / mol, due to the fact that the two free electrons are coupled to a single orbit. Because the transition from the term $O_2^1\Delta_g$ to the fundamental term $O_2^3\Sigma_g^-$ is a spin-off transition, the singlet oxygen molecule with the term $O_2^1\Delta_g$ is metastable and has a life span of up to several minutes, and after some sources up to 45 minutes.

Possible electronic transitions (see Fig.5):

- 1) $O_2^3\Sigma_g^- \rightarrow O_2^1\Sigma_g^+$
- 2) $O_2^1\Sigma_g^+ \rightarrow O_2^1\Delta_g$
- 3) $O_2^1\Delta_g \rightarrow O_2^3\Sigma_g^-$

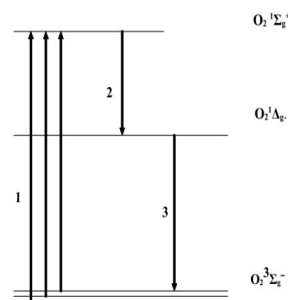


Figure 5.

Singlet oxygen-activated states can oxidize substrates that are not normally affected by molecular oxygen in the basic state. In the singlet state, the oxygen molecule has a pronounced electrophilic character, reacts rapidly with anions and unsaturated carbon bonds, and has high affinity for aromatic compounds.

CONCLUSIONS

Light-activated antimicrobial agents (LAAAs) act by generating reactive oxygen species with multiple targets toward microbial pathogens. Furthermore, titanium dioxide or zinc oxide coatings provide both reactive oxygen species and a hydrophilic, easy-to-clean surface, forming a microbial antiadherence barrier. These coatings prove to be promising to reduce microbial contamination in medical units. But, antimicrobial Coated Surfaces must be permanent, durable and operate under existing conditions in hospitals. The mode of action of the biocide should avoid the development of microbial resistance and, also, should be with prolonged action over time.

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