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Devices to fight catheter-related infections

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Abstract

Healthcare-Associated Infections (HAI) affect ~1.7 M people in the USA and 4.1 M in Europe, contributing to 99,000 and 37,000 deaths/year, respectively. Catheter-related infections are the most frequent cause of HAI, leading to life-threatening complications and colossal medical costs. Current prevention/treatment options – sterilization protocols, lock solutions, systemic antibiotic administration – are inefficient and lead to bacterial resistance, a huge threat to public health. This review addresses the existing solutions in the market – mostly catheter caps –, and emerging alternatives, to fight catheter-related infections. Graphene-based biomaterials arise as interesting weapons against these infections, particularly in combination with light: their photothermal and photodynamic properties boost their own antimicrobial action, allowing them to kill bacteria without contributing to bacterial resistance.

Keywords*: infection, catheters, medical devices, radiation, sterilization, graphene*

Resumo

As infeções associadas aos cuidados de saúde (IACS) afectam cerca de 1.7 M de pessoas nos E.U.A. e 4.1 M na Europa, contribuindo para cerca de 99,000 e 37,000 mortes/ano, respectivamente. Infecções associadas a cateteres são a causa mais frequente de IACS, originando complicações que colocam em risco a vida dos pacientes, além dos custos colossais associados. Actualmente, as opções de prevenção/tratamento – protocolos de esterilização, soluções de bloqueio dos cateteres, administração sistémica de antibióticos – são ineficientes e causam resistência bacteriana, uma grande ameaça para a saúde pública. Esta revisão da literatura explora as soluções existentes no mercado – maioritariamente tampas para cateteres –, e alternativas emergentes, para combater as infeções associadas a cateteres. Biomateriais à base de grafeno surgem como armas interessantes contra estas infeções, particularmente através da combinação com a luz: as propriedades fototérmicas e fotodinâmicas destes materiais estimulam a sua inerente acção antimicrobiana, permitindo que matem bactérias, sem contribuir para a resistência bacteriana.

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Introduction: the threat of catheter-related infections

Bacteria adhesion to the surface of medical devices is the onset of biofilm formation, making healthcare-associated infections (HAI) a colossal problem to tackle. HAI affect ~1.7 M people in the USA and 4.1 M in Europe, contributing to 99,000 and 37,000 deaths/year, respectively. Catheter-related bloodstream infections (CRBSIs) are the most frequent cause of HAI, the most serious complication in patients with prolonged central venous catheters (CVC) dependence [1, 2], and the most common indication for premature catheter replacement (30%–60%). They are also the costliest type of HAI: per case, a CRBSI costs an average of $45,814 ($30,919 - $65,245) and implies a hospital stay of 10.4 days on average, being 6.9 days at the intensive care unit. When the CRIs are caused by MRSA, the cost is even higher (averaging $58,000) as well as the hospital stay duration (averaging 15.7 days) [26]. This accounts for an economic burden of more than $23 B annually in the USA and €35.9 - €163.9 M in four European countries (France, Germany, Italy, and the UK) [3, 4]. The attributable mortality of CRBSIs has been estimated at 25% [5]. These CRBSIs are clinically defined as a systemic blood infection (bacteremia) where the catheter has been identified as the source of the infection [6], and where the pathogen on the catheter surface and in blood cultures is the same [5].

