Ann Ig 2019; 31: 461-473 doi:10.7416/ai.2019.2307

Potential antimicrobial effects of photocatalytic nanothecnologies in hospital settings

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Key words: Nanotechnologies, photocatalysis, Titanium dioxide, Enviromental disinfection, Healthcare associated infections
Parole chiave: Nanotecnologie, fotocatalisi, biossido di titanio, disinfezione ambientale, Infezioni correlate all'assistenza

Abstract

Background. *Recently, several advanced technologies have been considered to reduce the microbial load in hospital environments and control Healthcare Associated Infections (HAIs) incidence. New strategies for preventing HAIs have continuously evolved, including enforcement of hygiene procedures by novel liquid biocides or no-touch technologies, self-disinfecting surfaces coated by heavy metals or light-activated photosensitizers such as Titanium Dioxide (TiO_2) nanoparticles.*
Study design. *Review publications concerning the use of photocatalytic systems in hospital setting, focusing on products based on TiO_2.*
Methods. *Specific keywords combinations were analitically searched in PubMed and Scopus databases.*
Results. *Starting 80s-90s, over 2000 papers report "in vitro" studies on antimicrobial activity of TiO_2 photocatalysis on several microorganisms including bacteria, viruses, fungi, yeasts, and antibiotic resistant strains. Besides, at least 4 selected papers addressed the potentials of this approach by "in field" studies, showing a widespread pool of applications in hospital and healthcare settings. However, the low number of available experiences and their heterogeneity represent major limitations to achieve a comprehensive final overview on effectiveness and feasibility of these technologies.*
Conclusions. *Photocatalytic systems based on TiO_2 represent a promising strategy for hospital hygiene and HAI prevention. Additional "in field" studies are desirable in a next future to further evaluate and exploit this novel and interesting health technology.*