The majority (around ¾) of catheter-related infections are caused by Gram-positive organisms, and the remaining less than ¼ are Gram-negative (Figure 1) [1, 7]. Staphylococcus aureus, including methicillin-resistant S. aureus (MRSA), is the most common causative organism (3–74%), followed by Staphylococcus epidermidis (7–42%) and other coagulase-negative Staphylococci [8]. Reported rates of MRSA range from 2.3% to 27.3%, and up to 35% of colonized patients subsequently develop MRSA infections within 1 year [1, 9]. Fungal infections are also a concern, with Candida albicans being the predominant fungal species isolated from medical devices [10]. The severity of presentation and clinical consequences of CRBSI vary significantly in literature, ranging from 3.2% to 50%, and are related to the infecting organism: S. epidermidis CRBSI tends to present with atypical symptoms, while S. aureus CRBSI is more likely to require hospitalization or intensive care admission [11]. Polymicrobial infections accounted for 14% of CRBSIs and were associated with longer duration of prior catheter use [11]. Catheter salvage may be attempted if the infection is caused by coagulase-negative staphylococci, however if the causative microorganism is S. aureus and Candida spp., the catheter should be removed immediately, due to the high risk of metastatic infection and increased mortality [5]. S. aureus presents the highest risk of developing bacteremia [24] and a subsequent metastatic infection, being the prevalence of those during a S. aureus bacteremia of 5.7% to 75.3% [22]. It is therefore crucial to know the causative agent, so that it can be treated accordingly and with the antibiotics to which it is susceptible to [5].

Bacteria can access and colonize the catheter by different routes (Figure 2): (1) migration of microorganisms from the patient's skin through the catheter tract at the exit site; (2) pathogen colonization of the CVC hub or connector; (3) hematogenous seeding (from contaminated intravenous fluids); and (4) contamination of infused fluids [6, 12, 13]. Biofilm distribution is related with the duration of catheter placement. Colonization of the extraluminal surface, likely originating from the skin, predominates soon after insertion and in short-term catheters that have been in place less than 10 days. Colonization of the intraluminal surface occurs generally due to hub contamination and increases progressively with time, becoming predominant after 30 days of placement of long-term devices [6, 14, 15]. As such, bacteria can colonize the catheter hub and exit site (localized infection), and/or spread further along the subcutaneous tunnel to the lumen (systemic infection) [11]. In patients with CVCs, the major source of CRBSI is the bacterial biofilm formed in the inner surface of the CVC [12].

Similarly to other medical devices, the general mechanism of infection in catheters starts

with the adsorption of proteins at the surface. Planktonic bacteria migrate to the surface via Brownian motion, and due to different forces, including van der Waals and surface electrostatic charges and hydrophobic interactions, adhere reversibly to the conditioning films established. As the adherent bacteria multiply, form colonies and secrete extracellular polymeric substances (EPS), the process becomes irreversible and bacteria permanently anchor to catheter surface. These aggregates of bacteria protected from external disruptors, as