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Introduction

Innovation in preventing Healthcare Associated Infections (HAIs) represents a priority for public health (1-6). Indeed, the improvement of the strategies for breaking the transmission chain of HAIs in hospital environments is urgently required (7-9). Stewardship programs, educational and training of operators, implementation of hand and environmental hygiene, surveillance in reprocessing and control of antibiotic resistances are only some of the key issues playing a role in HAIs prevention (1, 10-23). Disinfection of the inanimate environment is a critical point to avoid spreading of HAIs and several antimicrobial techniques have been proposed to reduce microbial contamination on surfaces (16). Different approaches were considered, e.g.: i) chemical-based disinfection protocols, such as hydrogen peroxide steam, copper and silver coated surfaces (20-23); ii) biological-based strategies, such as probiotics or their products (e.g. biosurfactants) (17-19); iii) physical systems, as ultraviolet (UV) light (8, 19). Furthermore, the innovation in HAIs prevention can be classified into several categories, including: (a) new liquid surface disinfectants, such as cold atmospheric pressure plasma, peracetic acid-hydrogen peroxide combination, hydrogen peroxide liquid disinfectants, electrolyzed water, polymeric guanidine (20-27), (b) improved methods for applying disinfectants, as microfiber and ultra-microfiber cloths or mops are among the alternative tools for distributing liquid disinfectants on surfaces (28-30), (c) self-disinfecting surfaces by coating surfaces using heavy metals as copper or silver (7, 31), (d) light-activated photosensitizers such as nanosized titanium dioxide to surfaces and using UV light (32), and (e) no-touch (automated) technologies. No-touch surface or room decontamination technologies include: aerosolized hydrogen peroxide, hydrogen peroxide vapor systems, gaseous ozone, chlorine dioxide, saturated steam systems, peracetic acid/hydrogen peroxide fogging, mobile continuous ultraviolet devices, pulsed-xenon light devices, and high-intensity narrow-spectrum (405 nm) light (1, 33-39). These recent "no-touch" technologies have been shown to be useful for reducing bacterial contamination on surfaces (40). Several "no-touch" strategies and technologies for antimicrobial coatings have been described, such as: active eluting agents (e.g., ions or nanoparticles of silver, copper, zinc, or antibiotics, chloride, iodine); immobilized molecules that become active upon contact (e.g., quaternary ammonium polymers or peptides, chitosan); or light-activated molecules (e.g., TiO_2 or photosensitizers) (41-45). These innovative technologies offer an alternative for environmental hygiene, but their equipment, training, management, and personnel involvement, require further independent studies to establish the rapport between costs and benefits in their application (39). Moreover, in the last years, several antimicrobial agents with smaller sizes, called nanoparticles (NPs) were developed or integrated within available strategies. The main characteristics of nanoparticles are stability, homogeneity and broad spectrum of action on different microorganisms as well as the possibility of being linked with functional groups, increasing the antimicrobial effect. Indeed, it has been shown that copper, silver, titanium and gold nanoparticles show interesting disinfectant properties. Another advantage of the use of nanoparticles is the high surface-volume ratio which significantly increases their effectiveness compared to commonly used compounds (34). Either, nanoparticles can play an important role in enhancing the efficacy of routinely used treatments. This synergistic effect has been shown for different compounds (35, 36). An important potential of nanoparticle-based technologies is the relative larger surface area when compared to the volume of same material. Nanotechnologies are based on given volumes divided into smaller pieces to increase the functional surface area. Therefore, as particle size decrease, a greater portion of the atoms are found at the surface compared to those inside, leading to more chemically reactive compounds. Since growth and catalytic reactions can occur at surfaces, therefore a given mass of nanomaterial will be much more reactive than the similar mass of material made up of larger particles. It is also found that materials which are inert in their bulk form are reactive when produced in their nanoscale form (40). Therefore, NPs are being more and more often considered due to the growing recognition of their superior biocidal efficacy (e.g. silver, copper, zinc and titanium-NPs) (41-43). Example given, silver and copper have been used as additives in hospital fabrics, but several other applications have been proposed (44-46). Nanosilver is widely used as an antimicrobial additive in bandages, wound dressing and in urinary and intravenous catheters (45). The use of covering surface containing silver, copper and zinc are regulated within EU by the Biocidal Product Regulation (BPR, Regulation (EU) 528/2012) and by the Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH). Furthermore, the antimicrobial nanocomposites based on titanium dioxide (TiO_2) have been actively investigated (47). Titanium Dioxide, also known as titanium (IV) oxide or titania is the naturally occurring oxide of titanium, chemical formula TiO_2. It has been generally used as a pigment (Pigment White 6 - PW6- or CI 77891), independently of the catalytic potentials. Sourced from ilmenite, rutile and anatase, this compound has a wide range of applications, including paint, sunscreen and even widely diffused food colouring (E171). TiO_2 has substantial advantages over both chemical (NO, H_2O_2, small organic molecules) and metal (typically Ag)-based systems: i) titanium dioxide NPs showed a broad spectrum of activity against Gram-negative and positive-bacteria and fungi (48, 49) acting also against the multiple drug resistant strains (48); ii) titanium dioxide-polymer nanocomposites are intrinsically environmentally friendly and exert a non-contact biocidal action (49). Therefore, these applications allow no release of potentially toxic nanoparticles to the media still achieving disinfection (49-58). A wealth of information is present in literature demonstrating the efficacy of TiO_2 photocatalytic in the inactivation of various microorganisms including bacteria, viruses, fungi and yeasts. As stated by International Union of Pure and Applied Chemistry (IUPAC), photocatalysis is the change in the rate of a chemical reaction or its initiation under the action of ultraviolet, visible or infrared radiation in the presence of a substance the photocatalyst that absorbs light and is involved in the chemical transformation of the reaction partners (59). Basic mechanism relies on the formation of reactive oxygen species (ROS) (60). Besides the degradation of several groups of organic compounds and inorganic species, ROS have demonstrated bacterial inactivation capacity (61, 62). The mechanism of TiO_2 NP activity on microorganisms can be outlined as follows: i) the production of ROS (the superoxide anion, hydrogen peroxide, the hydroxyl anion, and hydroxyl radical); ii) cell wall damage and lipid peroxidation of the cell membrane caused by NP-cell attachment by electrostatic force owing to the large surface area of TiO_2 NPs; iii) ROS are thus responsible for the oxidation of many organic constituents of the microorganism, such as lipid per-oxidation, protein alteration and/or DNA damage (Fig. 1) (63, 64).