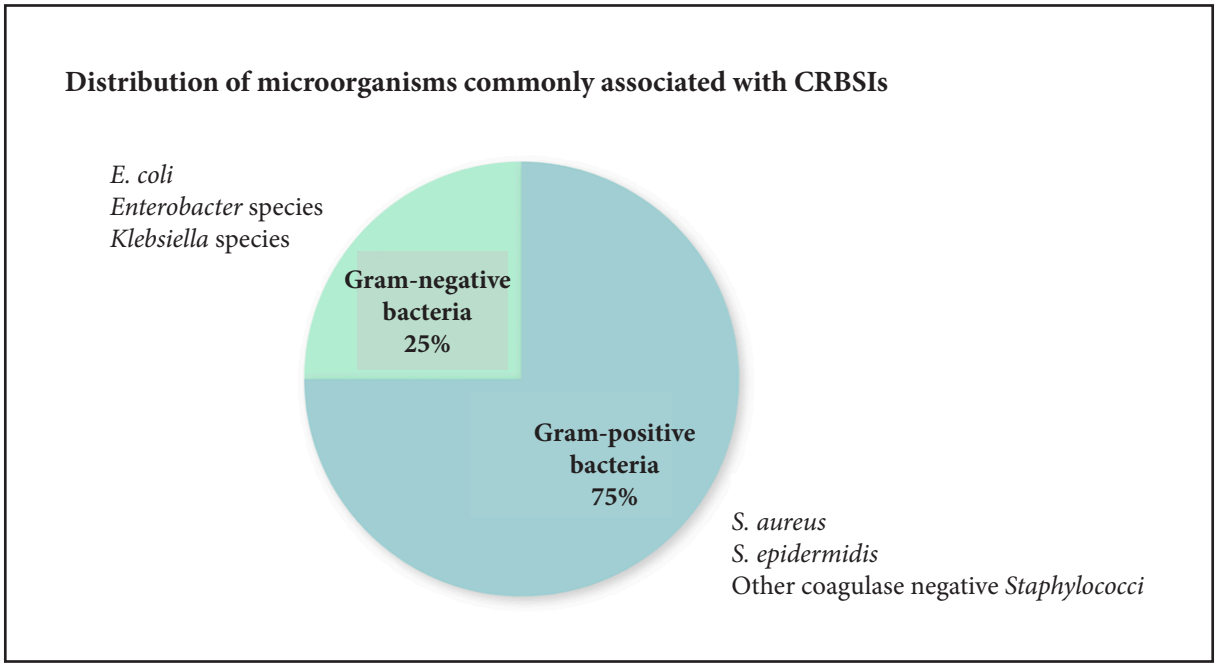


Figure 1. Microorganisms commonly associated with CRBSIs [7, 8, 11]

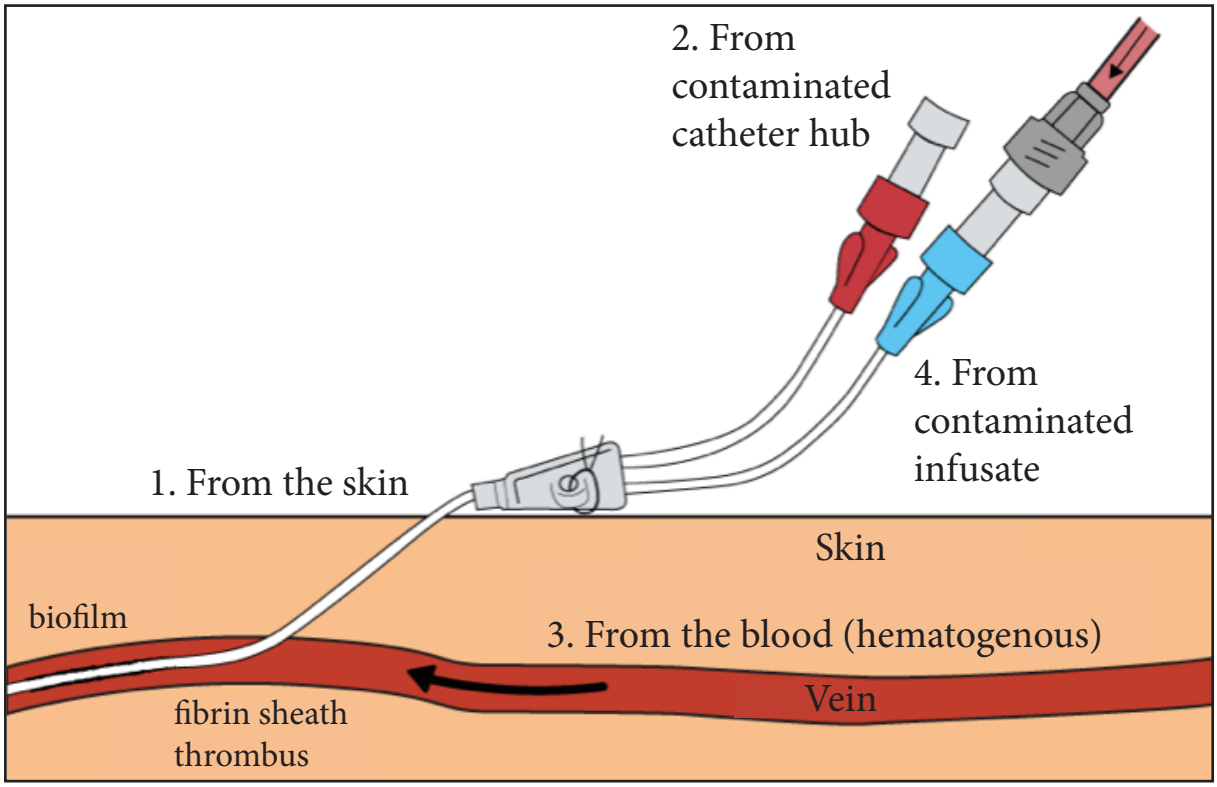


Figure 2. Potential routes of CRBSIs (adapted from [16])

drugs and the host immunity, are called biofilm. Bacteria living within a biofilm have different properties from the free-floating bacteria of the same species, as the dense and protective environment of the biofilm allows them to cooperate and communicate in different ways [17]. Biofilm bacteria also excrete toxins that can reversibly block important host defensive processes. After maturation and growth of the biofilm, single cells or aggregates of cells may detach from the biofilm due to fluid shear, or as a result of internal biofilm processes, leading to infection [8]. Biofilms also cause the deterioration of surface properties and functions, limiting the service life of the catheter [18].

As mentioned before, when signs of infection are observed, antibiotics are systemically administered, despite their low ability to disrupt formed biofilm. Biofilms at different stages of maturity showed different susceptibility to antibiotics, which may give rise to antibiotic resistance [9], an emergent public health issue responsible for more than 500,000 deaths/year worldwide, with costs to healthcare systems reaching around 1.1B € [19]. Antimicrobial resistance limits treatment options and increases the risk of infection-related morbidity and mortality. In addition, the use of traditional antibiotics exerts secondary effects on the healthy human microbiota, further contributing to antibiotic selection pressure and the risk of emergence and propagation of antimicrobial resistance [9].

Currently, measures to prevent or control infection in catheters rely on skin disinfection (in some hospitals and clinics following a strict sterilization protocol), and on the use of prophylactic topical antimicrobial ointments and dressings at the catheter exit site, associated with the use of anticoagulant and antimicrobial catheter locking solutions, in some types of catheters (with sodium citrate, for instance, which already has some antibacterial properties) [20, 21]. In some cases, catheter capping also occurs, functioning as a physical barrier between the interior of the catheter and the external environment. Despite this, bacterial infection still occurs, resulting in catheter replacement, possibly the only option to effectively eliminate the risk of further infection-associated problems. As such, a need exists for better, safer and antibiotic-free methods and systems, able to ensure a sterile access to the catheter, minimizing the possibility of the introduction/permanence of pathogenic organisms in the catheter lumen.

Existing technologies

Bacterial infection in catheters or in any other medical device starts by the attachment of a single bacteria to the surface. Endowing surfaces with antibacterial performance has therefore become of utmost importance to tackle HAIs. Strategies can focus on preventing bacteria from adhering to the surface (anti-adhesive) [22], killing the bacteria that manage to attach on the surface (contact-killing) [23-25], or eradicating early developed biofilm [10, 18, 26].

Commonly used polymeric materials in catheters production, namely silicone, polyurethane or latex, readily adhere bacteria, and so research has been dedicated to their surface modification and the development of antibacterial coatings [6, 18, 25-30]. These have been developed focusing on the incorporation and release of biocides, which include classical antimicrobial agents, such as silver compounds or ions, silver sulfadiazine, or chlorhexidine, and antibiotics, such as rifampin, or minocycline. Antibiotic-impregnated CVCs, for instance with rifampicin-miconazole [31] and chlorhexidine-silver sulfadiazine [32], have been shown to reduce the risk of infection and catheter colonization when comparing to standard catheters [31, 32]. For hemodialysis patients, for instance, there are already some alternative options in the market, as is the case of Arrowg+ard® Blue Acute HD catheter, commercialized by Teleflex Incorporated, a CVC that allows vascular access for acute hemodialysis, with chlorhexidine and chloracetate incorporated in the internal surface, and chlorhexidine and silver sulfadiazine on the external surface [33]. However, catheter tubing modification strategies rise concerns about coating stability, long-term efficiency, depletion of antimicrobial agent, or toxicity of leaching products [6, 32, 34]; not to mention the well-known risks of using antibiotics.