This paper reviews recent publications focusing on the use of photocatalytic systems based on TiO_2 in hospital setting.

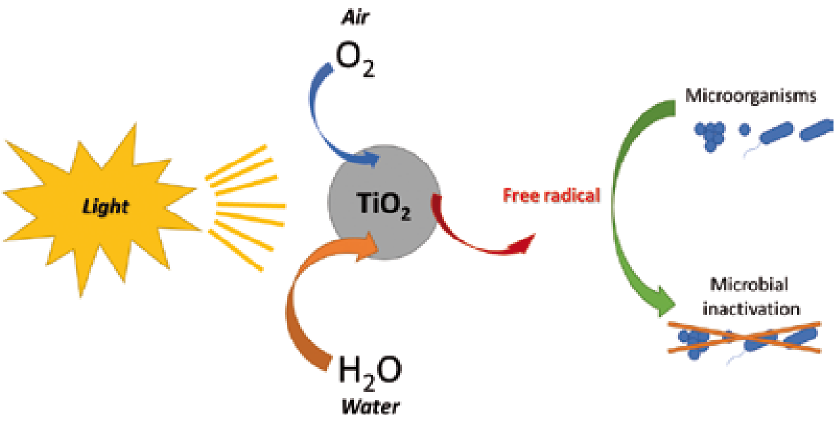

Figure 1 - Photocatalytic mechanisms based on TiO_2 and microbial inactivation through the production of reactive oxygen species.

Material and methods

The search strategy was developed according to the knowledge of the authors and the findings of previous reviews or original articles on photocatalytic nanotechnologies in hospital setting. Relevant literature on "*Titanium dioxide*" and "*photocatalysis*" and "*bacterial*" in several environments and microorganisms were collected through a systematic search of the following electronic databases (until 20 April 2019): MEDLINE via PubMed, Science direct and Scopus. The combination of the key word "*Titanium dioxide*" with any of the following terms was used for the search in the aforementioned databases: "*photocatalysis*", "*water*", "*air*", "*surfaces*" and "*bacterial*". The references of each article were examined to achieve additional relevant citations. Several inclusion criteria were considered to identify the eligible "*in field*" studies. Only English-based studies with detailed analytic study design were considered for this review. Studies considering "*in vivo*", "*in vitro*" and "*in field*" were included. Case reports, studies without a control group, studies with incomplete design (e.g. ecological studies) were excluded. Study selection was carried out using the following multistep exclusion process: two reviewers independently investigated the titles and the abstracts; then, the full text of any potentially includable study (when it seemed to meet the inclusion criteria or when the title and the abstract did not present adequate data for a clear decision) was obtained. The authors of the studies for which it was not possible to find the full text were directly contacted. During this multi-step exclusion process, reviewer consensus was obtained.

Results and discussion

A century of Titanium Dioxide

The increasing interest in photocatalysis activity of TiO_2 and its application in microorganism inactivation is deeply reflected in the scientific literature. Indeed, research related to "*Titanium dioxide*" and "*photocatalysis*" and "*bacterial*" has exponentially increased over the last decades (Fig. 2). TiO_2 powders were originally obtained from the natural minerals and have been commonly used as white pigments

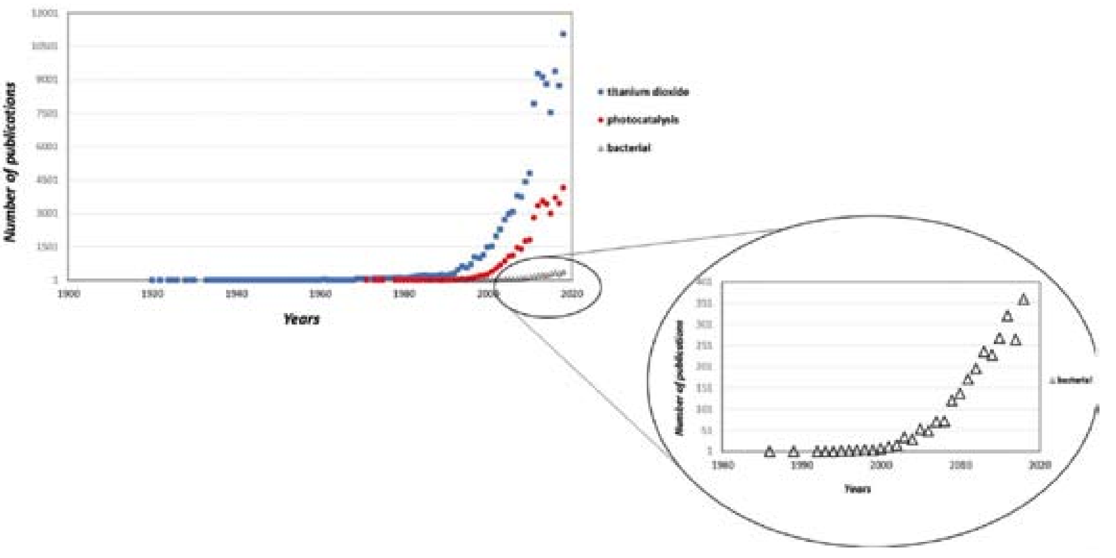

Figure 2 - The increasing interest in photocatalysis activity of TiO_2 and its application in microorganism inactivation is reflected by the scientific literature trend. Research related to "*Titanium dioxide*" and "*photocatalysis*" and "*bacterial*" has increased over the last decades.

from ancient times (65-67). Photocatalytic activity was known since the 1920s, fabrics and paints incorporating TiO_2 were modified after their exposure under sunlight (68). Interest in TiO_2 photocatalysis processes increased strongly when *Fujishima and Honda*, in 1972, discovered its photocatalytic mechanism in water (69). Subsequently, an extensive list of organic compounds, inorganic compounds, microorganisms, viruses and other compounds that could potentially be oxidized, reduced, transformed or inactivated by photocatalysis were tested (70). However, some disadvantages related to TiO_2-based photocatalys, were also reported, such as the higher recombination rate of electron-hole pairs or the relatively lower sensitivity to solar light (70). In order to overcome these limits, extensive studies were performed aiming to develop photocatalytic processes active under visible light and described as a second generation of photocatalysts (70, 71). Second-generation TiO_2 photocatalysts doped with either anions or cations have recently been shown to enhance photonic efficiencies of the reactions. Since the 1980s, the efficacy of photocatalysis was tested against several microorganisms harboring in different matrices (72-77). Efficacy of ROS generation by TiO_2 irradiated with metal halide lamp was demonstrated, already in 1985, and, in this preliminary application, *Escherichia coli* load was completely reduced (77). The following studies considered several microorganisms such as viral particles (e.g. MS2 phage, RNA bacteriophage, phil164), bacteria (e.g. *Staphylococcus aureus Escherichia coli,* total coliforms, *Salmonella, Pseudomonas aeruginosa* and *Listeria monocytogenes*), and spores of bacteria (e.g. *Bacillus subtilis*), fungi (e.g. *Fusarium, Candida albicans, Aspergillus niger*) and other parasites such as protozoa (e.g. *Cryptosporidium parvum*) (70, 78). Several hypotheses have been argued to draw the possible reaction pathways involved in titanium dioxide based photocatalytic disinfection (76).