Apart from modification of the catheter surface, other strategies have been followed, such as

modification of the catheter cap (Table 1). The catheter caps that are mostly used nowadays are made only of plastic material and so only act as a physical barrier to prevent microorganisms from entering the catheters hub. CurosTM, commercialized by 3M, is a cap containing isopropanol that allows disinfection of the outside part of catheter hubs [35, 36]. DualCap® Disinfection and Protection System, commercialized by MeritMedical, is a system composed of two caps designed to help prevent intraluminal contamination, as well as device cross-contamination, especially important for IV catheter use over extended dwell times [37]. SwabCap™ Disinfecting Cap, commercialized by ICU Medical, is a disinfecting cap for needlefree connectors, disinfecting both the top and threads of the connector with isopropanol [38]. BD PureHub™ Disinfecting Cap, commercialized by BD, is a disinfecting cap for swabbable needlefree luer connectors prior to access, acting as a physical barrier between line accesses and sterilizing also through the use of isopropanol [39]. ClearGuardTM HD, commercialized by ICU Medical, is an antimicrobial cap that disinfects the inner lumen of the catheter hub, as it contains a rod coated with chlorhexidine that extends into the catheter hub and that, upon contact with the lock solution, releases chlorhexidine, killing bacteria [40]. ClearGuard HD, for instance, has shown efficiency in reducing CRBSIs, both when compared with standard caps (use of ClearGuard HD caps reduced in 56% CRBSIs when used for 12 months and in 69% when used for 6 months, with also 43% fewer hospital admissions for BSI and 51% fewer hospitalization days for BSI [40]) and compared with Tego connectors plus Curos caps (ClearGuard HD caps significantly lowered the rate of CRBSIs in patients undergoing hemodialysis using CVCs [35]). The downside is that these continue to be single use and therefore expensive for continuous use (for example, ~ 4€ a pair for ClearGuard HD, replaced every hemodialysis session).

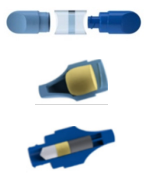
Technology	Description	Attach to open catheters	Disinfection inside the hub	Release of disinfecting agents	Reusable	Features	Refs.
3M™ Curos™ Disinfecting Cap	Cap for catheter hubs or Tego™ needle-free connectors, containing 70% isopropyl alcohol (IPA), disinfecting the surfaces of the hub/connector	✓	✗	✓	✗	- Disinfects external surfaces of catheter hub. - Disinfects in 1 minute. - Kills 99.99% of the most common pathogens. - Protects the lumen between sessions (up to 7 days). - Single use. - Antibiotic-free.	[35] [36]
DualCap® Disinfection and Protection System 	Cap for male luer connectors and needle-free valves that contain medical-grade sponges saturated with 70% IPA, disinfecting the surfaces of the device.	✗	✗	✓	✗	- Disinfects external surfaces of the connector or valve. - Cannot be attached to an open catheter hub. - Disinfects in 30secs. - Blocks 70% IPA from entering the patient's bloodstream. - Protects the lumen between sessions (up to 7 days). - Single use. - Antibiotic-free.	[37]

Table 1. Disinfecting catheter caps commercially available on the market

(continues in the next page)