An increasing interest in the application of the photocatalytic properties of TiO_2 for disinfection of water, air and surfaces was considered using different approaches (70, 79, 80). Over 20000 papers (n=22132) appear in the scientific literature databases when searching by "*water*" and "*titanium dioxide*" keywords. About 52% of these articles address the issue of the photocatalytic effect and the 5% specify some antibacterial properties. Several studies have reported TiO_2 applications for water purification. TiO_2-based photocatalysis in water shows a high oxidation power. Moreover, the generation of hydroxyl radicals through the partial oxidation of water revealed enough effective to kill microorganisms such as bacteria, destroy viruses, and remove alternative organic contaminants from water (76, 81, 82). This kind of photocatalytic technology seems a promising alternative to the traditional disinfection processes commonly adopted in the control of bacteria such as *Legionella spp* or *Pseudomonas spp* in hospital hot water systems (6, 83-85). Several factors, such as reactor design, water chemistry, and TiO_2 modifications can influence these disinfection processes and are not still fully optimized. Thus, even if photocatalysis is undoubtedly a desirable tool in dealing with microbial contamination of water sources, some aspects remain to be considered in terms of maximizing its efficiency (81). Considering air as another critical matrix in hospital settings, several papers (n=7322) appear in the literature with "*air*" and "*titanium dioxide*" keywords. About 42% articles address the issue of the photocatalytic effect, and about 3.6% considers its antibacterial properties. Studies on the photocatalytic technique for disinfection demonstrate its potentials for widespread applications in indoor air and environmental health, opening to novel perspectives for the microflora air control and indoor air quality (IAQ) (80, 86). Some pioneering works have investigated the disinfection of indoor air and the improvement of IAQ by photocatalytic techniques, also based on TiO_2 (81-86). More recently, photocatalytic self-cleaning activity was enforced by TiO_2 coated surfaces, so that this technology has been vastly improved in the last few years (87). Previous works showed how the hydrophilic or hydrophobic properties can be controlled by the photocatalytic process, making it possible to couple photocatalysis and photoinduced wettability to improve self-cleaning properties in a controllable way. TiO_2 photocatalytic self-cleaning activity can support further applications in hospital settings, considering an action not only as biological contaminants removal but also chemical pollutants such as volatile organic compounds (VOCs) (87, 88). In conclusion, the redox activity supported by TiO_2 photocatalysis was considered for very different applications ranging from disinfection to cleaning and decontamination, suitable in hospital settings as well as in several other frameworks, including food protection applications, wastewater treatments, pharmaceutical or laboratory processes and other life or occupational environments (40, 88, 89).

Titanium Dioxide in Hospital setting

Focusing on hospital settings, several *in vitro* studies have showed the potential effectiveness as semiconductor active in matrices such as water, air and surfaces and on various microorganisms (16, 32, 82, 90-93). Several materials, such as Polyvinyl Chloride (PVC), Polystyrene or Ceramics, were coated with TiO_2 -doped or not doped with ions- and were tested for antimicrobial activities on bacteria strains (93-95). In Bonetta *et al.*, the best antibacterial effect was observed at 180, 60, 30 and 20 min of exposure for *E. coli*, *S. aureus*, *P. putida* and *L. innocua* both in ceramics and in polystyrene (93). Moreover, among the different species that were tested *in vitro*, antimicrobial resistance (AMR) strains were included, highly recommended for hospital applications. Indeed, according to the World

Health Organization, antimicrobial resistance is becoming an increasingly serious threat to global health and seems to require the development of alternative systems in addition to the traditional disinfection and treatments that are already available (90-93). Some potential applications of TiO_2 on surfaces (PVC or polystyrene) have been addressed to AMR bacteria and some researches have shown their efficacy *in vitro* (94, 95). In Petti *et al.*, the PVC surfaces incorporated with nano-TiO_2 particles were contaminated with methicillin-resistant *Staphylococcus aureus* (MRSA) isolated from hospitalized patients using a mist sprayer to simulate the environmental contamination, showing the achievement of a benchmark threshold for surface-hygiene in hospitals (<1 CFU/cm^2) within 3 h of exposure to photocatalysis (94). A recent study has tested the antimicrobial activity of copper doped titanium dioxide nanotubes, showing up how 10^3 microorganisms (MRSA and extended-spectrum beta-lactamase *Escherichia coli*) per cm^2 can be inactivated in 24 hours (95).

Given the increasing interest in the above-mentioned innovative technologies for cleaning and disinfection of surfaces, several studies were performed to consider their applicability in hospital environments and support actions focused to prevent healthcare associated infections (HAIs) (1-9). However, to state the effectiveness of various cleaning, disinfecting and monitoring strategies, "*in field*" studies are needed to compare alternative disinfection and monitoring methods with each other and with traditional ones (7). Table 1 shows four studies, that were performed in hospital environment (95-99). These studies have tested the action of these new technologies by traditional microbiological methods both by considering different outcomes such as verifying the acquisition of infections and using epidemiological indicators such as odd ratio. In the first study dated 2006, the evaluation of the

Table 1 - Recent and selected studies performed in hospital environment

Paper	Result summary	References
Kim MH, et al. Environmental disinfection with photocatalyst as an adjunctive measure to control transmission of methicillin-resistant Staphylococcus aureus: A prospective cohort study in a high-incidence setting. BMC Infect Dis. 2018; 18(1):610.	Comparison of the acquisition rate of MRSA in patients, before and after hospitalization in an intensive care unit, on surfaces and walls treated with titanium dioxide. Odd Ratio of 0.37 (95% confidence interval, 0.14 – 0.99; p = 0.04)	100
De Jong B, et al. Pre-post evaluation of effects of a titanium dioxide coating on environmental contamination of an intensive care unit: the TITANIC study. J Hosp Infect. 2018; 99(3):256-262.	Prospective pilot study, in a controlled environment, to examine the effect of a titanium dioxide coating on microbial colonization on surfaces of an intensive care unit (In vitro and field data).	98
Reid M, et al. How Does a Photocatalytic Antimicrobial Coating Affect Environmental Bioburden in Hospitals? Infect Control Hosp. Epidemiol. 2018; 39(4):398-404.	Evaluation of a photocatalytic titanium dioxide-based antimicrobial coating on surfaces within an intensive care department. Odd ratio of 0.95 (95% CI, 0925 – 0977; p < 001)	99
Shintani H, et al, Sterilization efficiency of the photocatalyst against environmental microorganisms in a health care facility. Biocontrol Sci. 2006; 11(1):17-26.	Evaluation of the antimicrobial effect of a photocatalytic system with titanium dioxide-based membranes and a UV lamp inside a sanitary structure. High level of reduction of microbial charge in the presence of high humidity (60-70%).	97

antimicrobial effect was assessed adopting a photocatalytic system using titanium dioxide-based membranes and a UV lamp inside a sanitary structure room, showing the high level of reduction of the microbial load in the presence of high humidity (60-70%) (96). A prospective pilot study, performed in intense care unit, examined the effect of a titanium dioxide coating on microbial colonization, considering surfaces of an intensive care unit, but it did not confirm the same results observed *in vitro* (97). Indeed, during the *in-vitro* study, the log reduction was less than 2 in an 8 h period, but non-significant results have been achieved in the clinical environment. The discording results were explained by different reasons, including the absence of information on the characterization of the used product, the lower intensity of light respect to the *in vitro* studies and the lower control of variables in the environment also due to the higher risk of continuous contamination by bioaerosols or contact with healthcare workers or visitors (97). Conversely, in another study performed in intensive care department in a hospital, the photocatalytic titanium dioxide-based antimicrobial coating on surfaces exhibited a 2.5% reduction per day for treated surfaces (odd ratio of 0.95, 95% CI, 0925 – 0977; p < 001) (98). Finally, in a recent study dating 2018, the comparison of the acquisition rate of MRSA in patients, before and after hospitalization, showed a reduction thru the Odd Ratio analysis (0.37, 95% confidence interval, 0.14-0.99; p= 0.04) (99).