Technology	Description	Attach to open catheters	Disinfection inside the hub	Release of disinfecting agents	Reusable	Features	Refs.
SwabCap™ Disinfecting Cap 	Disinfecting cap for needlefree connectors. It disinfects both the top and threads of the connector for maximum protection. A 70% IPA sponge bathes both threads and top of connector.	✗	✗	✓	✗	- Disinfects the connector surface. - Provides continuous disinfection for up to 7 days, if not removed. - Sterile, individually packed. - Ensures swabbing compliance with easily identifiable colored caps. - Reduces in 34% HA-CLABSI. - Single use. - Antibiotic-free.	[38]
BD PureHub™ Disinfecting Dap 	Disinfecting cap for swabbable needle-free luer connectors prior to access, and acts as a physical barrier between line accesses. It disinfects with a sterilised 70% IPA solution.	✗	✗	✓	✗	- Disinfects in just one minute, providing a >4 log (99.99%) reduction in bacteria. - Provides a physical barrier for up to seven days. - It is compatible with needle-free luer connectors and supports compliance with disinfection protocols to deliver optimal patient outcomes. - Provides visual confirmation of compliance with disinfection protocol. - Reduces in 41% the risk of central-line associated bloodstream infection (CLABSI) - Single use. - Antibiotic-free.	[39]
ClearGuard™ HD 	HD catheter cap for hub disinfection. It features a rod that extends into the hub. Both the rod and the cap thread are coated with chlorhexidine that elutes from them to the lock solution, killing bacteria.	✓	✓	✓	✗	- Disinfects inside and outside the hub. - Kills >99.99% of the most common pathogens. - Protects the lumen between sessions (recommended use of max 3 days). - Safety to both patient and healthcare worker. - Compatible with different lock solutions (heparin, citrate and saline solution). - Single use. - Antibiotic-free. - Cannot be used in individuals allergic to chlorohexidine.	[40]

Nevertheless, and even though progresses have been made, complete elimination of bacteria is difficult to achieve [41, 42]. There are many requirements that infection-resistant materials must fulfill in order to be effective, including 1) antimicrobial activity against a broad spectrum which can be achieved by any combination of reduction or prevention of adherence of bacterial and fungal microorganisms; reduction or prevention of biofilm formation; bacteriostatic and/or bactericidal properties; 2) adequate, long-term duration of antimicrobial activity; 3) antimicrobial activity must be present on the outer and inner surfaces of the device; 4) the polymer modification must not affect the physical properties of the biomaterial, i.e. stability, durability, elasticity and strength, thrombogenicity, cytotoxicity [43-45]. Apart from the demanding conditions, randomized clinical trials to assess the efficacy of these surface treatments are still few, and implementation in the clinics may be hindered by the high costs associated with coated catheters [33].

3. Emerging technologies

The scientific community and catheter producing/selling companies have invested in the development of new strategies to fight catheter-related infections. The use of radiation, particularly UV light, is a well-established antimicrobial modality, and has been used in healthcare environments to kill microorganisms, including drug-resistant bacteria, and inactivate viruses. Apart from being used as an external sterilization lamp, UV light has also been integrated in the development of medical devices for catheter sterilization [46-48]. Some examples include apparatus that can sterilize externally the catheter hub, the interior lumen, and even the liquid passing through. A significant advantage of these devices lies on being antibiotic-free; however, the use of UV light is still a well-known human health hazard, being both carcinogenic and cataractogenic.

To increase efficacy and reduce the possibility of development of bacterial resistance, researchers have attempted the combination of features or wavelengths, for instance. It is the case of "UV-C catheter hub sterilization and data acquisition system", a device that uses UV-C light (short wavelength of 250–280 nm) [47], but of two different wavelengths. It uses 254 nm, which acts directly on the genetic material of the pathogenic organism, cleaving critical molecular bonds and rendering the pathogen incapable of reproduction or normal cellular activity, and 190 nm, which breaks diatomic oxygen and fosters the generation of ozone from the resulting monatomic oxygen, rapidly oxidizing any organic material it comes into contact with. The use of far-UV-C light (specifically 207 nm) has, however, been deemed safe for human cells, since due to its extremely short range in biological material, it cannot penetrate the human stratum corneum (the outer dead-cell skin layer, thickness 5–20 μm) nor even the cytoplasm of individual human cells, but in contrast, it can penetrate bacteria and viruses because these cells are physically much smaller [49].

The use of other safer wavelengths has been expanding, with near-infrared (NIR) light presenting high benefits when considering biomedical and healthcare applications. Its low interaction with biological components (particularly in the biological therapeutic window of 700–950 nm, where light tissue absorption and scattering is reduced) allows it to achieve a high penetration depth and minimal off-target heating [50, 51]. In this case, however, combination with other materials may be required in order to potentiate the effect and the interaction with the microorganisms.