While analysing all these studies, several limits emerged, as absence of information about the characteristics of the TiO_2 coating, e.g. morphology, microstructure, elemental state, or the quality of indoor lighting or microclimatic conditions. Moreover, also the ascertain of the presence or quality of the coating during the study seems a fundamental point. Indeed, the wear might have damaged or removed the coating from some of the tested surfaces, corrupting its efficacy. Heterogeneity of the study designs may also represent a major limit to obtain a complete and definitive overview on effectiveness of these technologies *in field* applications. Thus, a more complete control of the variables present directly in the hospital environment could be a clear key issue in assessing the effectiveness of this novel and promising technology in hospital settings.

Conclusions

The current challenges in HAIs and the increase of and AMR bacteria diffusion are engaging researchers in exploring the field of nanotechnologies and photocatalysis as a new source to improve hospital hygiene. Several studies are available, supporting the effectiveness of strategies based on TiO_2 materials or processes. However, health technology assessment studies are needed to evaluate the effectiveness of photocatalytic systems within a cost/benefit framework. Therefore, additional "*in field*" studies are desirable for the future, including *in vitro* preliminary experiments and consistent details on the control over the many variables present in hospital setting.

Funding
None
Competing Interests
None declared

Riassunto

Potenzialità antimicrobiche delle nanotecnologie fotocatalitiche in ambito ospedaliero

Stato dell'arte. Recentemente, negli ambienti dedicati all'assistenza sanitaria sono state introdotte nuove tecnologie in grado di ridurre il livello dei microrganismi sulle superfici, con l'obiettivo di limitare la diffusione dei microrganismi e a controllare l'incidenza delle infezioni correlate all'assistenza (ICA). Nuove strategie per la prevenzione delle ICA sono in continua evoluzione, come l'introduzione di alcuni disinfettanti superficiali liquidi, lo sviluppo di superfici auto-disinfettanti mediante rivestimenti che utilizzano metalli pesanti, le tecnologie "no-touch" e foto-sensibilizzatori attivati dalla luce come nanoparticelle di biossido di titanio (TiO_2) sempre utilizzate per rivestire le superfici.

Disegno dello studio. Scopo di questo lavoro è una revisione della letteratura sull'uso di sistemi fotocatalitici a base di TiO_2 in ambiente ospedaliero.

Metodi. L'analisi della letteratura è stata sviluppata attraverso database quali *PubMed* e *Scopus*, utilizzando parole chiave specifiche.

Risultati. Numerose informazioni sono presenti in letteratura e oltre 2000 studi "in vitro" considerano l'efficacia antimicrobica della TiO_2-fotocatalisi su vari microrganismi compresi batteri, virus, funghi e lieviti ed anche su ceppi con antibiotico resistenze multiple. Inoltre, almeno 4 articoli selezionati hanno affrontato le potenzialità di questo approccio con studi "sul campo", mostrando un ampio pool di applicazioni in ambito ospedaliero e sanitario. Tuttavia, il basso numero di esperienze disponibili e la loro eterogeneità rappresentano i maggiori limiti per ottenere una panoramica finale completa sull'efficacia e sulla fattibilità di queste tecnologie.

Conclusioni. I sistemi fotocatalitici basati su TiO2 rappresentano una strategia promettente per l'igiene ospedaliera e la prevenzione delle ICA. Ulteriori studi "sul campo" sono auspicabili in un prossimo futuro per valutare e ottimizzare questa nuova e interessante tecnologia in ambito sanitario.

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