The reusability of the devices is also an advantage as it can help lower the associated cost. So far, however, none of these devices has been widely implemented in the clinics.

Graphene-based materials: a profitable collaboration with light?

Graphene-based materials (GBMs) offer an opportunity for development of novel antimicrobial surfaces, particularly considering their ability to escape or delay antimicrobial resistance. This happens because they act through different mechanisms, making it harder for bacteria to adapt and develop resistance. Gra-

phene is a single sheet of carbon atoms packed together in a particular structure of hybridized sp2 bonds, possessing a hydrophobic and conductive nature. GBMs in general have an exquisite set of features, depending on their oxidation degree, platelet size, thickness and conductivity, which makes them of particular interest for antimicrobial [52] and biomedical [53] applications. Their remarkable broadband optical absorption ability (which arises from the closely spaced energy levels of the loosely held π electrons) makes them photothermal agents, generating heat upon light stimulation [18, 54-57], while their intrinsic oxidative potential and ability to induce oxidative stress makes them powerful photodynamic agents when stimulated by light irradiation [23, 58]. These two last properties make GBMs interesting materials for photothermal therapy – PTT and photodynamic therapy – PDT.

Even though also absorbing UV (200–380 nm) and visible (blue and red) light, the absorption of NIR irradiation by GBMs is of particular interest, for the abovementioned reasons. GBMs stimulation with NIR light has been shown to induce hyperthermia (temperature increase) both in the materials surface and on the supernatant, and oxidative stress in biological systems [10], via a reactive oxygen species (ROS)-independent (glutathione oxidation [24]) and ROS-dependent pathways (inducing the formation of ROS and further inducing ROS-mediated programed bacterial death [56]) [23, 59-61]. Bacteria are susceptible to temperature increase, which leads to increase in membrane permeability, facilitating the permeation of photothermal agents, photosensitizers and ROS into bacteria, thus acting more locally [47]. On the other hand, the presence of ROS can also contribute to increase the permeability of damaged bacterial membranes, making them more sensitive to heat, and thus accelerating the leakage of intracellular content from bacteria [48].

GBMs can be used as photothermal agents or photosensitizers, either alone [52, 62] or in combination with other photothermal agents/photosensitizers, namely metallic nanoparticles [63, 64], antibiotics [65], or photosensitizers (as chlorin e6) [66], and so their use in the development of smart light-activated antibacterial platforms is only starting. The possibility of tuning parameters as the irradiation time, light source type and optical power, amount of graphene, distance between the light source and the GBMs, among others, widens their potential use for biomedical applications. Higher temperatures are generally translated into higher bactericidal performances; however, safety may be compromised. Combination of GBMs with other photothermal agents/photosensitizers has been explored to potentiate even more the antibacterial action.

Therefore, combination of GBMs and NIR light appears as a promising strategy to improve the antibacterial performance of medical devices. GBMs have been impregnated onto fabrics of face masks, for instance, in combination with TiO and subjected to UV LEDs, or combined with antibiotics.

Conclusions

Catheter-related bloodstream infections (CRBSIs) affect millions of people and are a significant cause of morbidity and mortality among them. CRBSIs have the highest economic impact of all healthcare associated infections, being estimated at a total cost of around $45,000 per case for the US healthcare system. The use of antibiotics to fight CRIs has caused bacterial resistance to rise, with the World Health Organization defining it as a global public health problem that should be tackled with high priority.

Some options in the market to reduce catheter-related infections have potential, avoiding the use of antibiotics and reducing these infections up to 65%, however their high cost and need for recurrent replacement makes them prohibitively expensive, a significant barrier for clinical acceptance. Devices for catheter sterilization are under development, greatly supported by the use of UV light as a way to replace the use of antibiotics and making it reusable. Graphene-based materials arise as potential collaborators in this fight, particularly when combined with NIR light, opening the possibility of developing smart,

more efficient and safer antibacterial devices, without contributing to bacterial resistance.

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